Desarrollo de Nuevas Reacciones Multicomponente basadas en la activación de isonitrilos. Aplicaciones en biomedicina

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DOCTORAT EN QUÍMICA ORGÀNICA

DESARROLLO DE NUEVAS REACCIONES MULTICOMPONENTE BASADAS EN LA ACTIVACIÓN DE ISONITRILOS. APLICACIONES EN BIOMEDICINA.

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Memòria presentada per Nicola Kielland per optar al títol de doctor per la universitat de Barcelona

Directores:

Prof. Rodolfo Lavilla, Prof. Fernando Albericio Palomera

Doctorand
Nicola Kielland

NICOLA KIELLAND
2011

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La dirección del trabajo ha sido llevada a cabo por el Dr. Rodolfo Lavilla Grifols, a quien quiero mostrar mi agradecimiento por su orientación, ayuda y amistad. Siempre me ha aconsejado lo mejor para mi formación de científico y para mi futuro profesional.

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Contribución personal a las publicaciones presentadas en la presente tesis doctoral

Capítulo 1: Recent progress in non-classical isocyanide-based MCRs.

in "Isocyanide Chemistry - Applications in Synthesis and Material Science", WILEY, ed. V.G. Nenaidenko, Accepted for publication

Autores: Rosario Ramón, Nicola Kielland, Rodolfo Lavilla

Mi contribución ha consistido en la búsqueda de bibliografía de las secciones dos y tres, la sistematización y ordenamiento de esas referencias, y en la redacción de los textos y figuras correspondientes. Así mismo, he participado en la discusión de los diferentes enfoques preliminares, en la corrección y en la redacción final, en colaboración con la Dra. Rosario Ramón y el Dr. Rodolfo Lavilla.

Capítulo 2. Boron-Based Dipolar Multicomponent Reactions: Simple Generation of Substituted Aziridines, Oxazolidines and Pyrrolidines.

Chemistry, a European Journal **2010**, *16*, 7904-7915.

Autores: N. Kielland, F. Catti, D. Bello, N. Isambert, I. Soteras, F. J. Luque, R. Lavilla

En relación a la parte experimental, he colaborado en el estudio de las condiciones de reacción, y en el "screening" de los 4 componentes, habiendo descrito la mayoría de experimentos con isonitrilos, boranos y dipolarófilos. He llevado a cabo la caracterización de un buen número de compuestos así como la elucidación estructural de los mismos por métodos espectroscópicos. He desarrollado íntegramente los estudios en fase sólida. He participado en los estudios computacionales y en la escritura del manuscrito.

Capítulo 3. Recent Developments in Reissert-Type Multicomponent Reactions.

in "Synthesis of Heterocycles via Multicomponent Reactions II",
Topics in Heterocyclic Chemistry, Vol.25, eds. R. V. A. Orru, E. Ruijter
Springer, Berlin, 2010, pp 127–168. ISBN: 978-3-642-15454-6
Autores: N. Kielland, R. Lavilla

Mi contribución ha consistido en la búsqueda de bibliografía, la sistematización y ordenamiento de esas referencias, y en la redacción de los textos y figuras correspondientes. Así mismo, he participado en la discusión de los diferentes enfoques preliminares, en la corrección y en la redacción final del capítulo, en colaboración con el Dr. Rodolfo Lavilla.

Capítulo 4. Multicomponent Access to Functionalized Mesoionic Structures Based on TFAA Activation of Isocyanides: Novel Domino Reactions

European Journal of Organic Chemistry **2009**, 617–625
Autores: M. J. Arévalo, N. Kielland, C. Masdeu, M. Miguel, N. Isambert, R. Lavilla

Tras el descubrimiento inicial de la transformación por parte de la Dra. Arévalo, mi participación ha consistido en el "screening" de isonitrilos, azinas y anhídridos fluorados. Este último componente ha presentado un trabajo especial, ya que muchos compuestos no son comerciales, lo que ha requerido unas labores de síntesis específicas. También he trabajado en la interpretación mecanística, procesos de post-condensación con nucleófilos, y en las tareas de redacción y revisión del manuscrito.

Capítulo 5. Synthesis and Properties of Oligonucleotides Carrying Isoquinoline Imidazo[1,2-a]azine Fluorescent Units

Bioconjugate Chemistry **2010**, *21*, 1622–1628
Autores: S-P. Rentero, N. Kielland, R. Lavilla, R. Eritja

Mi participación ha consistido en el diseño de experimentos, la preparación del aducto multicomponente y en asistir a la Dra. S-P. Rentero en la síntesis en fase sólida de los oligonucleótidos asi como en su conjugación. He participado en los análisis de

estabilidad de los conjugados y también el la redacción del manuscrito, en concreto las secciones de introducción y procesos multicomponente.

Adenda: Mesoionic acid fluorides as new biosensors for histamine bioimaging

(Preliminary draft to be sent for publication)

Autores: Nicola Kielland, Marc Vendrell, Rodolfo Lavilla, Young-Tae Chang

He desarrollado toda la parte experimental, incluyendo la preparación de los sensores, los experiemtos de *screening* con diferentes analitos, las pruebas de selectividad así como gran parte de los ensayos biológicos y de espectroscopía. He diseñado gran parte de la experimentación en química y en biología. He participado también en la redacción del manuscrito.

Nicola Kielland

Revisado por el Dr. Rodolfo Lavilla

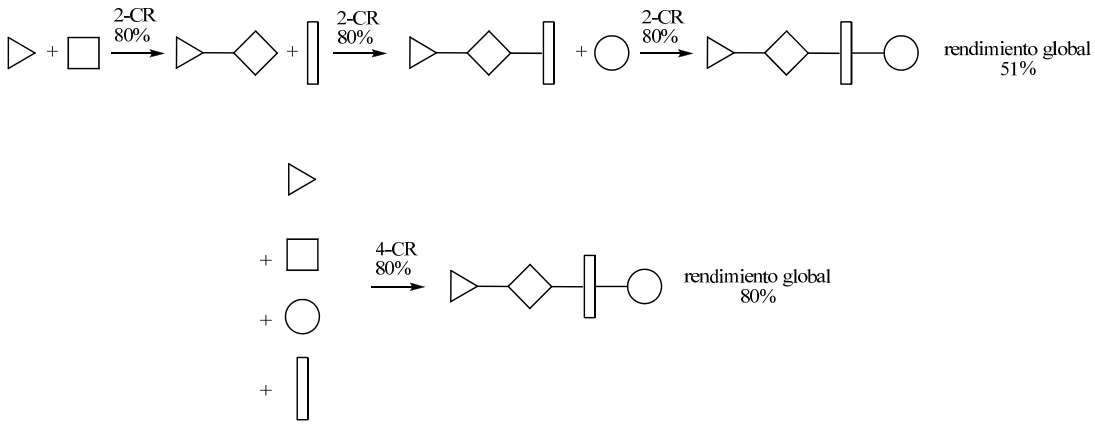
Desarrollo de nuevas reacciones multicomponente basadas en la activación de isonitrilos. Aplicaciones en biomedicina.

Nicola Kielland

1. Introducción

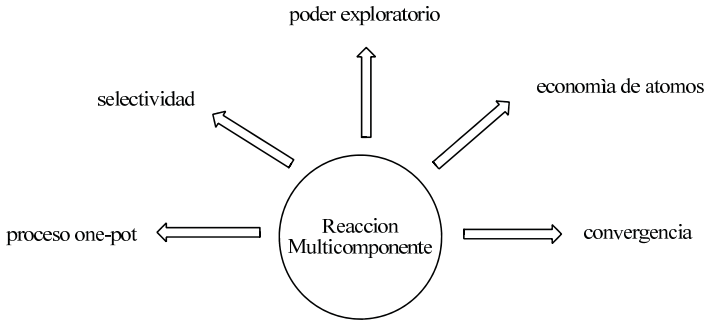
1. Desarrollo de nuevas Reacciones Multicomponente

Una reacción multicomponente (MCR) se define como un proceso en el cual tres o más reactivos forman un aducto final a través de un mecanismo de reacción unificado.[1] El esqueleto del producto obtenido tiene que estar constituido por la mayoría de los átomos de los reactivos empleados. Las MCRs presentan muchas ventajas en comparación con las síntesis convencionales, en las cuales el producto final se obtiene utilizando una secuencia multietapa con formación de un sólo enlace en cada paso. Por contraposición, las MCRs son procesos convergentes y, en consecuencia, muy convenientes en términos de rendimientos globales (asumiendo valores comparables en cada paso) y de carácter práctico (Esquema 1).



Esquema 1. Síntesis clásica y síntesis multicomponente.

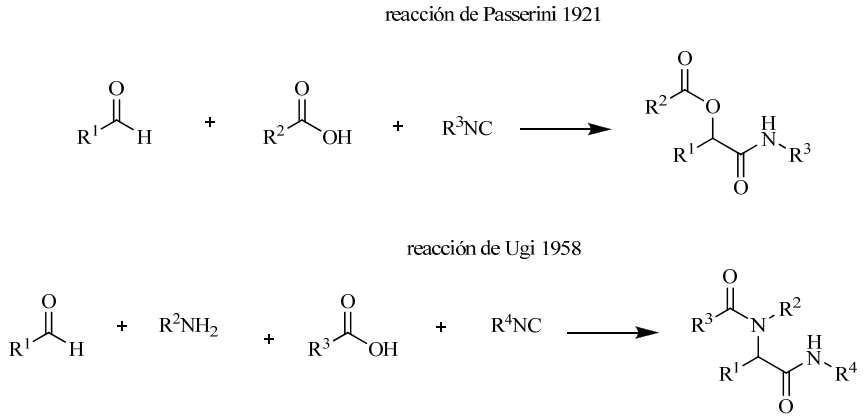
Además las MCRs son conceptualmente procesos *one-pot*, y requieren un solo *workup*, un único proceso de purificación, lo que implica un considerable ahorro de solventes y reactivos (grupos protectores, agentes activantes etc.). En este aspecto, muchos procesos de este tipo están caracterizados de una excelente economía de átomos, y desde un punto de vista teórico, se acercan mucho a los criterios de síntesis ideal.[2] (Esquema 2).



Esquema 2. Ventajas de las MCRs

Teniendo en cuenta que cada componente añade un elemento de diversidad al aducto final, una sola MCR es capaz de generar un número muy alto de productos.[3] Esta consideración suscitó un gran interés en el empleo de estos procesos para generar

librerías de compuestos de elevada diversidad estructural (típicas de *diversity-oriented synthesis).*[4] Sin embargo las primeras librerías generadas con las MCRs clásicas (las reacciones de Ugi[5] o de Passerini[6], esquema 3) no produjeron los resultados esperados en biomedicina. Esto es principalmente debido al hecho que esos aductos no tenían las características adecuadas que hoy en día se buscan en los fármacos.[7] Estas consideraciones evidenciaron la necesidad de descubrir nuevos procesos multicomponente que permitieran sintetizar, no solamente un número elevado de productos, sino también una gran diversidad en términos de tipología esqueletal. De este modo, se enfocó la investigación hacia a productos de tipo *drug-like,* privilegiando la generación de una mayor variabilidad en la conectividad. Actualmente, muchas estructuras son fácilmente accesibles usando esta metodología, y las MCRs se utilizan masivamente en síntesis de productos bioactivos y también en ciencia de materiales.

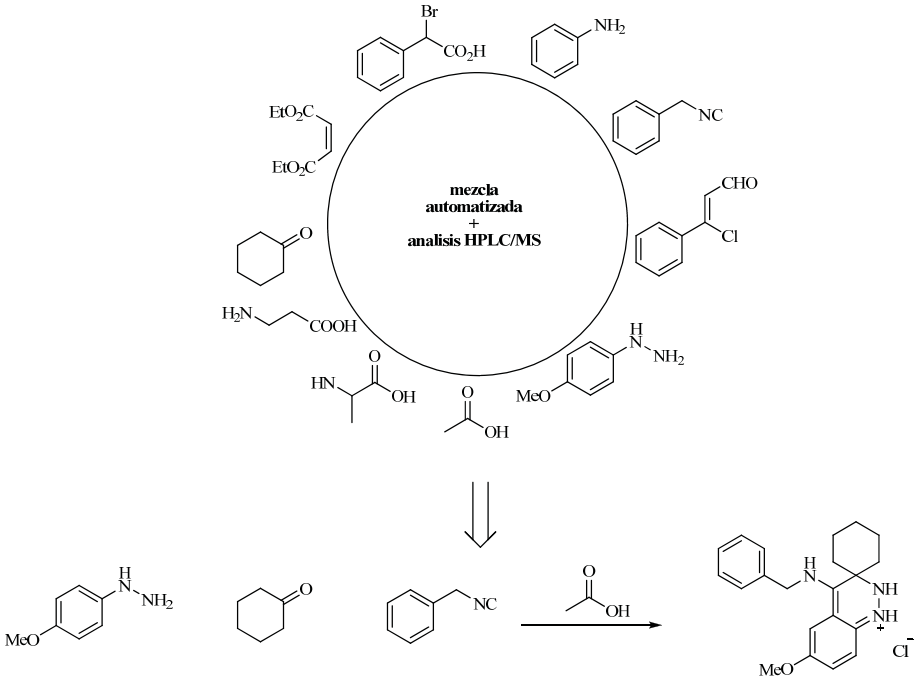


Esquema 3. Las reacciones de Passerini y de Ugi.

La historia de las MCRs se halla estrictamente ligada a los estudios de reactividad de los isonitrilos. Este grupo funcional se caracteriza por tener una estructura de tipo carbenoide,[8] y muestra al mismo tiempo la capacidad de interaccionar con electrófilos y

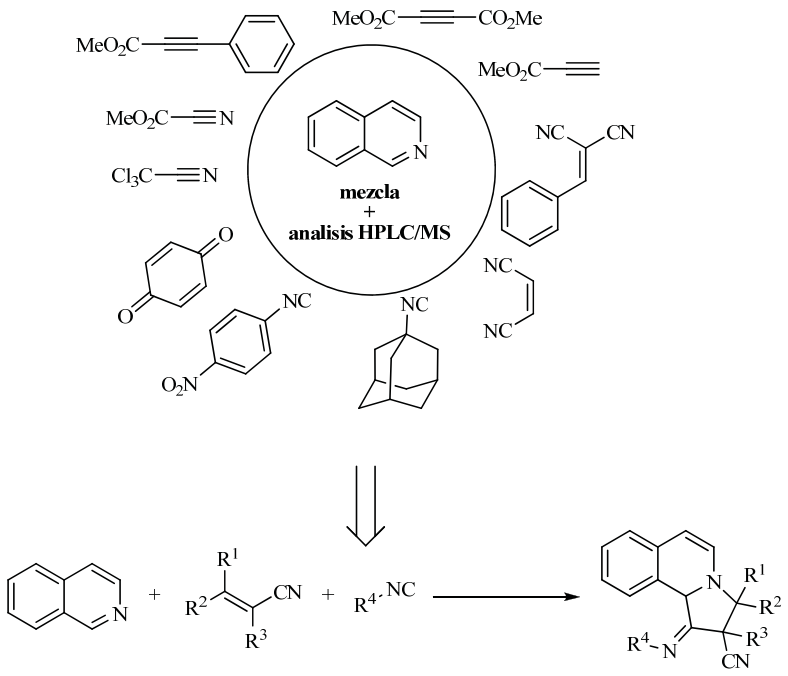
con nucleófilos. Consecuentemente los isonitrilos representan un tipo estructural privilegiado en este tipo de procesos. Los ejemplos más representativos son las reacciones de Ugi y de Passerini,[5,6] indudablemente las transformaciones más fructíferas en el campo de las MCRs, y que siguen siendo de gran interés, como demuestran las continuas publicaciones sobre post-modificaciones de sus aductos,[9] variantes intramoleculares, procesos tándem, macrociclaciones,[10] diseño de nuevas reacciones basadas en variaciones mecanisticas,[11] y el desarrollo de métodos para generar sus componentes *in situ*.[12-14]

Las MCRs son, en muchos casos, procesos muy complejos desde el punto de vista mecanístico. La coexistencia de más de dos componentes en el seno de reacción introduce mucha variabilidad en las posibilidades de interacción entre los reactantes. Además las mismas combinaciones pueden dar resultados diferentes variando las condiciones de reacción (solventes, temperaturas, presencia de catalizadores, etc.). Se han empleado varios métodos para el descubrimiento sistemático de nuevas MCRs con suerte diversa. Por ejemplo Weber utilizó un sistema automatizado para mezclar diez compuestos con diferentes grupos funcionales en todas las combinaciones posibles y los aductos resultantes se analizaron por HPLC/MS. De esta forma descubrió una nueva reacción entre cetonas, isonitrilos e hidracinas para proporcionar 2,3-dihidrocinnolinas (Esquema 4).[15]



Esquema 4. Método de Weber para el descubrimiento de nuevas MCRs.

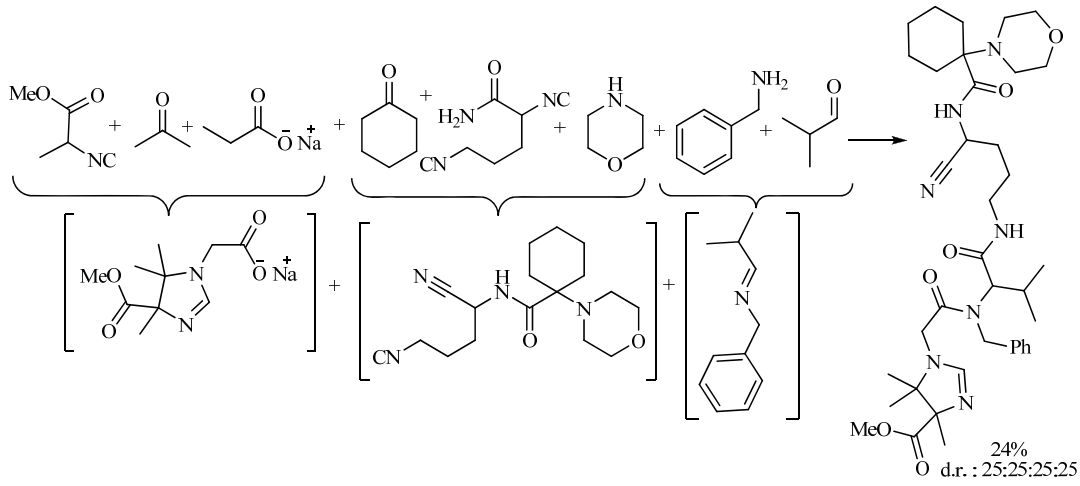
En un experimento similar, Mironov empleó un método semi-racional, combinando isoquinolinas con varios aceptores de Michael y diversos nucleófilos, como potenciales promotores para una reacción en cascada (Esquema 5).[16,17] De esta forma descubrió un nuevo método de activación de isoquinolinas en procesos de tipo Reissert, utilizando olefinas *gem*-diactivadas. Sin embargo los esfuerzos invertidos para el desarrollo de nuevas MCRs por métodos combinatorios no han llevado, hasta la fecha, a unos resultados de impacto elevado.



Esquema 5. Método de Mironov para el descubrimiento de nuevas MCRs

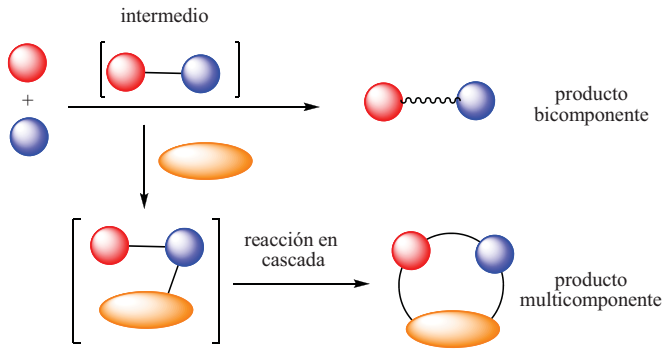
Un método alternativo para generar nuevos aductos multicomponente es la unión de MCRs conocidas en procesos de tipo tándem. Los ejemplos más famosos son los procesos de hasta ocho componentes desarrollados por Orru y colaboradores.[18] En estas transformaciones existen grupos funcionales inertes en una primera etapa, y que reaccionan selectivamente en la siguiente. Ello permite unificar varios procesos de tipo *one pot*. De esta manera, se ha descrito la síntesis multicomponente de 2-imidazolinas y *N*-(cianometil)amidas basada en la unión de MCRs de isonitrilos (Esquema 6). Aunque estos protocolos, estrictamente hablando, se consideran más procesos secuenciales que

MCRs propiamente dichas, los resultados obtenidos ponen de manifiesto la complejidad que se puede alcanzar selectivamente en un solo paso con este tipo de aproximación.



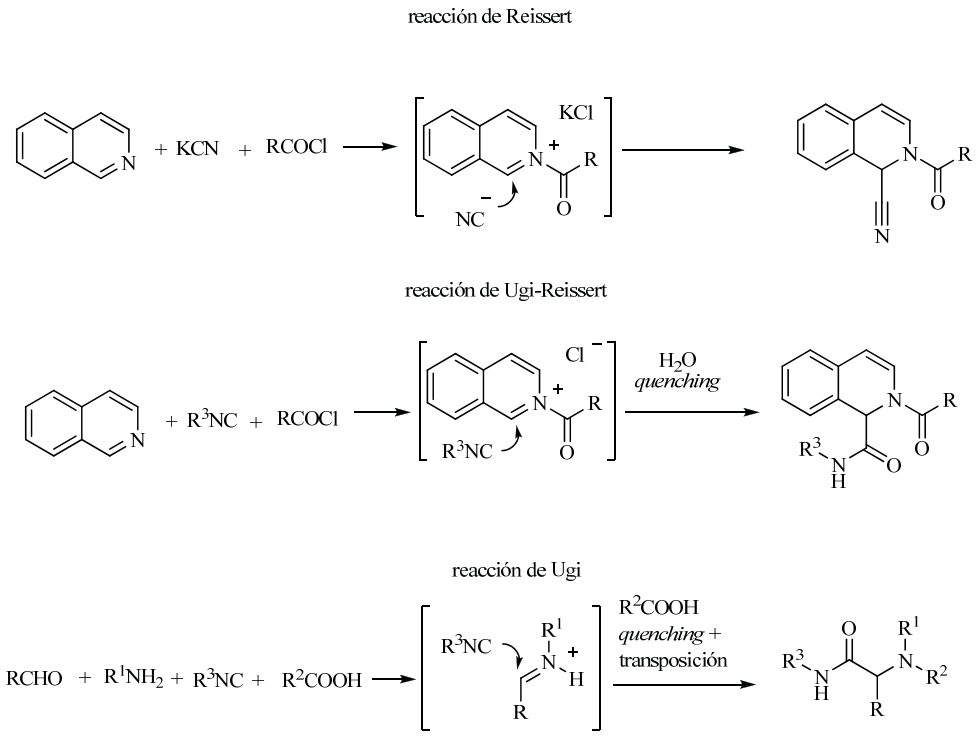
Esquema 6. Desarrollo de nuevas MCRs por unión de MCRs conocidas.

Sin embargo la estrategia más fructífera en el desarrollo de nuevas MCRs es una aproximación racional de tipo mecanístico, que se basa en el diseño de nuevos procesos mediante hipótesis razonables de previsión de reactividad. En un caso típico, una especie química es activada por un segundo reactivo para originar un intermedio de reacción que será atrapado por un tercer reactante para dar lugar al aducto final después de una serie de eventos más o menos larga y compleja (Esquema 7).



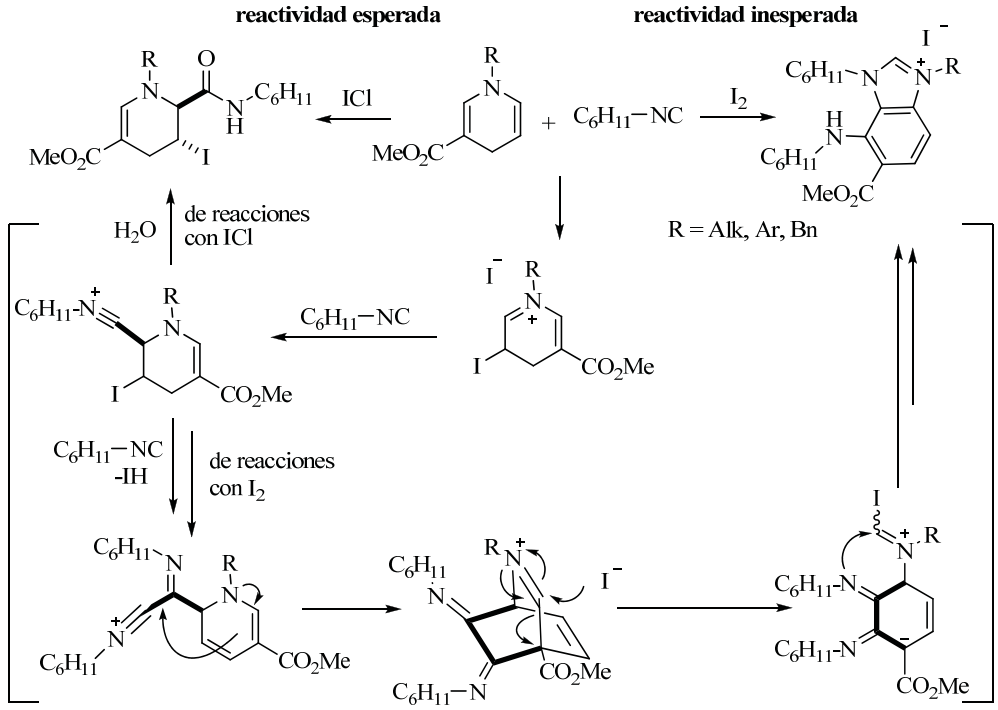
Esquema 7. Diseño racional de nuevas MCRs.

Usualmente se puede interferir en el mecanismo de procesos conocidos intentando atrapar los intermedios de reacciones de dos componentes con una tercera especie. En muchos casos, este tipo de experimentos ha originado la reactividad esperada dando lugar a interesantes variantes multicomponente de los procesos originales. Por ejemplo, en nuestro laboratorio se describió la síntesis de dihidroazinas-α-cabamoiladas por modificación de la reacción de Reissert.[19,20] En este proceso, el anión cianuro de la reacción clásica ha sido sustituido por un isonitrilo, originando una nueva transformación de tres componentes a partir de una reacción conocida. En este contexto, se puede comparar el intermedio azinio con el análogo iminio, generado en procesos de tipo Ugi. Por analogía con dichas reacciones el proceso se ha denominado reacción de Ugi-Reissert (Esquema 8).



Esquema 8. La reacción de Ugi-Reissert: un ejemplo de diseño racional de MCR.

Sin embargo, en algunos casos, la previsión inicial de reactividad no se observa, y una pequeña variación en las condiciones de reacción puede desencadenar una cascada de eventos completamente distinta. Por ejemplo en nuestro laboratorio se desarrolló la síntesis de tetrahidropiridinas yodo-carbamoiladas por reacción de dihidropiridinas con isonitrilos en presencia de ICl.[21] Sorprendentemente el empleo de yodo en esta transformación llevó a una inesperada cascada de reacción con formación final de una sal de benzimidazolio (Esquema 9).[22]

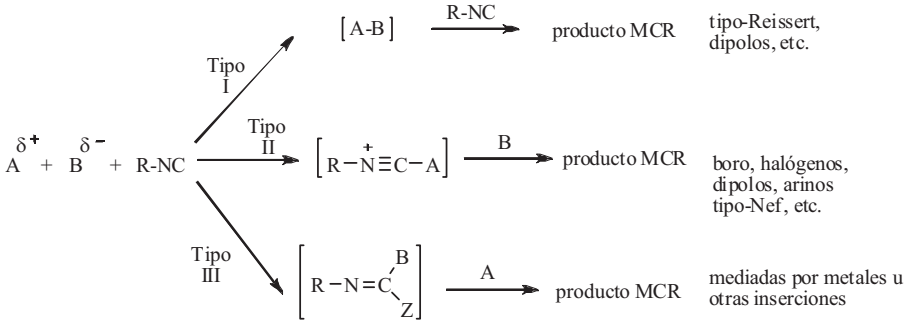


Esquema 9. Reacción de isonitrilos, dihidropiridinas y fuentes de I^+: procesos esperados e inesperados.

Desarrollo de nuevas MCRs basadas en activación de isonitrilos

La química de los isonitrilos sigue siendo de interés fundamental en la síntesis orgánica. Como se ha mencionado, la capacidad para interaccionar con electrófilos y con nucleófilos hace de este grupo el sustrato clave en muchos procesos multicomponente. Su reactividad más clásica se expresa con iones iminio u oxocarbenio como especies electrófilicas. Estas combinaciones llevan a procesos de tipo Ugi o Passerini que siguen teniendo una enorme utilidad sintética. En tiempos recientes, la interacción con otros tipos de electrófilos ha permitido sintetizar una gran variedad de aductos de interés farmacéutico. En una aproximación esquemática propuesta por nuestro grupo, es posible clasificar las MCRs basadas en isonitrilos en tres tipos (Esquema 10).[23] Las reacciones de

tipo I se refieren a procesos en los cuales los isonitrilos reaccionan como nucleófilos con aductos originados mediante una interacción de dos componentes para dar un intermedio activado. Las reacciones de tipo II incluyen procesos en los cuales los isonitrilos se activan directamente por un componente electrofilico para dar un intermedio que reacciona en una segunda etapa con un tercer componente. Las reacciones de tipo III cubren los procesos que no se pueden englobar en las categorías precedentes, e incluyen principalmente interacciones con metales y procesos de inserción de isonitrilos. (Esquema 10).



Esquema 10. Modalidades de reacción de los isonitrilos.

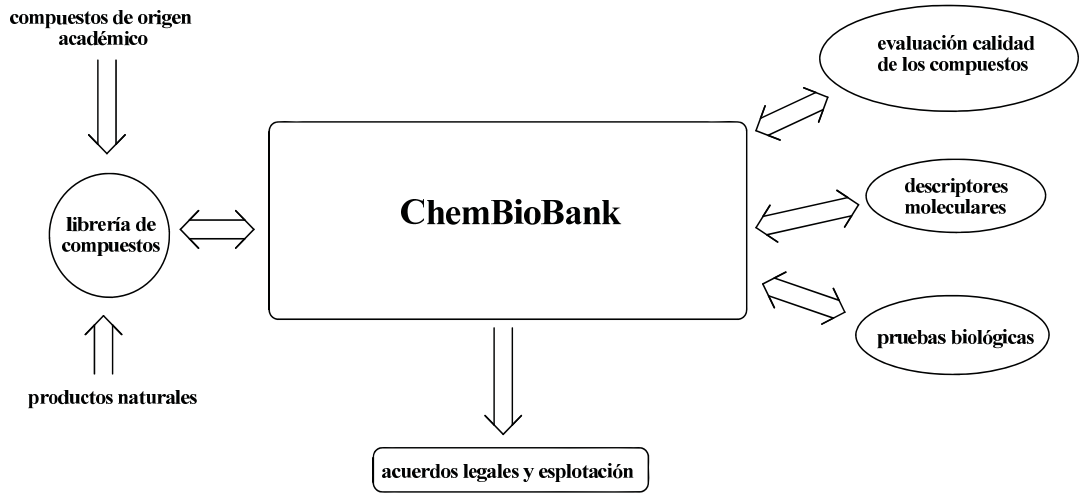
Las reacciones de tipo I son las más estudiadas hasta ahora. A este grupo pertenecen muchos procesos clásicos, comprendiendo transformaciones de tipo Ugi, Passerini y Van Leusen. Este hecho se fundamenta principalmente en la escasa nucleofilia de los isonitrilos en comparación con otras especies. De ese modo, en la mayoría de los casos un componente nucleófilo se activará por un electrófilo para dar un intermedio que interaccionará posteriormente con el isonitrilo. Los casos en los cuales los isonitrilos son activados directamente (tipo II) son mucho menos frecuentes, y representan un campo de investigación casi inexplorado y capaz de generar productos

nuevos de forma sencilla y directa. Un número aún más bajo de procesos se pueden atribuir al tipo III. Ello es debido a la tendencia de los isonitrilos a dar complejos estables con metales (con raras excepciones), lo cual normalmente impide procesos catalíticos, y muchas reacciones de este grupo son secuencias tándem más que verdaderas MCRs, o requieren el uso exclusivo de algunas especies muy impedidas estéricamente.

3. Aplicaciones en biomedicina de productos de MCRs

En tiempos recientes, la química combinatoria y la síntesis en paralelo han tenido un gran impacto en las estrategias para el descubrimiento de nuevos fármacos. En este contexto, el intenso desarrollo de las MCRs ha hecho de esta clase de transformaciones una de las metodologías más fructíferas en el campo de la química médica. Las nuevas aproximaciones para el diseño de MCRs privilegian la síntesis de compuestos heterocíclicos pequeños que contengan subestructuras frecuentes en fármacos y productos naturales. Adicionalmente, los mismos heterociclos representan una clase de compuestos muy productiva en MCRs.[24] De esta forma los aductos de estos nuevos procesos incorporan desde el principio las características favorables para su eventual uso como fármacos.[7] El desarrollo de nuevos procesos MCR basados en heterociclos sigue siendo una empresa muy exigente en ciencia básica. Otro reto formidable, sobre todo en ambitos de investigación pública, se basa en desarrollar aplicaciones y usos en biomedicina para los nuevos aductos MCRs así generados. Para ello, recientemente se han puesto a punto algunos métodos sistemáticos basados en la generación de bibliotecas de compuestos químicos, principalmente de origen académico, y su caracterización por métodos virtuales y experimentales de *screening*. Una iniciativa prometedora en este campo es el ChemBioBank, desarrollado por el Parc Cientific de Barcelona (PCB-UB),

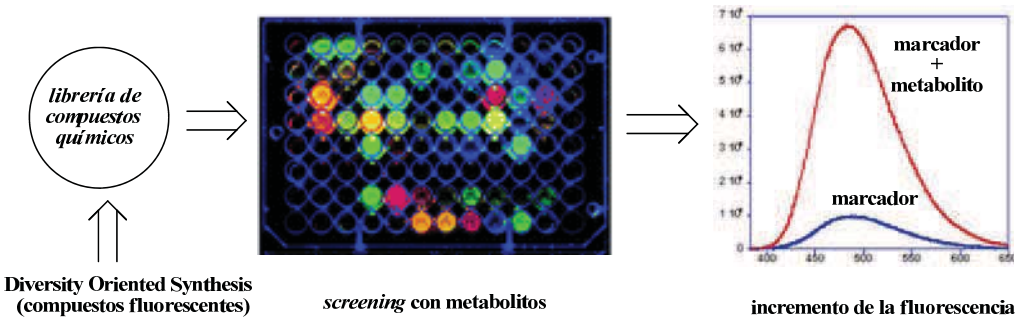
en colaboración con la Universidad de Santiago de Compostela (USC), y el Instituto Municipal d'Investigació Mèdica (IMIM) (Esquema 11).[25]



Esquema 11. Estructura y función del ChemBioBank.

Los métodos combinatorios para el desarrollo de nuevas aplicaciones desde librerías de compuestos han tenido éxito también en otros campos de la biomedicina. Por ejemplo, el grupo del Prof. Chang ha desarrollado una estrategia para el descubrimiento de nuevos marcadores biológicos utilizando librerías[i] de aductos fluorescentes. Esta tecnología llamada *Diversity Oriented Fluorescent Library Approach* (DOFLA)[26] permite de analizar los cambios de fluorescencia de las moléculas en presencia de hasta 90 analitos de interés biológico (Esquema 12).

[i] En esta tesis se usará la palabra "librería" como sinónimo de "quimioteca" o "colección de compuestos". Por una disquisición sobre la semántica del término ver: R. Hoffmann (2001), Not a Library, *Angew. Chem. Int. Ed.* ***40***, 3337-3340.



Esquema 12. *Diversity Oriented Fluorescent Library Approach* (DOFLA), desarrollado en el laboratorio del prof. Chang.

Además de estas metodologías sistemáticas, se pueden identificar nuevas aplicaciones mediante la participación en proyectos interdisciplinares. En nuestro laboratorio, gracias a varias colaboraciones con otros grupos, se han descrito nuevos *hits* frente a diversas dianas terapéuticas que implicaban nuevos *scaffolds* sin necesidad de ningún cribado sistemático. En este aspecto la participación activa en congresos y conferencias, y el diálogo con otros grupos de investigación ha sido un factor clave; sin embargo el desarrollo de métodos sistemáticos para estudiar las propiedades de librerías de compuestos podría dar lugar a un incremento importante en la cantidad y la calidad de las aplicaciones.

Objetivos

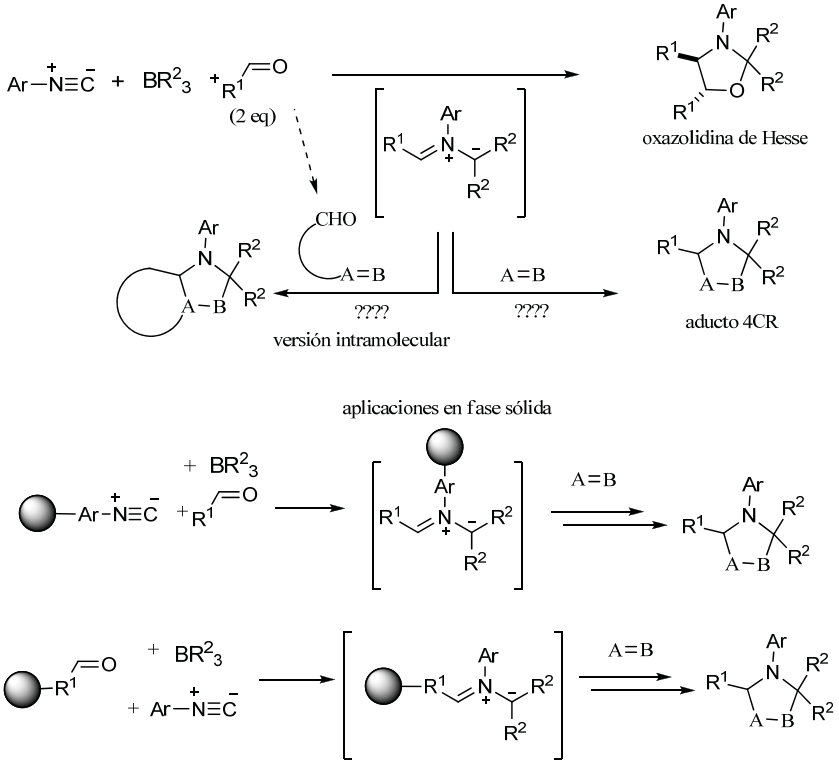
1- Desarrollo de nuevas MCRs basadas en la activación de isonitrilos con organoboranos.

1.1- Se plantea llevar a cabo un estudio bibliográfico sistemático sobre la reactividad de los isonitrilos, con particular énfasis sobre resultados recientes y procesos innovadores (Capítulo 1).

1.2- Se estudiará y modificará la síntesis de oxazolidinas descrita por Hesse en una comunicación del 1965.[27] En estos trabajos, Hesse sugiere la activación del isonitrilo por un borano para originar, mediante interacción con un aldehído, un intermedio de tipo dipolar (Esquema 13). Ese iluro de azometino es atrapado por otro equivalente de aldehído para dar lugar, de manera estereoselectiva, al aducto de oxazolidina *trans*. Sin embargo las tecnologías de los años sesenta no permitieron determinar la estereoquímica del producto final por RMN, sino que se analizó por correlación química (hidrólisis). Además de una validación del proceso, se pretende asignar las estereoquímicas de los productos por métodos espectroscópicos. Así mismo, se ampliarán los rangos de boranos, de aldehídos y de isonitrilos. Se ensayará también la diferenciación de los dos equivalentes de aldehído para dar lugar a oxazolidinas mixtas.

Adicionalmente se pretende explorar la reactividad del intermedio iluro de azometino con diversos dipolarófilos y ampliar los rangos de los componentes, así como desarrollar diferentes procesos en fase sólida (para facilitar la purificación), y

aproximaciones intramoleculares. Se utilizaran métodos computacionales para explicar la selectividad intrínseca de la reacción y elaborar una justificación razonable de los resultados experimentales (Capítulo 2).

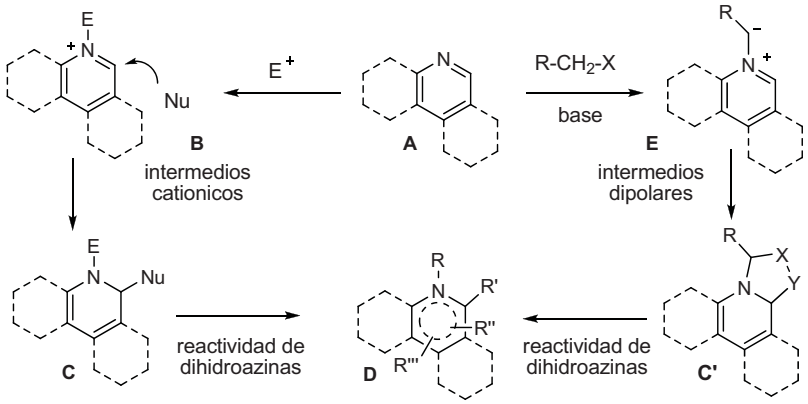


Esquema 13. Plan de modificacion de la sintesis de oxazolidinas de Hesse.

2- Estudio de reactividad de isonitrilos y azinas en presencia de nuevos agentes activantes. Aplicaciones en biomedicina.

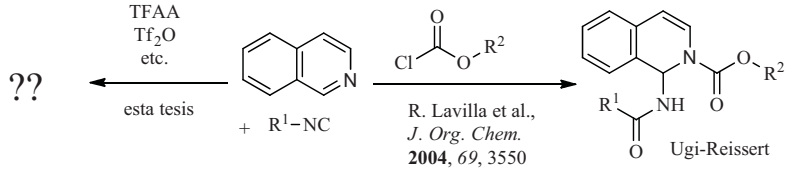
2.1- Se plantea realizar una revisión bibliográfica de la reactividad de las azinas en química multicomponente, centrada en los procesos de tipo Reissert (Esquema 14).

(Capítulo 3). Ello nos permitirá contextualizar la problemática de la metodología y sus aplicaciones a la síntesis de moléculas de interés en biomedicina.



Esquema 14. Reactividad típica de azinas.

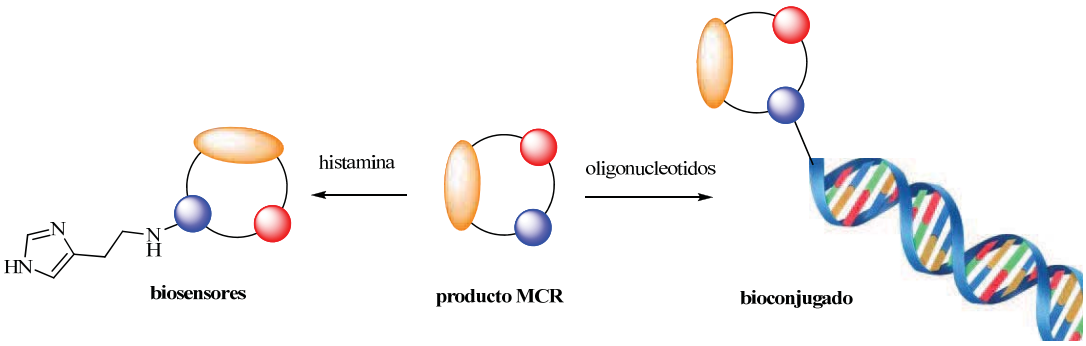
2.2- Un resultado relevante desarrollado en nuestro laboratorio describe la interacción de isoquinolinas con isonitrilos y cloroformiatos. Se trata de una reacción de de tipo Ugi-Reissert que origina aductos tricomponente con estructura de dihidroazina-α-carbamoilada. En esta tesis, se pretende desarrollar una nueva MCR basada en la activación alternativa de isonitrilos por diferentes agentes electrofílicos para su interacción con azinas (Esquema 15).



Esquema 15. Posibles escenarios de la interacción isonitrilos activados y azinas.

En este contexto se investigará la reactividad de azinas e isonitrilos en presencia de nuevos agentes activantes. Con este propósito se emplearan anhídridos de diferente electrofilia (Tf_2O, TFAA, así como otros anhídridos halogenados) con el intento de modular la reactividad del sistema. Se compararan los resultados experimentales con los precedentes bibliográficos del laboratorio sobre la reacción de Ugi-Reissert. Se explorarán los posibles perfiles mecanísticos del proceso. También se pretende establecer las estructuras de los aductos, el rango de aplicación de la MCR, así como la reactividad potencial de los aductos.

2.3- Se pretende la exploración de algunas aplicaciones de los aductos MCR, obtenidos por estos métodos, en el campo de la biomedicina (Esquema 16). En este contexto, resultan particularmente atractivos los proyectos interdisciplinares, como son la formación de bioconjugados con biomoléculas (oligonucleótidos, Capítulo 5), y el desarrollo de biosensores de metabolitos (histamina, Capítulo 6).



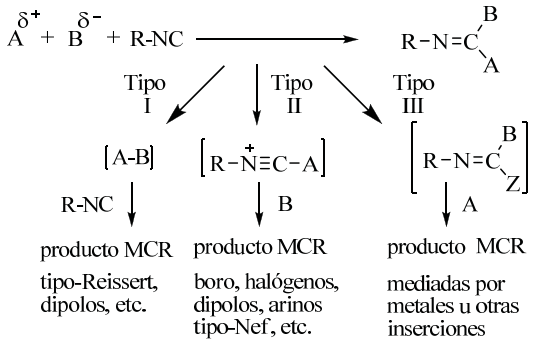
Esquema 16. Aplicaciones en biomedicina.

Capítulo 1: Recent progress in non-classical isocyanide-based MCRs.

in "Isocyanide Chemistry - Applications in Synthesis and Material Science", WILEY, ed. V.G. Nenaidenko, Accepted for publication

Autores: Rosario Ramón, Nicola Kielland, Rodolfo Lavilla

El capítulo describe una amplia colección de procesos multicomponente basados en isonitrilos, excluyendo las variaciones mecanísticas de los procesos de tipo Ugi o Passerini. Se ordenan los procesos en tres secciones. La primera parte trata de las reacciones de isonitrilos con complejos derivados de la interacción de nucleófilos y reactivos complementarios. La segunda sección describe la reactividad derivada de la activación directa de isonitrilos con electrófilos, seguida de la incorporación de un tercer reactante. En la sección 3 se resumen los procesos que no pueden ser incluidos en las partes anteriores, principalmente procesos de inserción directa del isonitrilo y metalaciones (Esquema 17). Esta clasificación no se basa en una descripción mecanística precisa de procesos particulares, sino en principios básicos de reactividad de isonitrilos a fin de establecer una clasificación útil de tipos de transformaciones. Para detalles de los diferentes procesos se remite al lector a la consulta de revisiones bibliográficas o a los trabajos originales.



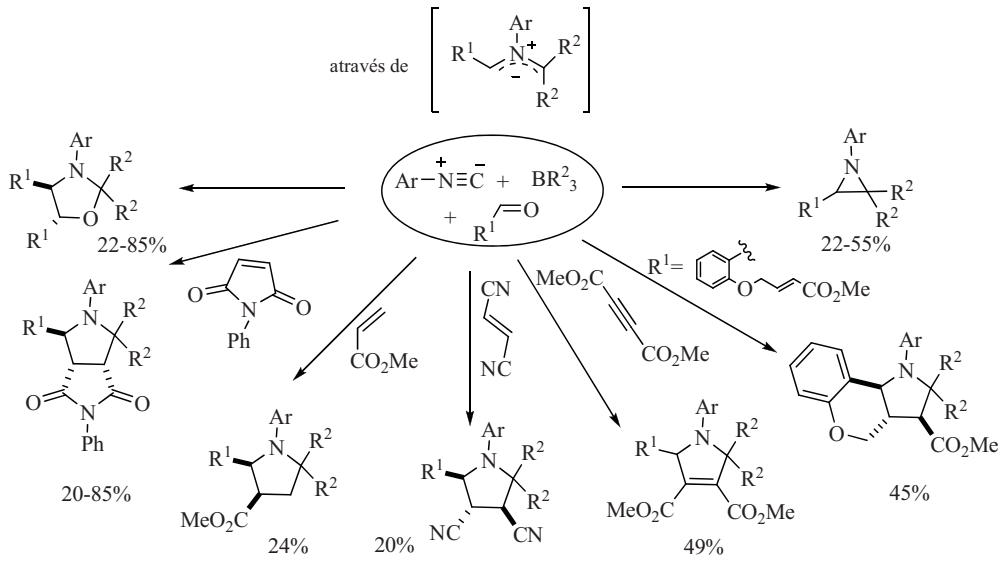
Esquema 17. Clasificación de la reactividad de los isonitrilos.

Capítulo 2. Boron-Based Dipolar Multicomponent Reactions: Simple Generation of Substituted Aziridines, Oxazolidines and Pyrrolidines.

Chemistry, a European Journal **2010**, *16*, 7904-7915.

Autores: N. Kielland, F. Catti, D. Bello, N. Isambert, I. Soteras, F. J. Luque, R. Lavilla

En este capítulo se describen nuevas MCRs de aldehídos, isonitrilos, organoboranos y dipolarófilos para generar de forma eficiente varios *scaffolds* como aziridinas, oxazolidinas y pirrolidinas diversamente sustituidas (Esquema 18). Esta química inspirada por una comunicación breve de Hesse en 1965 es simple y requiere condiciones suaves.



Esquema 18. Síntesis de aziridinas, oxazolidinas y pirrolidinas por MCRs de isonitrilos, boranos, aldehídos y dipolarofílos.

El proceso describe la interacción de isonitrilos, boranos y aldehídos para generar un iluro de azometíno, que reacciona en una cicloadición con un segundo equivalente de aldehído para formar oxazolidinas. Se ha logrado sustituir el segundo equivalente de aldehído por una amplia selección de dipolarofilos y sintetizar, de ese modo, pirrolidinas sustituidas de una forma alternativa a las síntesis tradicionales. Se ha investigado la reactividad de cada componente. Adicionalmente se han hecho consideraciones sobre la estereoquímica observada en la formación de oxazolidinas y de aductos de cuatro componentes con el soporte de estudios computacionales, que han permitido identificar los factores que gobiernan el resultado de la MCR. También se describen los rangos de reactividad de cada componente y se han considerado los mecanismos razonables del proceso. Finalmente se ha desarrollado una versión intramolecular de la reacción y versiones en fase sólida de estos procesos (usando aldehídos e isonitrilos soportados en resinas convenientemente funcionalizadas) aportando nuevas posibilidades de síntesis. En conclusión, los resultados obtenidos constituyen una innovación sustancial, validan el descubrimiento original de Hesse y describen nuevas vías de reactividad en la interacción de boranos, isonitrilos y compuestos carbonílicos.

Capítulo 3. Recent Developments in Reissert-Type Multicomponent Reactions.

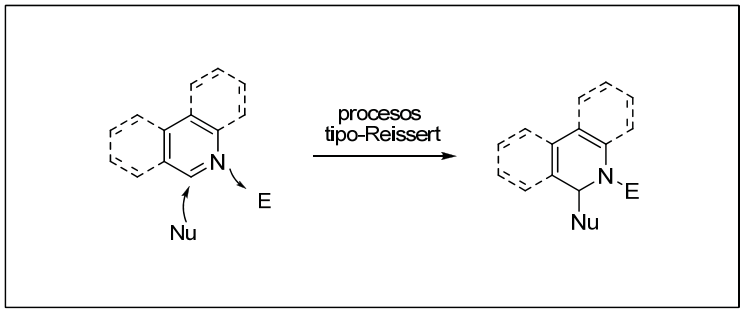
in Synthesis of Heterocycles via Multicomponent Reactions II,

Topics in Heterocyclic Chemistry, Vol.25, eds. R. V. A. Orru, E. Ruijter

Springer, Berlin, 2010, pp 127–168. ISBN: 978-3-642-15454-6

Autores: N. Kielland, R. Lavilla

El capítulo trata de la reacción de Reissert como el origen de una amplia familia de MCRs que involucran azinas, agentes activantes electrófilos y nucleófilos, para dar dihidroazinas *N*,α-disustituidas. Se ha enfocado la revisión en base a la reactividad general de las especies implicadas, clasificando los procesos de manera consecuente. La primera parte trata de interacciones de nucleófilos con azinas activadas, incluyendo versiones asimétricas. Se describen las clases más comunes de agentes activantes, de nucleófilos y de azinas. La segunda sección se centra en procesos en los cuales las azinas están activadas por reactantes capaces de generar intermedios de tipo dipolar. Estas especies reaccionan típicamente con dipolarófilos, y evolucionan (mayoritariamente en cicloadiciones [3+2]) hacia los productos finales. Se dedica la última sección a la química de los isonitrilos que, en este contexto, generan un altísimo grado de complejidad, modulando largas cascadas de eventos. También se describe la reactividad de las dihídroazinas obtenidas en reacciones de tipo multicomponente (Esquema 19).



Esquema 19. Procesos tipo-Reissert.

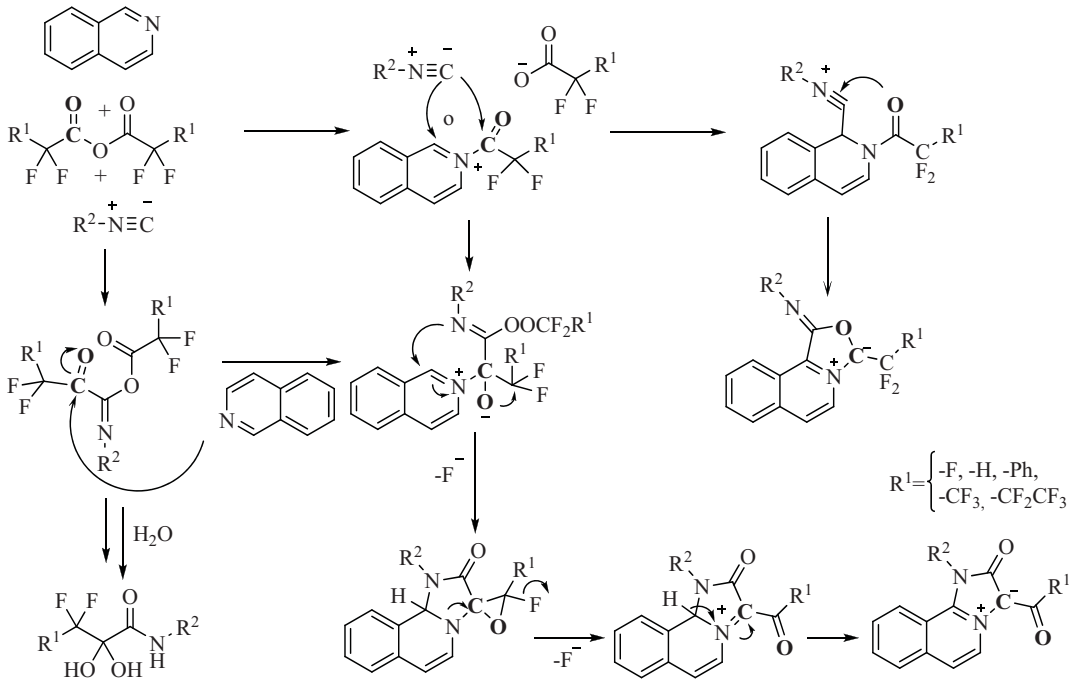
Capítulo 4. Multicomponent Access to Functionalized Mesoionic Structures Based on TFAA Activation of Isocyanides: Novel Domino Reactions

European Journal of Organic Chemistry **2009**, 617–625

Autores: M. J. Arévalo, N. Kielland, C. Masdeu, M. Miguel, N. Isambert, R. Lavilla

En este capítulo se describe una nueva MCR de azinas con TFAA (anhídrido trifluoroacético) e isonitrilos para dar fluoruros de ácido mesoiónicos en un proceso dominó. La introducción de TFAA como agente activante en reacciones de tipo Ugi-Reissert modifica drásticamente la reactividad del sistema, en consecuencia el proceso descrito representa una nueva MCR, más que una variante de procesos Ugi-Reissert. Esta reacción tiene un carácter general, tolera una amplia gama de sustituyentes en cada componente y la conectividad de los átomos en los aductos finales sugiere una secuencia mecanística sin precedentes. En este aspecto, es interesante notar como la reacción puede iniciarse por dos caminos alternativos. Ambas vías (activación del isonitrilo y ataque nucleofílico de la isoquinolina,[28] o activación de la isoquinolina[19,29] y ataque nucleofílico del isonitrilo) tienen precedentes en procesos análogos descritos en la literatura, y confluyen hacia a un intermedio común. (Esquema 20) El grupo funcional sintetizado en la mayoría de las reacciones es un fluoruro de acido mesoiónico: un tipo estructural inédito en la literatura y que presenta características de gran interés. Los aductos muestran la reactividad esperada con nucleófilos (alcoholes, tioles o aminas), permitiendo la introducción de un componente sintético adicional. En este contexto, la novedad más

relevante reside en la baja reactividad del fluoruro, posiblemente disminuida por la presencia del dipolo; consecuentemente, esta especie resulta muy estable. Ello ha posibilitado su aislamiento, caracterización, así como su almacenamiento, lo que ha devenido un factor clave en sus aplicaciones, que se basan en su reactividad en disolventes acuosos, tampones básicos o incluso en cultivos celulares.



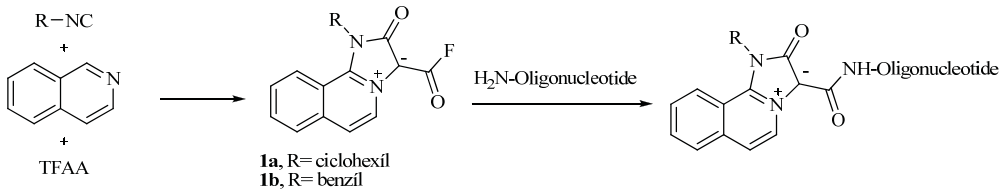
Esquema 20. Síntesis de fluoruros de acido, cetonas o aldehídos mesoiónicos por MCR de azinas, isonitrilos y anhídridos fluorados.

Capítulo 5. Synthesis and Properties of Oligonucleotides Carrying Isoquinoline Imidazo[1,2-a]azine Fluorescent Units

Bioconjugate Chemistry **2010**, *21*, 1622–1628

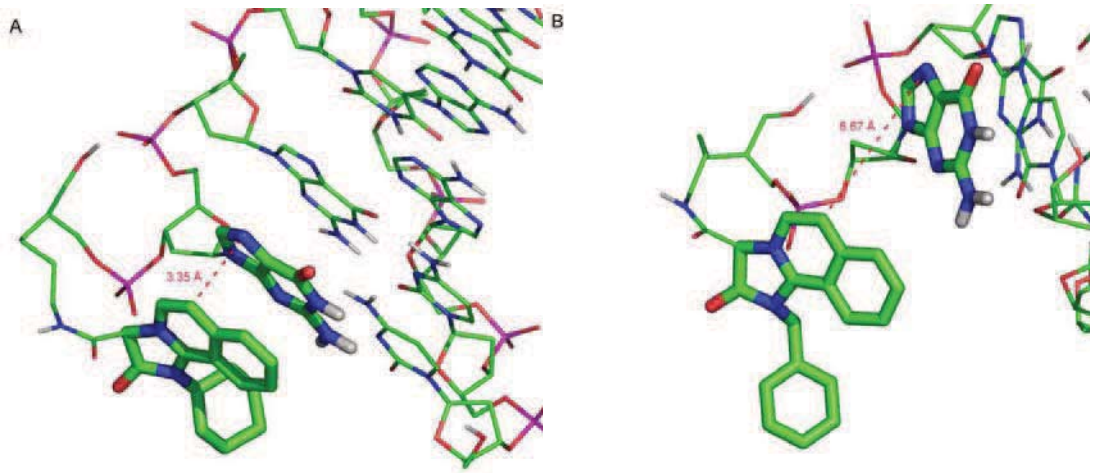
Autores: S-P. Rentero, N. Kielland, R. Lavilla, R. Eritja

En este capítulo se describe la síntesis de conjugados de oligonucleótidos con nuevos marcadores fluorescentes de estructura tipo imidazo[1,2-*a*]azina (descritos en el capítulo 4). Se detalla la preparación de esos oligonucleótidos modificados por incorporación del fluoróforo ligado a la posición 3' o 5', a través de un espaciador aminado, en fase solución. La síntesis de los oligonucleótidos se lleva a cabo en fase sólida por métodos automatizados. Los conjugados se obtienen con alto grado de pureza (Esquema 21). Se han preparado derivados con diversa longitud de secuencia. Los oligonucleótidos autocomplementarios marcados forman dímeros estables. El análisis de las curvas de punto de fusión demuestra que el dímero de ADN modificado con el marcador de fluorescencia ligado a una de las extremidades presenta un ligero aumento en la estabilidad de la doble hélice. Adicionalmente la desnaturalización provoca un aumento en la fluorescencia. Estudios de cultivos celulares han permitido observar la internalización de los oligonucleótidos marcados en células HeLa, en presencia de agentes de transfección.



Esquema 21. Síntesis de bioconjugados de oligonucleótidos con nuevos marcadores fluorescentes con estructura tipo imidazo[1,2-*a*]azina.

Estudios preliminares de modelización molecular sugieren modos de interacción específicos entre residuos del fluoróforo con la última base de la secuencia (Esquema 22). Ello puede ser de interés en el diseño de nuevos marcadores que den lugar a conjugados con propiedades optimizadas.

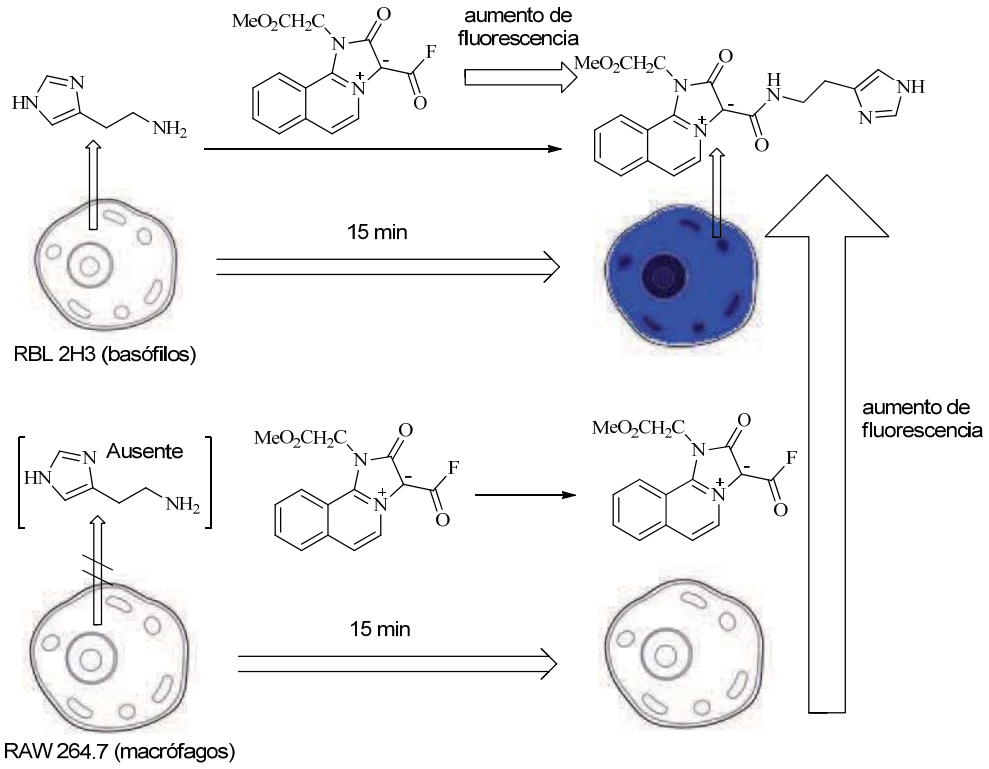


Esquema 22. Conformaciones más favorables de los conjugados **1a** y **1b** (esquema 21). En figura se explicitan la guanina terminal de la secuencia nucleotidica y la triazina con líneas más gruesas. Las distancias entre la guanina y el derivado de isoquinolina están indicadas.

Adenda

Mesoionic acid fluorides as new biosensors for histamine bioimaging

En este capítulo se describe el desarrollo de un nuevo biosensor de histamina aplicando los dipolos descritos en el capítulo 4 a la metodología DOFLA (Esquema 23). Estos estudios se han llevado a cabo en los laboratorios del Singapore Bioimaging Consortium (Biopolis) en colaboración con el grupo del Prof. Chang. La formación de un aducto covalente entre los fluoruros de ácido mesoiónicos con histamina causa un sensible aumento en la intensidad de fluorescencia y un desplazamiento ratiométrico del máximo de emisión. El proceso es selectivo frente a varios metabolitos, incluyendo otros neurotrasmisores. Se ha evidenciado experimentalmente el papel clave de la cinética de la reacción en la selectividad del proceso. Se ha empleado el sensor para marcar células RBL 2H3 (basófilos, que almacenan histamina) frente a células RAW 264.7 (macrófagos, sin histamina). También se ha usado el sensor para detectar cambios en los niveles de histamina en células RBL 2H3 (estimulando, por vía inmunitaria, la liberación de histamina) o en células RAW 264.7 (induciendo la formación de histamina con thapsigargina). En definitiva, se ha desarrollado un nuevo biosensor para la visualización de histamina en células funcionales.



Esquema 23. Nuevos biosensores de histamina: marcaje de células RBL 2H3 (basófilos) frente a células RAW 264.7 (macrófagos).

1 Recent progress in non-classical isocyanide-based MCRs

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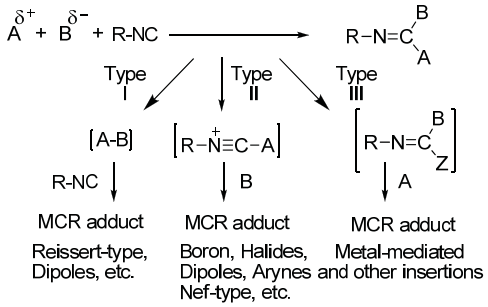
Abstract The chapter reviews a wide set of isocyanide-based multicomponent reactions, unrelated with mechanistic variations of Ugi- or Passerini-type processes. The first section deals with the isocyanide attack upon complexes arising from the interaction of nucleophiles with electrophiles, and the second involves the activation of isocyanides by electrophilic agents to generate species that will subsequently react with nucleophiles. Lastly, in section 3, we briefly comment on formal isocyanide insertion processes, mainly metalations.

Keywords isocyanides, multicomponent reactions, domino reactions, electrophilic activation.

1.1 Introduction

The use of isocyanides in organic chemistry is having a huge impact on the general approach to the synthesis of bioactive compounds [1-2]. The unique “carbene-like” structure of this functional group allows the incorporation of two other species (normally an electrophile and a nucleophile) in the same process, which makes it a privileged reactant in multicomponent reactions (MCRs) [3]. This strategy allows a large number of chemically diverse drug-like scaffolds to be prepared quickly and in mild conditions, and enables diversity-oriented synthesis to compete with and complement standard multistep target-oriented synthesis. The most classical use of isocyanides involves interaction with iminium or oxocarbenium ions as the electrophilic species, combinations that lead to the well-known Ugi-, van Leusen- and Passerini-like processes as well as mechanistically related variations [1,2,4]. Apart from these, the recent exploration of many other electrophilic partners has generated a large number of MCRs, often in-

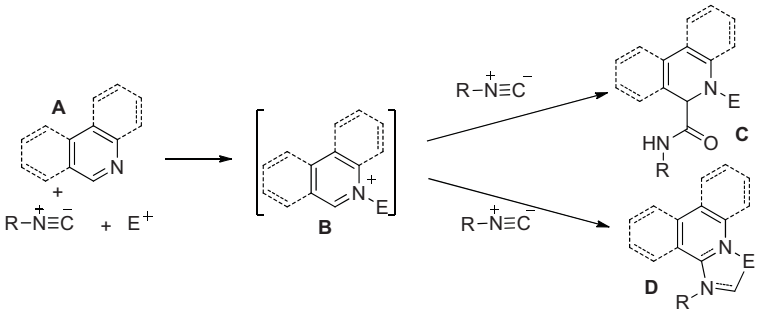
volving complex reaction cascades and leading to a variety of new adducts of great pharmaceutical interest. A schematic outline of the reactivity trends of isocyanides and the types of processes covered in the review are depicted in Scheme 1. The mechanistic guidelines used in the chapter are based on well-stated concepts and serve mainly to classify the reactions. In this respect, type I processes are those in which the isocyanide attacks the complex formed between the electrophilic and nucleophilic partner; type II includes the activation of the isocyanide by electrophilic agents to generate the reactive species towards the nucleophiles, and finally type III deals with insertion processes not covered above, mainly metalation-driven. A comprehensive coverage is not intended, and we refer to reviews and major studies for detailed explanations.



Scheme 1 Isocyanide reactivity: classical and alternative activating agents.

1.2 Type I MCRs. Isocyanide attack upon activated species

In this section we analyze a broad family of reactions that feature as the key step isocyanide addition upon activated species generated by interaction of the two complementary reactants. A relevant class of reactions belonging to this type involves the use of azine-derived cations as surrogates of the iminium intermediates in Ugi MCRs. These Reissert-type processes, where the azine formally replaces the imine, have been recently reviewed in the context of MCRs [5]. In this way, azines can be activated by a variety of electrophilic reactants, generating an azinium salt, the target of the isocyanide attack in a second step, to be followed by the final trapping of the nitrilium ion. Some mechanistic detours, however, lead to alternative connectivity patterns (Scheme 2).

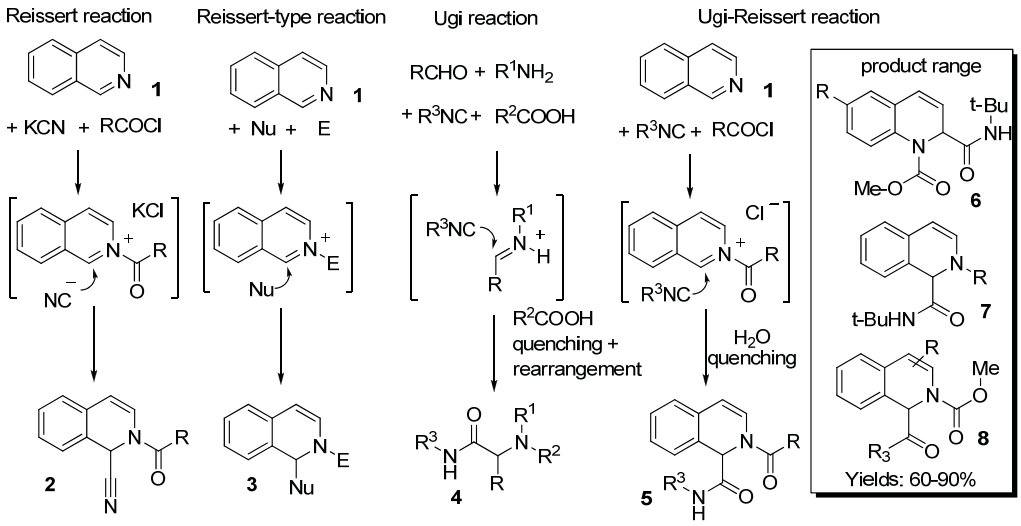


Scheme 2 Azine-isocyanide MCRs

Several activating agents have been studied in this context. Due to the coexistence of two nucleophilic species in the reaction mixture (azine and isocyanide), more than one reaction pathway is theoretically possible. Here we discuss the most commonly found scenario, where the azine is activated by the electrophile (the activation of isocyanides will be treated in section 1.3 below) to generate intermediate **B**, often in a reversible process. The isocyanide subse-

quently attacks at the α position of these cationic species and generates a product of general structure **C**, after being intercepted by a quencher (normally water). An alternative pathway involves an isocyanide attack upon the electrophile-derived moiety in **B**, its nucleophilic carbon becoming attached to this residue. After a final cyclization, compounds of general structure **D** are formed (Scheme 2).

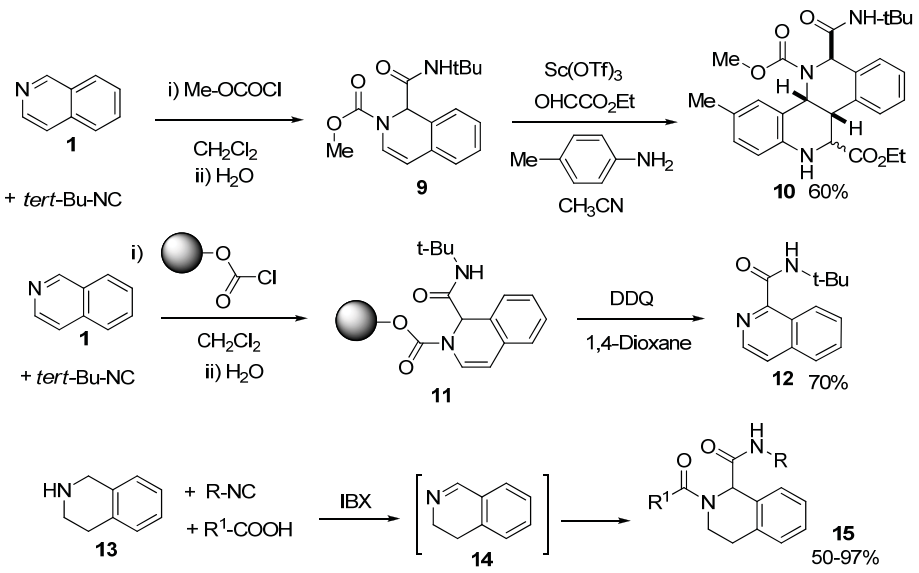
In this way, when isoquinoline **1** is activated by a chloroformate, isocyanides attack at the α position of the azine, and after aqueous trapping of the nitrilium intermediate, the carbamoylated dihydroisoquinolines **5** are obtained in a single step [6]. This process has been termed Ugi-Reissert reaction because of its mechanistic similarity with the parent transformations (Scheme 3).



Scheme 3 Analogies between Reissert and Ugi MCRs

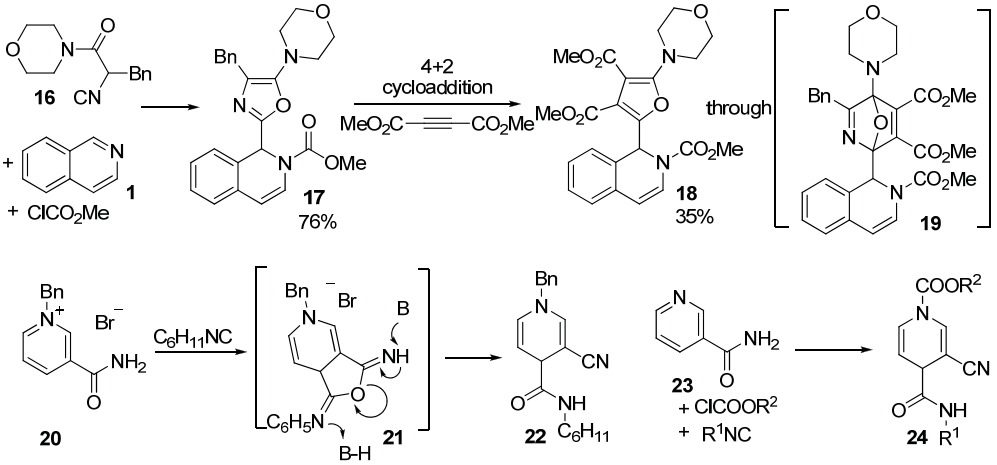
The Ugi-Reissert reaction is quite general and affords α–carbamoylated dihydroazines **6-8** in good to high yields. The range of isocyanides is diverse and the activating electrophilic reagents includes chloroformates, acid chlorides, tosyl chloride and even $(Boc)_2O$. In contrast, the choice of azines is restricted to diversely substituted isoquinolines and quinolines. Interestingly, the resulting products can be used as starting materials for Povarov reactions, leading to highly complex products in a two-step tandem reaction to afford the polyheterocyclic adduct **10** by interaction with aldehydes, anilines and $Sc(OTf)_3$ (Scheme 4) [7]. A solid-phase Ugi-Reissert reaction on a chloroformate resin has also been described. The α-carbamoylated isoquinoline **11** is then cleaved from the resin by oxidation with DDQ [6]. Zhu recently reported an alternative method to obtain products with a similar structure by a Ugi reaction. The novelty in this case is the use of IBX to generate imine **14** *in situ* by oxidation of terahydroisoquinoline **13**. Remarkably, IBX has proven to be chemically compatible with all the other components, and the process takes place as a true MCR (Scheme 4)[8].

4



Scheme 4 *Ugi-Reissert* MCRs: a solid-phase version, post-synthetic transformations, and analogous processes.

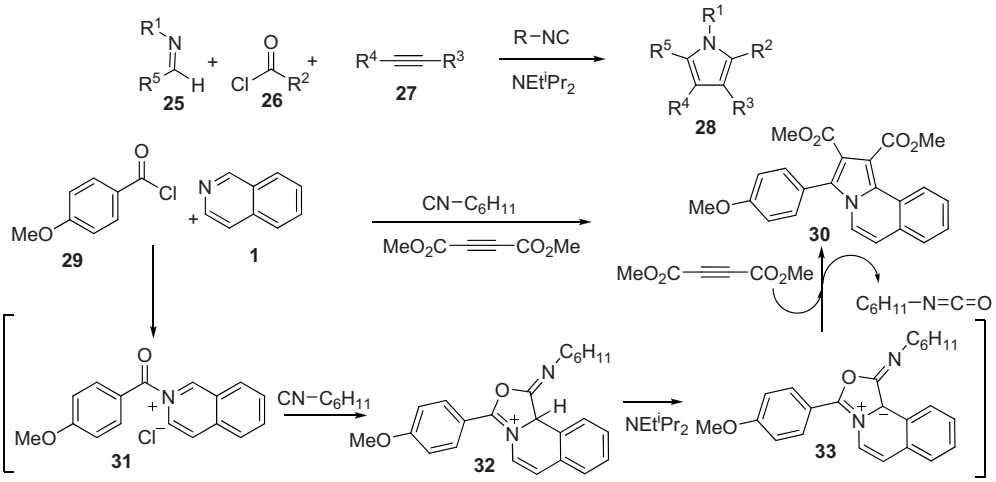
With respect to the trapping of the intermediate nitrilium ions, Zhu designed a new class of MCRs in which these species are intramolecularly trapped by a carboxamido group to generate substituted oxazoles [9-11]. On applying this strategy an interesting transformation was reported using the functionalized isocyanide **16**, which on interaction with isoquinoline and methylchloroformate afforded oxazole **17** in good yields [12]. The latter compound can finally react in several cycloadditions to yield furan **18** after rearrangement of intermediate **19** (Scheme 5). The use of the same approach allowed the direct addition of isocyanides to nicotinamide salt **20** (incidentally, the direct isocyanide addition to other pyridinium salts is not feasible). However, in this case the different substitution pattern of the carboxamido group led to isomerization of the putative intermediate **21** to the cyano-carbamoyl derivative **22**. Interestingly this process is also efficient in a *one-pot* Reissert-Ugi reaction (Scheme 5) [13].



Scheme 5 Internal trapping of the nitrilium intermediate by carboxamido groups

The Arndtsen group described a related process involving imines or isoquinolines, acid chlorides, alkynes and isocyanides to yield highly substituted pyrroles in a single step [14]. Although none of the isocyanide atoms end up at-

tached to the final product, their role in the mechanism appears to be crucial. After activation of the imine (or isoquinoline) the isocyanide attack generates a nitrilium ion that is quickly trapped by the carbonyl group of the activating agent to give the cationic intermediate **32**. Dipole **33** is then formed by proton loss, and reacts with dimethylacetylene dicarboxylate to yield pyrrole **30** through a cycloaddition-cycloelimination process in which an equivalent of isocyanate is released (Scheme 6).



Scheme 6 Arndtsen pyrrole synthesis

One of the main restrictions of the Reissert type processes is the limited reactivity of pyridines. These azines, in sharp contrast with (iso)quinolines, are practically inert, and special conditions are needed to activate them. Recently Corey and coworkers investigated the use of triflic anhydride for this purpose [15]. Under these conditions, several nucleophiles have been able to react in Reissert-type processes with pyridine to afford the γ-substituted dihydropyridines **37** (Scheme 7). The same reaction in presence of isocyanides affords a mixture of γ-carbamoylated dihydropyridines **38** and **39** together with the corresponding oxidized products **38'** and **39'**in a low overall yield. A major problem found here is the massive degradation of isocyanide, therefore milder activating agents were tested, and the use of trifluoroacetic anhydride (TFAA) was considered. Surprisingly, when mixing pyridine with TFAA and cyclohexylisocyanide, the expected α-carbamoylated dihydropyridine **40** was not detected, while the mesoionic acid fluoride **42** was isolated. Isoquinolines were proved to be even better reactants in these conditions, affording the corresponding dipoles in high yields [16]. The unusual connectivity of the atoms in these products suggests a different kind of mechanism at work (Scheme 8).

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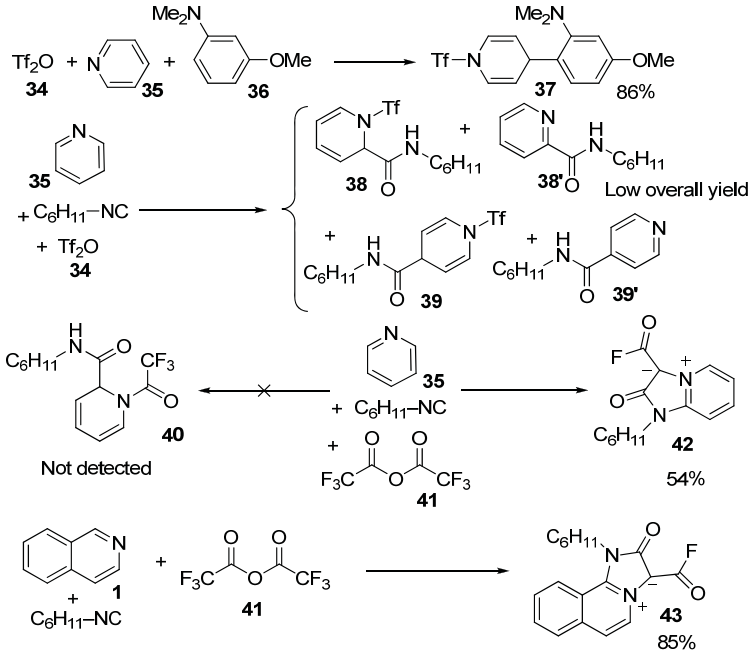
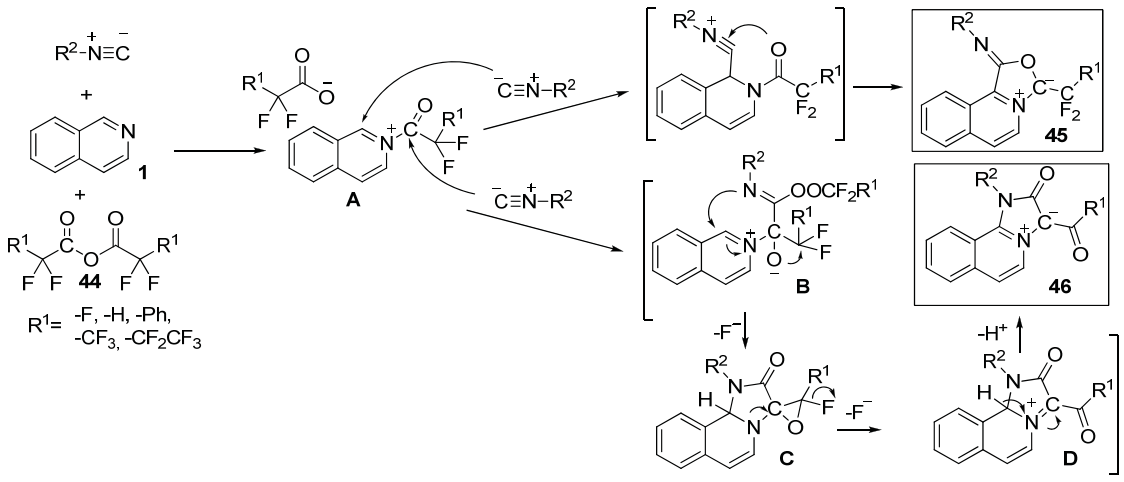


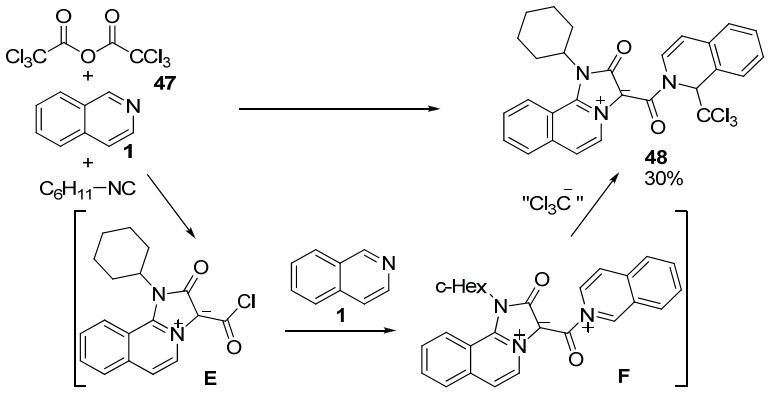
Scheme 7 Tf_2O- and TFAA-promoted isocyanide-azine MCRs

A reasonable mechanistic explanation involves the activation of the azine by the trifluoroacetic anhydride to generate the isoquinolinium salt **A** (Scheme 8). The expected isocyanide attack at the α-position of the isoquinoline should generate a nitrilium ion, finally leading to dipoles **45**, which have been obtained as byproducts in some of these reactions. This kind of cascade has been previously described in the Arndtsen pyrrole synthesis [14]. However, the main route here goes through the isocyanide addition upon the carbonyl group of the trifluoroacetyl moiety, generating adduct **B**. This intermediate triggers a domino process that starts with an attack of the isocyanide nitrogen on the α-position of the isoquinoline and is followed by closure of the epoxide ring with loss of a fluorine anion leading to **C**. Subsequently, a second fluorine atom is lost by the opening of the epoxide intermediate and formation of a new carbonyl group (**D**), and a final proton loss yields dipole **46** (Scheme 8).



Scheme 8 Mechanistic proposals for MCR of azines, isocyanides and TFAA

The scope of the reaction is quite general. Apart from TFAA, diversely substituted difluoroacetic anhydrides are also reactive, yielding the corresponding carbonyl compounds, including ketones and aldehydes. Trichloroacetic anhydride leads to dipole **48** through an even more complex reaction cascade: the expected mesoionic acid chloride **E** is more reactive than the acid fluoride analogue, being able to activate a second equivalent of isoquinoline. The new isoquinolinium ion (**F**) is then attacked by a trichloromethyl anion, leading to dipole **48** (Scheme 9) [16, 17].



Scheme 9 Cascade reaction of azines and isocyanides promoted by TCAA

The dipolar acid fluorides **46**, although stable enough to be isolated and characterized, are reactive towards nucleophiles and conveniently afford amides, esters and thioesters on interaction with amides, alcohols and thiols, respectively [16]. This property, together with their natural fluorescence, has been successfully applied to the selective labeling of oligonucleotides [18].

Distinct activating agents can also promote Reissert-type reactions with isocyanides. The reaction of chlorothioimidates **49** with pyridines and isocyanides leads to the fused imidazolium salt **50** (Scheme 10). The reaction proceeds through the usual activation-isocyanide attack pathway to generate a nitrilium intermediate that is intramolecularly trapped to afford the imidazolium salt **50**. An analogous reaction with double isocyanide insertion yielding derivative **51** has also been described [19]. In a related work, Berthet reported the double incorporation of isocyanides into pyridine through triflic acid activation to yield the bicyclic azolium salt **53** [20]. Fluorine has also been used as an activating agent in a two-component reaction leading to α-carbamoylated pyridine **54**, or triazole **55** on trapping with TMS-azide [21-22]. Electron-deficient alkenes are also suitable activating agents in Reissert-type reactions. For instance, the Michael acceptor **56** activates isoquinoline, and the isocyanide attack at the α-position of the azine followed by intramolecular trapping of the resulting nitrilium ion leads to polycycle **57** in average to good yields [23-25]. Analogously, the reaction of isocyanide with isoquinolinium dipole **59**, (obtained by treatment of salt **58** with isothiocyanate) triggers a reaction cascade yielding pyrroloisoquinoline **60**, pyrroloquinolines and indolizines (Scheme 10) [26].

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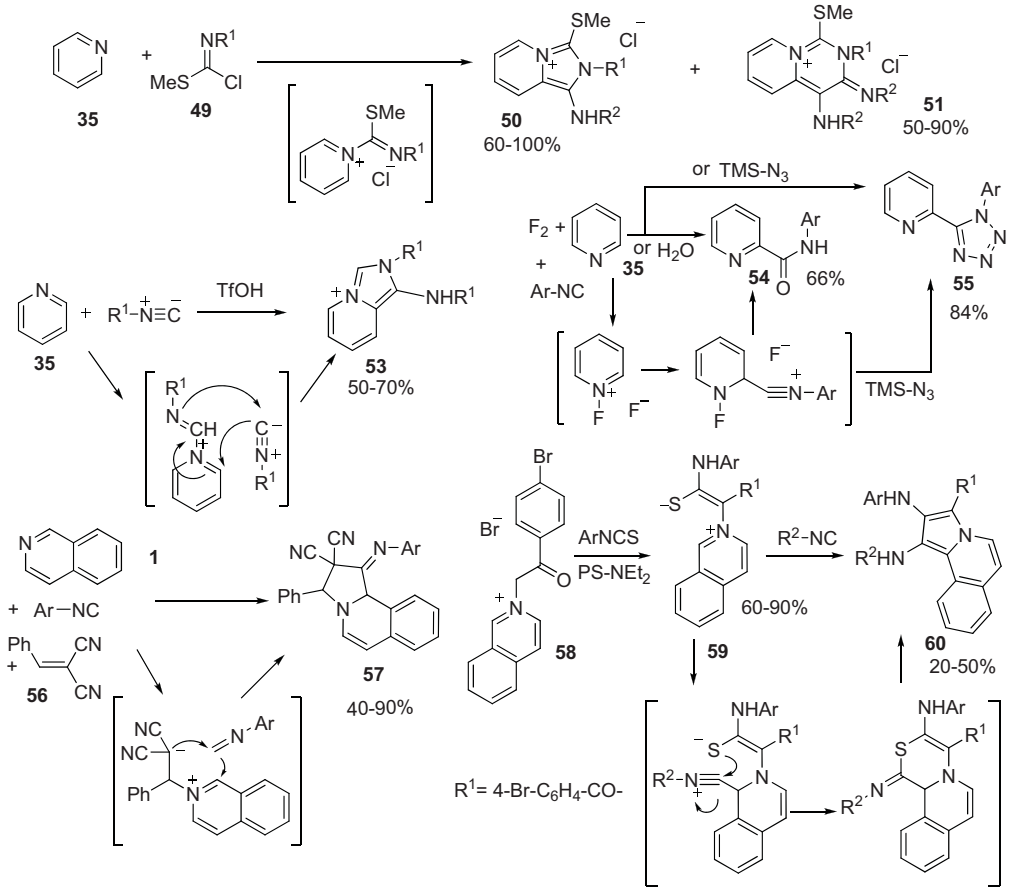
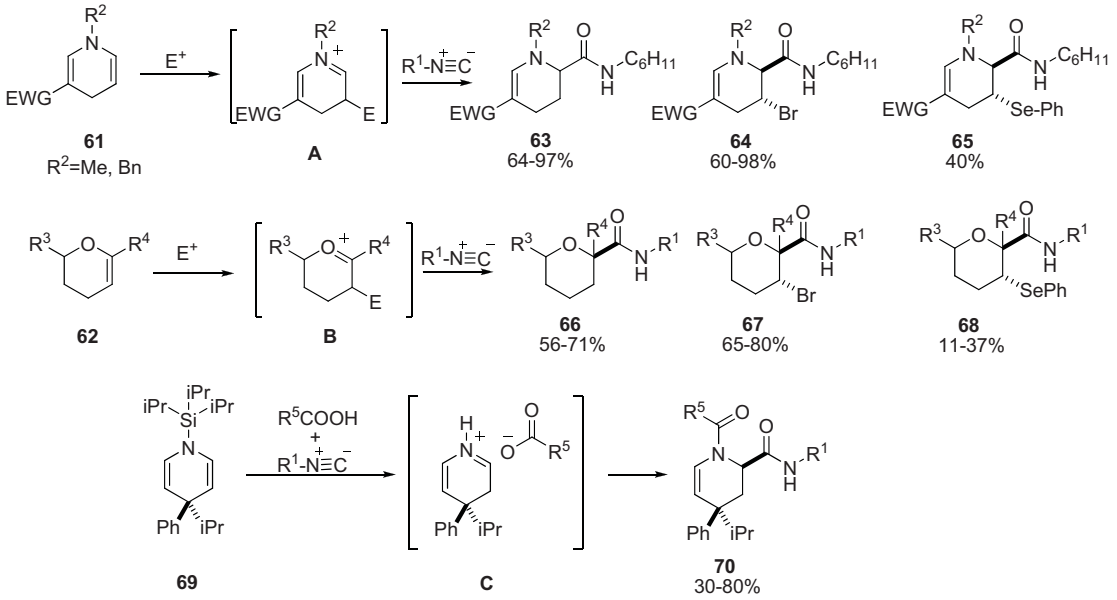


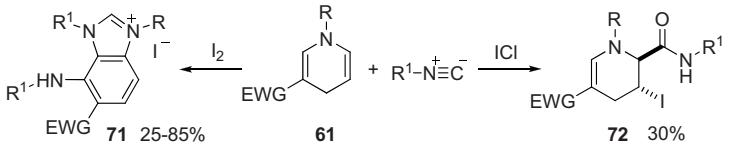
Scheme 10 Isocyanide-azine MCRs promoted by various activating agents

The same reactivity principle has been applied to electron-rich double bond functionalities. Thus, the interaction of electrophilic reagents with dihydropyridines and cyclic enol ethers generates reactive iminium species that can react with isocyanides. This enables the hydro-, halo- and seleno-carbamoylation of activated olefin moieties present in DHPs **61** and cyclic enol ethers **62** to be conveniently carried out with *p*-toluenesulfonic acid (as the proton source), bromine and phenylselenyl chloride as electrophilic inputs to afford heterocyclic systems **63**-**68** (Scheme 11) [27-28]. Wanner et al. reported a straightforward method for the transformation of *N*-silyl DHPs **69** to polysubstituted tetrahydropyridines **70** using a carboxylic acid and an isocyanide (Scheme 11) [29]. The mechanism involves an initial protodesilylation to form the dihydropyridinum salt **C** which, once attacked by the isocyanide, yields the MCR adduct.



Scheme 11 Hydro-, halo- and seleno-carbamoylation of DHPs and cyclic enol ethers

Interestingly, the use of iodine in an attempted iodocarbamoylation of DHPs led to benzimidazolium salts **71**; in sharp contrast, iodine monochloride (ICl) afforded the expected β-iodo-α-carbamoylated tetrahydropyridine **72** (Scheme 12) [30]. The former transformation is unprecedented and quite general in scope, allowing several substituents at the nitrogen and β-carbon of the DHP as well as a wide range of isocyanides.



Scheme 12 Reactions of isocyanides, DHPs and different iodonium sources

Although the mechanism is far from well-established, a reasonable pathway starts with the formation of the iodo-dihydropyridinium ion **74**, (Scheme 13). The consecutive attack of two isocyanide units followed by HI elimination gives rise to the nitrilium ion **B**, which suffers an intramolecular trapping by the enamine unit to form the bicyclic system **C**. An iodide-mediated fragmentation may generate the iodoiminium **D**, which, through ring closure and aromatization steps, yields the final benzimidazolium salts **75**. These compounds have been determined as moderate inhibitors of human Prolyl Oligopeptidase (an enzyme involved in the metabolism of neuropeptides, whose activity is altered in several mental illness), thus constituting a promising new scaffold for targeted drug design [31].

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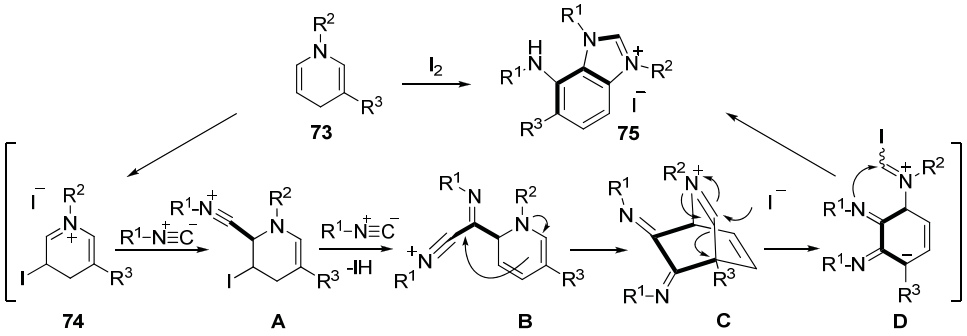
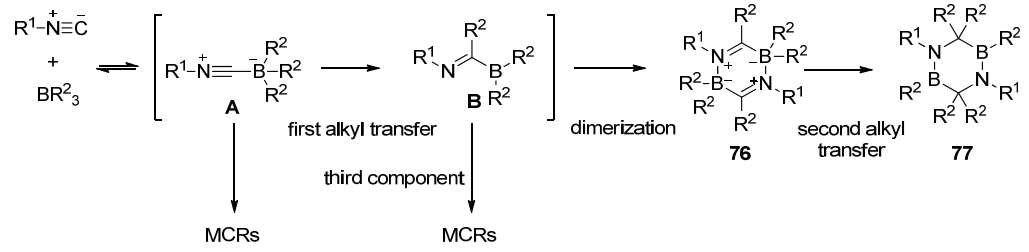


Scheme 13 Mechanistic hypothesis for the generation of benzimidazolium salts **75**

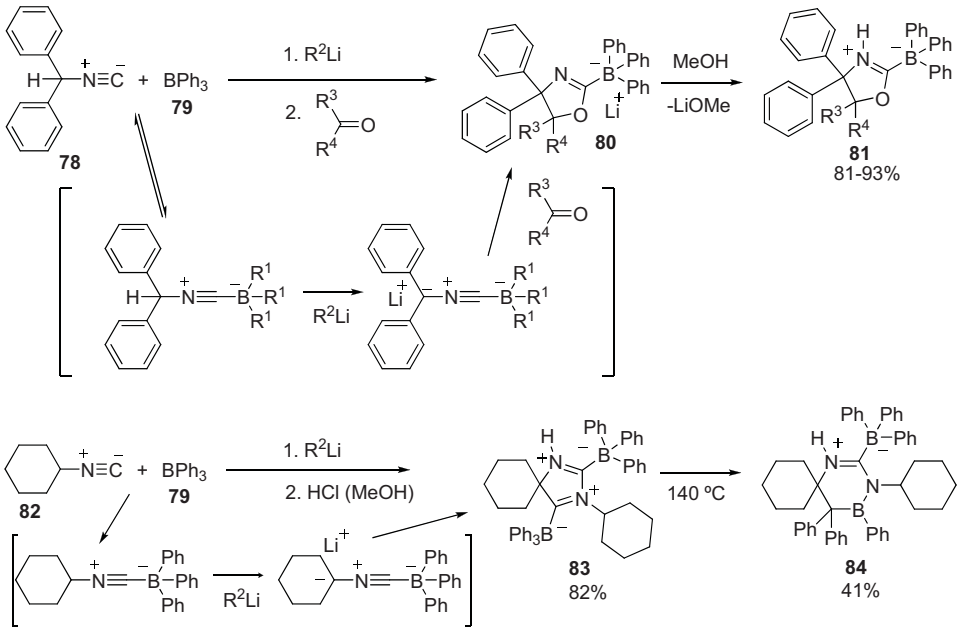
1.3 Type II MCRs. Isocyanide activation

Processes in this section include the transformations triggered by the initial activation of isocyanides and the subsequent reaction of these species with a third component. In this context, the interaction between boranes and isocyanides was first studied in the sixties and showed promising results, only to lie dormant until recently. The process is triggered by the nucleophilic attack of the isocyanide upon the borane, and the initial complex **A** quickly evolves by an alkyl transfer from the boron atom to the isonitrile carbon to generate the iminoborane **B** (Scheme 14). In absence of other components this intermediate dimerizes to generate diazadiborinine **76** as a stable compound; a second alkyl transfer may then be induced by heating to afford the saturated analogue **77** [32-37]. The reactive nature of intermediates **A** and **B** enables the participation of appropriate components to yield a rich variety of MCRs, as discussed below.



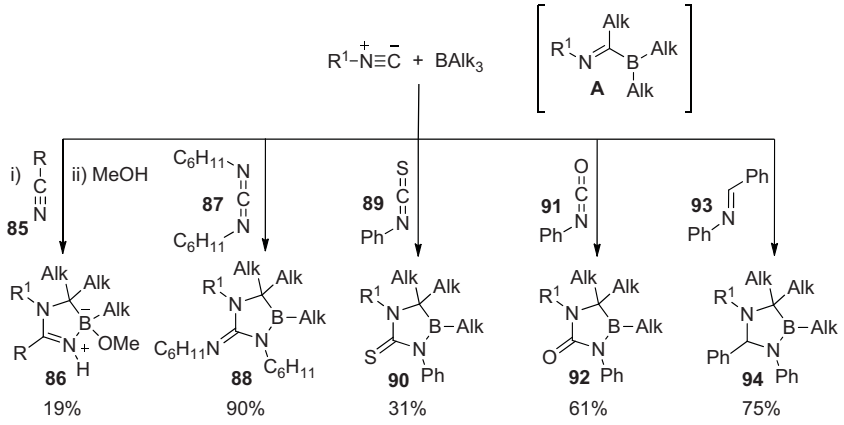
Scheme 14 Isocyanide-borane interaction

When using isocyanide **78**, intermediates of type **A** are generated on interaction with BPh_3, and can be further activated by addition of organolithium compounds (Scheme 15). The resulting dipolar lithium salt can then react with ketones or aldehydes in formal 3+2 cycloadditions, to afford the cyclic iminoborane salt **80** or its protonated analogue **81** after treatment with methanol. The same reaction using cyclohexylisocyanide **82** evolves through a dimerization step to yield the spiro compound **83**, which rearranges to dipole **84** upon heating [38].



Scheme 15 Dipolar species from isocyanides and BPh_3

In the presence of distinct substrates, the reaction pathway diversifies into different reaction mechanisms. In this way, iminoboranes **A** (Scheme 16), arising from the reaction between an isocyanide and trialkylboranes, are able to interact with several reactive species through formal 3+2 cyclodditions.



Scheme 16 Formal 3+2 cycloadditions with iminoboranes

Therefore, when nitrile **85** is mixed with an isocyanide and trialkylborane, diazaborolidine **86** is generated in a single step through the intermediacy of iminoborane **A**. The analogous products **88**, **90**, and **92** can be synthesized using carbodiimide **87**, isothiocyanate **89** or isocyanate **91**, repectively. The saturated analogue **94** can be obtained with imines. During these processes a second alkyl group is transferred from boron to the terminal carbon of the isocyanide (Scheme 16) [39-40]. On the other hand, alcohols, thiophenols and anilines can also react with iminoborane **A** to afford the acyclic borane adducts **95-97** with good yields (Scheme 17) [41].

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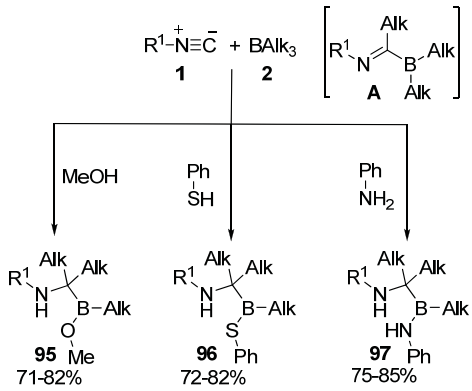
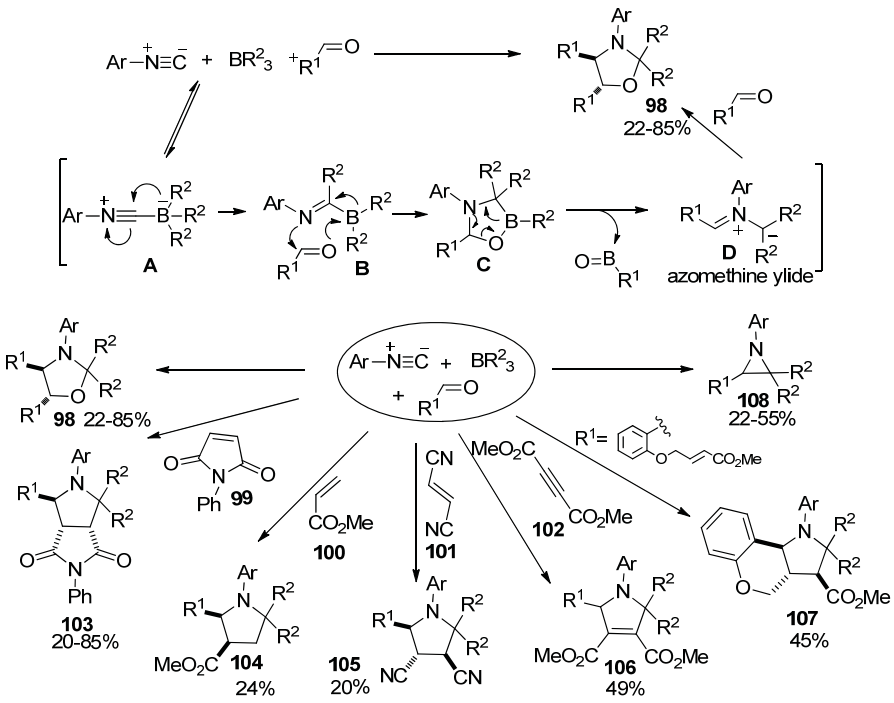


Scheme 17 Reaction of isocyanides and alkylboranes with methanol, phenol or aniline

Interestingly, when aldehydes are used, a more complex reaction cascade takes place. Thus, by mixing aromatic isocyanides, alkylboranes and aldehydes, oxazolidines **98** (Scheme 18) are synthesized in mild conditions. The reaction was first reported by Hesse in 1964 [42], and not revisited until 2010, when the original discovery was expanded into a whole family of MCRs, leading to structurally diverse drug-like scaffolds [43]. The first steps of this process closely resemble the previous reactions involving boranes and isocyanides and result in the formation of iminoborane **B**. Likewise, a formal cycloaddition with a molecule of aldehyde and the transfer of a second alkyl group from the boron atom leads to an oxazaborolidine **C**, which further evolves to an azomethine ylide intermediate **D** with loss of boroxine. In the final step, a second molecule of aldehyde reacts in a cycloaddition to yield oxazolidine **98** with excellent *trans* diasteroselectivity. In presence of a dipolarophile as a fourth component, the azomethine ylide reacts to afford different types of scaffolds. In these conditions phenylmaleimide **99,** methyl acrilate **100**, fumaronitrile **101**, and dimethyl acetylenedicarboxylate **102** yield the respective pyrrolidine derivatives **103**-**106**. The processes shows moderate diastereoselectivity and typical isomer distribution lies in the range of a 4:1 ratio. When an aromatic aldehyde bearing a dipolarophile moiety was used, an intramolecular version of the process took place, affording the fused heterocyclic system **107** in a single step. When aldehydes bearing electro-donating groups are used, the affinity of the generated azomethine ylide intermediates for dipolarophiles is reduced; in these conditions, the formation of aziridine **108** is predominant with respect to the formation of oxazolidine **98** (Scheme 18).



Scheme 18 MCRs involving isocyanides, alkylboranes, aldehydes and dipolarophiles (major diasteromers shown)

As several routes can compete for the final distribution of the possible products, the overall yield of these processes is highly dependent on the electronic properties of the components, and some combinations afford complex mixtures whose purification is difficult. To overcome this problem, a solid-phase version of these processes was developed in which the isocyanide resin **109** was reacted with phenylmaleimide **99**, triethylborane and *p*-chlorobenzaldehyde **110** (Scheme 19), leading to the pure 4CR adduct **111** after washing of the resin and subsequent cleavage with TFA [43]. Analogously, oxazolidine **112** was obtained in high yield without further purification. Finally, aziridine **115** was obtained by reaction of the solid-supported aldehyde **113** with *p*-methoxyisocyanide **114** and triethylborane, after cleavage with sodium methoxide and removal of the unreacted aldehyde with a scavenger. The use of solid-supported reagents not only allows the expected products to be acquired in a pure form, but also significantly improves the range of substituents compatible with the process. For instance, the use of unprotected phenols in solution would not be feasible in presence of borane reagents, while an attempt of synthesize aziridine **115** in solution using 4-formylbenzoate would lead to the formation of the corresponding oxazolidine. Yet both problems can be solved using the solid-phase approach, and the expected adducts **111**, **112** and **115** are conveniently formed.

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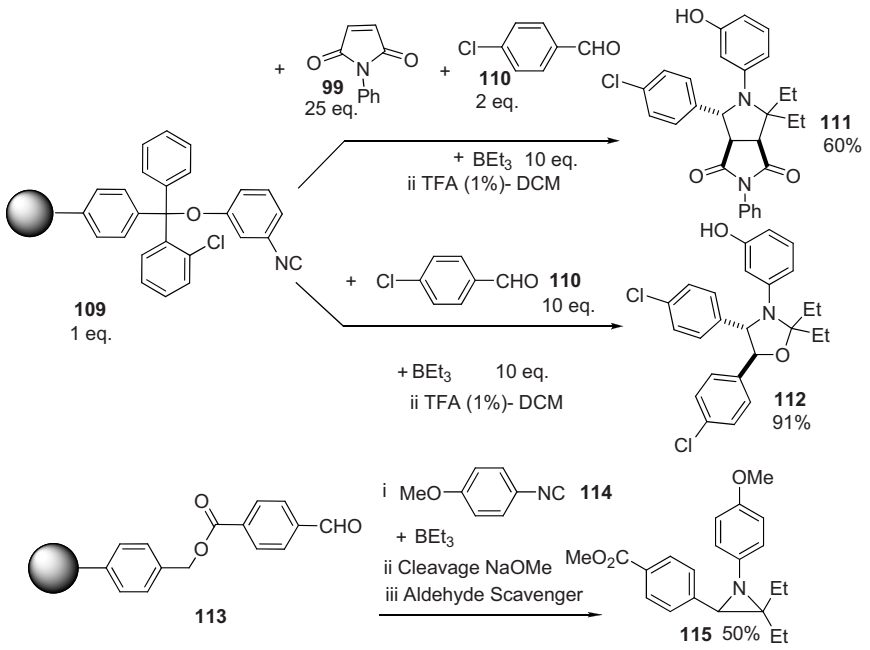
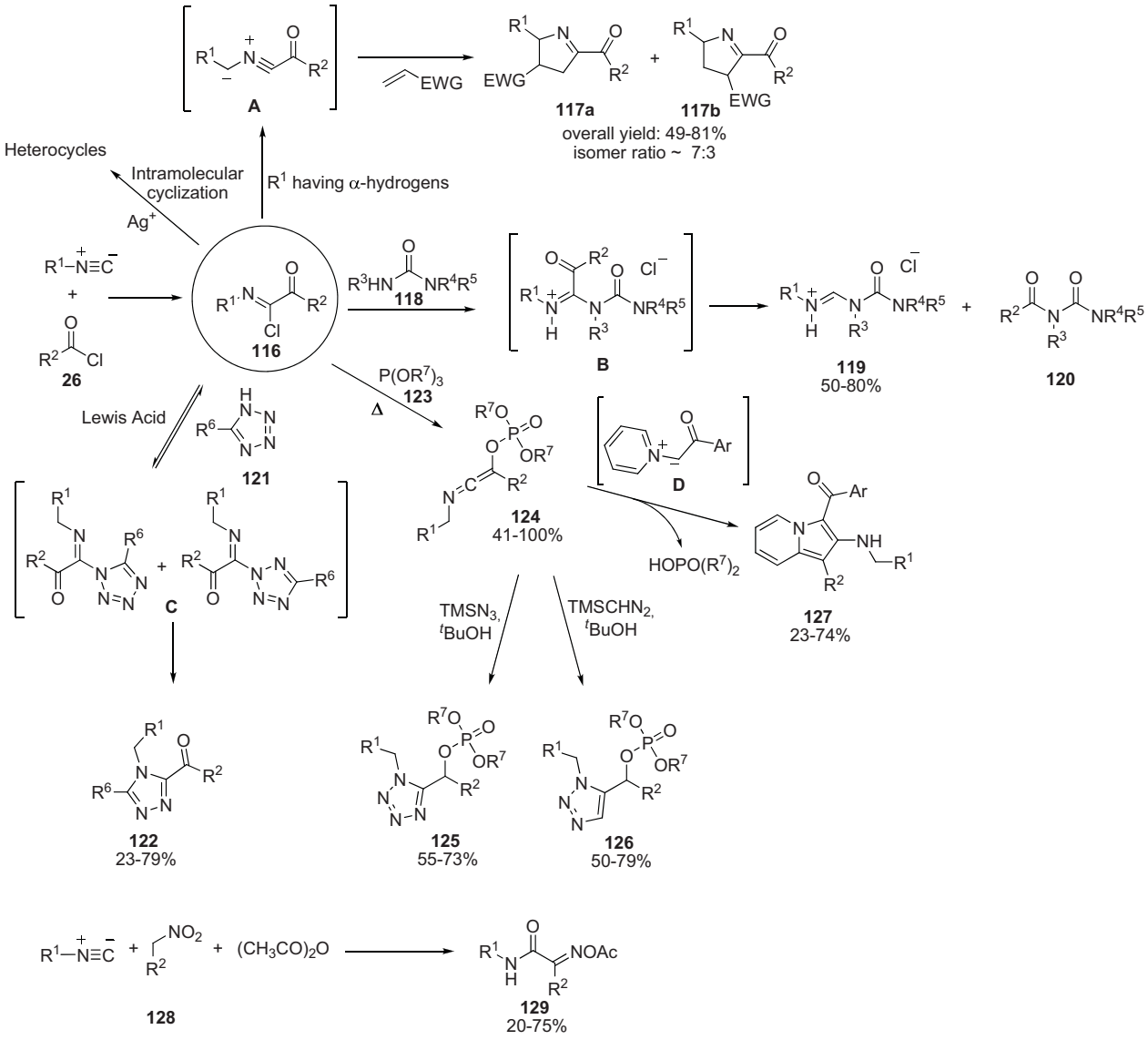


Scheme 19 Solid-supported boron-based MCRs

A wide range of MCRs have been described based on the Nef isocyanide reaction [44-45]. The α-addition of acyl chlorides to isocyanides leads to the formation of imidoyl chlorides (Nef adducts), whose interaction with different nucleophiles form the final adducts [46]. The synthesis of a large number of heterocycles based on the intramolecular cyclization of *C*-acylnitrilium ions, derived from imidoyl chlorides, has been exhaustively reviewed by Livinghouse [47-48]. The treatment of imidoyl chloride **116** with a base gives rise to the dipolar intermediate **A**, which can be trapped by a dipolarophile to afford the corresponding pyrroline derivatives **117** (Scheme 20) [49]. Finn et al. described the synthesis of formamidine urea salts **119** via the trapping of the imidoyl chloride **116** by substituted ureas **118**. Notably, the reaction is somewhat restricted to acid chlorides, not working or affording lower yields with other lectrophilic activating agents [50]. A wide application of these formamidine salts **119** has since been described with the development of useful protocols involving the exchange reaction of the imine fragment with nitrogen nucleophiles (aromatic and aliphatic primary amines, hydrazines, hydrazides and hydroxylamines) [51]. In this context, the addition of thiols to generate thiocarbamates, deprotonation/alkylation sequences or amide fragment exchange have also been reported (Scheme 20) [52].

The scope of the Nef-MCRs has been expanded by the group of El Kaïm. Thus, the reactivity of the Nef adducts with tetrazoles **121** and the subsequent Huisgen rearrangement under Lewis acid activation lead to 1,2,4-triazol derivatives **122** (Scheme 20) [53]. An other interesting 3CR was described as an application of the Perkow reaction in which the addition of trialkylphosphites **123** to imidoyl chloride adducts **116** afforded the keteneimine adducts **124**. The reactivity of such compounds allowed several post-condensations [54], for instance, the formation of phosphorylated tetrazoles **125** from the reaction of keteneimines derivatives **124** and trimethylsilyl azide, and the generation of phosphorylated triazoles **126** using trimethylsilyl diazomethane [55]. Additionally, keteneimines undergo dipolar cycloadditions with pyridinium ylides **D** generated *in situ* to afford indolizine derivatives **127** (Scheme 20) [56]. The same group reported the first MCR between nitro compounds **128**, acylating agents and isocyanides to yield α-oximinoamides **129** [57-58].



Scheme 20 Reactions of imidoyl chlorides arising from a Nef-isocyanide process

Bossio et al. reported the α-addition of *N*-chloramines, generated from aromatic amines and chloramine T **130**, to isocyanides to give *N*-tosylguanidines **131** (Scheme 21). Imidazole derivatives were obtained after the cyclization of *N*-tosylguanidines in acidic media [59-60]. Similarly, isocyanide dihalides can be regarded as synthetic equivalents of imidoyl chlorides in reactions with nucleophiles or in MCRs. The synthesis of these compounds, which proceeds by halogenation of isocyanides or isothiocyanates, has been reviewed [61]. Different reactions of dihalogenated isocyanides have been extensively described, resulting in carbodiimides, chloroformamidines, thioesters, guanidines, isoureas, isothioureas and five- and six-membered heterocycles [62-64]. More recently, some authors have reported innovative applications of dihalogenated isocyanides in the synthesis of natural products [65, 66]. An illustrative example of this chemistry is the substituted tetrazole synthesis based on the addition of azide to the dihalogenated isocyanide **132**, followed by the incorporation of a second component in a palladium-catalyzed coupling [67].

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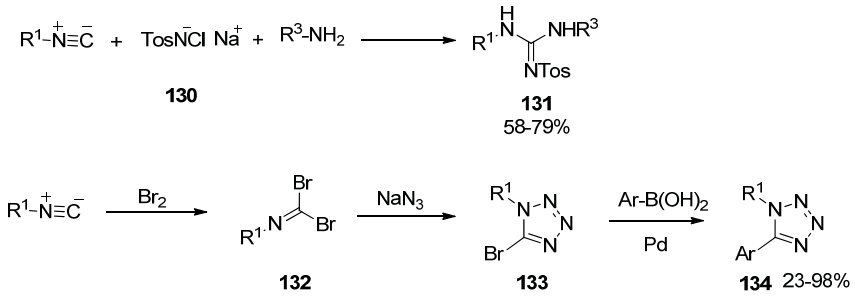
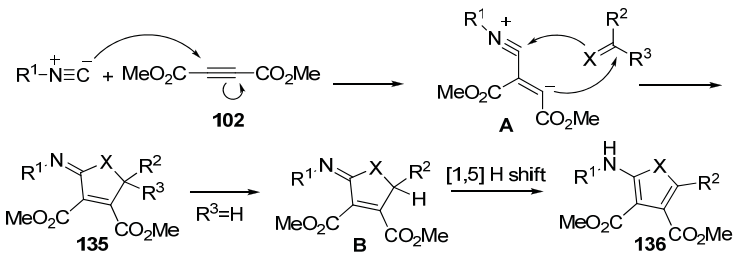
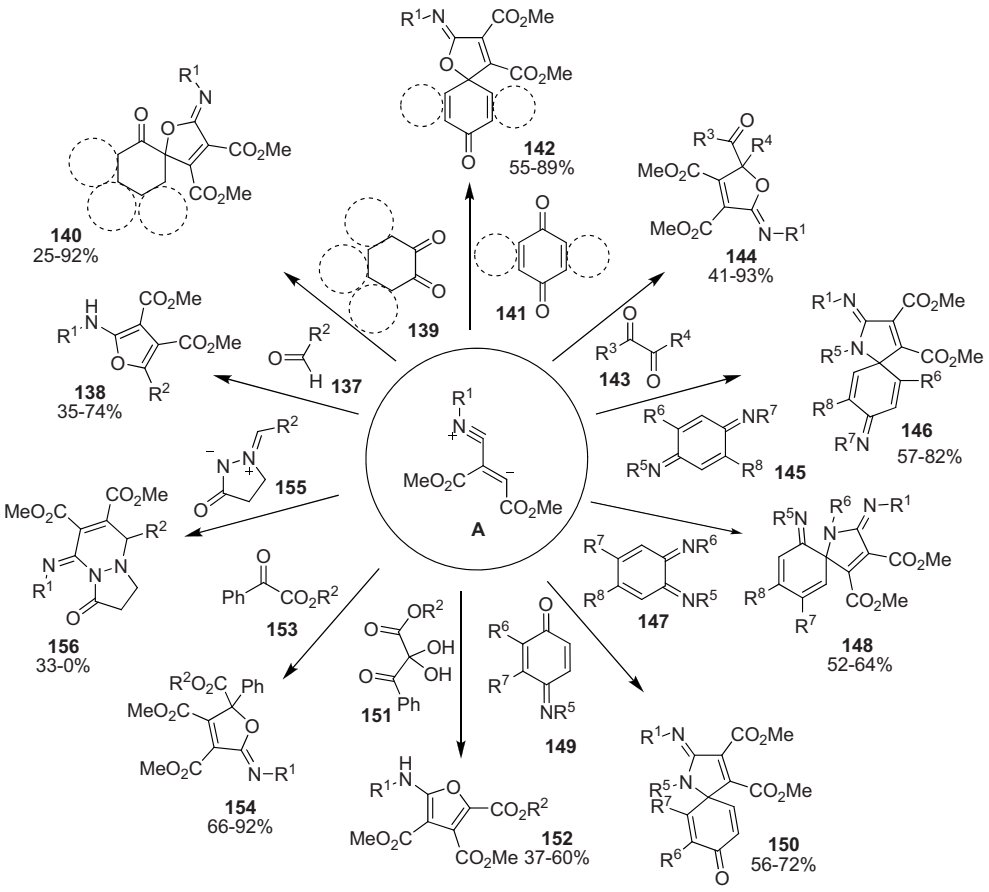


Scheme 21 Reactions of isocyanide dihalides and related compounds

A rich chemistry arises from the interaction of aromatic and aliphatic isocyanides with dimethyl acetylenedicarboxylate (DMAD) [68]. Nair et al. described a family of 3CRs based on the trapping of the resulting zwitterionic intermediate **A** with different electrophilic species to afford compounds **135** (Scheme 22) [69]. Interestingly, when R^3=H, a [1,5] hydrogen shift takes place to yield the heteroaromatic amino derivative **136**. The process is extremely versatile and distinct electrophiles are engaged in these transformations. Apart from aldehydes, the addition of 1,2 and 1,4-quinones yielded dihydrofuranone derivatives **140** and **142**, respectively (Scheme 23). Iminolactones **144** were obtained from acyclic 1,2-diones **143** [70]. Several spirofused γ-iminolactams **146**, **148** and **150** were synthesized following the addition of the zwitterionic intermediates to quinonediimides **145** or **147,** and to quinonemonoimides **149**, respectively [71]. The use of vicinal tricarbonyl compounds **151** as electrophiles was reported in the synthesis of furan derivatives **152** [72]. Alkyl phenylglyoxylates **153** were employed to trap zwitterionic intermediates and a subsequent cycloaddition yielded highly functionalized derivatives **154** [73]. The reaction of intermediate **A** with 1,3-dipolar compounds **155** produced pyrazolo[1,2-a]pyrazinone derivatives **156** (Scheme 23) [74].

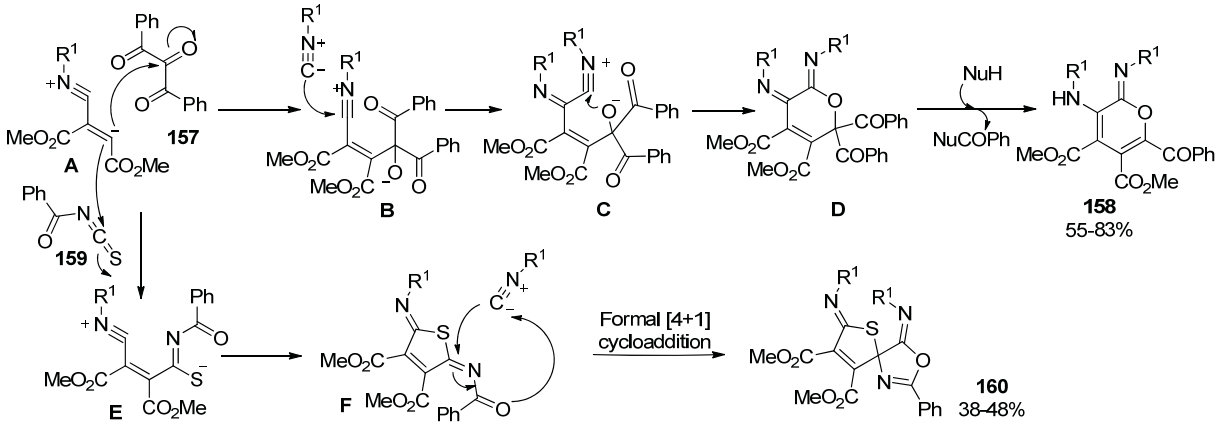


Scheme 22 Mechanistic proposal for the formation of compounds **135** and **136**



Scheme 23 Reactions of isocyanide-DMAD zwitterion with a range of electrophiles

Notably, the incorporation of two molecules of isocyanide was observed in processes involving the interaction of zwitterionic intermediate **A** with vicinal tricarbonyl compound **157** [72,] or with squaric acid derivatives [75], thus constituting a formal 4CR (Scheme 24). The reaction may take place though the formation of intermediate **B** after the nucleophilic addition of dipole **A** to the carbonyl compound. The attack of an excess of isocyanide on these species affords the corresponding betaine **C**, which eventually undergoes a cyclization to afford the iminolactone **158** with loss of a phenylcarbonyl residue. Yavari et al. reported a related reaction, where benzoylisothiocyanate **159** is employed as the electrophilic partner. In this process, the final isocyanide addition-cyclization events lead to the spiroheterocyclic derivatives **160** through the intermediacy of species **E** and **F** (Scheme 24) [76].



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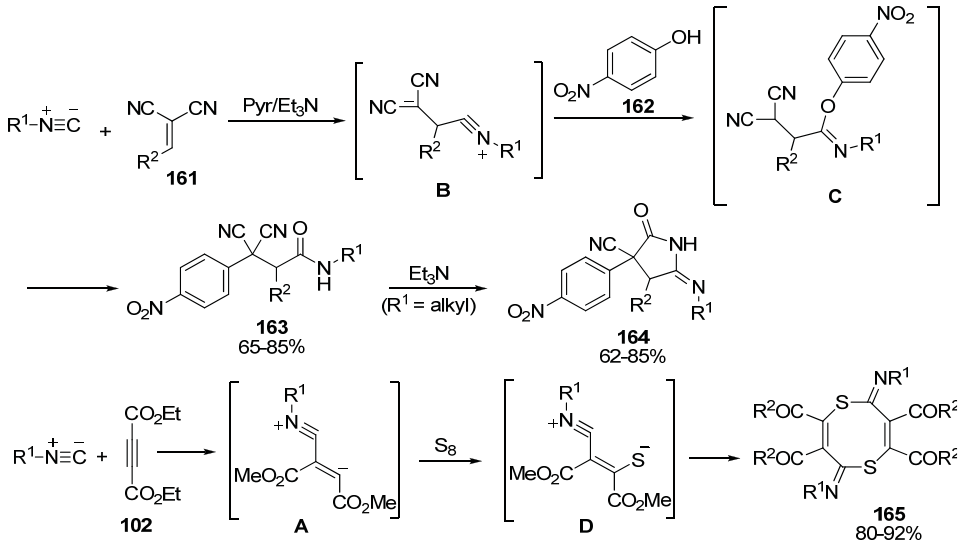
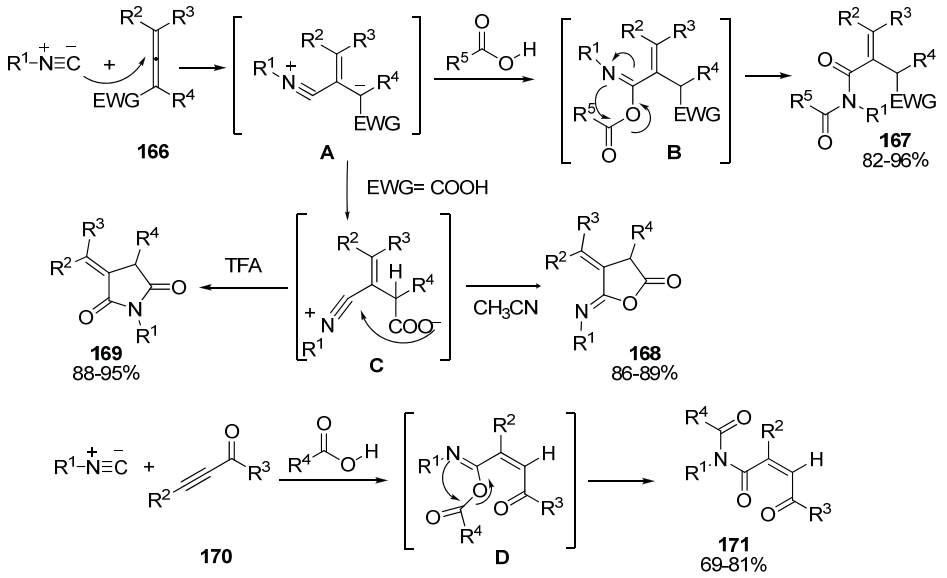
Scheme 24 Reactions of isocyanide-DMAD zwitterion with two equivalents of isocyanide

Alternative trappings of zwitterionic intermediates type **A-B** (Scheme 25**)** with several CH or NH acids, or with electron-deficient olefins, have been recently reviewed [77]. Mironov et al. described the formation of a dipolar intermediate between isocyanides and *gem*-dicyano olefins **161**, followed by an intermolecular nucleophilic attack of 4-nitrophenol **162** to afford propionamides **163** after a Smiles rearrangement and tautomerization (Scheme 25). These adducts were obtained only when R^1 was an aromatic group, since if this substituent is an alkyl chain, cyclization occurs spontaneously to give succinimides **164** [78]. A remarkable reaction of the zwitterionic intermediate **A** on treatment with elemental sulphur, leading to the formation of eight-membered-ring cyclic thioimidic esters **165** in excellent yields, was reported by Alizadeh et al. (Scheme 25) [79].



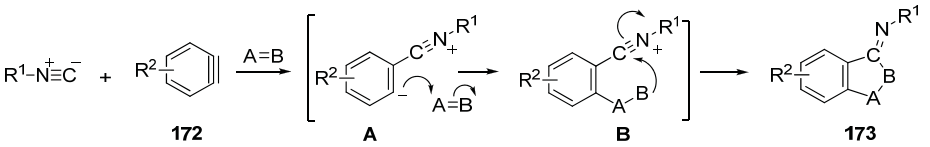
Scheme 25 MCRs from dipolar isocyanide-derived intermediates

The zwitterionic nitrilium intermediate **A**, formed between an isocyanide and electron-deficient allenes **166**, can be trapped by carboxylic acids, affording interesting 3CR adducts **167**, after an *O* to *N* acyl shift (Scheme 26). A mechanistic variation involving an allenoic acid affords 5-iminodihydrofuran-2-one derivatives **168** by the intramolecular nucleophilic attack of the carboxylate anion in intermediate **C**. When the reaction was carried out in the presence of TFA, pyrrolidine 2,5-dione derivatives **169** were obtained instead [80]. More recently, the same authors described a similar reaction between isocyanides, acetylenic esters or ketones **170** and carboxylic acids to afford derivatives **171**, with high regio-and stereoselectivity [81].



Scheme 26 Reaction between isocyanides, allenes and electrophiles

The highly electrophilic character of arynes, which is due to the low-lying LUMO, enables isocyanide addition and subsequent formation of a zwitterionic nitrilium intermediate **A**, which may trap a variety of electrophiles to yield a structurally diverse array of compounds (Scheme 27). This fruitful research line has been developed by Yoshida and co-workers, resulting in several benzoannulated nitrogen or oxygen heterocycles **173**. Thus, arynes **172**, prepared *in situ* from 2-(trimethylsilyl)phenyl triflate derivatives, react with isocyanides and aliphatic or aromatic aldehydes to afford benzoiminofurans **174** (Scheme 28) [82]. The use of sulfonylimines gives rise to 2-iminoisoindolines **175** [83], whereas ketones and benzoquinones have been employed in the synthesis of iminofurans **176** and spiro-benzofuran derivatives **177** [84].



Scheme 27. Mechanistic rationale for the aryne-isocyanide MCRs

Interestingly, Allan et al. expanded the scope of the electrophiles by using substituted phenyl esters (lineal, branched and cyclic), leading to phenoxyiminoisobenzofurans **178** (Scheme 28). A final treatment of the reaction with an aqueous solution of oxalic acid promoted the hydrolysis of these adducts afforded *o*-ketobenzamides **179**. Finally, the authors described the use of electron-deficient alkynes as an electrophilic third component of this MCR to give iminoindenones **180** [85]. A regioselective synthesis of polysubstituted isoquinolines **182** and pyridines **183** though this methodology was described by Sha et al. (Scheme 29). The trapping of the zwitterionic intermediate **A** with a terminal alkyne **181** affords imine species that undergo rearrangement to **C** via a [1,5] hydride shift. Finally, intermediate **C** can react with another unit of benzyne **172** to give isoquinolines **182** or with a second molecule of alkyne **181** to yield pyridines **183** [86].

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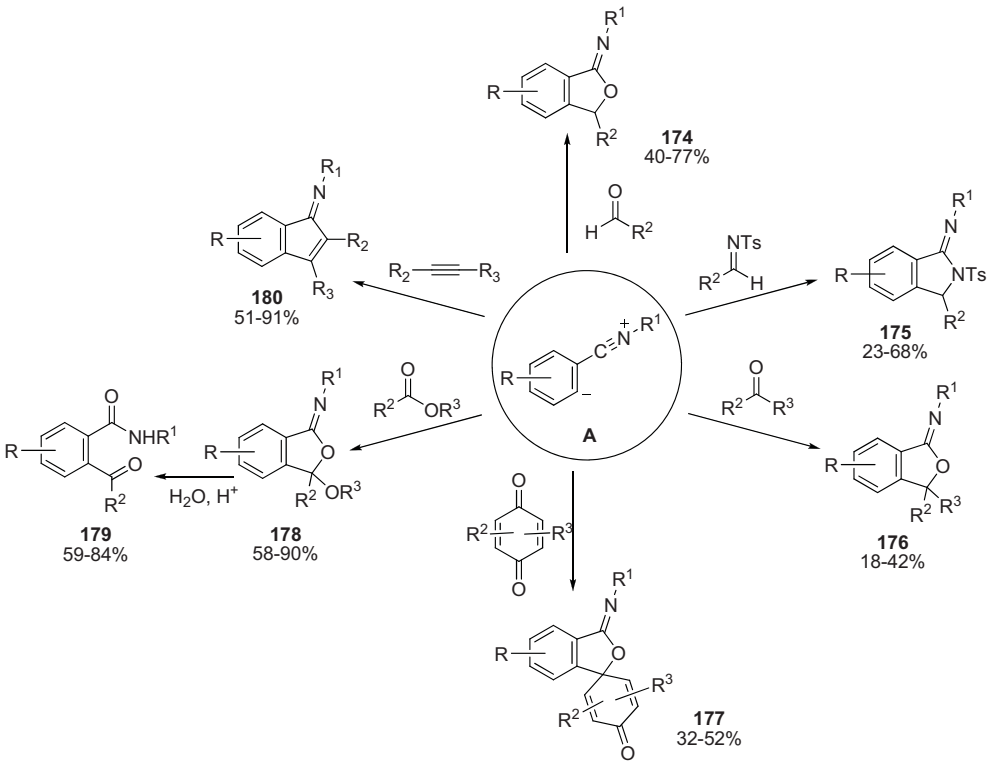
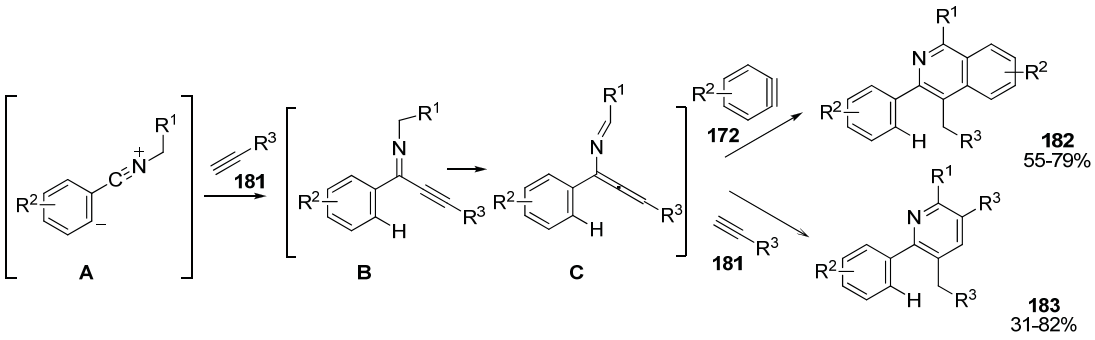
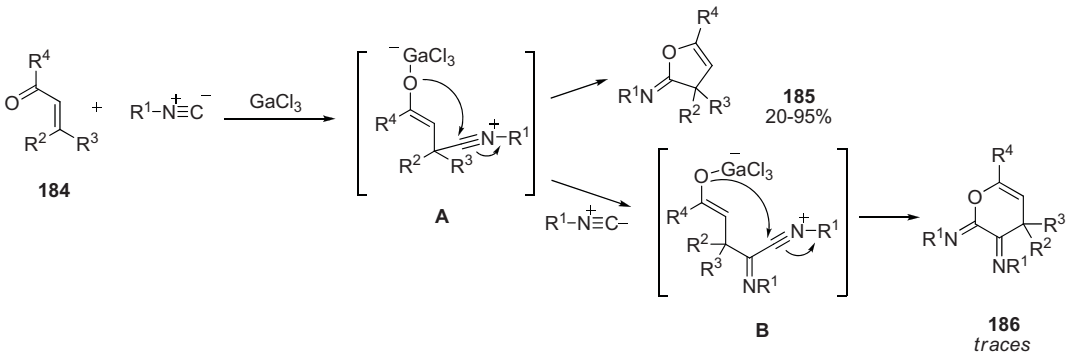


Scheme 28 MCRs between isocyanides, arynes and electrophiles

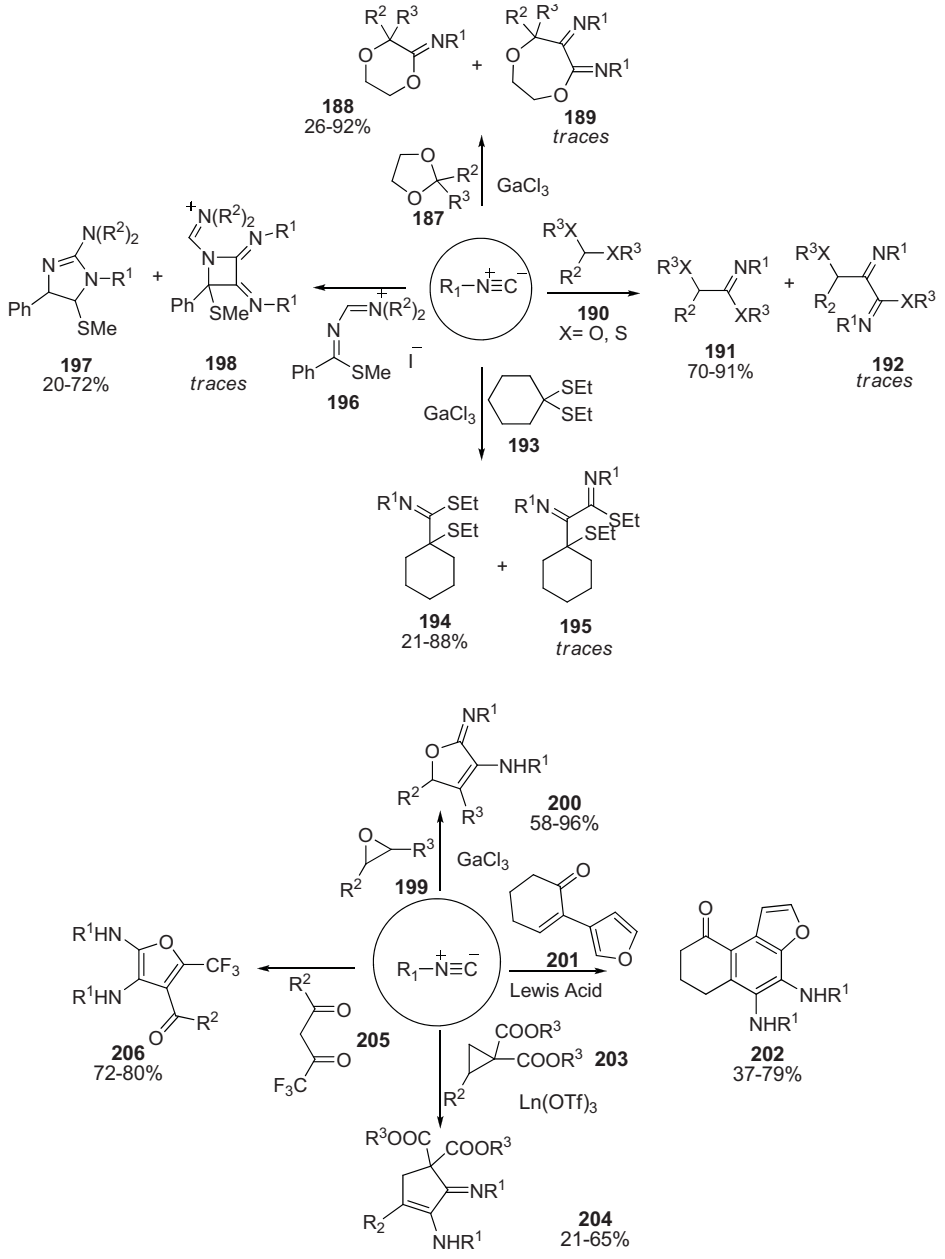


Scheme 29 Benzyne-isocyanide mediated synthesis of isoquinolines and pyridines

Chatani et al. have described a family of Lewis acid-catalyzed formal [4+1] cycloadditions of α,β-unsaturated carbonyls **184** and isocyanides [87, 88] and mechanistically related insertions of isocyanides into C-O and C-S bonds of cyclic and acyclic ketals and dithioacetals (Scheme 30) [89-92]. In all cases, the adducts arising from the incorporation of one unit of isocyanide (**185**, **188**, **191**, **194** and **197**) were isolated as the major products, although compounds displaying a double isocyanide insertion **186**, **189**, **192**, **195** and **198** were also found [93]. Notably, the latter compounds may predominate in certain circumstances, for instance, 2,5-dihydrofurans **200** were obtained from disubstituted epoxides **199** [94], 7,8-dihydronaphtho[2,1-b]furan-9(6*H*)-one derivatives **202** from enones **201** [95], cyclopentenedicarboxylates **204** from cyclopropane rings **203** [96] and diaminofuran derivatives **206** from trifluorobutane-2,4-diones **205** [97] (Scheme 31).

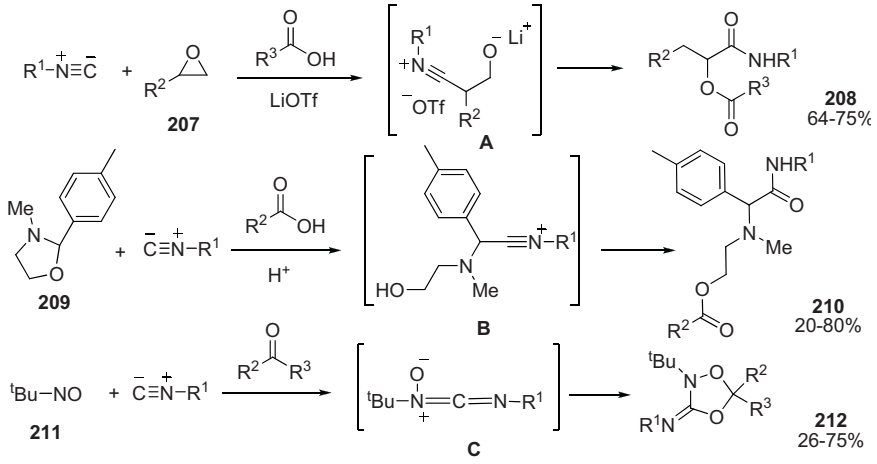


Scheme 30 $GaCl_3$-catalyzed single and double isocyanide insertion processes



Scheme 31 Single and double isocyanide insertion processes

A MCR between epoxides **207**, isocyanides and carboxylic acids under LiOTf catalysis furnishes the α-acyloxyamide adduct **208** (Scheme 32) [98, 99]. The chemistry of oxazolidines **209** provides an interesting 3CR to afford *N*-acyloxyethylamino acid amides **210** [100]. In both cases, the isocyanide attack gives rise to nitrilium ions that end up trapped by the carboxylates, as in the Ugi and Passerini MCRs. More recently, a modified version of this process has used TfOH as the catalyst, and thiols and tetrazoles instead of carboxylic acids. A formal four-component version was described through the *in situ* preparation of *N*-alkyloxazolidines from *N*–alkylethanolamines and carbonyl compounds [101]. Additionally, the interaction of nitroso compound **211**, isocyanides and ketones has been reported to yield 3-imino-1,4,2-dioxazolidines **212** by activation of the isonitrile (Scheme 32) [102].

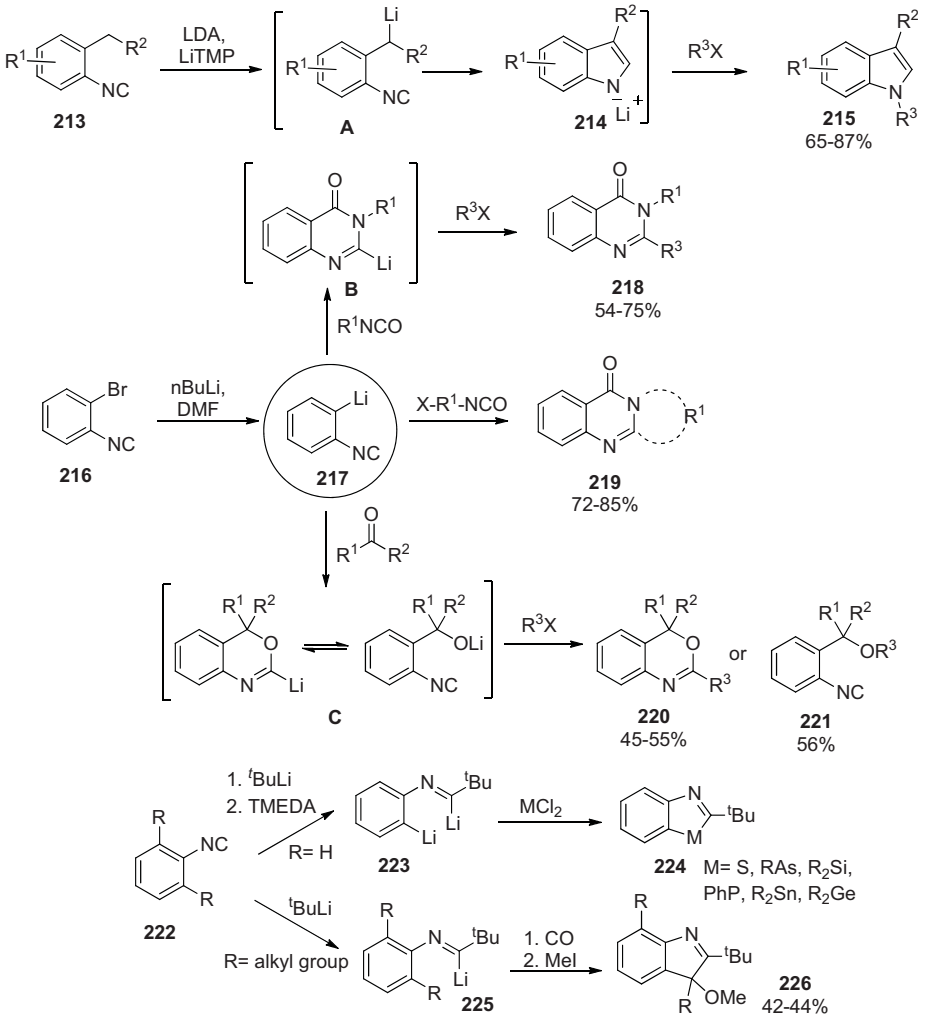


Scheme 32 Isocyanide-MCRs with epoxides, oxazolidines and nitroso compounds

1.4 Type III MCRs. Formal isocyanide insertion processes

An enormous body of work is devoted to metal-mediated transformations of isocyanides. Although the nature of many of these processes is sequential, the overall synthetic outcome is typical of MCRs and, for this reason, we present some representative cases in this section. Also included are other processes not clearly assigned to previous reaction types, especially insertions into heteroatom-heteroatom bonds. In this context, Meijere et al. have recently carried out a comprehensive overview of the use of isocyanides in the synthesis of a wide range of nitrogen heterocycles based on the cyclization of metalated isocyanides [103]. Also, the synthesis of indoles via isocyanide-mediated transformations has been reviewed and includes many useful MCRs involving metal-based or radical reactions [104]. *o*-Methylphenyl isocyanides **213** and *o*-bromophenyl isocyanides **216** are lithiated and engaged in sequential reactions with different electrophiles to trap the initially formed organometallic intermediate (Scheme 33). Selective metalation of isocyanide **213** with LDA in the presence of 2,2,6,6-tetramethylpiperidide affords 3-unsubstituted indole anions **214**, which can be selectively alkylated with a variety of electrophiles, such as epoxides, alkyl halides or acid chlorides, to yield the *N*-substituted derivatives **215** [105]. *o*-Lithiophenyl isocyanides **217**, obtained from the lithiation of **216** with *n*-BuLi, react with isocyanates, aldehydes and ketones and then with a second electrophile to afford quinazolin-4-ones **218**, benzoxazines **220** and *o*-isocyanobenzylalcohol derivatives **221**, respectively. The use of functionalized isocyanates triggers a domino cyclization to yield *N*-functionalized intermediates **219** [106, 107]. The α-addition of organolithium reagents to isocyanides provides metalated aldimines **223** or

225, which can undergo subsequent cyclization to heteroaromatic derivatives **224** or substituted indolenines **226**, after the customary trapping with metalodihalides and related species ($PhPCl_2$, SCl_2, $MeAsCl_2$, Me_2SnCl_2, etc.) [108, 109] or carbon monoxide/MeI [110], respectively (Scheme 33).



Scheme 33 Representative MC processes involving metalated isocyanides

Fujiwara et al. described an innovative synthesis of selenium derivatives via an isocyanide-MC protocol promoted by several nucleophiles, such as lithiated secondary amines **227**, organolithium derivatives **228** or alcohols **229**. These species on interaction with elemental selenium and isocyanides triggered a selenoimidoylation process (Scheme 34) [111-113]. Afterwards, in a sequential manner, the generated intermediate was trapped with butyl iodide to provide isoselenoureas **230**, selenoimidates **231** and selenocarbonimidates **232**, respectively, in suitable yields. Recently, the synthesis of benzoselenazoles **233** from *o*-arylisocyanides **216**, selenium and several nucleophiles under copper (I) catalysis was described. It should be noted that when the same reaction was carried out in the absence of the catalyst, selenoureas **234** were obtained instead. However, in the presence of tellurium, the use of lithiated secondary amines is required to obtain the desired benzotellurazoles **235** [114]. The synthesis of selenoureas **234** following a sequential strategy from amines, isocyanides and selenium has also been described (Scheme 34) [115,116].

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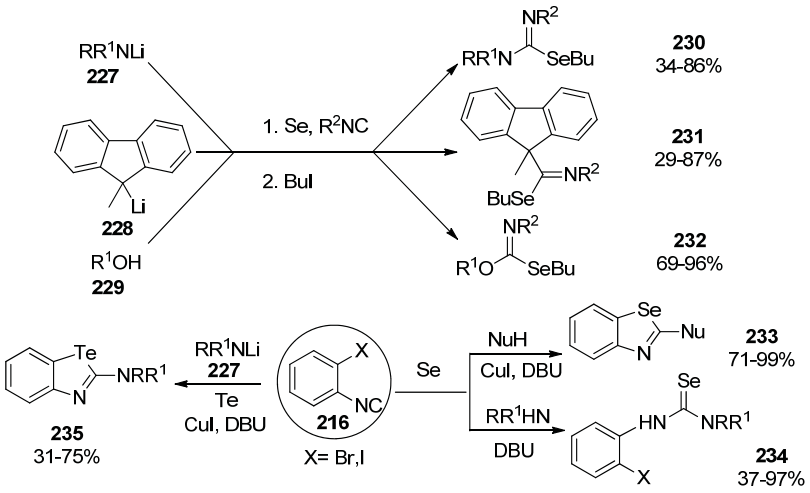
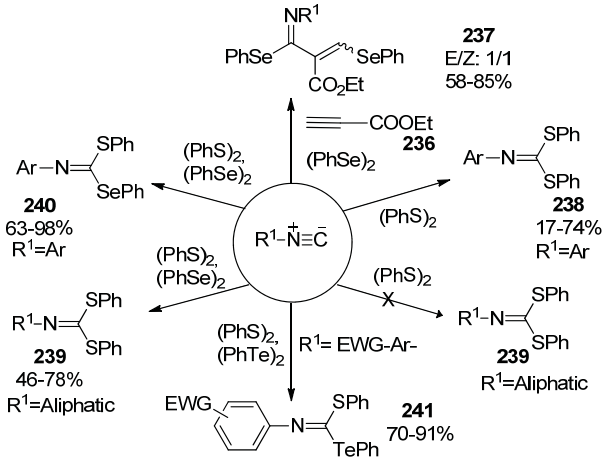


Scheme 34 Se- and Te-promoted MCRs with isocyanides and nucleophiles

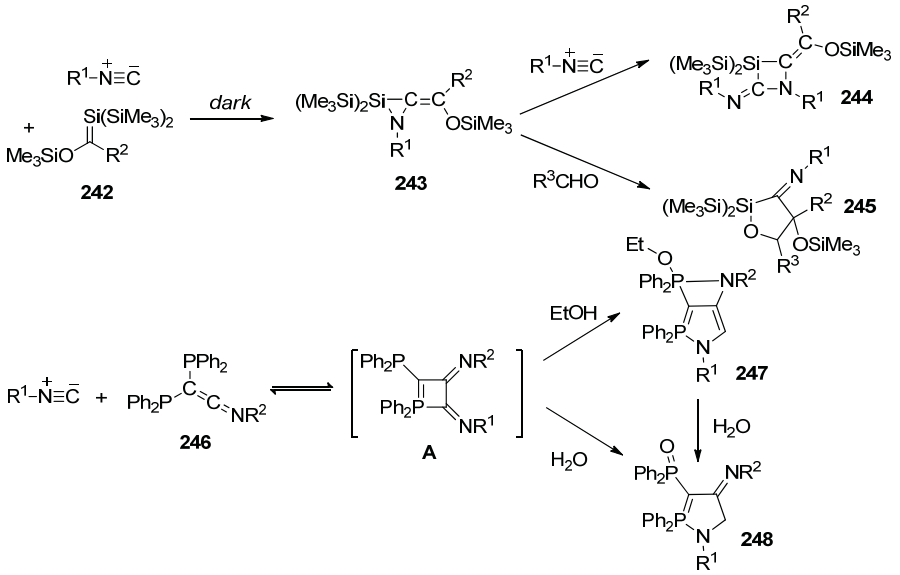
Ogawa et al. have extensively explored the incorporation of substituted thio, telluro and seleno groups into isocyanides. An interesting MCR between isocyanides, electron-deficient alkynes (such as ethyl propiolate) and diphenyl diselenide afforded adducts **237** (Scheme 35) [117]. A selective double chalcogenation of isocyanides with disulfides, diselenides and ditellurides was similarly carried out. In this way, bisthiolated derivatives **238** were directly obtained from aromatic isocyanides, while the corresponding aliphatic derivatives **239** required a modified method using a disulfide-diselenide mixture. In contrast, the reaction of aromatic isocyanides with these reactants selectively yielded thioselenatated adducts **240** [118]. Analogously, the corresponding thiotellurated products **241** were obtained only when aryl isocyanides bearing electron-withdrawing groups were employed (Scheme 35) [119]. Intramolecular cyclization of *o*-vinyl- or *o*-alkynyl-arylisocyanides with organic dichalcogenides is an efficient method for the synthesis of interesting and useful heterocyclic compounds [120-122].



Scheme 35 Chalcogenation of isocyanides

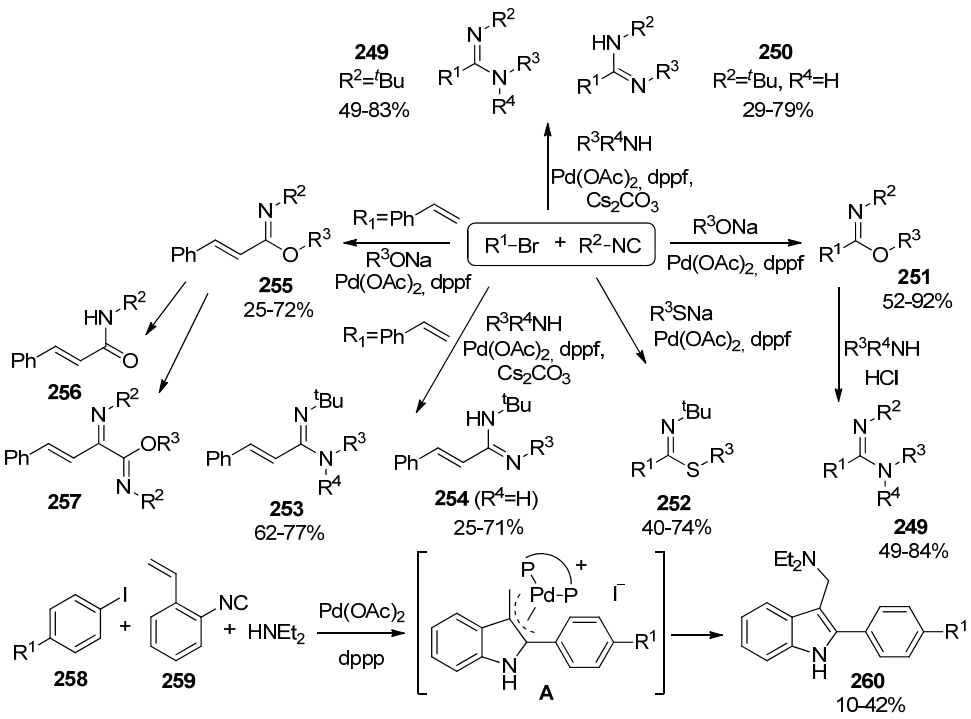
The ring-opening of silaaziridines **243**, generated from the interaction between isocyanides and silenes **242**, was carried out with another equivalent of the starting isocyanide or with an α,β-unsaturated aldehyde, to afford the corresponding heterocyclic systems **244** and **245**, respectively (Scheme 36) [123, 124]. The insertion of isocyanides into silicon-silicon bonds was also reported [125, 126]. A novel 3CR between isocyanides, diphosphinoketenimines

246 and ethanol or water affords azaphosphaheterocycles **247** and **248**, respectively (Scheme 36). The mechanism probably involves the formation of the unstable four-membered ring **A** through a formal [1+3] cycloaddition. In the presence of ethanol, compound **247** is obtained, whereas water leads to the related system **248** (Scheme 36) [127].



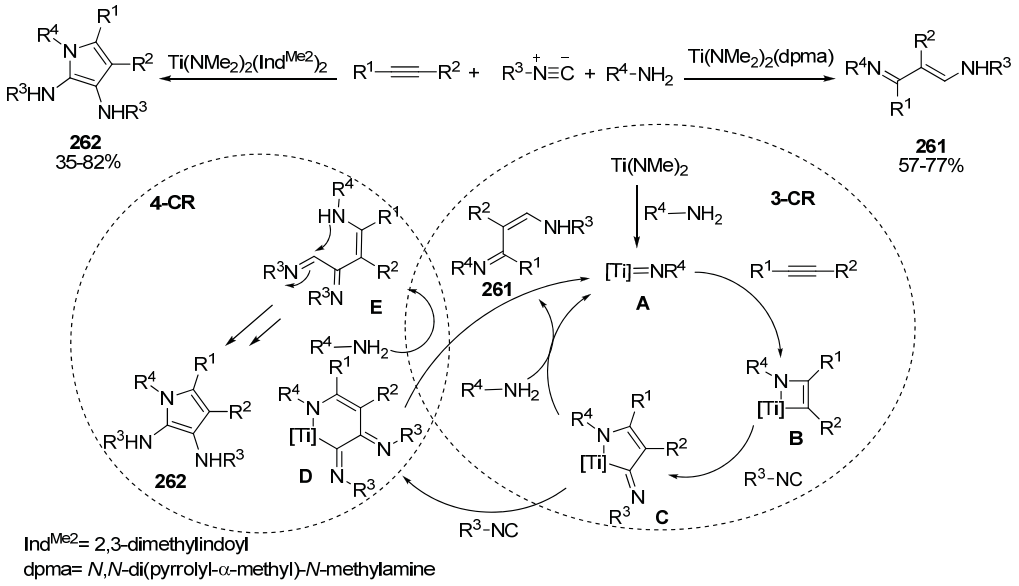
Scheme 36 Isocyanide-MCRs involving Si and P reactants

Several MCRs involving the use of isocyanides in transition metal-catalyzed processes have been reported in the literature [128]. Whitby et al. disclosed the synthesis of amidines, imidates and thioimidates through the interaction between isocyanides, aryl halides and nucleophilic species under palladium catalysis. The synthesis of amidines **249** and **250**, from secondary and primary amines respectively, was carried out in this way, the process being almost limited to *tert*-butylisocyanide (Scheme 37) [129]. The reaction with sodium ethoxide afforded imidates **251** in moderate to high yields. Analogously, the use of thiols allowed the formation of thioimidates **252**. Treatment of imidates **251** with amines and acetic acid conveniently afforded amidines **249** and overcame the limitation of different isocyanides used in the syntheses described above [130]. Subsequently, α,β-unsaturated amidines **253**-**254** and imidates **255** were prepared from alkenylbromides, the resulting imidates **255** proving unstable and spontaneously evolving to amides **256** through hydrolysis. Double isocyanide insertion compounds **257** were also isolated in these transformations [131]. Due to the coordinating nature of the isocyanide, these processes, which are catalytic in the transition metal, are especially delicate and the optimization of the reaction conditions becomes a critical issue [132]. In a related study, the synthesis of 2,3-disubstituted indoles **260** in a 3CR was carried out via the interaction of *o*-alkenylphenyl isocyanide **259** with aryliodide **258**. The coupling of the alkenyl and isocyano groups affords the 3-(indolylmethyl)palladium complex **A** which, after the amine attack, yields the expected adduct **260** (Scheme 37) [133].



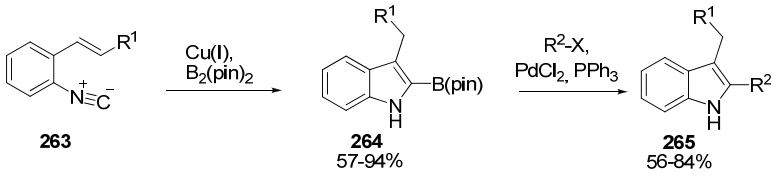
Scheme 37 Palladium-catalyzed isocyanide MCRs

Besides palladium, other transition metals have been used in isocyanide-MCRs, For instance, Odom et al. described 3-CR and 4-CR between isocyanides, alkynes and alkyl- or arylamines under titanium catalysis to yield diaminopyrroles **262** and iminoenamines **261** [134] (Scheme 38). The process may take place through a [2+2]-cycloaddition between a titanium imido complex **A** and an alkyne giving rise to the azatitanacyclobutene intermediate **B**, in which the insertion of isocyanide leads to the corresponding complex **C**. Cleavage of this species with an amine equivalent regenerates the iminotitanium intermediate and releases the α,β-unsaturated β-aminoimines **261**. A competitive pathway involves the insertion of a second unit of isocyanide into the aza-titanacycle intermediate **C** leading to the 2,3-diaminopyrroles derivatives **262** after the corresponding demetalation and cyclization steps. The latter MCR is predominant when using an excess of isocyanide [135].



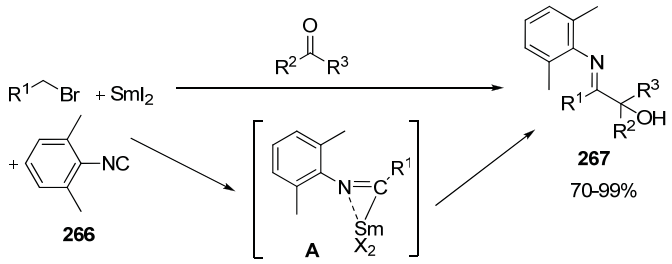
Scheme 38 Titanium-catalyzed isocyanide MCRs

Recently, Angelici et al. described an interesting process involving reactions of isocyanides with amines and oxygen under gold-catalysis [136-138]. A MC tandem reaction was employed by Chatani et al. to obtain diversely substituted indoles from arylisocyanides. The process takes place via the Cu(I)-catalyzed synthesis of a 2-boroindole derivatives **264**, and this borylative cyclization is linked in tandem to a Pd-mediated Suzuki coupling with arylhalides to afford indole derivatives **265** (Scheme 39) [139]. A silylative termination was also described.



Scheme 39 Copper-catalyzed borylative cyclization

A few multicomponent processes involving isocyanides and samarium have also been described. The reaction of 2,6-xylylisocyanide **266**, aldehydes or ketones and alkylbromides leads to α-hydroxy imines **267** in good to excellent yields. The process begins with the formation of organosamarium species arising from an interaction of the metal with the alkylbromide and isocyanide to generate intermediate **A**. The carbonyl compound is then added to the reaction mixture to yield the final adduct (Scheme 40) [140, 141].



Scheme 40 Tandem MC process promoted by SmI_2

1.5 Conclusions

This chapter has shown that the rich chemistry of isocyanides goes far beyond the famous Ugi and Passerini MCRs and in a representative overview, it has outlined useful transformations that exploit the inherent reactivity of this functional group. The potential of isocyanide-MCRs is currently being explored in different directions at a good pace. Interestingly, some recent work has focused on old and neglected results, applying modern techniques and approaches to achieve a completely renewed reactivity with substantially enhanced synthetic usefulness. It is reasonable to expect that the already high impact of isocyanide MCRs would be further developed with novel reactant combinations, and this will facilitate the preparation of complex organic compounds in a few steps, aiming for the ideal synthesis [142].

Acknowledgements We warmly thank all the members of our research group involved in this project for their enthusiasm and dedication. Financial support from the DGICYT (Spain, project BQUCTQ2009-07758), Generalitat de

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Boron-Based Dipolar Multicomponent Reactions: Simple Generation of Substituted Aziridines, Oxazolidines and Pyrrolidines

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In memory of Gerhard Hesse

Abstract: New multicomponent reactions of aldehydes, isocyanides, trialkylboron reagents and dipolarophiles have been developed as an efficient route to diverse scaffolds, including aziridines, oxazolidines and poly-substituted pyrrolidines. This chemistry, inspired by a report by Hesse in 1965, is simple and involves mild conditions. Computational studies provide a basis to investigate the stereochemical features observed in the formation of oxazolidines and four-component adducts, and permit identification of potential factors that might influence the outcome of the multicomponent reaction. Thus, a rational screening of all the components and reaction parameters is made to examine the manifold mechanistic pathways and establish the practical limits for standard applications. Finally, intramolecular and solid-supported versions of these reactions bring new synthetic possibilities and practical protocols. Overall, the results describe a new family of multicomponent reactions valuable not only for organic reactivity, but also for combinatorial chemistry and drug discovery.

Keywords: boranes · cycloaddition · heterocycles · isocyanides · multicomponent reactions

Introduction

Multicomponent reactions (MCRs) are domino processes in which three or more reactants interact to form an adduct in a single operation. MCRs constitute a fast-growing field of enormous importance in organic chemistry[1] as they embody many features of the ideal synthesis, such as atom and step economy, convergence and structural diversity.[2] Progress in this area has allowed the use of this methodology in target-oriented synthesis, parallelisation protocols and diversity-oriented synthesis, thus enabling the preparation of natural products and bioactive compounds.

Isocyanides are arguably the most prolific functional group for MCRs.[3] In recent times new and exciting results have brought great attention to this field.[4] In pursuing the development of new MCRs,[5] we considered the interaction of electrophilic boron reagents with isocyanides as the initial step to generate reactive intermediates amenable to further reactivity.[6] A literature search revealed a fascinating process described by Hesse and co-workers in 1965, which involves the generation of oxazolidines in useful yields from the interaction of alkylboranes, aldehydes and isocyanides.[7] The authors pointed out the intermediacy of an azomethine ylide, which may undergo a dipolar [3+2] cycloaddition with a second equivalent of the aldehyde to furnish the final adduct in a stereoselective manner (Scheme 1). Surprisingly, almost no references to this work have been reported.[8] The process, the keystone of which is the reaction between the isocyanide and the borane,[9] can be reshaped and, through different trappings of the dipolar intermediate, can provide a variety of scaffolds, thus exploiting the rich chemistry of azomethine ylides.[10,11]

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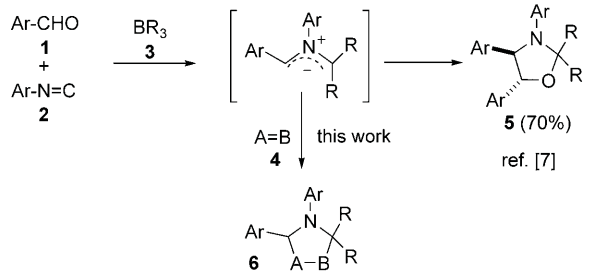


Scheme 1. Generation of five-membered N-heterocycles from the interaction of isocyanides, aldehydes, alkylboranes and dipolarophiles through azomethine ylides.

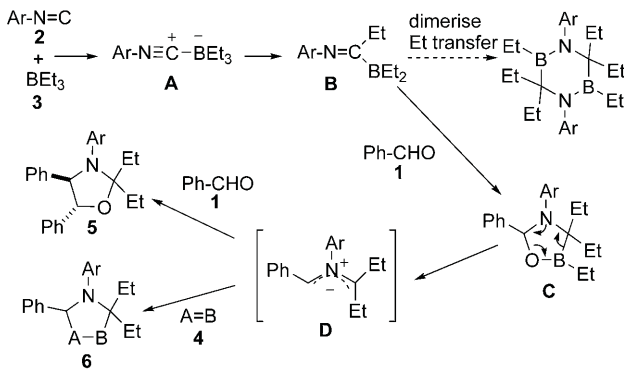
Herein, we report a new set of MCRs involving aldehydes, isocyanides, trialkylboron reagents and dipolarophiles that is well suited to affording a variety of scaffolds comprising aziridines, oxazolidines and poly-substituted pyrrolidines. We used computational studies to unravel the mechanistic details of the stereochemical preferences of the processes. Lastly, we established the scope and limitations of the new MCRs, and also devised intramolecular and solid-supported versions of these reactions.

Results and Discussion

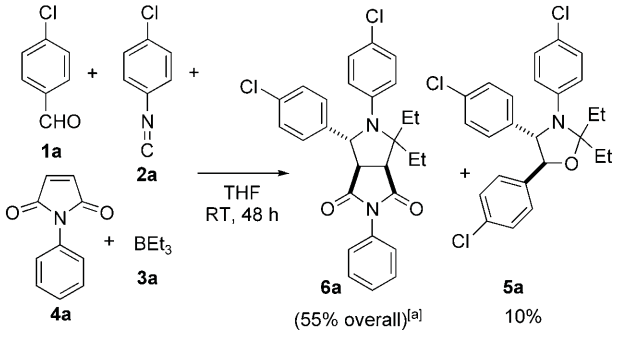
Mechanistic proposal: The suitability of the MCR involving the interaction of four reactants (aldehydes, isocyanides, trialkylboranes and dipolarophiles) to become a productive process depends on three critical factors: firstly, the feasibility of the domino process that links the four chemical inputs to yield the desired cycloaddition;[12] secondly, the generality of the process, which is mainly determined by the range of reactivity for each component; and lastly, the reaction parameters required for achieving useful transformations under mild conditions. These issues are particularly challenging due to the number and nature of the reactive species presumably engaged in the mechanism, and the manifold evolutionary pathways they may follow. Thus, as illustrated in Scheme 2, the process could start with the formation of an initial adduct **A** arising from the addition of isocyanide **2** to borane **3**, which after alkyl migration would yield an iminoborane **B**, which could dimerise and then either undergo a second ethyl migration[9] or, in the presence of aldehyde **1**, could form an oxazaborolidine intermediate (**C**) en route to the azomethine ylide **D**. Finally, this dipole could efficiently trap a second equivalent of the aldehyde to yield the oxazolidine **5**. Nevertheless, the remarkable bond-forming efficiency[1c] of the MCR could be improved if it allowed incorporation of the dipolarophile species **4**, which would lead to the highly substituted pyrrolidine derivatives **6**, representing the formation of one C–N and four C–C bonds in a single event.[13]

The main feature of the process deals with a practically unexplored access route to azomethine ylides, which may tackle some synthetic niches difficult to reach through known methodologies. However, the drawbacks of the new reaction are related to the double incorporation of the alkyl groups from the borane, and the competition between the aldehyde and the dipolarophile for trapping the azomethine ylide. The oxazolidine adduct contains two different moieties from the starting aldehyde, so its formation can be regarded as a chemo-differentiating reaction, a burgeoning family of processes with great synthetic potential.[14] Moreover, the new MCRs are susceptible to many side reactions, such as the aforementioned (and undesired) formation of the isocyanide–borane complexes,[9] the interaction of the isocyanide with the dipolarophile,[3c,15] and Passerini-type reactions promoted by the Lewis acidity of the borane.[16]

As proof of concept, we reacted an equimolecular mixture of *p*-chlorobenzaldehyde (**1a**), *p*-chlorophenyl isocyanide (**2a**), triethylborane (**3a**) and *N*-phenylmaleimide (**4a**) in THF at room temperature, to obtain the four-component-reaction (4CR) adduct **6a** as a 4:1 mixture of two stereoisomers (the minor isomer being the *all-cis* epimer) in an overall yield of 55% together with lesser amounts (≈10%) of the corresponding *trans*-oxazolidine **5a** (Scheme 3). The relative stereochemistry of compounds **5a** and **6a** was established by NMR methods (the NOEs being of diagnostic value). Incidentally, the structural assignment for the oxazolidine derivative agrees with that reported by Hesse, which he obtained by using chemical correlation studies.[7]



Scheme 2. Mechanistic proposal.



Scheme 3. 4CR leading to pyrrolidine derivative **6a**. [a] 4:1 isomeric ratio, whereby **6a** is the major isomer and the minor isomer is the *all-cis* compound.

Computational analysis: Quantum chemistry computations were performed to gain insight into the stereochemical preferences of the chemical processes involved in these MCRs. To this end, a series of model compounds that includes methylborane, phenyl isocyanide, benzaldehyde and *N*-phenylmaleimide was considered in calculations, and the relative free energies between chemical reactants, products and transition states (TSs) were determined at the MP2/6-311G-(d,p)+[CCSD-MP2/6-31G(d)] level (see the Experimental and Computational Section).

*Formation of azomethine ylide **D***: According to the reaction mechanism (Scheme 2), the iminoborane intermediate **B**, generated after alkyl migration in the initial adduct **A**, in the presence of aldehyde **1** yields the azomethine ylide **D** via the oxazaborolidine intermediate **C**. For the model compounds considered in the present computations, formation of oxazaborolidine **C** is highly favourable (-17.9 kcal mol^{-1}), but the exothermicity of this process is counterbalanced by the energy required to open the oxazaborolidine ring to yield the azomethine ylide **D**. As a result, the ylide **D** is slightly stabilised relative to the separated reactants (intermediate **B** and benzaldehyde; see Figure 1). The orientation of the two benzene rings in **D** defines two configurations denoted here as **D**-*cis* and **D**-*trans*, which mimic the W- and S-type configurations of ylides (Figure 2). The **D**-*tran*s species is marginally favoured (0.4 kcal mol^{-1}) compared to the **D**-*cis* form. Accordingly, both species can a priori participate in the reaction with either another molecule of aldehyde to yield oxazolidine **5** or with dipolarophile **4** to generate adduct **6**.

*Formation of oxazolidine **5***: The azomethine ylide **D** can react with benzaldehyde to yield oxazolidine **5**, which can exist in two stereoisomeric arrangements (*trans* and *cis*, see Scheme 3). Formation of **5** is predicted to be very favourable (around -42 kcal mol^{-1}; see Figure 1), *trans*-**5** being favoured by 2.4 kcal mol^{-1} relative to *cis*-**5**. When the [3+2] cycloaddition involves the azomethine ylide **D**-*cis*, the TS leading to *trans*-**5** is destabilised by 7.0 kcal mol^{-1} relative to the separate reactants, whereas the TS yielding *cis*-**5** is further destabilised by 2.6 kcal mol^{-1} (Figure 1). Such a difference can be attributed to two factors. First, the more eclipsed approach of the reactants in the TS *cis*-**5**, as noted in the Newman projection along the forming C–C bond (see Figure 3). Second, the larger steric repulsion due to the approach of the benzene rings in the TS *cis*-**5**, as noted in the short contact between the hydrogen atoms of the benzene rings (2.31 Å; see Figure 3). On the other hand, when the cycloaddition takes place starting from the ylide **D**-*trans*, there is an additional destabilisation (by around 2 kcal mol^{-1}) in the TSs leading to oxazolidine **5**, which reflects the increased eclipsed character of the incoming reactants (note also the short H···H contact, 2.27 Å, found in TS *trans*-**5**; see Figure 3). Overall, the results indicate that the stereoselective formation of *trans*-**5** (Scheme 3) can be attributed to the kinetic preference associated with the *trans* cycloaddition pathway originating from the reaction of benzaldehyde with the **D**-*cis* form of the azomethine ylide.

Inspection of the geometries of the most favoured TSs reveals the asynchronicity of the bond formation in the cycloaddition reaction leading to *trans*-**5** (i.e. the lengths of the forming C–C and C–O bonds are 2.15 and 2.42 Å, respectively), which is in contrast with the similar lengths (C–C:

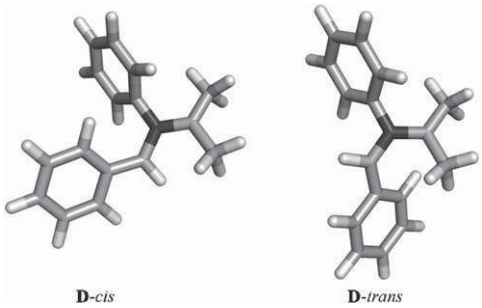


Figure 2. Representation of the *cis* and *trans* forms of the azomethine ylide **D**.

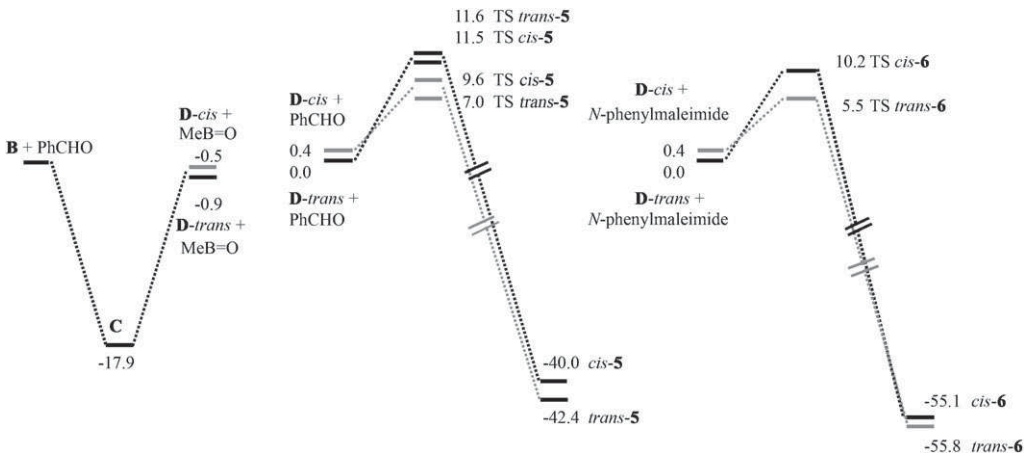


Figure 1. Diagram of the free energy differences [kcal mol^{-1}] for the chemical species involved in the formation of oxazolidine **5** and pyrrolidine **6**.

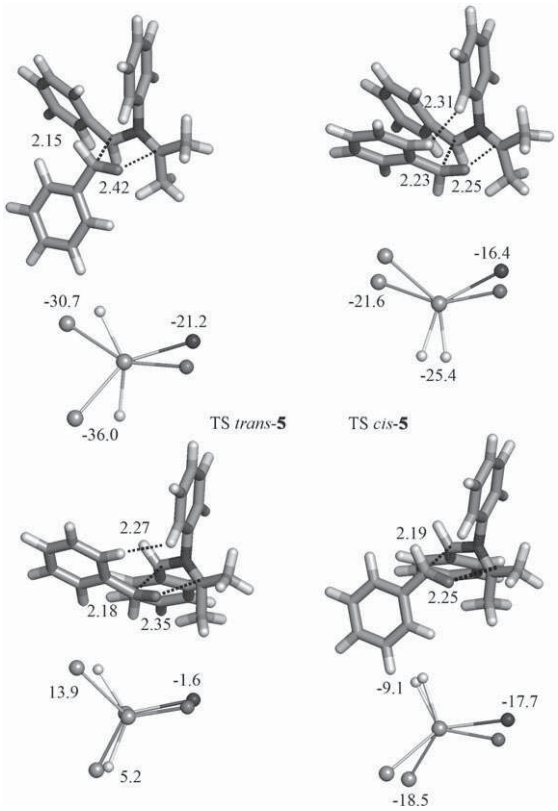


Figure 3. Representation of the TSs leading to *trans* and *cis* forms of oxazolidine **5** formed from (top) **D**-*cis* and (bottom) **D**-*trans* forms of the azomethine ylide. Newman projections viewed from along the forming C(benzaldehyde)–C(ylide) bond are also shown (distances and torsional angles are in Å and degrees, respectively).

2.23 Å; C–O: 2.25 Å) found in the TS leading to *cis*-**5**. These trends, which differ from the negligible asynchronicity found for the corresponding [3+2] cycloaddition between benzaldehyde and nitrile-containing carbon ylides reported in previous studies,[17] most likely reflect the influence of the substituents attached to the ylide **D** and the steric effects arising from the aromatic ring bound to the nitrogen atom of the ylide.

Formation of pyrrolidine ***6***: The azomethine ylide **D** may interact with *N*-phenylmaleimide to afford the desired pyrrolidine **6**, which can display two possible stereoisomeric arrangements (*trans*, *cis*) for the C-phenyl ring coming from intermediate **D** with respect to the maleimide ring, the *trans*-**6** adduct being the major component (ratio 4:1) of the mixture (see Scheme 3). The interaction between the ylide and the dipolarophile is conditioned by the presence of the bulky benzene rings, which thus only enables the approach of the reactants through a reactive pathway where the benzene rings adopt an *anti* orientation. Accordingly, the reaction of *N*-phenylmaleimide with the **D**-*cis* ylide exclusively affords *trans*-**6**, whereas reaction with **D**-*trans* yields *cis*-**6**. Computations point out that the formation of pyrrolidine **6** is highly exothermic (around 55 kcal mol^{-1}), and the pyrrolidine *trans*-**6** is predicted to be 0.7 kcal mol^{-1} more favourable than the *cis*-**6** adduct (Figure 1). Remarkably, the TS leading to *trans*-**6** is favoured by 4.7 kcal mol^{-1} compared to that associated with the formation of *cis*-**6**. In the two TSs, there is a steric contact between the *N*-phenyl ring in the ylide and the *N*-phenylmaleimide moiety (distances of 2.31 and 2.45 Å in TS *trans*-**6** and TS *cis*-**6**, respectively; see Figure 4). However, the more eclipsed approach of the reactants in TS *cis*-**6** explains the larger stability of the TS *trans*-**6**.

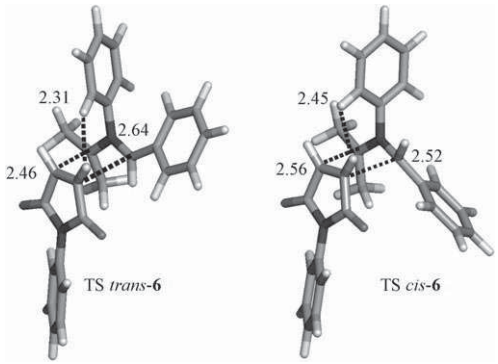


Figure 4. Representation of the TSs leading to *trans* and *cis* forms of pyrrolidine **6** (distances are in Å).

Overall, the results point out that the stereochemical preferences in the formation of oxazolidine **5** and pyrrolidine **6** are dictated by the kinetically more favoured TS, which corresponds to the one leading to *trans*-**5** and *trans*-**6**, respectively. Notably, the latter is predicted to be 1.5 kcal mol^{-1} more favourable than the former, which agrees qualitatively with the larger amount found for pyrrolidine **6** (see Scheme 3). Nevertheless, the preceding discussion also suggests that the precise outcome of the MCR may be very sensitive to the nature of the substituents attached to both isocyanide and aldehyde, the differential stabilisation played by the solvent on the [3+2] cycloaddition, and the chemical features of the dipolarophile, which might affect the relative stability of the *cis* and *trans* species of the ylide **D** and the competitive reaction of the ylide with either the aldehyde or the dipolarophile.

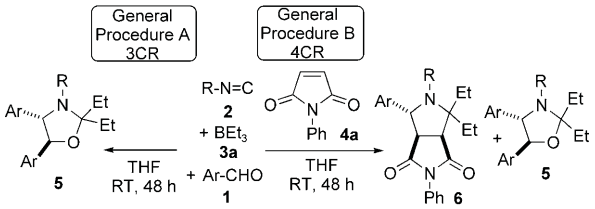
Reaction scope: Upon surveying the reaction conditions, we found that the best solvents were diethyl ether (Et_2O) and THF; no reaction occurred in toluene, dichloromethane, DMF, CH_3CN or MeOH. Surprisingly, water (50% in THF) is well tolerated and it is even possible to run the MCR in micellar systems (H_2O/sodium dodecyl sulfate). The reaction proceeds within a useful temperature range: from −20 to +20 °C. At lower temperatures, there is no noticeable reactivity, whereas at higher values, the starting materials severely decompose (the formation of isocyanide–borane adducts is presumably favoured). Therefore, all the following experiments were run at room temperature, after pre-mixing the four components at 0 °C. Microwave irradiation seems to increase the formation of oxazolidines, consequently lowering

the amount of the 4CR adduct. The use of a set of additives including Lewis acids, bases, ligands and dehydrating agents such as scandium(III) trifluoromethane sulfonate (scandium triflate, $Sc(OTf)_3$), $Mg(ClO_4)_2$, *N*,*N*-diisopropylethylamine (DIPEA), 2-chloropyridine[18] or molecular sieves (4 Å), respectively, precludes the reaction. In contrast, the chemistry proceeds normally with galvinoxyl and with limited exposure to oxygenated atmospheres (no effect on the yields and selectivity), which seems to rule out a radical process.

Isocyanide range: We determined the range of reactivity for each component by using comparable sets of reactants and reaction conditions. Starting with isocyanides **2**, we found that only the aromatic derivatives were productive under the mild conditions tested. For example, *p*-methoxyphenyl isocyanide (**2b**) was efficiently incorporated into oxazolidine **5b** and the 4CR adduct **6b** (Table 1, entries 1 and 2, respectively). As usual, we obtained epimeric mixtures (≈7:3) of the 4CR adducts, the major stereoisomers being depicted in Table 1. *p*-Tolyl (**2c**) and phenyl isocyanides (**2d**) afforded the expected adducts in somewhat lower yields (Table 1, entries 3 and 4). Halo-substituted aromatic derivatives also reacted in a convenient manner (Table 1, entries 5–7), whereas the deactivated 4-ethoxycarbonyl derivative (**2f**, Table 1, entry 8) was considerably less reactive and the 3- and 4CR adducts could only be detected in minute amounts. Cyclohexyl (**2g**), cyclohexenyl (**2h**), benzyl (**2i**) and deactivated isocyanides, such as tosylmethyl isocyanide (**2j**), were inert under the usual conditions or gave rise to complex mixtures (Table 1, entries 9–12). As revealed in Table 1, the best yields were obtained with electron-rich benzene rings, which may reflect the need for nucleophilicity at both the C-terminal atom of the isocyanide and at the N atom of intermediate **B** (Scheme 2).[19] The stability of the resulting azomethine ylide may also be important for the viability of the MCRs, as it would presumably restrict the process to the presence of aromatic rings in the dipole.

Aldehyde range: Regarding the aldehydes (Table 2), we found that aromatic derivatives afforded the best conversions in both three-component reactions (3CRs; oxazolidines **5**) and 4CRs (pyrrolidines **6**). *p*-Chlorobenzaldehyde (**1a**, Table 2, entries 1 and 2) yielded the corresponding adducts in good amounts, and methyl 4-formylbenzoate (**1b**, Table 2, entries 3 and 4) was also productive. Benzaldehyde (**1c**, Table 2, entry 5) and even the electron-rich *p*-methoxybenzaldehyde (**1d**, Table 2, entry 6) afforded the corresponding MCR adducts, although in lower yield in the latter case. Among the heteroaromatic aldehydes, furfural (**1e**, Table 2, entry 7) yielded the corresponding adduct **6g**, whereas pyridine-3-carbaldehyde (**1f**, Table 2, entry 8) gave predominantly the oxazolidine **5h** in low yield; the 4CR adduct was only detected under these conditions (general

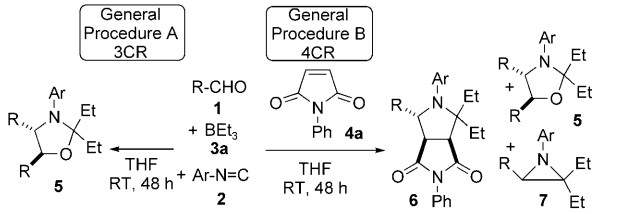
Table 1. Range of isocyanides **2**.



Entry[a]	Procedure	R	Adduct	Yield[b]
1	A	4-MeO-C_6H_4- (**2b**)	**5b**	85
2	B	4-MeO-C_6H_4- (**2b**)	**6b**[c]	68
3	A	4-Me-C_6H_5- (**2c**)	**5c**	67
4[d]	A	C_6H_5- (**2d**)	**5d**	22
5	A	4-Cl-C_6H_4- (**2a**)	**5a**	65
6[e]	B	4-Cl-C_6H_4- (**2a**)	**6a**	55
7	A	4-F-C_6H_4- (**2e**)	**5e**	36
8[f]	B	4-EtO_2C-C_6H_4- (**2f**)	**5f/6c**	traces
9	A	cyclohexyl- (**2g**)	–	–
10	A/B	1-cyclohexenyl- (**2h**)	–	–
11	A	benzyl- (**2i**)	–	–
12	A	tosylmethyl- (**2j**)	–	–

[a] The reactions were performed following the standard procedure A or B to form respectively **5** or **6** with *p*-chlorobenzaldehyde **1a** as the aromatic aldehyde input. [b] Overall yield of isolated product. [c] Adducts **6** were generated as ≈7:3 diastereomeric mixtures, from which the major epimer was isolated and characterised. The major epimer corresponds to the depicted relative stereochemistry. [d] The reaction was performed with BBu_3 (**3b**). [e] In this experiment, oxazolidine **5a** was also generated (10%). [f] This experiment was attempted with methyl-4-formylbenzoate **1b** as the aldehyde component.

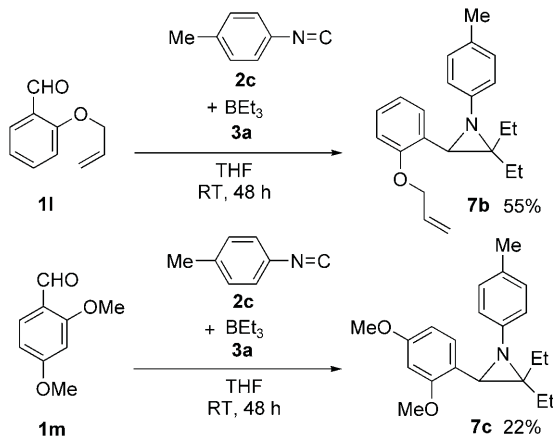
Table 2. Range of aldehydes **1**.



Entry[a]	Procedure	R	Adduct	Yield[b]
1	A	4-Cl-C_6H_4- (**1a**)	**5b**	85
2	B	4-Cl-C_6H_4- (**1a**)	**6b**[c]	68
3	A	4-MeO_2C-C_6H_4- (**1b**)	**5g**	50
4	B	4-MeO_2C-C_6H_4- (**1b**)	**6d**	24
5	B	C_6H_5- (**6e**)	**6e**	55
6[d,e]	B	4-MeO-C_6H_4- (**1d**)	**6f/7a**	25/4
7[d]	B	2-furyl- (**1e**)	**6g**	20
8[d]	A	3-pyridyl- (**1f**)	**5h**	62[f]
9	B	CH_2=CH- (**1g**)	**6h**	40
10[d]	B	Ph-CH=CH- (**1h**)	**6i**[g]	71
11	B	C_5H_{11}-C≡C- (**1i**)	**6j**	63
12	A/B	$(Me)_3C$- (**1j**)	–	–
13	A	EtO_2C- (**1k**)	**5i**	7

[a] The reactions were performed following the standard procedure A or B to form respectively **5** or **6**; *p*-methoxyisocyanide (**2b**) was used as the aromatic isocyanide input if not stated otherwise. [b] Overall yield of isolated product. [c] Adducts **6** were generated as ≈7:3 diastereomeric mixtures, from which the major epimer was isolated and characterised. The major epimer correspond to the depicted relative stereochemistry. [d] *p*-Chlorophenyl isocyanide (**2a**) was used as the aromatic isocyanide input. [e] Aziridine **7a** was also isolated in this experiment. [f] Following procedure B, the expected 4CR adduct was detected in minute amounts, whereas the oxazolidine **5h** adduct was obtained in 15% yield. [g] Obtained as a 7:3 mixture of stereoisomers, from which the minor adduct was isolated and characterised.

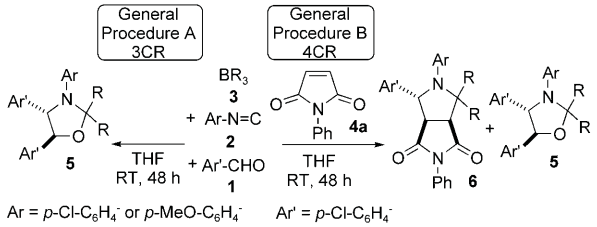
procedure B). However, this oxazolidine was conveniently generated (62%) when the 3CR protocol (general procedure A) was used, which probably means that this electrophilic aldehyde overrides maleimide as the dipolarophile input, thereby preventing the 4CR process. Interestingly, formyl groups linked to non-aromatic sp^2- or sp-hybridised carbon atoms were also reactive. Thus, acrolein (**1g**), cinnamaldehyde (**1h**) and oct-2-ynal (**1i**) readily afforded the expected MCR adducts (Table 2, entries 9–11).[20] In contrast, pivalaldehyde (**1j**) was not reactive (Table 2, entry 12) and ethyl glyoxylate (**1k**) gave low yields of the corresponding oxazolidine (**5i**, Table 2, entry 13). These results clearly indicate that electron-withdrawing substituents in aromatic rings seem to favour the MCRs, by rendering the carbonyl group more electrophilic and stabilising the anionic site in the dipole. Interestingly, strong electron-donor substituents, such as the *p*-MeO group, also provided the 4CR adduct albeit in lower yields. In this experiment the aziridine **7a** (Table 2, entry 6) was also isolated whereas the corresponding oxazolidine was not detected, probably due to the low reactivity of this aldehyde as dipolarophile in [3+2] cycloadditions. Confirming this result, the 2-allyloxy derivative **1l** and 2,4-dimethoxybenzaldehyde (**1m**) afforded aziridines **7b** and **7c**, respectively (Scheme 4), most likely by electrocyclisation of the azomethine ylide intermediate.[21,22] Overall, the reactivity pattern of aldehydes seems to parallel that of the carbonyl precursors of the azomethine ylides generated by conventional methods (e.g. condensation, decarboxylation, prototropy, carbene insertion); the aromatic derivatives are the most widely used for preparative purposes.[10]



Scheme 4. Aziridine formation from *o*-alkoxybenzaldehydes.

Boron reagent range: The borane component is the main limitation in this MCR: we only found acceptable reactivity by using the commercially available ethyl (**3a**) and butyl (**3b**) boranes (Table 3, entries 1 and 2). However, borane itself afforded minute amounts of the expected adduct (as a somewhat unstable compound), together with the benzylic alcohol from the reduction of the aldehyde (Table 3, entry 3).[23] Triphenyl boron (**3d**),[24] 9-benzyl-BBN (**3e**; 9-BBN: 9-borabicyclo[3.3.1]nonane) and $BF_3{\cdot}Et_2O$ (**3f**) led to complex mixtures (Table 3, entries 4–6). Whether these MCRs can be improved with more suitable reaction conditions, namely by minimising unproductive side reactions, remains to be determined.

Table 3. Set of boron reagents.

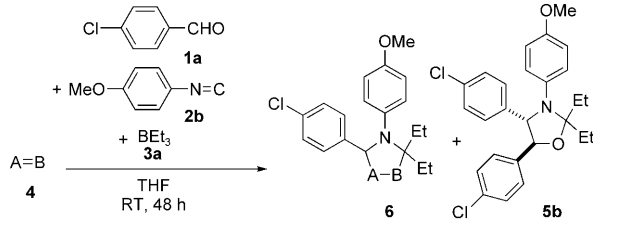


Entry[a]	Procedure	R	Adduct	Yield[b]
1	A	Et (**3a**)	**5a**	65
2	A	Bu (**3b**)	**5j**	40
3[c]	B	H (**3c**)	**6k**[d]	3
4	B	C_6H_5- (**3d**)	–	–
5	B	9-benzyl-BBN (**3e**)	–	–
6	B	F (**3f**)	–	–

[a] The reactions were performed following the standard procedures A or B to form respectively adducts **5** or **6** with *p*-chlorobenzaldehyde as the aromatic aldehyde input and *p*-chlorophenyl isocyanide as the isocyanide input if not stated otherwise. [b] Overall yield of isolated product. [c] *p*-Methoxyphenyl isocyanide was used in this experiment. [d] Adduct **6k** was generated as a ≈4:1 diastereomeric mixture.

Dipolarophile range: Regarding the dipolarophile **4** (Table 4), we obtained the highest yields of the 4CR adducts using *N*-phenylmaleimide (**4a**, Table 4, entry 1), which is the reference compound in many dipolar cycloadditions. It should be noted that azomethine ylides preferentially react with electron-deficient dipolarophiles.[25] As such, dimethyl acetylenedicarboxylate (**4b**, Table 4, entry 2), dimethyl fumarate (**4c**, Table 4, entry 3) and fumaronitrile (**4d**, Table 4, entry 4) were found to be reactive in our system. The 4CR adducts were isolated (although the adduct from acetylene dicarboxylate was somewhat unstable), and in all applicable cases the stereochemistry of the dipolarophile was conserved (7:3 mixtures of isomers in Table 4, entries 1, 3 and 4). Methyl acrylate (**4f**, Table 4, entry 5) afforded the 4CR adduct **6o** (24%, Figure 5) together with oxazolidine **5b** as the major compound (76%). The structure of **6o** was unambiguously assigned by diagnostic correlations from NMR experiments (^1H, ^{13}C, COSY, HSQC, HMBC, NOESY). In this case, the non-symmetrically substituted dipolarophile behaves in a particular manner, as it not only affords a *cis* stereochemistry, but seemingly alters the regiochemistry (taking into account the expected polarity in this type of process). Literature precedents on cycloadditions involving acrylates and azomethine ylide intermediates generally report low selectivity profiles, and in most cases the predominant regiochemistry is opposite to that observed in our system.[26] Diethyl azodicarboxylate (**4e**, Table 4, entry 6) also reacted conveniently but again the slight instability of the adduct prevented its full characterisation. The assay

Table 4. Set of dipolarophile reagents **4**.



Entry	A = B	Adduct	Yield[a]
1	*N*-phenylmaleimide (**4a**)	**6b**[b]	85
2	MeO_2C-C≡C-CO_2Me (**4b**)	**6l**[b]	49[c]
3	dimethyl fumarate (**4c**)	**6m**[d]	26
4	fumaronitrile (**4d**)	**6n**[b]	20[e]
5	methyl acrylate (**4f**)	**6o/5a**	24/76
6	EtO_2C-N=N-CO_2Et (**4e**)	**6p**	34
7	1,4-naphthoquinone (**4g**)	–	traces
8	ethyl 3-coumarincarboxylate (**4h**)	**5b**	58
9	diethyl benzylidenemalonate (**4i**)	**5b**	35
10[f]	norbornene (**4j**)	–	–
11[f]	2,3-dihydrofuran (**4k**)	–	–

[a] Overall yield of isolated product. [b] Adducts **6** were generated as ≈7:3 diastereomeric mixtures, from which the major epimer was isolated and characterised. The major epimer corresponds to the depicted relative stereochemistry. [c] Unreacted aldehyde was recovered (50%). [d] Obtained as an inseparable 6:4 mixture of stereoisomers. [e] Unreacted aldehyde was recovered (78%). [f] In these entries, 4-ethoxycarbonylphenyl isocyanide (**2f**) and methyl 4-formylbenzoate (**1b**) were used as the isocyanide and aldehyde components, respectively.

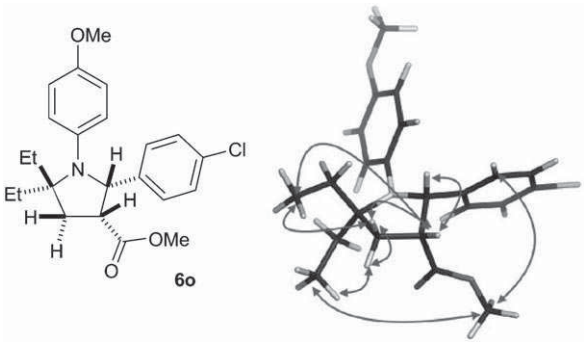
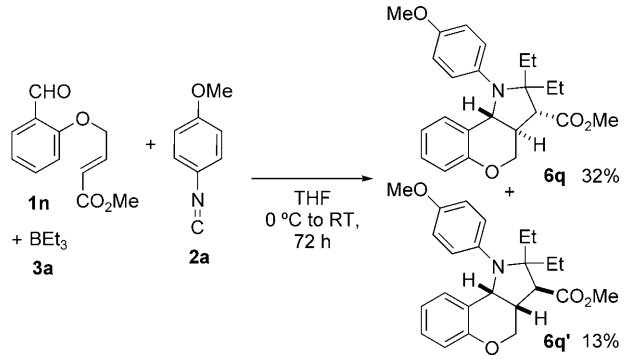


Figure 5. 4CR adduct **6o**. Diagnostic correlations in the NOESY spectrum.

with 1,4-naphthoquinone (**4g**, Table 4, entry 7) afforded a complex mixture in which the expected adduct together with its oxidation product were each detected in minute amounts.

On the other hand, when more sterically hindered dipolarophiles, such as ethyl 3-coumarincarboxylate (**4h**, Table 4, entry 8) and diethyl benzylidenemalonate (**4i**, Table 4, entry 9) were used, the oxazolidine **5b** was the only isolated product. Two examples of inverse electron-demanding cycloaddition were attempted by using non-activated (electron-rich) dipolarophiles, namely norbornene (**4j**, Table 4, entry 10) and 2,3-dihydrofuran (**4k**, Table 4, entry 11).[25] In both cases, to adjust the polarity of the process, 4-ethoxycarbonylphenyl isocyanide (**2f**) and methyl 4-formylbenzoate (**1b**) were used as reaction partners. However, no productive reaction was detected under the mild conditions used, and only the corresponding oxazolidines were formed. As noted above, the complexity of the mechanism promotes competition between two species (the aldehyde and the nominal dipolarophile) for trapping the dipole, which limits the use of the less reactive dipolarophiles. Moreover, the need to perform the processes at room temperature (cycloadditions with azomethine ylides are typically conducted at much higher temperatures) to avoid side reactions diminishes the feasibility of some combinations, particularly those involving the less reactive species.

Intramolecular MCRs: We also explored the possibility of promoting intramolecular MCRs by taking advantage of the structural diversity provided by this methodology and the extraordinary success recently achieved in this field.[10c,f,27] Again, the mild conditions demanded use of electron-deficient olefin moieties (for instance, the deactivated *o*-allyloxybenzaldehyde (**1l**) failed to give any pyrrolidine adduct, and afforded the aziridine **7b** instead; see Scheme 4). Hence, aldehyde **1n**[28] was chosen as an alternative substrate (Scheme 5). Rewardingly, the MCR yielded the chromenopyrrolidine adducts (**6q** and **6q′**) in an overall yield of 45%, as a 2:1 mixture of stereoisomers displaying *trans* and *cis* ring fusions, respectively.



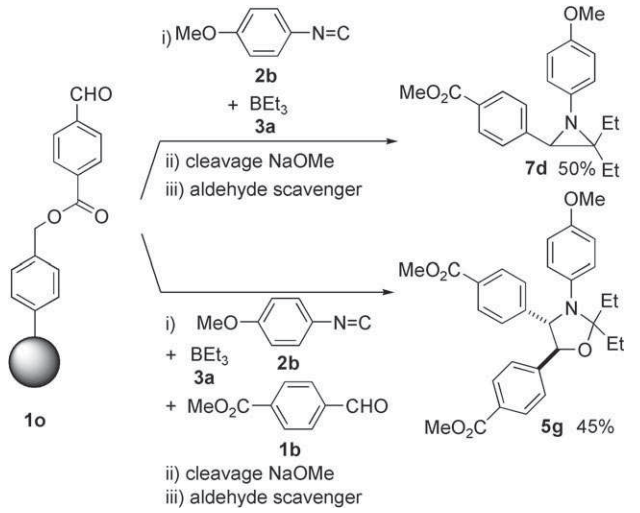
Scheme 5. Intramolecular MCR.

Recent precedents to access these heterocyclic systems used different methodologies to generate the azomethine ylide.[29] However, the method presented here seems to be the most straightforward for the introduction of two alkyl substituents at position 2 of the tricyclic scaffold.[30]

Solid-supported MCRs: Many side reactions do take place in these MCR processes and the undesired by-products, together with remaining starting materials (usually aldehyde and dipolarophile), can produce very complex mixtures, as noted in the HPLC profile of the crude organic extract from the experiment leading to **6f** (see the Supporting Information). Therefore, the purification of the expected adducts is extremely challenging, especially in cases with low yields. Solid-phase versions of MCRs[31] might be a practical and ef-

ficient way to facilitate removal of undesired products and minimise the impact of side reactions. For instance, supporting the aldehyde component on a resin would secure its role as the azomethine ylide precursor, and would prevent it from acting as a dipolarophile. Remarkable work in the area has shown the possibility of conducting dipolar cycloadditions in the solid phase.[32] Hence, we decided to link the aldehyde to a suitable resin, generate the azomethine ylide and quench the reaction in situ with the dipolarophile, or promote the selective formation of the aziridine and oxazolidine systems. In this way, only the desired products would remain attached to the resin, ideally to furnish pure samples after the cleavage. Also, it is conceivable to generate the linked dipolar intermediate, to elute all other compounds and, in a sequential manner, promote the cycloaddition step without interferences.

To explore these possibilities, we first linked 4-formylbenzoic acid to hydroxymethyl polystyrene resin, and afterwards we added the borane **3a** and isocyanide **2b** and stirred the resin at room temperature (Scheme 6). After



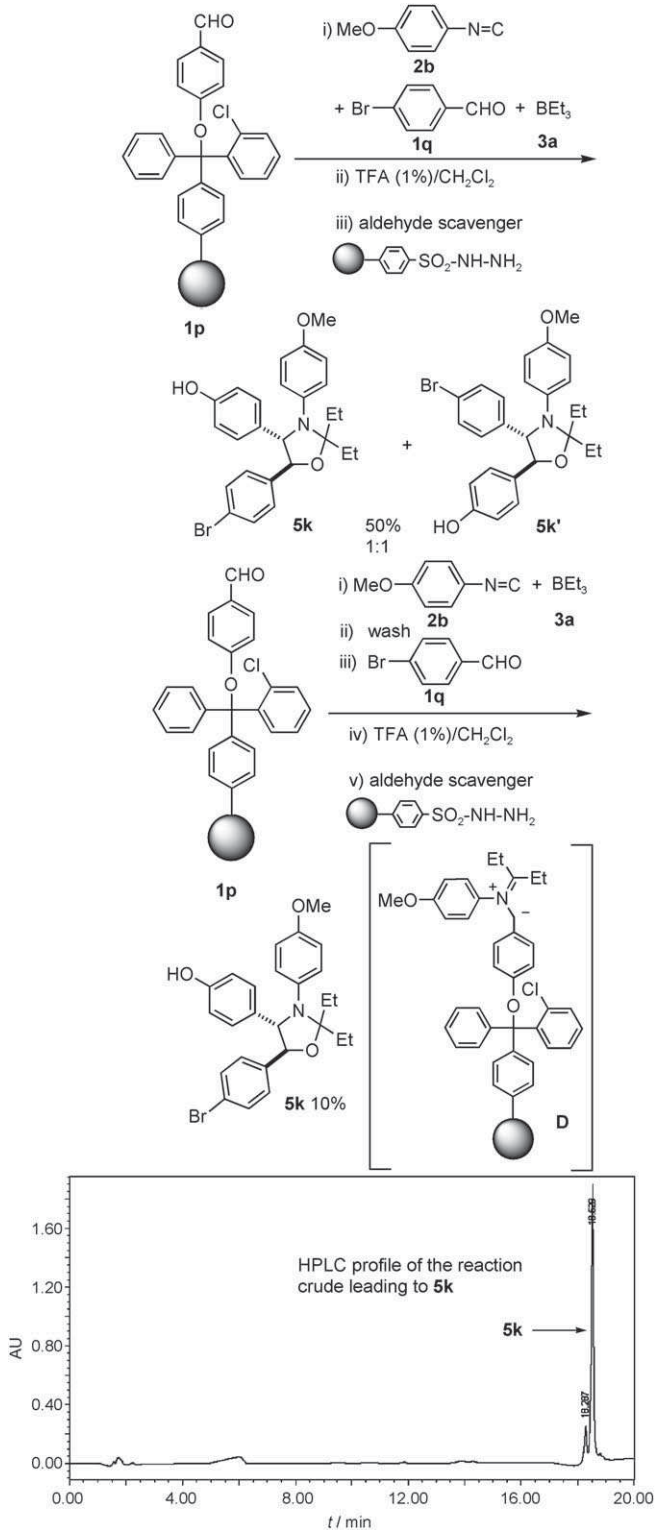
Scheme 6. Solid-supported versions of the MCRs.

standard washings and a mild sodium methoxide cleavage, the corresponding aziridine **7d** was obtained in 50% yield. Remarkably, this compound cannot be formed in solution, as the aldehyde efficiently traps the dipole once generated, which leads to the corresponding oxazolidine **5g**. In another experiment, we specifically promoted the latter reaction, which took place smoothly upon interaction with the aldehyde component **1b**. The resulting product was identical in all aspects to that previously obtained in the solution phase. The yields were calculated upon the loading of the aldehyde onto the resin. In spite of using excesses of the non-supported components, we could not accomplish quantitative transformations, which probably reflects some practical limitations in reaching sterically crowded regions in the solid support. However, the use of a solid-supported scavenger[33] efficiently removes the unreacted aldehyde, and affords the pure MCR adducts.

We then promoted the formation of "mixed oxazolidines" in a 4CR using two different aldehydes. A solution-phase approach would be unproductive, because at least four compounds would be generated (two from homo-combinations plus two from hetero-couplings). In an initial assay, we first linked 4-hydroxybenzaldehyde to a 2-chlorotrityl chloride resin, and then reacted it with borane **3a**, *p*-bromobenzaldehyde (**1q**) and isocyanide **2b**.

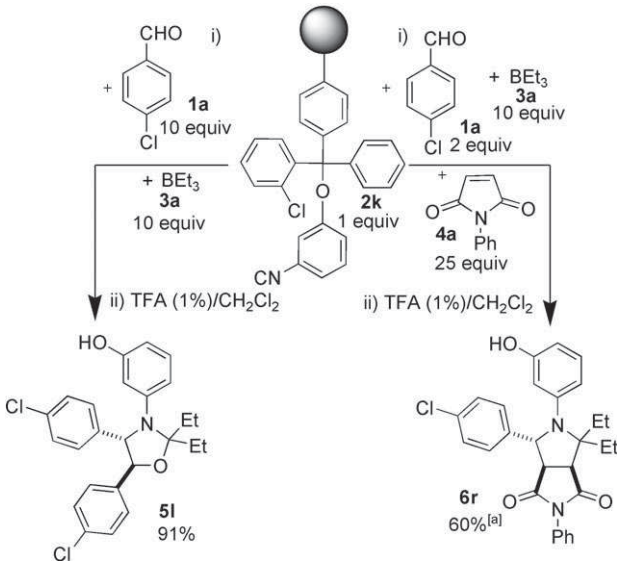
After the usual sequence of elutions, cleavage and a final treatment with a solid-supported aldehyde scavenger, we obtained a nearly equimolecular mixture of the two hetero-coupled oxazolidines **5k** and **5k′** which were not separated (Scheme 7). This suggested that two azomethine ylides had been generated: one from the aldehyde in solution, trapped by the linked aldehyde, and vice versa. To solve this problem, we performed the reaction in a sequential manner, and the protocol was modified to include washings after the generation of the linked dipole **D**, then we added the solution of aldehyde **1q**, and let the reaction proceed (Scheme 7). In this way, we managed to selectively prepare the mixed oxazolidine **5k** (10%, unoptimised). The low yield may be attributable to the manipulation of the azomethine ylide. Remarkably, this methodology allows the selective generation of solid-supported azomethine ylides and their interactions with dipolarophiles in a sequential manner. The high purity of the crude reaction mixture obtained in this experiment compared to that obtained with previous solution-phase processes is noteworthy (see the Supporting Information). Interestingly, this approach distinguishes between two pseudo-equivalent partners in chemo-differentiating ABB′-type processes, and consequently can significantly improve the synthetic applications of these useful procedures.[14,34]

A first attempt to perform a 4CR using the solid-supported aldehyde **1o** (Scheme 6), *p*-methoxyphenyl isocyanide (**2b**), *N*-phenylmaleimide (**4a**) and triethylborane (**3a**) afforded a complex mixture, probably due to the degradation of the desired adduct during the cleavage with sodium methoxide (based on mass spectrometry evidence). We then attempted the same reaction with the aldehyde-loaded resin **1p** (Scheme 7) and, although we did detect the expected 4CR adduct, the overall yield was very low. We then decided to use a solid-supported isocyanide[35] to avoid the dimerisation process of the intermediate **B** (see Scheme 2). The 2-chlorotrityl resin was loaded with *N*-(3-hydroxyphenyl)formamide and the resulting polymer was subjected to dehydration by using the Hulme protocol, to yield the solid-supported isocyanide **2k**.[35a] The loading of the solid-supported formamide was then evaluated with a TFA cleavage protocol. In a parallel experiment, the cleavage of the solid-supported isocyanide **2k** afforded the same starting formamide. Thus, we roughly estimated the loading of **2k** to be about 0.4 mmol g^{-1}, which suggests that the isocyanide or the formamide is partially cleaved during the dehydration process. A mixture of this isocyanide-functionalised resin and *p*-chlorobenzaldehyde (**1a**) was added to a solution of triethyl-



Scheme 7. Solid-phase approaches to mixed oxazolidines. TFA: trifluoroacetic acid.

borane in THF and stirred for 48 h (Scheme 8). After cleavage with 1% TFA–dichloromethane, the pure oxazolidine **5l** was obtained in 91% yield. In another experiment, the solid-supported isocyanide **2k** was reacted with triethylborane (**3a**), *p*-chlorobenzaldehyde (**1a**) and *N*-phenylmaleimide (**4a**) in a 4CR; standard TFA cleavage afforded the expected adduct **6r** (60%) in a stereoselective manner.[36] Thus, we have conducted all our new MCRs in the solid phase, thereby showing the feasibility of this strategy to facilitate access to pure compounds.



Scheme 8. MCRs using solid-supported isocyanide. [a] 4:1 isomeric ratio, whereby **6r** is the major isomer and the minor isomer is the *all-cis* compound.

Conclusion

Based on an initial report by Hesse and co-workers, we have designed and implemented a family of MCRs involving the interaction of isocyanides, aldehydes, boranes and dipolarophiles to yield pyrrolidine, aziridine and oxazolidine adducts in a single step, with high atom economy and bond-forming efficiency. These scaffolds have relevant presence in bioactive compounds. Moreover, oxazolidines are also found in pro-drugs as protected forms of 1,2-aminoalcohols.[37] Incidentally, this approach can also stereoselectively furnish these compounds after the customary hydrolysis of the oxazolidine precursors. Calculations performed for model compounds indicate that the stereochemical preferences in the reaction outcome are dictated by the TSs that are more favoured kinetically, which correspond to those leading to *trans* stereochemistries in the cycloaddition of the azomethine ylide **D**-*cis* with either the aldehyde or dipolarophile. However, these studies also show that the precise evolution of the MCRs may be subtly modulated by factors such as the nature of the substituents attached to both the isocyanide and the aldehyde units, or the chemical features of the dipolarophile. This has allowed a rationalisation of the manifold mechanistic pathways and established the practical limits for standard reactions. Furthermore, intramolecular and solid-supported versions of these processes have been developed

and, in the latter cases, the controlled environment achieved using linked substrates allows selective reactions, and facilitates purification. Our future work will follow along these lines, namely, to increase the reactivity range of some components (particularly the boranes)[38] and to expand the synthetic usefulness and scaffold variability for this complex family of MCRs.

Experimental and Computational Section

General procedure A: A solution of isocyanide (1 mmol, 1 equiv) and aldehyde (2 mmol, 1 equiv) in THF (2 mL) was added slowly to a solution of trialkylborane in THF (1 M, 1.2 mmol, 1.2 equiv) at 0 °C. After 3 min of stirring at this temperature, the ice bath was removed and the reaction mixture was stirred for 48 h at room temperature. An aqueous saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2×5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the oxazolidine **5**.

General procedure B: A solution of isocyanide (1 mmol, 1 equiv) and aldehyde (1 mmol, 1 equiv) in THF (2 mL) was added slowly to a solution of trialkylborane in THF (1 M, 1.2 mmol, 1.2 equiv) at −10 °C. Subsequently the dipolarophile was added to the mixture. After 3 min of stirring at this temperature, the cooling bath was removed and the reaction was stirred for 48 h at room temperature. An aqueous saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2×5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the adduct **6**.

General procedure C: For the synthesis of aziridines in the solution phase, the stoichiometry of general procedure A was modified (aldehyde, 1 mmol, 1 equiv). After chromatographic purification, the corresponding aziridine **7** was obtained.

General procedure D (solid-phase approach, supported aldehyde): A solution of isocyanide (1.39 mmol, 8 equiv) and aldehyde (8 equiv) in THF (3 mL) was added to the solid-supported aldehyde (200 mg, loading 0.82 mmol g^{-1}, 174 μmol). The resulting suspension was added to a borane solution in THF (1 M, 3.48 mmol, 20 equiv) in a falcon tube at 0 °C. The bath was removed and the reaction mixture was stirred for 48 h at room temperature. The mixture was then transferred to a solid-phase syringe, and washed with dichloromethane (3×5 mL). The cleavage was made depending on the nature of the resin. The unreacted aldehyde was scavenged with a suspension of *p*-toluenesulfonylhydrazide polymer-bound in dichloromethane. In this way, oxazolidines **5** and aziridines **7** (without adding the aldehyde in solution) were obtained.

General procedure E (solid-phase approach, supported isocyanide): A solution of aldehyde (1.39 mmol, 17 equiv) in THF (3 mL) was added to the solid-supported isocyanide (200 mg, 3-isocyanophenylether 2-chlorotrityl polymer-bound, loading 0.4 mmol g^{-1}, 80 μmol). The resulting suspension was added to a borane solution in THF (1 M, 3.48 mmol, 20 equiv) in a falcon tube at 0 °C. The bath was removed and the reaction mixture was stirred for 48 h at room temperature. The mixture was then transferred to a solid-phase syringe, and washed with dichloromethane (3×5 mL). The cleavage was made through cleavage procedure B (see below). In this way, oxazolidines **5** and the four-component adducts **6** (adding the corresponding dipolarophile, 25 equiv) were obtained.

Cleavage A: Hydroxymethyl polystyrene resin: The resin-bound product was suspended in THF (2 mL). A solution of NaOMe in MeOH (0.5 M, 1 mmol, 5.7 equiv) was then added and the reaction mixture was stirred for 24 h. Afterwards, the solid was removed by filtration washing with dichloromethane (2 mL). H_2O (2 mL) was added and the mixture was extracted with dichloromethane (2×5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure.

Cleavage B: 2-Chlorotrityl polystyrene resin: The resin-bound product was treated with TFA (1%) in dichloromethane (5×3 mL×1 min). The mixture was dropped directly onto an extraction funnel with an aqueous saturated $NaHCO_3$ solution (10 mL). After extraction with dichloromethane (3×10 mL), the combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure.

Computational studies: Full geometry optimisations were performed with the B3LYP[39] functional and the 6-31G(d)[40] basis set. The nature of the stationary points was verified by inspection of vibrational frequencies within the harmonic oscillator approximation. Intrinsic reaction coordinate calculations were carried out to check the connection between TSs and minimum-energy structures.[41] Single-point calculations were carried out at the MP2/6-311G(d,p)[42] level to determine the relative energies. Higher-order electron correlation effects were estimated from coupled-cluster singles and doubles (CCSD) calculations with the 6-31G(d) basis set. The final estimate of the electronic energies was determined by combining the MP2/aug-cc-pVDZ energy with the difference between the energies calculated at both CCSD and MP2 levels with the 6-31G(d) basis (denoted in the text as MP2/6-311G(d,p)+[(CCSD-MP2)/6-31G(d)]. Finally, zero-point, thermal and entropic corrections evaluated within the framework of harmonic oscillator rigid-rotor models at 1 atm and 298 K using the B3LYP/6-31G(d) vibrational frequencies (scaled by a factor of 0.96)[43] were added to estimate the free energy differences in the gas phase. Calculations were performed with Gaussian 03.[44]

Acknowledgements

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Supporting Information

Boron-Based Dipolar Multicomponent Reactions: Simple Generation of Substituted Aziridines, Oxazolidines and Pyrrolidines

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General. Hydroxymethylpolystyrene resin (100-200 mesh, 0.98 mmol/g, bach no. A27786) was purchased from Novabiochem. 2-Chlorotrityl chloride resin (100-200 mesh, 1.56 mmol/g Cl/g resin, lot no. 2812) was purchased from Iris Biotech GmbH. Unless stated otherwise, all solution phase reactions were carried out under argon in dried glassware. Commercially available reactants were used without further purification. Thin-layer chromatography was conducted with Merck silica gel 60 F254 sheets and visualized by UV and $KMnO_4$ solution. Silica gel (particle size 35– 70 μm) was used for flash column chromatography. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Varian Mercury 400 spectrometer (at 400, 100 and 376 MHz, respectively). NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^{1}H NMR spectra are reported as follows: chemical shift (d/ppm), multiplicity, coupling constant (Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to the solvent peak of $CDCl_3$ set at d = 77.0 ppm. ^{19}F NMR spectra are referenced to TFA as external reference (–78.5 ppm). IR spectra were recorded with a Thermo Nicolet Nexus spectrometer and are reported in frequency of absorption (cm^{-1}). HPLC analysis were performed on a Waters Alliance 2695 separations module (Empower software) connected to a Waters PDA2996 photodiode array detection (PDA) system (190-800 nm) and using a *Symmetry* column (C18, 5 μm, 4.6 × 150 mm).

General Procedure A: A solution of isocyanide (1 mmol, 1 eq.) and aldehyde (2 mmol, 1 eq.) in THF (2 mL) was added slowly into a solution 1M of trialkylborane in THF (1.2 mmol, 1.2 eq.) at 0 ºC. After 3 min stirring at this temperature, the ice bath was removed and the reaction mixture was stirred for 48 h at room temperature. A saturated solution of Na_2CO_3 (10 ml) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, Hexanes/Ethyl acetate) to yield the pure oxazolidine.

General Procedure B: A solution of isocyanide (1 mmol, 1 eq.) and aldehyde (1 mmol, 1 eq.) in THF (2 mL) was added slowly into a solution 1M of trialkylborane in THF (1.2 mmol, 1.2 eq.) at -10 ºC. Subsequently the dipolarophile was added to the mixture. After 3 min stirring at this temperature, the cooling mixture bath was removed and the reaction was stirred for 48h at room temperature. A saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, Hexanes/Ethyl acetate).

General Procedure C: For the synthesis of aziridines in solution phase, the stoichiometry of the general procedure A was modified (aldehyde, 1 mmol, 1 eq.).

General procedure D (solid-phase approach, supported aldehyde): A solution of isocyanide (1.39 mmol, 8 eq.) and aldehyde (8 eq.) in 3 mL of THF was added to the solid-supported aldehyde (200 mg, loading 0.82 mmol/g, 174 μmol). The resulting suspension was added over a 1M borane solution in THF (3.48 mmol, 20eq) in a falcon tube at 0ºC. The bath was removed and the reaction was stirred for 48 h at room temperature. The mixture was then transferred to a solid-phase syringe, and washed with DCM (3 × 5 mL). The cleavage was made depending on the nature of the resin. The unreacted aldehyde was scavenged using *p*-toluenesulfonylhyrazide polymer-bound in DCM solution. In this way, oxazolidines **5** and aziridines **7** (without adding the aldehyde in solution) were obtained.

General procedure E (solid-phase approach, supported isocyanide): A solution of aldehyde (1.39 mmol, 17 eq.) in 3 mL of THF was added to the solid-supported isocyanide (200 mg, of 3-isocyano)phenylether 2-chlorotrityl polymer bound, loading 0.4 mmol/g, 80 μmol). The resulting suspension was added over a 1M borane solution in THF (3.48 mmol, 20eq) in a falcon tube at 0ºC. The bath was removed and the reaction was stirred for 48 h at room temperature. The mixture was then transferred to a solid-phase syringe, and washed with DCM (3 × 5 mL). The

cleavage was made using procedure B. In this way, oxazolidines **5** and the 4-component adducts **6** (adding the corresponding dipolarophile, 25 eq.) were obtained.

Cleavage A: Hydroxymethyl polystyrene resin: the resin-bound product was suspended in THF (2 mL). A solution 0.5M of NaOMe in MeOH (1 mmol, 5.7 eq.) was then added and the reaction was stirred for 24 h. Afterwards, the solid was removed by filtration washing with DCM (2 mL), H_2O (2 mL) was added and the mixture was extracted with DCM (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure.

Cleavage B: 2-Chlorotrityl polystyrene resin: the resin-bound product was treated with TFA (1%) in DCM (5 × 3mL × 1min). The mixture is dropped directly onto an extraction funnel with sat. aq. $NaHCO_3$ (10 mL). After extraction with DCM (3 × 10mL) the combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure.

2-(4-formylphenoxy)ethyl polystyrene resin: Hydroxymethylpolystyrene resin (2.07 g, max loading 0.98 mmol/g) was washed with DMF (3 × 20 mL) , DCM (3 × 20 mL), and swelled in DCM (20 mL) for 1h. 4-formylbenzoic acid (1.21 g, 4 eq., 8.08 mmol), dicyclohexylcarbodiimide (1.67 g, 4 eq., 8.08 mmol) and DMAP (107 mg, 0.4 eq., 0.88 mmol) were added. After 16 h the resin was washed with DCM (3 × 20 mL), MeOH (3 × 20 mL), Et_2O (3 × 20 mL), and dried under vacuum. The final loading (0.82 mmol/g) was evaluated carrying out cleavage A procedure on 200 mg scale of resin.

(4-formyl)phenylether 2-Chlorotrityl polymer bound: 2-Chlorotrityl chloride resin (1,4 g, max loading 1.566 mmol/g) was washed with DMF (3 × 15 mL), DCM (3 × 15 mL) and swelled in DCM (15 mL) for 1h. DIEA (1.1 mL, 8 eq., 6.48 mmol) and 4-hydroxybenzaldehyde (100 mg, 1 eq., 0.81 mmol) were added and the reaction was left stirring for 3h. The final loading (0.59 mmol/g) was evaluated carrying out cleavage B procedure on 200 mg scale of resin.

(3-isocyano)phenylether 2-chlorotrityl polymer bound: 2-Chlorotrityl chloride resin (1,0 g, max loading 1.566 mmol/g) was washed with DMF (3 × 15 mL), DCM (3 × 15 mL) and swelled

in DCM (15 mL) for 1h. DIEA (1.4 mL, 8 eq., 8.24 mmol) and *N*-(3-hydroxyphenyl)formamide (137 mg, 1 eq., 1.03 mmol) were added. The reaction was left stirring overnight. Then the resin was washed with dry DCM (10 mL), and Et_3N (715 μL, 5 eq., 5.15 mmol), CCl_4 (496 μL, 5 eq., 5.15 mmol) and PPh_3 (1.35 g, 5 eq., 5.15 mmol) were added in this order to the resin. The reaction mixture was left stirring overnight, then washed with dry DCM (3 × 15 mL) and Et_2O (3 × 15 mL), dried under vacuum for 15 min. The solid supported isocyanide was conserved at 4 ºC under inert atmosphere.

Computational studies. Full geometry optimizations were performed with the B3LYP[1] functional and the 6-31G(d)[2] basis set, and the nature of the stationary points was verified by inspection of vibrational frequencies within the harmonic oscillator approximation. Intrinsic reaction coordinate calculations (IRC) were carried out to check the connection between the transition states and the minimum energy structures.[3] Single point calculations were carried out at MP2 level with the 6-311G(d,p)[4] basis set to determine the relative energies. Higher-order electron correlation effects were estimated from additional CCSD calculations with the 6-31G(d) basis set. The final estimate of the electronic energies was determined by combining the MP2/aug-cc-pVDZ energy with the difference between the energies calculated at both CCSD and MP2 levels with the 6-31G(d) basis (denoted in the text as MP2/6-311G(d,p)+[(CCSD-MP2)/6-31G(d)]. Finally, zero point, thermal, and entropic corrections evaluated within the framework of harmonic oscillator-rigid rotor models at 1 atm and 298 K using the vibrational frequencies at the B3LYP/6-31G(d) level scaled by a factor of 0.96[5] to estimate the free energy differences in the gas phase. Calculations were performed using Gaussian-03.[6]

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(4*RS*,5*RS*)-3,4,5-tris(4-chlorophenyl)-2,2-diethyloxazolidine (5a): General Experimental Procedure A. Isolated yield (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.79 (d, *J* = 8.8 Hz, 1H), 4.46 (d, *J* = 8.8 Hz, 1H), 2.35-2.14 (m, 2H), 2.08-1.96 (m, 1H), 1.95-1.82 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$,) δ = 142.3, 135.8, 134.3, 133.5, 128.9, 128.62, 128.60, 128.5, 128.3, 124.9, 119.4, 110.7, 100.6, 84.9, 70.9, 34.2, 28.6, 9.1, 7.5 ppm. IR (NaCl) *?* = 2974, 2937, 2879, 1595, 1493, 1462, 1408, 1331, 1193, 1090, 1013, 974, 955, 832, 817 cm^{-1}; MS (EI) *m/z* (%) = 461 (6), 460 (M^+, 7), 374 (86), 319 (12), 250 (17), 235 (24), 165 (20), 138 (100), 111 (30), 57 (20). HRMS: calcd for $C_{25}H_{25}Cl_3NO^+$ 460.0996, found 460.0993.

(4*RS*,5*RS*)-4,5-bis(4-chlorophenyl)-2,2-diethyl-3-(4-methoxyphenyl)oxazolidine (5b): General Experimental Procedure A. Isolated yield (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 9.2 Hz, 2H), 4.79 (d, *J* = 8.4 Hz, 1H), 4.47 (d, *J* = 8.8 Hz, 1H), 3.69 (s, 3H), 2.30-2.15 (m, 1H), 2.10-2.00 (m, 1H), 1.95-1.80 (m, 1H), 1.74-1.61 (m, 1H), 1.29 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.3, 137.0, 136.6, 136.2, 134.0, 133.3, 128.9, 128.7, 128.5, 128.2, 121.6, 114.0, 100.1, 85.5, 70.7, 55.3, 33.3, 29.8, 8.7, 7.9 ppm. IR (NaCl) *?* = 2971, 2935, 2878, 2832, 2510, 1490, 1463, 1244, 1089, 1072, 1013, 826 cm^{-1}. MS (EI) *m/z* (%) = 455 (M^+, 11), 426 (69), 370 (53), 246 (12), 231 (26), 134 (100). HRMS: calcd for $C_{26}H_{28}Cl_2NO_2^+$ 456.1492, found 456.1495.

(4*RS*,5*RS*)-4,5-bis(4-chlorophenyl)-2,2-diethyl-3-*p*-tolyloxazolidine (5c): General Experimental Procedure A. Isolated yield (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.80 (d, *J* = 8.8 Hz, 1H), 4.50 (d, *J* = 8.8 Hz, 1H), 2.30-2.22 (m, 1H), 2.20-2.10 (m, 1H), 2.19 (s, 3H), 2.03-2.10 (m, 1H), 1.85-1.72 (m, 1H), 1.27 (t, *J* = 7.6 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.2, 136.4, 136.3,

134.1, 133.2, 129.6, 129.2, 128.7, 128.6, 128.5, 128.3, 119.2, 100.4, 85.3, 70.7, 34.0, 29.3, 20.5, 8.9, 7.7 ppm. IR (NaCl) *?* = 2973, 2937, 2878, 1615, 1513, 1490, 1462, 1314, 1285, 1090, 1013, 975, 833, 817 cm^{-1}. MS (EI) *m/z* (%) = 439 (M^+, 8), 414 (67), 410 (100), 354 (93), 299 (10), 230 (11), 215 (18), 178 (15), 146 (7), 118 (67), 91 (31), 57 (9). HRMS: calcd for $C_{26}H_{28}Cl_2NO^+$ 440.1542, found 440.1543.

(4*RS*,5*RS*)-2,2-dibutyl-4,5-bis(4-chlorophenyl)-3-phenyloxazolidine (5d): General Experimental Procedure A. Isolated yield (22%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.10 (m, *J* = 7.2, 7.6 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 4.79 (d, *J* = 8.8 Hz, 1H), 4.49 (d, *J* = 8.8 Hz, 1H), 2.32-2.10 (m, 2H), 2.05-1.93 (m, 1H), 1.91-1.75 (m, 2H), 1.71-1.57 (m, 1H), 1.53-1.41 (m, 3H), 1.25-1.07 (m, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.6, 136.3, 136.1, 134.2, 133.2, 128.8, 128.6, 128.54, 128.52, 128.40, 119.9, 118.6, 100.2, 85.0, 70.7, 41.8, 36.1, 26.8, 25.0, 23.2, 22.7, 14.2, 13.9 ppm. IR (NaCl) *?* = 2954, 2869, 1598, 1490, 1331, 1088, 1013, 998, 831, 693 cm^{-1}. MS (EI) *m/z* (%) = 481 (M^+, 2), 424 (100), 340 (63), 305 (4), 248 (4), 214 (13), 178 (14), 125 (12), 104 (79), 77 (27), 57 (22). HRMS: calcd for $C_{29}H_{34}Cl_2NO^+$ 482.2012, found 482.2014.

(4*RS*,5*RS*)-4,5-bis(4-chlorophenyl)-2,2-diethyl-3-(4-fluorophenyl)oxazolidine (5e): General Experimental Procedure A. Isolated yield (36%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.85-6.78 (m, 2H), 6.75-6.68 (m, 2H), 4.80 (d, *J* = 8.7 Hz, 1H), 4.47 (d, *J* = 8.7 Hz, 1H), 2.31-2.20 (m, 1H), 2.19-2.06 (m, 1H), 1.98-1.86 (m, 1H), 1.82-1.71 (m, 1H), 1.27 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.4 (d, *J* = 240.0 Hz, 1C), 139.8 (d, *J* = 2.4 Hz, 1C), 136.1, 135.9, 134.2, 133.5, 128.8, 128.7, 128.6, 128.2, 120.5 (d, *J* = 7.6 Hz, 1C), 115.3 (d, *J* = 22.1 Hz, 1C), 100.3, 85.2, 70.9, 33.8, 29.3, 8.8, 7.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -123.8 ppm. IR (NaCl) *?* = 2974, 2938, 2879, 1508, 1490, 1462, 1328, 1228, 1090, 1014, 975, 831, 739 cm^{-1}. MS (EI) *m/z* (%) = 443 (M^+, 6), 414 (95), 358 (100), 323 (6), 303 (13),

232 (17), 219 (16), 178 (16), 122 (89), 95 (24), 57 (15). HRMS: calcd for $C_{25}H_{25}Cl_2FNO^+$ 444.1292, found 444.1292.

Dimethyl 4,4'-((4*RS*,5*RS*)-2,2-diethyl-3-(4-methoxyphenyl)oxazolidine-4,5-diyl)dibenzoate (5g): General Experimental Procedure A. Isolated yield (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 9.2 Hz, 2H), 6.66 (d, *J* = 9.2 Hz, 2H), 4.91 (d, *J* = 8.8 Hz, 1H), 4.59 (d, *J* = 8.8 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.68 (s, 3H), 2.30-2.17 (m, 1H), 2.14-2.02 (m, 1H), 1.95-1.82 (m, 1H), 1.75-1.63 (m, 1H), 1.32 (t, *J* = 7.6 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 166.8, 166.8, 154.3, 143.1, 143.0, 136.9, 130.1, 129.8, 129.7, 129.6, 127.7, 126.8, 121.6, 114.0, 100.4, 85.6, 71.1, 55.3, 52.1, 52.0, 33.2, 29.8, 8.7, 7.9 ppm. IR (NaCl) *?* = 2949, 1722, 1611, 1510, 1611, 1510, 1457, 1435, 1308, 1245, 1190, 1111, 1018, 770 cm^{-1}. MS (EI) *m/z* (%) = 503 (M^+, 12), 474 (100), 418 (46), 358 (4), 284 (22), 268 (14), 255 (13), 165 (7), 134 (28). HRMS: calcd for $C_{30}H_{34}NO_6^+$ 504.2381, found 504.2385.

(4*RS*,5*RS*)-3-(4-chlorophenyl)-2,2-diethyl-4,5-di(pyridin-3-yl)oxazolidine (5h): General Experimental Procedure A. Isolated yield (15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.48 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.45 (d, *J* = 2.0 Hz, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 7.57 (dt, *J* = 7.6, 2.0 Hz, 1H), 7.47 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.29 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.18 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 4.91 (d, *J* = 8.8 Hz, 1H), 4.60 (d, *J* = 8.8 Hz, 1H), 2.35-2.13 (m, 2H), 2.02-1.96 (m, 1H), 1.91-1.80 (m, 1H), 1.26 (t, *J* = 7.6 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.2, 149.7, 149.2, 148.7, 141.8, 134.7, 134.5, 132.6, 132.5, 128.8, 125.7, 123.8, 123.5, 120.0, 101.0, 83.7, 69.2, 34.1, 28.8, 9.0, 7.5 ppm. IR (NaCl) *?* = 2973, 2936, 2879, 1715, 1668, 1594, 1577, 1494, 1426, 1302, 1190, 1135, 1073, 1023, 973, 815, 713 cm^{-1}. MS (EI) *m/z* (%) = 393 (M^+, 7), 364 (100), 308 (53), 215 (13), 170 (45), 138 (11), 111 (14). HRMS: calcd for $C_{23}H_{25}ClN_3O^+$ 394.1681, found 394.1677.

(4*RS*,5*RS*)-diethyl 2,2-diethyl-3-(4-methoxyphenyl)oxazolidine-4,5-dicarboxylate (5i): General Experimental Procedure A. Overall yield (7%, isomer ratio 6:4); **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.89-6.85 (m, 2H), 6.81-6.78 (m, 2H), 4.79 (d, *J* = 7.9 Hz, 1H), 4.59 (d, *J* = 7.9 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.21-4.12 (m, 2H), 3.76 (s, 3H), 2.07-1.98 (m, 1H), 1.92-1.83 (m, 1H), 1.77-1.68 (m, 1H), 1.64-1.55 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.3 Hz, 3H), 0.75 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 170.0, 154.6, 137.0, 120.5, 114.5, 103.3, 77.4, 65.7, 61.8, 61.6, 55.6, 32.9, 29.6, 14.3, 14.3, 8.2, 7.7 ppm. IR (NaCl) *?* = 2962, 2929, 2873, 1734, 1653, 1514, 1465, 1369, 1242, 1147, 1097, 1024, 824 cm^{-1}. MS (EI) *m/z* (%) = 379 (M^+, 4), 350 (59), 311 (12), 238 (12), 208 (75), 162 (13), 134 (100). HRMS: calcd for $C_{24}H_{30}NO_4^+$ 396.2169, found 396.2154.

(4*RS*,5*RS*)-2,2-dibutyl-3,4,5-tris(4-chlorophenyl)oxazolidine (5j): General Experimental Procedure A. Isolated yield (40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 4.78 (d, *J* = 8.4 Hz, 1H), 4.43 (d, *J* = 8.4 Hz, 1H), 2.30-2.07 (m, 2H), 2.02-1.90 (m, 1H), 1.89-1.72 (m, 2H), 1.70-1.55 (m, 1H), 1.54-1.40 (m, 3H), 1.28-1.05 (m, 3H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.79 (t, 0.79 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.5, 136.1, 136.0, 134.5, 133.8, 129.2, 128.9, 128.8, 128.7, 128.6, 125.1, 119.7, 100.4, 85.1, 71.0, 41.9, 36.1, 27.0, 25.2, 23.4, 22.9, 14.4, 14.2; IR (NaCl) *?* = 2955, 2869, 1595, 1493, 1465, 1332, 1287, 1139, 1091, 1013, 831, 817 cm^{-1}. MS (EI) *m/z* (%) = 515 (M^+, 20), 454 (28), 413 (19), 491 (42), 190 (31), 167 (89), 149 (100), 114 (83), 83 (50), 80 (56), 60 (97). HRMS: calcd for $C_{29}H_{33}Cl_3NO^+$ 516.1622, found 516.1620.

4-((4*RS*,5*RS*)-5-(4-bromophenyl)-2,2-diethyl-3-(4-methoxyphenyl)oxazolidin-4-yl)phenol (5k): Prepared using a modified General Experimental Procedure D by adding first the isocyanide and the borane, and after 4 hours reaction time, the resin was washed with anhydrous THF (2 × 5 mL). p-Bormobenzaldehyde was added and the mixture was stirred overnight and washed with anhydrous THF (2 × 5 mL). Cleavage B. Isolated yield (10%). ^{1}H NMR (400 MHz,

$CDCl_3$) δ = 7.42 (d, *J* = 7.4 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 9.2 Hz, 2H), 6.70-6.64 (m, 4H), 4.79 (d, *J* = 8.7 Hz, 1H), 4.41 (d, *J* = 8.7 Hz, 1H), 3.69 (s, 3H), 2.26-2.15 (m, 1H), 2.10-1.97 (m, 1H), 1.92-1.77 (m, 1H), 1.71-1.57 (m, 1H), 1.29 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H) ppm. (One proton interchanging) ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.9, 154.0, 137.6, 137.3, 131.3, 129.7, 128.9, 128.5, 121.9, 121.6, 115.4, 113.8, 99.9, 85.7, 70.7, 55.3, 33.3, 29.8, 8.7, 7.9 ppm. IR (NaCl) *?* = 2930, 1597, 1510, 1487, 1462, 1244, 1164, 1070, 1036, 1009, 831 cm^{-1}. MS (EI) *m/z* (%) = 483 (6), 481 (M^+, 6), 452 (29), 454 (28), 396 (27), 398 (26), 297 (9), 261 (5), 226 (10), 162 (11), 134 (100), 107 (16), 77 (14), 57 (9). HRMS: calcd for $C_{26}H_{29}BrNO_3^+$ 482.1325, found 483.1294.

3-((4*RS*,5*RS*)-4,5-bis(4-chlorophenyl)-2,2-diethyloxazolidin-3-yl)phenol (5l): General Experimental Procedure E. Cleavage B. Isolated yield (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.93 (t, *J* = 6.9 Hz, 1H), 6.28 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.24 (dd, *J* = 7.9, 1.2 Hz, 1H) 6.21 (m, *J* = 1.9 Hz, 1H), 4.77 (d, *J* = 8.7 Hz, 1H), 4.47 (d, *J* = 8.7 Hz, 1H), 2.15-2.35 (m, 2H), 2.02-2.14 (m, 1H), 1.82-1.95 (m, 1H), 1.22 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H) ppm; (one proton interchanging). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.8, 145.3, 136.4, 136.0, 134.3, 133.3, 129.4, 128.9, 128.6, 128.4, 111.1, 106.8, 105.5, 100.7, 18.0, 70.9, 34.2, 28.7, 9.1, 7.5 ppm, (one carbon overlapped). IR (NaCl) *?* = 2968, 2939, 1711, 1676, 1596, 1491, 1456, 1381, 1180, 739, 691 cm^{-1}. MS (EI) *m/z* (%) = 441 (M^+, 23), 427 (20), 413 (15), 279 (9), 149 (26), 119 (29), 80 (100), 71 (30). HRMS: calcd for $C_{25}H_{26}Cl_2NO_2^+$ 442.1341, found 442.1345.

(3a*RS*,6*SR*,6a*SR*)-5,6-bis(4-chlorophenyl)-4,4-diethyl-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6a): General Experimental Procedure B. Overall yield (55%, isomer ratio 8:2). **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52-7.45 (m, 2H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 5.21 (d, *J* = 6.5 Hz, 1H), 3.61 (d, *J* = 10.5 Hz, 1H), 3.37 (dd, *J* = 10.5, 6.4 Hz, 1H), 2.26-2.12 (m, 1H), 2.10-1.95 (m, 2H), 1.92-1.79 (m, 1H), 1.32 (t, *J* =

7.2 Hz, 3H), 0.62 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.2, 175.1, 143.0, 140.5, 133.1, 131.6, 129.2, 129.0, 128.7, 128.6, 128.0, 126.9, 126.1, 123.0, 72.6, 65.4, 51.9, 35.1, 26.0, 9.3, 8.8 ppm, (one carbon overlapped). IR (NaCl) *?* = 2969, 2881, 1777, 1714, 1595, 1493, 1377, 1179, 1089, 745 cm^{-1}. MS (EI) *m/z* (%) = 492 (M^+, 1), 463 (5), 430 (3), 319 (9), 250 (19), 235 (29), 166 (20), 139 (100), 125 (94), 111 (74), 75 (36), 50 (17). HRMS: calcd for $C_{28}H_{27}Cl_2N_2O_2^+$ 493.1444, found 493.1435.

(3a*RS*,6*SR*,6a*SR*)-6-(4-chlorophenyl)-4,4-diethyl-5-(4-methoxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6b): General Experimental Procedure B. Overall yield (68%, isomer ratio 7:3). **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54-7.45 (m, *J* = 8.0 Hz, 2H), 7.44-7.35 (m, *J* = 7.2, 8.0 Hz, 3H), 7.34-7.28 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 6.69 (d, *J* = 9.2 Hz, 2H), 5.19 (d, *J* = 6.8 Hz, 1H), 3.70 (s, 3H), 3.62 (d, *J* = 10.4 Hz, 1H), 3.32 (dd, *J* = 10.4, 6.8 Hz, 1H), 2.15-2.03 (m, 1H), 2.00-1.85 (m, 2H), 1.80-1.65 (m, 1H), 1.32 (t, *J* = 7.6 Hz, 3H), 0.63 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.6, 175.5, 155.5, 140.8, 137.0, 134.2, 132.9, 131.8, 129.2, 128.8, 128.5, 126.2, 125.4, 113.8, 71.6, 65.1, 55.2, 52.1, 51.9, 33.3, 25.1, 9.3, 8.8 ppm. IR (NaCl) *?* = 3047, 2967, 2939, 2835, 1776, 1715, 1598, 1510, 1377, 1245, 1180, 1088, 829, 744 cm^{-1}. MS (EI) *m/z* (%) = 489 (M^+, 3), 462 (10), 461 (37), 460 (31), 459 (100), 312 (5), 268 (2), 162 (4). HRMS: calcd for $C_{29}H_{30}ClN_2O_3^+$ 489.1939, found 489.1934.

Methyl 4-((1*RS*,3a*SR*,6a*RS*)-3,3-diethyl-2-(4-methoxyphenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrol-1-yl)benzoate (6d): General Experimental Procedure B. Overall yield (24%, isomer ratio 8:2). **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.52-7.45 (m, 2H), 7.44-7.37 (m, 1H), 7.35-7.30 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 5.28 (d, *J* = 6.1 Hz, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.65 (d, *J* = 10.4 Hz, 1H), 3.36 (dd, *J* = 10.3, 6.65 Hz, 1H), 2.16-2.05 (m, 1H), 2.00-1.89 (m, 2H), 1.80-1.68 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.64 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.5, 175.4, 166.8, 155.5, 147.6, 137.0, 131.7, 129.9, 129.2, 129.1, 128.6,

127.1, 126.2, 125.2, 113.8, 71.6, 65.4, 55.1, 52.0, 51.9, 51.8, 33.2, 25.1, 9.3, 8.8 ppm. IR (NaCl) *?* = 2950, 1714, 1610, 1510, 1436, 1377, 1279, 1245, 1179, 1113, 1035, 775, 691 cm^{-1}. MS (EI) *m/z* (%) = 513 (M^+, 100), 459 (10), 414 (7), 324 (5), 270 (21), 243 (25). HRMS: calcd for $C_{31}H_{33}N_2O_5^+$ 513.23840, found 513.23811.

4,4-Diethyl-5-(4-methoxyphenyl)-2,6-diphenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6e): General Experimental Procedure B. Overall yield (55%, isomer ratio 8:2). **Major isomer (3a*RS*,6*SR*,6a*SR*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50-7.44 (m, 4H), 7.42-7.38 (m, 1H), 7.33-7.31 (m, 2H), 7.25-7.22 (m, 2H), 7.16-7.13 (m, 1H), 6.98-6.94 (m, 2H), 6.69-6.65 (m, 2H), 5.23 (d, *J* = 6.5 Hz, 1H), 3.68 (s, 3H), 3.63 (d, *J* = 10.3 Hz, 1H), 3.38 (dd, *J* = 10.3, 6.5 Hz, 1H), 2.15-2.06 (m, 1H), 1.99-1.89 (m, 2H), 1.79-1.69 (m, 1H), 1.34 (t, *J* = 7.3 Hz, 3H), 0.63 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0, 175.9, 155.4, 142.6, 137.7, 132.0, 129.4, 128.8, 128.8, 127.5, 127.3, 126.4, 125.3, 113.9, 71.7, 65.9, 55.4, 52.5, 52.2, 33.6, 25.5, 9.6, 9.0 ppm. IR (NaCl) *?* = 2967, 2930, 2840, 1713, 1510, 1453, 1377, 1244, 1179, 1034, 744, 692 cm^{-1}. *m/z* (%) = 454 (M^+, 7), 425 (100), 278 (6); HRMS: calcd for $C_{29}H_{30}N_2NaO_3^+$ 477.2149, found 477.2149. **Minor isomer (3a*RS*,6*RS*,6a*SR*)**: ^{1}H NMR ($CDCl_3$) δ 7.39-7.35 (m, 2H), 7.32-7.29 (m, 3H), 7.31-7.17 (m, 2H), 7.12-7.09 (m, 3H), 7.05-7.01 (m, 2H), 6.67-6.64 (m, 2H), 5.4 (d, 1H, *J* = 9.7), 3.72 (dd, 1H, *J* = 9.7, 1.6), 3.68 (s, 3H), 3.33 (d, 1H, *J* = 8.0), 2.29-2.20 (m, 1H), 2.04-1.95 (m, 1H), 1.90-1.81 (m, 1H), 1.76-1.65 (m, 1H), 1.04 (t, 3H, *J* = 7.4), 0.85 (t, 3H, *J* = 7.5); ^{13}C NMR ($CDCl_3$) δ 175.8, 174.8, 156.5, 137.8, 137.0, 132.1, 129.1, 128.5, 128.4, 128.3, 128.1, 128.0, 126.3, 113.6, 71.1, 65.6, 55.3, 52.2, 48.3, 28.3, 26.0, 10.0, 9.4; IR (NaCl) *?* = 2962, 2923, 2872, 1715, 1653, 1558, 1507, 1457, 1386, 1245, 1175, 1028, 767, 683 cm^{-1}. MS (EI) *m/z* (%) = 454 (M^+, 2), 425 (100), 278 (6). HRMS: calcd for $C_{29}H_{30}N_2NaO_3^+$ 477.2149, found 477.2145.

5-(4-Chlorophenyl)-4,4-diethyl-6-(4-methoxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6f): General Experimental Procedure B. Overall yield (25%, isomer ratio 8:2). **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52-7.45 (m, 2H), 7.44-7.37

(m, 1H), 7.36-7.30 (m, 4H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 5.20 (d, *J* = 6.4 Hz, 1H), 3.74 (s, 3H), 3.61 (d, *J* = 10.4 Hz, 1H), 3.40 (dd, *J* = 10.4, 6.4 Hz, 1H), 2.26-2.15 (m, 1H), 2.10-1.97 (m, 2H), 1.95-1.82 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 0.63 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.4, 175.4, 158.8, 143.4, 133.9, 131.7, 129.1, 128.6, 128.5, 127.7, 126.4, 126.1, 122.8, 114.2, 72.4, 65.6, 55.1, 52.2, 52.0, 35.3, 26.1, 9.3, 8.8 ppm. IR (NaCl) *?* = 2967, 2836, 1777, 1714, 1598, 1511, 1495, 1377, 1303, 1248, 1171, 1100, 1032, 832 cm^{-1}. MS (EI) *m/z* (%) = 488 (M^+, 7), 461 (69), 460 (56), 459 (100), 312 (17), 283 (8), 268 (8), 244 (4), 166 (10), 111 (6). HRMS: calcd for $C_{29}H_{30}ClN_2O_3^+$ 489.1939, found 489.1939.

(3a*RS*,6*SR*,6a*SR*)-5-(4-chlorophenyl)-4,4-diethyl-6-(furan-2-yl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6g): General Experimental Procedure B. Overall yield (25%, isomer ratio 6:4). **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55-7.45 (m, 2H), 7.44-7.37 (m, 1H), 7.35-7.30 (m, 3H), 7.13 (d, *J* = 9.2 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.25-6.22 (m, 1H), 6.16 (d, *J* = 3.2 Hz, 1H), 5.47 (d, *J* = 4.4 Hz, 1H), 3.73 (m, *J* = 10.2, 4.6 Hz, 1H), 3.63 (d, *J* = 10.0 Hz, 1H), 2.25-2.13 (m, 1H), 2.12-2.01 (m, 1H), 1.98-1.85 (m, 2H), 1.22 (t, *J* = 7.4 Hz, 3H), 0.61 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.1, 175.3, 153.2, 143.2, 142.0, 131.7, 129.2, 128.7, 128.6, 126.0, 121.5, 110.3, 108.1, 72.5, 59.9, 52.5, 49.3, 34.4, 25.6, 9.0, 8.7 ppm, (one quaternary carbon not detected). IR (NaCl) *?* = 2971, 2881, 1777, 1715, 1595, 1496, 1379, 1379, 1181, 1153, 1010, 735 cm^{-1}. MS (EI) *m/z* (%) = 448 (M^+, 6), 421 (69), 420 (51), 419 (100), 272 (18), 243 (12), 166 (11), 111 (8). HRMS: calcd for $C_{26}H_{26}ClN_2O_3^+$ 449.1626, found 449.1628.

4,4-Diethyl-5-(4-methoxyphenyl)-2-phenyl-6-vinyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6h): General Experimental Procedure B. Overall yield (40%, isomer ratio 8:2). **Major isomer (3a*RS*,6*RS*,6a*SR*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50-7.46 (m, 2H), 7.41-7.38 (m, 1H), 7.32-7.30 (m, 2H), 6.99-6.97 (m, 2H), 6.80-6.78 (m, 2H), 5.76-5.67 (m, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 4.67-4.64 (m, 1H), 3.77 (s, 3H), 3.50 (d, *J* =

10.2 Hz, 1H), 3.30 (dd, *J* = 10.2, 6.8 Hz, 1H), 2.04-1.96 (m, 1H), 1.92-1.85 (m, 1H), 1.81-1.63 (m 2H), 1.19 (t, *J* = 7.3 Hz, 3H), 0.59 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.7, 176.0, 155.7, 139.4, 137.6, 132.0, 129.3, 128.8, 126.5, 126.0, 118.3, 113.8, 71.6, 65.1, 55.5, 52.5, 49.8, 33.5, 24.8, 9.5, 8.9 ppm. IR (NaCl) *?* = 2967, 2924, 2873, 1715, 1509, 1457, 1376, 1245, 1180, 1036, 745, 688 cm^{-1}. MS (EI) *m/z* (%) = 404 (M^+, 11), 375 (100), 228 (8). HRMS: calcd for $C_{25}H_{29}N_2O_3^+$ 405.2173, found 405.2171. **Minor isomer (3a*RS*,6*SR*,6a*SR*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49-7.45 (m, 2H), 7.40-7.36 (m, 1H), 7.31-7.29 (m, 2H), 7.02-7.00 (m, 2H), 6.81-6.76 (m, 2H), 5.64-5.56 (m, 1H), 5.23 (dd, *J* = 17.8, 1.0 Hz, 1H), 5.13 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.62-4.58 (m, 1H), 3.77 (s, 3H), 3.53-3.49 (m, 1H), 3.26 (d, *J* = 8.2 Hz, 1H), 1.97-1.83 (m, 2H), 1.67-1.60 (m, 2H), 0.90-0.85 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.1, 175.4, 156.9, 136.9, 136.2, 132.2, 129.2, 129.0, 128.6, 126.7, 119.2, 113.5, 71.1, 64.2, 55.4, 51.2, 47.8, 27.9, 26.1, 9.41, 9.4 ppm. IR (NaCl) *?* = 2956, 2911, 1716, 1653, 1559, 1502, 1374, 1239, 1175, 1027, 720 cm^{-1}. MS (EI) *m/z* (%) = 404 (M^+, 6), 375 (100), 228 (5). HRMS: calcd for $C_{25}H_{29}N_2O_3^+$ 405.2173, found 405.2171.

5-(4-chlorophenyl)-4,4-diethyl-2-phenyl-6-styryltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6i): General Experimental Procedure B. Overall yield (71%, isomer ratio 7:3). **Major isomer (3a*RS*,6*RS*,6a*SR*)**: Data from a mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (m, 2H), 7.41 (m, 1H), 7.35-7.23 (m, 6H), 7.21 (m, *J* = 6.9 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.72 (d, *J* = 16.0 Hz, 1H), 6.08 (dd, *J* = 16.0, 6.9 Hz, 1H), 4.93 (t, *J* = 6.2 Hz, 1H), 3.55-3.40 (m, 2H), 2.20-2.00 (m, 2H), 1.98-1.80 (m, 2H), 1.02 (t, *J* = 7.0 Hz, 3H), 0.58 (t, *J* = 7.3 Hz, 3H) ppm. **Minor isomer (3a*RS*,6*SR*,6a*SR*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46-7.40 (m, 2H), 7.39-7.35 (m, 1H), 7.28-7.19 (m, 6H), 7.17 (m, *J* = 8.8 Hz, 3H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.00 (dd, *J* = 15.6, 8.0 Hz, 1H), 4.85 (t, *J* = 8.0 Hz, 1H), 3.62 (t, *J* = 8.4 Hz, 1H), 3.30 (d, *J* = 8.4 Hz, 1H), 2.16-2.05 (m, 1H), 2.00-1.87 (m, 1H), 1.75-1.56 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6, 174.8, 142.9, 136.5, 133.5, 131.9, 129.1, 128.9, 128.5, 128.4, 128.3, 127.6, 127.3,

126.7, 126.6, 126.4, 71.9, 63.0, 51.2, 48.1, 28.0, 27.7, 9.5, 8.9 ppm. IR (NaCl) *?* = 2968, 1776, 1711, 1595, 1491, 1378, 1178, 1093, 1007, 964, 747, 691 cm^{-1}. MS (EI) *m/z* (%) = 484 (M^+, 7), 458 (11), 457 (37), 456 (32), 455 (100), 166 (7), 141 (3), 111(4). HRMS: calcd for $C_{30}H_{30}ClN_2O_2^+$ 485.1990, found 485.1989.

4,4-Diethyl-6-(hept-1-ynyl)-5-(4-methoxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*] pyrrole-1,3(2*H*,3a*H*)-dione (6j): General Experimental Procedure B. Overall yield (63%, isomer ratio 6:4). **Major isomer (3a*RS*,6*SR*,6a*SR*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50-7.45 (m, 2H), 7.41-7.37 (m, 1H), 7.32-7.29 (m, 2H), 7.11-7.07 (m, 2H), 6.84-6.80 (m, 2H), 4.98-4.96 (m, 1H), 3.78 (s, 3H), 3.62 (dd, *J* = 9.3, 3.1 Hz, 1H), 3.5 (d, *J* = 9.3 Hz, 1H), 2.14-1.95 (m, 5H), 1.86-1.77 (m, 1H), 1.45-1.38 (m, 2H), 1.26-1.24 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H), 0.87-0.84 (m, 3H), 0.60 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.4, 175.9, 155.1, 138.0, 132.0, 129.3, 128.8, 126.3, 124.0, 114.0, 85.8, 80.2, 72.3, 55.6, 54.4, 52.6, 51.3, 31.4, 31.0, 28.3, 26.2, 22.3, 18.9, 14.1, 9.2, 8.9 ppm. IR (NaCl) *?* = 2962, 2934, 1716, 1653, 1511, 1457, 1378, 1246, 1181, 1037, 966, 747, 691 cm^{-1}. MS (EI) *m/z* (%) = 472 (M^+, 6), 443 (100), 162 (6). HRMS: calcd for $C_{30}H_{37}N_2O_3^+$ 473.2799, found 473.2811. **Minor isomer (3a*RS*,6*RS*,6a*SR*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50-7.44 (m, 2H), 7.40-7.38 (m, 1H), 7.35-7.32 (m, 2H), 7.08-7.06 (m, 2H), 6.82-6.80 (m, 2H), 4.92-4.89 (m, 1H), 3.78 (s, 3H), 3.57-3.53 (m, 1H), 3.27 (d, *J* = 8.3 Hz, 1H), 2.08-1.93 (m, 4H), 1.78-1.55 (m, 2H), 1.31-1.23 (m, 2H), 1.17-1.04 (m, 4H), 0.89-0.84 (m, 6H), 0.78 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.5, 174.6, 156.3, 137.5, 134.4, 129.2, 128.6, 126.8, 126.6, 113.6, 88.3, 76.2, 71.0, 55.5, 53.8, 52.4, 47.0, 30.8, 28.2, 27.7, 26.8, 22.3, 18.8, 14.0, 9.7, 9.2 ppm. IR (NaCl) *?* = 2958, 2934, 1717, 1508, 1375, 1249, 1182, 1034, 823, 746, 688 cm^{-1}. MS (EI) *m/z* (%) = 473 ($[M+H]^+$, 100), 396 (10), 230 (12). HRMS: calcd for $C_{30}H_{37}N_2O_3^+$ 473.2799, found 473.2803.

4-(4-chlorophenyl)-5-(4-methoxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6k): General Experimental Procedure B. Overall yield (3%, isomer ratio 7:3, unstable oil). **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50-7.39 (m, 3H), 7.37 (d, *J*

= 7.6 Hz, 2H), 7.35-7.30 (m, 2H), 6.91-6.87 (m, 2H), 6.73 (d, *J* = 9.3 Hz, 2H), 6.61 (d, *J* = 9.1 Hz, 2H), 4.90 (d, *J* = 9.8 Hz, 1H), 4.43 (d, *J* = 9.7 Hz, 1H), 3.89 (dd, *J* = 9.7, 8.4 Hz, 1H), 3.70 (s, 3H), 3.67-3.61 (m, 1H), 3.53 (dd, *J* = 9.7, 7.5 Hz, 1H) ppm. MS (EI) *m/z* (%) = 433 (M^+, 35), 421 (12), 314 (19), 286 (46), 188 (10), 235 (29), 161 (35), 160 (40), 136 (100), 125 (24), 83 (12). These data were obtained from slightly contaminated samples.

Dimethyl 5-(4-chlorophenyl)-2,2-diethyl-1-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole-3,4-dicarboxylate (6l): General Experimental Procedure B. Isolated yield (49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 6.72 (d, *J* = 9.1 Hz, 2H), 5.86 (s, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.61 (s, 3H), 2.71-1.91 (m, 3H), 1.70-1.57 (m, 1H), 1.28 (t, *J* = 7.3 Hz, 3H), 0.75 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.0, 163.3, 153.9, 143.0, 138.8, 137.2, 136.9, 133.5, 129.8, 128.5, 120.8, 114.4, 78.3, 70.3, 55.5, 52.6, 52.2, 33.3, 30.4, 10.2, 8.4 ppm. IR (NaCl) *?* = 1725, 1508, 1258 cm^{-1}. MS (EI) *m/z* (%) = 922 (100), 458 (20), 273 (20), 121 (70). HRMS: calcd for $C_{28}H_{29}ClNO_5^+$ 458.1729, found 458.1728. calcd for $C_{28}H_{28}ClNNaO_5$ 480.1548, found 480.1548.

Diethyl 5-(4-chlorophenyl)-2,2-diethyl-1-(4-methoxyphenyl)pyrrolidine-3,4-dicarboxylate (6m): General Experimental Procedure B. Isolated yield (26%, obtained as an inseparable 7:3 mixture of diastereoisomers. Data from the mixture). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 8.4 Hz, 2H, minor diast.), 7.22 (d, *J* = 8.5 Hz, 2H, major diast.), 7.18-7.12 (m, 4H), 6.93 (d, *J* = 9.1 Hz, 2H, minor diast.), 6.75 (d, *J* = 9.0 Hz, 2H, major diast.), 6.68 (d, *J* = 9.1 Hz, 2H, minor diast.), 6.64 (d, *J* = 9.0 Hz, 2H, major diast.), 5.21 (d, *J* = 11.1 Hz, 1H, minor diast.), 4.76 (d, *J* = 10.0 Hz, 1H, major diast.), 4.10 (t, *J* = 11.1 Hz, 1H, minor diast.), 3.84-3.79 (m, 1H, minor diast.), 3.73 (s, 3H, major diast.), 3.72 (s, 3H, minor diast.), 3.70-3.66 (m, 7H), 3.60 (s, 3H, major diast.), 3.36 (dd, *J* = 10.0, 11.9 Hz, 1H, major diast.), 3.17 (s, 3H, minor diast.), 2.16-2.06 (m, 1H, minor diast.), 1.91-1.80 (m, 1H, major diast.), 1.79-1.65 (m, 4H), 1.63-1.52 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H, minor diast.), 1.18 (t, *J* = 7.5 Hz, 3H, major diast.), 0.79 (t, *J* = 7.3 Hz, 3H, major diast), 0.72 (t, *J* = 7.5 Hz, 3H, minor diast.) ppm. IR (NaCl) *?* = 1738, 1508, 1251 cm^{-1}. MS (EI)

m/z (%) = 463 (33), 462 (32), 460 (100), 458 (24), 457 (7), 430 (6), 192 (11). HRMS: calcd for $C_{25}H_{31}ClN_3O_5^+$ 460.1885, found 460.1886.

(3*RS*,4*RS*,5*RS*)-5-(4-chlorophenyl)-2,2-diethyl-1-(4-methoxyphenyl)pyrrolidine-3,4-dicarbonitrile (6n): General Experimental Procedure B. Overall yield (20%, isomer ratio 6:4). **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 4.78 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 3H), 3.39 (d, *J* = 11.7 Hz, 1H), 3.12 (dd, *J* = 9.9, 11.7 Hz, 1H), 2.25-2.14 (m, 1H), 1.82-1.71 (m, 1H), 1.53-1.44 (m, 1H), 1.41-1.27 (m, 4H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.4, 135.6, 135.6, 134.7, 129.4, 128.6, 125.5, 116.9, 116.9, 114.3, 69.1, 66.7, 55.4, 41.3, 41.0, 33.5, 31.3, 9.6, 8.7 ppm. IR (NaCl) *?* = 2238, 1508, 1245 cm^{-1}. MS (EI) *m/z* (%) = 393 (14), 364 (100), 162 (16). HRMS: calcd for $C_{23}H_{25}ClN_3O$ 394.1681, found 394.1679.

(2*RS*,3*SR*)-methyl 2-(4-chlorophenyl)-5,5-diethyl-1-(4-methoxyphenyl)pyrrolidine-3-carboxylate (6o): General Experimental Procedure B. Overall yield (24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 5.07 (d, *J* =10.3 Hz, 1H), 3.74-3.66 (m, 4H), 3.61-3.51 (m, 1H), 3.22 (s, 3H), 2.50 (dd, *J* = 11.5, 12.7 Hz, 1H), 2.02-1.91 (m, 2H), 1.87-1.76 (m, 1H), 1.71-1.59 (m, 2H), 1.21 (t, *J* = 7.4 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.7, 153.8, 139.9, 138.9, 132.9, 129.3, 128.2, 122.0, 114.1, 68.6, 66.6, 55.5, 51.5, 46.6, 34.7, 31.6, 28.0, 9.9, 9.3 ppm. IR (NaCl) *?* = 1732, 1501, 1239 cm^{-1}. MS (EI) *m/z* (%) = 401 (10), 372 (100), 161 (12). HRMS: calcd for $C_{23}H_{29}ClNO_3$ 402.183, found 402.1818.

Diethyl 5-(4-chlorophenyl)-3,3-diethyl-4-(4-methoxyphenyl)-1,2,4-triazolidine-1,2-dicarboxylate (6p): General Experimental Procedure B. Overall yield (34%, slightly unstable oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 4.36-4.26 (m, 1H), 4.24-4.13 (m, 1H), 3.77 (s, 3H), 2.80-2.68 (m, 1H), 1.65-1.53 (m, 1H), 1.53-1.44 (m, 1H), 1.35-1.21 (m, 8H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.82 (t, *J* = 7.0 Hz, 3H) ppm. IR (NaCl) *?* = 1700, 1623, 1495, 1251 cm^{-1}. MS (EI) *m/z* (%) =

1001 (10), 922 (100), 512 (65), 490 (5), 321 (30), 246 (75), 192 (65), 121 (70). HRMS: calcd for $C_{25}H_{33}ClN_3O_5$ 490.2103, found 490.2094. calcd for $C_{25}H_{33}ClN_3O_5Na$ 512.1923, found 512.1913. calcd for $C_{50}H_{64}Cl2N_6O_{10}Na$ 1001.3953, found. 1001.3949.

Methyl-2,2-diethyl-1-(4-methoxyphenyl)-1,2,3,3a,4,9b-hexahydrochromeno-[4,3-*b*]pyrrole-3-carboxylate (6q): General Experimental Procedure B. Overall yield (45%, isomer ratio 7:3). **Major isomer (3*RS*,3a*RS*,9b*RS*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.09-7.04 (m, 1H), 7.00-6.75 (m, 5H), 6.65-6.60 (m, 2H), 4.62 (dd, *J* = 9.5, 5.3 Hz, 1H), 4.51 (d, *J* = 10.7 Hz, 1H), 4.16 (dd, *J* = 11.5, 9.5 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.95 (d, *J* = 12.3 Hz, 1H), 2.85-2.75 (m, 1H), 1.82-1.49 (m, 4H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.69 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9, 154.6, 153.8, 140.3, 128.0, 127.6, 125.1, 123.7 (br), 121.7 (br), 120.0, 116.2, 114.1 (br), 73.4, 71.4, 59.5, 55.6, 52.1, 51.3, 41.6, 33.3, 31.2, 9.7, 8.7 ppm. IR (NaCl) *?* = 2948, 2873, 2828, 1727, 1611, 1510, 1452, 1247, 1162, 1028, 752 cm^{-1}. MS (EI) *m/z* (%) = 395 (M^+, 20), 366 (100), 334 (15), 162 (20). HRMS: calcd for $C_{24}H_{30}NO_4^+$ 396.2169, found 396.2154. **Minor isomer (3*RS*,3a*RS*,9b*SR*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.08-6.97 (m, 4H), 6.84-6.82 (m, 2H), 6.79-6.77 (m, 1H), 6.72-6.68 (m, 1H), 5.37 (d, *J* = 8.9 Hz, 1H), 4.21 (dd, *J* = 11.8, 1.9 Hz, 1H), 4.12 (dd, *J* = 11.8, 2.5 Hz, 1H), 3.34 (d, *J* = 12.2 Hz, 1H), 3.21-3.15 (m, 1H), 1.97-1.86 (m, 1H), 1.81-1.71 (m, 1H), 1.55-1.42 (m, 2H), 0.72 (t, *J* = 7.5 Hz, 3H), 0.54 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 154.1, 153.9, 140.2, 129.2, 127.9, 127.0, 123.2, 121.3, 116.9, 114.5, 71.0, 66.2, 56.1, 55.6, 51.9, 48.9, 37.6, 31.5, 28.2, 9.5, 7.8 ppm. IR (NaCl) *?* = 2951, 2873, 1733, 1652, 1559, 1508, 1457, 1243, 1220, 1174, 1028, 752 cm^{-1}. MS (EI) *m/z* (%) = 396 ($[M+H]^+$, 100), 366 (10), 241 (15), 213 (20). HRMS: calcd for $C_{24}H_{30}NO_4^+$ 396.2169, found 396.2166.

(3a*RS*,6*SR*,6a*SR*)-6-(4-chlorophenyl)-4,4-diethyl-5-(3-hydroxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6r): Prepared using a modified General Experimental Procedure E, by adding 2 equivalents of the aldehyde and 25 equivalents of the dipolarophile (*N*-phenyl maleimide). Cleavege B .Overall yield (27%, isomer ratio 8:2).

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52-7.46 (m, 2H), 7.44-7.36 (m, 3H), 7.33-7.29 (m, 2H), 7.25-7.21 (d, *J* = 8.5 Hz, 2H), 6.96 (t, *J* = 8.1 Hz, 1H), 6.50 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.44 (t, *J* = 2.2 Hz, 1H), 6.33 (dd, *J* = 7.9, 2.1 Hz, 1H), 5.24 (d, *J* = 6.3 Hz, 1H), 3.61 (d, *J* = 10.5 Hz, 1H), 3.37 (dd, *J* = 10.5, 6.3 Hz, 1H), 2.12-2.29 (m, 1H), 2.00-2.11 (m, 2H), 1.88-1.98 (m, 1H), 1.32 (t, *J* = 7.3 Hz, 3H), 0.65 (t, *J* = 7.4 Hz, 3H) ppm; (one proton interchanging). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.5, 175.4, 155.9, 146.1, 141.1, 132.9, 131.6, 129.4, 129.3, 129.0, 128.8, 128.0, 126.1, 114.2, 108.8, 108.7, 72.7, 65.4, 52.0, 35.3, 29.7, 26.2, 9.4, 8.9 ppm, (one carbon overlapped). IR (NaCl) *?* = 2965, 2918, 1712, 1490, 1379, 1168, 1088, 1013, 744, 691 cm^{-1}. MS (EI) *m/z* (%) = 474 (M^+, 40), 457 (9), 399 (11), 327 (35), 319 (31), 175 (37), 135 (30), 124 (33), 97 (38), 84 (100). HRMS: calcd for $C_{28}H_{28}ClN_2O_3^+$ 475.1788, found 475.1791.

1-(4-Chlorophenyl)-2,2-diethyl-3-(4-methoxyphenyl)aziridine (7a): General Experimental Procedure C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.10 (s, 1H), 1.90-1.75 (m, 1H), 1.53-1.43 (m, 1H), 1.06 (t, *J* = 7.6 Hz, 3H), 1.03 (t, *J* = 7.6 Hz, 3H), 0.96-0.87 (m, 1H), 0.75-0.60 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.7, 149.4, 129.3, 128.8, 128.5, 126.5, 121.4, 113.6, 55.3, 54.3, 52.0, 24.5, 22.4, 11.1, 10.0 ppm. IR (NaCl) *?* = 2964, 2933, 2874, 1610, 1591, 1512, 1487, 1458, 1268, 1246, 1169, 1089, 1034, 830 cm^{-1}. MS (EI) *m/z* (%) = 315 (M^+, 35), 286 (15), 246 (15), 231 (55), 204 (6), 189 (11), 166 (42), 138 (12); 121 (100), 77 (9). HRMS: calcd for $C_{19}H_{23}ClNO^+$ 316.1463, found 316.1462.

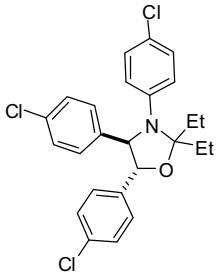
3-(2-(Allyloxy)phenyl)-2,2-diethyl-1-*p*-tolylaziridine (7b): General Experimental Procedure C. Isolated yield (55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.23 (m, *J* = 7.6, 1.6 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.15-6.02 (m, 1H), 5.41 (dm, *J* = 17.2 Hz, 1H), 5.28 (dm, *J* = 10.4 Hz, 1H), 4.61 (d, *J* = 5.2 Hz, 2H), 3.28 (s, 1H), 2.30 (s, 3H), 1.90-1.77 (m, 1H), 1.57-1.46 (m, 1H), 1.10-1.03 (m, *J* = 7.6 Hz, 6H), 1.00-0.87 (m, 1H), 0.81-0.68 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.1, 148.3, 133.5 130.6 129.3, 129.1, 127.7, 126.6, 120.2, 117.5, 110.6, 68.8, 53.6,

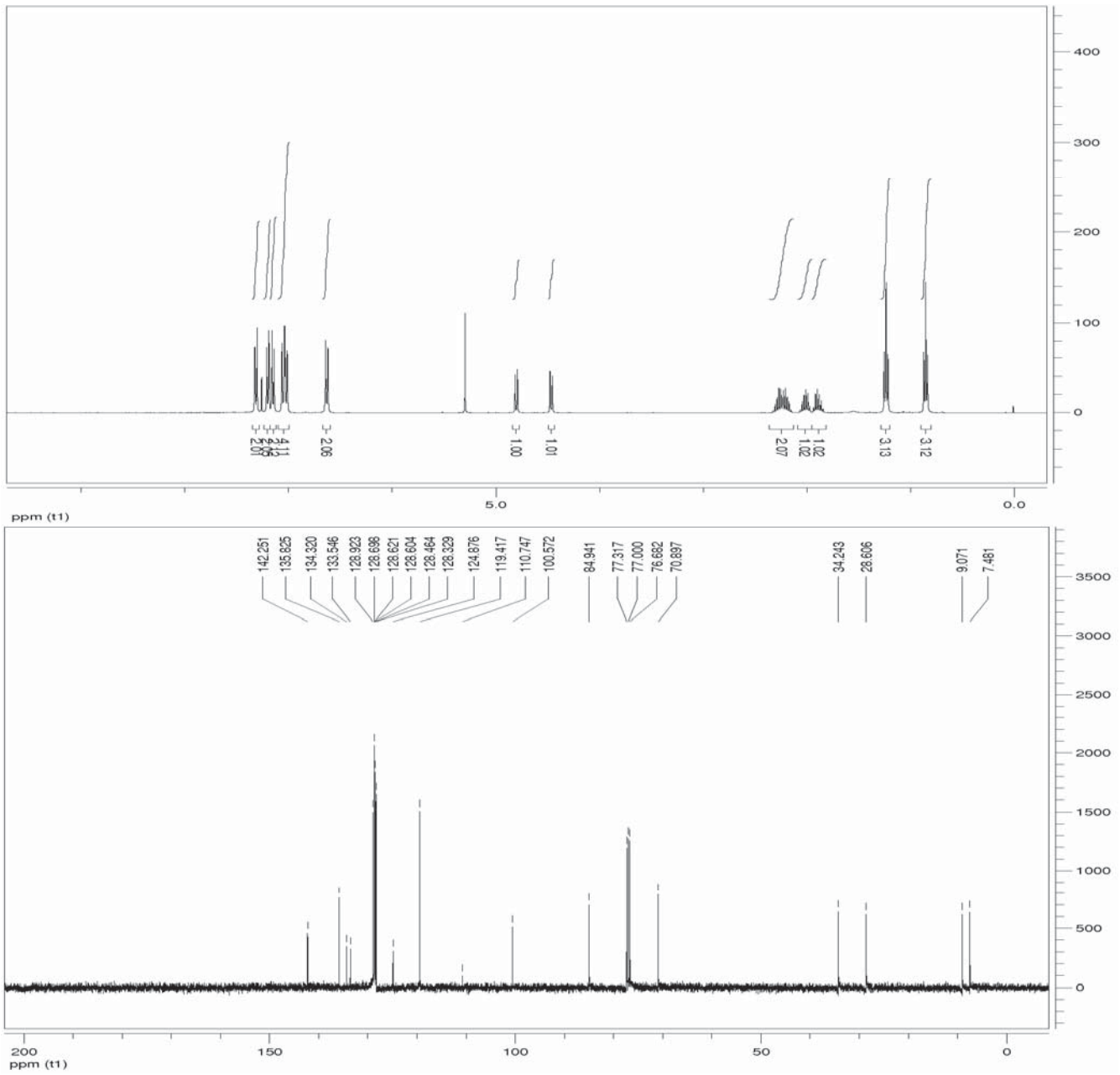
49.1, 24.6, 22.5, 20.7, 10.7, 10.0 ppm. IR (NaCl) *?* = 2965, 2935, 2874, 1610, 1586, 1491, 1451, 1422, 1312, 1267, 1242, 1112, 818, 752 cm^{-1}. MS (EI) *m/z* (%)= 321 (M^+, 48), 264 (38), 236 (13), 210 (33), 181 (32), 173 (33), 146 (100), 131 (47), 119 (29), 91 (91), 65 (18). HRMS: calcd for $C_{22}H_{28}NO^+$ 322.2165, found 322.2172.

3-(2,4-Dimethoxyphenyl)-2,2-diethyl-1-*p*-tolylaziridine (7c): General Experimental Procedure C. Isolated yield (22%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.50-6.43 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.14 (s, 1H), 2.29 (s, 3H), 1.90-1.75 (m, 1H), 1.55-1.45 (m, 1H), 1.10-1.01 (m, *J* = 7.6, 7.2 Hz, 6H), 0.96-0.85 (m, 1H), 0.75-0.61 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 159.0, 148.5, 130.5, 129.4, 129.3, 120.2, 119.0, 103.4, 98.0, 55.4, 55.1, 53.3, 48.8, 24.5, 22.4, 20.7, 10.5, 10.0 ppm. IR (NaCl) *?* = 2962, 2933, 1609, 1507, 1456, 1207, 1156, 1121, 1035, 819 cm^{-1}. MS (EI) *m/z* (%) = 325 (M^+, 13), 296 (4), 256 (3), 241 (8), 219 (17), 151 (100), 146 (20), 121 (12), 105 (8), 91 (14). HRMS: calcd for $C_{21}H_{28}NO_2^+$ 326.2115, found 326.2119.

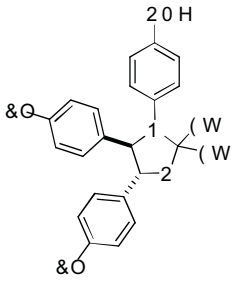
Methyl 4-(3,3-diethyl-1-(4-methoxyphenyl)aziridin-2-yl)benzoate (7d): Prepared using a modified General Experimental Procedure D (no aldehyde in solution was added). Cleavage A. Isolated yield (50%). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 6.87-6.77 (m, 4H), 3.19 (s, 3H), 3.77 (s, 3H), 3.16 (s, 1H), 1.86-1.74 (m, 1H), 1.51-1.39 (m, 1H), 1.10-1.00 (m, *J* = 7.6, 7.5 Hz, 6H), 0.99-0.88 (m, 1H), 0.81-0.69 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0, 155.0, 143.4, 143.3, 129.3, 128.7, 127.6, 121.0, 114.3, 55.5, 54.8, 52.0, 51.9, 24.2, 22.6, 11.1, 9.9 ppm. IR (NaCl) *?* = 2964, 2874, 2833, 1722, 1610, 1506, 1435, 1277, 1240, 1037, 831, 770 cm^{-1}. MS (EI) *m/z* (%) = 339 (M^+, 43), 310 (8), 255 (77), 204 (14), 162 (23), 149 (100), 135 (13), 121 (8), 77 (10). HRMS: calcd for $C_{21}H_{26}NO_3^+$ 340.1907, found 340.1909.

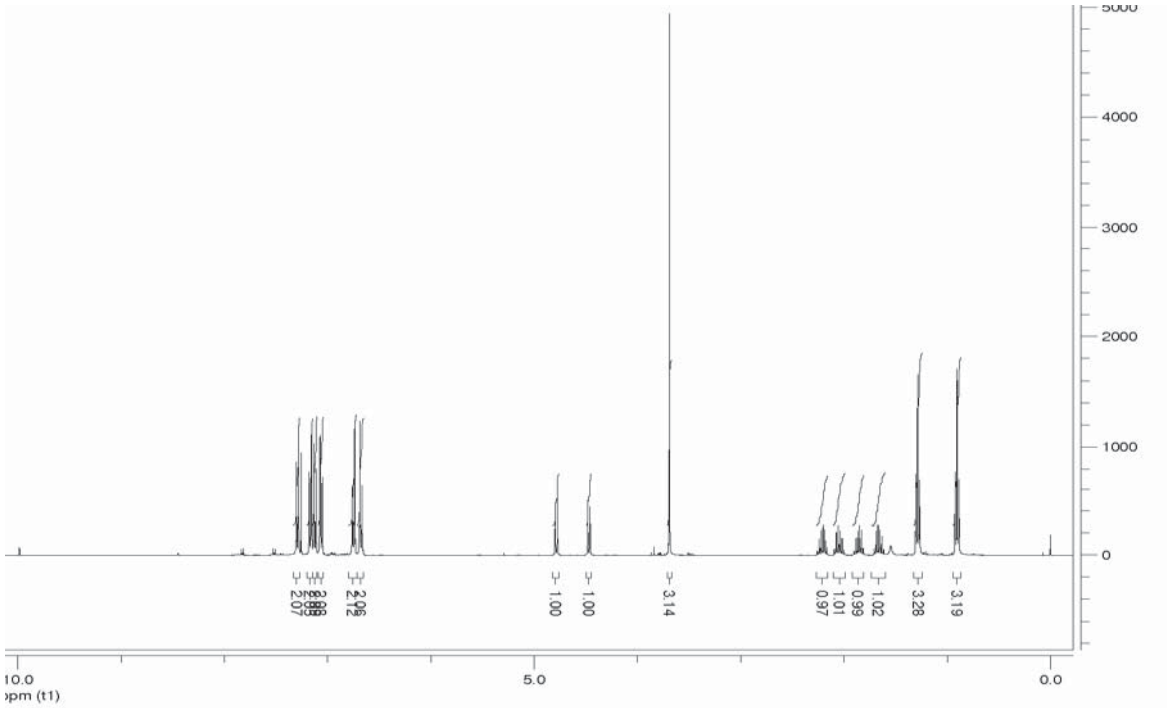
(4*RS*,5*RS*)-3,4,5-tris(4-chlorophenyl)-2,2-diethyloxazolidine (5a):

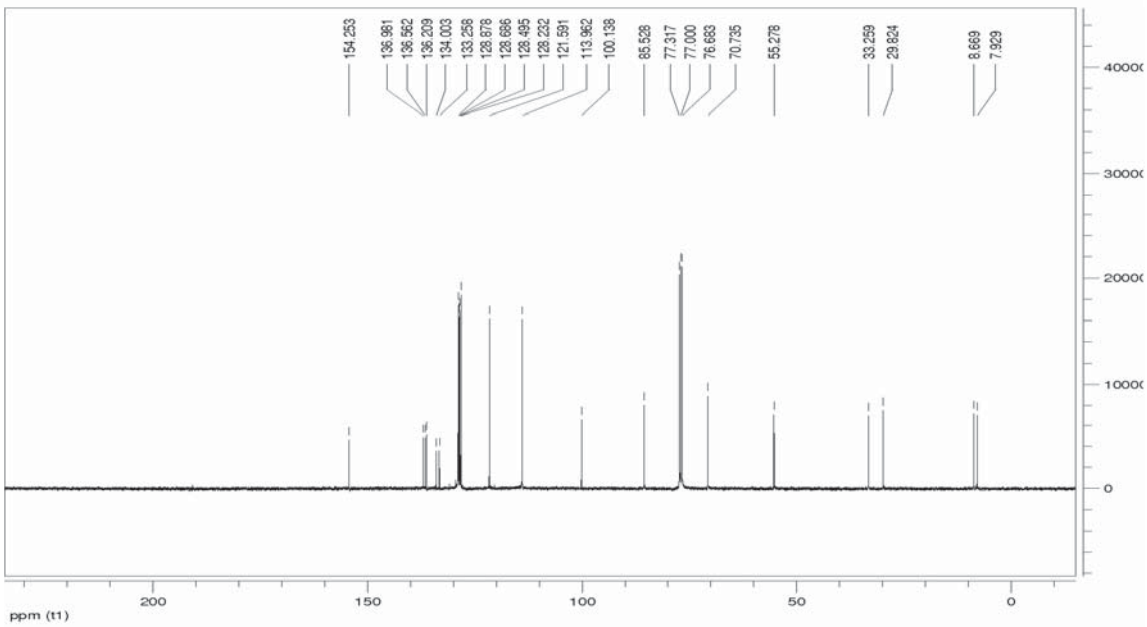




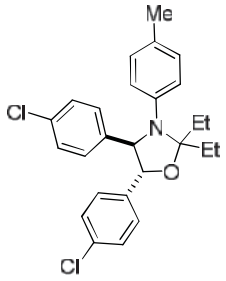
(4*RS*,5*RS*)-4,5-bis(4-chlorophenyl)-2,2-diethyl-3-(4-methoxyphenyl)oxazolidine (5b):

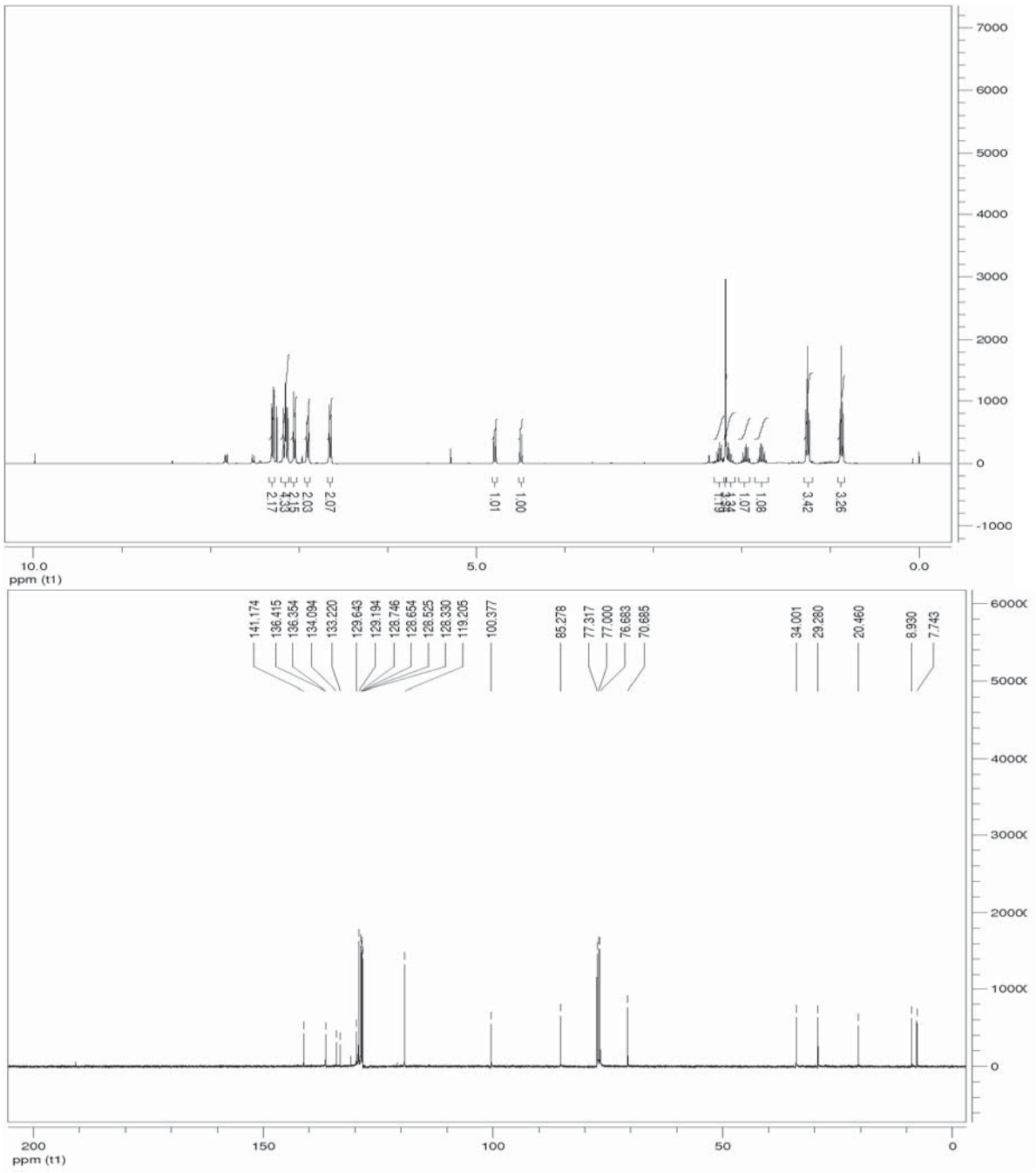




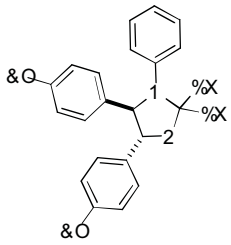


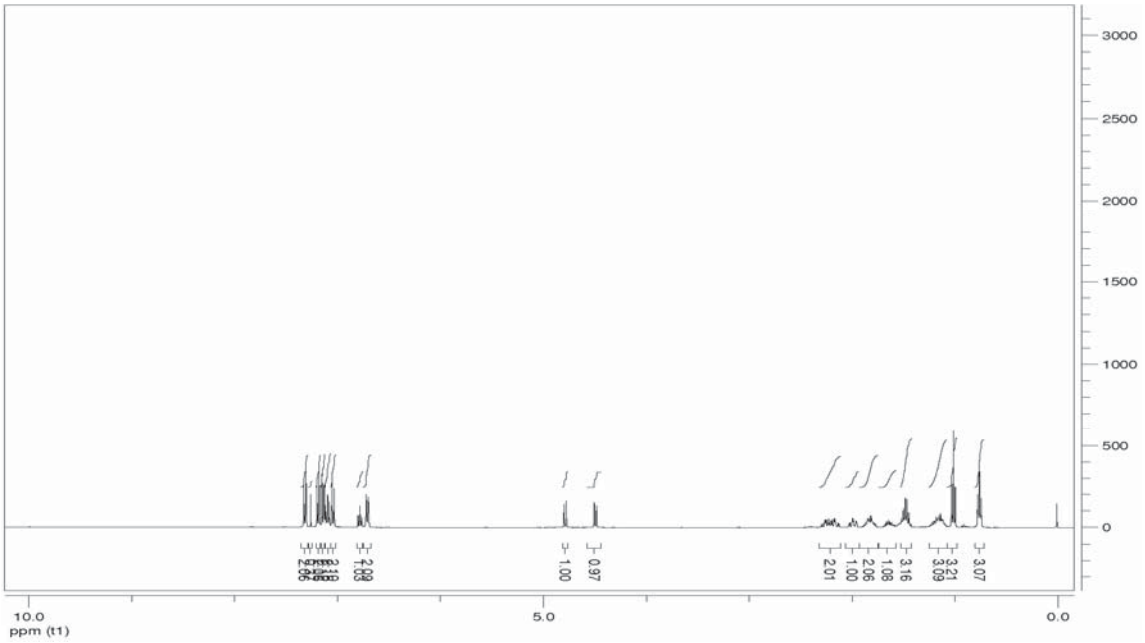
(4*RS*,5*RS*)-4,5-bis(4-chlorophenyl)-2,2-diethyl-3-*p*-tolyloxazolidine (5c):

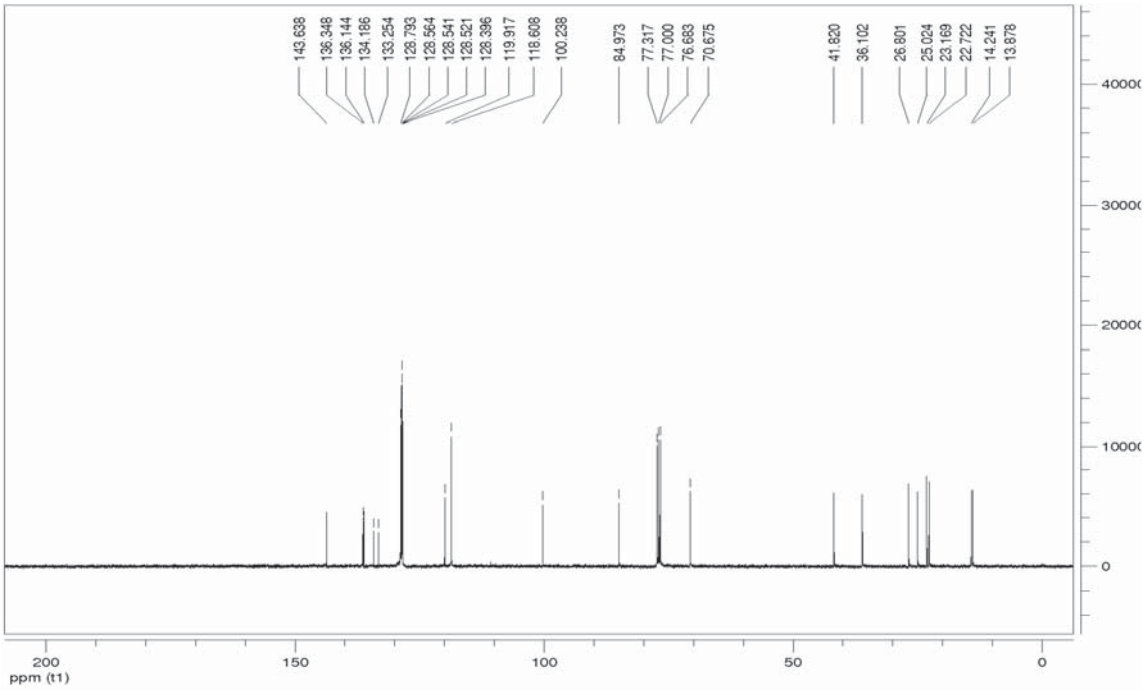




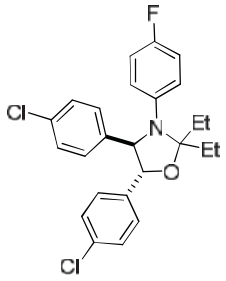
(4*RS*,5*RS*)-2,2-dibutyl-4,5-bis(4-chlorophenyl)-3-phenyloxazolidine (5d):

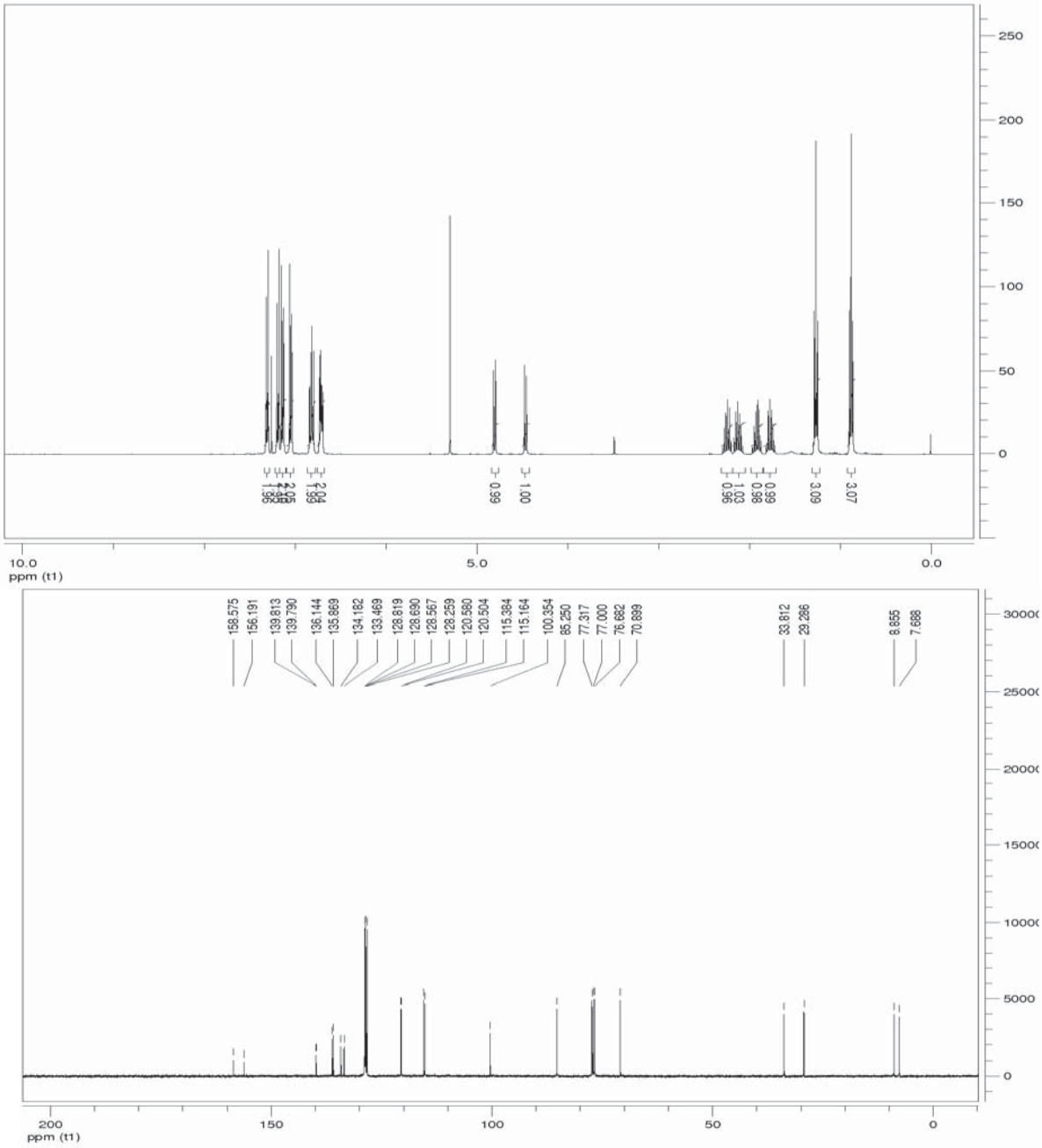




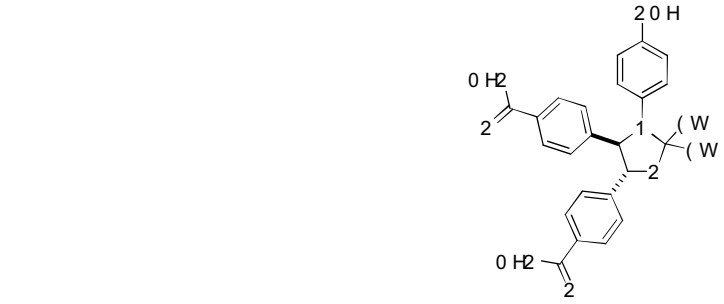


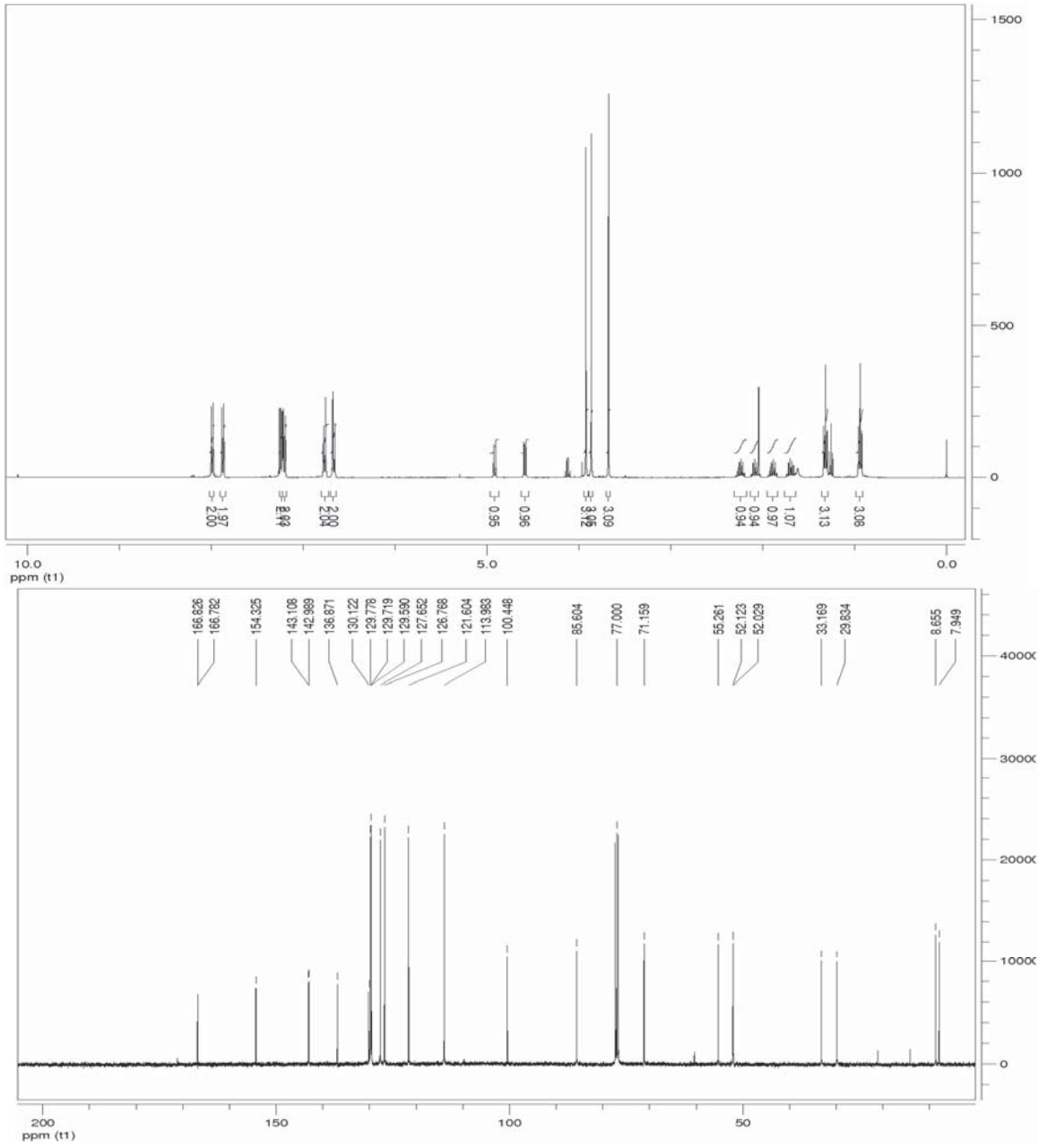
(4*RS*,5*RS*)-4,5-bis(4-chlorophenyl)-2,2-diethyl-3-(4-fluorophenyl)oxazolidine (5e):



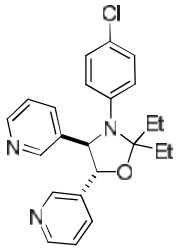


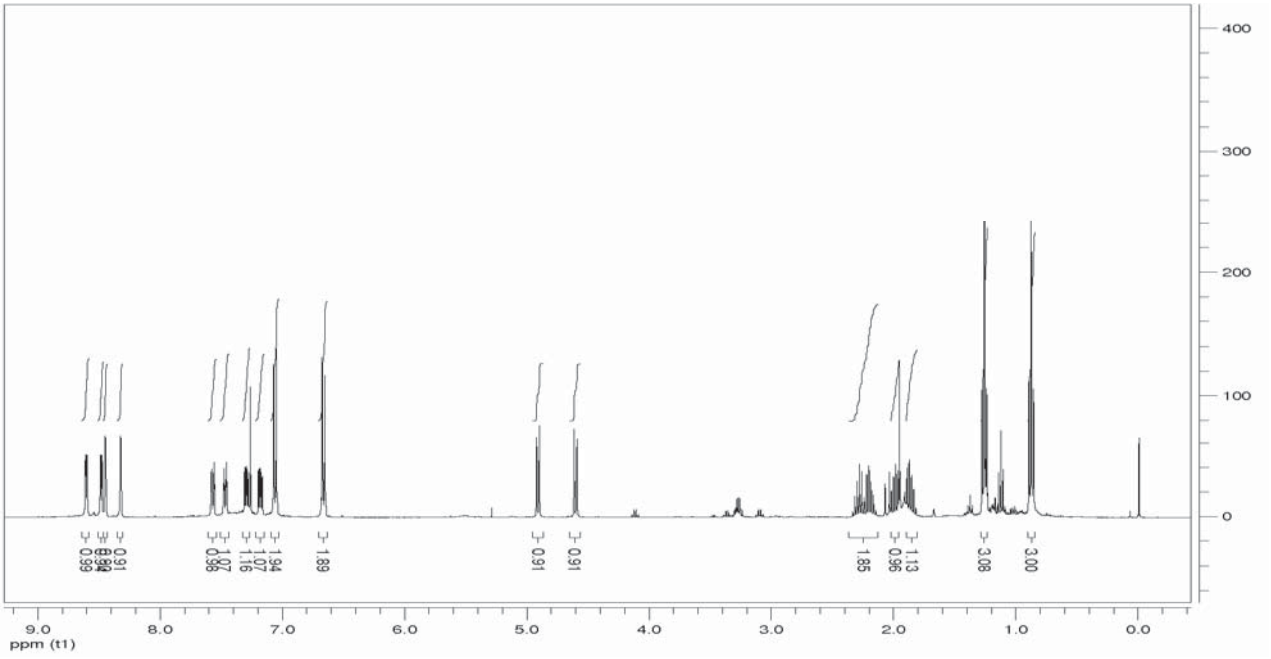
Dimethyl 4,4'-((4*RS*,5*RS*)-2,2-diethyl-3-(4-methoxyphenyl)oxazolidine-4,5-diyl)dibenzoate (5g):

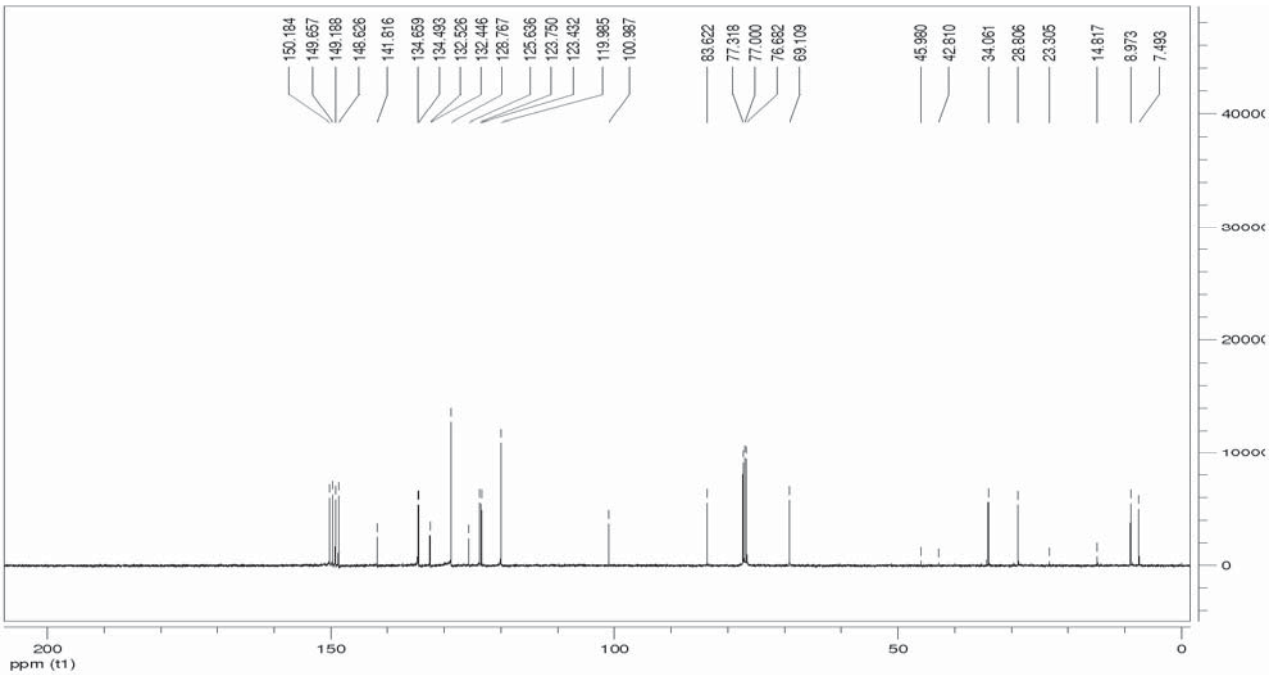




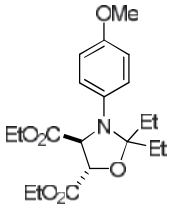
(4*RS*,5*RS*)-3-(4-chlorophenyl)-2,2-diethyl-4,5-di(pyridin-3-yl)oxazolidine (5h):

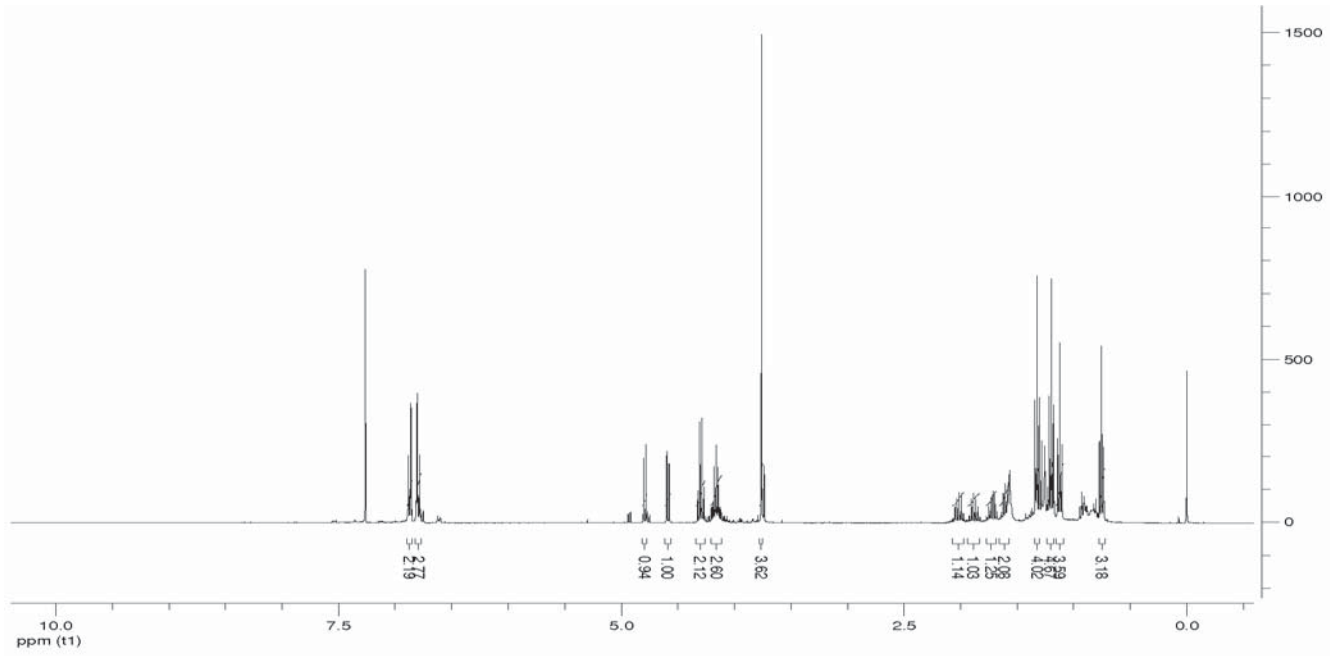


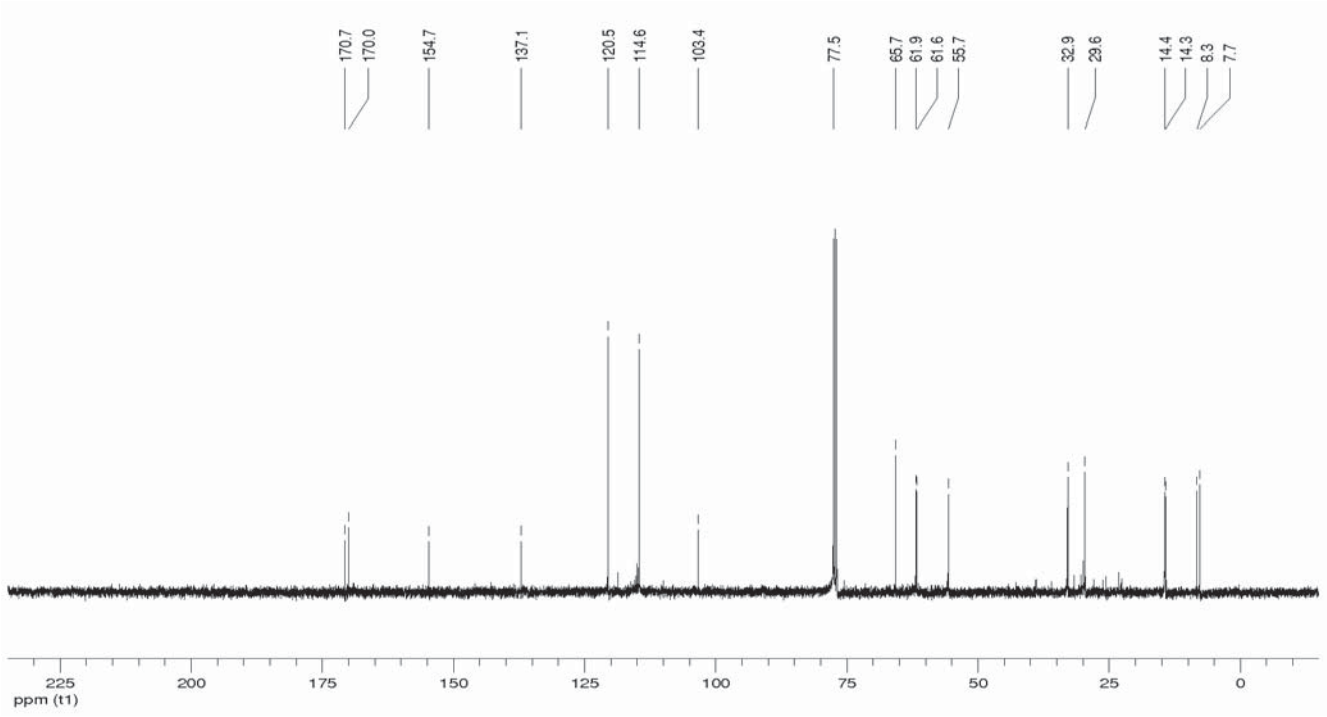




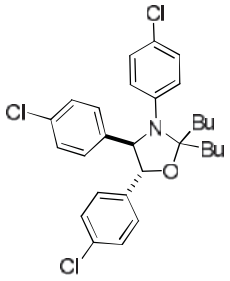
(4*RS*,5*RS*)-diethyl 2,2-diethyl-3-(4-methoxyphenyl)oxazolidine-4,5-dicarboxylate (5i):

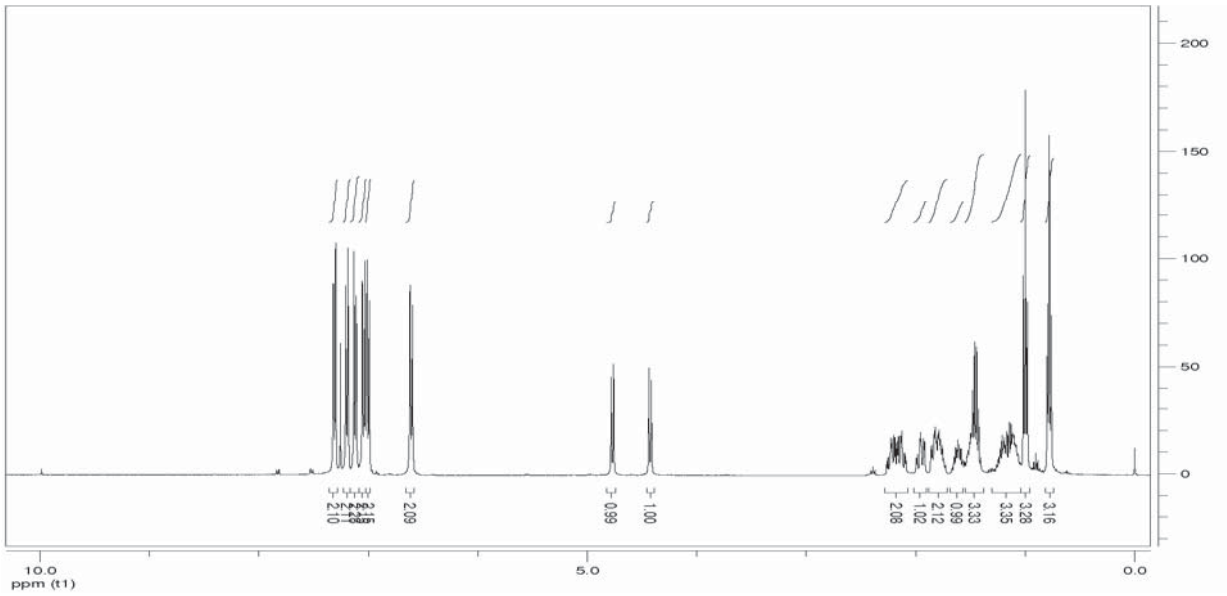


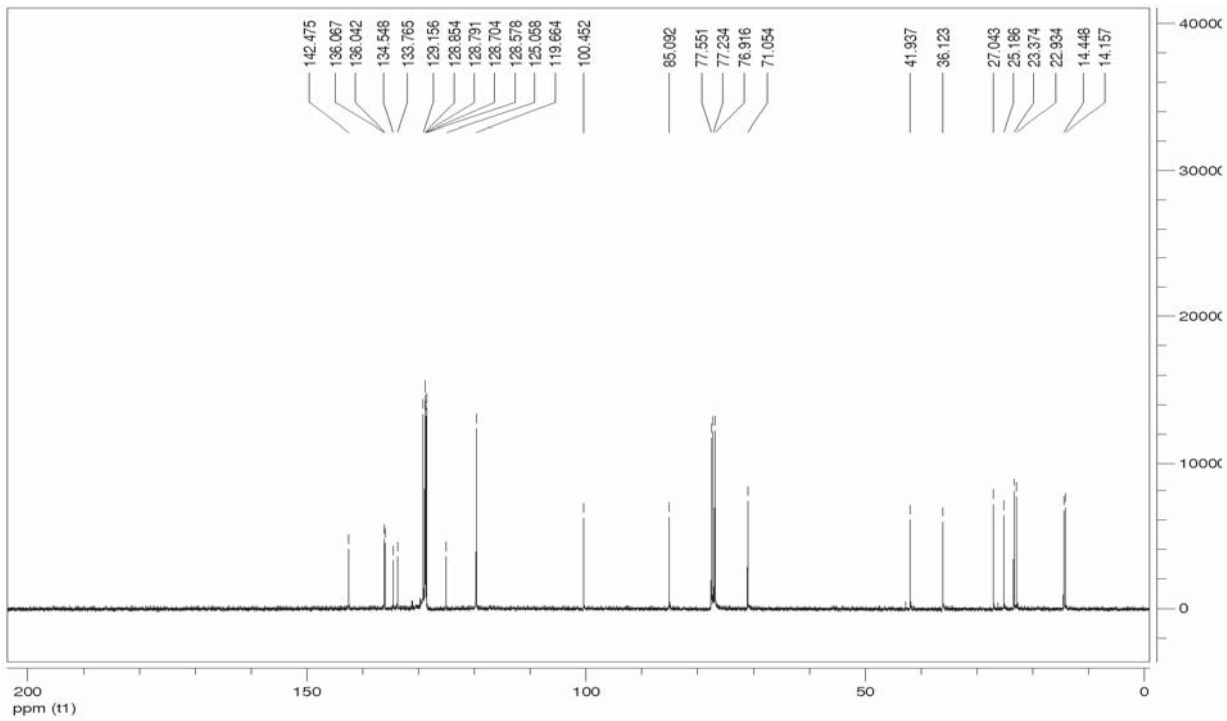




(4*RS*,5*RS*)-2,2-dibutyl-3,4,5-tris(4-chlorophenyl)oxazolidine (5j):

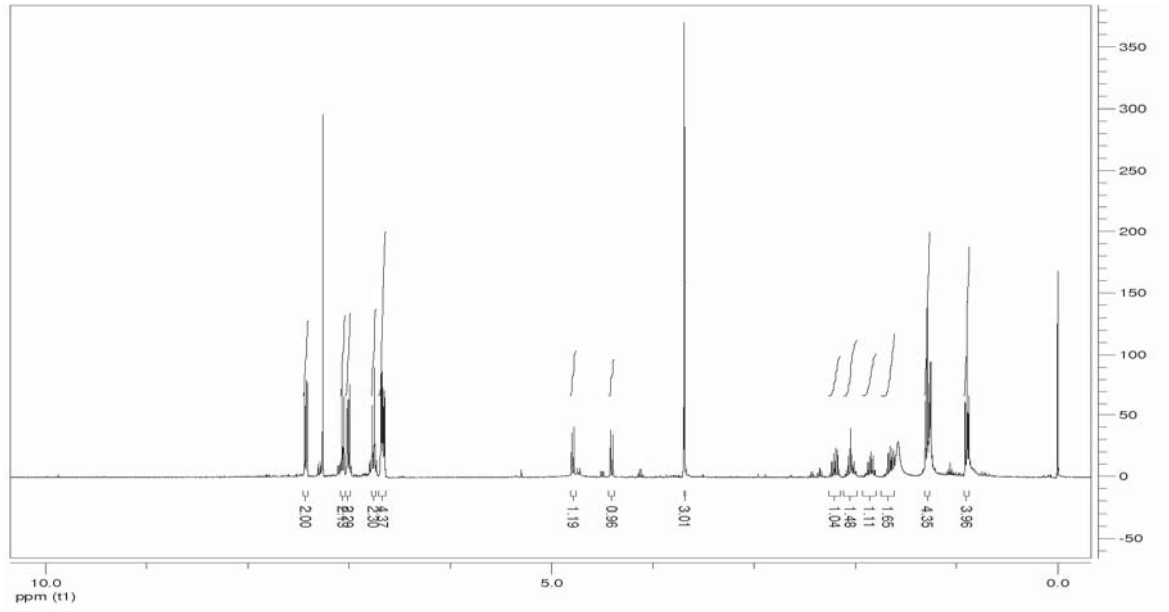


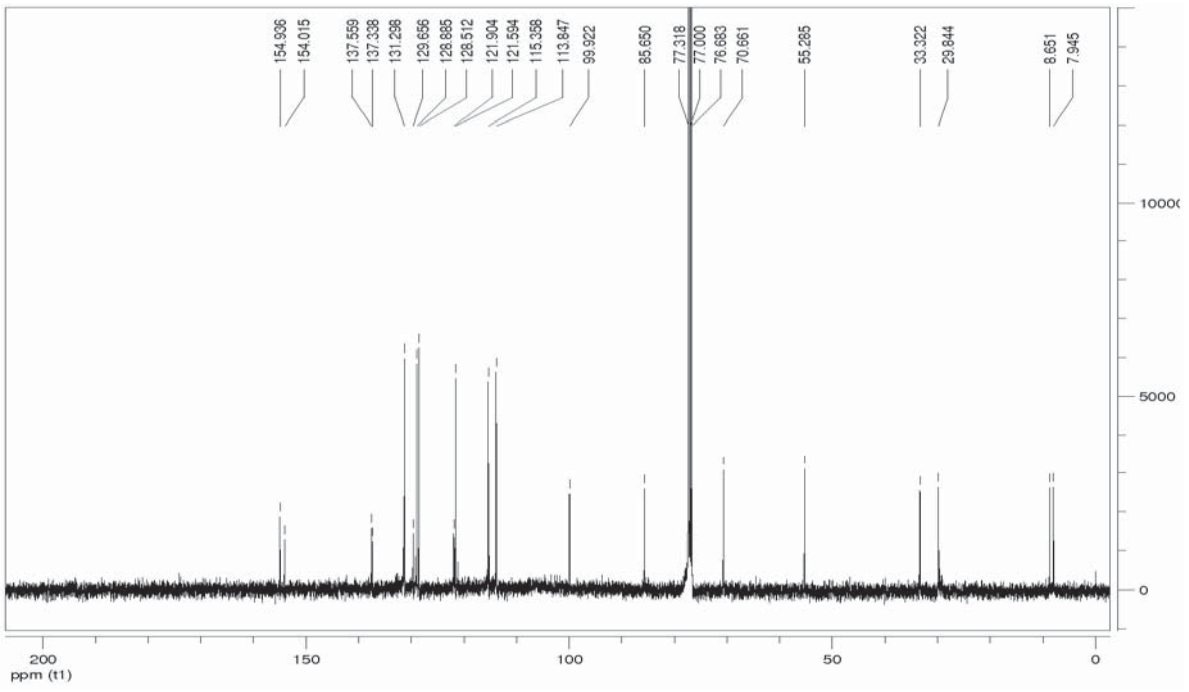




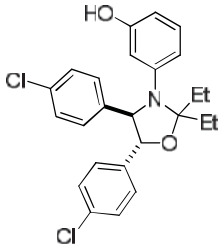
4-((4*RS*,5*RS*)-5-(4-bromophenyl)-2,2-diethyl-3-(4-methoxyphenyl)oxazolidin-4-yl)phenol

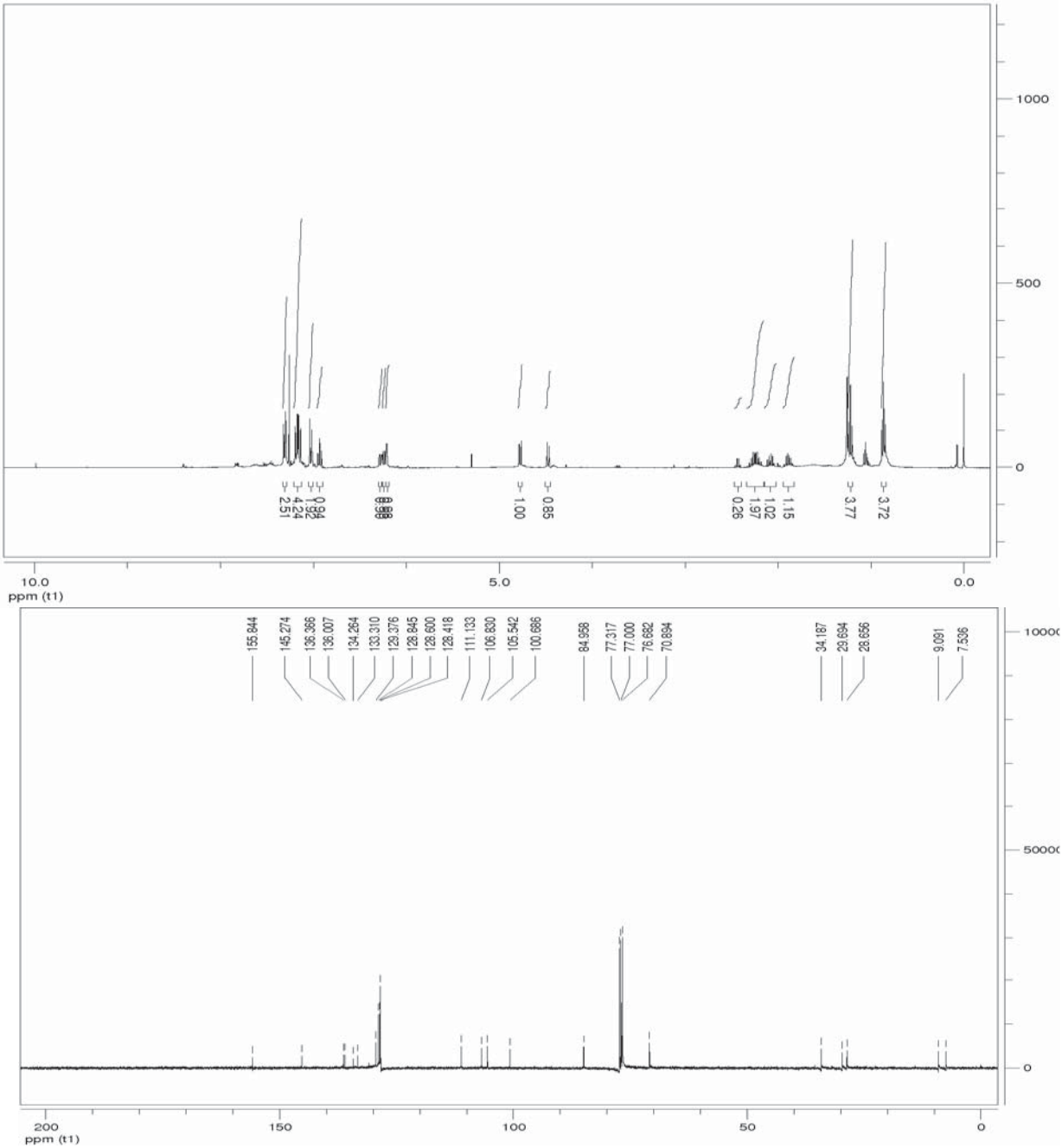
(5k):



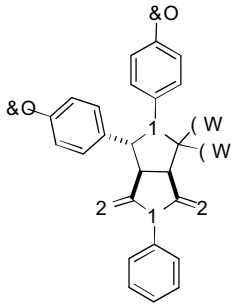


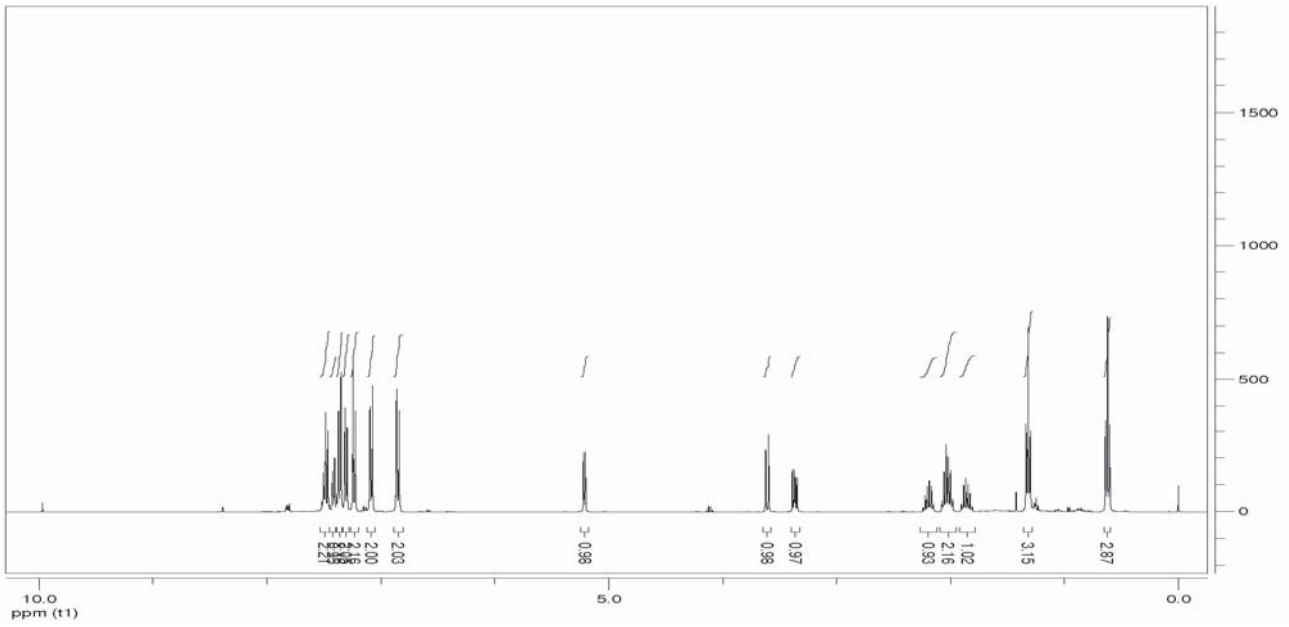
3-((4*RS*,5*RS*)-4,5-bis(4-chlorophenyl)-2,2-diethyloxazolidin-3-yl)phenol (5l):

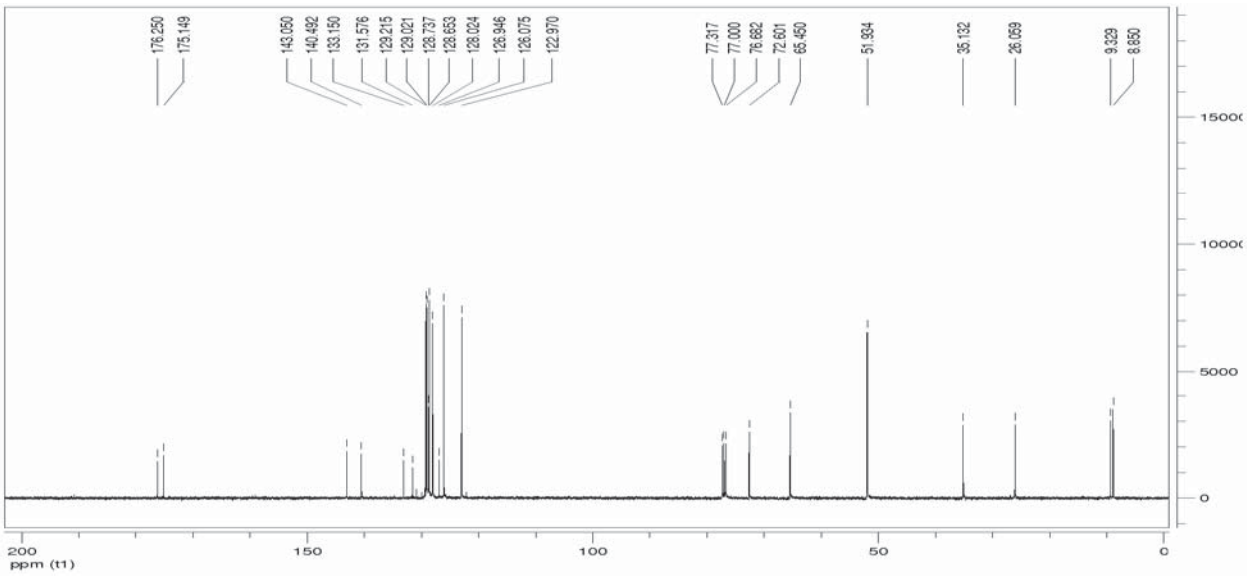




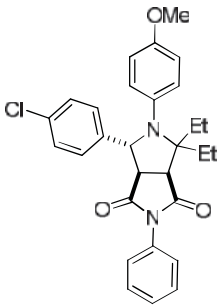
(3a*RS*,6*SR*,6a*SR*)-5,6-bis(4-chlorophenyl)-4,4-diethyl-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6a):

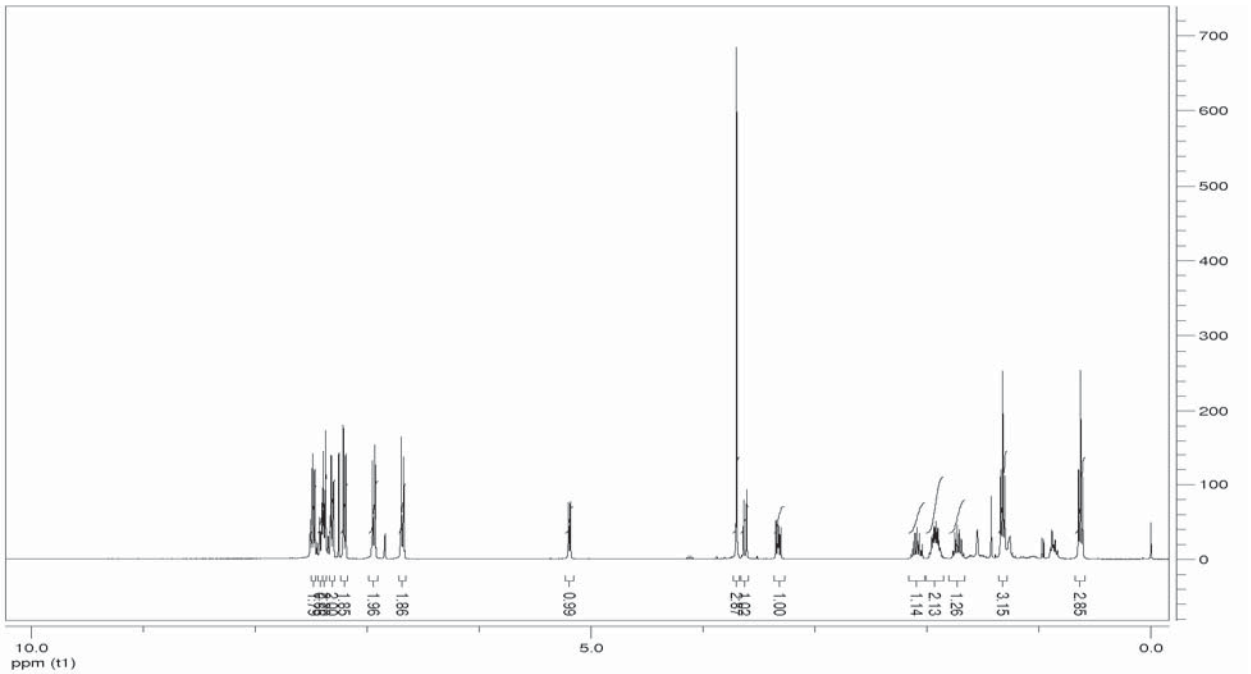


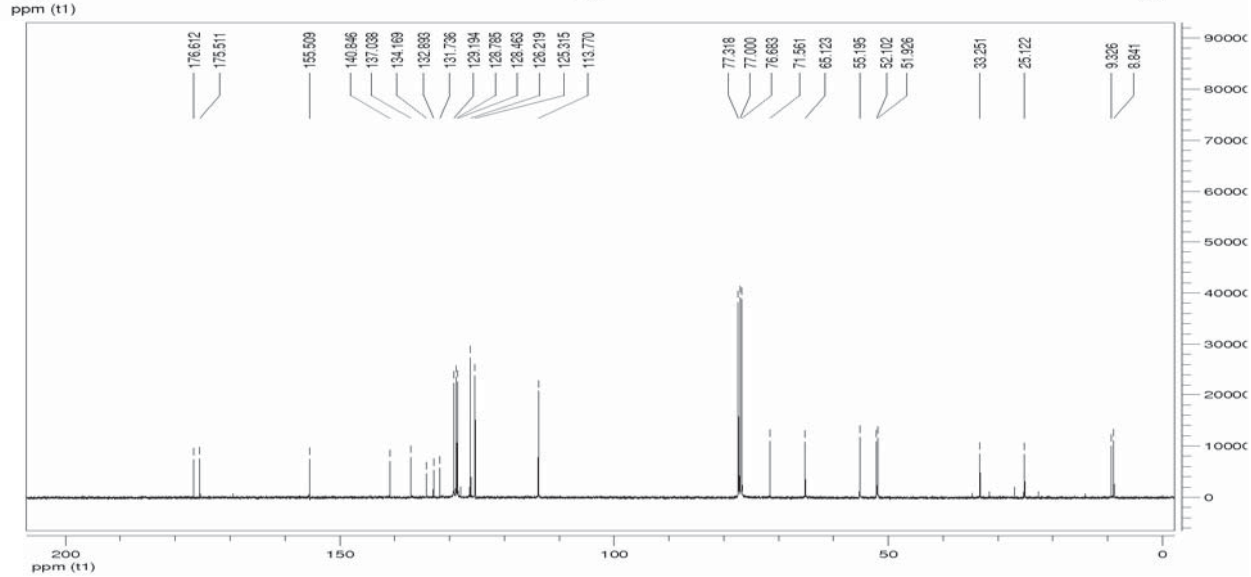




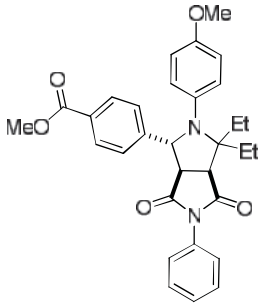
(3a*RS*,6*SR*,6a*SR*)-6-(4-chlorophenyl)-4,4-diethyl-5-(4-methoxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6b):

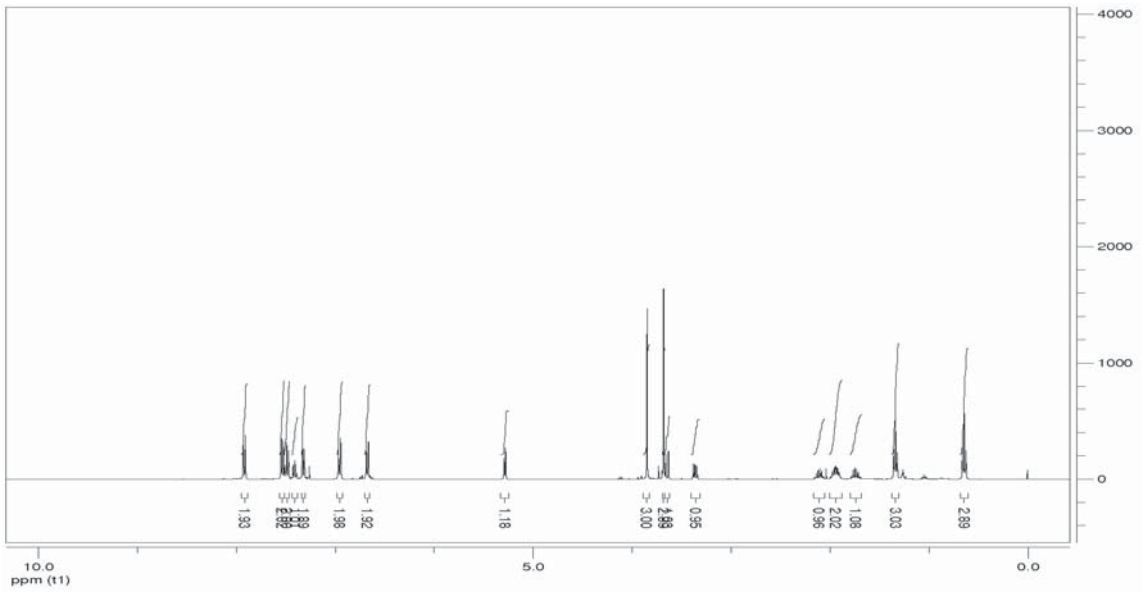


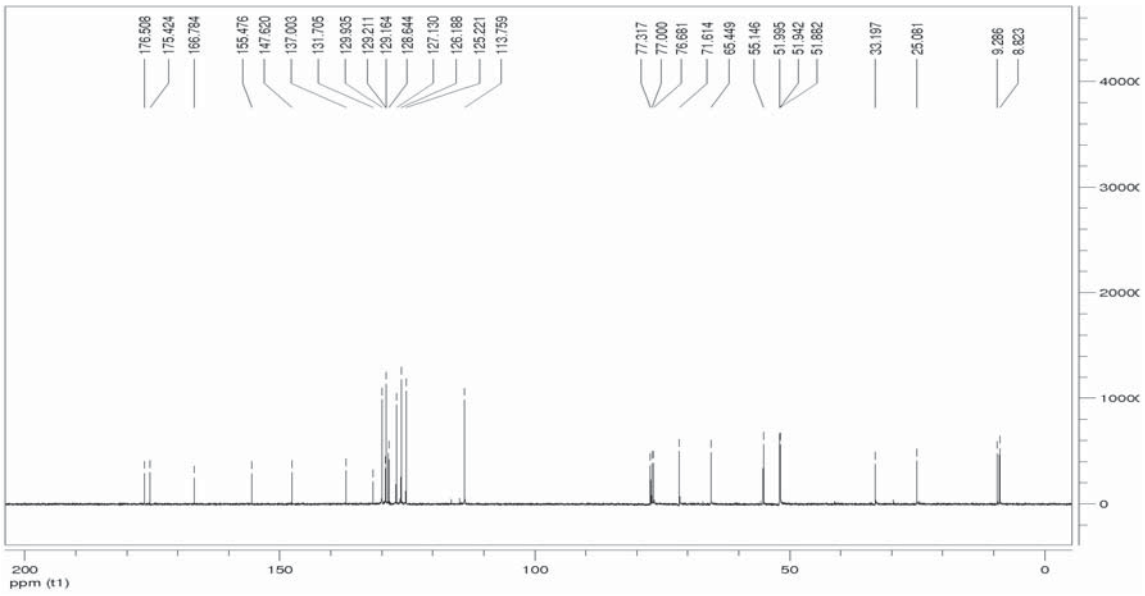




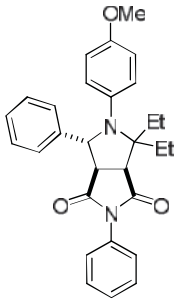
Methyl 4-((1*RS*,3a*SR*,6a*RS*)-3,3-diethyl-2-(4-methoxyphenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrol-1-yl)benzoate (6d):



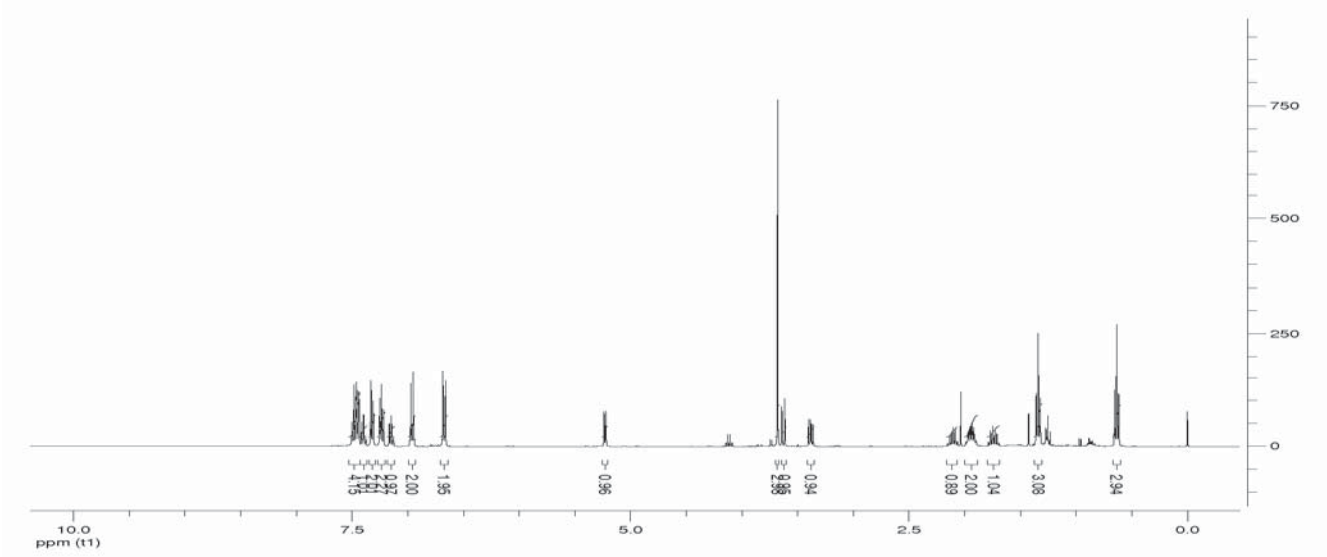


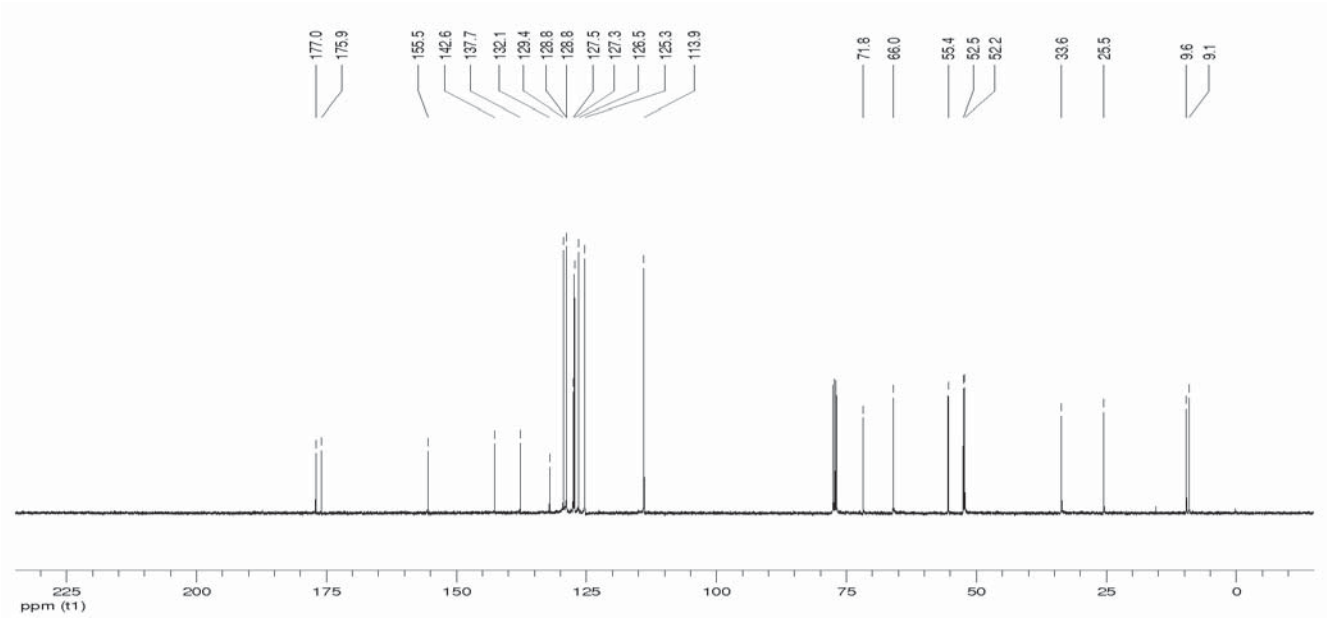


4,4-Diethyl-5-(4-methoxyphenyl)-2,6-diphenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3*aH*)-dione (6e):

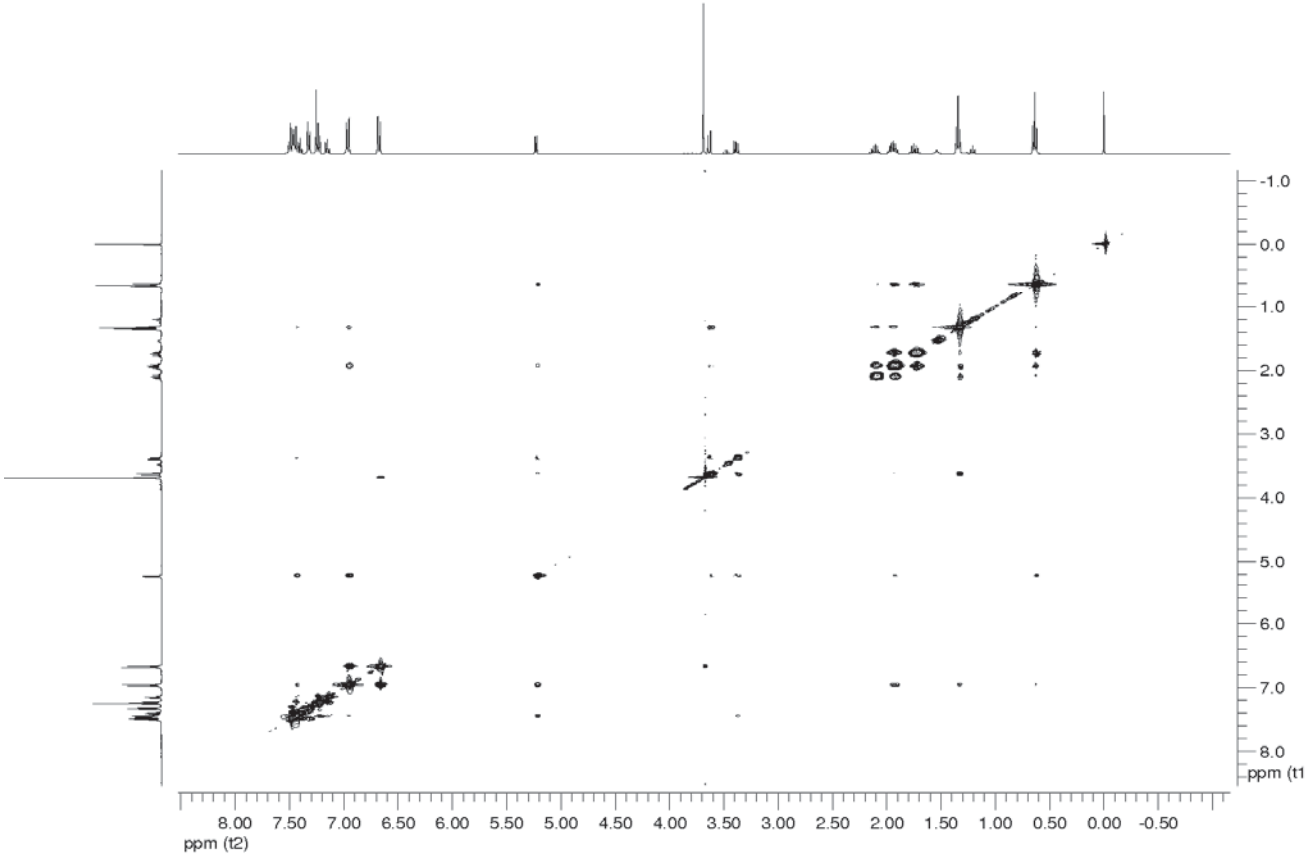


(major isomer)

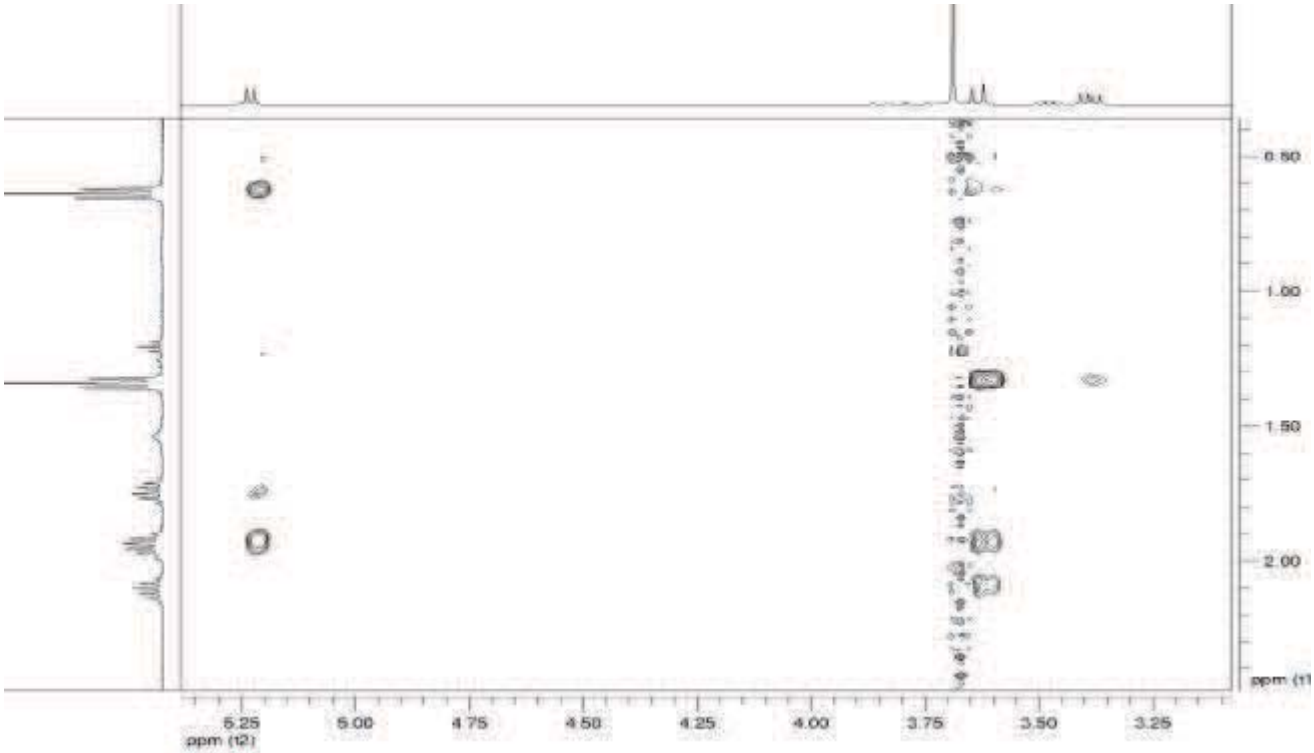


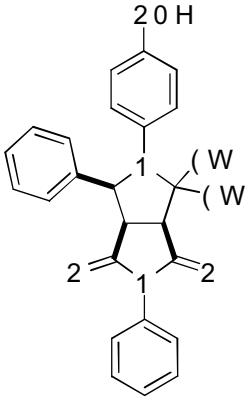


(NOESY spectra)

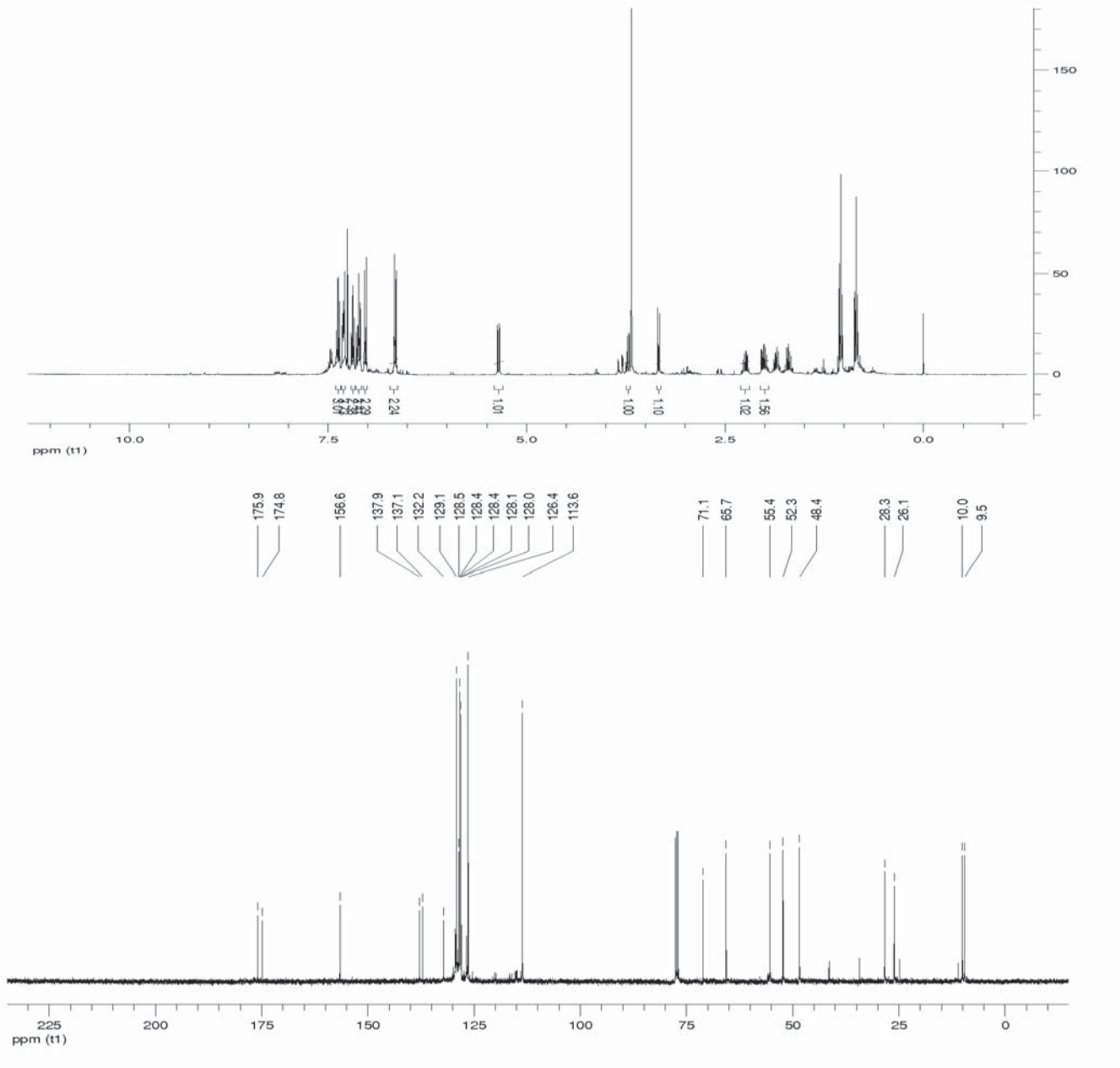


(NOESY spectra ampliation)

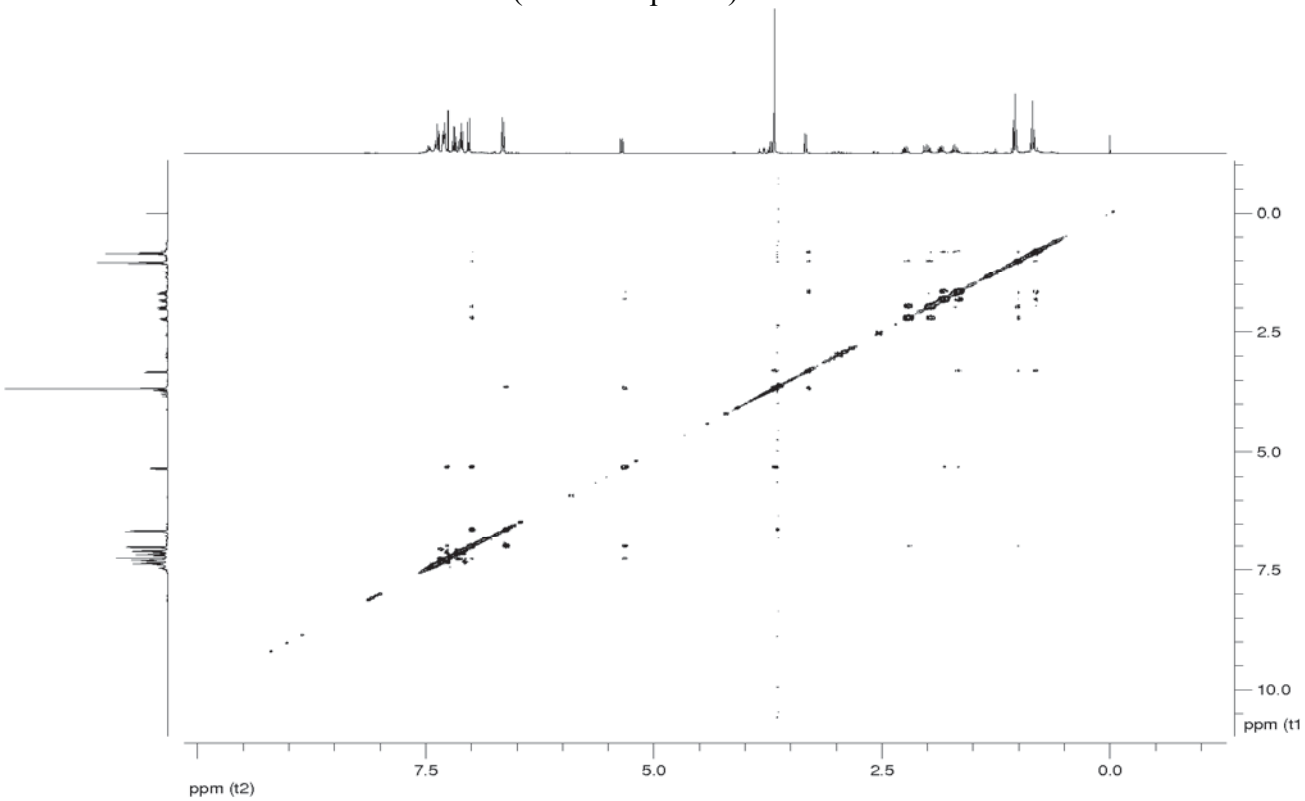




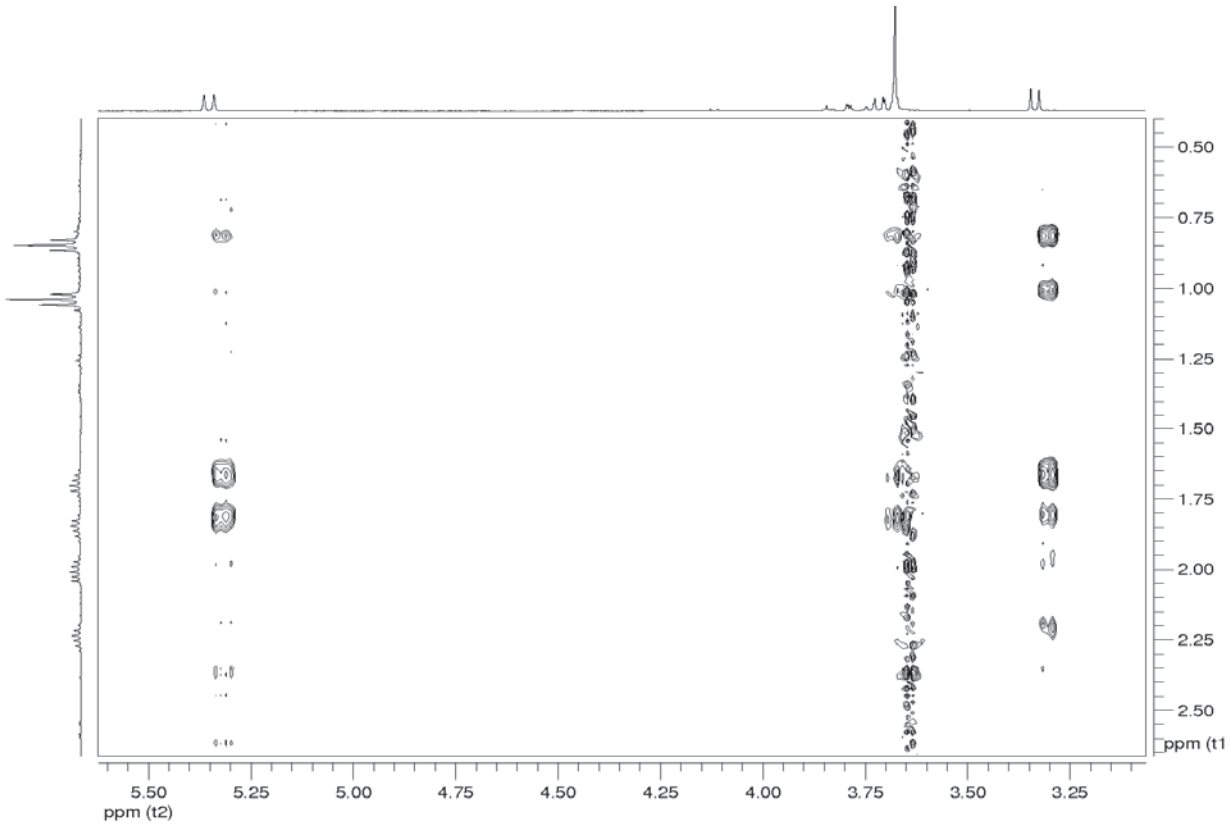
H PLQRULVRP HU



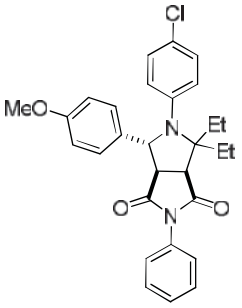
(NOESY spectra)

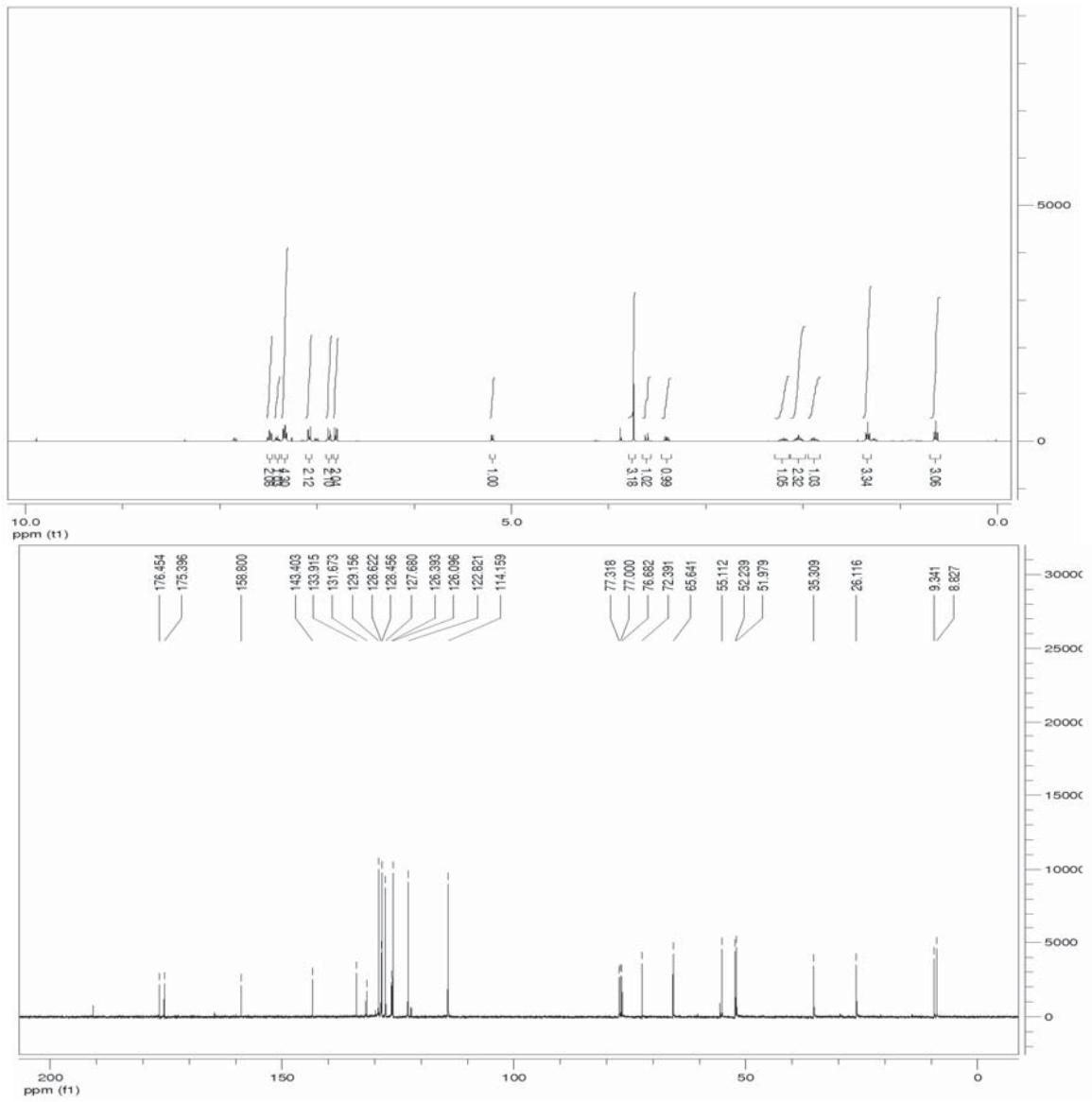


(NOESY spectra ampliation)

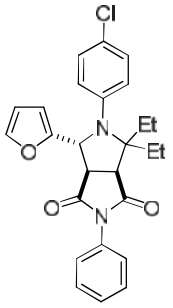


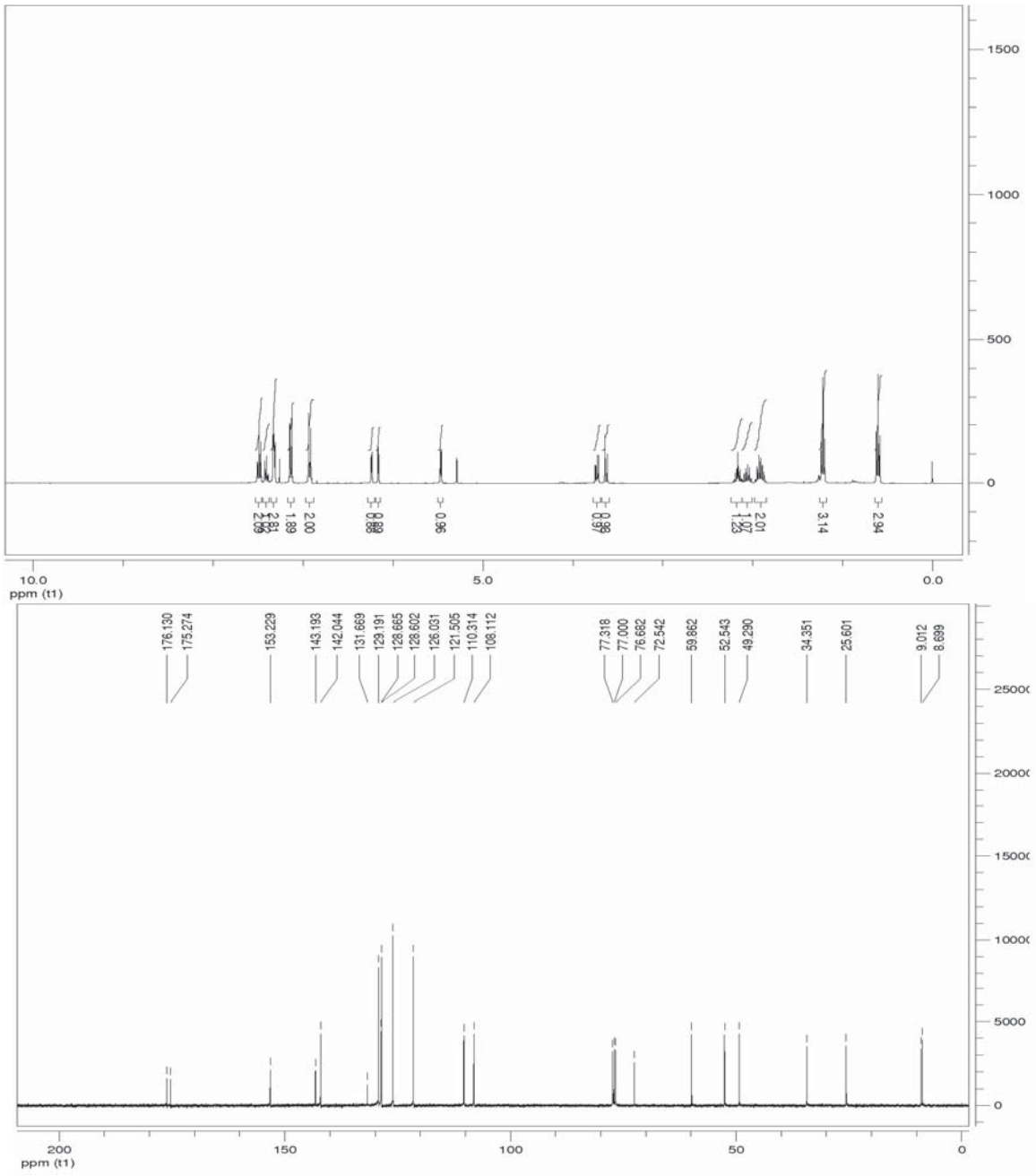
(3a*RS*,6*SR*,6a*SR*)-5-(4-Chlorophenyl)-4,4-diethyl-6-(4-methoxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6f):



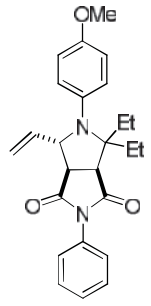


(3a*RS*,6*SR*,6a*SR*)-5-(4-chlorophenyl)-4,4-diethyl-6-(furan-2-yl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6g):

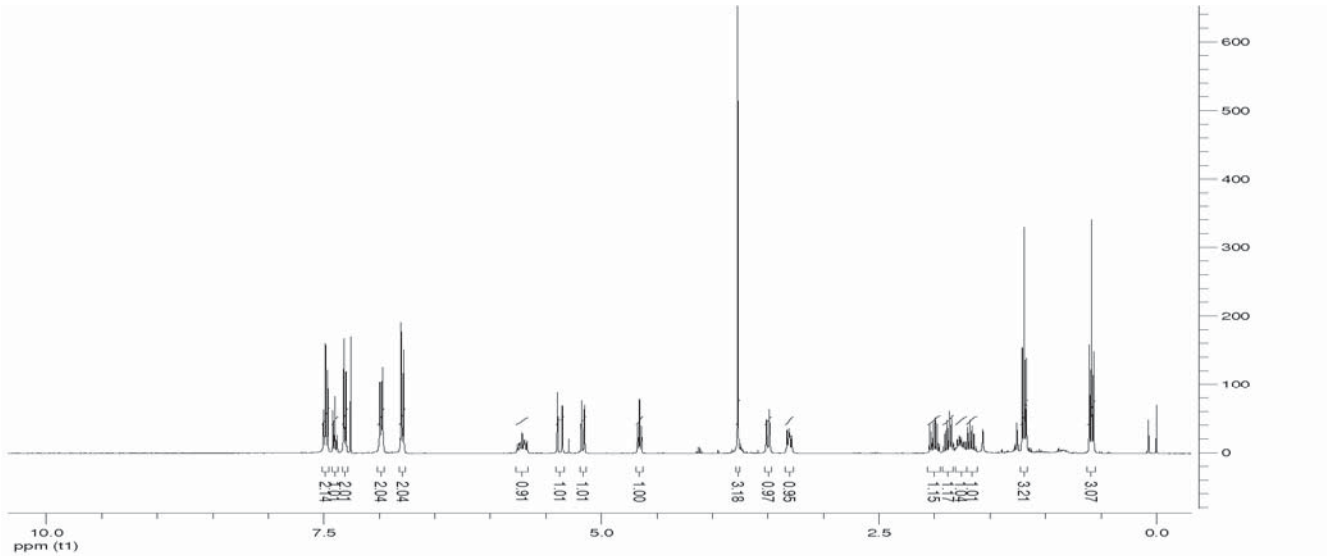


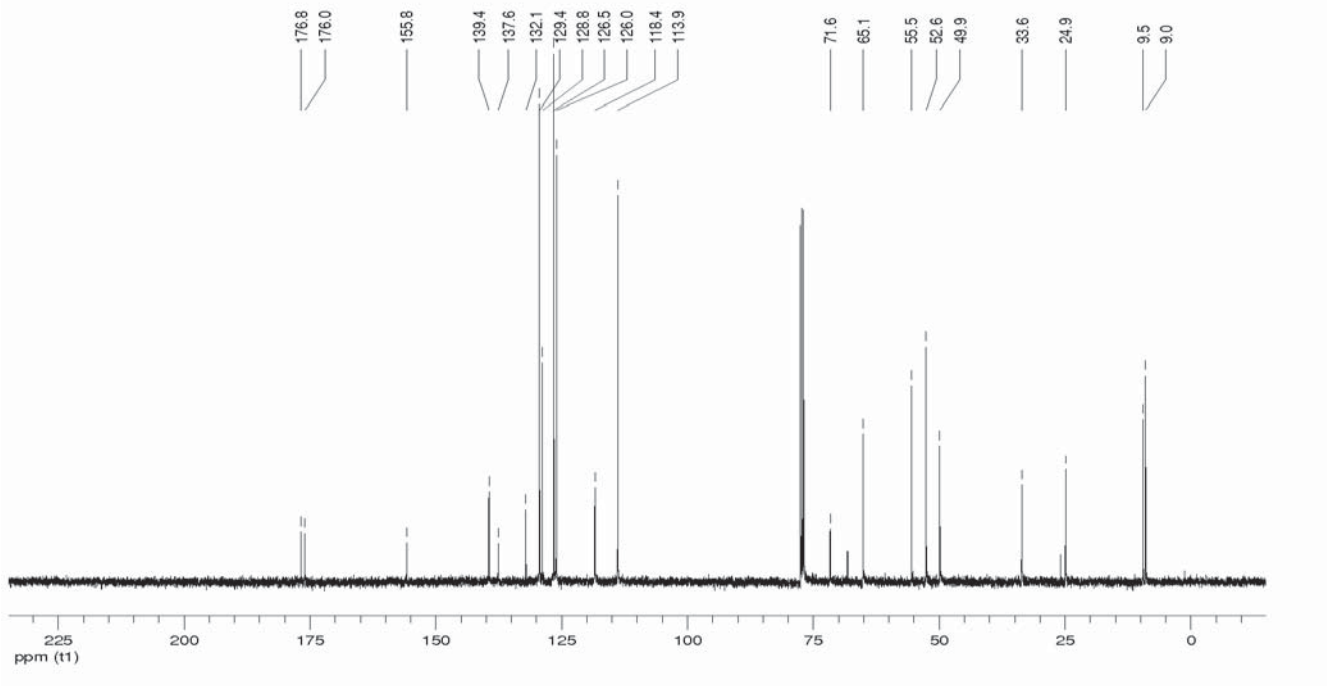


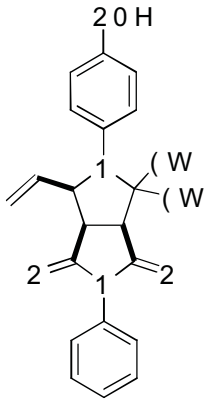
(3a*RS*,6*RS*,6a*SR*)-4,4-Diethyl-5-(4-methoxyphenyl)-2-phenyl-6-vinyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6h):



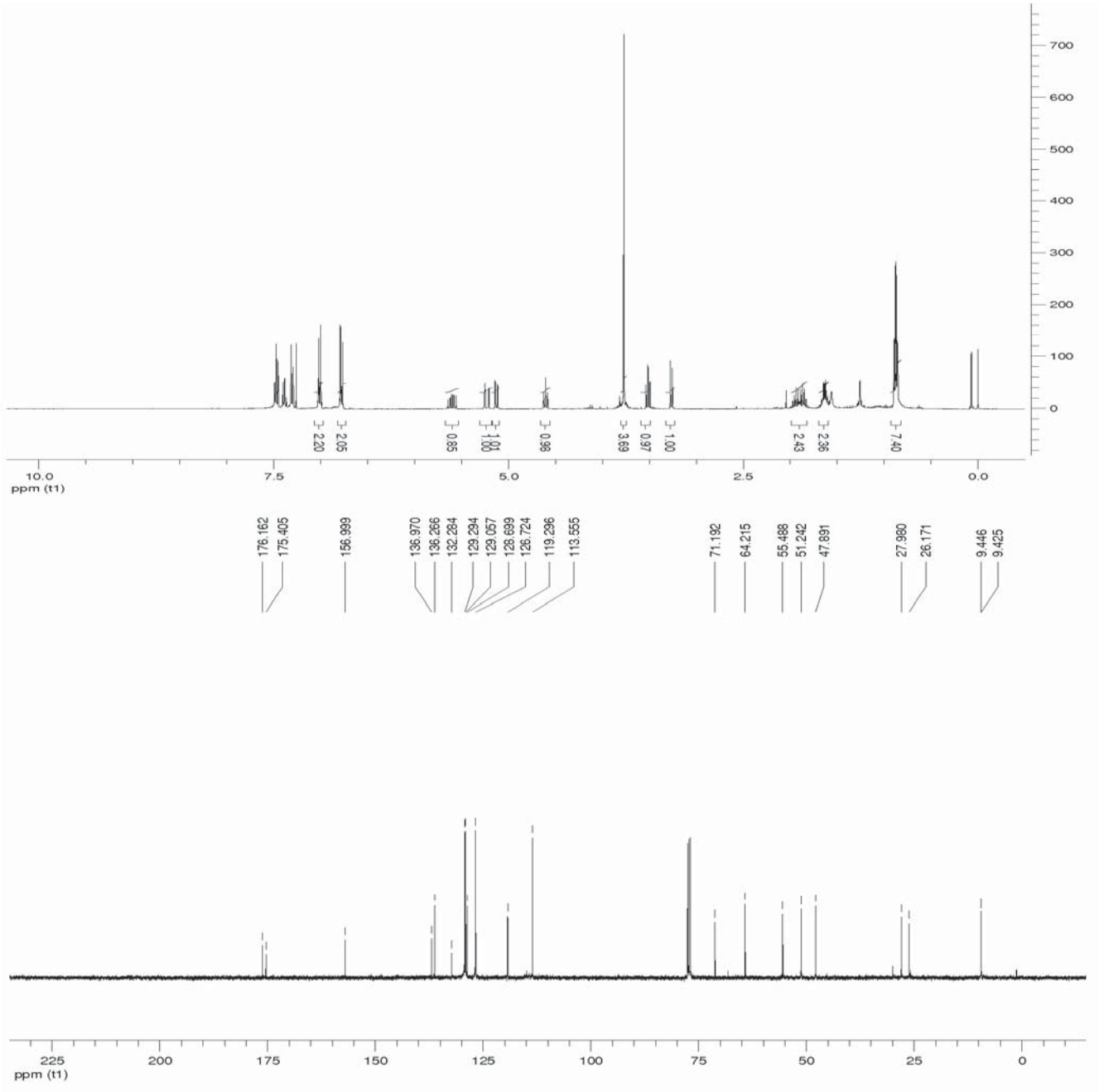
(major isomer)



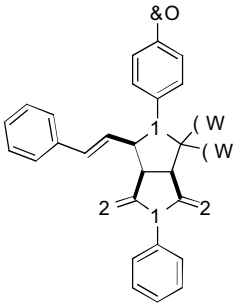


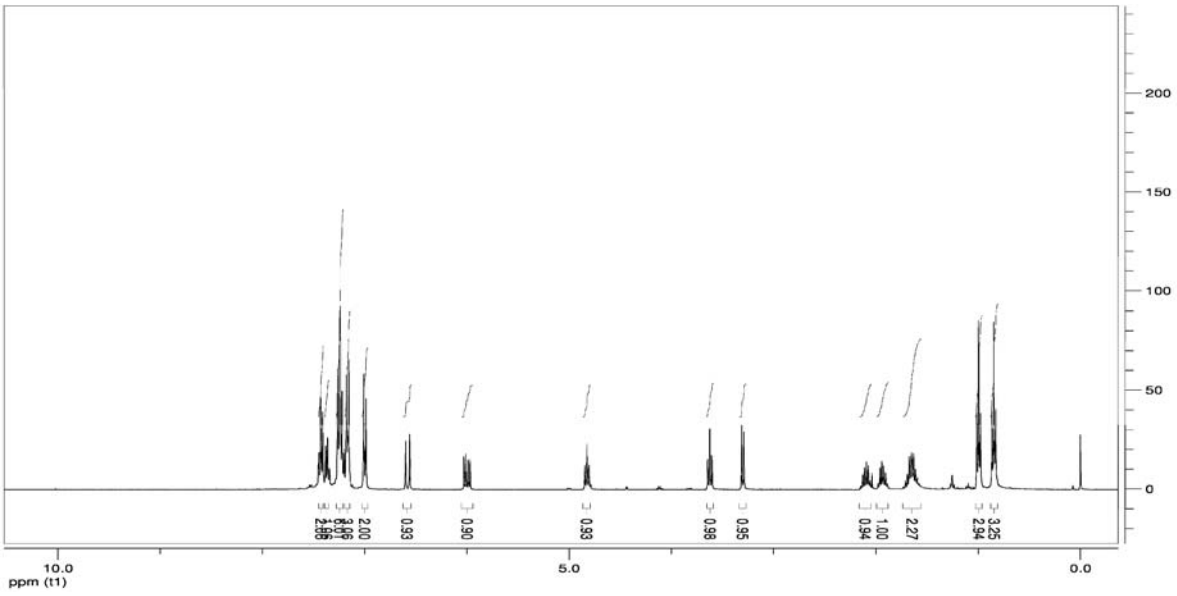


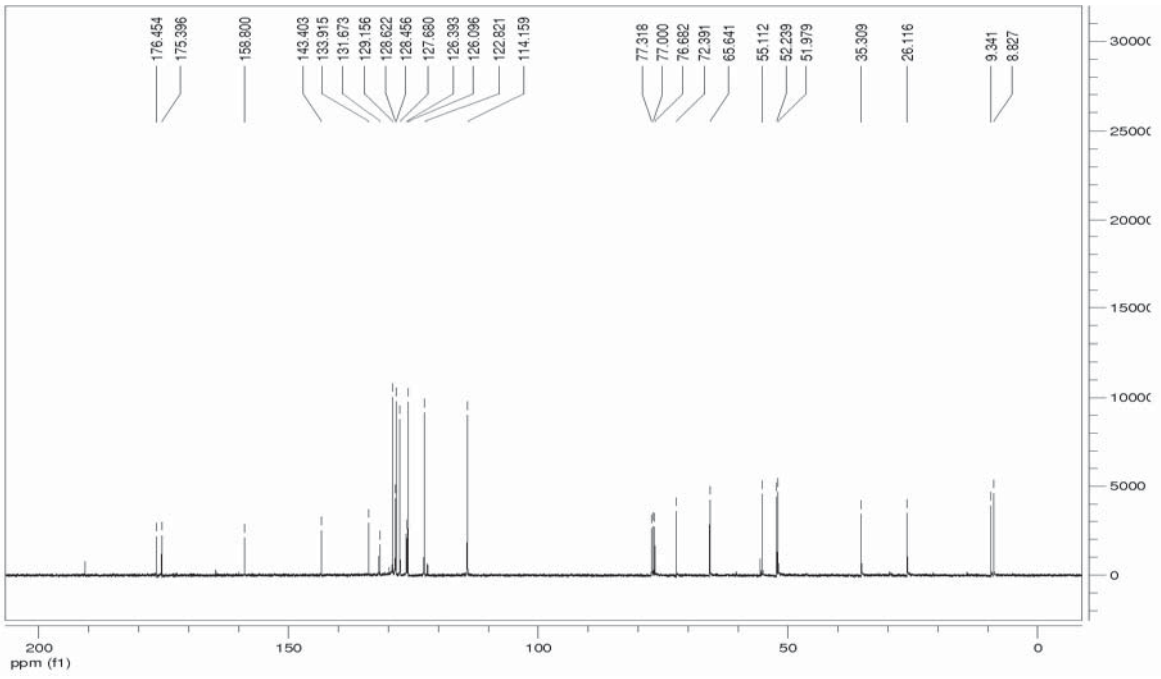
K PLQRULVRPHU



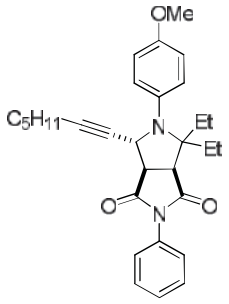
(3a*RS*,6*SR*,6a*SR*)-5-(4-chlorophenyl)-4,4-diethyl-2-phenyl-6-styryltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6i):



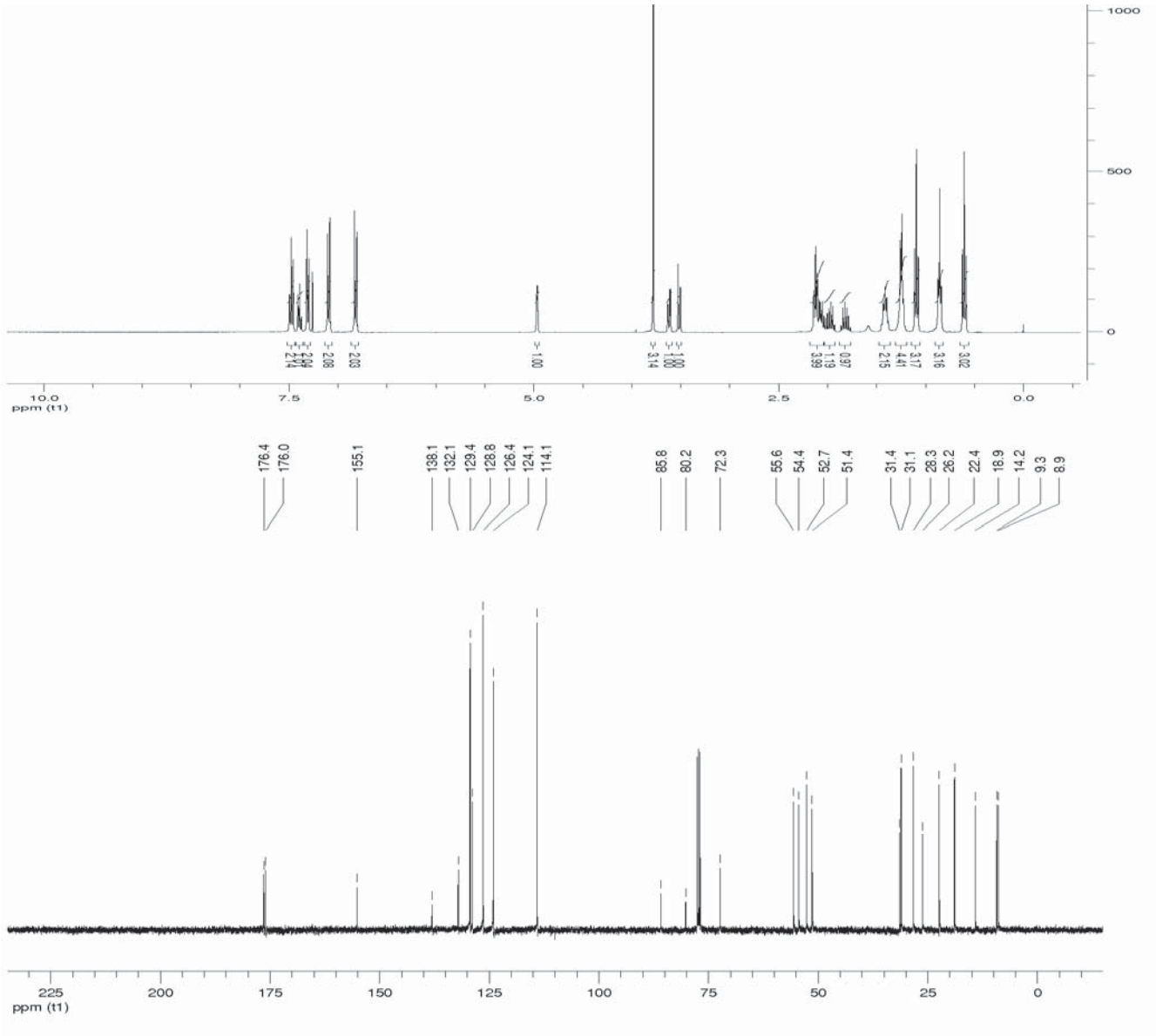


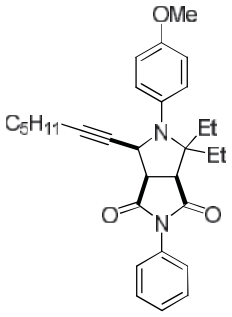


4,4-Diethyl-6-(hept-1-ynyl)-5-(4-methoxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6j):

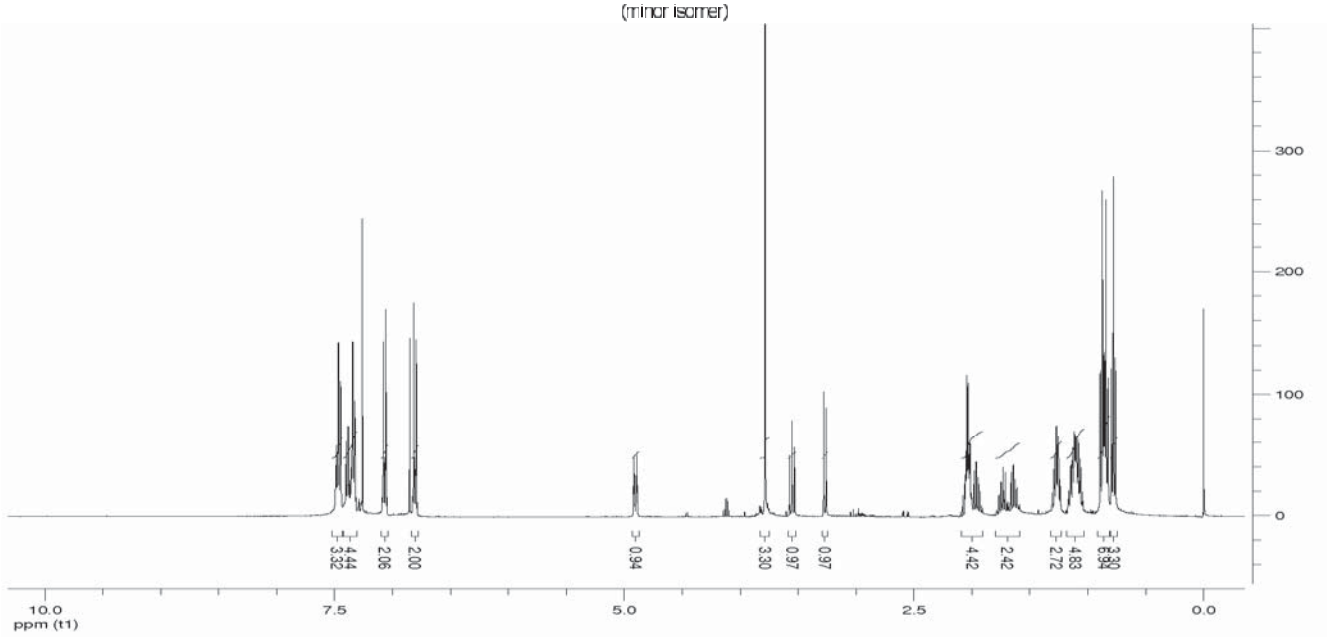


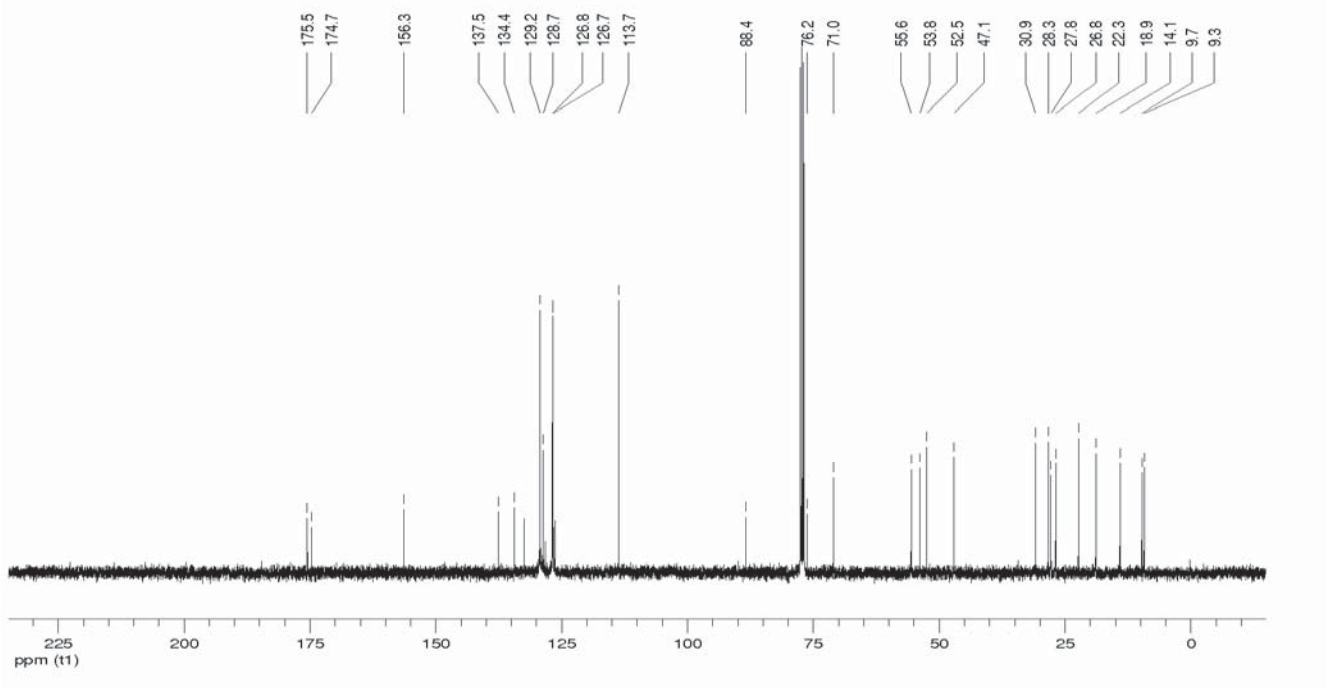
(major isomer)



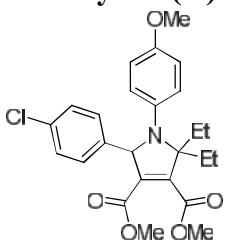


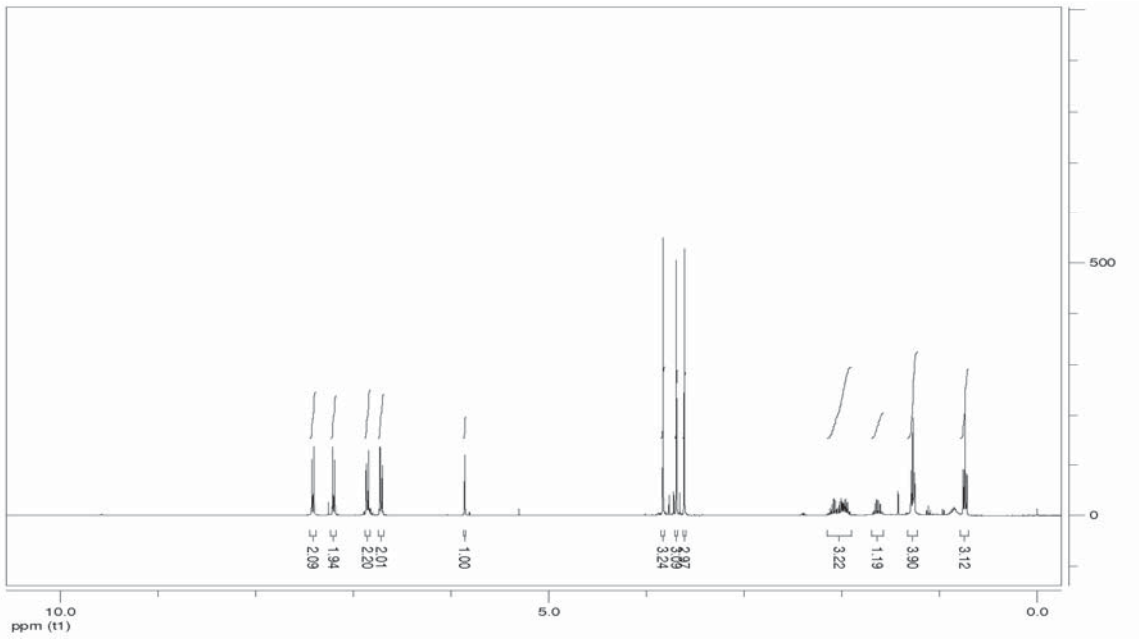
(minor isomer)

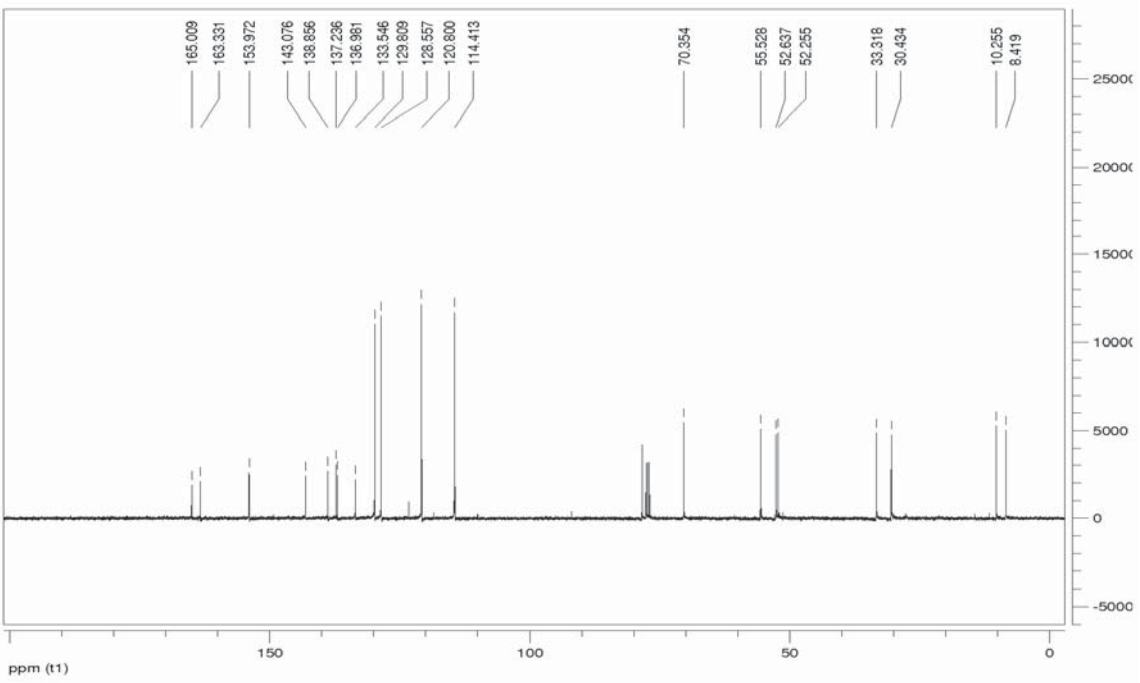




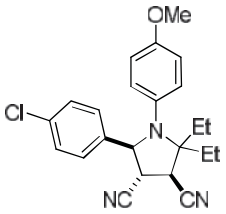
Dimethyl 5-(4-chlorophenyl)-2,2-diethyl-1-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole-3,4-dicarboxylate (6l):

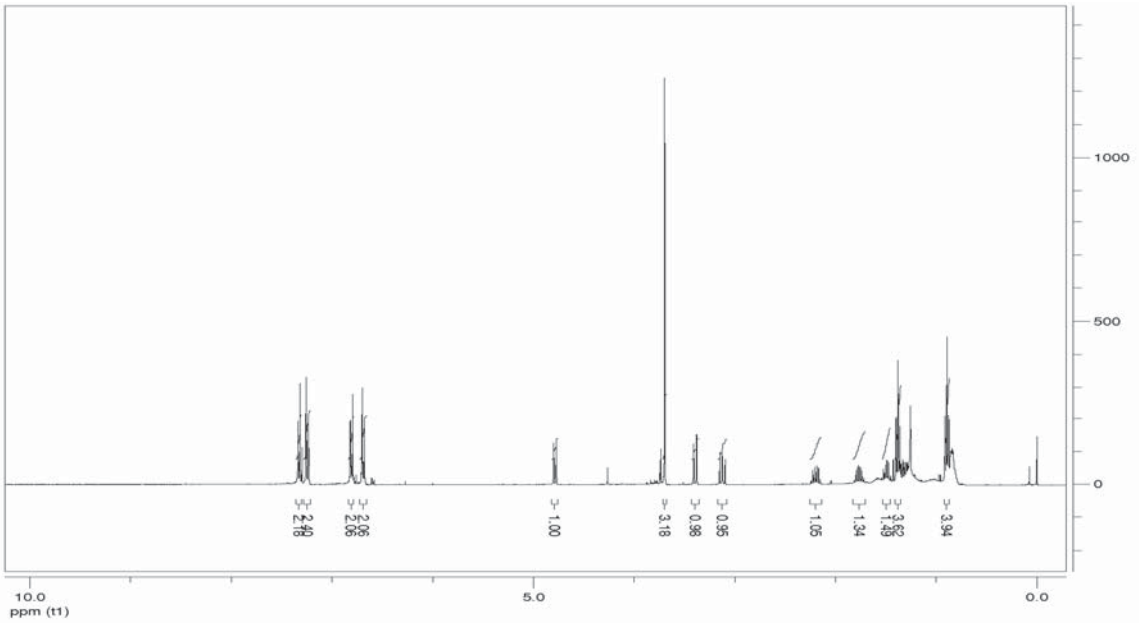


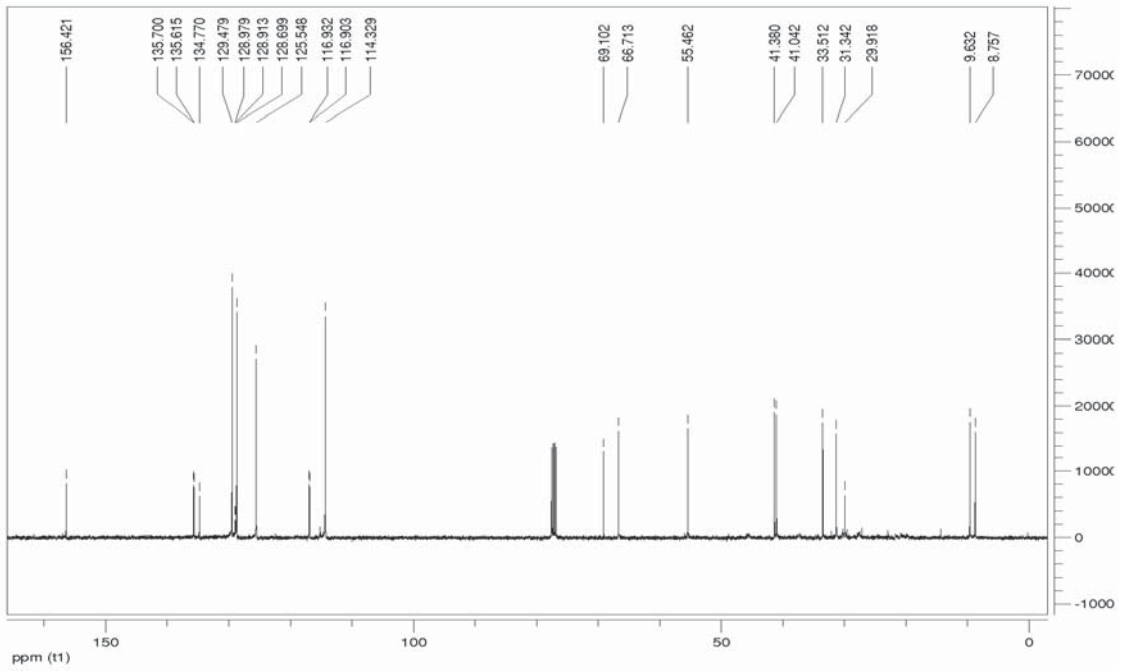




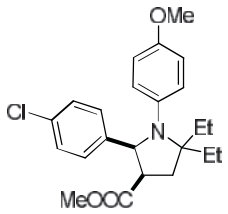
(3*RS*,4*RS*,5*RS*)-5-(4-chlorophenyl)-2,2-diethyl-1-(4-methoxyphenyl)pyrrolidine-3,4-dicarbonitrile (6n):

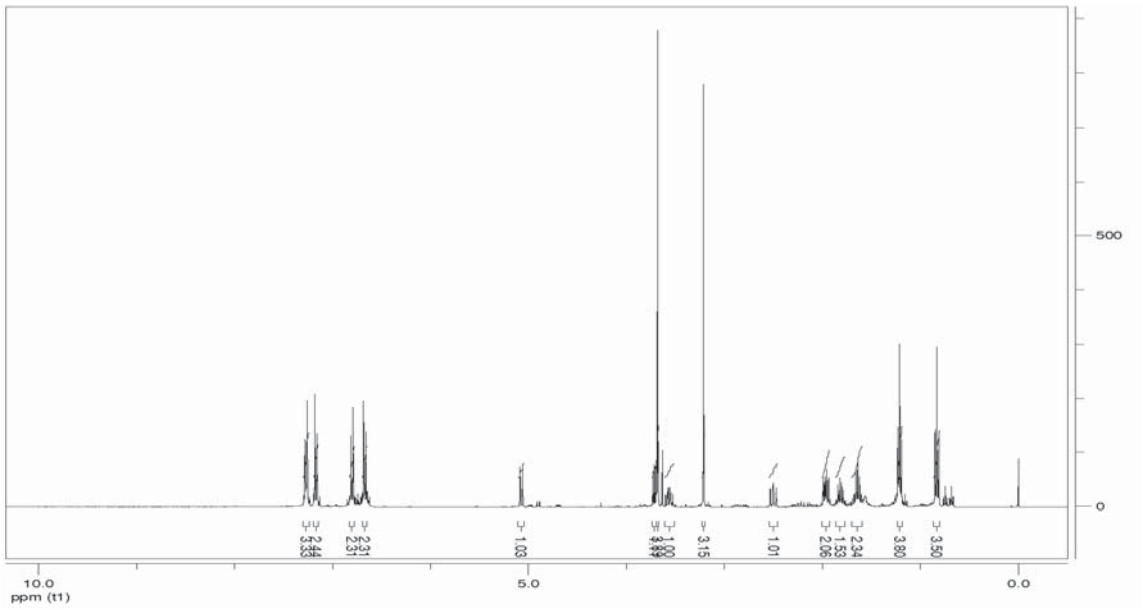


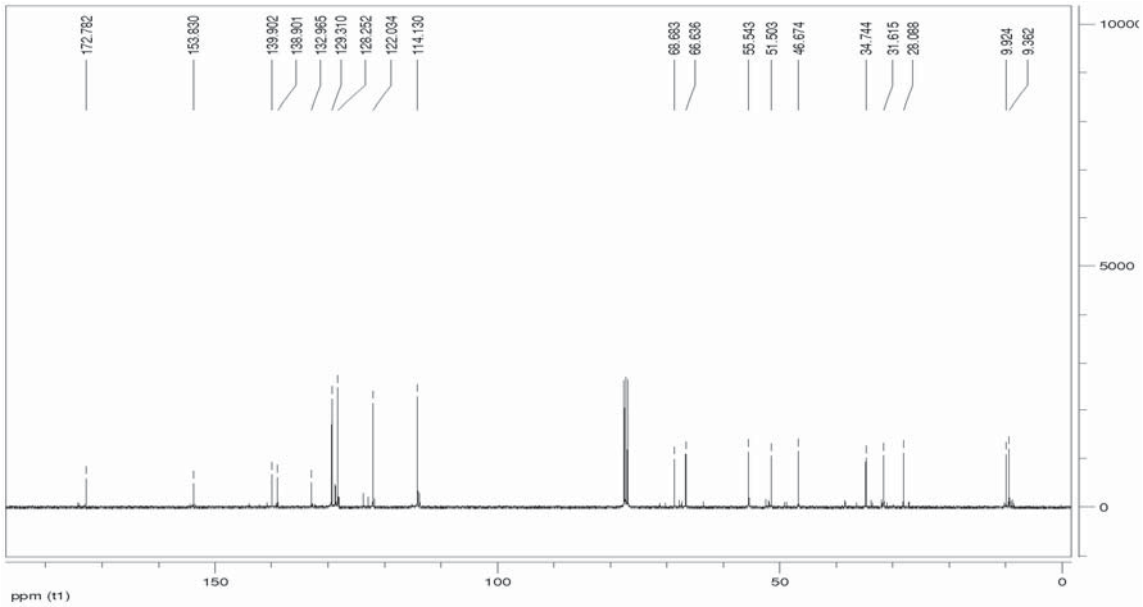




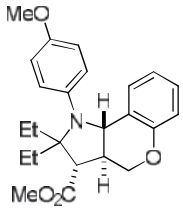
(2*RS*,3*SR*)-methyl 2-(4-chlorophenyl)-5,5-diethyl-1-(4-methoxyphenyl)pyrrolidine-3-carboxylate (6o):



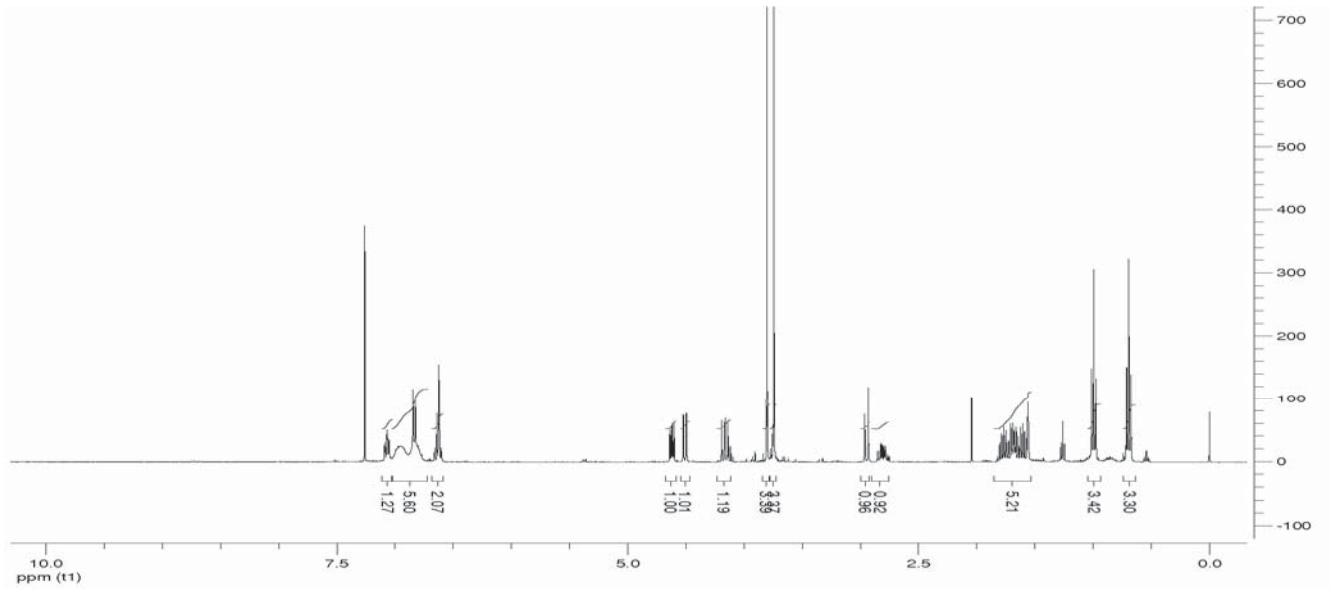


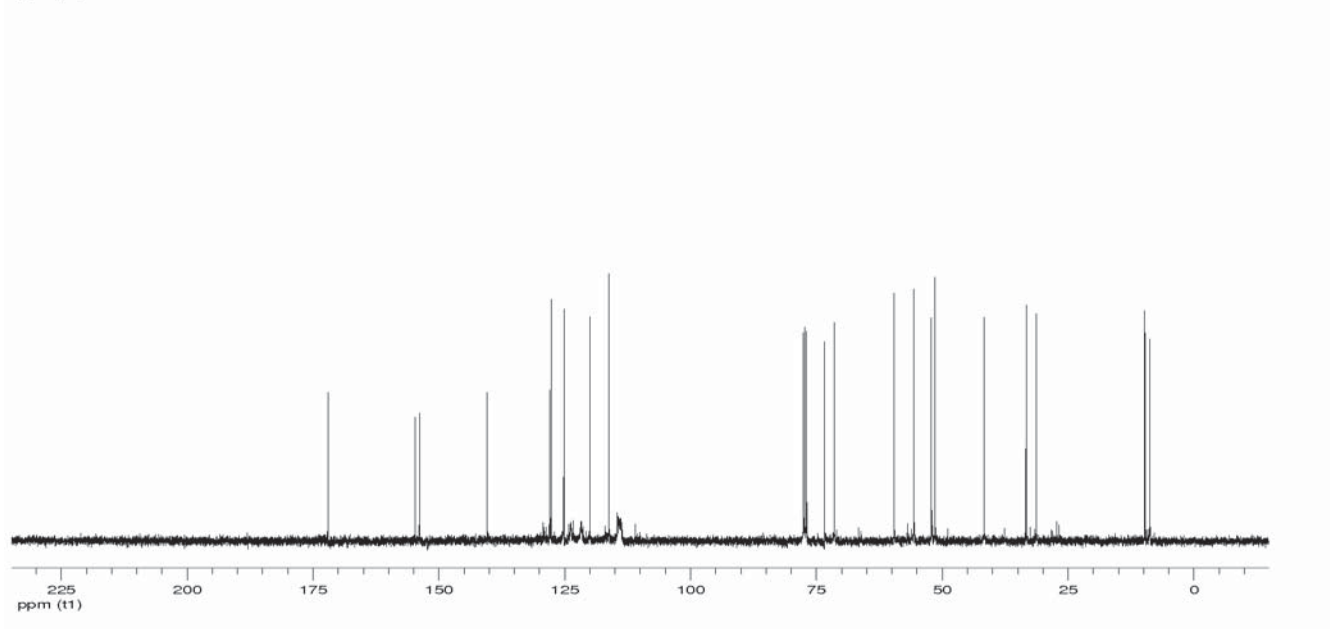


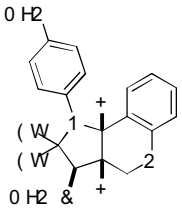
Methyl 2,2-diethyl-1-(4-methoxyphenyl)-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole-3-carboxylate (6q):



(major isomer) **6q**







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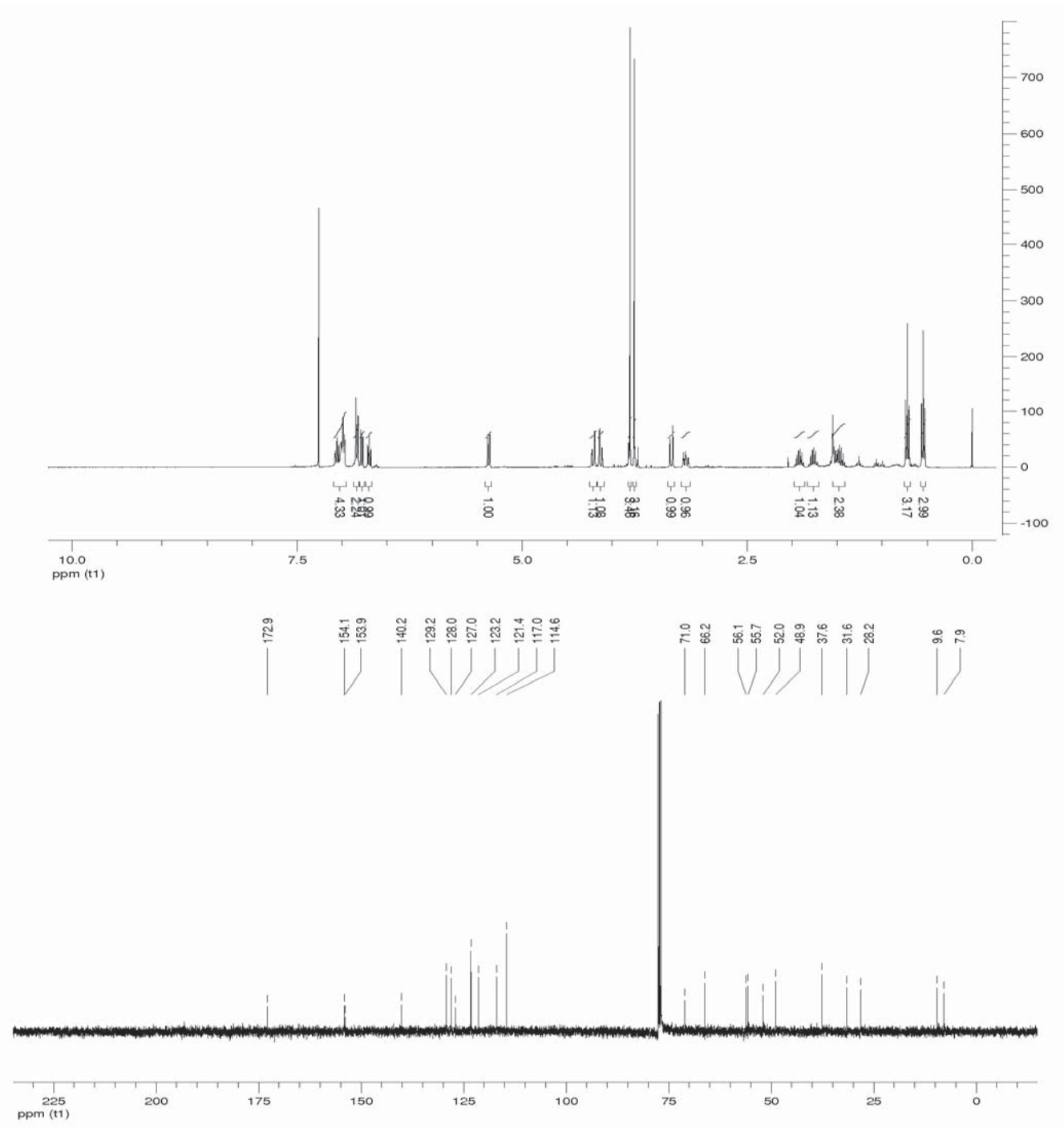
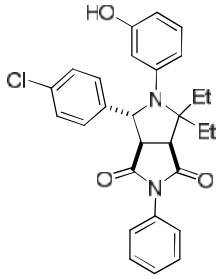
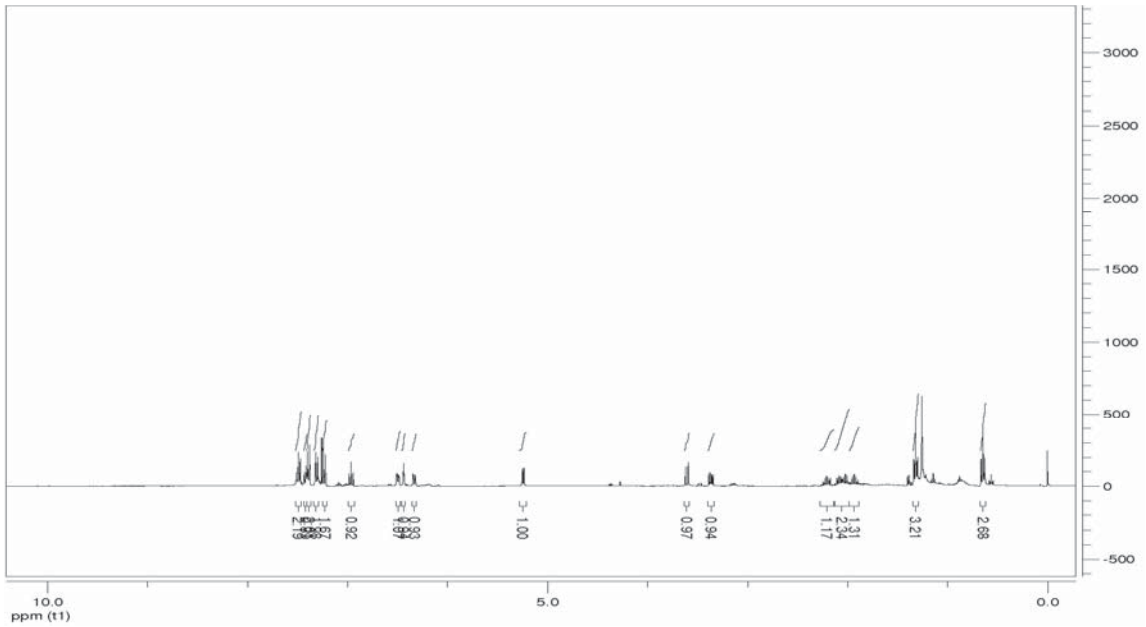
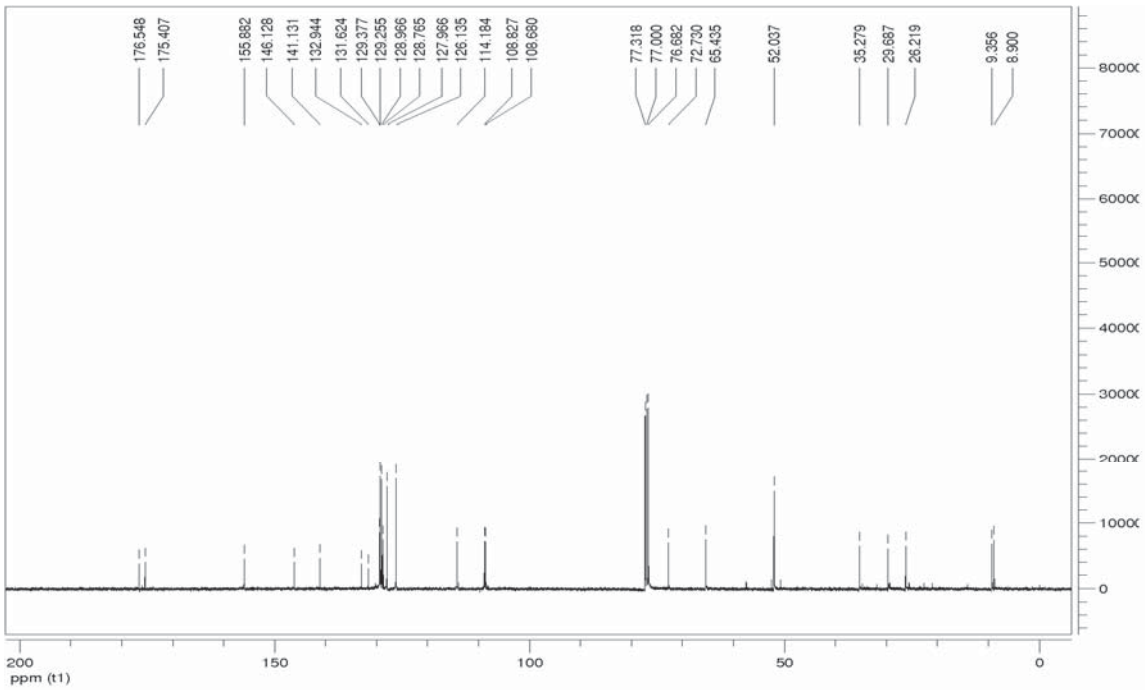


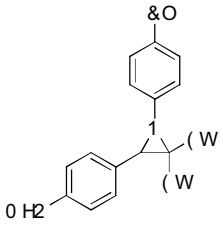
(3a*RS*,6*SR*,6a*SR*)-6-(4-chlorophenyl)-4,4-diethyl-5-(3-hydroxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6r):

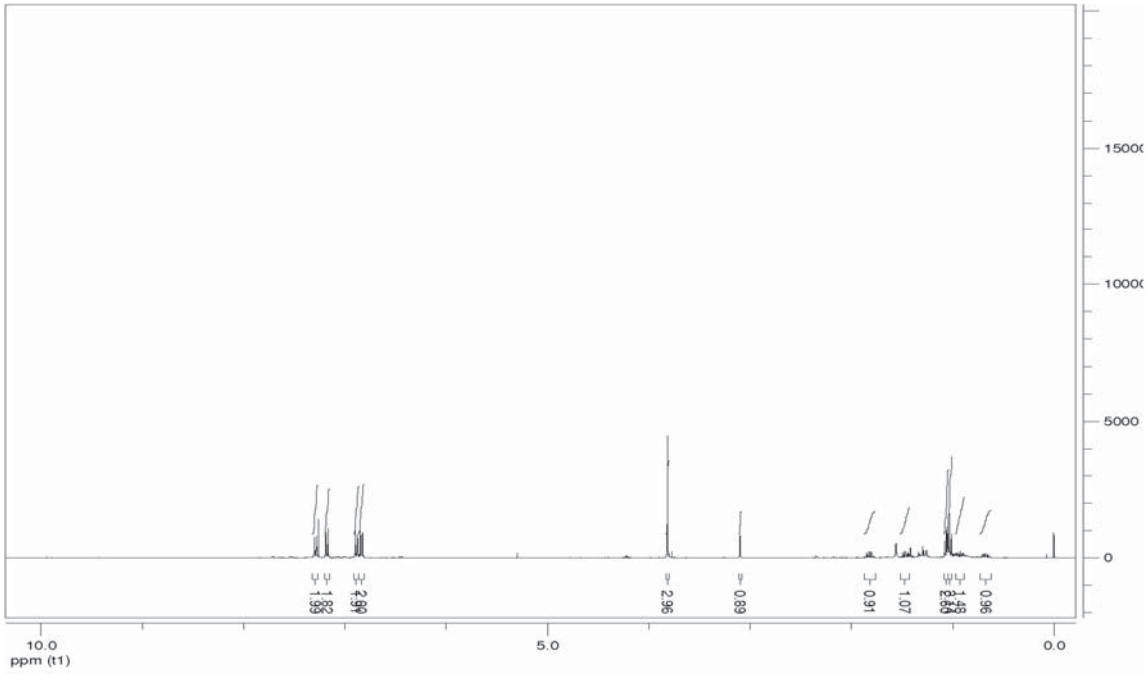


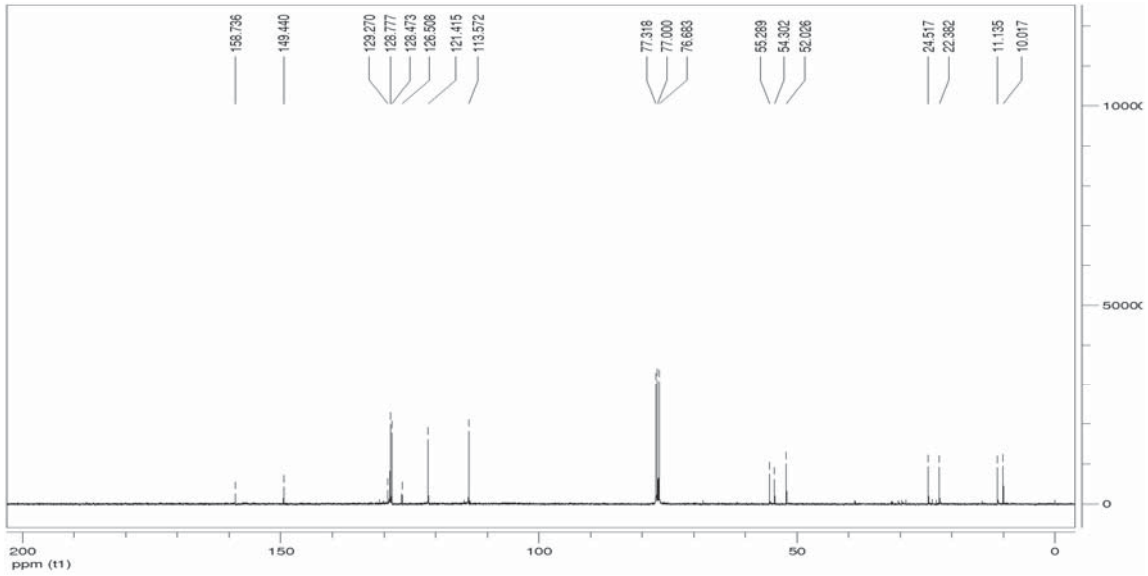




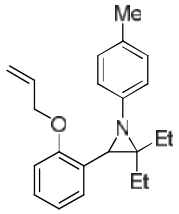
1-(4-Chlorophenyl)-2,2-diethyl-3-(4-methoxyphenyl)aziridine (7a):

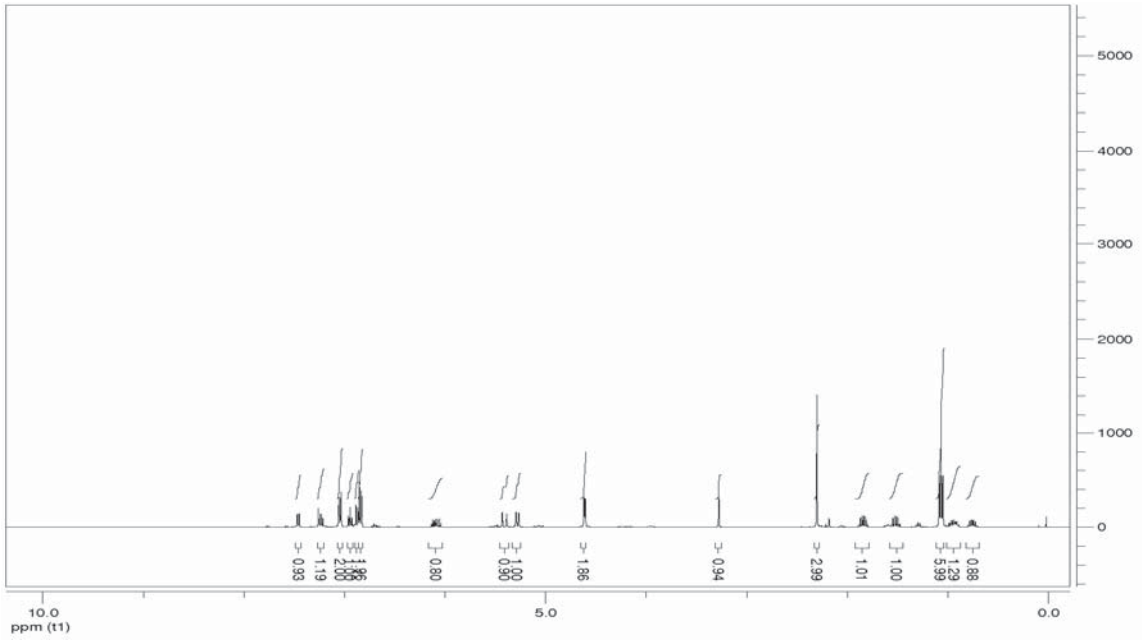


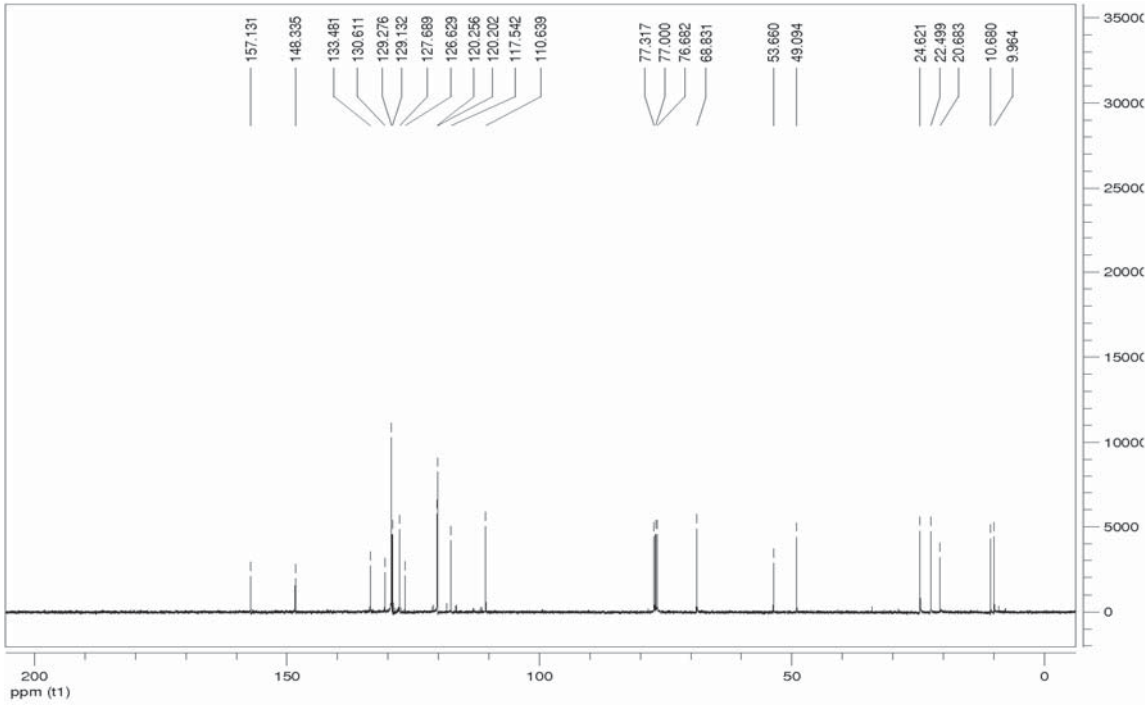




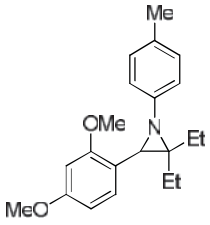
3-(2-(Allyloxy)phenyl)-2,2-diethyl-1-*p*-tolylaziridine (7b):

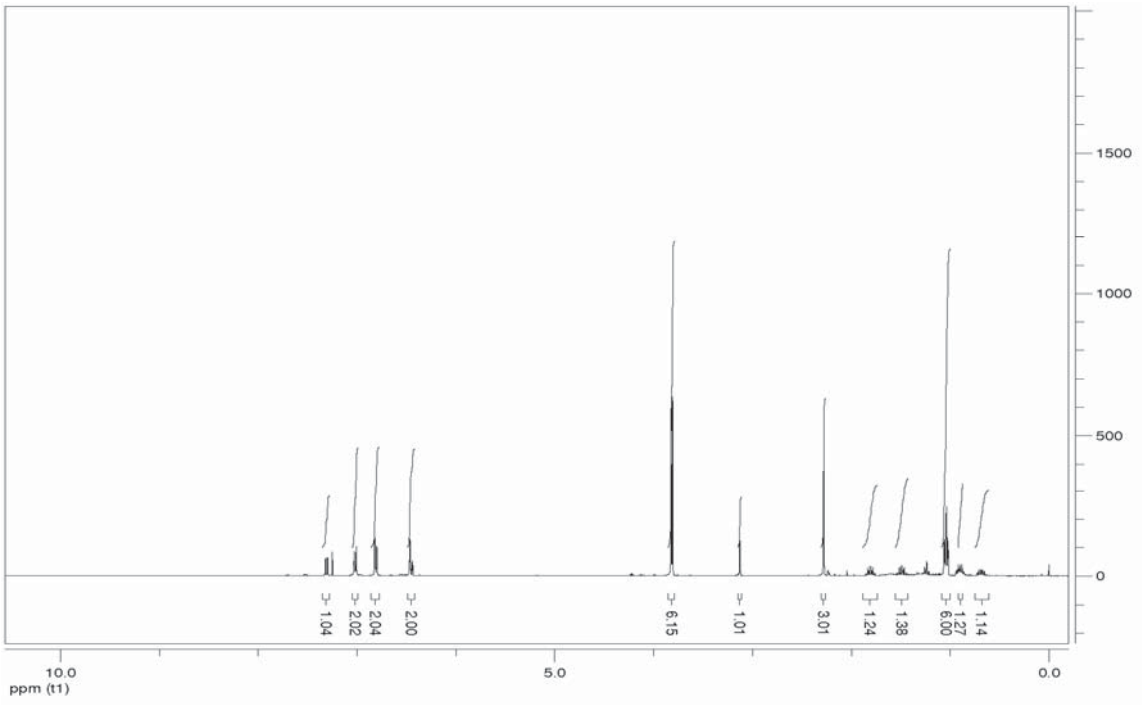


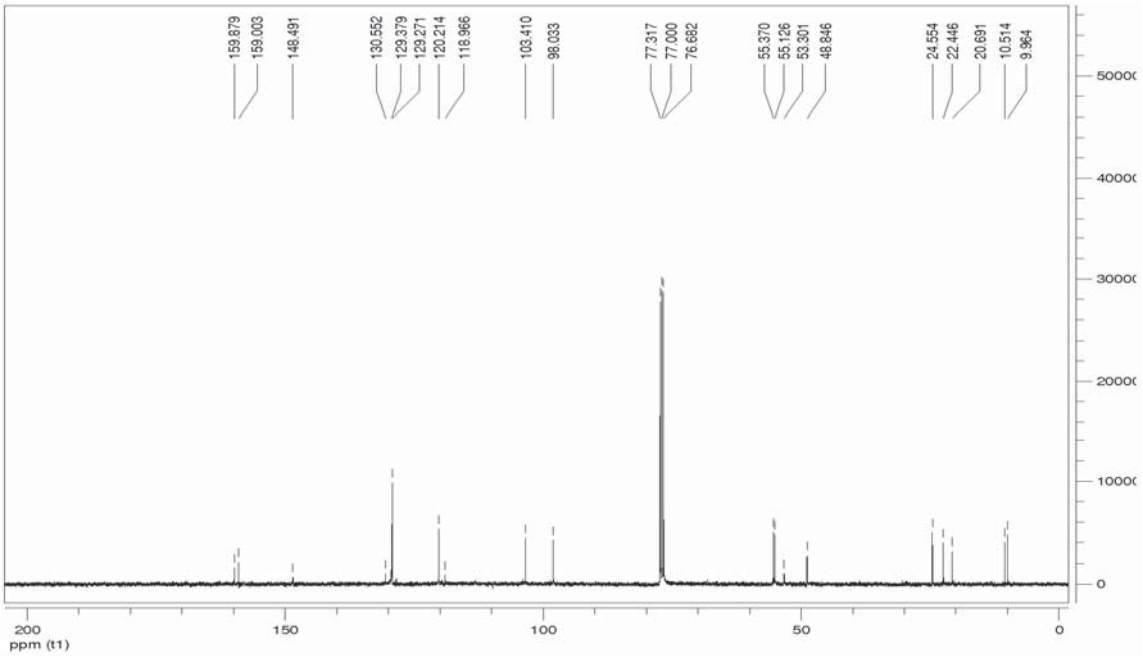




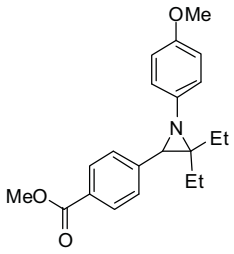
3-(2,4-Dimethoxyphenyl)-2,2-diethyl-1-*p*-tolylaziridine (7c):

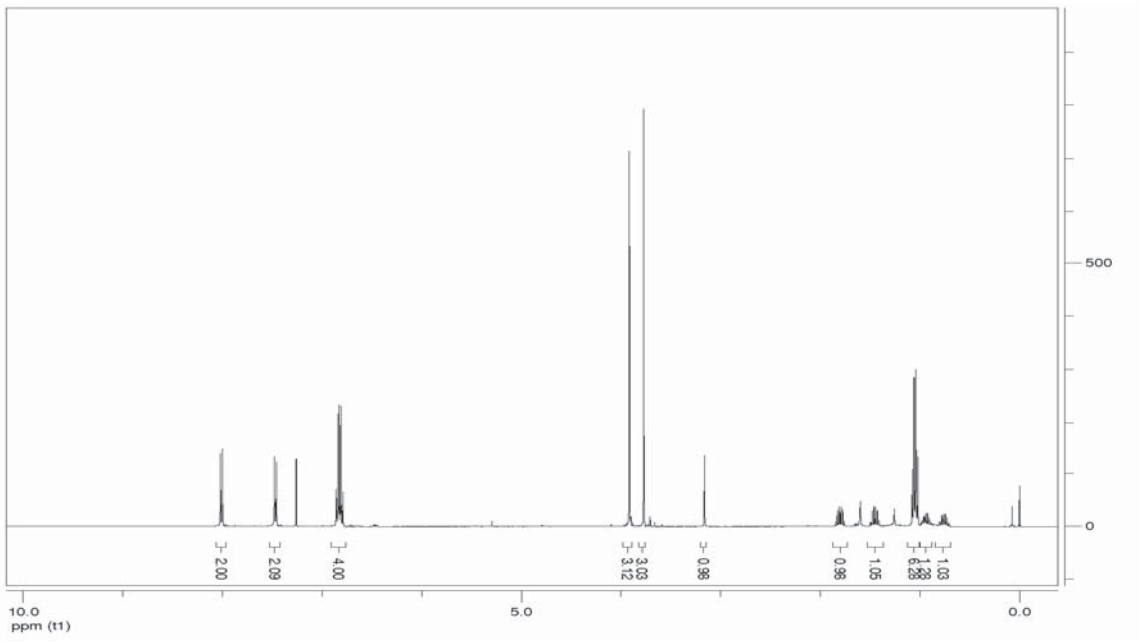


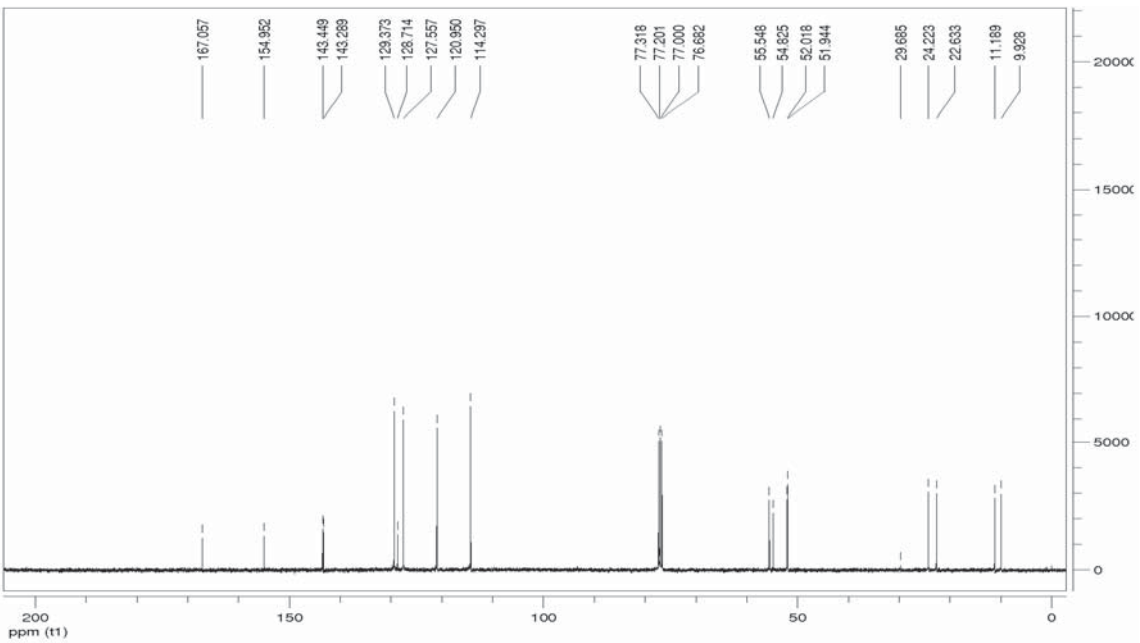




Methyl 4-(3,3-diethyl-1-(4-methoxyphenyl)aziridin-2-yl)benzoate (7d):







Computational methods: Geometrical and energetic data.

Benzaldehyde

C	-2.216809	-0.250855	0.000221
C	-1.736000	1.060550	0.000045
C	-0.361191	1.292131	-0.000265
C	0.533999	0.214578	-0.000433
C	0.045239	-1.101060	-0.000243
C	-1.326197	-1.331273	0.000071
H	-3.288200	-0.433501	0.000467
H	-2.430373	1.896077	0.000157
H	0.024875	2.309589	-0.000404
H	0.759178	-1.919149	-0.000380
H	-1.707743	-2.348620	0.000200
C	1.992223	0.468740	-0.000847
O	2.847571	-0.395875	0.000958
H	2.274107	1.545744	0.000998

Number of imaginary frequencies = 0
E(B3LYP/6-31G(d)) = -345.573441364 au

Oxazaborolidine intermediate C

C	1.544042	3.390357	0.845255
C	0.489521	2.478881	0.913325
C	0.375857	1.481065	-0.059485
C	1.313043	1.384880	-1.091602
C	2.361604	2.302529	-1.153641
C	2.479431	3.304046	-0.187489
H	1.631091	4.168121	1.598610
H	-0.246390	2.537498	1.710151
H	1.219311	0.593492	-1.827939
H	3.089230	2.231039	-1.956945
H	3.299008	4.015190	-0.238974
N	-0.701103	0.534065	0.025039
C	-1.924284	0.680819	-0.400216
B	-2.839664	-0.562530	0.102109
C	-2.360011	1.880938	-1.169784
H	-2.762987	1.545270	-2.133269
H	-3.199659	2.347617	-0.640699
H	-1.579849	2.627070	-1.342157
C	-3.693434	-1.287644	-1.071740
H	-4.196096	-2.180623	-0.676135
H	-4.483139	-0.639266	-1.478512
H	-3.075042	-1.620886	-1.918033
C	-3.769094	-0.028647	1.347060
H	-3.207418	0.463854	2.155589
H	-4.550792	0.673840	1.023614
H	-4.283301	-0.887918	1.798229
H	1.800715	-3.840157	-1.793565
C	1.827022	-3.137432	-0.964653
C	3.015746	-2.935653	-0.257301
C	0.669991	-2.449209	-0.601929
C	3.041238	-2.047186	0.818660
H	3.915527	-3.477147	-0.537821
C	0.693675	-1.548589	0.469114
H	-0.268765	-2.617103	-1.120095
C	1.881948	-1.358501	1.180535
H	3.959195	-1.895405	1.380372
C	-0.567071	-0.794437	0.847286
H	1.899905	-0.672732	2.024866
O	-1.706054	-1.470585	0.577062
H	-0.481420	-0.430165	1.890024

Number of imaginary frequencies = 0

E(B3LYP/6-31G(d)) = -814.714224109 au

Azomethine ylide D-*cis*

C	1.328597	-2.482354	1.295906
C	0.963338	-1.136872	1.264046
C	1.223602	-0.384232	0.119709
C	1.843361	-0.961215	-0.989683
C	2.205985	-2.307788	-0.950784
C	1.949113	-3.070060	0.191003
H	1.129105	-3.071372	2.186608
H	0.472032	-0.664165	2.108099
H	2.025724	-0.353334	-1.870751
H	2.681406	-2.762053	-1.815642
H	2.228992	-4.119480	0.218589
N	0.845514	1.018432	0.087208
C	1.807246	1.940759	-0.169334
C	3.251506	1.706386	0.168902
H	3.901818	2.074982	-0.635957
H	3.541470	2.264779	1.076434
H	3.492227	0.656954	0.344341
H	-3.022156	-2.021051	-1.621160
C	-2.981795	-1.154876	-0.964237
C	-4.148173	-0.692223	-0.350928
C	-1.760605	-0.516187	-0.766232
C	-4.070722	0.438849	0.468706
H	-5.097561	-1.194151	-0.514948
C	-1.653906	0.616165	0.079306
H	-0.885840	-0.888934	-1.286265
C	-2.855618	1.076878	0.678968
H	-4.966232	0.825020	0.950369
C	-0.453989	1.363588	0.359044
H	-2.814237	1.951166	1.325554
H	-0.572789	2.362851	0.755628
C	1.379641	3.339331	-0.466038
H	1.147958	3.936933	0.434407
H	2.182687	3.870704	-0.991492
H	0.471319	3.345226	-1.084399

Number of imaginary frequencies = 0
E(B3LYP/6-31G(d)) = -674.629898908 au

Azomethine ylide D-*trans*

N	0.515014	0.409490	-0.247376
C	0.346728	1.749427	-0.111925
C	1.170460	2.548874	0.857116
C	-0.783709	2.412034	-0.812104
H	1.598562	3.439434	0.376161
H	1.987364	1.974287	1.297942
H	0.545894	2.921871	1.686135
H	-0.537414	3.466074	-0.990424
H	-1.742994	2.388801	-0.262701
H	-0.982543	1.908000	-1.767747
C	-0.460216	-0.469997	-0.651488
H	-4.131029	0.760539	1.963269
C	-3.746302	0.176249	1.130241
C	-4.594627	-0.684607	0.433687
H	-5.643183	-0.768557	0.704756
C	-4.067770	-1.439722	-0.622541
H	-4.710061	-2.120750	-1.176348
C	-2.731148	-1.327893	-0.975079
C	-1.848248	-0.451395	-0.287802
C	-2.404006	0.305964	0.776515
H	-1.761148	0.950036	1.368497

H	1.126366	-1.682710	1.269430
C	1.992142	-1.281356	0.752410
C	3.255880	-1.854881	0.897376
H	3.383401	-2.718195	1.544420
C	4.352395	-1.319346	0.218030
H	5.334512	-1.770485	0.329674
C	4.184538	-0.207600	-0.611149
H	5.032064	0.200972	-1.154440
C	2.924652	0.372205	-0.758618
H	2.770529	1.226620	-1.410710
C	1.835345	-0.164250	-0.069138
H	-2.338872	-1.923861	-1.796422
H	-0.093218	-1.300744	-1.243051

Number of imaginary frequencies = 0
E(B3LYP/6-31G(d)) = -674.631432698 au

Transition state TS *trans*-5 (starting from D-*cis*)

N	-0.064541	-1.313878	0.360388
C	-0.241367	-1.722780	1.617064
C	0.548568	-2.863775	2.194601
C	-1.425738	-1.321663	2.443119
H	1.181475	-2.470845	2.999889
H	1.185376	-3.376481	1.475000
H	-0.132846	-3.593469	2.649113
H	-1.107864	-1.243151	3.485799
H	-2.199052	-2.101965	2.382568
H	-1.874690	-0.381492	2.137818
C	-0.644758	-0.118739	-0.154578
H	-5.004935	-1.841010	-0.463174
C	-4.341626	-0.989545	-0.596213
C	-4.841655	0.214922	-1.091536
H	-5.895286	0.316409	-1.336174
C	-3.961462	1.283435	-1.283725
H	-4.328042	2.224732	-1.686112
C	-2.611816	1.153993	-0.969735
C	-2.091930	-0.047602	-0.442653
C	-2.989262	-1.121954	-0.281513
H	-2.620080	-2.081844	0.066440
H	-0.156009	-2.690930	-1.899994
C	0.861614	-2.490894	-1.578061
C	1.952859	-2.923650	-2.331876
H	1.785026	-3.475845	-3.252208
C	3.254199	-2.646054	-1.906284
H	4.101812	-2.980995	-2.497641
C	3.464424	-1.932870	-0.724362
H	4.475198	-1.707888	-0.395566
C	2.379546	-1.497219	0.037967
H	2.507369	-0.932718	0.955334
C	1.084721	-1.787146	-0.393805
C	0.135296	3.333115	0.189521
C	0.813196	4.344016	-0.491622
C	2.195341	4.259688	-0.673166
C	2.890633	3.164426	-0.153787
C	2.210117	2.156566	0.527569
C	0.819452	2.215077	0.689142
C	0.073912	1.156241	1.455171
O	0.684870	0.351542	2.224250
H	0.264705	5.202808	-0.870901
H	2.727711	5.046914	-1.200637
H	3.969988	3.102299	-0.271409
H	2.750529	1.322033	0.960609
H	-0.937093	3.415115	0.352605

H	-1.938055	1.988091	-1.141660
H	-0.946509	1.492476	1.725609
H	-0.041488	0.247018	-0.979434

Number of imaginary frequencies = 1
E(B3LYP/6-31G(d)) = -1020.19668831 au

Transition state TS *cis*-5 (starting from D-*cis*)

N	-1.371653	0.251080	0.476193
C	-1.179187	-0.126822	1.745134
C	-2.328340	-0.541259	2.619811
C	0.085595	0.187245	2.484725
H	-2.180266	-1.591491	2.898457
H	-3.304448	-0.445555	2.145608
H	-2.324905	0.046316	3.546193
H	0.221172	-0.559873	3.270817
H	0.005286	1.172952	2.966938
H	0.965805	0.197003	1.847673
C	-0.284749	0.412593	-0.429914
H	0.982518	4.576001	1.323286
C	1.205631	3.766929	0.631743
C	2.313805	3.852221	-0.211440
H	2.968816	4.718402	-0.175513
C	2.559953	2.813476	-1.112392
H	3.412131	2.867022	-1.785369
C	1.722270	1.702338	-1.159210
C	0.612886	1.586005	-0.298433
C	0.364976	2.655347	0.585146
H	-0.514572	2.629654	1.221196
H	-3.069972	2.026204	-0.513608
C	-3.405627	1.004342	-0.663673
C	-4.597236	0.730213	-1.335780
H	-5.204435	1.549791	-1.709727
C	-5.005088	-0.591787	-1.529093
H	-5.931770	-0.802353	-2.055808
C	-4.219458	-1.641569	-1.048656
H	-4.531833	-2.670733	-1.202967
C	-3.027567	-1.379486	-0.370714
H	-2.393954	-2.171989	0.016651
C	-2.634114	-0.052680	-0.178691
C	2.460450	-1.674693	-1.516271
C	3.846425	-1.757906	-1.644962
C	4.649599	-1.850961	-0.505784
C	4.052099	-1.874469	0.757046
C	2.665864	-1.795735	0.881814
C	1.851739	-1.675480	-0.252758
C	0.357501	-1.657052	-0.137666
O	-0.222919	-2.002216	0.945069
H	4.299760	-1.758348	-2.633287
H	5.730162	-1.917476	-0.602095
H	4.669371	-1.967436	1.647430
H	2.192190	-1.857717	1.856187
H	1.835906	-1.620625	-2.406951
H	1.932276	0.906236	-1.865117
H	-0.644984	0.302085	-1.449198
H	-0.133896	-1.912774	-1.094582

Number of imaginary frequencies = 1
E(B3LYP/6-31G(d)) = -1020.19638671 au

Transition state TS *cis*-5 (starting from D-*trans*)

N	1.568043	-0.048945	-0.844697
C	2.344418	-1.017801	-1.348270
C	3.557887	-1.530220	-0.629486

C	2.320265	-1.342142	-2.819618
H	3.478066	-2.622620	-0.573805
H	3.681043	-1.142096	0.379655
H	4.465491	-1.300357	-1.204795
H	1.322364	-1.455519	-3.237071
H	2.850123	-2.283083	-2.984323
H	2.848477	-0.554638	-3.380899
C	0.323887	0.229979	-1.452868
H	0.413148	0.174819	-2.530734
H	-2.346677	3.797147	-2.636769
C	-1.977730	3.184604	-1.817749
C	-2.395350	3.433930	-0.509084
H	-3.094356	4.238615	-0.297286
C	-1.912360	2.626317	0.522009
H	-2.245118	2.792525	1.543520
C	-1.021881	1.586907	0.259678
C	-0.559619	1.338520	-1.050000
C	-1.074712	2.157172	-2.078986
H	-0.747848	1.984541	-3.102419
H	2.532936	2.337094	-0.238822
C	2.341276	1.732310	0.641977
C	2.590752	2.229970	1.921790
H	2.988590	3.233875	2.039690
C	2.328604	1.441713	3.043883
H	2.522491	1.831505	4.039316
C	1.816014	0.151873	2.885484
H	1.609387	-0.464432	3.755962
C	1.560637	-0.351824	1.609468
H	1.158386	-1.346510	1.458698
C	1.826384	0.445165	0.495467
C	-1.349056	-2.470859	1.014002
C	-2.383176	-2.476618	1.948843
C	-3.588545	-1.827826	1.667853
C	-3.752694	-1.181624	0.440142
C	-2.716285	-1.174221	-0.492113
C	-1.495113	-1.805480	-0.212874
O	0.677484	-2.488441	-1.000420
H	-2.256574	-3.003211	2.892046
H	-4.397407	-1.836178	2.394041
H	-4.689503	-0.680733	0.209104
H	-2.849350	-0.668565	-1.445436
H	-0.426150	-3.012321	1.199314
H	-0.699998	0.954790	1.077551
C	-0.404245	-1.863569	-1.234447
H	-0.789848	-1.822165	-2.270909

Number of imaginary frequencies = 1
E(B3LYP/6-31G(d)) = -1020.19659688 au

Transition state TS *trans*-5 (starting from D-*trans*)

N	-0.961319	-0.939215	0.787526
C	-0.665120	-2.206172	1.081530
C	-1.660417	-3.319054	0.940475
C	0.565854	-2.535097	1.880746
H	-1.256089	-4.058138	0.237110
H	-2.637461	-3.002662	0.579126
H	-1.791682	-3.828520	1.904520
H	0.686269	-3.620072	1.929505
H	0.455217	-2.163565	2.912549
H	1.479727	-2.117920	1.463670
C	0.070294	0.024774	0.722803
H	0.822330	-0.172669	1.476550
H	0.971614	4.359940	2.020919

C	0.438018	3.725856	1.317282
C	-0.320347	4.295232	0.293299
H	-0.384072	5.374974	0.188942
C	-0.988055	3.457148	-0.602060
H	-1.570366	3.884216	-1.414830
C	-0.907064	2.071160	-0.479294
C	-0.166278	1.474461	0.563290
C	0.510964	2.340812	1.447569
H	1.104002	1.912098	2.251967
H	-3.052321	0.326450	1.835795
C	-3.218539	0.023624	0.806730
C	-4.419974	0.313560	0.157431
H	-5.204727	0.842753	0.690446
C	-4.609715	-0.072099	-1.170958
H	-5.545413	0.156543	-1.673706
C	-3.598053	-0.753955	-1.852716
H	-3.746053	-1.058338	-2.885169
C	-2.392657	-1.048983	-1.214192
H	-1.585360	-1.585787	-1.705220
C	-2.217185	-0.653078	0.113946
C	3.361119	-1.585784	-0.437105
C	4.714520	-1.313475	-0.240920
C	5.193231	-0.006244	-0.361952
C	4.308278	1.023665	-0.691377
C	2.954666	0.750314	-0.887794
C	2.462454	-0.555748	-0.748988
C	1.010185	-0.869861	-0.986573
O	0.593959	-2.069617	-0.978401
H	5.400701	-2.123645	-0.004988
H	6.248702	0.206563	-0.212308
H	4.674242	2.041883	-0.799284
H	2.271531	1.553888	-1.150855
H	0.518273	-0.134593	-1.651169
H	2.977693	-2.600169	-0.378289
H	-1.416276	1.451881	-1.207803

Number of imaginary frequencies = 1
E(B3LYP/6-31G(d)) = -1020.20218834 au

Oxazolidine *trans*-5

C	3.633262	0.728941	-2.028472
C	2.408699	0.434837	-1.428941
C	2.343489	-0.363206	-0.269626
C	3.560941	-0.832404	0.266444
C	4.776086	-0.546369	-0.349448
C	4.827078	0.236685	-1.504086
H	3.644677	1.349204	-2.921339
H	1.504625	0.840557	-1.865804
H	3.560699	-1.411192	1.182449
H	5.693334	-0.929258	0.091261
H	5.777573	0.466502	-1.976684
N	1.117290	-0.647477	0.362980
C	0.784102	-2.007085	0.894407
C	1.116898	-2.131693	2.389399
H	0.633017	-1.328873	2.953753
H	0.753558	-3.093105	2.767247
H	2.192889	-2.073065	2.575937
H	0.830782	3.854871	2.445301
C	0.342043	3.432938	1.570832
C	-0.387004	4.257583	0.711186
C	0.453434	2.067552	1.308809
C	-1.001755	3.707245	-0.414277
H	-0.469998	5.322040	0.914088

C	-0.160639	1.506528	0.182232
H	1.034667	1.428565	1.966922
C	-0.886283	2.341166	-0.676683
H	-1.567788	4.340546	-1.092414
C	-0.109041	0.012620	-0.085793
H	-1.366604	1.917478	-1.555746
C	-1.181078	-0.779999	0.707833
H	-1.243159	-0.361471	1.723857
C	-2.556569	-0.796538	0.084552
C	-3.532561	0.109418	0.514170
C	-2.863829	-1.689456	-0.949841
C	-4.792218	0.133003	-0.086991
H	-3.305357	0.799820	1.322651
C	-4.124490	-1.671385	-1.545645
H	-2.114544	-2.407963	-1.266266
C	-5.091281	-0.757854	-1.118564
H	-5.540726	0.842071	0.256667
H	-4.354181	-2.374211	-2.342387
H	-6.073832	-0.745562	-1.582967
C	1.360137	-3.163206	0.073471
H	0.904242	-4.096324	0.418484
H	1.119773	-3.028336	-0.985107
H	2.443778	-3.246284	0.177280
O	-0.637374	-2.093102	0.742499
H	-0.295991	-0.164775	-1.157853

Number of imaginary frequencies = 0
E(B3LYP/6-31G(d)) = -1020.27141465 au

Oxazolidine *cis*-5

C	4.103095	1.382438	-0.373123
C	2.874775	0.800570	-0.689858
C	2.271609	-0.120013	0.182619
C	2.928866	-0.420693	1.388387
C	4.165148	0.146569	1.690229
C	4.761642	1.052565	0.810854
H	4.546494	2.096374	-1.062618
H	2.384802	1.076501	-1.616922
H	2.448246	-1.082640	2.100178
H	4.652197	-0.104033	2.629171
H	5.718564	1.506255	1.053253
N	1.009222	-0.730151	-0.087772
C	0.979323	-2.165074	-0.479087
C	1.287137	-3.115389	0.676649
H	0.700598	-2.844520	1.558840
H	1.020229	-4.133567	0.376664
H	2.349682	-3.101409	0.933636
H	-1.158266	3.038388	2.321695
C	-1.009432	2.841739	1.263131
C	-1.258854	3.845621	0.324382
C	-0.569640	1.584920	0.851082
C	-1.058816	3.585725	-1.031476
H	-1.601026	4.824890	0.648737
C	-0.368018	1.313573	-0.507951
H	-0.374675	0.805627	1.579781
C	-0.610744	2.328607	-1.440703
H	-1.241628	4.361611	-1.770439
C	0.080549	-0.049937	-0.993006
H	-0.443329	2.134822	-2.498821
C	-1.040322	-1.140893	-1.158104
H	-1.332771	-1.162585	-2.216924
C	-2.301110	-0.968867	-0.331140
C	-2.433975	-1.546309	0.935593

C	-3.366434	-0.220569	-0.846736
C	-3.601245	-1.363766	1.678594
H	-1.625882	-2.155575	1.324621
C	-4.531729	-0.031943	-0.104668
H	-3.282085	0.221923	-1.836964
C	-4.652207	-0.603264	1.163553
H	-3.691552	-1.822046	2.660336
H	-5.347805	0.553714	-0.519895
H	-5.561949	-0.464024	1.741760
C	1.869905	-2.480296	-1.695189
H	1.710780	-3.517713	-2.005380
H	1.626245	-1.834331	-2.544821
H	2.928819	-2.345421	-1.453050
O	-0.390414	-2.369972	-0.834304
H	0.515943	0.086722	-1.998208

Number of imaginary frequencies = 0
E(B3LYP/6-31G(d)) = -1020.26377907 au

N-phenylmaleimide

C	1.575767	1.128840	0.239550
C	2.994144	0.652489	0.139809
C	2.994146	-0.652493	-0.139769
C	1.575769	-1.128825	-0.239608
N	0.762207	0.000005	-0.000020
H	3.826830	1.328482	0.286147
H	3.826833	-1.328496	-0.286048
O	1.195407	2.254843	0.476034
O	1.195411	-2.254842	-0.476031
C	-0.665961	0.000002	-0.000008
C	-1.362765	1.068344	-0.575797
C	-1.362750	-1.068344	0.575792
C	-2.756848	1.065791	-0.564574
H	-0.818916	1.896052	-1.014014
C	-2.756834	-1.065798	0.564589
H	-0.818890	-1.896050	1.014000
C	-3.458928	-0.000006	0.000013
H	-3.293495	1.900688	-1.006556
H	-3.293469	-1.900699	1.006580
H	-4.545329	-0.000009	0.000022

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Transition state TS *trans*-6

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C	0.413987	0.251987	1.389982
C	1.978468	-1.388997	0.881919
C	1.664685	0.912637	0.977813
N	2.594490	-0.128755	0.672909
O	2.513606	-2.475405	0.734176
O	1.902228	2.107139	0.894464
H	-0.015056	-1.890041	1.735623
H	-0.364328	0.813908	1.884266
H	7.595303	0.618031	-0.963675
C	6.572730	0.464998	-0.629592
C	5.985541	1.352492	0.273084
H	6.549298	2.202918	0.647461
C	4.677133	1.158325	0.713300
H	4.225047	1.851690	1.409981
C	3.934532	0.070344	0.233283
C	4.519282	-0.821515	-0.676941
H	3.956426	-1.674694	-1.032139
C	5.833974	-0.622764	-1.096174

H	6.278930	-1.325067	-1.796273
N	-1.429906	-0.739609	-0.670192
C	-0.432044	-1.660896	-0.888521
C	-0.674532	-3.133730	-0.700895
C	0.635508	-1.283077	-1.886431
H	-1.029110	-3.622649	-1.622606
H	-1.392280	-3.356805	0.090648
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H	0.172003	-0.940424	-2.825288
H	1.256574	-2.153778	-2.107942
H	1.308749	-0.485078	-1.558068
C	-1.159951	0.595824	-0.705957
H	-1.693346	5.076783	0.042604
C	-2.198018	4.137995	-0.169667
C	-3.588383	4.103060	-0.310570
H	-4.174877	5.012593	-0.214938
C	-4.212747	2.885169	-0.582960
H	-5.291565	2.843679	-0.710636
C	-3.470574	1.712150	-0.706954
H	-3.987742	0.791395	-0.945047
C	-2.066648	1.728186	-0.559300
C	-1.448208	2.974660	-0.295809
H	-0.370126	3.010374	-0.158671
H	-2.285292	-0.471925	1.870502
C	-2.987639	-0.996882	1.234154
C	-4.202410	-1.457130	1.744738
H	-4.438386	-1.293871	2.792252
C	-5.109564	-2.119466	0.916221
H	-6.054740	-2.473547	1.317575
C	-4.800444	-2.325721	-0.430275
H	-5.503290	-2.838379	-1.080624
C	-3.587494	-1.870801	-0.947223
H	-3.338351	-2.018681	-1.993572
C	-2.687535	-1.206387	-0.111501
H	-0.187521	0.836701	-1.101523

Number of imaginary frequencies = 1
E(B3LYP/6-31G(d)) = -1265.11246177 au

Transition state TS *cis*-6

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C	-1.203742	-2.107097	0.106989
C	-1.315563	-0.463894	-1.529514
N	-2.042751	-1.139222	-0.514824
O	-1.550147	-2.876926	0.987887
O	-1.771439	0.372919	-2.289783
H	0.855084	-2.761873	-0.393477
H	0.709365	-0.867158	-2.343737
H	-7.148460	-0.289670	0.691816
C	-6.104639	-0.463631	0.444936
C	-5.664416	-0.354070	-0.874521
H	-6.364841	-0.094024	-1.663863
C	-4.328382	-0.583376	-1.200605
H	-3.990821	-0.492509	-2.224381
C	-3.411446	-0.911406	-0.192126
C	-3.848801	-1.018098	1.135388
H	-3.147940	-1.289929	1.913520
C	-5.190755	-0.800935	1.443925
H	-5.519090	-0.892871	2.475952
N	2.021023	-0.007146	0.348074
C	1.351649	-0.673900	1.325078
C	2.066931	-1.681420	2.183263

C	0.095070	-0.105957	1.912173
H	2.462779	-1.218552	3.101296
H	2.894916	-2.178661	1.676916
H	1.343720	-2.441900	2.495557
H	0.326555	0.658845	2.669253
H	-0.461444	-0.906032	2.405990
H	-0.546966	0.369510	1.171550
C	1.460599	0.886644	-0.551865
H	2.036665	0.947268	-1.468290
H	-1.258982	4.467225	-1.627420
C	-0.635053	3.997340	-0.871831
C	-0.450179	4.615978	0.367508
H	-0.921331	5.571462	0.580732
C	0.353977	3.997364	1.326219
H	0.524567	4.476958	2.286912
C	0.959966	2.772305	1.054828
H	1.621617	2.328001	1.792638
C	0.764674	2.125447	-0.183821
C	-0.035803	2.772042	-1.148611
H	-0.214971	2.284899	-2.101143
H	2.715034	-1.947310	-1.436742
C	3.561092	-1.451897	-0.975916
C	4.864297	-1.809807	-1.329350
H	5.021508	-2.589349	-2.069349
C	5.956480	-1.174474	-0.737620
H	6.967518	-1.458213	-1.015200
C	5.745979	-0.169357	0.209081
H	6.591169	0.333909	0.669759
C	4.448300	0.198653	0.562934
H	4.271878	0.986983	1.288453
C	3.360055	-0.449539	-0.025097

Number of imaginary frequencies = 1
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Pyrrolidine *trans*-6

C	-1.940826	-1.444173	-0.425464
C	-0.436091	-1.288995	-0.547159
C	-0.182944	0.218172	-0.660314
C	-1.550096	0.866903	-0.499145
N	-2.511827	-0.154842	-0.359843
H	0.216917	0.512290	-1.635373
O	-2.563220	-2.484373	-0.379326
O	-1.793484	2.055296	-0.488028
C	-3.912054	0.090848	-0.182963
C	-4.335387	1.080930	0.709930
C	-4.847863	-0.658998	-0.902985
C	-5.698690	1.320344	0.875301
H	-3.605205	1.664658	1.256908
C	-6.208764	-0.416639	-0.720455
H	-4.513892	-1.430492	-1.585484
C	-6.639024	0.572806	0.164734
H	-6.023616	2.093640	1.565736
H	-6.933317	-1.004166	-1.277357
H	-7.700598	0.760420	0.299842
H	-0.106693	-1.842092	-1.431764
C	0.407464	-1.785115	0.698626
C	0.842039	0.533122	0.483444
H	0.245534	0.761329	1.376546
C	-0.397125	-1.754737	2.014738
H	-1.213540	-2.481930	1.983037
H	0.268350	-2.011295	2.844320
H	-0.834116	-0.775144	2.230661

C	0.890886	-3.219441	0.466979
H	1.493968	-3.310990	-0.440094
H	1.484422	-3.584569	1.310896
H	0.011733	-3.863275	0.360090
N	1.503462	-0.763091	0.775859
C	2.736368	-1.081061	0.108312
C	3.706794	-1.771260	0.850459
C	3.029929	-0.748385	-1.223541
C	4.921372	-2.143244	0.276364
H	3.492822	-2.001405	1.889976
C	4.254315	-1.103794	-1.792033
H	2.311766	-0.197413	-1.820873
C	5.202081	-1.808869	-1.049707
H	5.655255	-2.680625	0.871381
H	4.463477	-0.829360	-2.822741
H	6.152572	-2.086432	-1.496864
C	1.767866	1.724736	0.302959
C	2.884764	1.866446	1.141202
C	1.483078	2.746852	-0.610038
C	3.712631	2.982491	1.043747
H	3.107874	1.091732	1.867765
C	2.312622	3.867473	-0.705441
H	0.588824	2.698283	-1.222404
C	3.433475	3.986799	0.113918
H	4.577589	3.067760	1.696404
H	2.072004	4.650342	-1.419889
H	4.079125	4.857628	0.037187

Number of imaginary frequencies = 0
E(B3LYP/6-31G(d)) = -1265.18993200 au

Pyrrolidine *cis*-6

C	-1.933484	-1.587730	-0.865016
C	-0.472044	-1.450238	-1.262158
C	-0.263454	0.046397	-1.464370
C	-1.424374	0.696910	-0.704534
N	-2.391261	-0.314157	-0.482625
H	-0.407058	0.347259	-2.508953
O	-2.591663	-2.606375	-0.856326
O	-1.566203	1.861001	-0.414078
C	-3.692078	-0.062048	0.062005
C	-3.831577	0.788440	1.164091
C	-4.815374	-0.668085	-0.510874
C	-5.100909	1.031750	1.687044
H	-2.959641	1.263855	1.595633
C	-6.077523	-0.424033	0.028816
H	-4.699054	-1.332383	-1.357983
C	-6.225940	0.426428	1.125349
H	-5.206421	1.696500	2.539842
H	-6.947225	-0.900366	-0.415080
H	-7.212257	0.616450	1.539440
H	-0.296148	-2.038576	-2.165712
C	0.547654	-1.893888	-0.143059
C	1.202039	0.322060	-1.058153
H	1.776343	0.225468	-1.995321
C	-0.131201	-2.015757	1.239579
H	-0.927714	-2.765868	1.217828
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C	1.138071	-3.253062	-0.560276
H	1.674973	-3.169202	-1.511465
H	1.829243	-3.656773	0.181986
H	0.318390	-3.968654	-0.687484

N	1.544876	-0.773031	-0.142766
C	2.904366	-0.966818	0.189729
C	3.289957	-1.798000	1.262830
C	3.934796	-0.304461	-0.509774
C	4.630769	-1.986775	1.587463
H	2.538917	-2.290184	1.866643
C	5.273907	-0.488037	-0.166748
H	3.703226	0.374511	-1.320238
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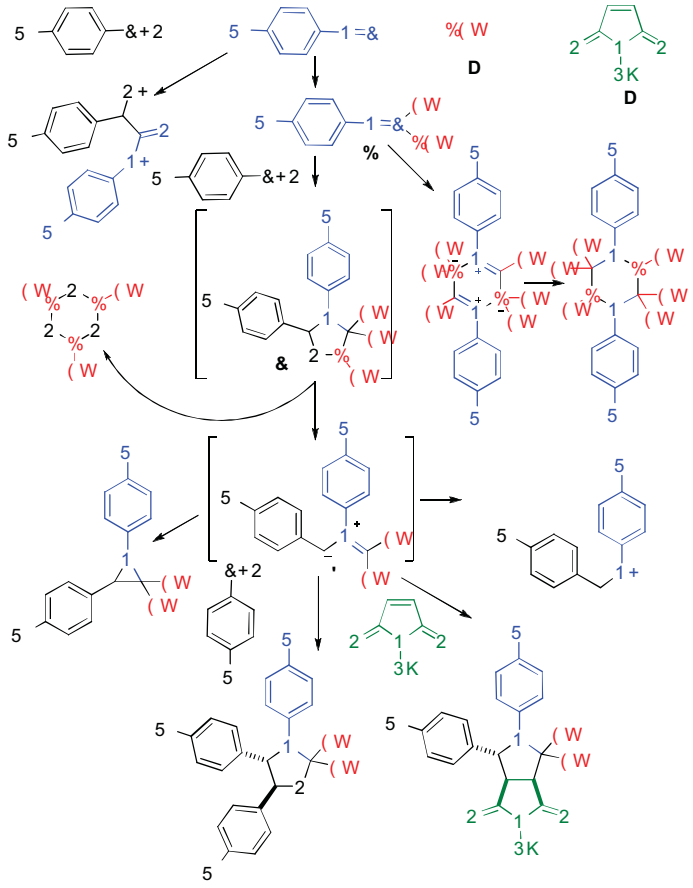
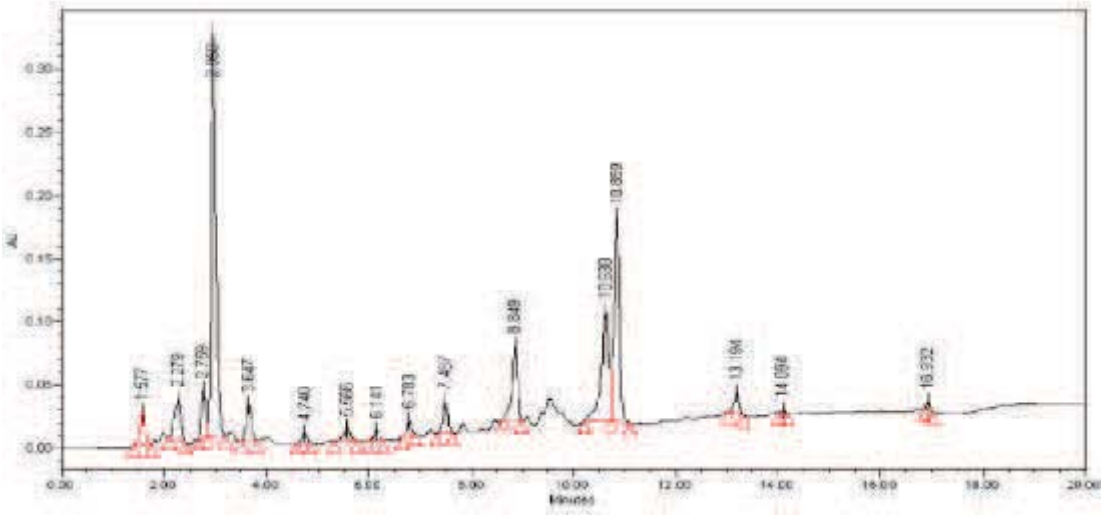
H	4.882701	-2.639194	2.419884
H	6.036302	0.043173	-0.731118
H	6.684089	-1.477346	1.138528
C	1.480051	1.716599	-0.507448
C	1.445466	1.992723	0.862370
C	1.761168	2.756864	-1.400079
C	1.677839	3.286234	1.328669
H	1.248080	1.186815	1.562325
C	1.986443	4.053127	-0.937521
H	1.804928	2.551710	-2.468578
C	1.945148	4.321543	0.431330
H	1.652095	3.485242	2.396907
H	2.200748	4.849924	-1.644953
H	2.126853	5.328820	0.796520

Number of imaginary frequencies = 0
E(B3LYP/6-31G(d)) = -1265.19154883 au

Competing processes taking place in a typical MCR



HPLC profile of the reaction crude from the experiment leading to the 4CR adduct 6f.



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Recent Developments in Reissert-Type Multicomponent Reactions

Nicola Kielland and Rodolfo Lavilla

Abstract The chapter reviews the classic Reissert reaction, the keystone of a broad family of multicomponent reactions involving azines, electrophilic reagents and nucleophiles to yield *N*,α-disubstituted dihydroazine adducts. The first sections deal with the standard nucleophilic attack upon activated azines, including asymmetric transformations. Section 5 focuses on the generation of dipolar intermediates by azine activation, and on their subsequent transformation; chiefly in cycloadditions. Lastly, Sect. 6 is primarily devoted to a special branch of this chemistry involving isocyanides. It also covers the reactivity of dihydroazines and reviews the mechanistic proposals for related reactions.

Keywords Azines · Isocyanides · Multicomponent reactions · Reissert reaction

Contents

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Abbreviations

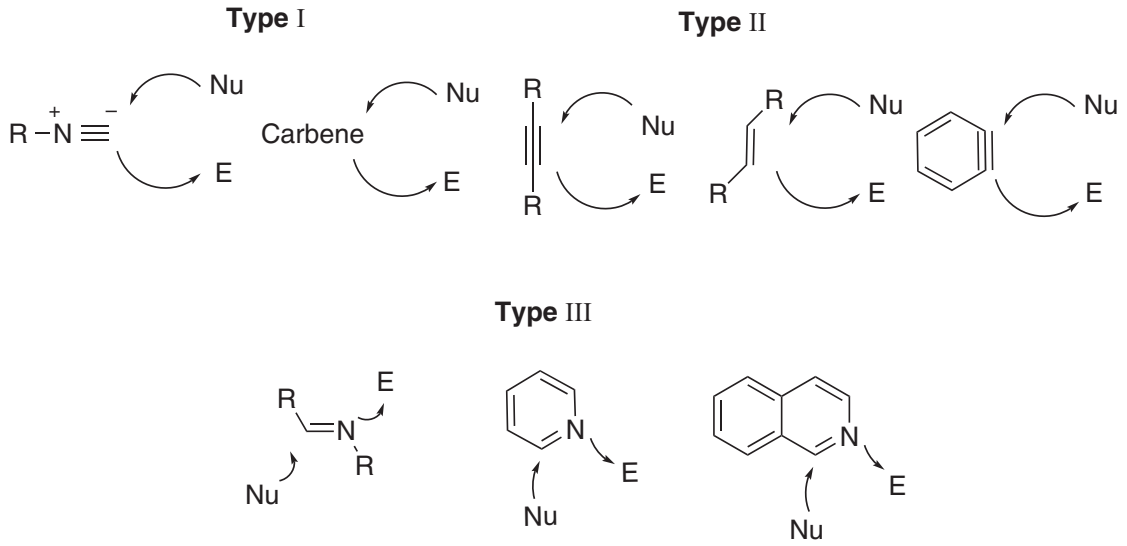
3CR	Three component reaction
4CR	Four component reaction
Al_2O_3	Alumina
Boc	*tert*-Butoxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
Cbz	Carbobenzyloxy
CO_2	Carbon dioxide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	Dihydropyridine
E	Electrophile
FMOC	9*H*-fluoren-9-ylmethoxycarbonyl
HF	Hydrogen fluoride
IBX	2-Iodoxybenzoic acid
ICl	Iodine monochloride
KOH	Potassium hydroxide
LDA	Lithium diisopropylamide
MC	Multicomponent
m-CPBA	*m*-Chloroperoxybenzoic acid
MCR	Multicomponent reaction
NMDA	*N*-methyl D-aspartate
Nu	Nucleophile
O_3	Ozone
PINAP	*N*-(alkyl(phenyl)methyl)-4-(2-(diphenylphosphino)naphthalen-1-yl) phthalazin-1-amine
$POCl_3$	Phosphorus (V) oxychloride
TCAA	Trichloroacetic anhydride
Tf_2O	Triflic anhydride
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMS-CN	Trimethylsilyl cyanide
TMS-N_3	Trimethylsilyl azide
TOSMIC	*p*-Toluenesulfonylmethyl isocyanide

1 Introduction

Multicomponent reactions (MCRs) have recently become a fruitful route to synthesizing diverse scaffolds in single-step operations [1, 2]. Perhaps the most attractive strategy in this field, and one which is widely employed, is the use of reactants bearing functional groups featuring complementary (ambivalent) reactivity: those

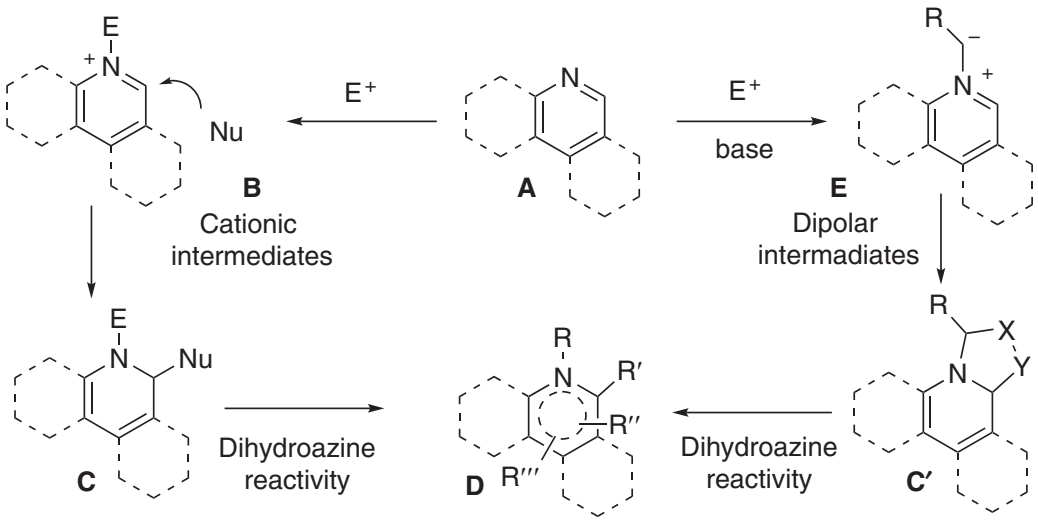
which can interact with two or more distinct species. Isocyanides are the paradigmatic example of Type I MCR reagents (see Type I in Scheme 1). Their *carbene-like* electronic structure enables formal addition of nucleophilic and electrophilic partners, thereby leading to MCRs. Other functional groups display this behavior, and combinations of these constitute the core of a family of MCRs marked by high bond-forming efficiency and structural diversity [3]. Electron-deficient alkenes and alkynes have often been employed with this purpose in MCRs. Arynes, in which the nucleophile and the electrophile react at two contiguous positions, are another relevant group (Type II in Scheme 1). Imines, which have a nucleophilic nitrogen linked to an electrophilic carbon atom, are among the most used components in many classic MCRs and also participate in processes of this type. As such, azines could be regarded as heterocyclic surrogates of imines and thus, are a useful source of reactive inputs for this chemistry (Type III in Scheme 1, Reissert reactions in a broad sense). This is especially relevant, since nitrogen heterocycles are ubiquitous common motifs in natural products, drugs, and bioactive compounds; involving these species in MCRs has, therefore, important consequences in organic synthesis [4].

The interaction of the azine nitrogen with electrophiles is normally fast and could display a reversible nature, while the addition of a nucleophile at the position α of the activated heterocyclic system **B** implies the loss of aromaticity and is often the rate determining step of the reaction. The resulting substituted dihydroazines **C** display a rich reactivity, and may be subsequently transformed into a variety of heterocyclic systems **D** with diverse oxidation degrees [5, 6]. Alternatively, reaction of azines with several activating agents can generate azinium ylides **E**, species which can undergo [3+2] cycloadditions with dipolarophiles (Scheme 2). In some cases the result of these combinations produces reactive intermediates, triggering complex cascade reactions [7]. This chemistry has enabled practical syntheses of alkaloids and heterocyclic structures as well as pilot scale production of major drugs and synthetic intermediates.

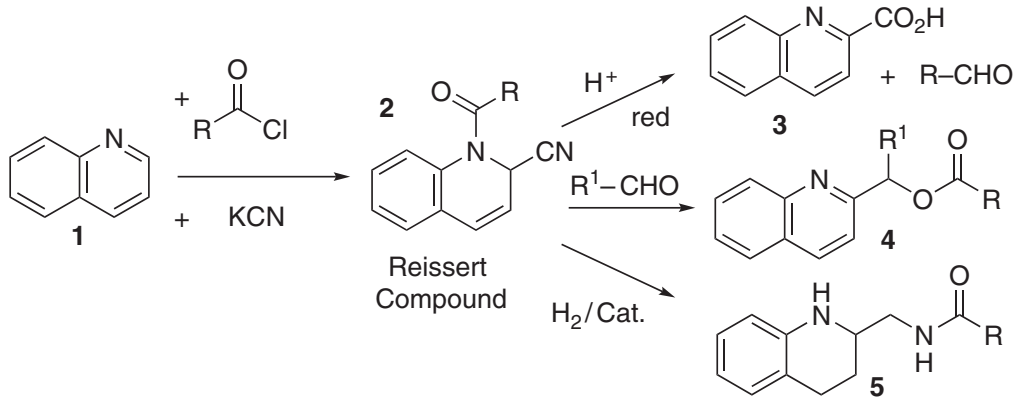


Scheme 1 Examples of common complementary reactants used in MCRs

In 1905, Arnold Reissert described the addition of cyanide to the α-position of a quinoline (**1**, Scheme 3) activated by an acylating agent [8–14]. The resulting substituted dihydroquinoline **2**, generally called a Reissert compound, can be hydrolyzed with aqueous HCl to afford the quinoline-2-carboxylic acid **3** and an equivalent of the aldehyde, after spontaneous dismutation of the intermediate dihydroazine derivative. Reissert originally performed the reaction in aqueous media; however, under these conditions, the acid chlorides hydrolyze quickly. To overcome this limitation, in 1940, Woodward explored the reaction in sulfur dioxide, using several aromatic acyl chlorides [15, 16]. Later, Fischer extended the acyl chloride range to include aliphatic derivatives using benzene as solvent, demonstrating that hydrolysis of these adducts was a useful way to convert the acid chlorides used as activating agents into aldehydes [17–19]. Interestingly, reactions of Reissert compounds with aldehydes or ketones bring new synthetic possibilities (see Scheme 3). For instance, the nucleophilic α-amidonitrile moiety of the



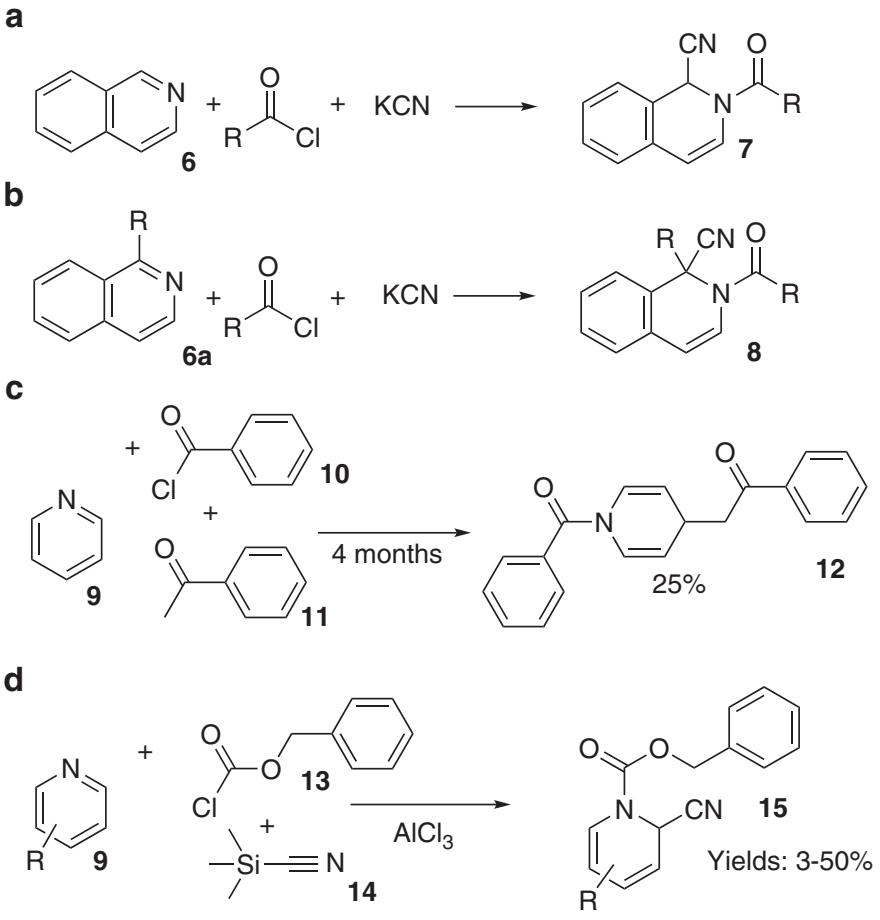
Scheme 2 Azine activation modes



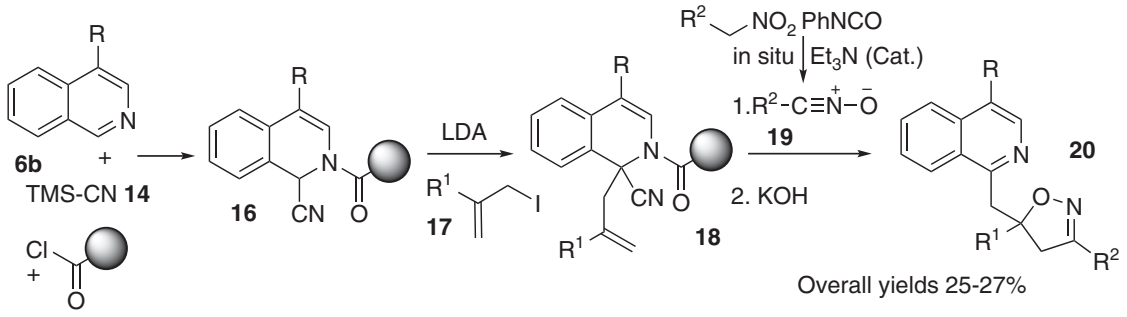
Scheme 3 Reissert reactions and post-condensation transformations

dihydroquinoline **2** can attack the carbonyl of aldehydes or ketones to afford the substituted quinoline ester **4** (after an acyl shift and subsequent cyanide elimination) [20–23]. Alternatively, the catalytic hydrogenation of the Reissert adduct afforded the tetrahydroquinoline **5** with concomitant migration of the acyl group to the primary amine moiety [24]. Indeed, the chemistry and synthetic uses of the Reissert adducts have been covered in several reviews [25, 26].

Apart from quinolines, isoquinolines (Scheme 4a, b) are also excellent substrates, even when substituted at position 1 [27–29]. The group of Popp extensively explored the azine range of the Reissert reaction: 1-azapyrene, 2-azafluoranthene, diazaaromatic systems, benzimidazoles, quinazolines, and even the analogous oxygen system of 2-benzopyrylium salts, all of which made suitable substrates for this process [30–35]. More recently, Reissert compounds of imidazolium and imidazolinium salts have been employed to synthesize new carbene complexes [36]. Although pyridines do not afford the expected adduct under classic Reissert conditions, *N*-alkylpyridinium salts do work [37]. Similarly, carbonyl derivatives such as acetophenone **11** have been used as nucleophiles in a regioselective addition through the *N*-acylpyridinium salt intermediate, demonstrating that non-cyanide nucleophiles could be employed in Reissert-type reactions (Scheme 4c) [38].



Scheme 4 Isoquinolines and pyridines in Reissert reactions and related processes



Scheme 5 Solid-phase Reissert reaction

In 1987, Popp et al. described the first Reissert reaction with pyridine as substrate using TMS-CN (**14**), in the presence of a catalytic amount of aluminum chloride [39]. Further modifications included the use of diethylaluminiumcyanide and tri-*n*-butyltin cyanide as alternative cyanide sources (Scheme 4d) [29, 40, 41].

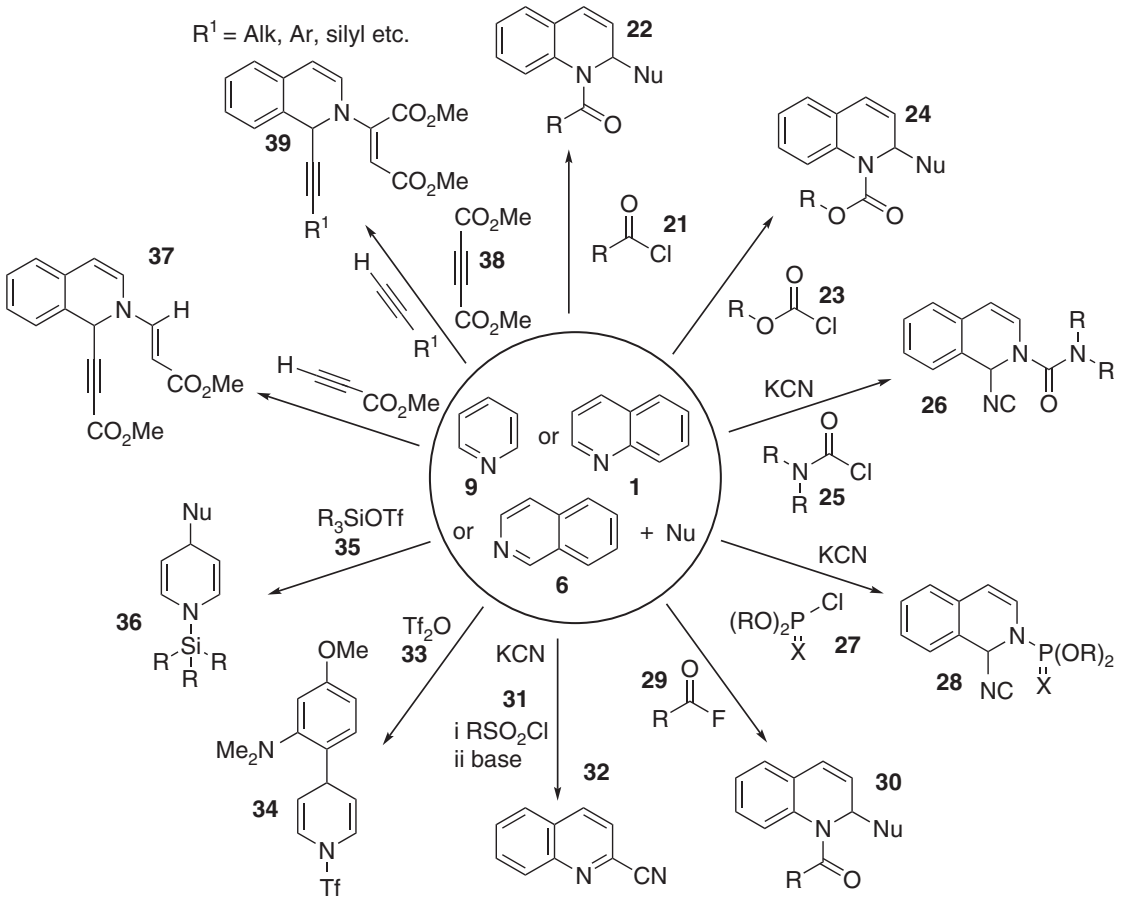
In 1996 the Kurth group described the first sold-phase Reissert reaction (Scheme 5) [42, 43]. Activation of a carboxylic acid functionalized resin to the corresponding acyl chloride, followed by treatment with isoquinoline and TMS-CN (**14**) afforded the resin-linked Reissert adduct **16**. This intermediate was subsequently alkylated at the α-position by treatment with LDA and alkyl iodides **17**. Some of these adducts were further manipulated, and finally the substituted isoquinolines **20** were conveniently released using a traceless cleavage with KOH/THF.

This account reviews recent advances in Reissert-type transformations, focusing on the use of different reactants, asymmetric versions of the process, and also on dipole-related reactivity and on the participation of activated azines in isocyanide-MCRs.

2 Range of Activating Agents in Reissert-Type Reactions

Besides the classic Reissert process, a wide range of modifications have been described. Structural variations on each component have been extensively screened, and several approaches have been designed based on the interaction of azines, activating agents, and nucleophiles to yield substituted dihydroazines or related compounds. This chapter does not provide an exhaustive list of these many transformations; rather, it offers a general overview of the field (Scheme 6).

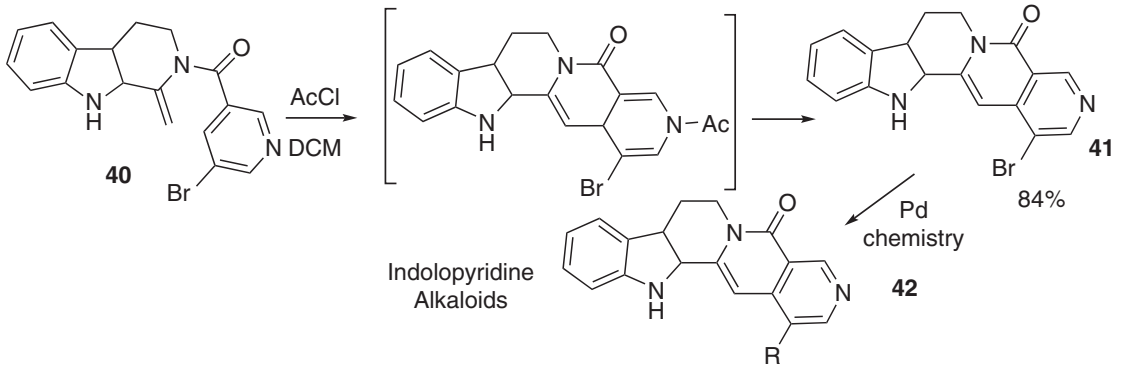
Different types of activating agents have been employed in Reissert-related reactions (Scheme 6). In many cases, it is mandatory to generate, or even isolate, the corresponding azinium salt intermediate, and sequentially proceed with the nucleophilic addition. Moreover, since the former step often takes place selectively and at a fast rate, the transformation can be performed in a multicomponent manner without any functional group interference.



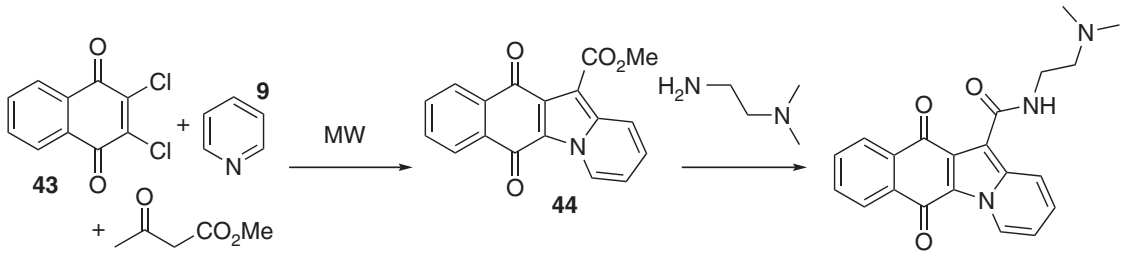
Scheme 6 Range of activating agents used in Reissert processes

Acid chlorides **21** and chloroformates **23** are the most commonly used activating agents and the preferred reagents for evaluating the reactivity of other components in new Reissert-type processes. For example, in studies on the total synthesis of the indolopyridine alkaloids **42**, acetyl chloride was used in the key step to prepare the common synthetic intermediate **41**. In this case, an enamide moiety intramolecularly attacks the in situ generated *N*-acylazinium salt, and the Reissert adduct is spontaneously oxidized and hydrolyzed to regain aromaticity in the last step (Scheme 7) [44, 45].

N,N-dialkyl- or diaryl-carbamoyl chlorides **25** are far less frequently used in this chemistry, although they were successfully employed by Popp in a Reissert-related process [28]. This group also investigated the use of chlorophosphates and chlorothiophosphates **27** as activating agents. The resulting Reissert analogs can be converted by base treatment into anions that can be alkylated or undergo elimination to isoquinaldonitrile [46]. Interestingly, acid fluorides have also been used [47]. Reissert compounds arising from sulfonyl chlorides are often unstable; however, the corresponding 2-substituted azines **32** can be obtained by treating the crude product of these reactions with a mild base [48]. Triflic anhydride (**33**) has been successfully used for promoting the incorporation of less reactive nucleophiles. The Corey group



Scheme 7 Synthesis of indolopyridine alkaloids based on a Reissert-type process

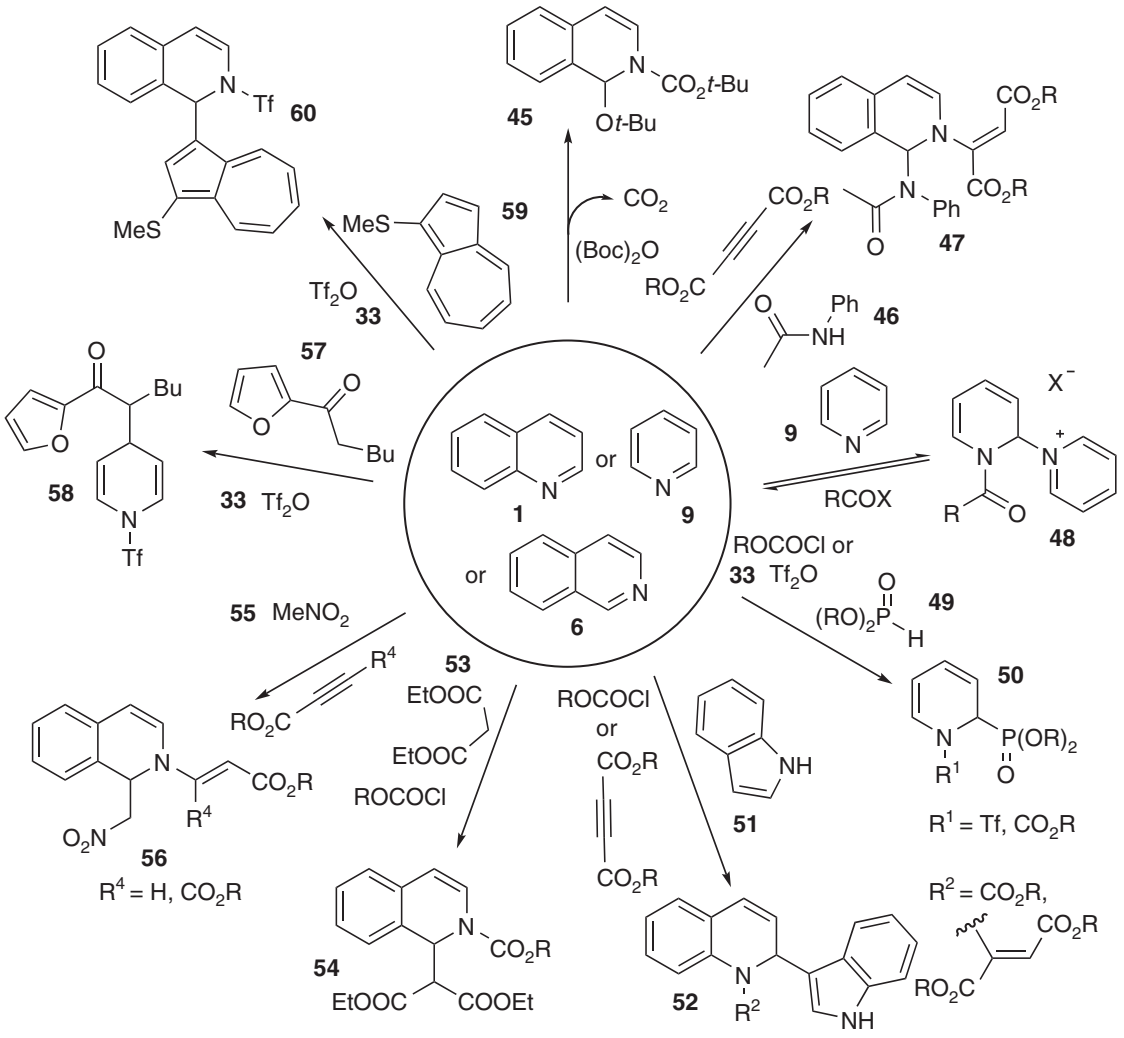


Scheme 8 Reissert-type cascade promoted by an activated double bond

used this activating agent in a direct arylation of pyridines that did not require an organometallic species [49]. The bulky trialkylsilyloxytriflates **35** have been used to activate pyridines in the presence of Grignard reagents: they protect the α-position of the azine, thereby leading to γ-regioselective nucleophilic attack. Additional examples of these activating agents are discussed in the following sections of this chapter. Substituted alkynes such as **38** (normally with electron-withdrawing groups) constitute a common class of activating agents. They interact with azines to form dipoles that can react in cycloadditions (see Sect. 5). However, in some cases, the anion moiety can trap a proton, generating an azinium species, which then enables subsequent nucleophilic addition. For instance, adducts **37** and **39** (Scheme 6) have been obtained by using a terminal alkyne as the nucleophile, in reactions catalyzed by copper or gold chlorides [50, 51]. Appropriately substituted π-acceptors such as **43** can also activate azines, through addition–elimination processes, consequently promoting cascade reactions based on Reissert chemistry (Scheme 8)[52].

3 Range of Nucleophiles in Reissert-Type Reactions

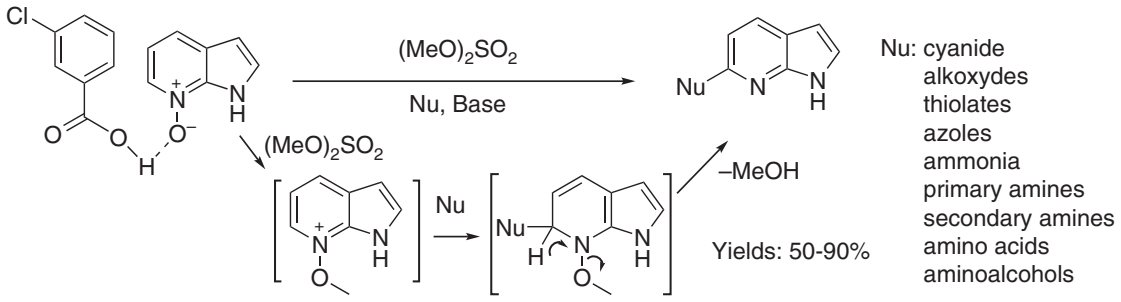
The range of nucleophiles used in these processes is very wide (Scheme 9). Although alcohols and amines cannot be directly used – as they would quickly trap the electrophilic partner, and therefore, bypass the intervention of the azine – the literature does contain a few examples of sequential use of these compounds.



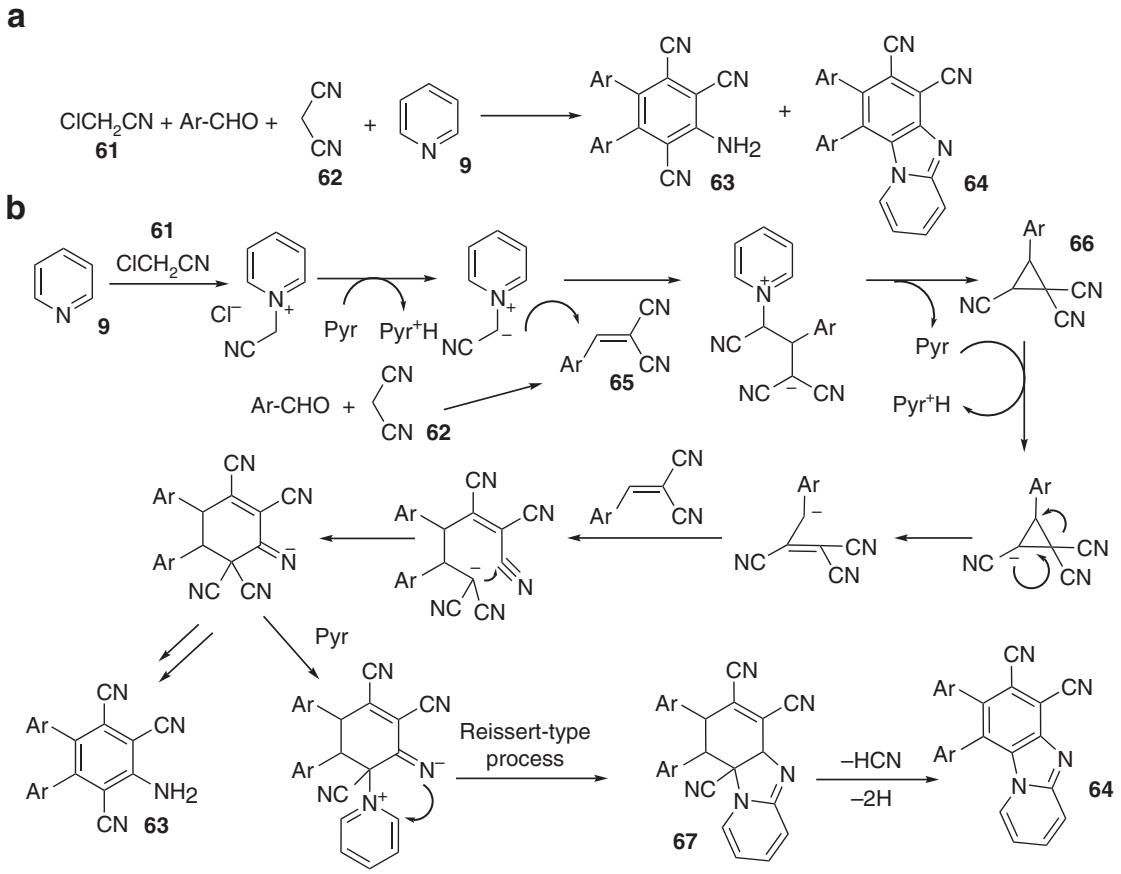
Scheme 9 Range of nucleophiles used in Reissert-type reactions

This entails preformation of the activated azinium ion and subsequent reaction of the nucleophile to generate the desired adduct [53–56]. In this regard, an interesting possibility is the use of symmetric carbonates. For example, the dihydroisoquinoline **45** (Scheme 9) was synthesized using this strategy. The nucleophilic alkoxide is released during the interaction between the azine and Boc_2O with loss of CO_2. Adduct **45** is an efficient *tert*-butoxycarbonylation reagent for phenols, aromatic and aliphatic amines in the absence of bases under mild conditions [57, 58].

Even poor nucleophiles such as the amides **46** can react with azines in the presence of alkynes as activating agents [59, 60]. Various nucleophiles (including alkoxides, thiols, amines and nitrogen heterocycles) were recently employed in a related process with *N*-oxide azaindoles (Reissert–Henze reaction, Scheme 10). In the process, the oxygen is alkylated with dimethyl sulfate and, after the nucleophilic attack, methanol is released to aromatize the initial adduct [61, 62]. Following similar mechanistic trends, *N*-heteroatom-activated azines afford the corresponding substituted adducts. Likewise, *N*-tosylated isoquinoline [63, 64] and *N*-fluoropyridinium salts [65] are also reactive substrates in Reissert–Henze type processes.

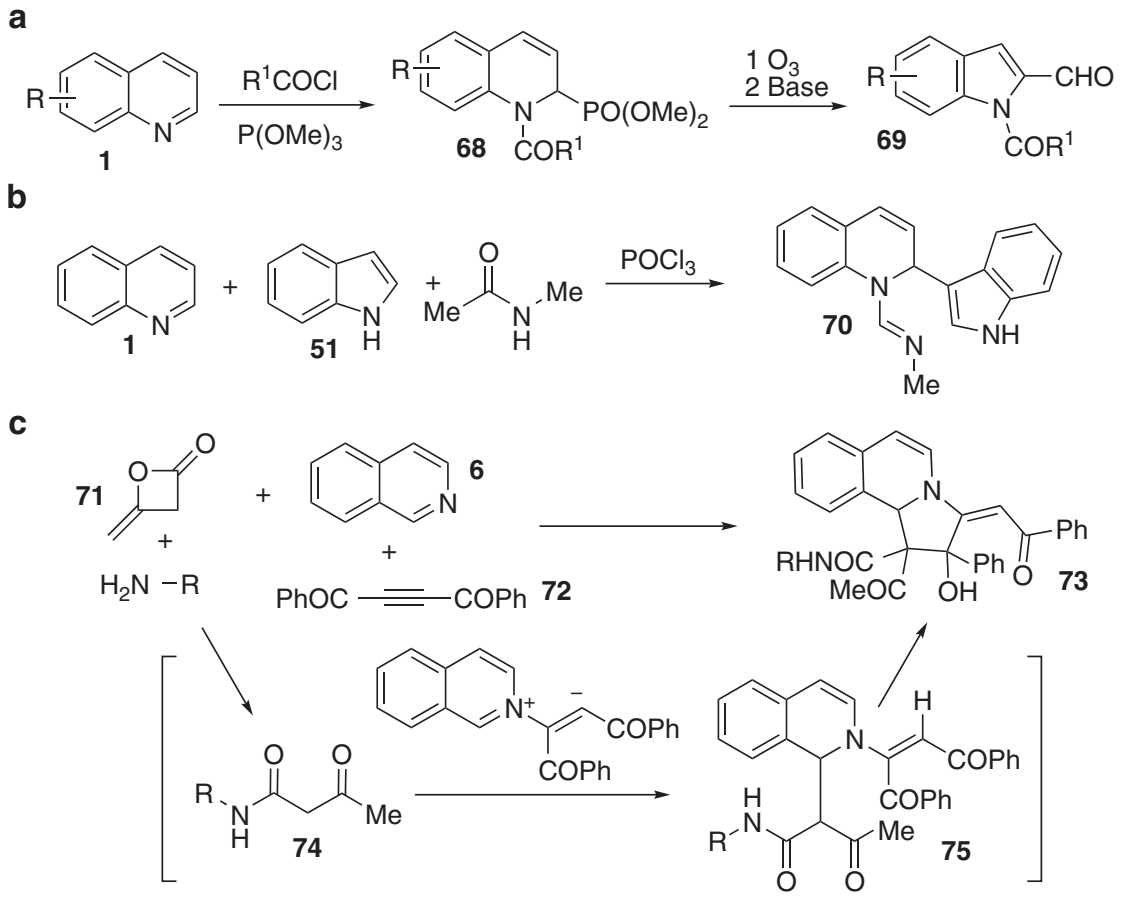


Scheme 10 Nucleophiles used in the Reissert–Henze reaction



Scheme 11 Cascade process terminating with a with Reissert-type reaction

In a chemodifferentiating ABB' process [66], King and coworkers characterized the adduct **48**, arising from the nucleophilic attack by pyridine upon an *N*-acylpyridinium intermediate (Scheme 9) [67]. The Yan group described an impressive cascade reaction involving chloroacetonitrile (**61**), malononitrile (**62**), aromatic aldehydes and pyridine (**9**, Scheme 11a). Alkylation and Knoevenagel-type reactions are suitably engaged with conjugate additions, cyclopropane ring formation and subsequent ring-opening to finish with an intramolecular Reissert-type reaction, leading to the complex heterocyclic system **64** (Scheme 11b). The different roles played by pyridine in this sequence are noteworthy [68].



Scheme 12 Phospho- and carbo-Reissert-type processes

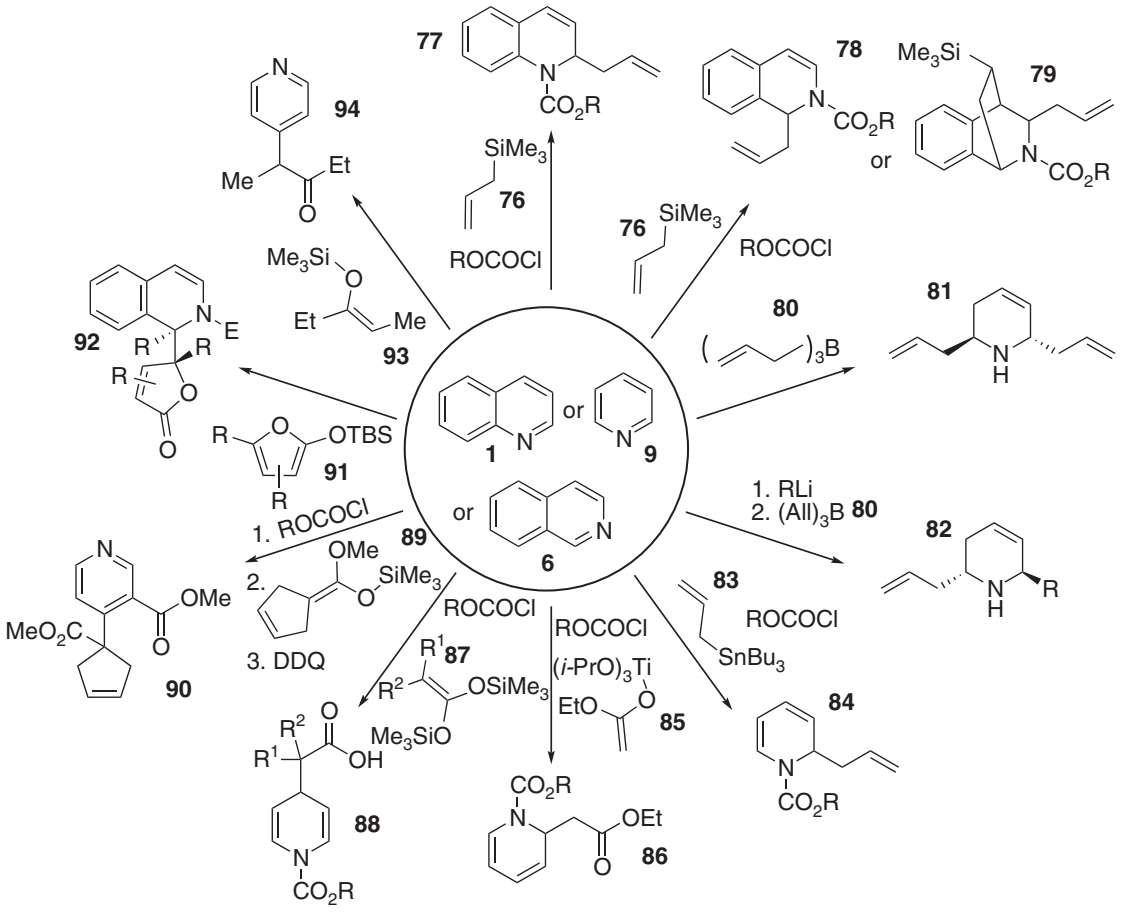
Dialkyl phosphites such as **49** (Scheme 9) have been reacted as nucleophiles with activated pyridines [69, 70]. The first examples of this chemistry involved either *N*-alkyl-pyridinium salts in the presence of DDQ, or pyridine and terminal alkynes as activating agents in a one-step protocol. The reaction proceeds under mild conditions that include Al_2O_3 catalysis. Quinolines **1** and chloroformates afford the expected adducts **68**. The latter structures can be easily oxidized with O_3 to provide the substituted indoles **69** (Scheme 12a). Isoquinolinephosphonates obtained this way have been used in Wittig–Horner chemistry. The whole sequence offers ready access to alkyl substituted isoquinolines [71]. Analogously, silyl substituents have been introduced into *N*-acylated pyridines by using silylcuprates [72].

Several classes of carbon nucleophiles have been successfully used in these systems, reflecting the utility of Reissert chemistry for derivatizing azines via carbon–carbon bond formation. Apart from cyanide anion, other classes of carbon nucleophiles have been explored. For instance, addition of indole (**51**) to *N*-acylazinium salts proceeds selectively at the α-position (Scheme 9). Pyrrole, quinolines and isoquinolines all behave similarly [73–76]. A related reaction, yielding adduct **70** (Scheme 12b) has also been described. In this case, azine activation is promoted by Vilsmeier reagents (generated by reaction of amides with $POCl_3$) [77]. β-Dicarbonyls are reactive inputs in this chemistry, and dialkyl malonates **53**

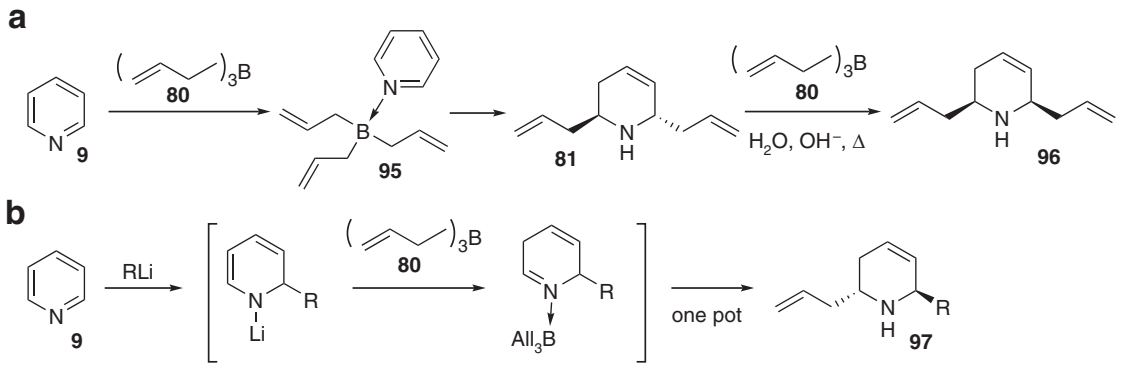
have been added to quinolines and isoquinolines in the presence of chloroformates [78]. In a related 4CR (Scheme 12c), the dicarbonyl **74** is first generated in situ by interaction of diketene **71** and a primary amine, then reacts with an isoquinoline dipole (presumably via proton transfer and nucleophilic addition) to give intermediate **75**, which by intramolecular addition of the acidic methine, provides the final adduct **73** [79, 80]. Nitroalkanes **55**, (Scheme 9) are also reactive as carbon nucleophiles in Reissert-type processes [81, 82]. Use of stronger activating agents such as triflic anhydride (**33**) enables functionalization of pyridines with electron-rich aromatic rings, as well as azulene derivatives (**59**), pyrroles, allylstannanes, and even substituted ketones **57** [49, 83, 84].

Allyl groups can be easily attached to azines through the standard activation-nucleophilic attack approach. Quinoline (or isoquinoline) smoothly reacts with chloroformate and allylsilanes (**76**) in the presence of iodine or triflate catalysts (Scheme 13). Using two equivalents of silane reagent in the isoquinoline reaction, gives adduct **79** [85–87].

Triallylborane **80** reacts both as activating agent and nucleophile. Interestingly, due to the lability of the N–B bond, the process leads to N–H derivatives, ready for further derivatization. A noteworthy transformation is the double allylation of pyridines by triallylboron **80** leading to the tetrahydropyridine derivative **81**.



Scheme 13 Activated alkenes and related species as nucleophiles in Reissert chemistry

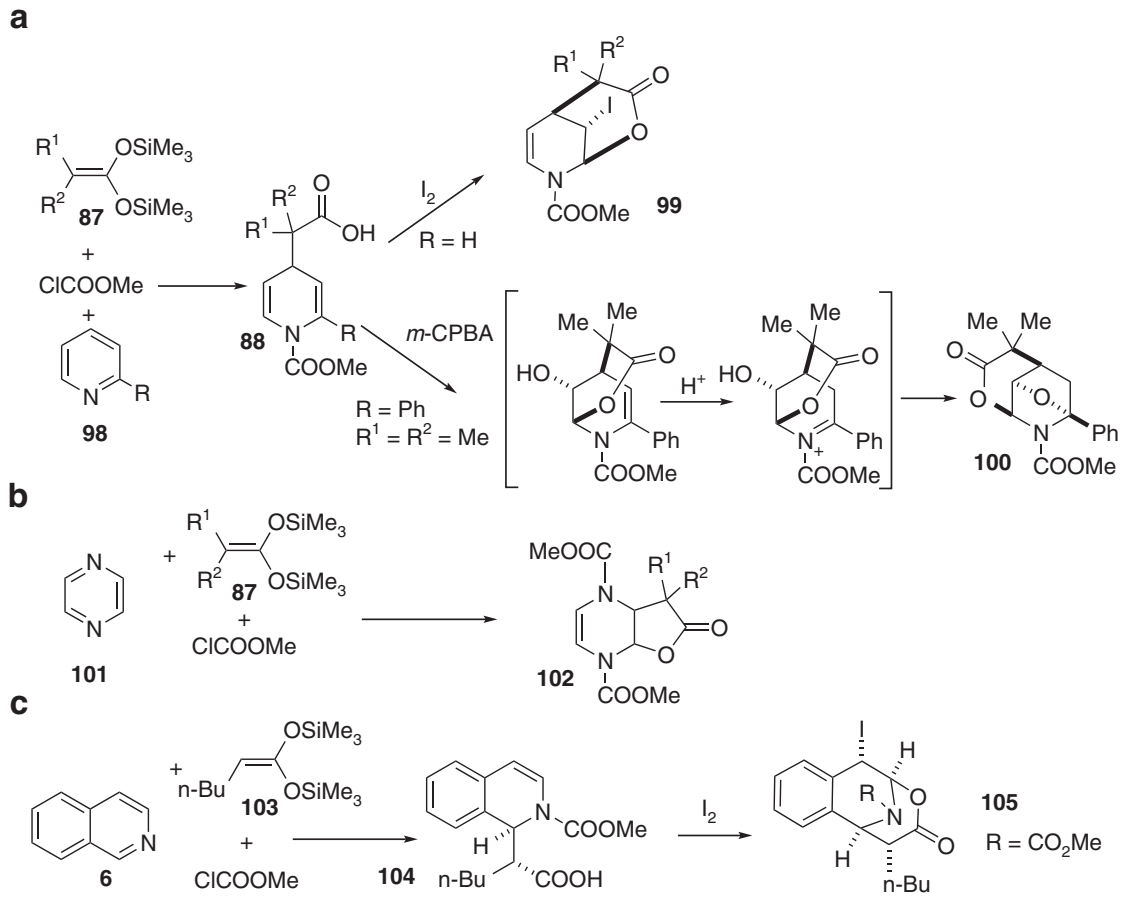


Scheme 14 Allylboration of pyridine

After coordination with the azine nitrogen, the activated complex **95** (Scheme 14a) undergoes a stereoselective diallylation to afford the *trans*-2,6-diallyl-tetrahydropyridine (**81**). Furthermore, **81** can be transformed into its *cis*-isomer (**96**) by heating. Isomerization can also occur at a dihydropyridine (DHP) intermediate following incorporation of an alkyl group via organometallic attack upon a pyridine in a one-pot transformation (Scheme 14b) [88–90].

An alternative method for allylating pyridines entails use of the corresponding organometallic reagents. For example, allyltin derivatives (**83**, Scheme 13) offer good yields and regioselectivity [91]. Moreover, interaction of chiral ligands of bisoxazoline type with allylzinc derivatives and *N*-acylpyridinium salts enables selective transformations, although with poor enantiomeric excesses [92]. A variety of enol derivatives have been used as functionalized nucleophiles in these processes, including titanium- and silicon-enolates **85** [93]. Addition of the ketene silyl acetal **89** to quaternized methyl nicotinate, followed by oxidation with DDQ, yields the γ-substituted pyridine **90**, an advanced intermediate in the total synthesis of (±)-sesbanine (Scheme 13) [94, 95]. Reaction of isoquinolines, silyloxyfurans **91** and activating agents have yielded diverse isoquinolinobutyrolactones with excellent diastereoselectivity, even for α-substituted azine substrates (Scheme 13). Furthermore, use of a chiral auxiliary has enabled formation of single stereoisomers in excellent yields [96]. The Rudler and Langer groups have developed this approach by using 1,1-bis(trimethylsilyloxy)ketene acetals **87** [97]. This versatile reactant can promote further bond-forming events, as the resulting carboxylic acid moiety may react as a nucleophile, trapping the iminium ion generated from the dihydroazine upon interaction with an external electrophile. The sequential addition–lactonization process can be induced by halogens or epoxidizing agents (Scheme 15a). Several azines (e.g., pyrazines and isoquinoline) react under these conditions to afford δ- or γ-lactones, thereby reflecting the generality of the methodology (Scheme 15b, c) [98–106].

Charette recently described an innovative activation protocol in which lactams, in the presence of triflic anhydride (**33**), react with pyridines to afford the pyridinium imidate **107** in good yield. Subsequent addition of metal enolates to this species leads to 2-substituted tricyclic dihydropyridines, advanced intermediates for the total synthesis of the natural alkaloid (±)-tetraponerine T4 (**109**, Scheme 16) [107].

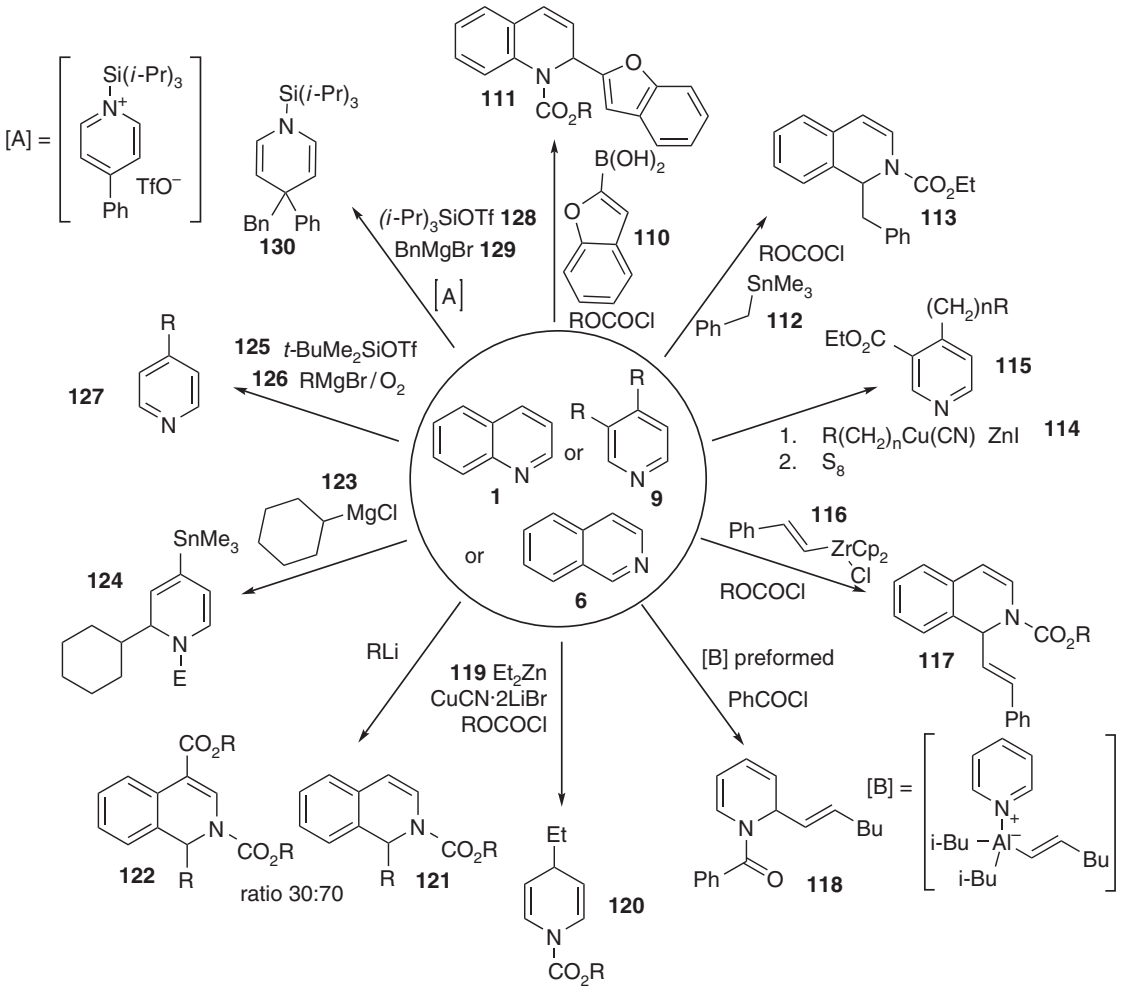


Scheme 15 Sequential Reissert–lactonization processes

Scheme 16 Charette's activation protocol

Besides lithium, zinc and tin derivatives (see Scheme 13), other types of organometallic reagents have been used as nucleophiles in related processes (Scheme 17). Yoon described a 3CR, resembling a Petasis process, in which isoquinolines or quinolines are reacted with activating agents and boronic acids to yield the expected α-arylated dihydroazines **111** [108].

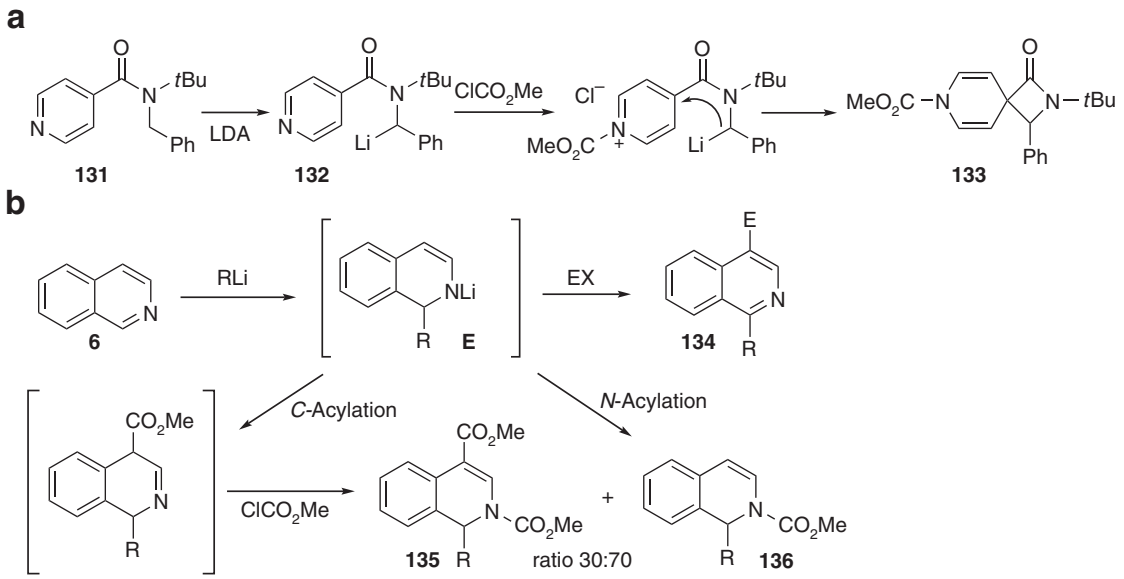
Azines have been benzylated via the corresponding organostannanes [91, 109, 110], and alkylated or arylated via the organocuprate precursors [111–113]. Vinylation of isoquinolines or quinolines with alkenylzirconocene chlorides **116** proceeds in excellent yields. Interestingly, an analogous reaction of a reduced derivative, catalyzed by a copper (I) salt in the presence of a chiral amine ligand, furnishes the corresponding adduct **117** in an enantioselective manner. (Scheme 17) [114].



Scheme 17 Organometallic addition to activated azines

In a related process, pyridines, vinyl alanes, and acid chlorides are reacted to afford the MC adduct **118** [115]. Also, reaction of pyridines, chloroformates, and organozinc reagents proceeds with high yields and regioselectivity in position γ [116]. Organolithium compounds are also useful nucleophiles, reacting with activated azine derivatives under standard conditions. In this respect, Clayden has developed remarkably elegant cyclizations of *N*-benzylpyridine- and quinoline-carboxamides, promoting the in situ formation of the carbanion (by deprotonation with a base) with subsequent azine activation with chloroformates (Scheme 18a) [117]. This route provides ready access to the spiro β-lactam system **133**.

Sequential reaction of azines with alkyl lithium compounds and chloroformates usually affords the expected Reissert-type products **136**, together with minor amounts of doubly acylated compounds **135** (Scheme 18b). Isoquinoline is likely to react directly with the alkyl-lithium compound to generate the alkylated lithio-enamine intermediate **E**, and this species may account for the formation of dihydroisoquinolines **135** and **136**, through interaction with the electrophilic partner. Mamane recently expanded this concept by replacing the acylating agent with different electrophiles. These combinations lead exclusively to isomers **134** (Scheme 18) [118–120].

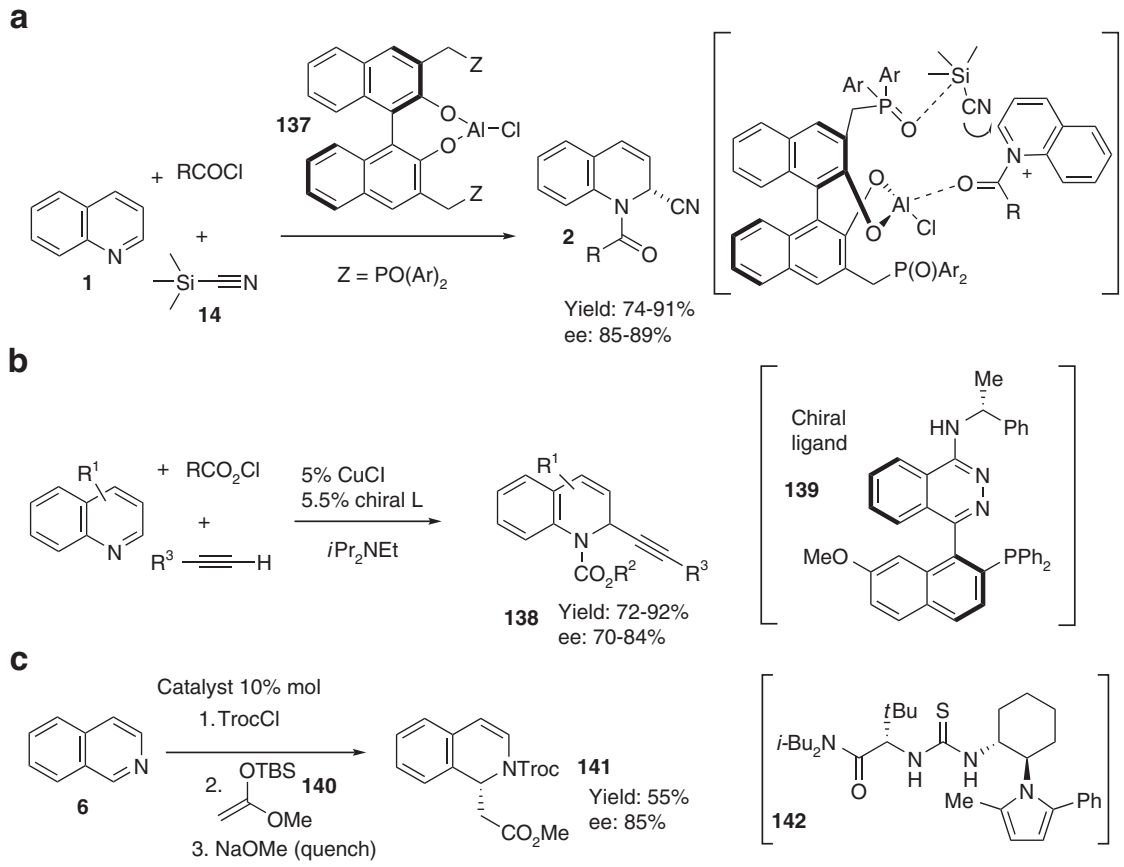


Scheme 18 Reaction of organolithium compounds with azines and electrophiles

Grignard reagents also have been explored as nucleophiles in these types of processes. The regioselectivity of the addition of these reagents to acylated pyridines strongly depends on the substrates [121]. However, the nucleophilic attack can be directed to the γ-position by using a stoichiometric organocuprate derivative or catalytically, with small amounts of copper iodide. Alternatively, the attack can be guided to the α-position by blocking the γ-site with a bulky substituent, regioselectively providing adduct **124** (Scheme 17) [122, 123]. To improve the poor regioselectivity often observed in nucleophilic additions of organometallics to pyridinium salts, the Akira group employed *tert*-butyldimethylsilyl triflate **125** as activating agent (Scheme 17). This bulky reagent efficiently protects the α-positions of the pyridine ring, and consequently, the Grignard reagent selectively attacks the γ-position. Furthermore, the silyl group can be easily removed, and oxidation of the dihydropyridine adduct smoothly regenerates the aromatic azine nucleus. Directed substitution has also been investigated in quinolines. Although this reaction is considerably more challenging, Mani achieved a 60:40 ratio of γ-substituted to α-substituted product [124]. More recently, Wanner had success with γ-substituted pyridines, obtaining even in these cases the corresponding adducts with excellent γ-regioselectivity [125].

4 Asymmetric Reissert-Type Processes

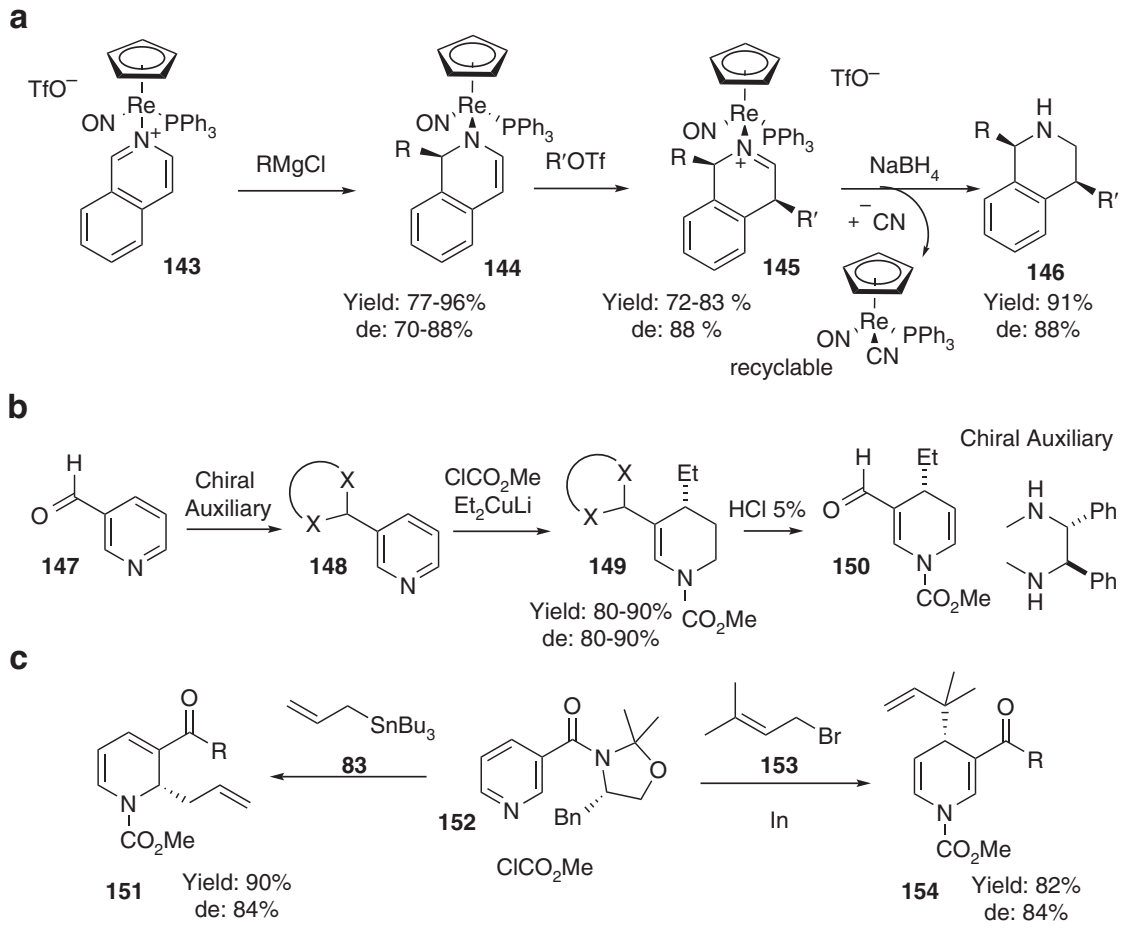
The need of enantiopure compounds has fuelled the development of asymmetric transformations in this field. This is especially challenging due to the mechanistic complexity of MCRs and to the lability of the dihydroazine moieties of the final adducts. Nevertheless, significant progress has been reported in the area. Shibasaki



Scheme 19 Catalytic enantioselective Reissert-type processes

recently described the first catalytic enantioselective Reissert reactions of quinolines (and isoquinolines) using the bifunctional aluminum catalyst **137** (Scheme 19a). The Lewis acidic and basic sites of the catalyst are critical for its coordination to the *N*-acylazinium salt and for directing the nucleophile with facial selectivity. In this manner, excellent yields and enantioselectivities of the desired Reissert adducts were obtained [126–129]. This process allowed the preparation of a potent NMDA receptor antagonist [130]. A few years later, an analogous catalyst was used to promote the first enantioselective Reissert reaction of pyridine derivatives [131]. Arndtsen recently described the copper catalyzed reaction of pyridines or quinolines with terminal alkynes and acylating agents to yield the dihydroazine adducts **138**. Several chiral ligands were analyzed, and the best results were obtained with the PINAP derivative **139**, reaching enantiomeric excesses greater than 80% with excellent chemical yields (Scheme 19b) [132]. In this context, Feringa et al. recently described the catalytic enantioselective addition of dialkylzinc reagents to 4-methoxypyridine [133]. Moreover, thiourea organocatalyst **142** has enabled enantioselective addition of silyl enol esters to activated *N*-acylisoquinolinum salts, conveniently providing the corresponding adduct **141** (Scheme 19c) [134].

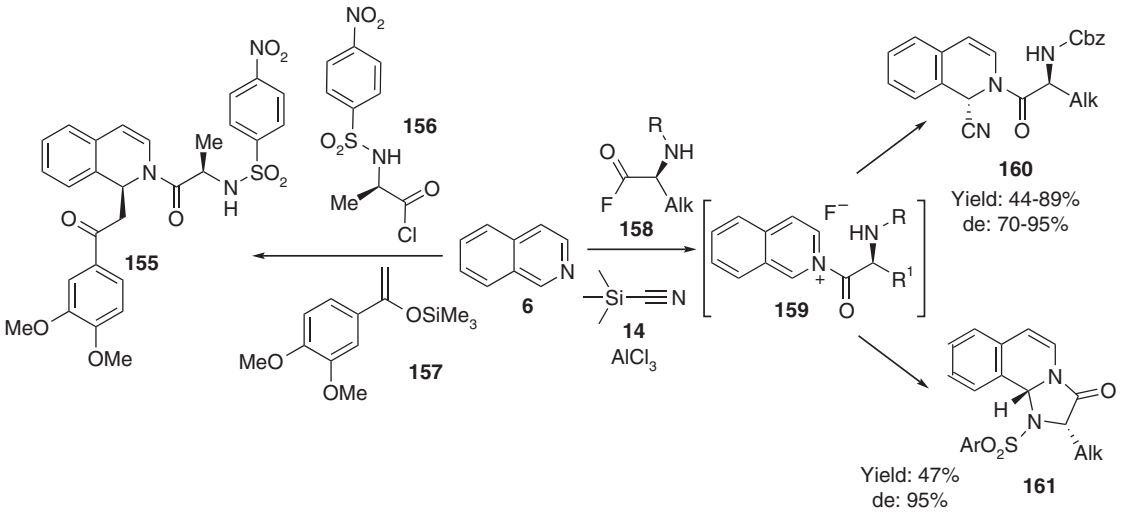
In a different approach, chiral auxiliaries have been widely used in Reissert-type chemistry to provide practical access to enantiopure addition adducts. For example, the stereoselective addition of cyanide to isoquinoline or quinoline with a modified



Scheme 20 Chiral auxiliaries linked to the azine moiety

Evan's-type chiral oxazolidinone as the activating agent has been described [135]. Gladysz reported coordination of the azine nitrogen to a chiral metal complex as an efficient tool for activating the azine and promoting the diastereoselective addition of a Grignard reagent (Scheme 20a) [136, 137]. Pyridine carboxyaldehyde (**147**) has been used as the azine input in asymmetric processes; its condensation with chiral diols or diamines affords the chirally modified pyridine derivatives **148**, which can be activated for stereoselective addition. The synthetic sequence ends with hydrolytic removal of the auxiliary (Scheme 20b) [111]. Yamada reported a regio- and diastereo-selective process to prepare enantiopure α- and γ-substituted addition adducts based on the use of a chiral oxazolidine linked to the nicotinic moiety involving either the allyl tin derivative **83** (which leads to attack at the more reactive α-sites) or an allyl indium reagent (which affords the γ-substituted isomers **154**), both of which offer good diastereomeric excess (Scheme 20c) [138, 139].

In a different context, chiral reagents have been implemented in this chemistry. For instance, Liebscher and Itho developed the use of chiral acylating agents such as amino acid-fluorides **158** and -chlorides **156**, respectively, (Scheme 21). The outcome of the reaction of isoquinoline (**6**), TMS-CN (**14**) and *N*-protected α-amino acid fluorides is dictated by the nature of the protecting group: whereas Cbz- and

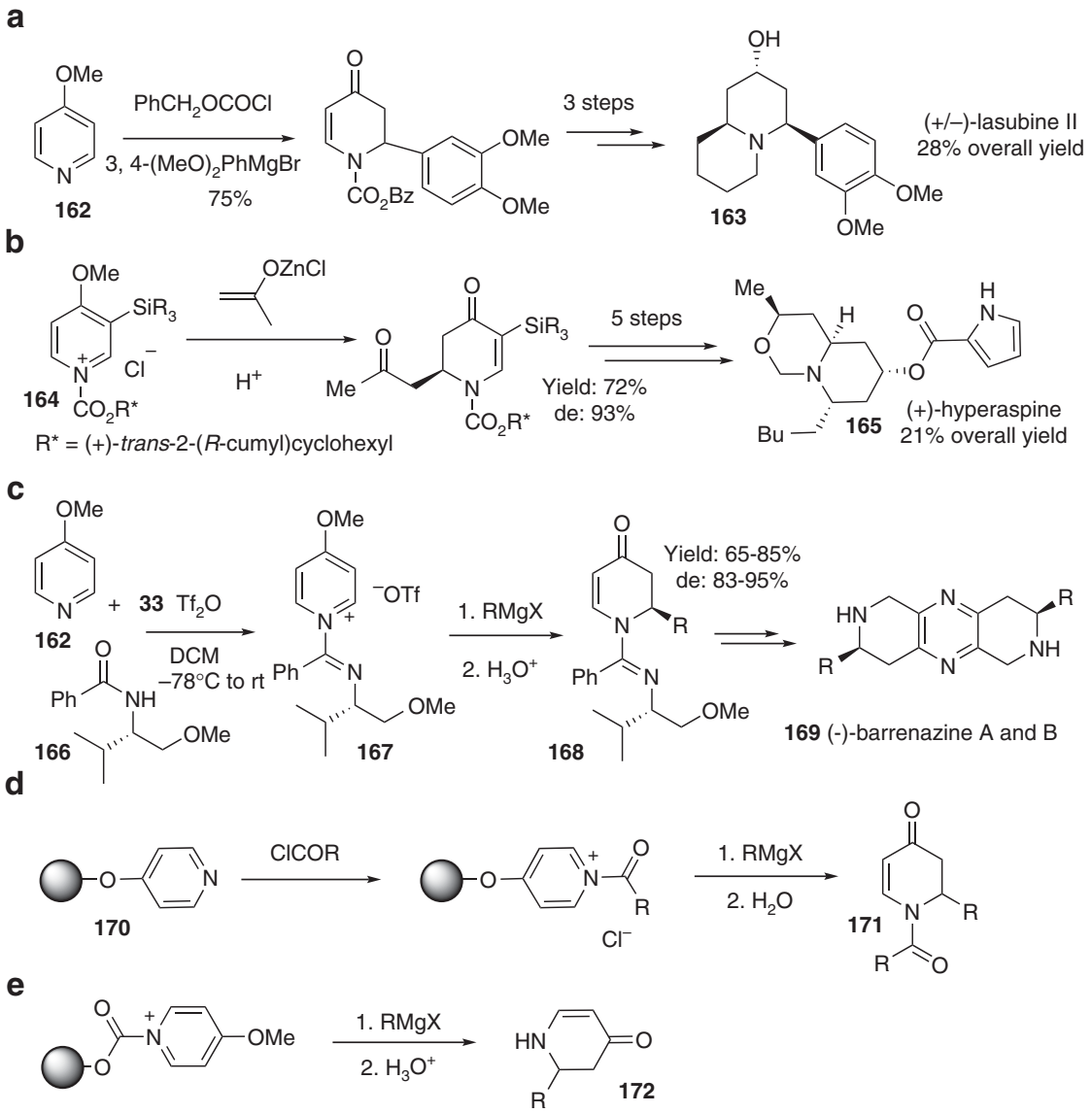


Scheme 21 Acid fluorides and chlorides in asymmetric Reissert-type processes

FMOC-protected amino acid fluorides afford the expected Reissert adducts **160** with a good stereoselectivities, the α-sulfonylamino acid fluorides undergo cyclization to adduct **161** [47, 140, 141]. Itho's protocol is amenable to using silyl enol ethers **157** as nucleophiles [142]. Gibson has used bulky asymmetric acid chlorides as substrates in a Reissert reaction with TMS-CN; the corresponding Reissert compound was then treated with aldehydes and sodium hydride to obtain the enantiopure adducts **4** (Scheme 3) [143].

An area that deserves special attention is the Comins methodology, which exploits the reactivity of *p*-methoxypyridine (**162**) in Reissert-type reactions (Scheme 22). This powerful and versatile synthetic approach represents an important tool for the preparation of natural products [144, 145]. The activation-nucleophilic addition protocol generates *N*-substituted-tetrahydropyridones, arising from the hydrolysis of the enol ether moiety of the initial adduct. This strategy was employed to prepare (±)-lasubine II (**163**) in three steps, using a Grignard reagent as nucleophile in the Reissert-type reaction (Scheme 22a) [146]. Chiral chloroformates provide the corresponding enantiopure adducts, which are versatile building blocks for the synthesis of alkaloids belonging to different groups. In this way, *p*-methoxypyridines can be further functionalized; the use of activating agents such as (+)-*trans*-2-(*R*-cumyl)cyclohexyl chloroformate can direct the attack of organometallic species to afford the expected adducts with good diastereomeric excesses. (+)-Hyperaspine (**165**) was obtained in six steps using this strategy (Scheme 22b) [147]. Charette recently published an asymmetric version of a protocol using a chiral amide-derived activating group (Scheme 22c). First, 4-methoxypyridine (**162**) was reacted with triflic anhydride (**33**) and the chiral amide **166** to generate in situ the salt **167**. Subsequent addition of a Grignard reagent yielded the tetrahydropyridone **168**, which is an advanced intermediate in the total synthesis of (-)-barrenazines A and B (**169**) [148, 149].

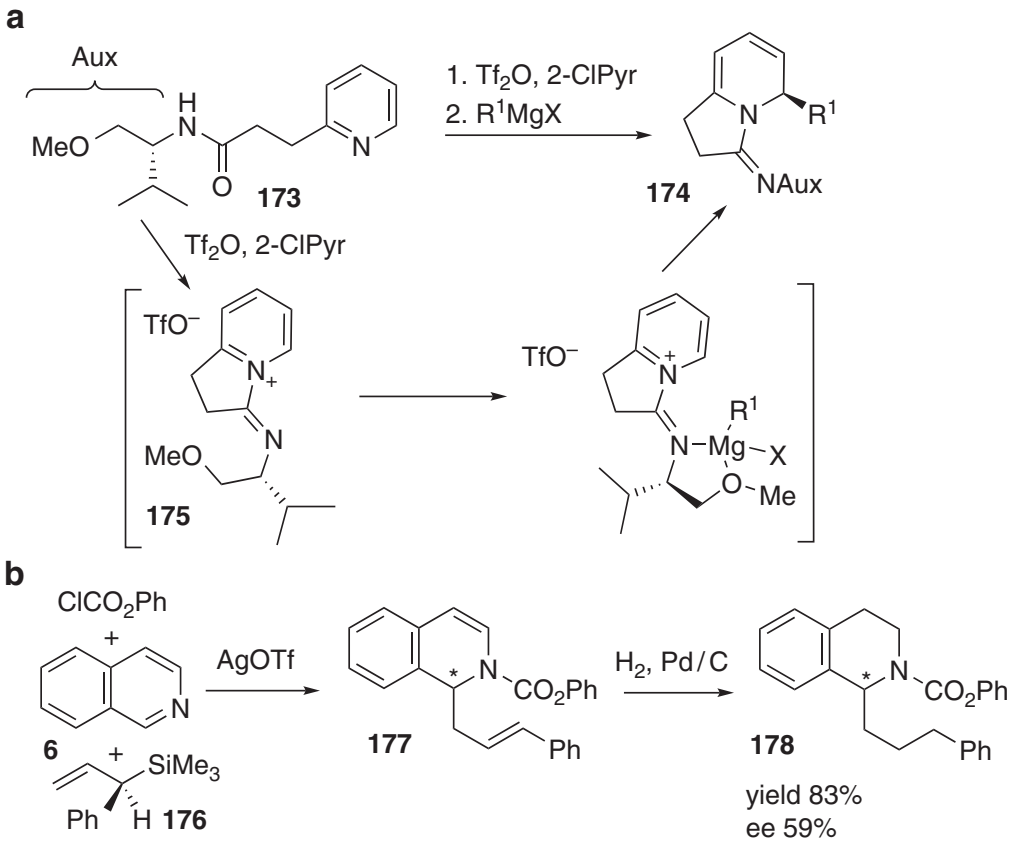
Incidentally, although in a different context, this Reissert-type chemistry has also been done on solid phase. In this regard, Munoz loaded a 4-hydroxypyridine



Scheme 22 Use of 4-methoxypyridines in activation–addition protocols

onto a Wang resin, and then reacted the resulting solid-supported pyridine **170** with acid chlorides and Grignard reagents to obtain the *N*-acyl-2-substituted-tetrahydro-4-pyridones **171**, which were isolated after cleavage under mild acidic conditions (Scheme 22d). A synthetic variant in which the 4-methoxypyridine is activated by the resin, produces the final adduct **172**, released as the corresponding N–H pyridone derivative (Scheme 22e) [150–154].

Coordinating groups have been introduced in the chiral activating agent, to direct the attack of the organometallic reagents. Charette has shown that the ether moiety in adduct **175** can coordinate with the Mg atom of a Grignard compound, and thereby guide the nucleophilic attack to one face of the azine (Scheme 23a) [155, 156]. Finally, the chirality can be directly transmitted from the nucleophile. Yamaguchi successfully employed this approach, using the chiral allylsilane **176** to prepare enantioenriched dihydroisoquinoline **178** (Scheme 23b) [157].



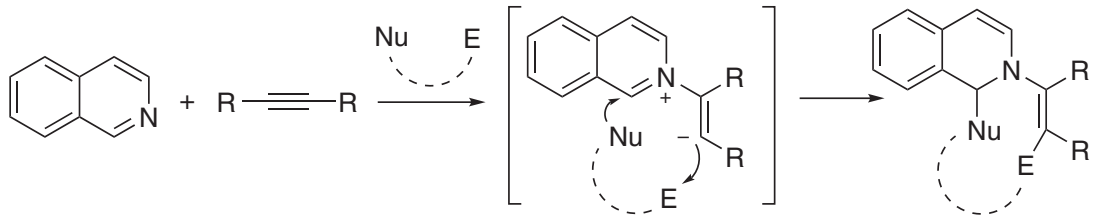
Scheme 23 Use of coordinating chiral auxiliaries and chiral nucleophiles

In summary, a wide variety of methods are available to prepare enantiopure Reissert-type adducts. Depending on the synthetic requirements, the use of chiral auxiliaries, enantioselective catalysis or chiral reagents may be the most suitable option.

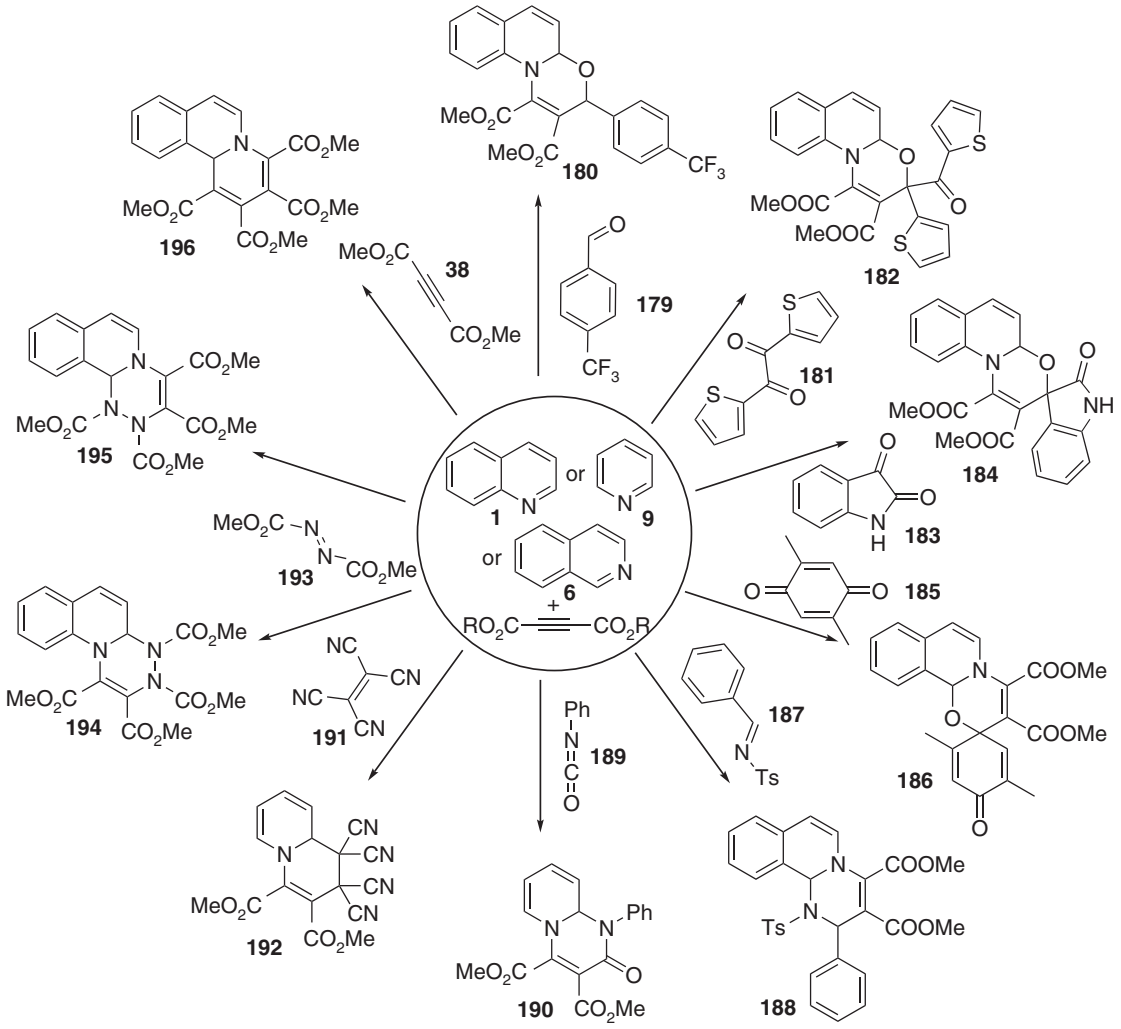
5 Dipole Formation and Domino Reactions

Dipoles enable a rich variety of transformations, with a considerable impact in organic synthesis; among them dipolar cycloadditions are especially productive. In some cases, complex domino reactions, processes in which the product of one elemental step is the reactant of the next one, are the result of apparently simple combinations.

When the reaction of an azine with activating agents involves the conjugate addition of a Michael acceptor or related species, a dipole is generated. Huisgen's systematic studies on dipolar cycloadditions include several reactions of this kind [158, 159]. The dipolar intermediates can react with other complementary partners, typically in concerted processes, or can trigger complex domino reactions. The most widely used activating agents for this chemistry are substituted alkynes (Scheme 24).



Scheme 24 Dipole formation from reactions of azines and substituted alkynes

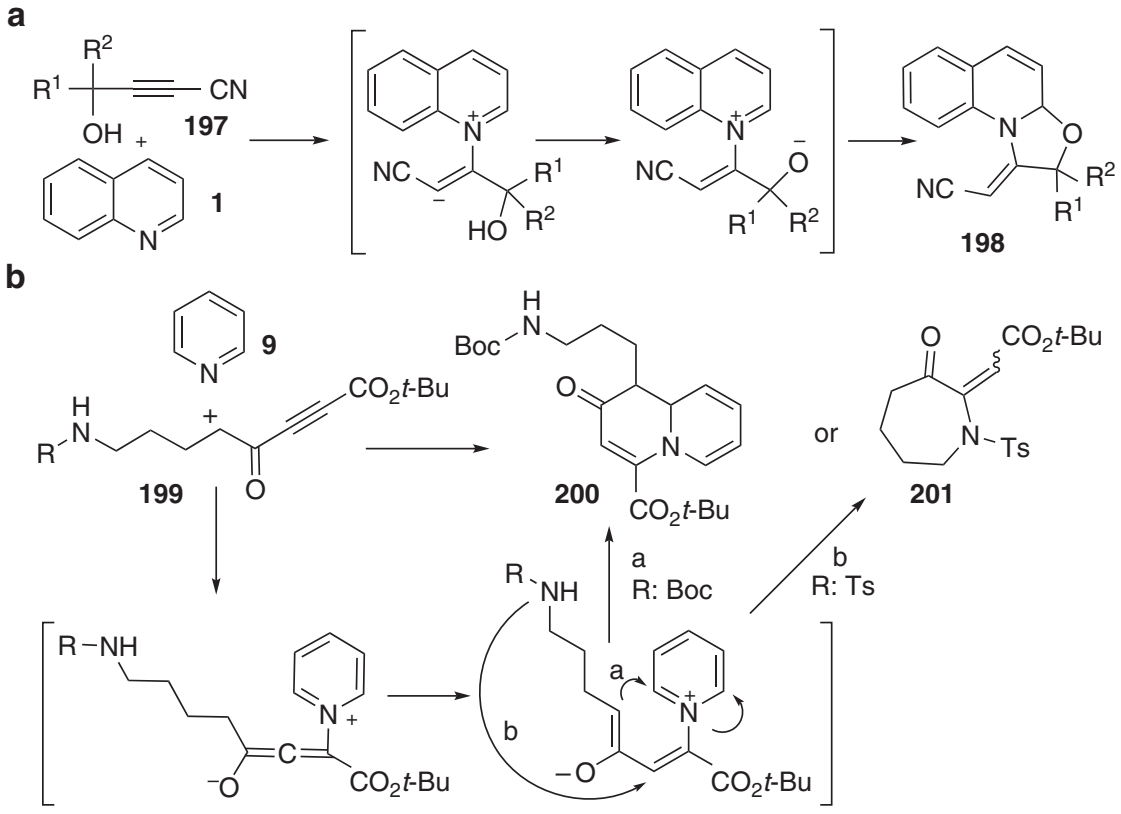


Scheme 25 MCRs involving dipolar intermediates

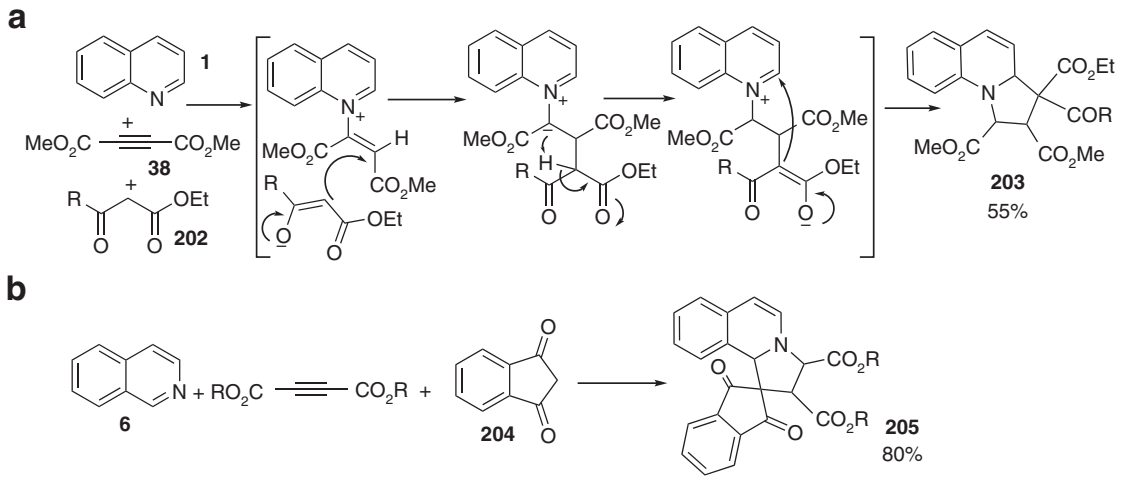
Scheme 25 shows representative examples of various chemotypes that can be generated with this simple and efficient strategy. Practically, all common azines and Michael acceptors react in these processes, and the range of the third component is also extremely wide. Aldehydes (such as **179**), ketones and α-dicarbonyls (such as **181**) afford the expected products in good yields; moreover, the cyclic carbonyl derivatives **183** and **185** lead to spiro-polyheterocycles **184** and **186**, respectively [160]. Interestingly, activated imines (such as **187**) are also reactive, which naturally

leads to 4CRs involving azines, alkynes, aldehydes, and amines. Isocyanates **189** yield the cyclic amides **190**. Tetracyanoethylene **191** is another good substrate, affording the highly substituted quinolizine **192** in a single step [161–170]. The reaction with azodicarboxylates **193** has been described by Huisgen in his comprehensive review [158, 159]. In the absence of a third component, two equivalents of alkyne can react to form adduct **196** in a chemodifferentiating ABB' process [66]. This historically relevant reaction was reported in a review by Krohnke in 1953 [171]. The Mironov group recently described an innovative approach for a combinatorial search for new MCRs based on this rationale, which enabled then to discover novel mechanistically related processes [172]. In this context, the Ma group described interesting related reactions involving other kinds of *N*-heterocycles [173, 174].

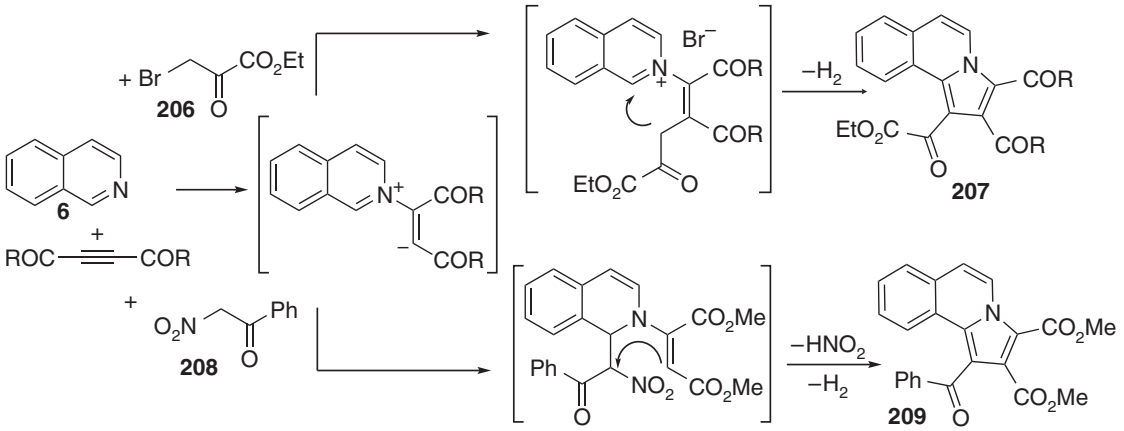
Modified versions of these reactions also have been described. Particularly attractive are the processes in which some of the components are linked. For instance, 4-hydroxybut-2-ynenitrile (**197**, Scheme 26a) contains both the activating alkyne moiety and the nucleophilic alcohol: thus, once the dipole is generated, a proton shift gives raise to the alkoxide anion ready to trap the azinium ion in an intramolecular manner to yield adduct **198** [175–178]. Similarly, an enolate (derived from the reaction of Michael acceptor **199** and pyridine) can trap the intermediate azinium moiety, to afford the quinolizidine ring system **200**. Interestingly, subtle changes in the substitution pattern of the reactive inputs can completely modify the reaction pathway. For instance, a tosyl group at the nitrogen



Scheme 26 Dipolar processes with bifunctional substrates



Scheme 27 β-Dicarbonyls in dipolar processes

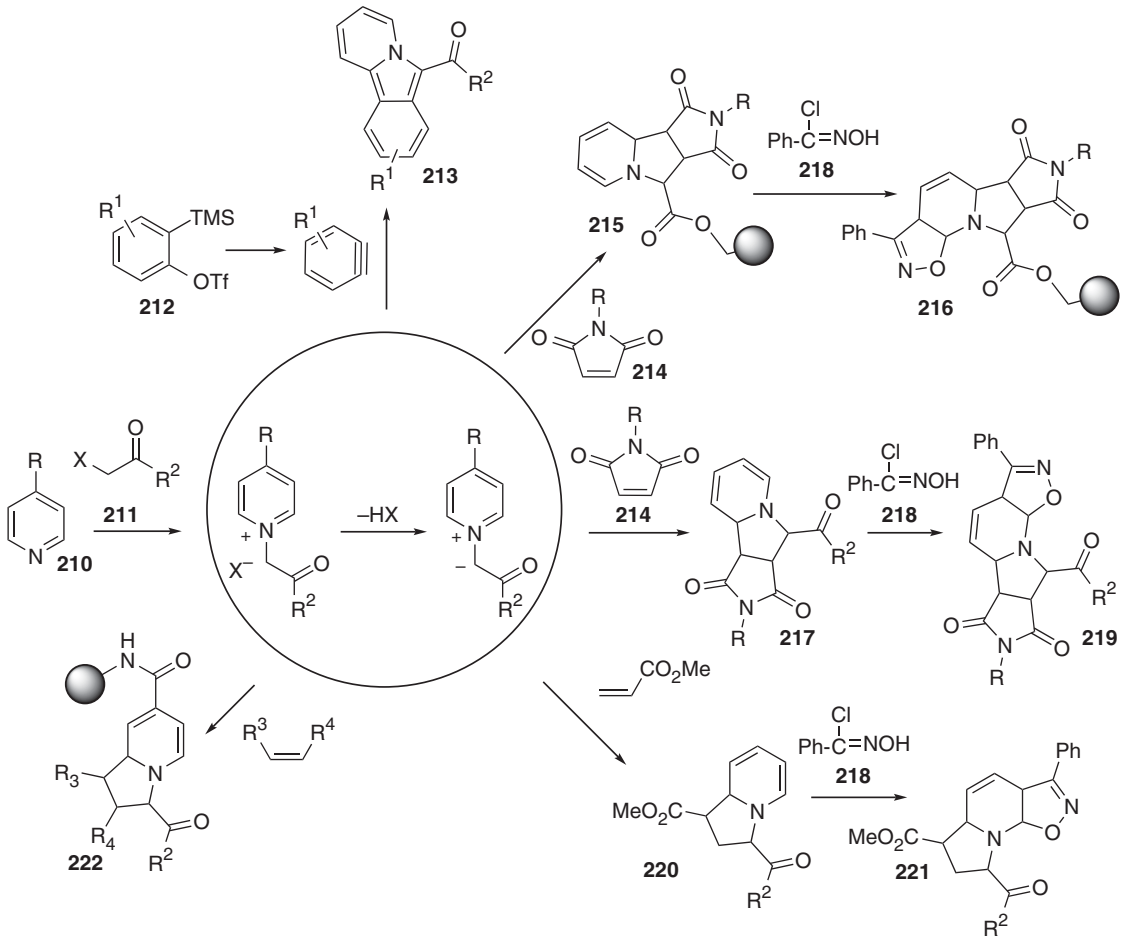


Scheme 28 Access to pyrroloisoquinolines via dipolar MCRs of azines

of the aminoalkyne **199** leads to the azepinone **201** (i.e., pyridine acts as leaving group in the dipole), whereas a Boc substituent in this reagent, leads to the normal dipolar process, affording the quinolizine **200** (Scheme 26b) [179].

Likewise, β-dicarbonyls **202** [180] react with quinolines and the acetylene dicarboxylates **38** to produce the pyrroloquinolines derivatives **203** in a single step (Scheme 27a), whereas the cyclic derivatives **204** lead to the corresponding spiro-compound **205** (Scheme 27b) [181, 182].

Distinct functional groups with acidic hydrogens can also promote these transformations. For instance, benzoylnitromethane (**208**) or ethyl bromopyruvate (**206**) react with isoquinoline (**6**) and acetylenedicarboxylates via the same dipolar mechanism to generate a pyrrolo[2,1-*a*]isoquinoline scaffold. However, in these cases, after closure of the 5-membered ring, a double-bond formation via dehydrogenation or nitrous acid elimination yields the fully aromatic ring systems **207** and **209** (Scheme 28) [82, 183].



Scheme 29 Azine-based dipolar [3+2] cycloadditions

Alkylation of the azine input with α-haloketones **211** or related compounds yields a different type of dipole (Scheme 29). Thus, the initially generated azinium salt, having highly acidic methylene hydrogens, can provide species suitable for undergoing [3+2] cycloadditions with a variety dipolarophiles. Interestingly, the resulting adducts (**215**, **217**, and **220**), featuring a dihydroazine moiety, may be engaged in a second cycloaddition with a nitrile oxide (**218**), leading to the final polycyclic products (**216**, **219**, and **221**, respectively) with high diastereoselectivity. The Huang group successfully introduced arynes (generated from the corresponding *o*-silylaryltriflates **212**) as dipolarophiles in this chemistry. Using this method, they obtained benzoindolizine **213**, which displays a scaffold frequently found in highly fluorescent materials, and is also a structural analog of the antitumor agent batracyclin [184]. These [3+2] cycloadditions occur also with other common dipolarophiles such as maleimides and substituted alkenes. Solid-supported versions of these processes have also been described [185–187].

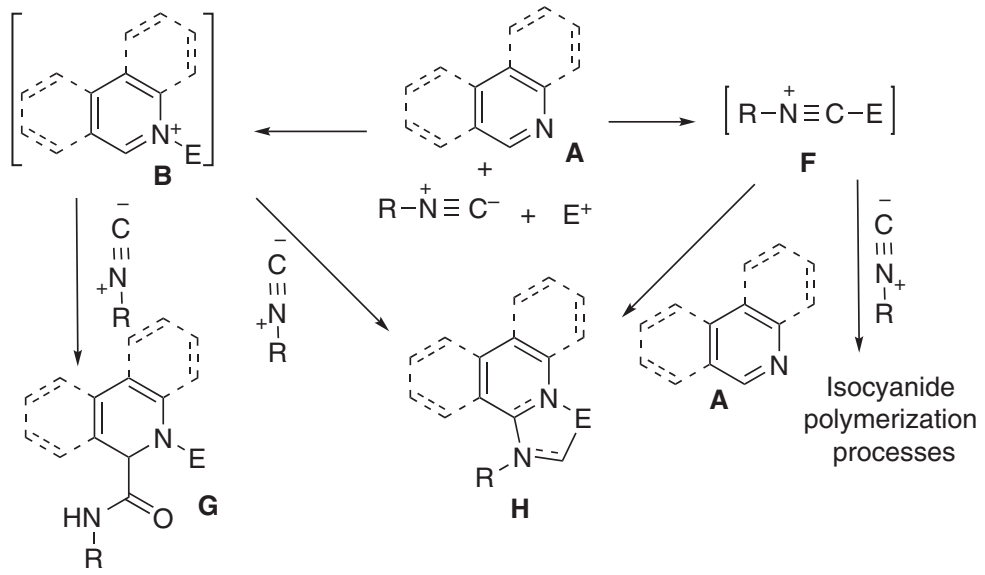
The structural variety obtained through the methodologies listed in this section is quite remarkable. The high bond-forming efficiency displayed in these transformations is also noteworthy. Most likely, the above mentioned features would be crucial to extend the use of this family of reactions in diversity oriented synthesis.

6 MCRs Involving Azines and Isocyanides

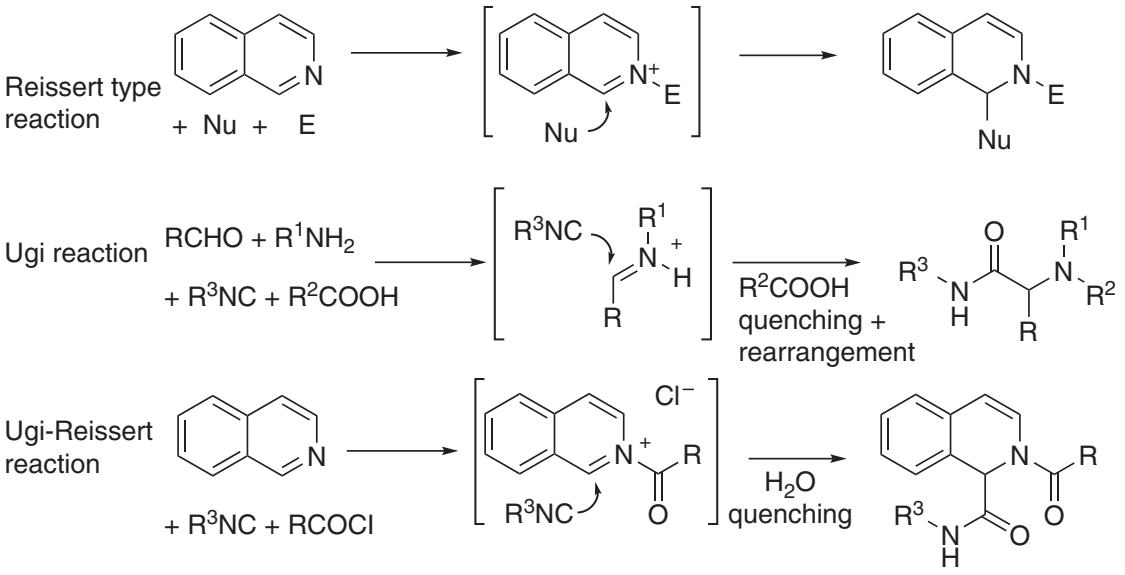
Use of isocyanides in Reissert-type MCRs greatly amplifies the complexity that can be generated in a single step. Indeed, the well-known *carbene-like* reactivity of isocyanides, combined with the rich chemistry of azines enables a wealth of transformations and cascade processes (Scheme 30). The synthetic outcome of these reactions is often controlled by the electronic effects of the substituents on the respective inputs. In Reissert-type chemistry, isocyanides typically react as nucleophiles, affording products of the general structure **G**. The carbon atom of the isocyanide normally ends up directly connected to the α-carbon of the azine. Alternatively, the isocyanide may attack the carbonyl of the acylazinium salt. In this case, an "imine-type" intermediate would be generated, and its nucleophilic nitrogen could promote a cyclization yielding adducts **H**. The same kind of structure can arise if the isocyanide reacts first with the activating agent and then with the azine nitrogen. Also, the intermediate formed by interaction of an isocyanide with an electrophilic partner can lead to undesired (in this context) polymerization processes (Scheme 30).

The mechanism leading to adduct **G** presents clear analogies with that of the well established Ugi MCR, in which the isocyanide attacks the electrophilic carbon of an iminium ion; for this reason, this process could be called the *Ugi–Reissert* reaction (Scheme 31). However, in this transformation, the adduct arises after a final hydration of the nitrilium ion, instead of undergoing the Mumm rearrangement as in the traditional Ugi reaction [188]. The novelty here lies in the use of *N*-acylazinium salts as a new source of reactive iminium ions for Ugi-type processes.

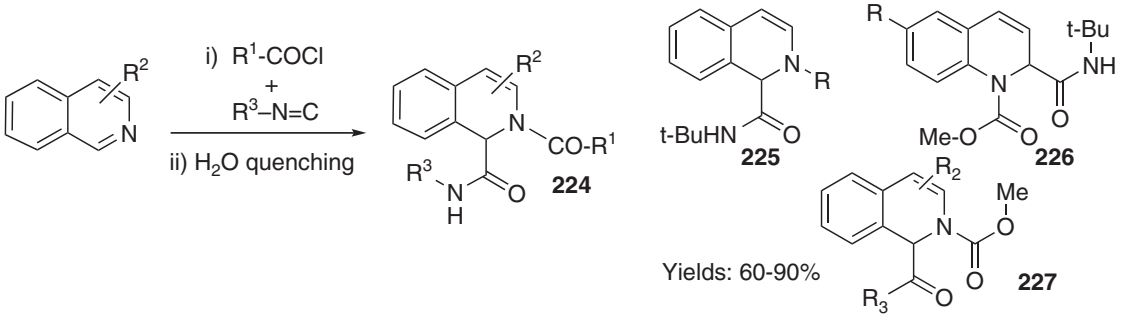
The *Ugi–Reissert* reaction is quite general [188]; it accepts a wide array of isocyanides, azines (excluding pyridine and derivatives lacking unsubstituted α-positions) and activating agents (chloroformates, acid chlorides, anhydrides,



Scheme 30 Azine-isocyanide MCRs



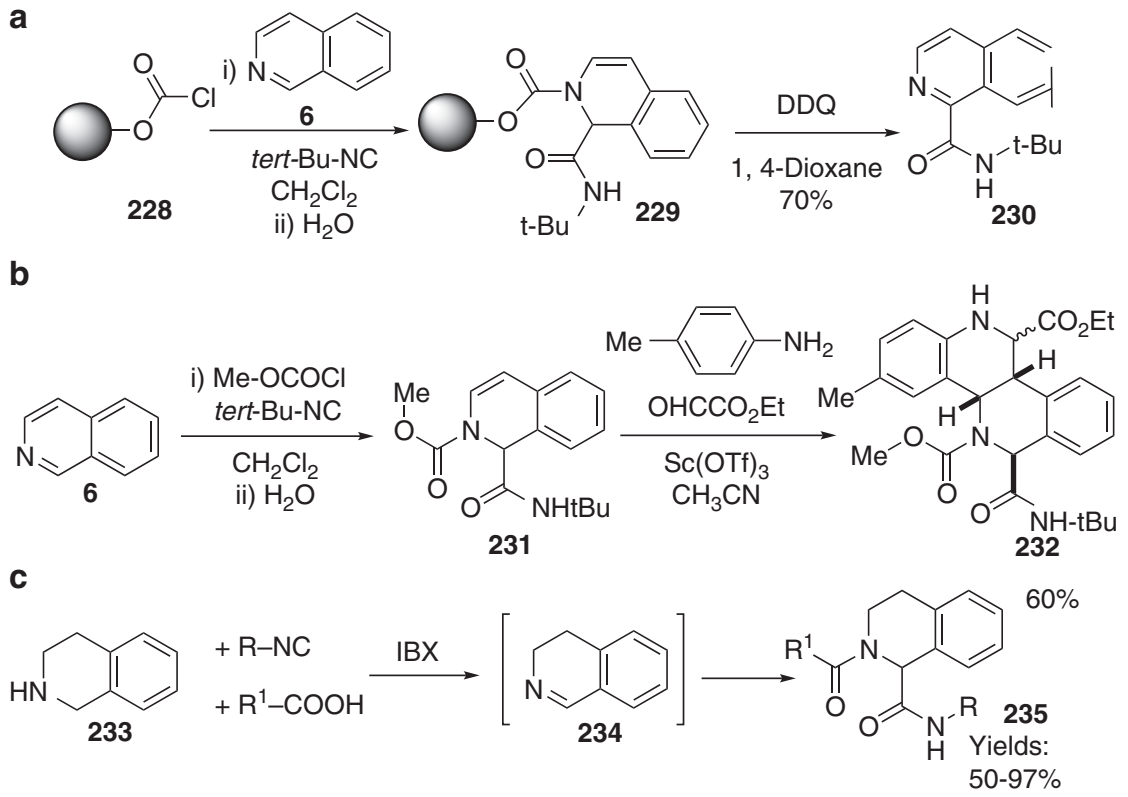
Scheme 31 Analogies between Reissert and Ugi MCRs



Scheme 32 The *Ugi–Reissert* reaction and representative adducts

and tosyl chlorides), affording the corresponding adducts in good to moderate yields (Scheme 32). In these reactions, the intermediate nitrilium ion is assumed to be stabilized via coordination with the nucleophilic species (either the carbonyl group or the chloride counter ion) and to be hydrolyzed via quenching during aqueous work up.

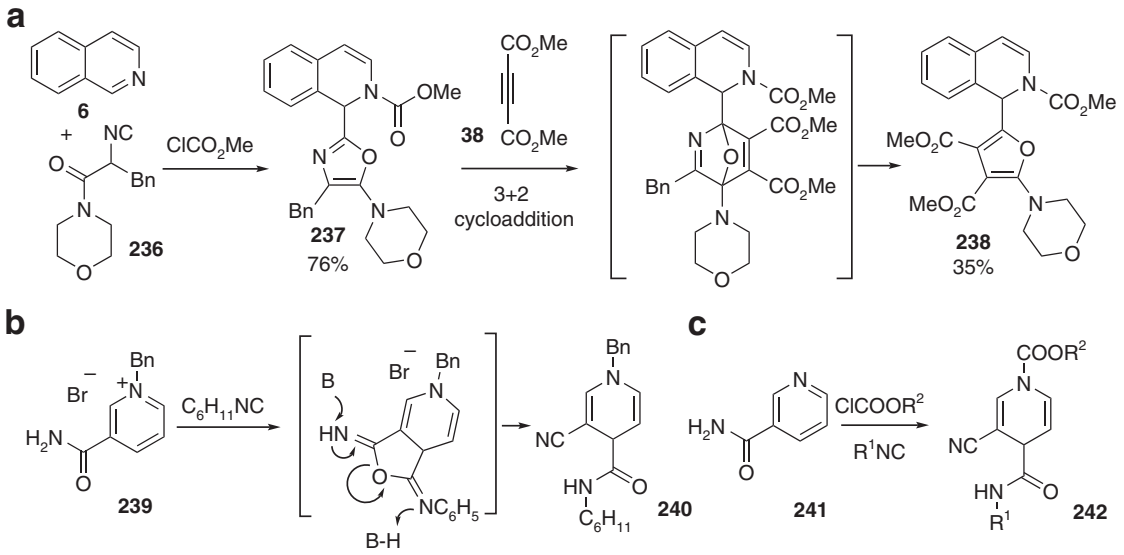
A solid-phase *Ugi–Reissert* reaction on chloroformate resin, has been reported. The product, the α-carbamoylated isoquinoline **230**, is released by oxidative cleavage (Scheme 33a). Interestingly, the enamide moiety in the adduct can be exploited to perform this process in tandem with a Povarov MCR [189, 190]. In this way, by interaction of dihydroisoquinoline **231** with aldehydes, anilines and a suitable Lewis acid catalyst, the polyheterocyclic system **232** was prepared (Scheme 33b). The Zhu group devised an innovative approach for the synthesis of this class of compounds. They employed the heterocyclic amine **233**, which was oxidized in situ to the dihydroisoquinoline **234** with IBX, to undergo the classic Ugi reaction. Remarkably, all the components are chemically compatible, allowing the sequence to proceed as a true MCR (Scheme 33c) [191].



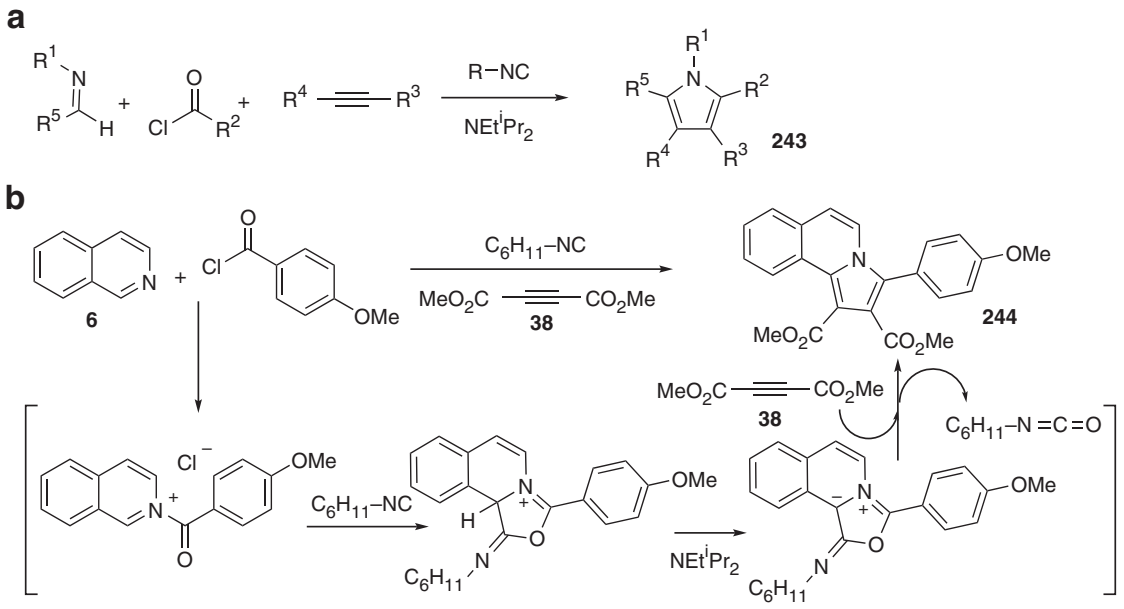
Scheme 33 *Ugi–Reissert* MCRs: a solid-phase version, post-synthetic transformations, and analogous processes

Zhu and coworkers implemented a family of Ugi-type MCRs, based on intramolecular trapping of the intermediate nitrilium ion by a carboxamido group, to prepare diversely substituted oxazoles as versatile synthetic intermediates [192–194]. They later reported an interesting example of the *Ugi–Reissert* process using this feature (**237**, Scheme 34a) [195]. This strategy enabled the direct addition of isocyanides to the *N*-alkyl nicotinamide salts **239**. However, the different substitution pattern of the carboxamido group, led to a different outcome: isomerization of the putative bis-iminofurane intermediate to the cyano-carbamoyl derivative **240**. Remarkably, the process is also efficient in a Reissert-type reaction (Scheme 34b, c) [196].

In a similar context Arndtsen developed a new pyrrole synthesis from alkynes, acid chlorides either imines or isoquinolines, based on the reactivity of isocyanides (Scheme 35a) [197]. Although all atoms from the isocyanide are excluded from the final structure, its role in the reaction mechanism is crucial. The process takes place through the activation of the imine (isoquinoline) by the acid chloride to generate the reactive *N*-acyliminium salt, which is then attacked by the isocyanide to furnish a nitrilium ion. This cationic intermediate coordinates with the neighboring carbonyl group to form a münchnone derivative, which undergoes a [3+2] cycloaddition followed by subsequent cycloelimination of the isocyanate unit, to afford the pentasubstituted pyrrole adducts **243** and **244** (Scheme 35a, b).

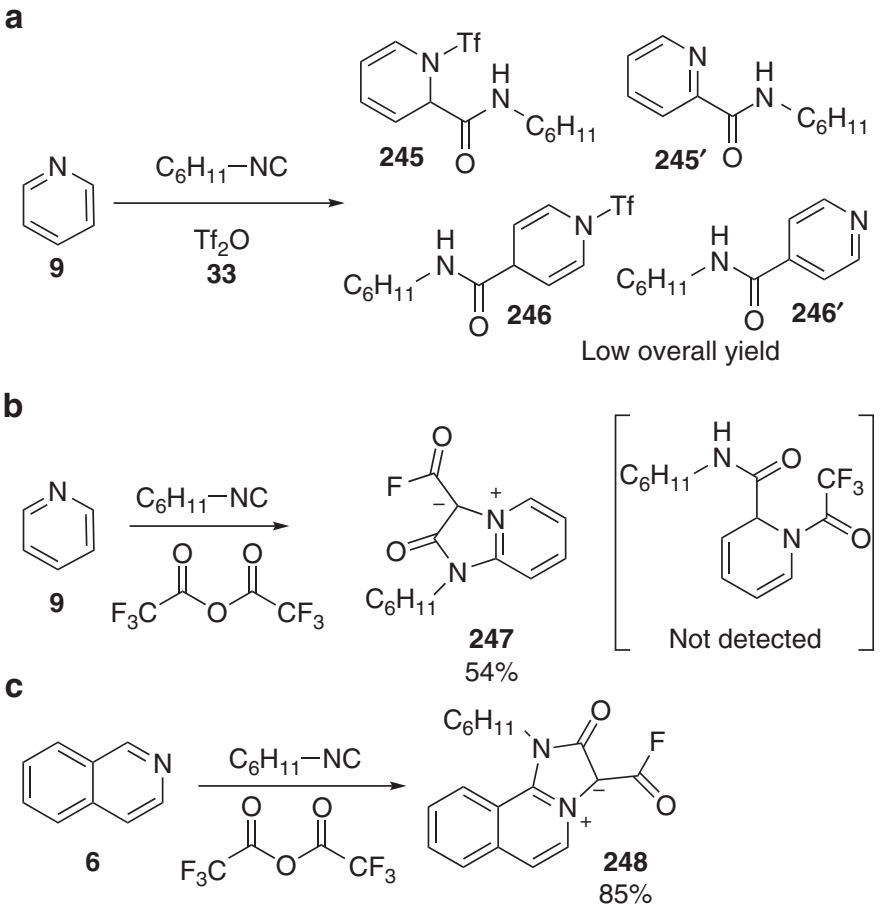


Scheme 34 Internal trapping of the nitrilium intermediate by carboxamido groups



Scheme 35 Arndtsen pyrrole synthesis

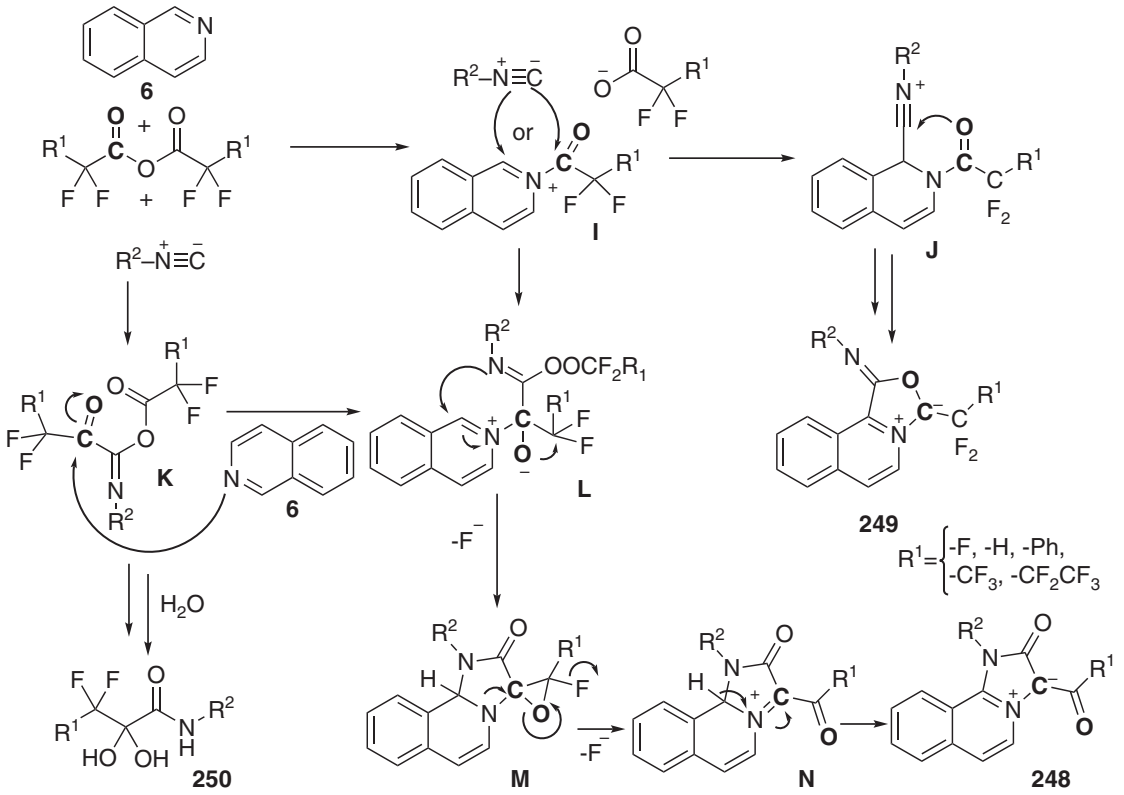
In many of the precedent reactions, pyridines are inert, and activation of this fundamental heterocycle remains problematic. To overcome this problem, more powerful activating agents have been tested. For instance, Corey explored the use of triflic anhydride (**35**) as an efficient method to link a variety of nucleophiles to the pyridine γ-position (see **34**, Scheme 6) [49]. This reaction in the presence of isocyanides affords a mixture of the α-and γ-carbamoylated dihydropyridines **245** and **246** together with the corresponding oxidized products **245′** and **246′**, respectively, in low overall yield (Scheme 36a). A major problem here is the massive degradation of the isocyanide under these rather drastic conditions. Trifluoroacetic



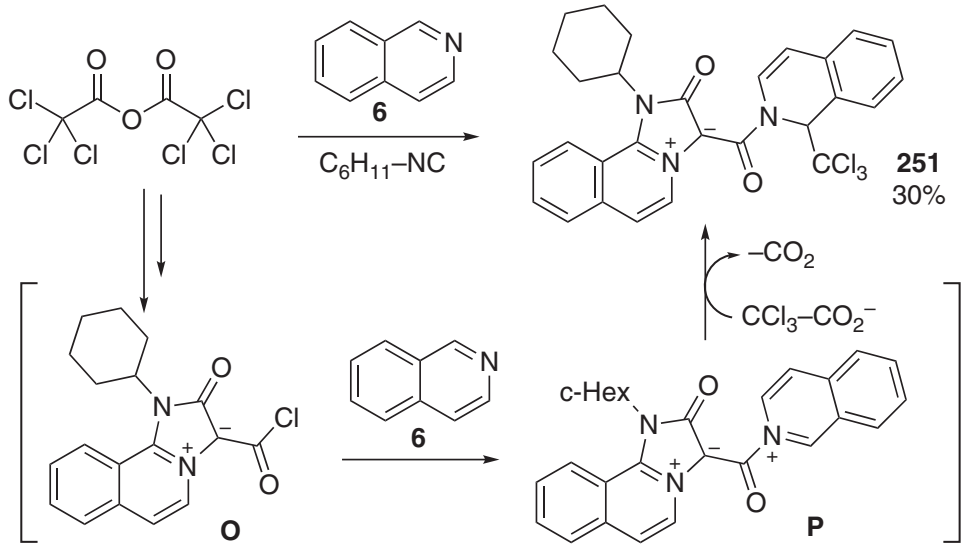
Scheme 36 Tf_2O- and TFAA-promoted isocyanide-azine MCRs

anhydride (TFAA) was then evaluated as a milder surrogate. Surprisingly, the reaction did not yield the expected Ugi–Reissert product, but instead gave the mesoionic acid fluoride **247** (Scheme 36b). Isoquinoline behaves similarly affording the analogous product **248**, although in higher yields (Scheme 36c) [198].

The unusual connectivity pattern of the dipoles **247** and **248**, whereby the isocyanide nitrogen is linked to the α-carbon of the azine, suggests a markedly distinct reaction mechanism (Scheme 37) to that of the *Ugi–Reissert* reaction. A reasonable mechanistic proposal may involve the formation of the *N*-acylazinium salt **I**, which would then be attacked at its α-position by the isocyanide, then leading to the Arndtsen-type dipoles **249** (which have been isolated in some cases). Alternatively, the isocyanide can attack the activated carbonyl group in **I**, triggering a cascade leading to the generation and subsequent transformation of intermediate **L**. This species can undergo cyclization, followed by ring closure to epoxide **M**, rearrangement, formal elimination of HF, and aromatization, to yield dipole **248**. Yet another possibility is that the isocyanide attacks the anhydride to form the intermediate **K**, a direct precursor of the dipolar species **L**. This mode of activation for isocyanides has been investigated by El Kaim, who promoted a series of useful transformations based on this reactivity, leading to products such as trifluoropyruvamides **250** (R = F) [199–201].

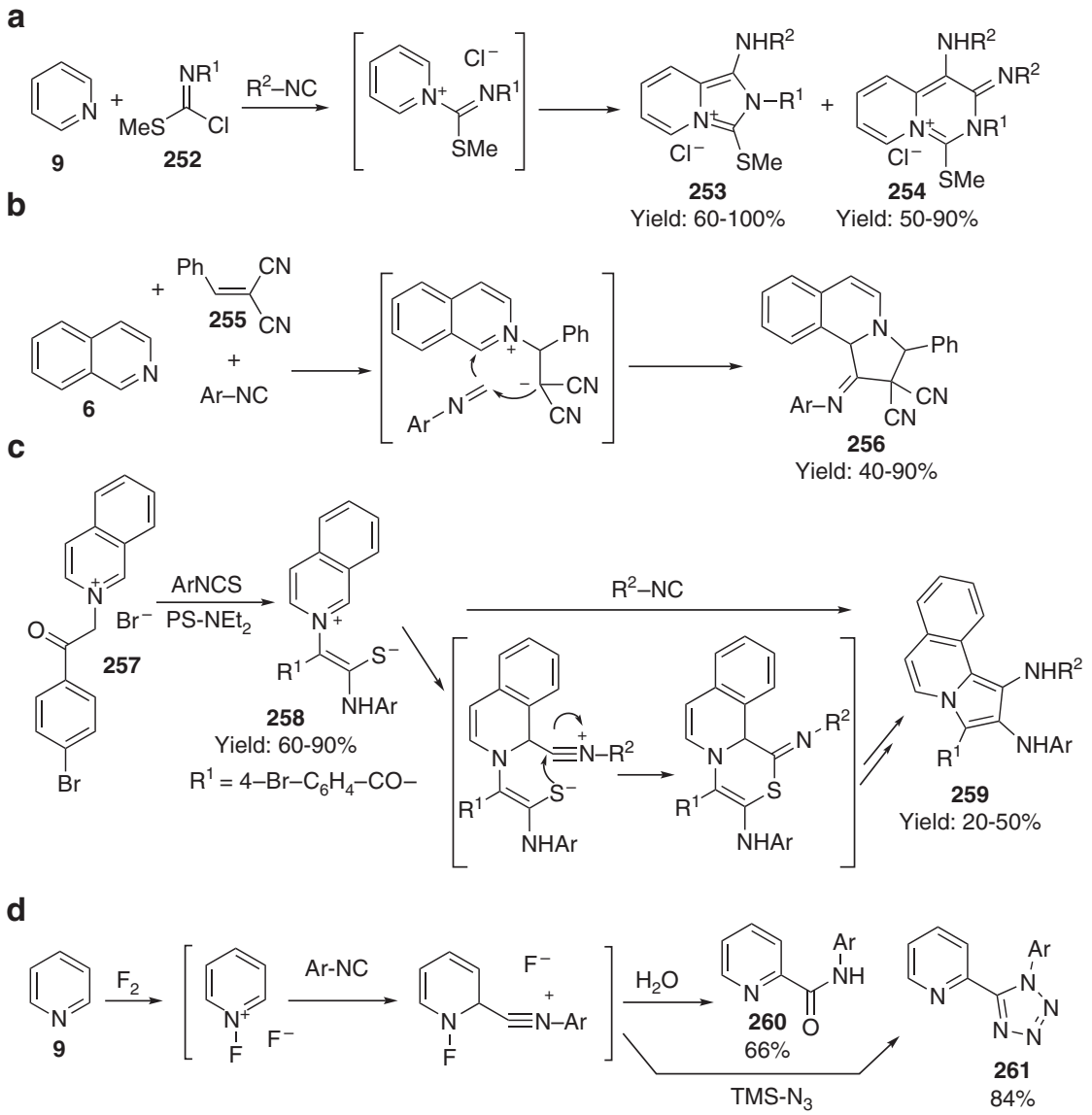


Scheme 37 Mechanistic proposals for the MCR of azines, isocyanides, and TFAA



Scheme 38 Cascade reaction of azines and isocyanides promoted by TCAA

The scope of the reaction is quite general, allowing reasonable variation for each component. Apart from TFAA, substituted difluoroanhydrides also react, yielding the expected derivatives with diverse groups attached to the exocyclic carbonyl moiety. Chlorinated anhydrides are less reactive: and only trichloroacetic anhydride (TCAA) leads to dipole **251** in moderate yield (Scheme 38). A new



Scheme 39 Isocyanide-azine MCRs promoted by various activating agents

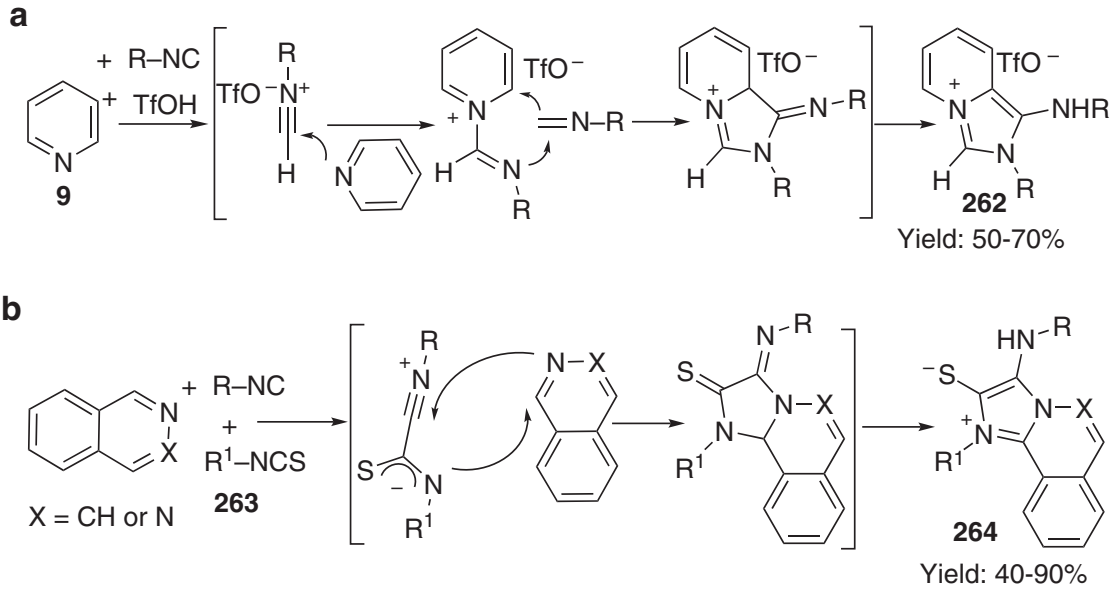
domino reaction derives, in this case, from the higher reactivity of the putative acid chloride adduct **O**, which can interact with another isoquinoline unit to generate a new *N*-acylisoquinolinium cation **P**, which in turn may undergo an α-trichloromethylation [198, 202].

Other electrophilic reagents have been used to activate azines in isocyanide-promoted reactions. For example, reaction of the methyl chlorothioimidates **252** with pyridines and isocyanides provides convenient access to the fused imidazolium salts **253** (Scheme 39a). The isocyanide attacks the α-carbon of the activated pyridinium salt, and the resulting intermediate is then trapped by the nitrogen of the activating agent to yield the product. The competing reaction of double isocyanide insertion to give **254** has also been described [203]. Substituted alkenes also react efficiently in analogous processes. For example, pyrroloisoquinoline derivative **256** was obtained in a straightforward manner by interaction of isoquinoline, Michael

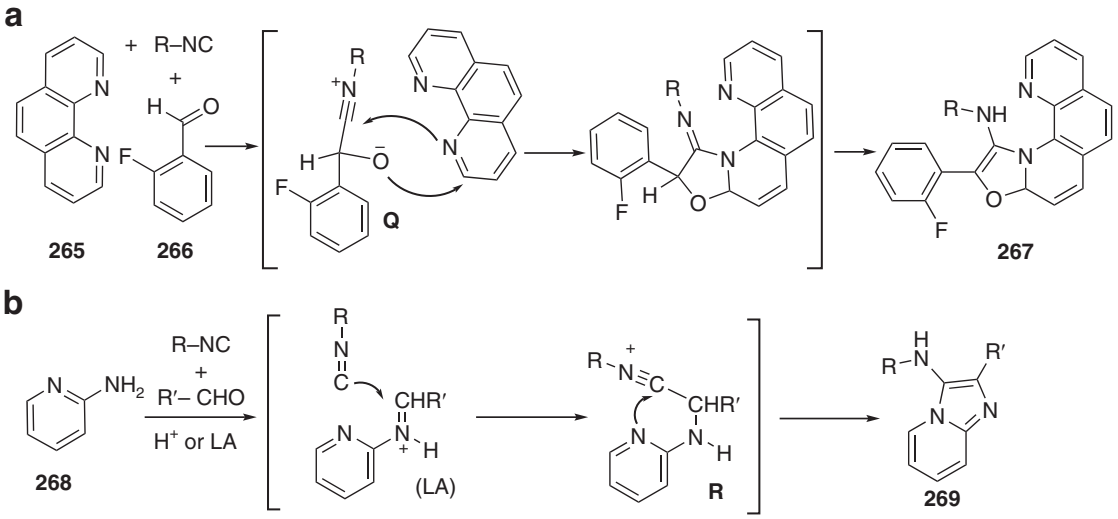
acceptor **255** and aromatic isocyanides (Scheme 39b) [172, 204, 205]. Similarly, Ley reported that reaction of an isocyanide with the isoquinolinium dipole **258** (generated from the interaction of the salt **257** with isothiocyanate) initiates a sequence yielding amino-substituted pyrroloisoquinolines (**259**), pyrroloquinolines and indolizines (Scheme 39c) [206]. Fluorine has also been used as activating agent in a bicomponent processes in which pyridine and isocyanides react to form the picolinamides **260** or the tetrazoles **261**, whereby the intermediate nitrilium ion is hydrolyzed or trapped with TMS-N_3, respectively (Scheme 39d) [207, 208].

Alternative activating pathways are based on the coordination of the isocyanide to the electrophilic reagent to furnish a nitrilium intermediate, which is the actual reactive species attacked by the azine (see intermediate **K** in Scheme 37) [201]. In this regard, Berthet described the reaction of azines and isocyanides with triflic acid to obtain the imidazopyridinium salts **262**, presumably through a cascade involving double isocyanide incorporation. Interestingly, one equivalent of the isocyanide generates the initial electrophilic intermediate, which goes on to be attacked by the azine, and subsequently, the second equivalent of the isocyanide acts as the next nucleophile; the sequence terminates upon nucleophilic ring closure promoted by the amidine nitrogen (Scheme 40a) [209]. Related processes, in which the isocyanide is activated by acidic species, have been described by Shaabani [210–212]. Similar connectivity patterns arise from the interaction of azines with TOSMIC or isocyanoacetate [213, 214]. This reactivity (isocyanide activation) was further exploited by Mironov et al., who reacted isocyanides with isothiocyanates and azines (isoquinolines or phtalazines) to prepare compounds **264** (Scheme 40b).

Mechanistically related processes include the reaction of isocyanides with aldehydes for in situ generation of the activated species, which is then attacked by the azine (Scheme 41a). This strategy has been harnessed in a convenient synthesis of



Scheme 40 MCRs involving isocyanide activation mechanisms

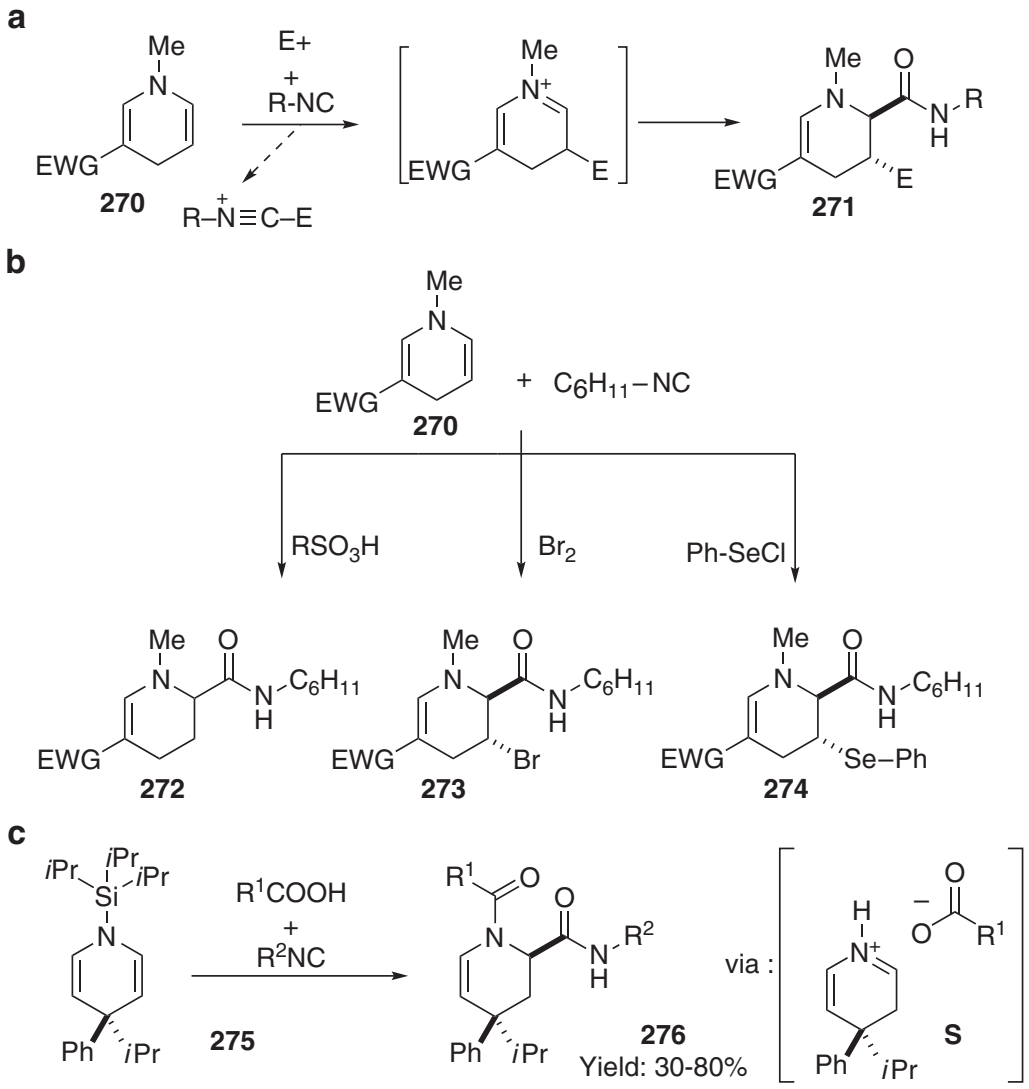


Scheme 41 Additional isocyanide-activation processes

the fused dihydrooxazoles **267**: the dipolar intermediate **Q** activates the azine, whereas the alkoxide attacks as the nucleophile; the final product is obtained after a proton shift [215]. The Bienaymé-Blackburn-Groebcke MCR – in which an α-amino-azine, an aldehyde and an isocyanide react to yield the fused imidazo-azine systems **269** (Scheme 41b) – could be considered in this section, as the heterocyclic nitrogen of the azine intramolecularly attacks the activated nitrilium species **R**, which is formed by addition of the isocyanide to the in situ generated imine. In fact, this MCR constitutes the most reliable access to these products. The process has been widely modified in each component, and has enabled the preparation of a wide range of bioactive compounds [216–222].

Alternative reaction pathways exploring different synthetic possibilities have been studied. For instance, electron-rich dihydroazines also react with isocyanides in the presence of an electrophile, generating reactive iminium species that can then be trapped by the isocyanide. In this case, coordination of the electrophile with the isocyanide must be kinetically bypassed or reversible, to enable productive processes. Examples of this chemistry include the hydro-, halo- and seleno-carbamoylation of the DHPs **270**, as well as analogous reactions of cyclic enol ethers (Scheme 42a) [223, 224]. *p*-Toluenesulfonic acid (as proton source), bromine and phenylselenyl chloride have reacted as electrophilic inputs, with DHPs and isocyanides to prepare the corresponding α-carbamoyl-β-substituted tetrahydropyridines **272**–**274** (Scheme 42b). Wanner has recently, implemented a related and useful process that exploits *N*-silyl DHPs (**275**) to promote interesting MCRs. These substrates are reacted with a carboxylic acid and an isocyanide in an *Ugi–Reissert*-type reaction, that forms the polysubstituted tetrahydropyridines **276** with good diasteroselectivity (Scheme 42c) [225]. The mechanism involves initial protiodesilylation to form the dihydropyridinum salt **S**, which is then attacked by the isocyanide, en route to the final adducts.

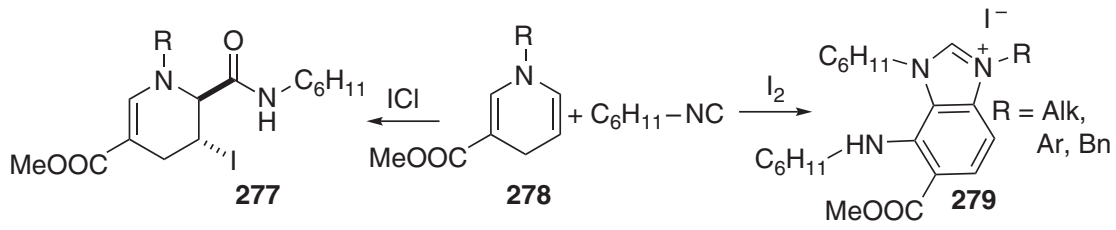
Suprisingly, the use of iodine in an attempted iodocarbamoylation of a DHP led instead to the benzimidazolium salt **279**; in contrast, iodine monochloride (ICl)



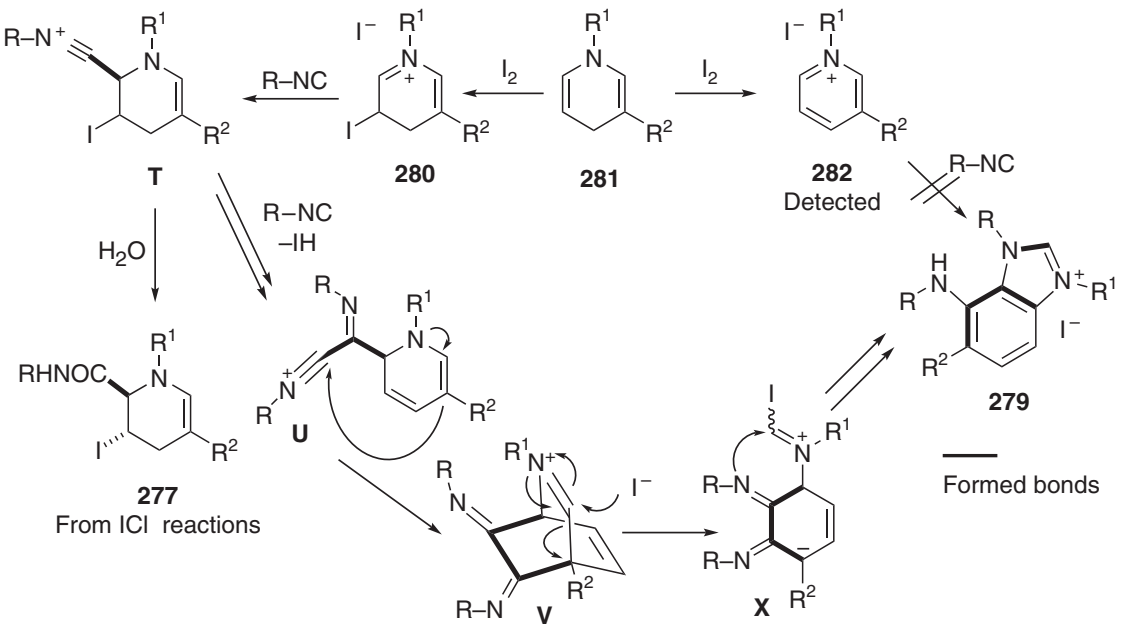
Scheme 42 Hydro-, halo- and seleno-carbamoylation of dihydropyridines

afforded the expected iodo-carbamoylated tetrahydropyridine **277** (Scheme 43) [226]. The scope of this unprecedented transformation was studied through systematic variation of the substituents and was found to be quite general: aliphatic, aromatic, and benzylic isocyanides have been reacted with a variety of DHPs bearing several electron-withdrawing groups (Scheme 43). The use of labeled precursors (^{2}H-DHPs and ^{13}C-isocyanides) provided meaningful data for establishing a mechanistic rationale.

Although isolated in small amounts, the pyridinium salts **282** (arising from the iodine-mediated oxidation of DHPs **281**) do not afford benzimidazolium salts **279** in the presence of isocyanides. A likely pathway may start with the iodo-dihydropyridinium intermediate **280**, which can be formed by interaction of iodine with the reactive double bond of the DHPs (Scheme 44). The isocyanide may subsequently attack these species to generate the nitrilium ion **T**, which interacts with a second equivalent of isocyanide to form cation **U**. This intermediate undergoes an intramolecular trapping by the enamine unit to close the bicyclic system **V**



Scheme 43 Reactions of isocyanides, DHPs and different iodonium sources



Scheme 44 Mechanistic proposal for the formation of benzimidazolium salts **279**

(Scheme 44). Iodoiminium **X** may then be formed by iodide-mediated fragmentation, possibly evolving through ring closure and subsequent aromatization to yield the final product **279**. In the presence of ICl, the halocarbamoylated tetrahydropyridine **277** is formed by the standard hydrolysis of nitrilium ion **T**. Therefore, the nature of the free anion in the mixture appears to be critical for stabilizing the nitrilium species and consequently promoting the formation of either **279** or **277**. Furthermore benzimidazolium salts **279** were tested in screening assays, looking for new inhibitors for human Prolyl Oligopeptidase, (an enzyme expressed in the central nervous system and involved in mental disorders), and some derivatives displayed potent and selective inhibitory activities [227].

As a final remark for this section, it is evident that the complexity of some processes together with the strikingly different synthetic outcomes, originated by slight changes in the reactants, reflects our low capacity of prediction for these MCRs. Therefore, more experimental work is needed to generate enough data that may enable a future rationalization for these fascinating cascades.

7 Conclusions

Reissert's initial discovery sparked research that continues to provide ever-growing combinations of azines, activating agents, and nucleophiles for countless synthetic applications. The structure of azines enables reactions with at least two other components, thus making them a privileged class of reactants for the development of new MCRs. The combination of azines with other types of bidentate compounds, such as alkenes and isocyanides, can trigger complex cascade reactions, elegantly leading to the corresponding MC-adducts in a single step. These products often feature intricate connectivities and structural motifs, that are nearly impossible to construct through classical stepwise approaches. The Reissert reaction and mechanistic variations thereof provide ready access to several types of *N*-heterocyclic systems, including the most common scaffolds found in natural products and bioactive compounds. Furthermore, the modularity of this chemistry makes it very attractive for generating the structural diversity sought in drug discovery. Future work in this area should expand the already great impact of these methodologies on organic synthesis.

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Multicomponent Access to Functionalized Mesoionic Structures Based on TFAA Activation of Isocyanides: Novel Domino Reactions

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The reactions of azines (isoquinolines, pyridine) with TFAA and isocyanides in a new domino process yield mesoionic acid fluorides with an imidazo[1,2-*a*]azine core. This multicomponent reaction has a general character, tolerating a wide range of substitution patterns on each component, and displays an unprecedented arrangement of reaction pathways. The protocol allows the incorporation of a fourth synthetic input by the reaction of a suitable nucleophile (alcohols, thiols, amines) with the acid fluoride moiety.

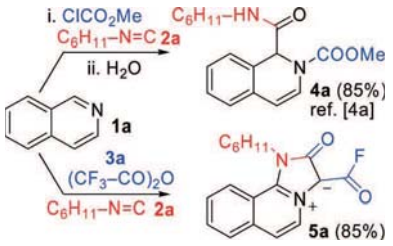
Introduction

Multicomponent reactions (MCRs, domino processes in which three or more starting materials interact to form an adduct) are specially attractive in organic synthesis because they maximize complexity and convergency while using structurally simple substrates in a single operation.[1] This approach is particularly beneficial for the preparation of libraries of compounds in which short synthetic sequences are mandatory. In this context, the participation of heterocyclic structures is critical as heterocycles are the most common motifs found in natural products and drugs, and are often considered privileged substructures.[2] The rich and intrinsic reactivity of heterocyclic systems brings fascinating possibilities to the design and implementation of domino reactions. However, the manifold evolutionary pathways of such complex systems make reliable predictions difficult and call for detailed mechanistic and synthetic experimentation. Therefore the development of new and efficient MCRs involving the participation of important heterocycles remains a challenging task in organic synthesis due to their wide-ranging applications in medicinal chemistry.[3]

Results and Discussion

Reactivity Studies

Continuing our interest in the development of MCRs based on heterocycles,[4] herein we report the direct functionalization of azines (pyridine, isoquinoline, etc.) with isocyanides and acylating agents to form new mesoionic structures.[5] We previously disclosed an efficient Ugi–Reissert reaction involving the interaction of isoquinolines, chloroformates and isocyanides in which the activated azine is carbamoylated at the α-position by the isocyanide to give dihydroazines such as **4a** (Scheme 1).[4a] Arndtsen and Mironov and their co-workers recently described related processes involving, respectively, acid chlorides and isothiocyanates in isocyanide MCRs.[6]



Scheme 1. Interaction of isoquinoline, acylating agents and isocyanides.

Several azines (pyridines for instance) are, however, inert under these conditions. In our search for more potent activation reagents to overcome this limitation and also to introduce a new point of diversity, we considered the use of triflic anhydride (Tf_2O), which was recently introduced by Corey and Tian to activate pyridines in the presence of C-nucleophiles.[7] However, its interaction with pyridine and isocyanides led to a mixture of α- and γ-carbamoylated *N*-triflyl-1,2- and 1,4-dihydropyridines and their oxidation products (the corresponding pyridines) in low overall yields, together with significant isocyanide polymerization. We then investigated the reactivity of trifluoroacetic anhydride (TFAA) in these systems. On mixing isoquinoline (**1a**) with

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Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

cyclohexyl isocyanide (**2a**) and TFAA (**3a**) in dry THF, we isolated the mesoionic acid fluoride **5a** as a stable crystalline solid in 25% yield (Scheme 1).

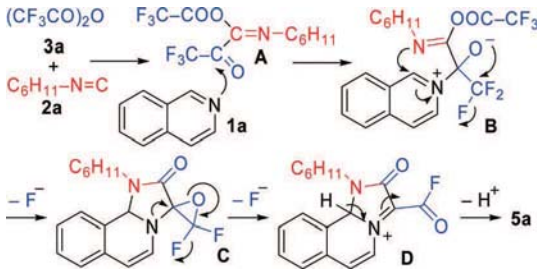
Optimization of the process led us to perform the reaction in anhydrous CH_2Cl_2 with isoquinoline, TFAA and the isocyanide in a stoichiometric ratio of 1:2:3, which increased the yield of **5a** up to 85%. The structure of this compound was unambiguously established by spectroscopic methods and confirmed by X-ray diffraction (Figure 1).[8] A related dipole has been prepared by Moody et al. through a stepwise synthesis by the intramolecular reaction of a carbenoid with the nitrogen atom of a pyridine.[9]

Figure 1. View of the X-ray crystal structure of **5a**.

Mechanistic Proposal

Regarding the constitution of acid fluoride **5a**, the connectivity between the three components indicates the occurrence of a completely different process, overriding the known pathway leading to the Ugi–Reissert products **4**. Note that the isocyanide moiety is linked to the isoquinoline ring through the N atom in the acid fluoride **5a**, whereas in the former process, which leads to **4a**, the bonding occurs through the C terminal atom. A plausible mechanistic explanation may involve the initial activation of the isocyanide by the TFAA, previously described by El Kaïm and co-workers,[10a,10b] to afford an adduct **A**. They have successfully developed this chemistry to promote a variety of useful transformations based on the reactivity of the trifluoropyruvamide intermediates.[10c,10d] In our system, this species undergoes nucleophilic attack by the isoquinoline to generate a reactive dipole **B**, which may evolve by intramolecular addition of the imine moiety to the α-position of the azinium ion and by fluoride elimination promoted by the oxyanion. The highly reactive amino epoxide intermediate **C** (or related species) would then undergo a ring-opening/rearrangement sequence, presumably triggered by the now nucleophilic heterocyclic nitrogen, to form the acyl fluoride **D**, which affords the dipole **5a** after proton loss (Scheme 2). Alternatively, TFAA activation of the isoquinoline ring followed by isocyanide attack upon the carbonyl may also lead to the epoxide intermediate **C**.[10e]

To the best of our knowledge, there are no precedents for the formation of an acid fluoride moiety from a trifluoroacetoxy group, although some elementary steps are reminiscent of known processes.[11] The overall anionic domino reaction consists of an orchestrated series of events in which electrophilic and nucleophilic species are precisely engaged to guarantee the formation of the C–C, C–N and C–O bonds. Several features of this mechanism remain hypothetical. However, the detection by MS of putative intermediates **B** and **C** (Scheme 2) together with species related to intermediates **A** in modified experiments (lower temperatures, short reaction times, exclusion of aqueous quenching) supports this proposal. Interestingly, the order of addition of the reactants does not substantially modify the synthetic outcome or the yield of the process. In this way, we have tested the addition of the isocyanide to a mixture of isoquinoline and TFAA (**5a**, 85%), the addition of TFAA to a solution of isoquinoline and the isocyanide (**5a**, 72%) and, finally, the addition of isoquinoline to a mixture of the isocyanide and TFAA (**5a**, 65%). These results may be consistent with a type II MCR[1c] in which a series of equilibria are affected by a final irreversible step.



Scheme 2. Mechanistic proposal for the formation of acid fluoride **5a**.

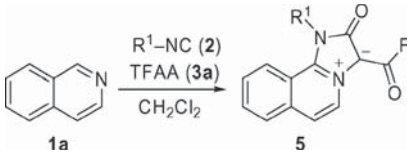
To test the scope of the reaction, a systematic screening of the three components was performed to fully exploit the synthetic possibilities of the transformation and to determine its practical limits.

Reaction Scope – Isocyanide Range

A representative set of isocyanides **2** were treated under the usual conditions with TFAA (**3a**) and isoquinoline (**1a**). The results show that the MCR is quite general with alkyl and benzyl isocyanides affording the expected dipoles **5** in reasonable yields (Table 1, entries 1–3). Note that even moderate yields are synthetically useful reactions taking into account the multicomponent nature of the process and the number of bonds formed. Notable exceptions are *tert*-butyl isocyanide (**2d**, entry 4, presumably because of the steric hindrance linked to the N atom) and the less nucleophilic isocyanide TOSMIC (**2e**, entry 5). In this experiment, the only new product was the hydrate of the *N*-tosylmethyltrifluoropyruvamide. This compound has previously been obtained by hydrolysis of the TFAA-activated isocyanide.[10b]

Interestingly, methyl isocyanoacetate (**2f**, entry 6) displays the expected reactivity although in a lower yield (**5d**, 21%). Remarkably, the formation of the Arndtsen-type dipole **6a** (14%; Figure 2)[6a] by TFAA activation of the iso-

Table 1. Reaction scope of the isocyanides **2** in the MCR.



Entry[a]	R^1	Adduct	Yield [%][b]
1	*c*-C_6H_{11} (**2a**)	**5a**	85
2	*n*Bu (**2b**)	**5b**	80
3	Bn (**2c**)	**5c**	65
4	*t*Bu (**2d**)	–	–
5	*p*$TolSO_2CH_2$ (**2e**)	–	–
6	MeO_2CCH_2 (**2f**)	**5d**	21[c,d]
7	4-ClC_6H_4 (**2g**)	**5e**	20
8	4-$MeOC_6H_4$ (**2h**)	**6b**	23
9	2,6-$Me_2C_6H_3$ (**2i**)	**5f**	26

[a] All reactions were performed following the standard procedure. [b] Isolated yield. [c] Dipole **6a** was also isolated. [d] Isoquinoline, TFAA and the isocyanide were allowed to react in a 1:1:1 stoichiometric ratio.

quinoline was also detected in this reaction, which suggests that competing pathways are operating (Scheme 3). This tendency is increased with 4-$MeOC_6H_4NC$ (**2h**, entry 8) in which the formation of **6b** (Figure 2) predominates. The diminished reactivity of the electron-rich intermediate **A** may divert the cascade towards the Arndtsen route. However, with less activated aromatic rings (**2g** and **2i**, entries 7 and 9) the expected mesoionic compounds are successfully obtained, albeit in lower yields. In these cases, the reduced nucleophilicity of the aniline-type nitrogen atoms in intermediates **B** (Scheme 2) may render the imidazole ring-closure less efficient than with aliphatic analogues and therefore account for the decrease in the overall yield. However, we still lack conclusive evidence to fully explain the behaviour of aromatic isocyanides.

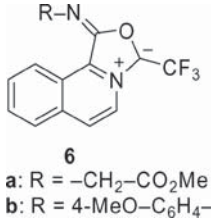
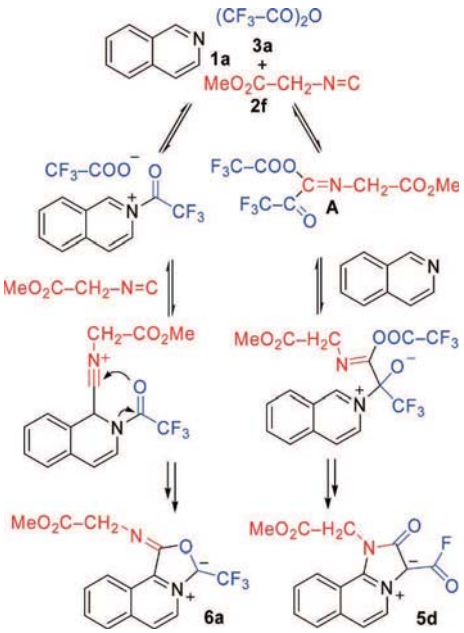


Figure 2. Additional mesoionic compounds isolated in the MCRs.

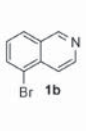
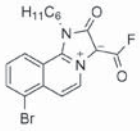
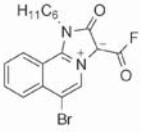
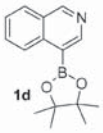
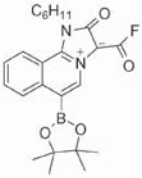
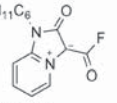
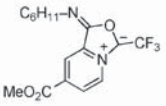
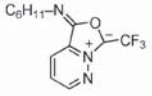
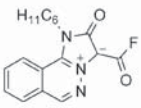


Scheme 3. Competitive reaction pathways leading to dipoles **5d** and **6a**.

Reaction Scope – Azine Range

Next, we examined the scope of reactive azines in the MCR (Table 2). Differently substituted isoquinolines (**1b**–**1d**, entries 1–3) gave the adduct **5** in good-to-moderate

Table 2. Reaction scope of the azines **1** in the MCR.

Entry[a]	Azine	Adduct	Yield (%)[b]
1	 1b	5g 	35
2	 1c	5h 	82
3	 1d	5i 	69
4	 1e	5j 	40
5	 1f COOMe	6c 	20
6	 1g OMe	–	–
7	 1h	–	–
8	 1i	6d 	54
9	 1j	5k 	traces

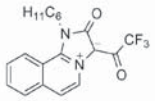
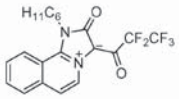
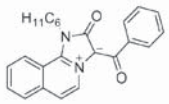
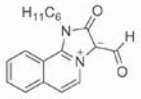
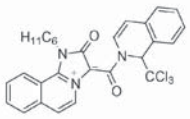
[a] All reactions were performed following the standard procedure. [b] Isolated yield.

yields, including the 4- and 5-bromo derivatives and the 4-boronate. Remarkably, pyridine (**1e**, entry 4), which is inert in Ugi–Reissert conditions,[4a] gave the adduct **5j**. Methyl isonicotinate (**1f**, entry 5) and 4-methoxypyridine (**1g**, entry 6) did not afford the corresponding acid fluorides **5**, the former yielding the corresponding Arndtsen dipole (**6c**, 20%). The rationale for these results may relate to the nucleophilic competition between the azine and the isocyanide in their reaction with TFAA and the relative reactivity of the resulting species: the intermediate azinium ion **B** and the corresponding *N*-acylazinium salt. In this respect, a somewhat restricted reaction window may appear as a consequence of the balance between the nucleophilicity of the azine and the electrophilicity of the azinium intermediate **B**. Thermodynamic aspects and the relative rates of the elementary steps involved in this manifold process may also determine the final outcome (Scheme 2 and Scheme 3). Quinoline (**1h**, entry 7) did not react under the standard conditions. Taking into account the similar reactivity of this heterocycle with isoquinoline, this suggests a steric requirement that does not allow substitution at the α-positions of the azine, presumably because of the structural and reactivity properties of the intermediate azinium ions **B** (Scheme 2). Pyridazine (**1i**, entry 8) showed different behaviour, forming the Arndtsen dipole **6d** (54%), whereas phthalazine (**1j**, entry 9) afforded a complex mixture in which **5k** was detected (MS evidence). In some cases, minor amounts of dipoles arising from the incorporation of two isocyanide units were generated.[12]

Reaction Scope – Anhydride Range

The third component in the reaction procedure was also examined (Table 3). Aside from TFAA, which leads to acid fluorides (Table 1 and Table 2), the results obtained show that for doubly α-fluorinated anhydrides (**3b**–**3e**, entries 1–4) the reaction is quite general and affords several different patterns of substitution, such as fluorinated ketones (**5l**, **5m**), aryl ketones (**5n**) or aldehydes (**5o**). Unfortunately the use of mixed anhydrides (to integrate the moiety deriving from the fluorinated acid precursor in a more efficient manner) was not successful.[13] Trichloroacetic anhydride (**3f**, entry 5)[10c] gives the amide **5p** in a yield of 30% in a remarkable process in which up to seven bonds are formed (Figure 3).[14] This MCR does not stop at the corresponding acid chloride (detected by MS), which, being more reactive than its fluoride counterpart, keeps the domino process alive, and by reacting with another equivalent of isoquinoline generates an *N*-acylisoquinolinium salt. This reactive intermediate then undergoes nucleophilic addition of a trichloromethyl anion (presumably generated in situ by decarboxylation of the trichloroacetate)[15] to finally yield **5p** (Scheme 4). The less electrophilic dichloroacetic anhydride (**3g**, entry 6) did not show any reactivity under the standard conditions tested and probably sets the activation threshold for the acylating component.

Table 3. Reaction scope of the anhydrides **3** in the MCR.

Entry[a]	Acid anhydride		Adduct	Yield (%)[b]
1	$(C_2F_5CO)_2O$ **3b**	**5l**		38
2	$(C_3F_7CO)_2O$ **3c**	**5m**		45
3	$(PhCF_2CO)_2O$ **3d**	**5n**		41
4	$(CHF_2CO)_2O$ **3e**	**5o**		32
5	$(CCl_3CO)_2O$ **3f**	**5p**		30
6	$(CHCl_2CO)_2O$ **3g**	–	–	–

[a] All reactions were performed following the standard procedure. [b] Isolated yield.

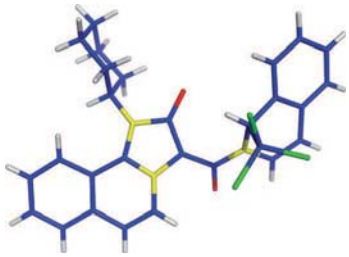
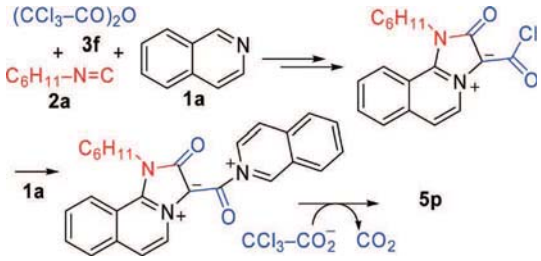


Figure 3. View of the X-ray crystal structure of **5p**.

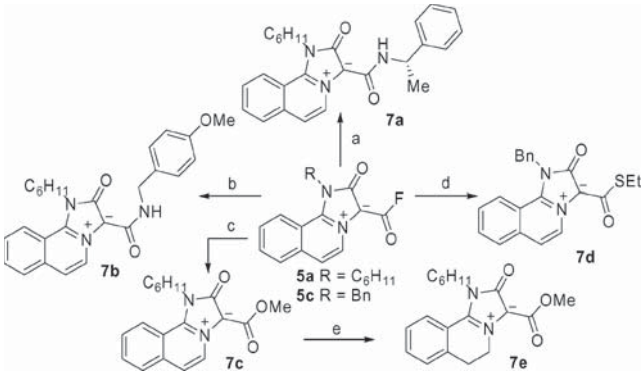


Scheme 4. MCR with trichloroacetic anhydride leading to **5p**.

Dipole Derivatization

Although remarkably stable (for instance, dipole **5a** does not react with acetylenedicarboxylate esters in [3+2] cycloaddition reactions),[9] the acid fluoride function present in dipoles **5** displays the expected reactivity and affords the corresponding mesoionic derivatives **7a**–**7d** on reaction with

nucleophiles (amines, alcohols and thiols). Interestingly, the isoquinolinium moiety can be selectively reduced, as shown by the formation of the dihydroisoquinoline derivative **7e** (Scheme 5).



Scheme 5. Reactivity of acid fluoride **5a**. Reagents and conditions: a) (*S*)-(–)-1-phenylethylamine, Et_3N, DCM (99%); b) *p*-methoxybenzylamine, Et_3N, DCM (75%); c) MeOH (excess), Et_3N, DCM (82%); d) EtSH (excess), DMAP, pyridine (62%); e) H_2, Pd/C, MeOH (85%).

Conclusions

We have described a new azine MCR based on the activation of isocyanides by anhydrides. This unique domino transformation, which features elements of the Ugi–Reissert, Chichibabin and organofluorine processes, yields mesoionic imidazo[1,2-*a*]azine (isoquinoline, pyridine) cores displaying a β-dicarbonyl moiety. These structures bear a close resemblance to neutral imidazoazines, a privileged scaffold of great importance in medicinal and combinatorial chemistry because of its broad spectrum of biological activities.[16] Our approach nicely complements the Bienaymé–Blackburn–Groebke reaction[17] and, although with some restrictions, allows the preparation of the heterocyclic scaffold directly from the azine, ready to be functionalized with a fourth component. Further studies are underway to fully understand the mechanistic implications of this unique transformation and to expand its synthetic outcome.

Experimental Section

General: Unless stated otherwise, all reactions were carried out under argon in dried glassware. Commercially available reactants were used without further purification. Reaction temperatures were controlled by an IKA temperature modulator. Thin-layer chromatography was conducted with Merck silica gel 60 F_{254} sheets and visualized by UV and $KMnO_4$ solution. Silica gel (particle size 35–70 μm) was used for flash column chromatography. ^1H, ^{13}C and ^{19}F NMR spectra were recorded with a Varian Mercury 400 spectrometer (at 400, 100 and 376 MHz, respectively). Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^1H NMR spectra are reported as follows: chemical shift (*δ*/ppm), multiplicity, integration and coupling constant (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to the solvent peak of $CDCl_3$ set at δ = 77.0 ppm. ^{19}F NMR spectra are referenced to TFA as external reference (–78.5 ppm). IR spectra were recorded with a Thermo Nicolet Nexus spectrometer and are reported in frequency of absorption (cm^{-1}).

General Procedure for the Multicomponent Reaction: The acid anhydride (3 mmol, 3 equiv.) and isocyanide (2 mmol, 2 equiv.) were added to a solution of the corresponding azine (1 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (5 mL) at –30 °C. Stirring was continued for 3 min at this temperature, then the cooling bath was removed and the reaction mixture was stirred for 14 h at room temperature. A saturated solution of Na_2CO_3 (10 mL) was added and the mixture extracted with dichloromethane (2 × 5 mL). The combined organic extracts were washed with brine (10 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the pure mesoionic compound.

1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5a): Obtained as a white solid (85%), m.p. 257 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.21 (d, *J* = 7.2 Hz, 1 H), 8.27 (d, *J* = 7.2 Hz, 1 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 7.80–7.72 (m, 2 H), 7.43 (d, *J* = 7.2 Hz, 1 H), 4.78 (m, 1 H), 2.89 (m, 2 H), 2.02–1.42 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 153.2 (d, *J* = 312 Hz), 135.2, 133.6, 131.1, 129.2, 128.9, 123.9, 123.6, 116.3, 115.8, 90.9 (d, *J* = 81 Hz), 59.2, 29.8, 26.5, 25.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 14.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2923, 1739, 1674, 1502, 1412, 1130 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon_0$) = 240 (4.44), 284 (4.47), 344 (4.13) nm. MS (EI): *m*/*z* (%) = 312 (9) $[M]^+$, 292 (8), 264 (4), 252 (34), 230 (29), 210 (100), 154 (36), 128 (13). HRMS: calcd. for $C_{18}H_{18}FN_2O_2^+$ 313.1352; found 313.1349.

1-Butyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5b): Obtained as a yellow solid (80%, purified by crystallization from CH_2Cl_2/Et_2O), m.p. 205–206 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.23 (d, *J* = 7.2 Hz, 1 H), 8.37 (d, *J* = 7.6 Hz, 1 H), 7.92–7.97 (m, 1 H), 7.70–7.90 (m, 2 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 4.52 (t, *J* = 7.6 Hz, 2 H), 1.89 (m, 2 H), 1.84–1.95 (m, 2 H), 1.03 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 156.24 (d, *J* = 316 Hz), 134.8, 133.3, 131.4, 129.6, 128.8, 124.1, 123.2, 122.4, 115.8, 90.2 (d, *J* = 82 Hz), 41.7, 31.0, 20.2, 13.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 11.8 ppm. IR (NaCl): $\tilde{\nu}$ = 1747, 1683, 1639, 1518, 1412, 1044, 747 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log\varepsilon_0$) = 248 (4.24), 291 (4.38), 366 (3.82) nm. MS (EI): *m*/*z* (%) = 286 (26) $[M]^+$, 269 (38), 252 (16), 238 (17), 224 (26), 210 (100), 154 (51), 128 (27), 101 (14). HRMS: calcd. for $C_{16}H_{16}FN_2O_2^+$ 287.1190; found 287.1191.

1-Benzyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]-isoquinolin-4-ium-3-ide (5c): Obtained as a white solid (65%), m.p. 257–258 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.30 (d, *J* = 7.2 Hz, 1 H), 8.24 (d, *J* = 8.8 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 8.0, 7.6 Hz, 1 H), 7.52 (d, *J* = 7.2 Hz, 1 H), 7.21–7.38 (m, 5 H), 5.74 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 153.1 (d, *J* = 312 Hz), 135.0, 133.2, 131.5, 129.5, 128.5, 128.3, 126.4, 126.3, 124.1, 123.9, 123.1, 116.3, 116.1, 90.2 (d, *J* = 83 Hz), 45.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 12.2 ppm. IR (NaCl): $\tilde{\nu}$ = 3135, 2993, 1744, 1687, 1520, 1417, 1433, 1041, 1026, 937, 742, 649 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log\varepsilon_0$) = 239 (3.99), 290 (4.05), 363 (3.50) nm. MS (EI): *m*/*z* (%) = 320 (27) $[M]^+$, 300 (7), 231 (10), 170 (5), 153 (6), 128 (6), 91 (100), 65 (11). HRMS: calcd. for $C_{19}H_{14}FN_2O_2^+$ 321.1033; found 321.1045.

3-(Fluorocarbonyl)-1-(2-methoxy-2-oxoethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5d): In this experiment the stoichiometry of the reagents was modified: isoquinoline (360 mg,

2.78 mmol, 1 equiv.), TFAA (0.393 mL, 2.78 mmol, 1 equiv.) and isocyanide (0.253 mL, 2.78 mmol, 1 equiv.) were added in that order. After the extractions silica and Na_2SO_4 were added to the organic extracts and left to stir for 1 h and then were filtered through Celite. The precipitate was washed with AcOEt, and the collected filtrates were combined. The solvent was removed under reduced pressure and the residue was washed with Et_2O (10 mL) to yield the dipole as a brown solid (176.9 mg, 21%), m.p. 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (d, J = 6.8 Hz, 1 H), 8.04 (d, J = 8.4 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.83 (m, J = 7.2, 8.0 Hz, 1 H), 7.76 (m, J = 8.4, 7.2 Hz, 1 H), 7.56 (d, J = 7.2 Hz, 1 H), 5.31 (s, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 157.1, 152.9 (d, J = 310.5 Hz), 135.0, 133.3, 131.6, 129.8, 128.9, 124.1, 122.3, 116.6, 116.4, 90.7 (d, J = 81 Hz), 53.5, 43.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 13.3 ppm. IR (NaCl): $\tilde{\nu}$ = 1746, 1699, 1522, 1441, 1419, 1364, 1224, 1042, 937, 748 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 246 (4.35), 277 (4.24), 363 (4.23) nm. MS (EI): m/z (%) = 302 (100) [M]$^+$, 215 (25), 195 (16), 168 (11), 156 (19), 140 (11), 128 (18), 115 (7), 101 (7). HRMS: calcd. for $C_{15}H_{12}FN_2O_4^+$ 303.0775; found 303.0776.

1-(4-Chlorophenyl)-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5e): Obtained as a yellow solid (20%), m.p. 225–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (d, J = 6.8 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.74 (m, J = 7.2, 7.6 Hz, 1 H), 7.65 (d, J = 8.8 Hz, 2 H), 7.59 (d, J = 7.2 Hz, 1 H), 7.39–7.50 (m, 3 H), 7.31 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 153.1 (d, J = 314 Hz), 136.9, 134.3, 133.3, 132.5, 131.7, 131.0, 130.2, 129.3, 128.6, 124.1, 123.5, 116.7, 115.8, 90.1 (d, J = 83 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 12.4 ppm. IR (NaCl): $\tilde{\nu}$ = 1740, 1670, 1415, 1001, 805, 739 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 251 (4.03), 291 (4.06), 363 (3.67) nm. MS (EI): m/z (%) = 340 (100) [M]$^+$, 319 (46), 265 (31), 230 (16), 203 (8), 175 (5), 111 (17), 75 (18). HRMS: calcd. for $C_{18}H_{11}ClFN_2O_2^+$ 341.0487; found 341.0496.

1-(2,6-Dimethylphenyl)-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5f): Obtained as a yellow solid (26%), m.p. 214–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (d, J = 7.2 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.68–7.75 (m, 1 H), 7.58 (d, J = 7.2 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 1 H), 7.35–7.40 (m, 1 H), 7.30–7.39 (m, 2 H), 7.09 (d, J = 8.8 Hz, 1 H), 2.09 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 153.16 (d, J = 311 Hz), 137.1, 133.1, 132.3, 131.7, 130.8, 129.8, 129.6, 128.4, 127.0, 124.2, 122.1, 116.3, 116.2, 90.6 (d, J = 83 Hz), 18.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 12.0 ppm. IR (NaCl): $\tilde{\nu}$ = 2918, 2850, 1747, 1743, 1703, 1514, 1413, 997, 748, 665 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 263 (3.96), 292 (3.91), 363 (3.82) nm. MS (EI): m/z (%) = 334 (50) [M]$^+$, 314 (100), 299 (11), 285 (24), 271 (12), 258 (89), 245 (20), 232 (30), 217 (16), 103 (17), 77 (31). HRMS: calcd. for $C_{20}H_{16}FN_2O_2^+$ 335.1190; found 335.1198.

7-Bromo-1-cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5g): Obtained as a white waxy solid (35%), m.p. 275 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (d, J = 7.6 Hz, 1 H), 8.24 (d, J = 8.4 Hz, 1 H), 8.08 (d, J = 7.6 Hz, 1 H), 7.93 (d, J = 7.2 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 4.74 (m, 1 H), 2.88 (m, 2 H), 2.02–1.42 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 152.8 (d, J = 313 Hz), 134.7, 132.1, 129.1, 124.7, 123.6, 122.9, 120.9, 117.2, 114.6, 90.8 (d, J = 81 Hz), 59.3, 29.5, 26.2, 24.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 15.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2930, 1739, 1706, 1502, 1405, 1155 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 247 (4.66), 294 (4.79), 348 (4.31) nm. MS (EI): m/z (%) = 390 (7) [M]$^+$, 370 (10), 344 (4), 308 (28), 288 (100), 234 (11), 209 (7), 153 (41), 127 (21). HRMS: calcd. for $C_{18}H_{17}BrFN_2O_2^+$ 391.0457; found 391.0453.

6-Bromo-1-cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1*a*]isoquinolin-4-ium-3-ide (5h): Obtained as a purple solid (82%), m.p. 196–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1 H), 8.34 (dd, J = 8.4, 0.8 Hz, 1 H), 8.30 (d, J = 8.3 Hz, 1 H), 7.92 (ddd, J = 8.3, 7.1, 1.0 Hz, 1 H), 7.84 (ddd, J = 8.4, 7.2, 1.3 Hz, 1 H), 4.77 (s, 1 H), 2.87 (m, 2 H), 2.09–1.91 (m, 4 H), 1.87–1.70 (m, 2 H), 1.52–1.36 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 131.8, 129.8, 128.4, 124.5, 123.8, 120.2, 118.1, 116.3, 111.3, 59.3, 29.5, 26.2, 24.8 ppm (the signals of two quaternary carbon atoms were not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = 11.5 ppm. IR (NaCl): $\tilde{\nu}$ = 2925, 1706, 1505, 1417 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 245 (4.09), 294 (4.36), 353 (3.78) nm. MS (EI): m/z (%) = 392 (7) [M]$^+$, 390 (7) [M]$^+$, 372 (7), 370 (7), 310 (24), 308 (24), 290 (100), 288 (99), 234 (16), 232 (16). HRMS: calcd. for $C_{18}H_{17}BrFN_2O_2^+$ 391.0451; found 391.0452.

1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5i): Obtained as an off-white solid (69%), m.p. 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 8.87 (dd, J = 8.4, 0.8 Hz, 1 H), 8.24 (d, J = 8.2 Hz, 1 H), 7.82 (ddd, J = 8.3, 7.1, 1.0 Hz, 1 H), 7.73 (ddd, J = 8.4, 7.1, 1.2 Hz, 1 H), 4.79 (t, J = 11.6 Hz, 1 H), 2.90 (m, 2 H), 2.08–1.91 (m, 4 H), 1.50–1.36 (m, 2 H), 1.78 (m, 2 H), 1.42 (s, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159, 152 (d, J = 311 Hz), 137.8, 136.3, 131.6, 131.0, 129.6, 128.3, 123.6, 123.4, 115.7, 84.8, 59.3, 29.6, 26.2, 24.9 ppm (one signal overlapped, the signal of one quaternary carbon atom was not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = 10.60 ppm. IR (NaCl): $\tilde{\nu}$ = 2977, 2931, 2851, 1738, 1692, 1389, 1365, 1317, 1142 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 248 (4.01), 287 (4.13), 341 (3.74) nm. MS (EI): m/z (%) = 438 (7) [M]$^+$, 418 (7), 390 (8), 356 (17), 336 (100), 335 (24). HRMS: calcd. for $C_{24}H_{29}BFN_2O_4^+$ 439.2199; found 439.2204.

1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-4-ium-3-ide (5j): Obtained as a white solid (40%), m.p. 190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (d, J = 6.4 Hz, 1 H), 7.65 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.19 (d, J = 6.8 Hz, 1 H), 4.56 (m, 1 H), 1.97–1.48 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 153.0 (d, J = 311 Hz), 137.6, 132.3, 129.6, 115.7, 107.8, 90.3 (d, J = 64 Hz), 52.2, 30.0, 26.1, 25.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 9.5 ppm. IR (NaCl): $\tilde{\nu}$ = 2936, 1737, 1688, 1513, 1440, 1132 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 255 (4.22), 304 (3.86), 333 (3.82) nm. MS (EI): m/z (%) = 262 (10) [M]$^+$, 242 (9), 214 (13), 180 (34), 160 (100), 104 (29), 78 (32). HRMS: calcd. for $C_{14}H_{16}FN_2O_2^+$ 263.1190; found 263.1197.

1-Cyclohexyl-2-oxo-3-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5l): Obtained as a white solid (38%), m.p. 228 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (d, J = 7.2 Hz, 1 H), 8.26 (d, J = 7.6 Hz, 1 H), 7.90 (d, J = 7.6 Hz, 1 H), 7.78 (t, J = 7.2 Hz, 1 H), 7.74 (m, J = 7.6, 1.6 Hz, 1 H), 7.42 (q, J = 7.2 Hz, 1 H), 4.76 (m, 1 H), 2.85 (m, 2 H), 2.02–1.38 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3 (m), 158.6, 136.4, 134.2, 131.4, 128.9, 128.6, 124.9, 118.9, 116.0, 115.5, 58.9, 29.5, 26.2, 24.9 ppm (the signals of two quaternary carbon atoms were not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –79.1 ppm. IR (NaCl): $\tilde{\nu}$ = 2923, 1700, 1610, 1508, 1456, 1251, 1143 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 262 (4.24), 279 (4.28), 294 (4.32), 359 (4.22) nm. MS (EI): m/z (%) = 362 (15) [M]$^+$, 280 (58), 211 (100), 155 (23), 128 (13). HRMS: calcd. for $C_{19}H_{18}F_3N_2O_2^+$ 363.1320; found 363.1313.

1-Cyclohexyl-2-oxo-3-(2,2,3,3,3-pentafluoropropanoyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5m): Obtained as a white solid (45%), m.p. 235 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83

(d, J = 7.6 Hz, 1 H), 8.27 (d, J = 8.0 Hz, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 7.80 (t, J = 7.2 Hz, 1 H), 7.74 (t, J = 7.2 Hz, 1 H), 7.41 (d, J = 7.2 Hz, 1 H), 4.76 (m, 1 H), 2.86 (m, 2 H), 2.00–1.39 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (m), 158.4, 136.7, 134.2, 131.5, 128.9, 128.6, 124.9, 118.9 (m), 115.6, 115.4, 108.8, 103.3, 59.0, 29.5, 26.2, 24.8 ppm (the signal of one quaternary carbon atom was not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –85.6, –124.4 ppm. IR (NaCl): $\tilde{\nu}$ = 2930, 1693, 1597, 1514, 1450, 1213, 1123 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 280 (4.29), 361 (4.24), 371 (4.21) nm. MS (EI): m/z (%) = 412 (13) $[M]^+$, 330 (36), 211 (100), 155 (21), 128 (12). HRMS: calcd. for $C_{20}H_{18}F_5N_2O_2^+$ 413.1282; found 413.1280.

3-Benzoyl-1-cyclohexyl-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5n): Oxalyl chloride (0.136 mL, 1.6 mmol, 3 equiv.) was slowly added to a suspension of potassium difluoro(phenyl)acetate (677.2 mg, 3.2 mmol, 6 equiv.)[18] in toluene (1.5 mL) at 0 °C. The reaction was left to stir under nitrogen at room temp. for 2 h and then heated at reflux for 2 h to yield difluoro(phenyl)acetic anhydride, which was used without purification. The mixture containing the anhydride was then cooled to –78 °C. At this temperature, CH_2Cl_2 (4 mL), cyclohexyl isocyanide (0.131 mL, 1.1 mmol, 2 equiv.) and isoquinoline (70.5 mg, 0.533 mmol, 1 equiv.) were added in that order. After 3 min, the dry ice bath was removed and the reaction mixture was left to stir for 24 h. An aqueous saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were washed with brine (10 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was washed with Et_2O (6 mL) to yield **5n** (81.1 mg, 41%) as a yellow solid, m.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.99 (d, J = 7.6 Hz, 1 H), 8.28 (br., 1 H), 7.86–7.95 (m, 1 H), 7.82 (m, 2 H), 7.73 (m, 2 H), 7.39–7.49 (m, 4 H), 4.80 (br., 1 H), 2.85 (m, 2 H), 1.90–2.10 (m, 4 H), 1.70–1.80 (m, 1 H), 1.30–1.50 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9, 159.7, 140.0, 134.2, 131.0, 130.4, 128.9, 128.7, 128.6, 128.5, 127.8, 125.4, 123.8, 116.2, 115.1, 104.73, 59.0, 29.8, 26.5, 25.1 ppm. IR (NaCl): $\tilde{\nu}$ = 3128, 2926, 2854, 1675, 1587, 1557, 1509, 1447, 1410, 1366, 1345, 1321, 1227, 1140, 1026, 977, 809, 740, 650 cm^{-1}. UV (CH_2Cl_2): λ_{max}(log ε_0) = 241 (3.32), 292 (3.25), 392 (3.22) nm. MS (EI): m/z (%) = 370 (34) $[M]^+$, 288 (100), 211 (15), 155 (12), 128 (9), 105 (24), 77 (18). HRMS: calcd. for $C_{24}H_{23}N_2O_2^+$ 371.1754; found 371.1763.

1-Cyclohexyl-3-formyl-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5o): Difluoroacetic anhydride (0.500 mL, 5 mmol, 5 equiv.) and cyclohexyl isocyanide (0.096 mL, 1 mmol, 1 equiv.) were added to a solution of the corresponding azine (100 mg, 0.78 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (5 mL) at –30 °C. After stirring for 3 min at this temperature, the dry ice bath was removed and the reaction mixture was stirred for 14 h at room temperature. A saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography [SiO_2, hexanes/ethyl acetate (1:5)] to yield **5o** (73.7 mg, 32%) as a white solid, m.p. 242 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 9.64 (d, J = 7.2 Hz, 1 H), 8.28 (m, 1 H), 7.89 (d, J = 7.6 Hz, 1 H), 7.74 (m, 2 H), 7.40 (d, J = 7.2 Hz, 1 H), 4.79 (m, 1 H), 2.86 (m, 2 H), 2.00–1.42 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 161.9, 133.3, 130.4, 128.8, 128.7, 124.2, 123.5, 122.3, 116.1, 115.5, 104.5, 58.6, 29.7, 26.2, 24.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2923, 1668, 1617, 1514, 1450, 1354, 1149 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 265 (4.44), 294 (4.42), 354 (4.36) nm. MS (EI): m/z (%) = 294 (27) $[M]^+$, 212 (100), 184 (46), 155 (23), 128 (16). HRMS: calcd. for $C_{18}H_{19}N_2O_2^+$ 295.1447; found 295.1446.

1-Cyclohexyl-2-oxo-3-[1-(trichloromethyl)-1,2-dihydroisoquinolin-2-ylcarbonyl]-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5p): Obtained as a white solid (30%), m.p. 141.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (d, J = 7.2 Hz, 1 H), 8.75 (m, 1 H), 8.39 (m, 1 H), 8.20–7.90 (m, 5 H), 7.82–7.60 (m, 4 H), 6.45 (br. d, J = 7.2 Hz, 1 H), 4.84 (br. s, 1 H), 2.84 (br. s, 2 H), 2.02–1.41 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 171.3, 162.2, 158.6, 133.5, 132.4, 131.6, 129.9, 129.0, 128.8, 128.5, 128.3, 126.4, 124.9, 124.6, 124.2, 122.4, 122.3, 116.5, 114.9, 113.9, 96.3, 58.7, 41.8, 29.8, 26.2, 24.9 ppm. IR (NaCl): $\tilde{\nu}$ = 3430, 2923, 1643, 1617, 1508, 1454, 1245 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 271 (4.67), 349 (4.99), 362 (4.95) nm. MS (EI): m/z (%) = 422, 328 (7), 293 (25), 246 (16), 211 (100), 176 (38), 155 (25), 128 (17). HRMS: calcd. for $C_{28}H_{25}Cl_3N_3O_2^+$ 540.1012; found 540.0987.

(2-Methoxy-2-oxoethylimino)-3-(trifluoromethyl)-1,3-dihydrooxazolo[4,3-*a*]isoquinolin-4-ium-3-ide (6a): In this experiment the order of addition was modified. The isocyanide (0.281 mL, 3.10 mmol, 2 equiv.), TFAA (0.658 mL, 4.64 mmol, 3 equiv.) and isoquinoline (200 mg, 1.55 mmol, 1 equiv.) were added in that order to yield under the standard conditions the dipole **6a** as a white solid (70.5 mg, 14%), m.p. 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.2 Hz, 1 H), 7.95–8.05 (m, 1 H), 7.85–7.92 (m, 1 H), 7.68–7.76 (m, 2 H), 7.46 (d, J = 7.2 Hz, 1 H), 5.36 (s, 2 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 153.2, 131.1, 130.1, 129.8, 128.8, 121.9, 121.8, 121.7, 121.6, 119 (q, J = 264 Hz), 116.5, 53.4, 43.3 ppm (the signal of one quaternary carbon atom was not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –59.4 ppm. IR (NaCl): $\tilde{\nu}$ = 3138, 2955, 2926, 1751, 1676, 1639, 1523, 1477, 1449, 1220, 1126, 1064, 647 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 236 (4.17), 286 (4.25), 357 (4.17) nm. MS (EI): m/z (%) = 324 (100) $[M]^+$, 305 (10), 266 (12), 237 (20), 217 (18), 197 (10), 168 (11), 142 (9), 128 (13). HRMS: calcd. for $C_{15}H_{12}F_3N_2O_3^+$ 325.0794; found 325.0802. The acid fluoride product **5d** (23.5 mg, 5%) was also obtained in this experiment.

(4-Methoxyphenylimino)-3-(trifluoromethyl)-1,3-dihydrooxazolo-[4,3-*a*]isoquinolin-4-ium-3-ide (6b): In this experiment the typical stoichiometry was modified: isocyanide (1 equiv., TFAA 1 equiv.), isoquinoline (1 equiv.) The product **6b** was obtained as a white solid (23%), m.p. 196–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.2 Hz, 1 H), 7.81 (d, J = 8.4 Hz, 1 H), 7.59 (m, J = 7.6, 7.2 Hz, 1 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.37 (m, J = 9.2 Hz, 2 H), 7.34 (m, J = 7.2 Hz, 1 H), 7.28 (m, J = 9.2 Hz, 1 H), 7.14 (m, J = 8.8 Hz, 2 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 154.7, 151.6, 133.3, 131.5, 130.0, 129.1, 128.4, 126.2, 124.0, 123.8, 116.4, 116.1, 116.0, 55.92 ppm (the signals of two quaternary carbon atoms were not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –76.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2957, 2924, 1753, 1672, 1607, 1469, 1443, 1252, 1122, 666 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 265 (3.72), 295 (3.70), 334 (3.36), 371 (3.52) nm. MS (EI): m/z (%) = 358 (100) $[M]^+$, 337 (40), 261 (20), 218 (25), 191 (8), 128 (8), 92 (9), 77 (10). HRMS: calcd. for $C_{19}H_{14}F_3N_2O_2^+$ 359.1002, found 359.1008.

1-(Cyclohexylimino)-7-(methoxycarbonyl)-3-(trifluoromethyl)-1,3-dihydrooxazolo[3,4-*a*]pyridin-4-ium-3-ide (6c): Obtained as a white solid (20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 4.0 Hz, 1 H), 7.87 (s, 1 H), 7.58 (dd, J = 6.8, 1.7 Hz, 1 H), 4.53 (m, 1 H), 3.96 (s, 3 H), 2.08–2.25 (m, 2 H), 1.65–2.00 (m, 5 H), 1.20–1.50 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 154.1, 131.7, 126.9, 123.6, 122.2 (q, J = 270 Hz), 114.8, 108.0, 53.04, 52.6, 30.2, 25.8, 25.0 ppm (the signal of one quaternary carbon atom was not

detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.0 ppm. IR (NaCl): $\tilde{\nu}$ = 2956, 2867, 1718, 1510, 1301, 1198, 1112, 970, 760 cm^{-1}. MS (EI): *m*/*z* (%) = 342 (98) $[M]^+$, 301 (38), 260 (100), 240 (12), 81 (10). MS (ESI): *m*/*z* = 343 [M + H], 342 $[M]^+$.

5-(Cyclohexylimino)-7-(trifluoromethyl)-5,7-dihydrooxazolo[3,4-*b*]-pyridazin-8-ium-7-ide (6d): Obtained as a yellowish oil (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 5.2 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.15 (dd, *J* = 8.8, 5.2 Hz, 1 H), 4.63 (m, 1 H), 2.04–1.25 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 142.5, 128.3, 121.5 (q, *J* = 264 Hz), 120.2, 115.2, 51.9, 30.7, 25.8, 25.2 ppm (the signal of one quaternary carbon atom was not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.8 ppm. MS (EI): *m*/*z* (%) = 285 (11) $[M]^+$, 203 (67), 177 (41), 120 (32), 95 (100), 69 (49), 55 (58).

(*S*)-1-Cyclohexyl-2-oxo-3-(1-phenylethylcarbamoyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (7a): Triethylamine (0.053 mL, 0.38 mmol, 2 equiv.) was added to a solution of **5a** (50 mg, 0.19 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (2 mL) under nitrogen. After stirring for 2 min (*S*)-(–)-α-methylbenzylamine (0.029 mL, 0.23 mmol, 1.2 equiv.) was added dropwise and the reaction mixture was stirred at room temperature overnight. A saturated solution of brine (7 mL) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography [SiO_2, hexanes/ethyl acetate (1:3)] to yield **7a** (77.9 mg, 99%) as a gum. $[a]_D^{20}$ = +56.35 (*c* = 2.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.88 (d, *J* = 7.2 Hz, 1 H), 8.94 (d, *J* = 7.6 Hz, 1 H), 8.22 (br. s, 1 H), 7.85 (m, 1 H), 7.60–7.80 (m, 2 H), 7.47 (m, 2 H), 7.35 (m, 3 H), 7.20 (m, 1 H), 5.30 (m, 1 H), 4.9 (br. s, 1 H), 2.95 (br. s, 2 H) 2.00–2.1 (m, 4 H), 1.75–1.85 (br., 1 H), 1.59 (d, *J* = 7.2 Hz, 3 H) 1.45–1.55 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 158.9, 145.2, 131.9, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 127.0, 126.3, 124.5, 122.7, 116.7, 115.1, 59.14, 48.4, 30.1, 26.5, 25.3, 23.5 ppm. IR (NaCl): $\tilde{\nu}$ = 2929, 2854, 1653, 1624, 1534, 1506, 1452, 1415, 1369, 1214, 742, 699 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log\varepsilon_0$) = 249 (3.96), 270 (3.99), 2.96 (4.00), 371 (3.88) nm. MS (EI): *m*/*z* (%) = 413 (49) $[M]^+$, 396 (23), 294 (41), 266 (38), 227 (82), 211 (100), 184 (92), 155 (55), 120 (62), 105 (70). HRMS: calcd. for $C_{26}H_{28}N_3O_2^+$ 414.2176; found 414.2180.

1-Cyclohexyl-3-(4-methoxybenzylcarbamoyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (7b): By using the same procedure as above with *p*-methoxybenzylamine, **7b** (75%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (d, *J* = 7.2 Hz, 1 H), 8.85 (m, 1 H), 8.19 (m, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.64 (m, 2 H), 7.31 (m, 3 H), 6.83 (m, 2 H), 4.84 (m, 1 H), 4.55 (d, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H), 2.84 (m, 2 H), 2.02–1.39 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 158.6, 131.6, 129.0, 128.8, 128.5, 128.3, 124.2, 122.4, 122.3, 122.2, 116.5, 114.9, 113.9, 96.3, 58.7, 55.2, 41.8, 29.8, 26.2, 24.9 ppm (the signal of one quaternary carbon atom was not detected). IR (NaCl): $\tilde{\nu}$ = 3429, 2923, 1645, 11617, 1508, 1412, 1245, 1028 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon_0$) = 262 (4.45), 288 (4.33), 348 (4.24) nm. MS (EI): *m*/*z* (%) = 429 (56) $[M]^+$, 294 (17), 266 (23), 211 (40), 184 (43), 155 (22), 121 (100). HRMS: calcd. for $C_{26}H_{28}N_3O_3^+$ 430.2131; found 430.2124.

1-Cyclohexyl-3-(methoxycarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo-[2,1-*a*]isoquinoline-4-ium-3-ide (7c): Triethylamine (0.4 mL, 3.2 mmol, 10 equiv.) was added to a solution of **5a** (100 mg, 0.3 mmol, 1 equiv.) in MeOH (5 mL) under nitrogen and the reaction mixture was heated at reflux overnight. Then the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (5 mL). The mixture was extracted with brine (4 × 5 mL) and the combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography [SiO_2, hexanes/ethyl acetate (1:1)] to yield **7c** (88.0 mg, 82%) as a white glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, *J* = 7.6 Hz, 1 H), 8.24 (m, 1 H), 7.86 (d, *J* = 8.6 Hz, 1 H), 7.70 (m, 2 H), 7.37 (d, *J* = 7.6 Hz, 1 H), 4.80 (m, 1 H), 3.93 (m, 3 H), 2.96 (m, 2 H), 2.02–1.41 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 158.0, 132.3, 129.8, 128.6, 128.5, 123.9, 123.0, 122.9, 116.2, 115.1, 95.0, 59.0, 51.1, 29.6, 26.3, 24.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2930, 1783, 1655, 1597, 1463, 1200, 1072 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon_0$) = 262 (4.42), 287 (4.52), 344 (4.18) nm. MS (EI): *m*/*z* (%) = 324 (21) $[M]^+$, 242 (78), 210 (100), 184 (22), 154 (33), 128 (16). HRMS: calcd. for $C_{19}H_{21}N_2O_3^+$ 325.1552; found 325.1547.

1-Benzyl-3-(ethylthiocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]-isoquinolin-4-ium-3-ide (7d): DMAP (10 mg, 81.8 μmol, 0.5 equiv.) and ethanethiol (0.5 mL, 9.6 mmol, 61.4 equiv.) were added to a solution of **5c** (50.0 mg, 0.156 mmol, 1 equiv.) in pyridine (2 mL). The reaction mixture was left to stir for 40 h under an inert atmosphere at room temp. A saturated solution of Na_2CO_3 (6 mL) was added and the mixture was extracted with dichloromethane (2 × 3 mL). The combined organic extracts were washed with brine (6 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was washed with Et_2O (6 mL) to yield **7d** (35.1 mg, 62%) as a yellow solid M.p. 224–225 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (d, *J* = 7.3 Hz, 1 H), 8.21 (d, *J* = 8.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 1 H), 7.23–7.37 (m, 5 H), 5.75 (s, 2 H), 3.08 (m, *J* = 7.4 Hz, 2 H), 1.39 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.5, 158.2, 153.3, 132.6, 132.2, 130.5, 129.4, 129.0, 128.3, 128.1, 126.4, 124.7, 123.7, 116.2, 115.7, 102.2, 45.52, 21.96, 15.31 ppm. IR (NaCl): $\tilde{\nu}$ = 2923, 1747, 1673, 1593, 1520, 1455, 1406, 1347, 917 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log\varepsilon_0$) = 241 (3.88), 271 (3.92), 298 (3.96), 380 (3.86) nm. MS (EI): *m*/*z* (%) = 362 (29) $[M]^+$, 301 (92), 273 (18), 91 (100). HRMS: calcd. for $C_{21}H_{19}N_2O_2S^+$ 363.1161, found 363.1169.

1-Cyclohexyl-3-(methoxycarbonyl)-2-oxo-2,3,5,6-tetrahydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (7e): Pd/C (10%, 15 mg) was added to a stirring suspension of **7c** (35.8 mg, 0.110 mmol) in MeOH (3 mL) under hydrogen at atmospheric pressure. After 48 h the hydrogen atmosphere was removed, CH_2Cl_2 (1 mL) was added and the solution was filtered through Celite. A saturated solution of Na_2CO_3 (6 mL) was added and the mixture was extracted with dichloromethane (2 × 3 mL). The combined organic extracts were washed with brine (6 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the pure reduced mesoionic ester as a white solid (30.6 mg, 85%), m.p. 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.49 (m, 3 H), 7.35–7.40 (m, 1 H), 4.60 (m, *J* = 6.8, 6.6 Hz, 2 H), 4.26 (m, 1 H), 3.84 (s, 3 H), 3.07 (m, *J* = 6.9, 6.6 Hz, 2 H), 2.80–3.00 (m, 1 H), 1.90–2.00 (m, 2 H), 1.80–1.88 (m, 2 H), 1.60–1.70 (m, 1 H), 1.20–1.40 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.54, 158.25, 153.86, 133.08, 130.60, 128.77, 127.84, 124.76, 120.89, 97.49, 57.76, 50.79, 42.07, 29.37, 28.34, 26.09, 24.89 ppm. IR (NaCl): $\tilde{\nu}$ = 2932, 2855, 1743, 1646, 1456, 1384, 1339, 1201, 1166 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log\varepsilon_0$) = 251 (3.70), 297 (4.00), 384 (3.90) nm. MS (EI): *m*/*z* (%) = 326 (23) $[M]^+$, 244 (100), 212 (53), 186 (15), 156 (23), 130 (22), 116 (15), 103 (9). HRMS: calcd. for $C_{19}H_{23}N_2O_3^+$ 327.1703; found 327.1705.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all new compounds.

Acknowledgments

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[14] Crystallographic data for **5p**: $C_{28}H_{24}Cl_3N_3O_2$, M_r = 540.85, monoclinic, space group *P*21/*n*, *a* = 9.8728(2), *b* = 24.8023(5), *c* = 10.1993(2) Å, *V* = 2420.67(8) Å^3, *T* = 100(2) K, *d* = 1.484 Mg m^{-3}, 0.412 mm^{-1}, 58646 reflections measured, 7086 unique reflections (R_{int} = 0.064), R_1 = 0.0405, wR_2 = 0.0866. CCDC-684677 contains the supplementary crystallographic data for **5p**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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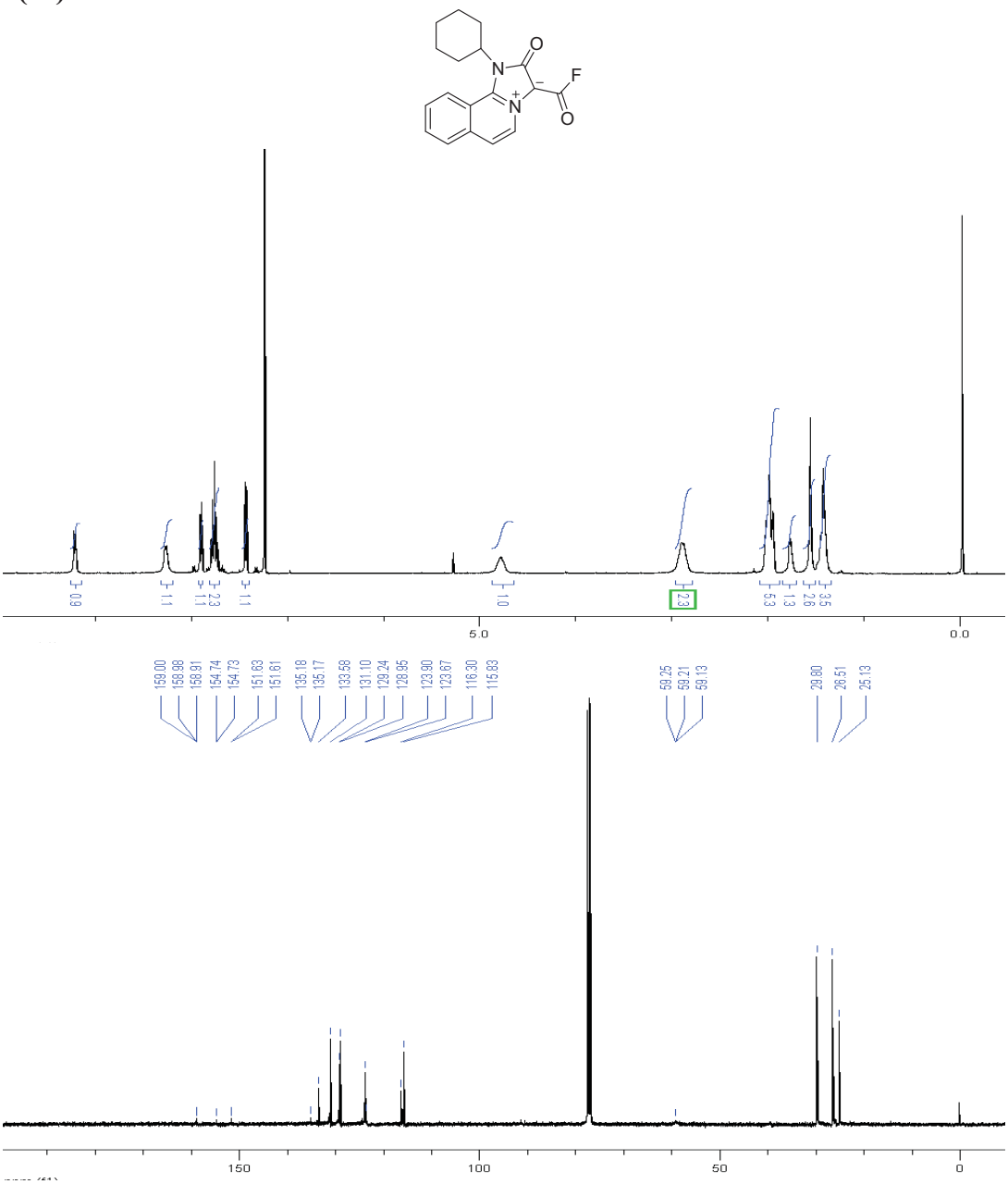
SUPPORTING INFORMATION

Title: Multicomponent Access to Functionalized Mesoionic Structures Based on TFAA Activation of Isocyanides: Novel Domino Reactions

Author(s): María José Arévalo, Nicola Kielland, Carme Masdeu, Miriam Miguel, Nicolas Isambert, Rodolfo Lavilla*

Ref. No.: O200801084

1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5a)



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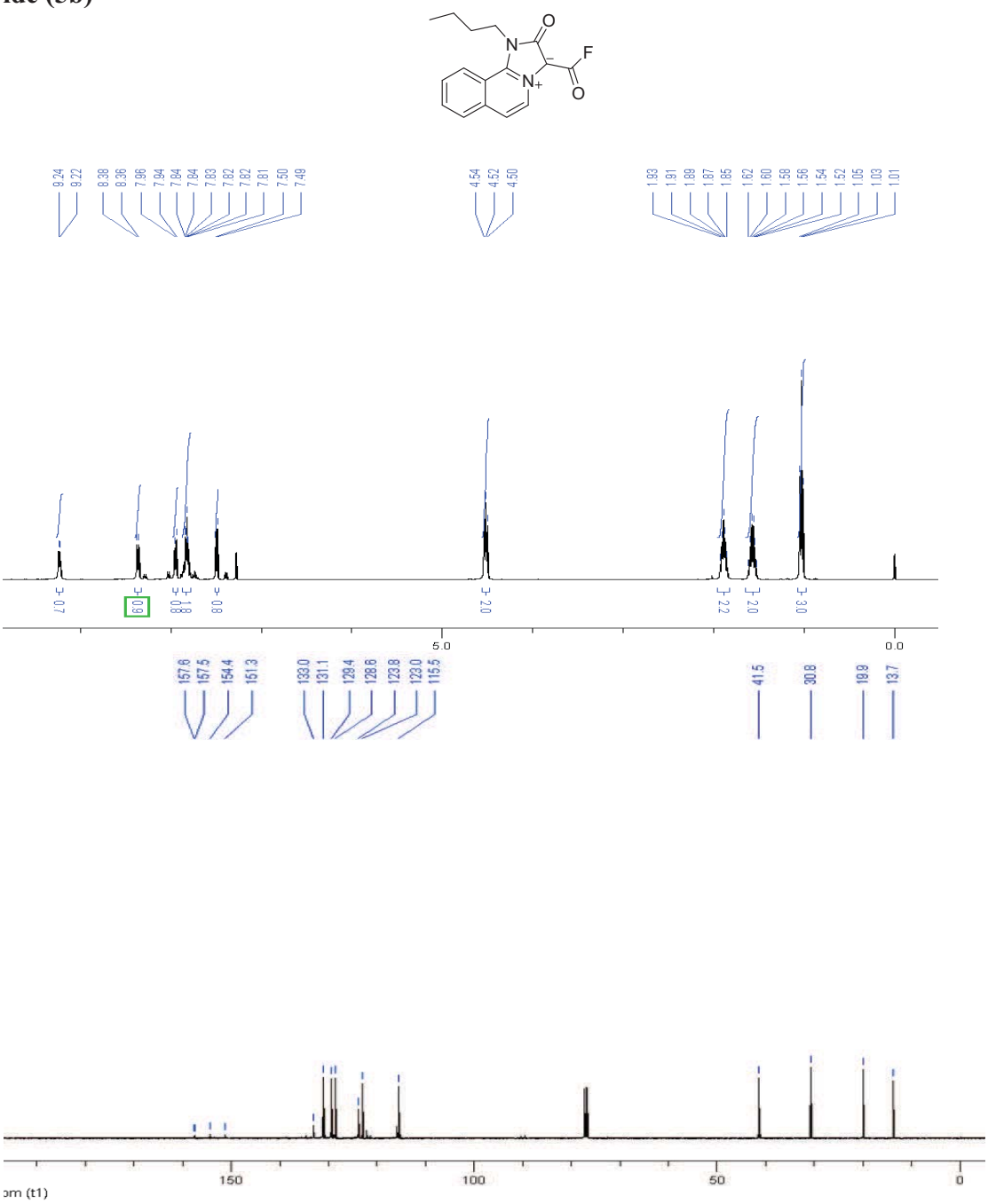

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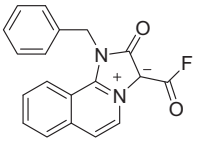

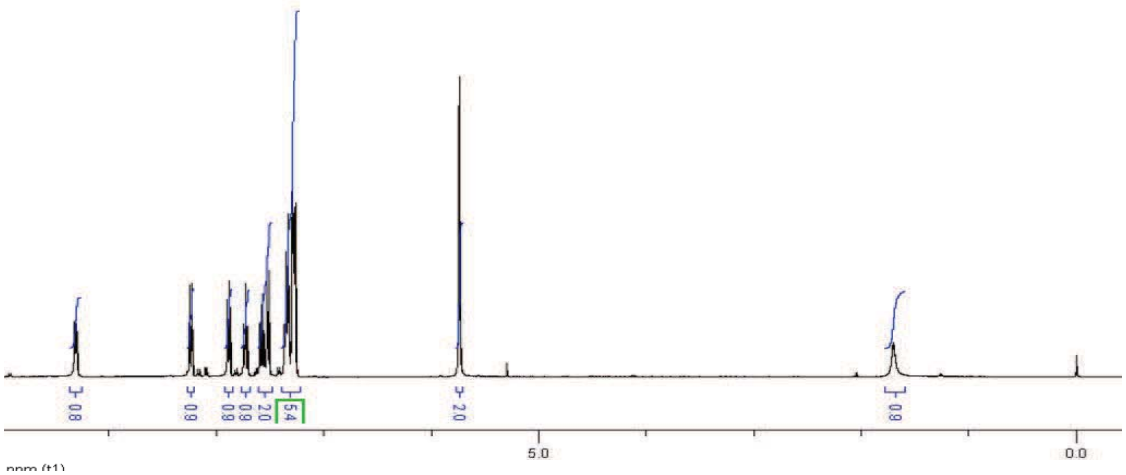

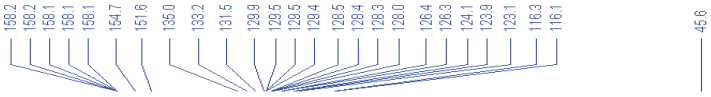

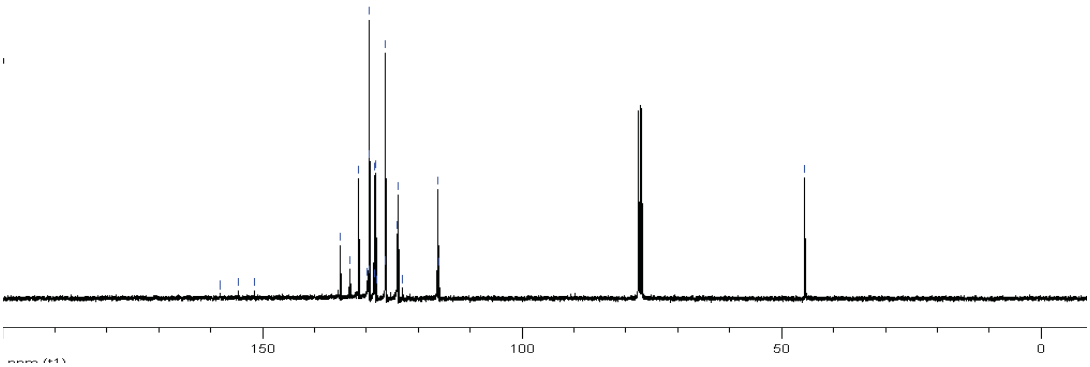

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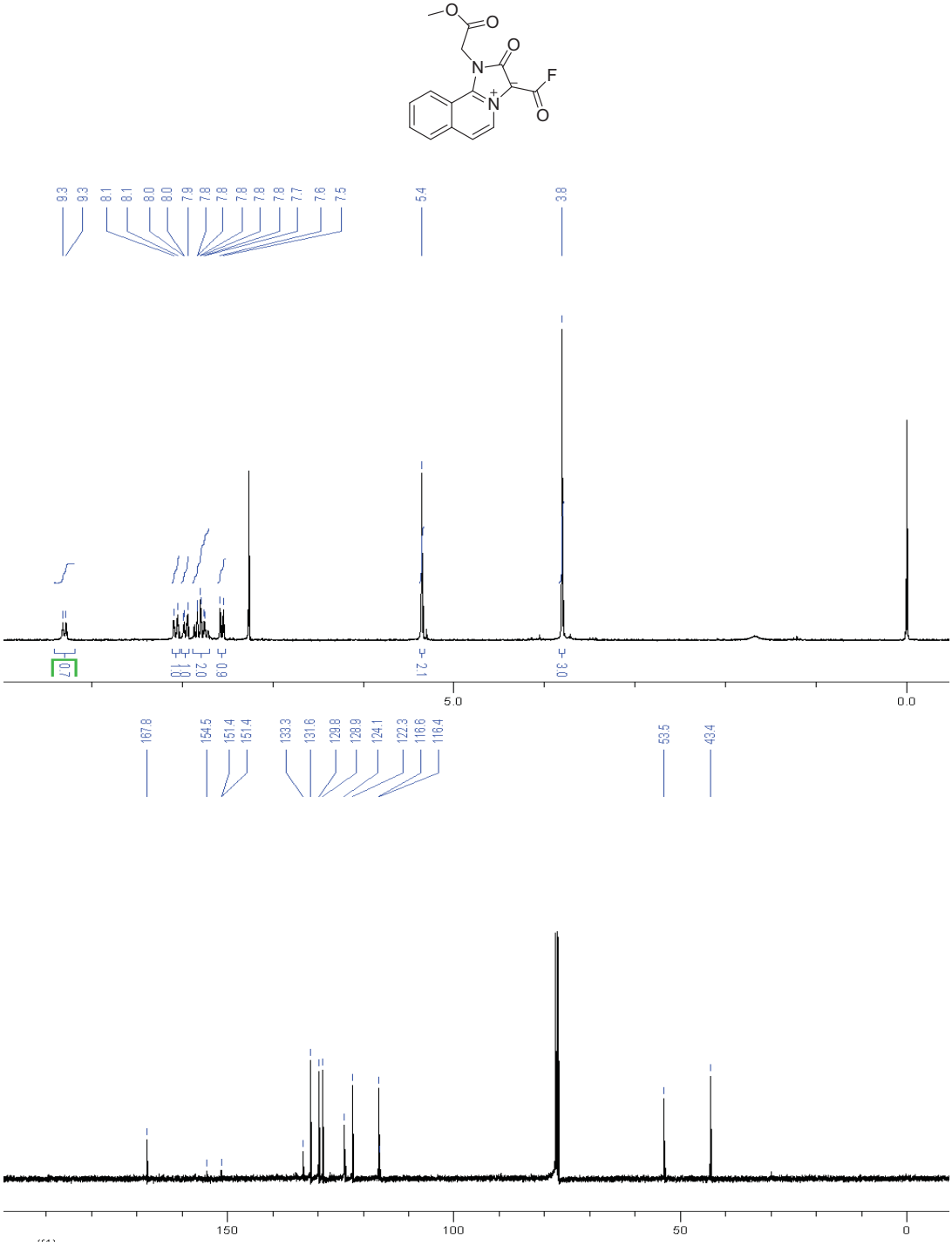

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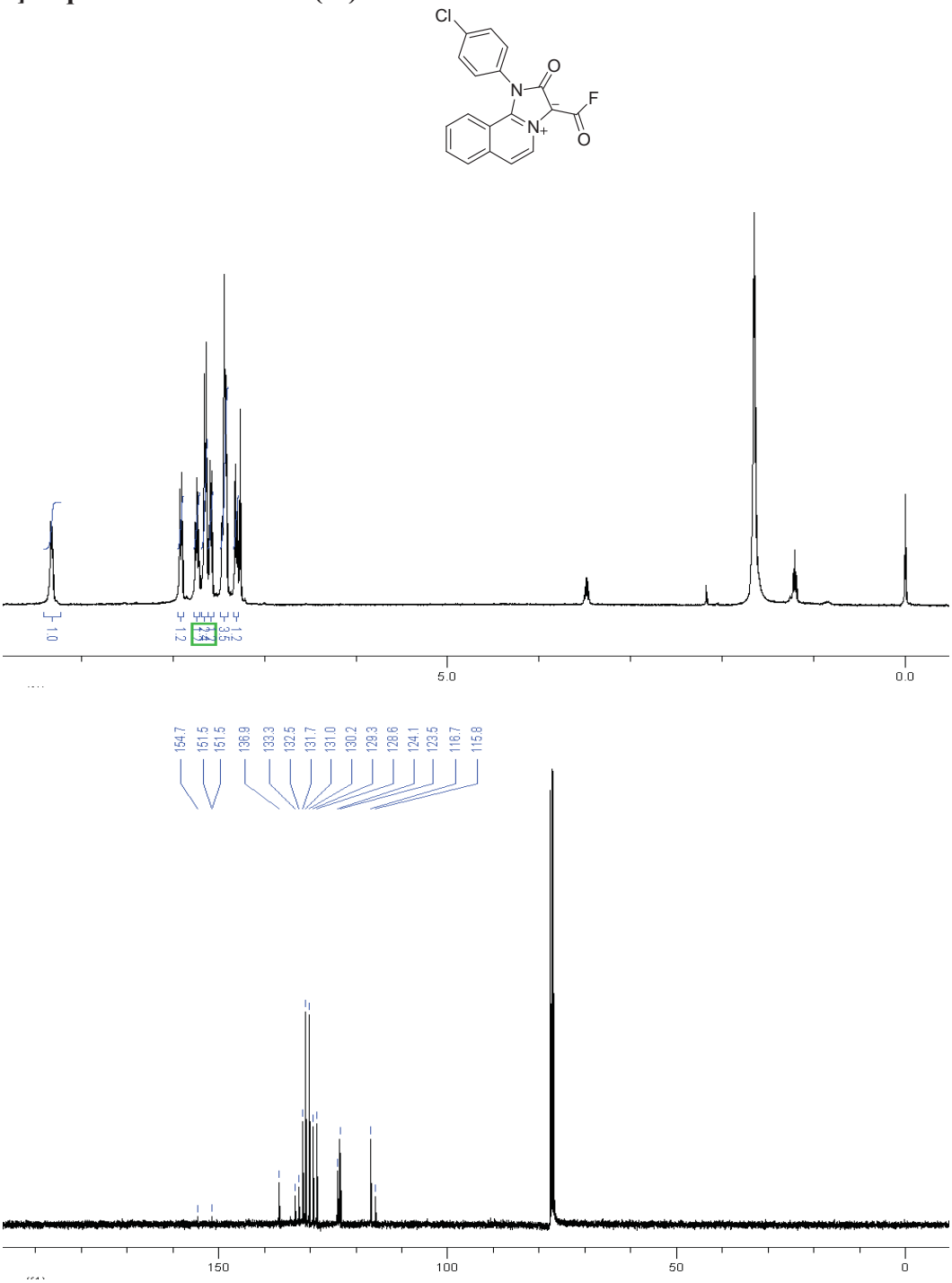

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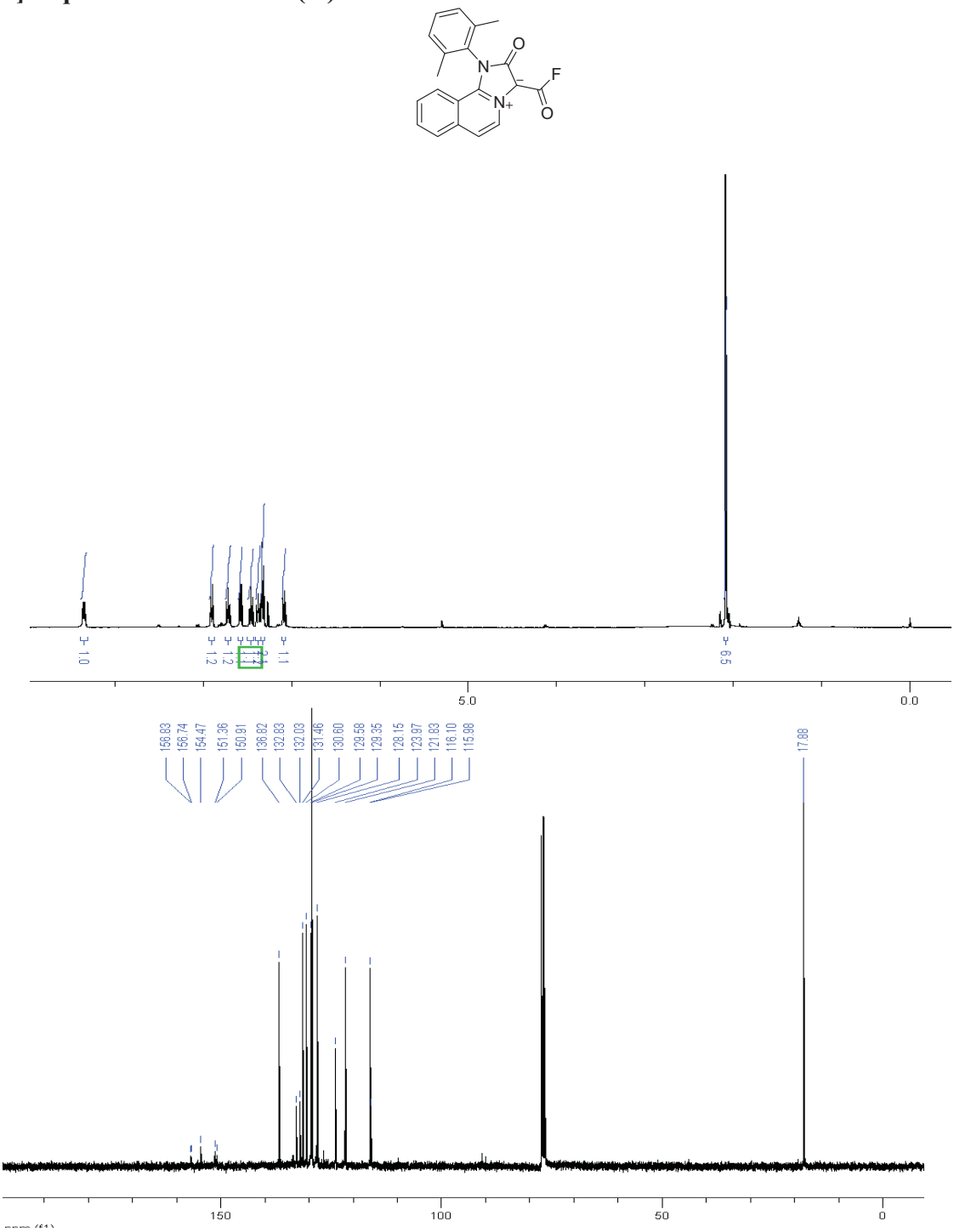
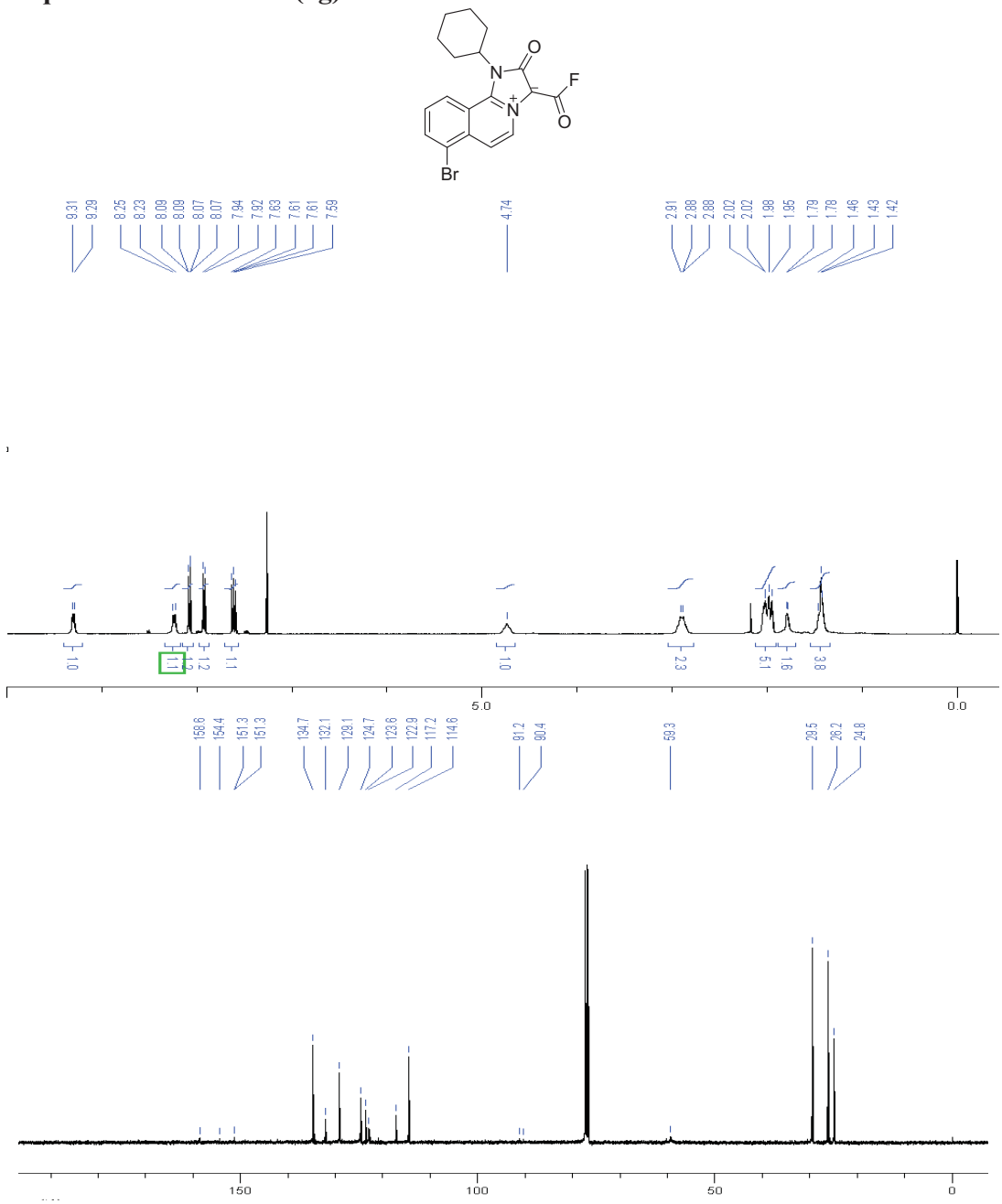
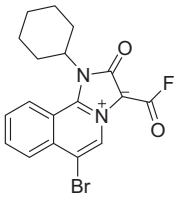
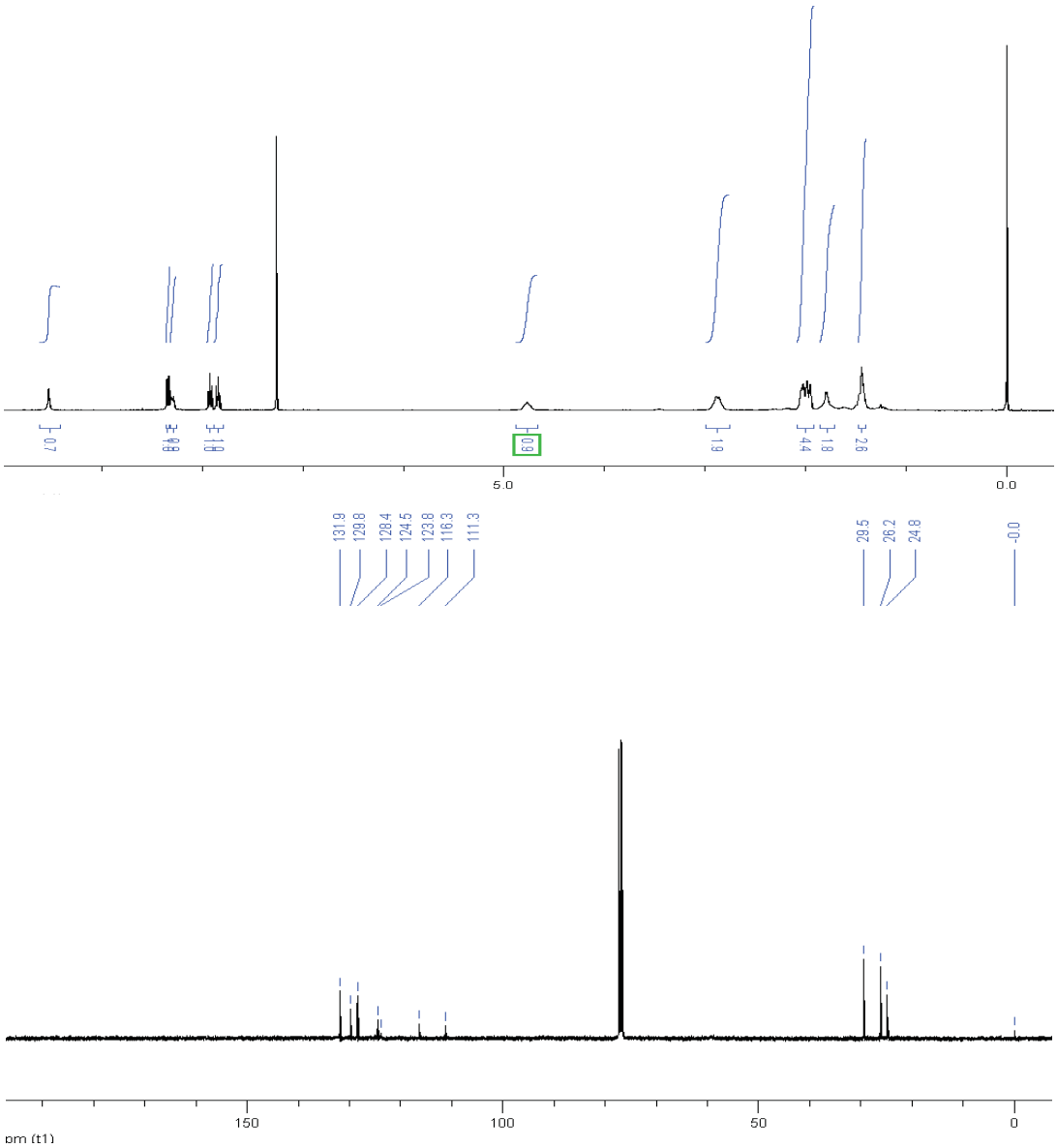


7-Bromo-1-cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5g)

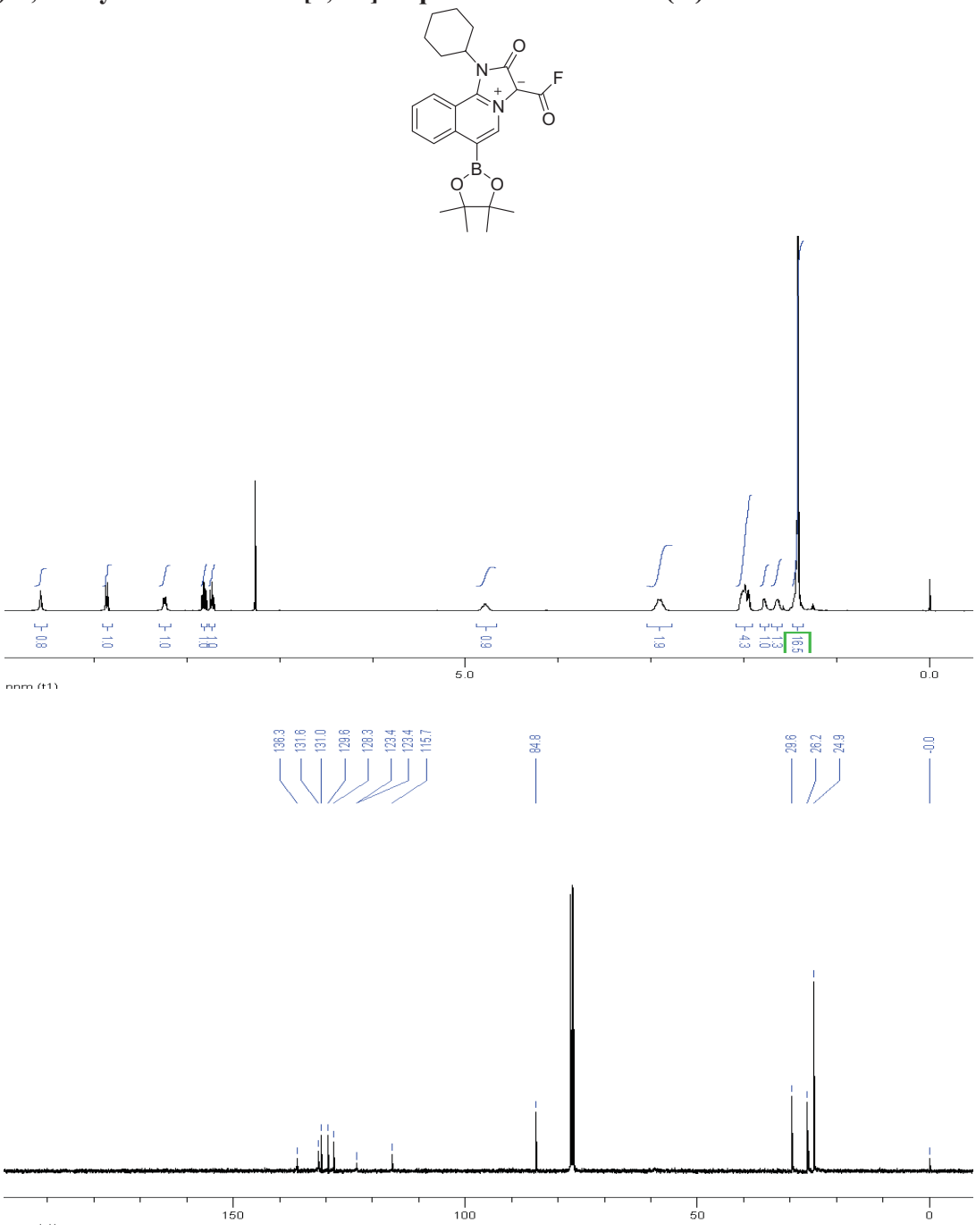


6-Bromo-1-cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5h)





1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5i)



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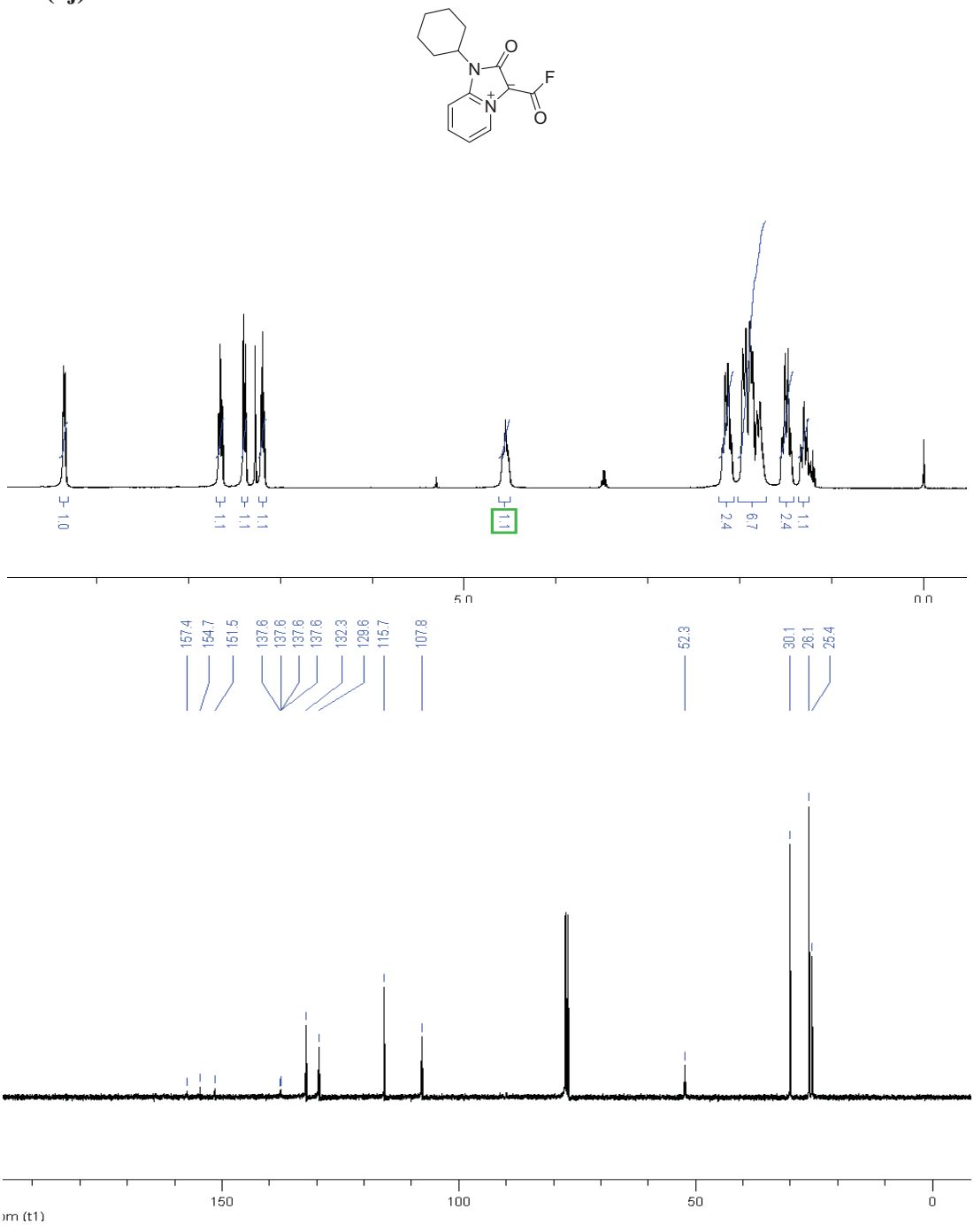
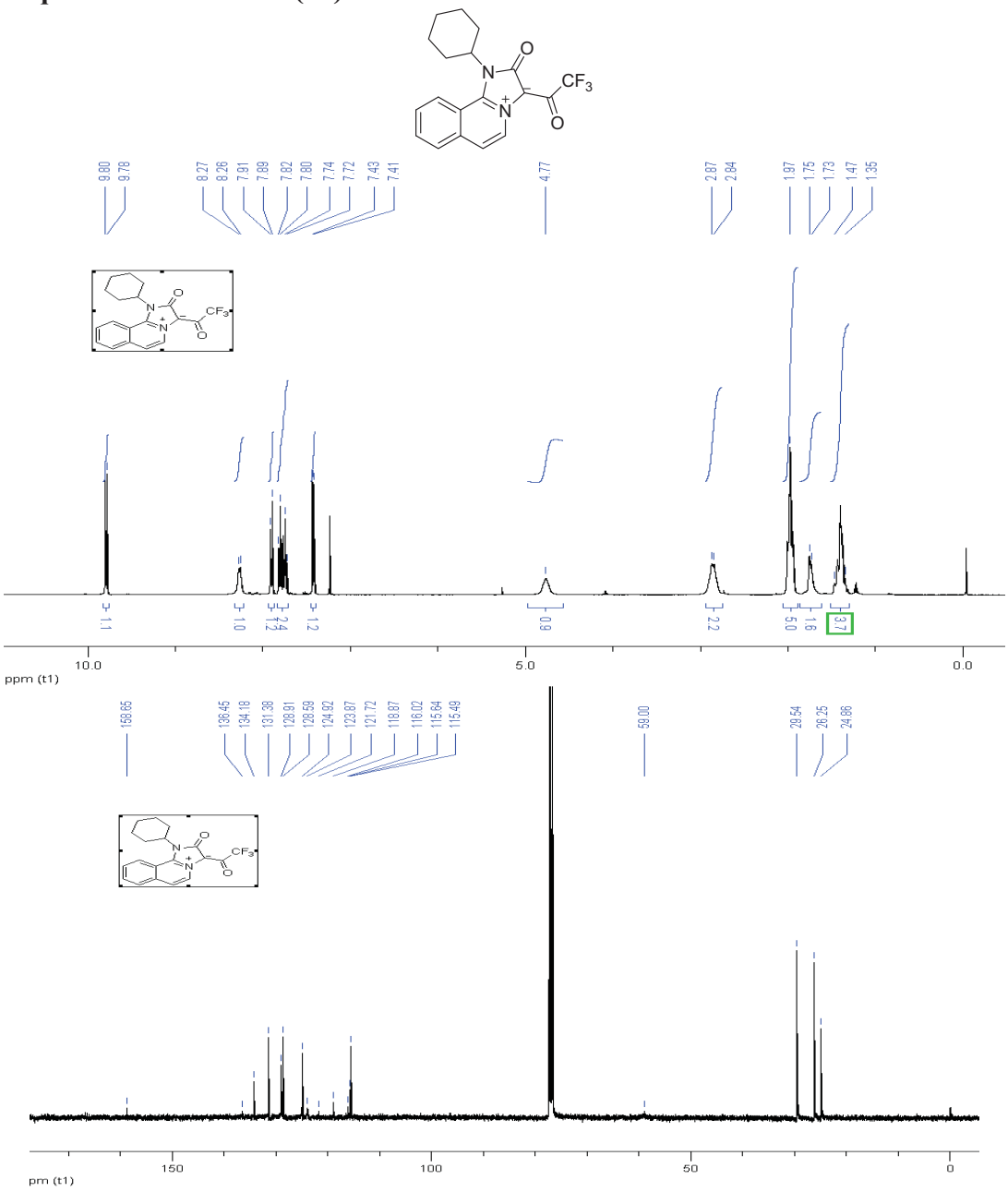
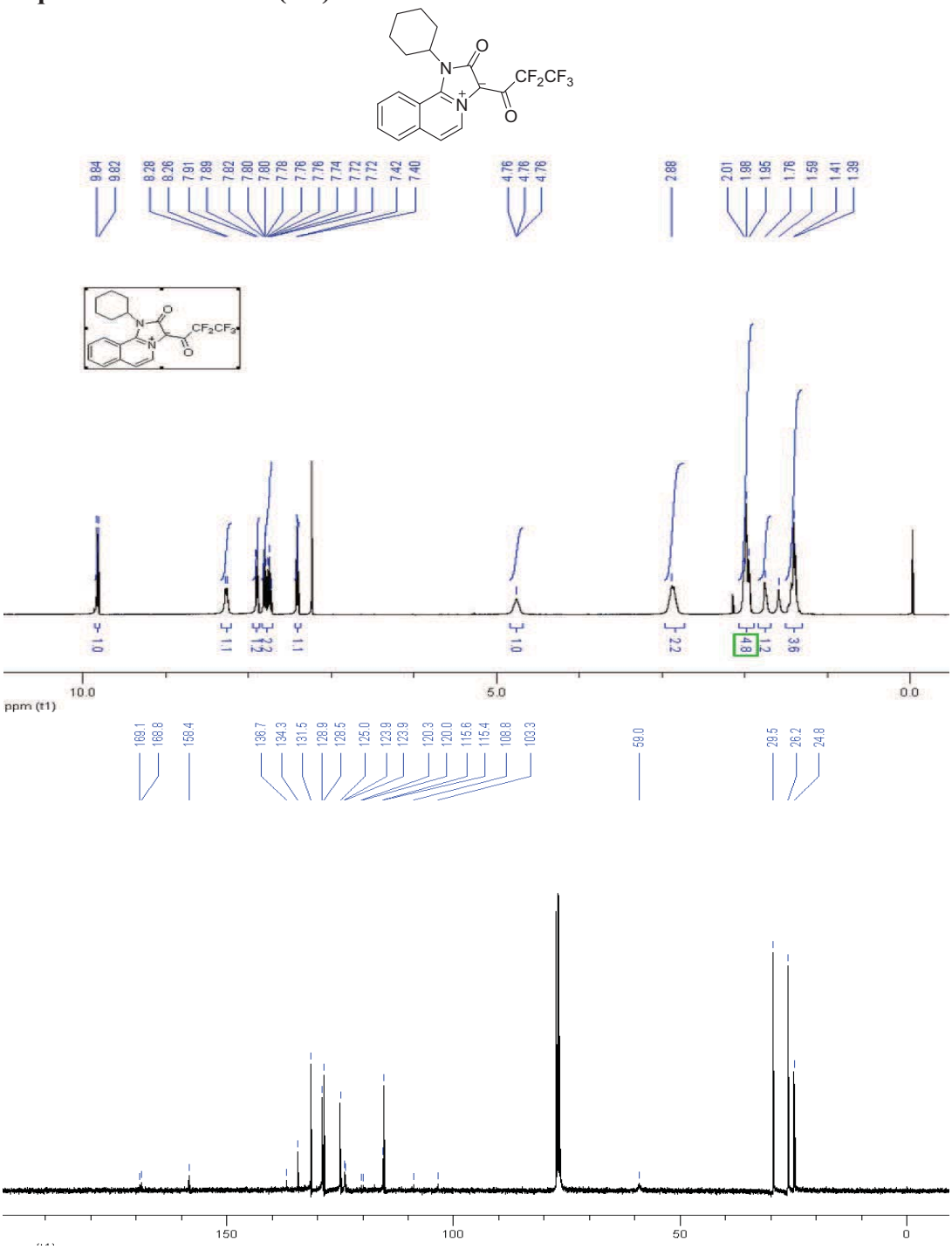


1-Cyclohexyl-2-oxo-3-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5k)



1-Cyclohexyl-2-oxo-3-(2,2,3,3,3-pentafluoropropanoyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5m)



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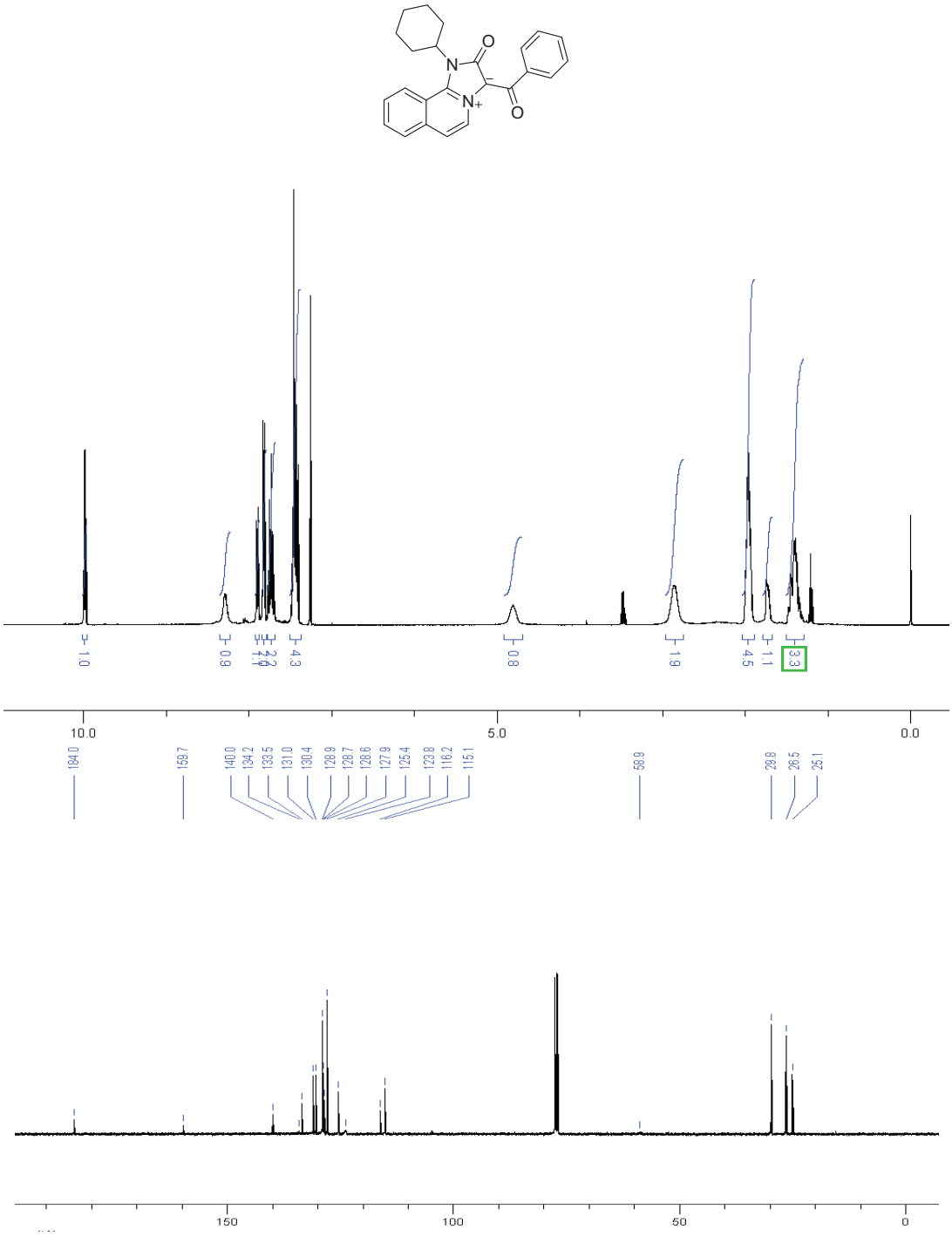

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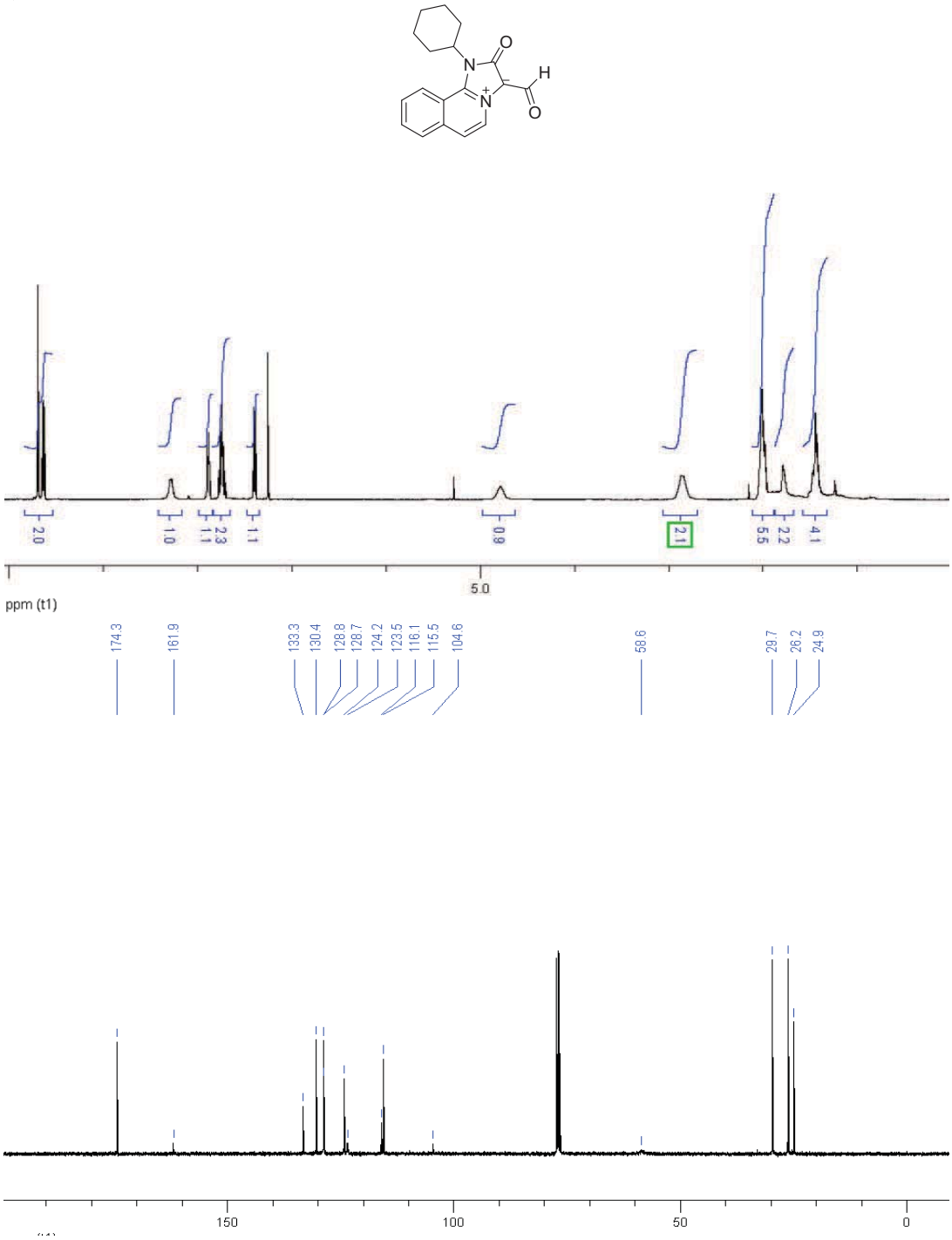

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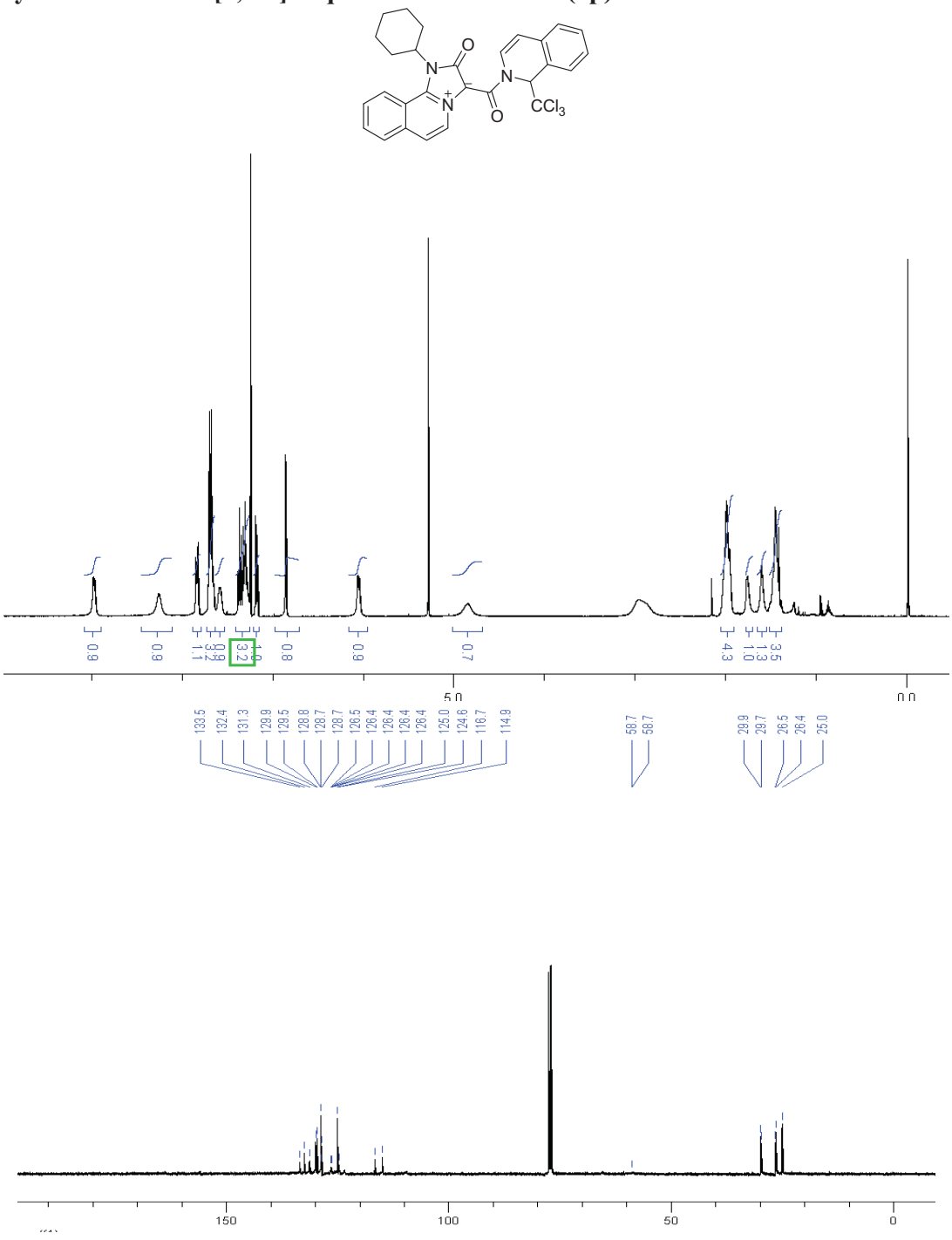

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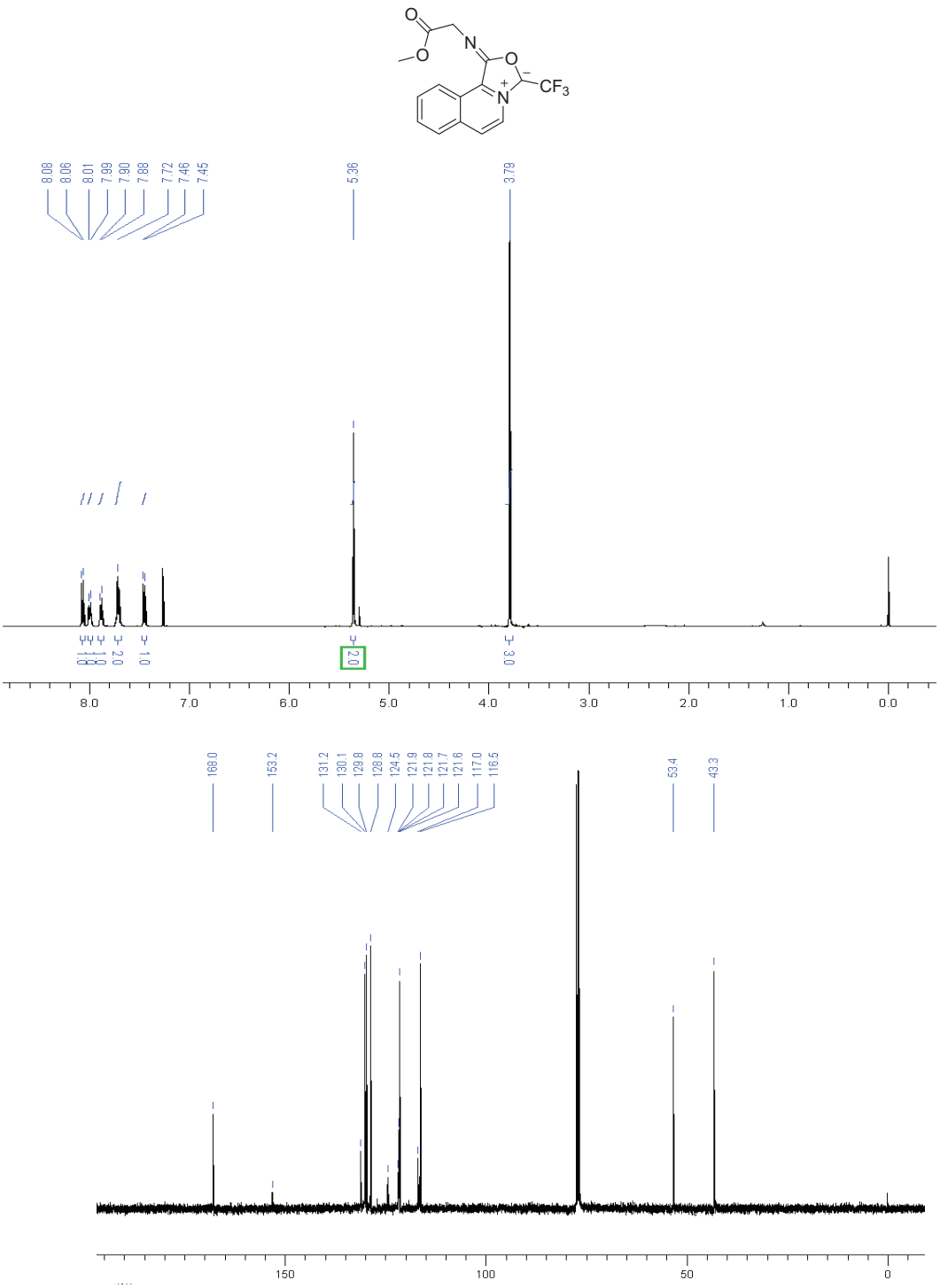

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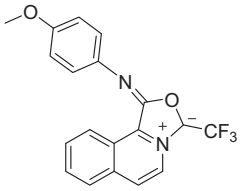

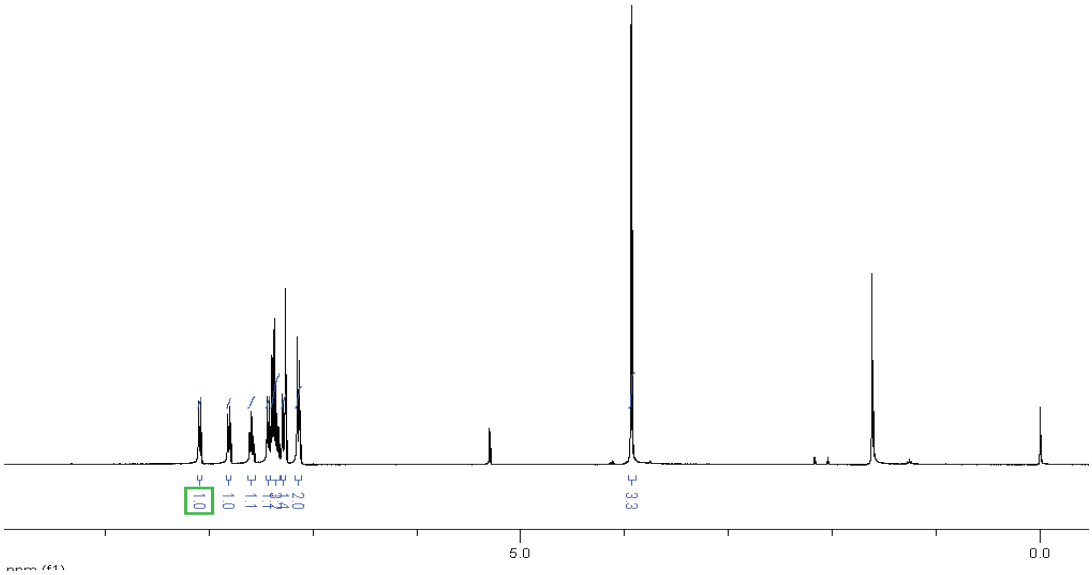

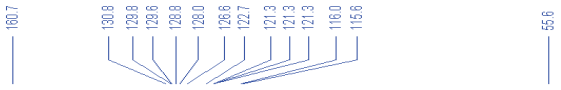

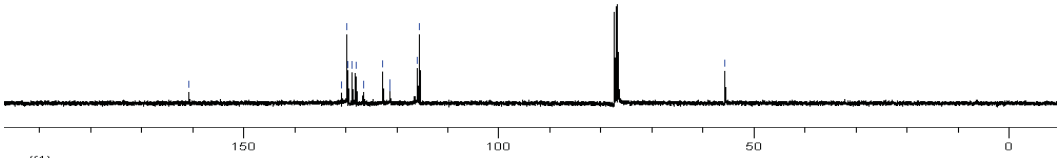

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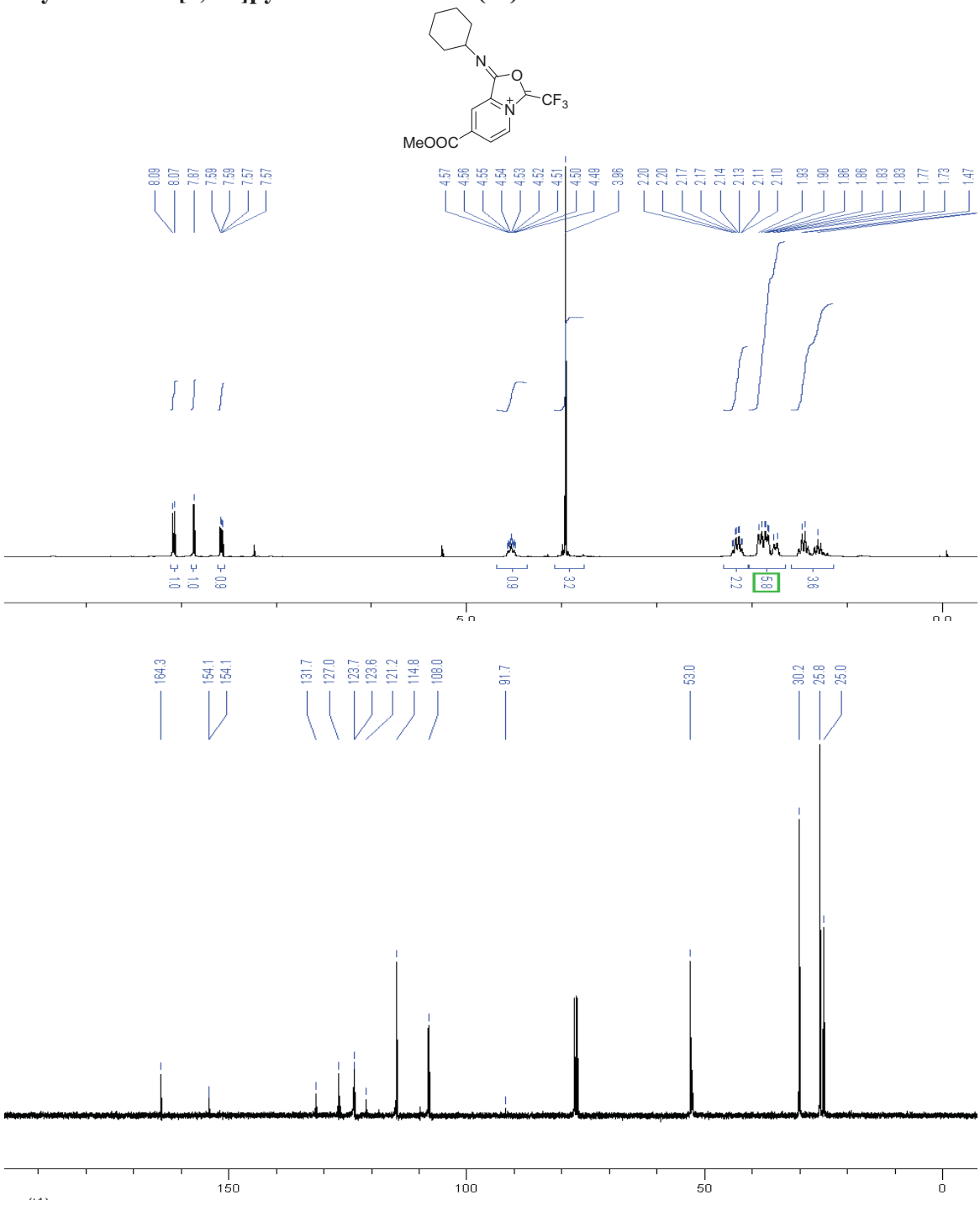
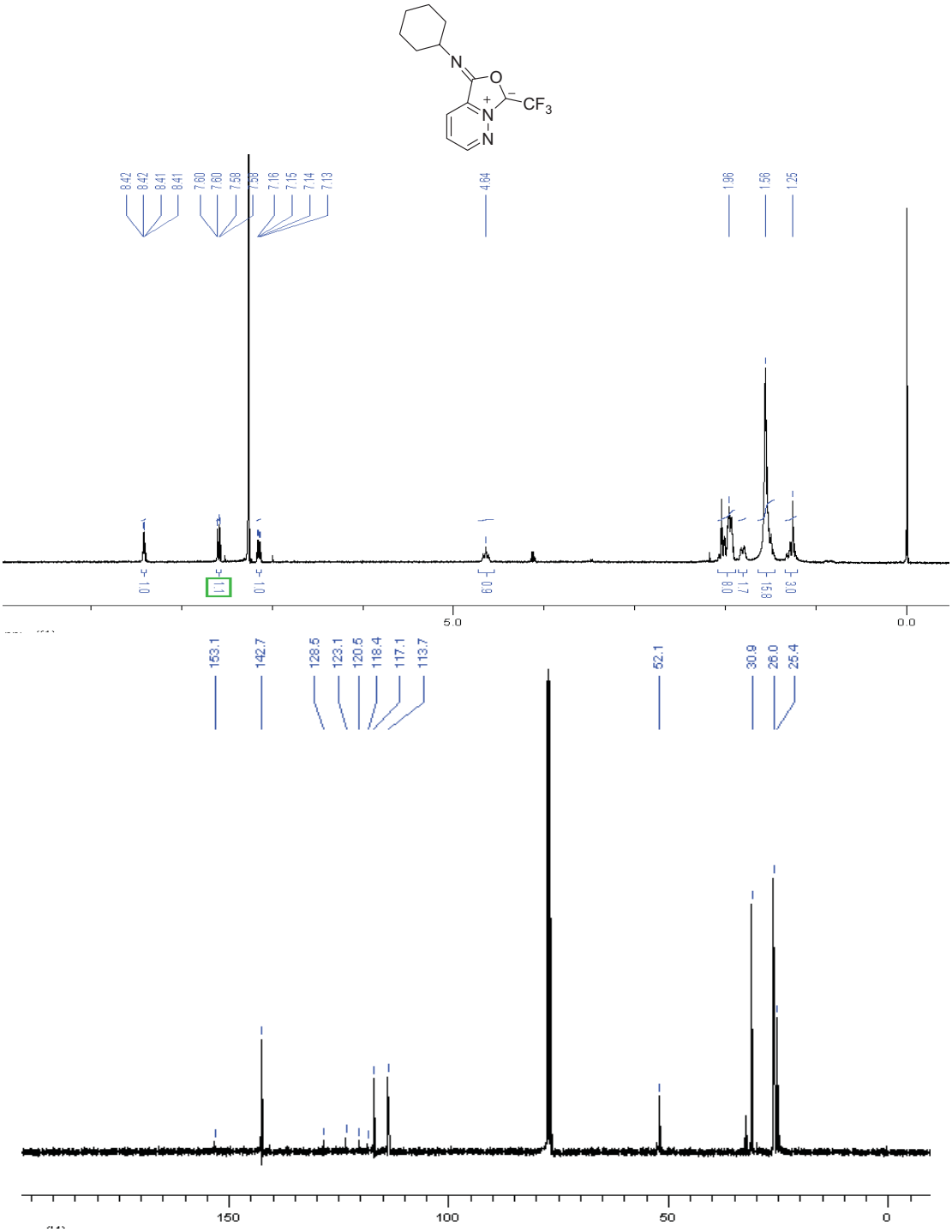
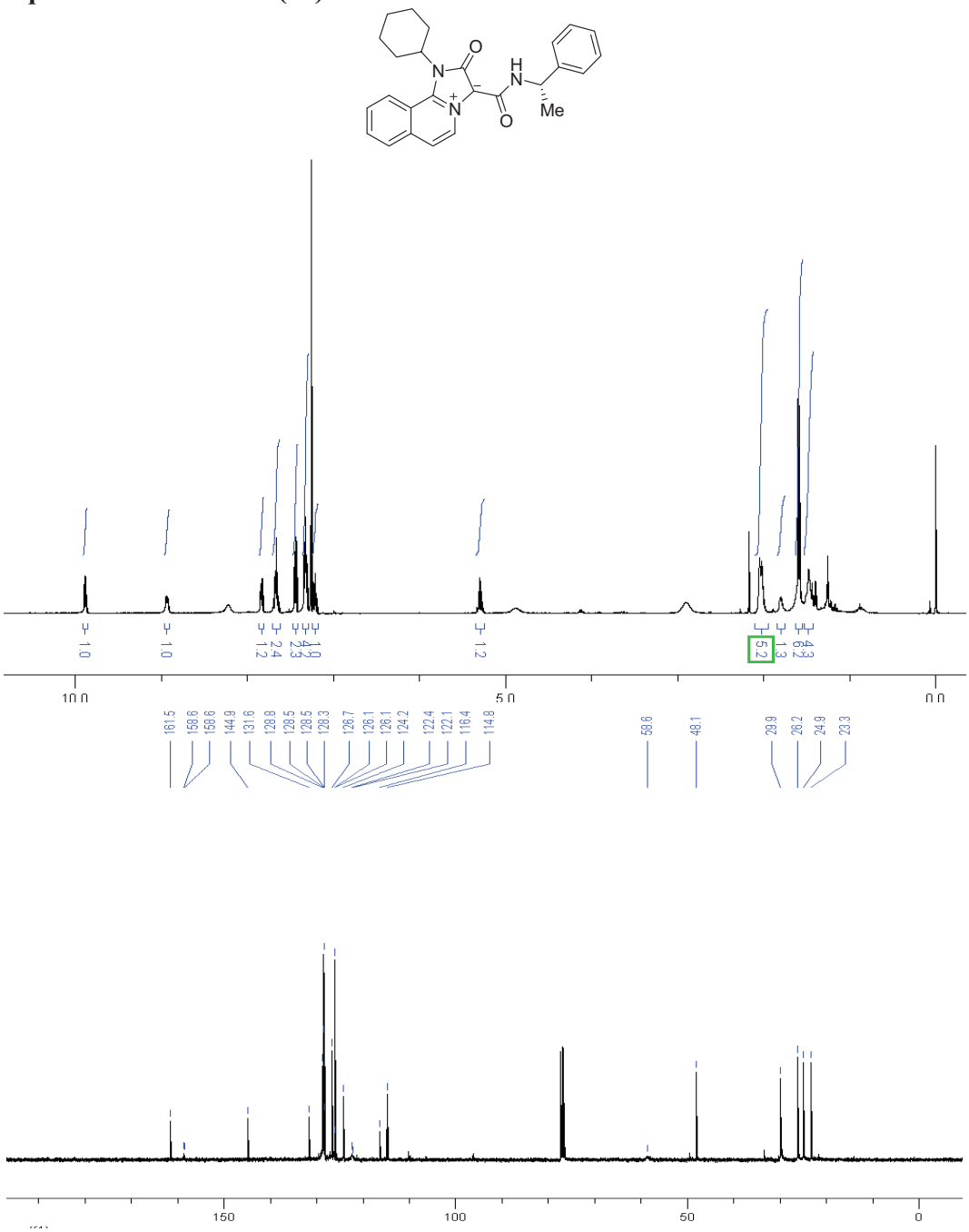


5-(Cyclohexylimino)-7-(trifluoromethyl)-5,7-dihydrooxazolo[3,4-*b*]pyridazin-8-ium-7-ide (6d)



(*S*)-1-Cyclohexyl-2-oxo-3-(1-phenylethylcarbamoyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (7a)



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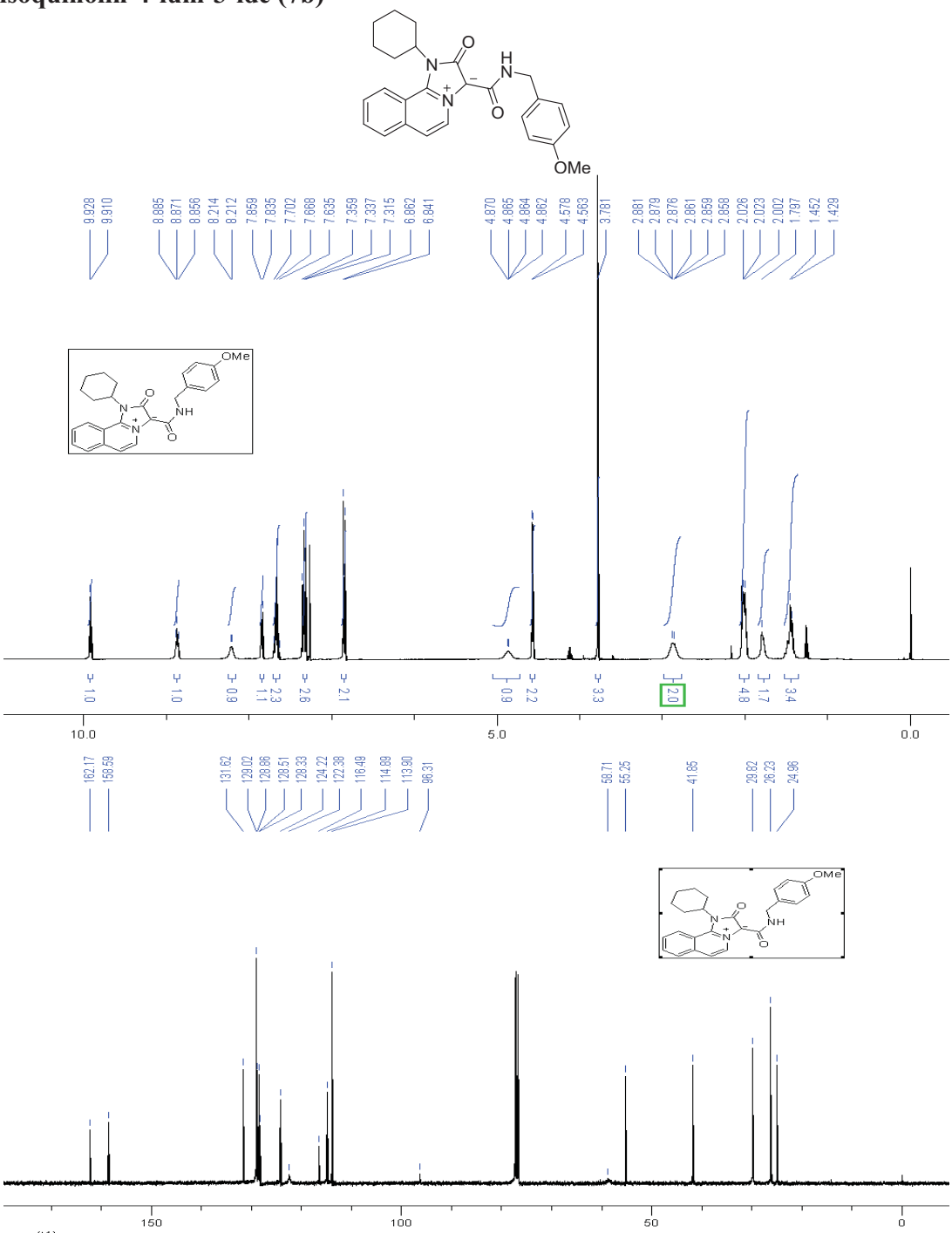

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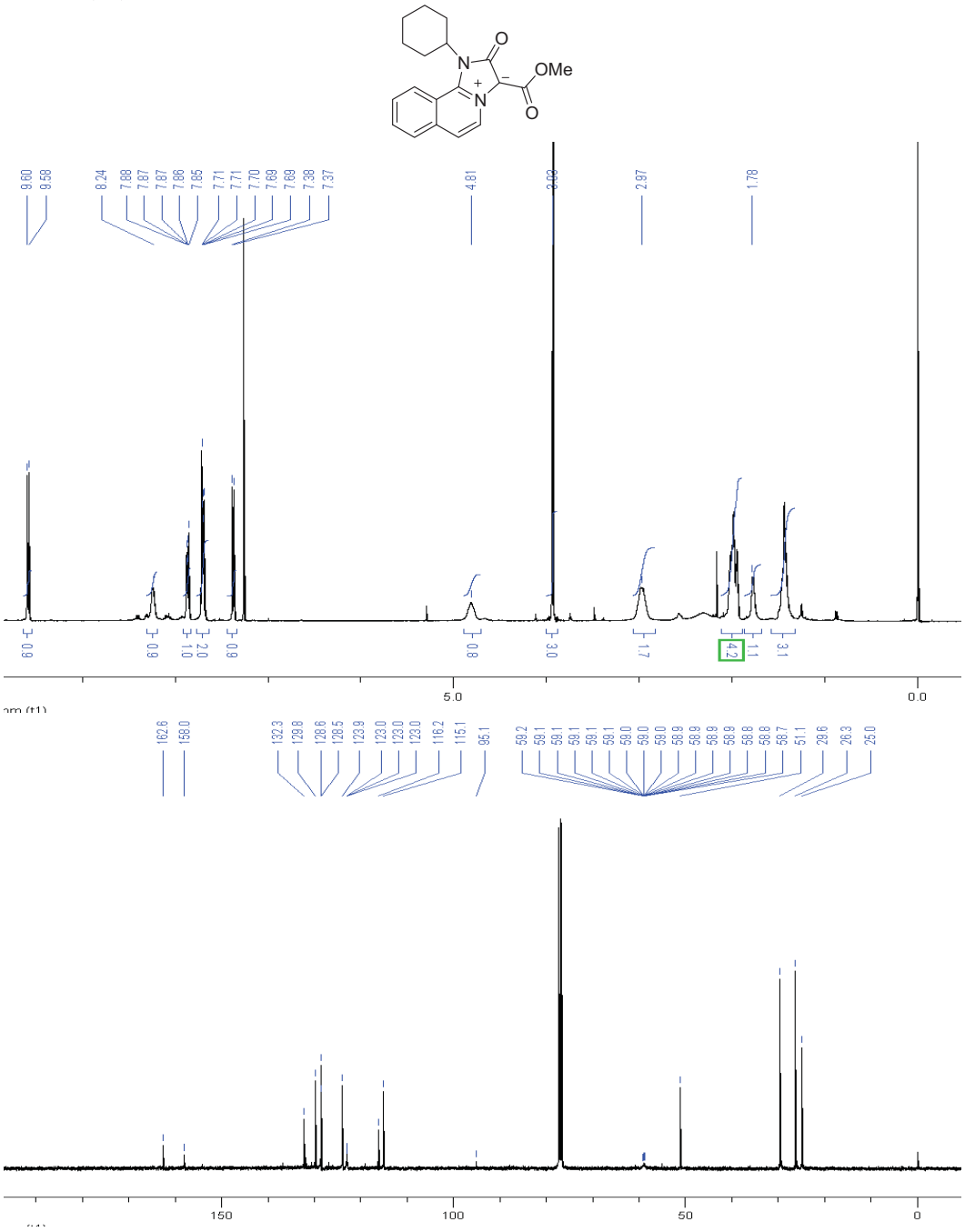

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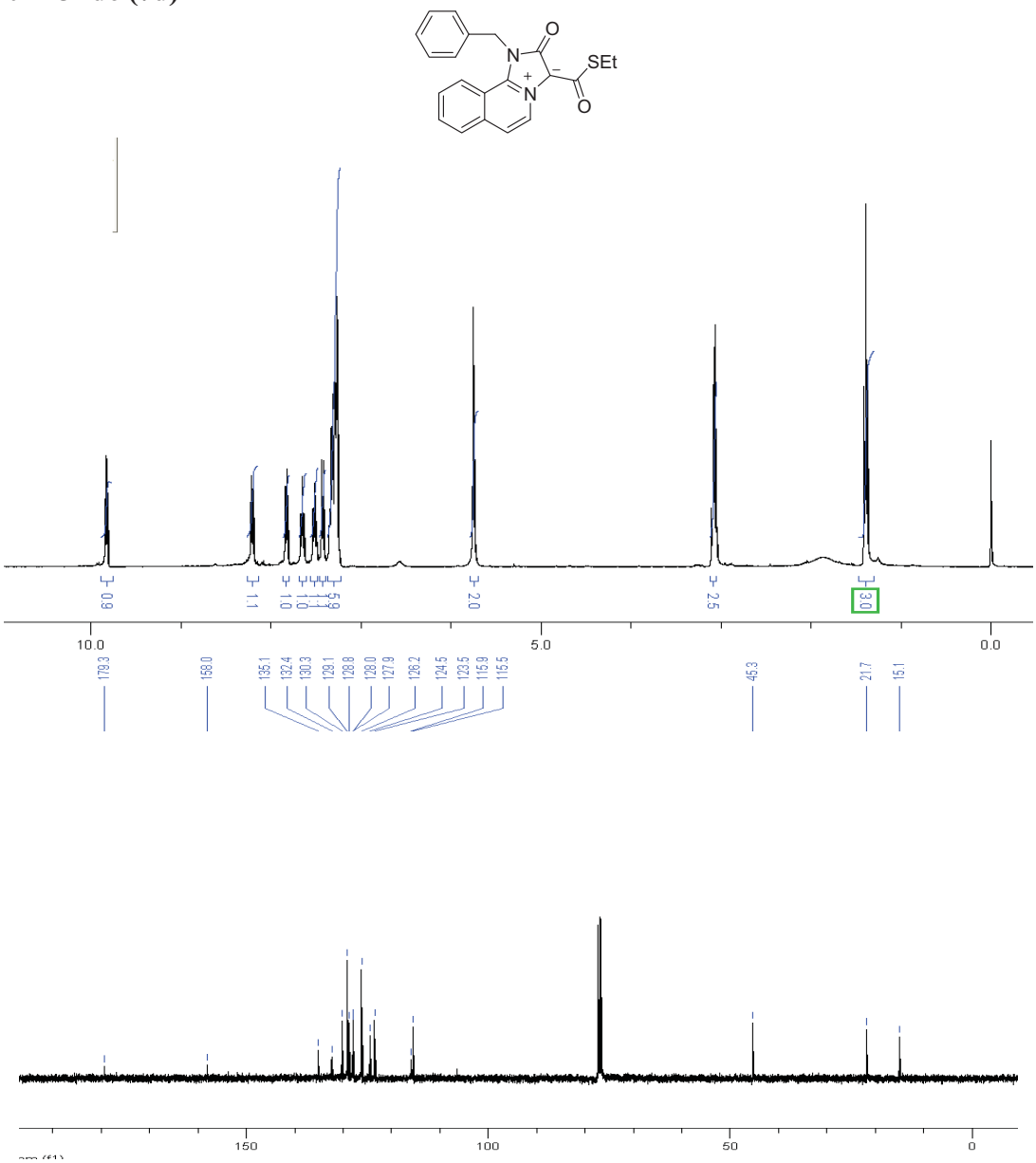

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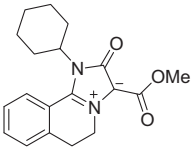

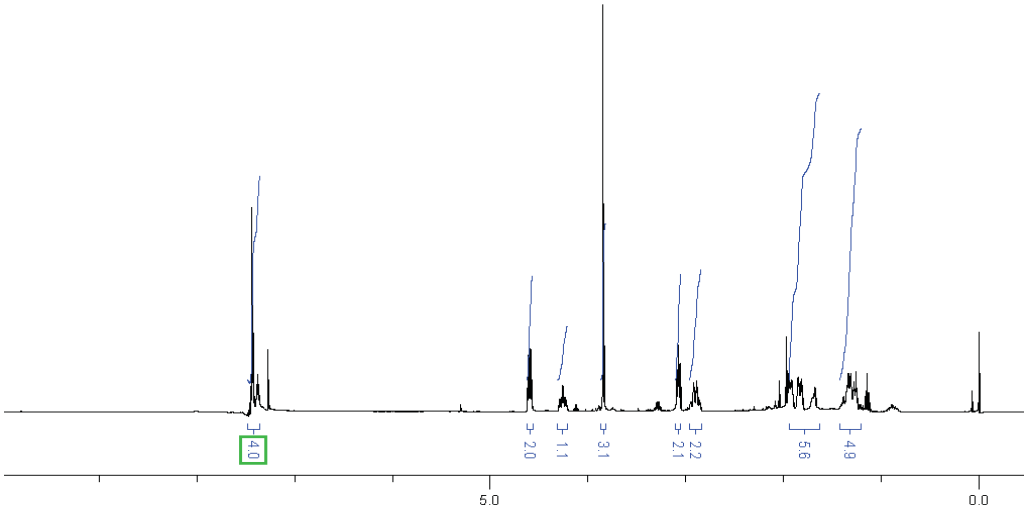

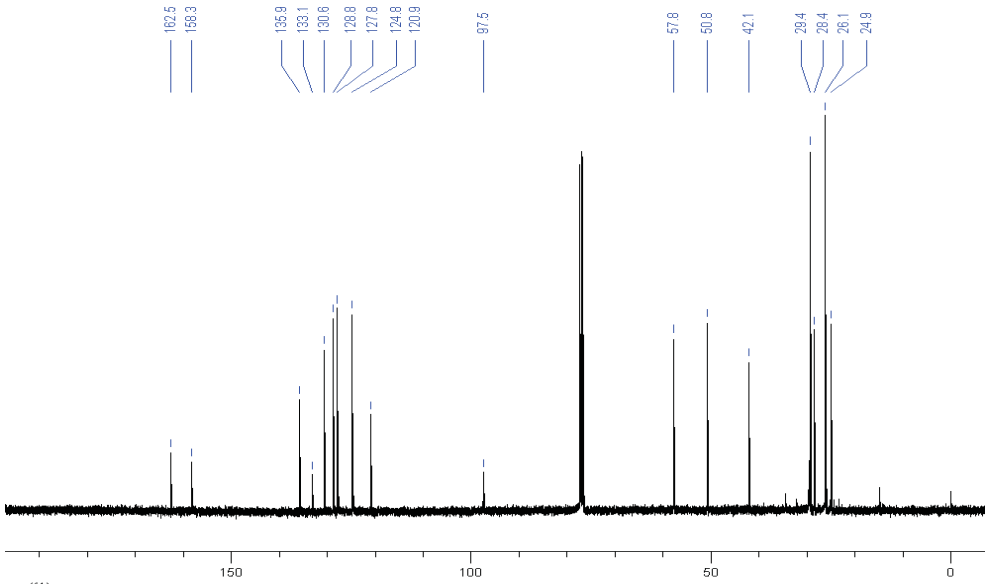

Synthesis and Properties of Oligonucleotides Carrying Isoquinoline Imidazo[1,2-*a*]azine Fluorescent Units

Sónia Pérez-Rentero,[†] Nicola Kielland,[‡] Montserrat Terrazas,[†] Rodolfo Lavilla,*[,‡,§] and Ramon Eritja*[,†]

Institute for Research in Biomedicine, IQAC−CSIC, CIBER-BBN Networking Centre on Bioengineering, Biomaterials and Nanomedicine, Baldiri Reixac 10, 08028 Barcelona, Spain, Institute for Research in Biomedicine, Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Baldiri Reixac 10−12, 08028 Barcelona, Spain, and Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Avda Joan XXIII s/n, 08028 Barcelona, Spain. Received February 18, 2010; Revised Manuscript Received June 28, 2010

Oligonucleotides carrying novel fluorescent compounds with a dipolar isoquinoline imidazo[1,2-*a*]azine core were prepared. Analysis of the melting curves demonstrates that DNA duplexes carrying these fluorescent labels at their ends have a slight increase in DNA duplex stability. The UV absorption and fluorescent properties of the oligonucleotide conjugates were analyzed. The fluorescent label is sensitive to duplex formation, as cooperative melting curves are also observed at 366 nm and fluorescence has a large increase upon denaturation. Cell uptake studies allow observation of these fluorescently labeled oligonucleotides internalized into HeLa cells.

INTRODUCTION

There is a considerable interest in the development of new dyes and the introduction of these into biomolecules such as peptides, proteins, and nucleic acids (*1*). Furthermore, the development of new methodologies for the selective and straightforward modification of biomolecules is having an increasing impact on biopharmaceuticals. When fluorescent molecules are attached to biomolecules that are not fluorescent, the resulting new entity acquires the fluorescent properties. Thus, fluorescent labels allow sensitive and selective detection of a specific component of complex biomolecular assemblies. Fluorescence-labeled oligonucleotides have large numbers of applications in several fields, such as biotechnology (*2*), cell biology (*3*), molecular biology (*4*), and biophysics (*5*). Therefore, the development of new fluorescent labels for oligonucleotides is of particular relevance (*6, 7*).

Recently, we described the synthesis of a new class of fluorescent mesoionic acid fluorides using a multicomponent strategy. The reaction involves the participation of an azine, an isocyanide, and a fluorinated anhydride and yields dipolar derivatives with an isoquinoline imidazo[1,2-*a*]azine core (see Scheme 1) (*8*). These compounds are fluorescent, and when trifluoroacetic anhydride is used, they contain a reactive acid fluoride group that can be used to introduce the fluorescent label, by means of amide formation, into biomolecules that carry amino groups. The modular character of this multicomponent reaction (MCR) (*9*) allows the convergent synthesis of a large variety of structural analogs in a single step. Thus, both the fluorescent and biological properties of the dye can be optimized for specific applications. In this respect, the present study determines the features of the conjugation of these stable dipolar acyl fluorides with oligonucleotides, a fruitful strategy often used in peptide synthesis (*10*), which to our knowledge is unprecedented in the oligonucleotide field.

Here, we report the conjugation of mesoionic acid fluorides **1a** and **1b** with oligonucleotides carrying alkyl amino groups (Scheme 2) and demonstrate that fluorescence-labeled oligonucleotides can be prepared in good yields directly from the reaction of amino-oligonucleotides and mesoionic acid fluorides in aqueous media. Dipoles **1a** and **1b**, bearing, respectively, cyclohexyl and benzyl groups as substituents at the imidazole nitrogen, were selected from a set of described analogues for the following reasons. First, they can be synthesized on a multigram scale with a simple methodology and are well characterized (X-ray, NMR, and spectroscopy); in addition, their substituents at the imidazole nitrogen (cyclohexyl and benzyl) featuring relevant differences in terms of shape, volume, polarity, and conformational behavior may confer to the corresponding bioconjugates distinct properties. Furthermore, both residues are chemically stable, unlikely to suffer degradation in physiological media, and, from an exploratory point of view, easy to replace by a wide number of analogues.

Our results indicate that the novel fluorescent oligonucleotides show potentially interesting properties for denaturation monitoring procedures as well as for cellular uptake studies.

EXPERIMENTAL PROCEDURES

The phosphoramidites and ancillary reagents used during oligonucleotide synthesis were from Applied Biosystems (PE Biosystems Hispania S.A., Spain) and Link Technologies Ltd. (Scotland). The rest of the chemicals were purchased from Aldrich, Sigma, or Fluka (Sigma-Aldrich Química S.A., Spain). 1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo-[2,1-*a*]isoquinolin-4-ium-3-ide (**1a**), 1-benzyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (**1b**), 1-cyclohexyl-3-(4-methoxybenzylcarbamoyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (**1c**), and 1-cyclohexyl-3-(methoxycarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (**1d**) were prepared following literature procedures (*8*) (Scheme 1).

Synthesis of Oligonucleotides. Oligonucleotide sequences A, 5′-CCAATTGG-3′; B, 5′-TTCCGGAA-3′; and C, 5′-CTCTCGCACCCATCTCTCTCCTTCT-3′ were prepared on an automatic Applied Biosystems 3400 DNA synthesizer on 0.2− or 1−μmol scale using commercially available chemicals. The

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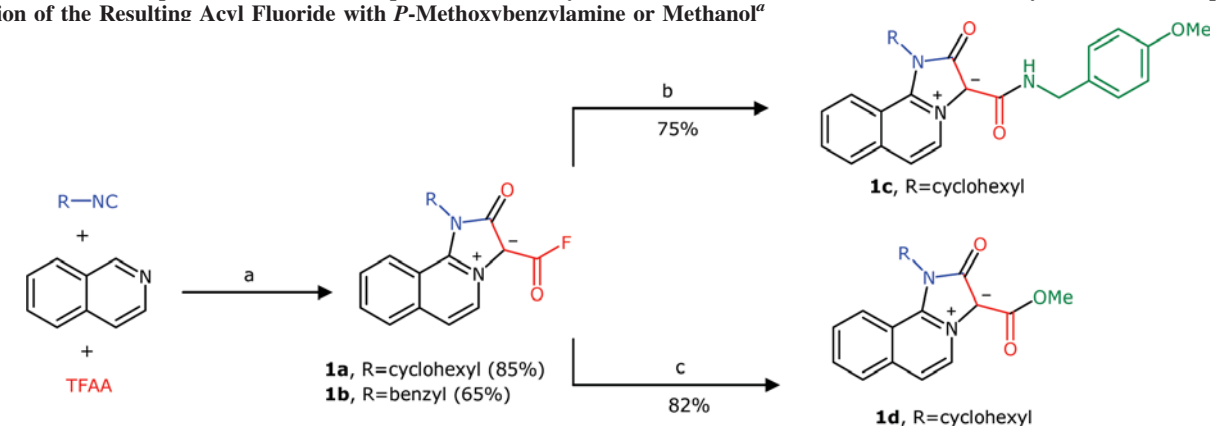
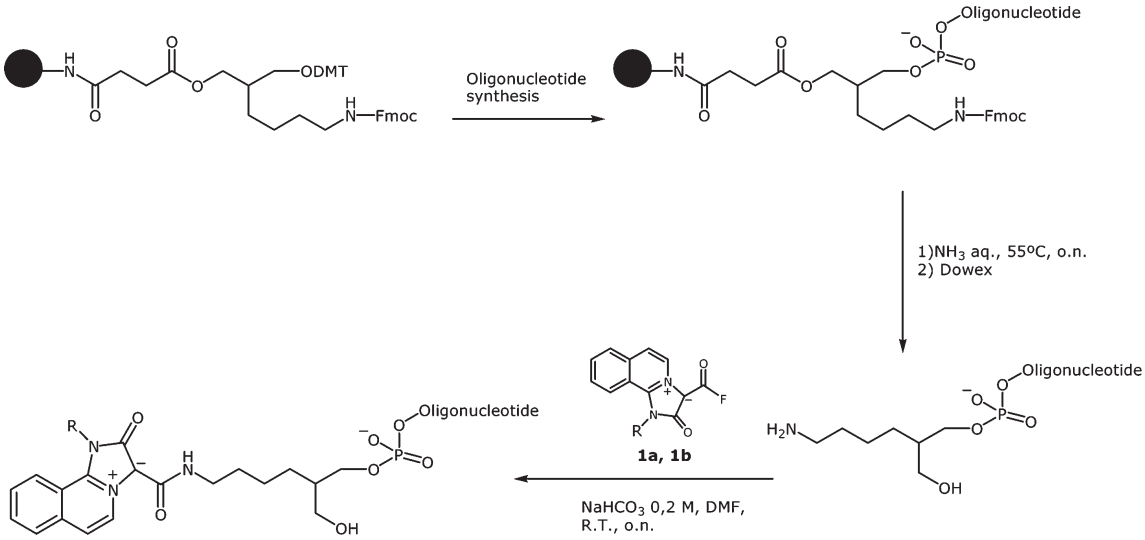
Scheme 1. Three-Component Reaction of Isoquinoline and Isocyanides in the Presence of Trifluoroacetic Anhydride and Subsequent Reaction of the Resulting Acyl Fluoride with *P*-Methoxybenzylamine or Methanol[a]



[a] Reagents and conditions: (a) CH_2Cl_2, 14 h, r.t.; (b) *p*-methoxybenzylamine, TEA, CH_2Cl_2 anh., r.t., overnight; (c) MeOH, TEA, reflux.

Scheme 2. Synthesis of Oligonucleotides Carrying a Derivative of Isoquinoline at the 3′-End



sequences were prepared with and without the amino group at the 3′-end. The synthesis was carried out using the standard phosphite triester methodology and a controlled-pore-glass support carrying the 2-(*N*-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}-4-aminobutyl)propane-1,3-diol linker (*11*) (Scheme 2) or in regular low-volume (LV200) polystyrene supports. The benzoyl (Bz) group was used to protect the amino group of dC and dA, and the isobutyryl (ibu) group to protect dG. Coupling yields were >95%. The last DMT group was removed at the end of the synthesis. The oligonucleotide was deprotected and cleaved from the support by treatment with aqueous concentrated ammonia for 12 h at 55 °C. Under these conditions, all protecting groups, including Fmoc, were removed to yield unprotected 3′-amino-oligonucleotide. The mixture was filtered, and the ammonia solution was concentrated to dryness. The residue was passed through a Dowex 50 × 4 (Na^+ form) column to exchange ammonium ions for Na^+ ions. The solution was analyzed by HPLC and used directly in the dye conjugation. Analytical HPLC solutions: Solvent A, 5% acetonitrile (MeCN) in 100 mM triethylammonium acetate (pH = 7); and solvent B, 70% MeCN in 100 mM triethylammonium acetate (pH = 7). Column: X-Bridge OST C18 (2.5 μm, 4.6 × 50 mm). Flow rate: 1 mL/min. Conditions for the analysis of octamers: 10 min linear gradient from 0−30% B at 60 °C; for the analysis of 25mer: 4 min linear gradient from 0−12% B, then 6 min linear gradient from 12−50% B at 60 °C. The desired oligonucleotides eluted at 2.5−3.5 min. Alternatively, oligonucleotides were purified by HPLC (see below).

Octamer sequence A (200 nmol scale): 33% yield (5 OD_{260}) t_R = 2.6 min. Octamer sequence A 3′-NH_2 (1 μmol scale): 47% yield (36 OD_{260}), t_R = 2.6 min. MALDI-TOF MS *m/z* (negative mode, THAP-CA, $[M-H]^-$) expected for $C_{85}H_{106}N_{31}O_{50}P_8$ 2617.8, found 2618.7. Octamer sequence B (200 nmol scale): 39% yield (6 OD_{260}) t_R = 3.2 min. Octamer sequence B 3′-NH_2 (1 μmol scale): 54% yield (42 OD_{260}), t_R = 3.2 min. MALDI-TOF MS *m/z* (negative mode, THAP-CA, $[M-H]^-$) calculated for $C_{85}H_{106}N_{31}O_{50}P_8$ 2617.8, found 2617.9. 25mer sequence C 3′-NH_2 (1 μmol scale): 58% yield 118 OD_{260}, t_R = 4.0 min. MALDI-TOF MS *m/z* (negative mode, THAP-CA, $[M-H]^-$) expected for $C_{244}H_{301}N_{73}O_{159}P_{25}$ 7600, found 7603.6.

General Protocol for Conjugation. The amino-oligonucleotides were reacted with 1-cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (**1a**) or 1-benzyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (**1b**) or with fluorescein isothiocyanate (**FITC**) (Isomer I, Sigma) as follows. Oligonucleotides (7 O.D.) were dissolved with 250 μL of an aqueous solution of 0.2 M $NaHCO_3$ (pH = 9). Then, 10 equiv of a solution of compound **1a** or **1b** or **FITC** in 0.25 mL of *N*,*N*-dimethylformamide (DMF) were added and the mixture was left to react for 8 h at room temperature. Then, 100 μL of an aqueous solution of 0.2 M $NaHCO_3$ (pH = 9) and an additional 10 equiv of compound **1a** or **1b** in 100 μL of DMF were added and the mixture was left overnight at room temperature. The mixtures were concentrated to dryness, and the residues were dissolved in 1 mL of H_2O. The solutions were purified by Sephadex G-25 (NAP-10

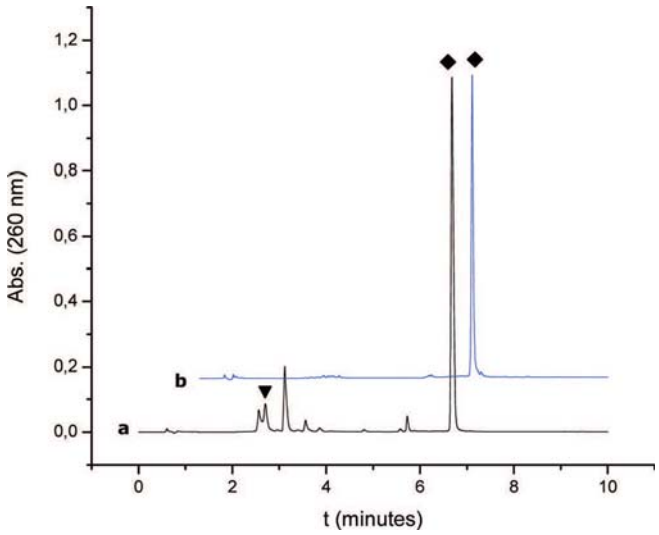


Figure 1. HPLC profiles of (a) the mixture obtained after the reaction with compound **1a** and amino-oligonucleotide sequence A to yield compound **2** (conversion 91%) and (b) purified compound **2**. HPLC conditions: 4 min linear gradient from 0−12% B, then 6 min linear gradient from 12−50% B at 60 °C. The desired oligonucleotide (compound **2**) eluted at 8.7 min (▼ stands for amino-oligonucleotide sequence A and ◆ stands for oligomer 2).

columns). The fractions containing oligonucleotides were analyzed by HPLC as described above (Figure 1). Octamer **5** and 25mer **6** were used in the next step without further purification. Octamers **2**−**4** were purified by HPLC on a Nucleosil 120C18 (10 μm, 200 × 10 mm) column. Flow rate: 3 mL/min. Conditions: 10 min linear gradient from 0−30% B, then a 10 min linear gradient from 30−100% B. The resulting products were desalted with Sephadex G-25 (NAP-5 Column). The coupling efficiency was determined by HPLC analyses (octamer **2** 91%, octamer **3** 91%, octamer **4** 94%, 25mer **6** 85%, octamer **5** (**FITC**) 94%. HPLC solutions as described above. Column: X-Bridge OST C18 (2.5 μm, 4.6 × 50 mm). Flow rate: 1 mL/min. Conditions: 4 min linear gradient from 0−12% B, then a 1 min linear gradient from 12−40% B, then 5 min linear gradient from 40−45% B at 60 °C. The purified oligomers were analyzed by MS (MALDI-TOF) and UV−vis (Table 1).

Octamer **2**: 39% yield (2.7 OD_{260}), t_R = 6.7 min, λ = 260 and 347 nm, MALDI-TOF MS *m/z* negative mode, THAP-CA, $[M-H]^-$ calculated for $C_{103}H_{122}N_{33}O_{52}P_8$ 2910.1, found 2911.8.

Octamer **3**: 54% yield (3.8 OD_{260}), t_R = 6.7 min, λ = 260 and 346 nm, MALDI-TOF MS *m/z* negative mode, THAP-CA, $[M-H]^-$ calculated for $C_{103}H_{122}N_{33}O_{25}P_8$ 2910.1, found 2906.8.

Octamer **4**: 26% yield (1.8 OD_{260}), t_R = 6.4 min, λ = 260 and 345 nm, MALDI-TOF MS *m/z* negative mode, THAP-CA, $[M-H]^-$ calculated for $C_{104}H_{118}N_{33}O_{52}P_8$ 2918.3, found 2914.9.

Octamer **5**: 84% yield (5.9 OD_{260}), t_R = 5.8 min, λ = 260 and 493 nm, MALDI-TOF MS *m/z* negative mode, THAP-CA, $[M-H]^-$ calculated for $C_{106}H_{128}N_{32}O_{55}P_8S$ 3008.9, found 3004.0.

25mer **6** (from 30 OD_{260}): 71% yield (21.3 OD_{260}), t_R = 8.3 min (4 min linear gradient 0−12% B, then 6 min linear gradient 12−50% B, at 60 °C), λ = 268 and 348 nm; MALDI-TOF MS *m/z* negative mode, THAP-CA, $[M-H]^-$ expected 7892.3, found 7870.2.

Melting Experiments. Melting experiments were performed in duplicate at concentrations ranging 1.5−14 μM of duplex. Solutions of each oligonucleotide were mixed in a solution containing 1 M NaCl and 100 mM sodium phosphate buffer pH = 7. The DNA concentrations were determined by UV-absorbance measurements (260 nm) at 80 °C, using the ε_{260} values calculated by the nearest-neighbor method for the DNA coil state. For octamer **5**, the ε_{260} value was calculated by the nearest-neighbor method as well and adding the contribution of fluorescein (the extinction coefficient of fluorescein (measured as FITC) at 260 nm is around 13.7 mM^{-1} cm^{-1}). Samples were heated at 90 °C for 5 min, allowed to cool slowly to room temperature to induce annealing, and then kept overnight in a refrigerator (4 °C).

Melting curves were recorded by heating the samples with a temperature controller from 15 to 80 °C at a constant rate of 1 °C/min and monitoring the absorbance at 260 nm. During the experiment, when the temperature was below 25 °C, argon was flushed to prevent water condensation on cuvettes. Absorption spectra and melting experiments (absorbance vs temperature) were recorded in 1 cm path-length cells. Melting curves were analyzed by computer-fitting the denaturation data, using *Meltwin 3.5* software. Melting temperatures (T_m) decreased with the concentration *c*, as expected for a bimolecular reaction (*12*). The plot of $1/T_m$ vs ln *c* was linear, giving a slope and a *y*-intercept, from which ΔH, ΔS, and ΔG were obtained (Table 2).

Fluorescence Analysis. Fluorescence spectra were measured in solutions containing 1 M NaCl and 100 mM sodium phosphate buffer (pH = 7) at a concentration of 2.3 μM. Excitation was set at 345 nm for octamers **2**−**4** and 493 nm for octamer **5**. Fluorescence spectra were measured before (F_D) and after (F_{RC}) duplex denaturation to yield relative fluorescence intensity (F_{RC}/F_D)). Results are shown in Figure 2 and Table 4.

Flow Cytometry Experiments. HT-29 cells were incubated for 8 h with dipole **1c** at concentrations of 2 μM, 5 μM, 10 μM, 20 μM, and 40 μM in a low glucose DMEM (Biological Industries) medium in the absence of phenol red. A blank control was also prepared. The supernatant was separated and placed in falcon tubes. The cells were treated with trypsin and placed in the corresponding falcon tubes. Each tube was centrifuged for 4 min at 2000 rpm. The supernatant was removed and PBS (500 μL) was added to each tube. The samples were treated with a propidium iodide solution (5 μL of a 1 μg/mL solution) and analyzed with a Cell Lab Quanta SC cytometer (Beckman Coulter).

Confocal Microscopy Experiments. HT-29 cells were incubated with dipole **1c** and **1d** (20 μM) for 2 h in a DMEM medium without phenol red. The living cells were treated with the plasmatic membrane marker WGA (Texas Red-x)-D (excitation at 595 nm, emission 615 nm). After 15 min, the cells were analyzed in vivo with a Leica TCS SP2 confocal microscope (excitation at 350 nm, emission between 400 and 500 nm). In these experiments, a blank control with the cells in the absence of dipole **1c** or its conjugate was analyzed. The intensity of the laser was adjusted in order to prevent detection of autofluorescent processes. Products **1c** and **1d** were detected in the cytoplasmatic region and they formed well-defined aggregates (see Supporting Information). Using the same procedure, HeLa cells were incubated with **1c** and oligonucleotide **6** (20 μM) for 4 h. While **1c** showed the same result as in the previous experiment, no fluorescence was detected using oligonucleotide **6**. In the presence of Lipofectamine 2000, oligonucleotide **6** penetrated the cytoplasmatic region.

RESULTS AND DISCUSSION

Synthesis and Thermodynamic Properties of Fluorescence Labeled Oligonucleotides. Small ligands can be incorporated into synthetic oligonucleotides at specific sites by preparing oligonucleotides carrying aliphatic amino groups and performing a conjugation reaction with the carboxylic derivatives of the ligands (*11, 13, 14*). This strategy was used to incorporate the acyl fluorides derivatives **1a** and **1b** into oligonucleotides (Scheme 2). Oligonucleotide sequences (Table 1) carrying an amino group at the 3′-end were assembled using a controlled

Table 1. Mass Spectra and UV Maxima of Fluorescent Oligonucleotides Prepared in This Study

#	sequence (5′−3′)	MS (expected)	MS (found)	UV_{max}, nm
2	CCAATTGG-NHCO-**1a**	2910.1	2911.8	260, 347
3	TTCCGGAA- NHCO-**1a**	2910.1	2906.8	260, 346
4	CCAATTGG-NHCO-**1b**	2918.3	2914.9	260, 345
5	TTCCGGAA-NHCO-**FITC**	3008.9	3004.4	260, 493
6	CTCTCGCACCCATCTCTCTCCTTCT NHCO-**1a**	7892.3	7870.2	267, 348

Table 2. Thermodynamic Parameters for Duplex-to-Random-Coil Transitions[a]

#	Duplex	T_m [°C][b]	ΔH [kcal/mol]	ΔS [kcal/mol.K]	ΔG [kcal/mol]	$\Delta\Delta G$[c][kcal/mol]
	$^{5'}$CCAATTGG$^{3'}$	33.3	−119.5	−340.5	−18.0	0
2	$^{5'}$CCAATGG-**1a**$^{3'}$	41.1	−116.8	−322.5	−20.6	1.3
4	$^{5'}$CCAATGG-**1b**$^{3'}$	34.0	−103.7	−288.3	−17.7	−0.15
	$^{5'}$TTCCGGAA$^{3'}$	31.8	−107.5	−303.0	−17.2	0
3	$^{5'}$TTCCGGAA-**1a**$^{3'}$	44.2	−107.0	−287.8	−21.2	2

[a] (1 M NaCl and 100 mM sodium phosphate buffer at pH = 7). ΔG is calculated at 25 °C, with the assumption that ΔH and ΔS do not depend on temperature; analysis was carried out with melting temperatures obtained from denaturation curves. [b] T_m calculated at 4 μM duplex concentration. [c] ΔG (modified octamer) − ΔG (unmodified octamer)/2 fluorescent molecules.

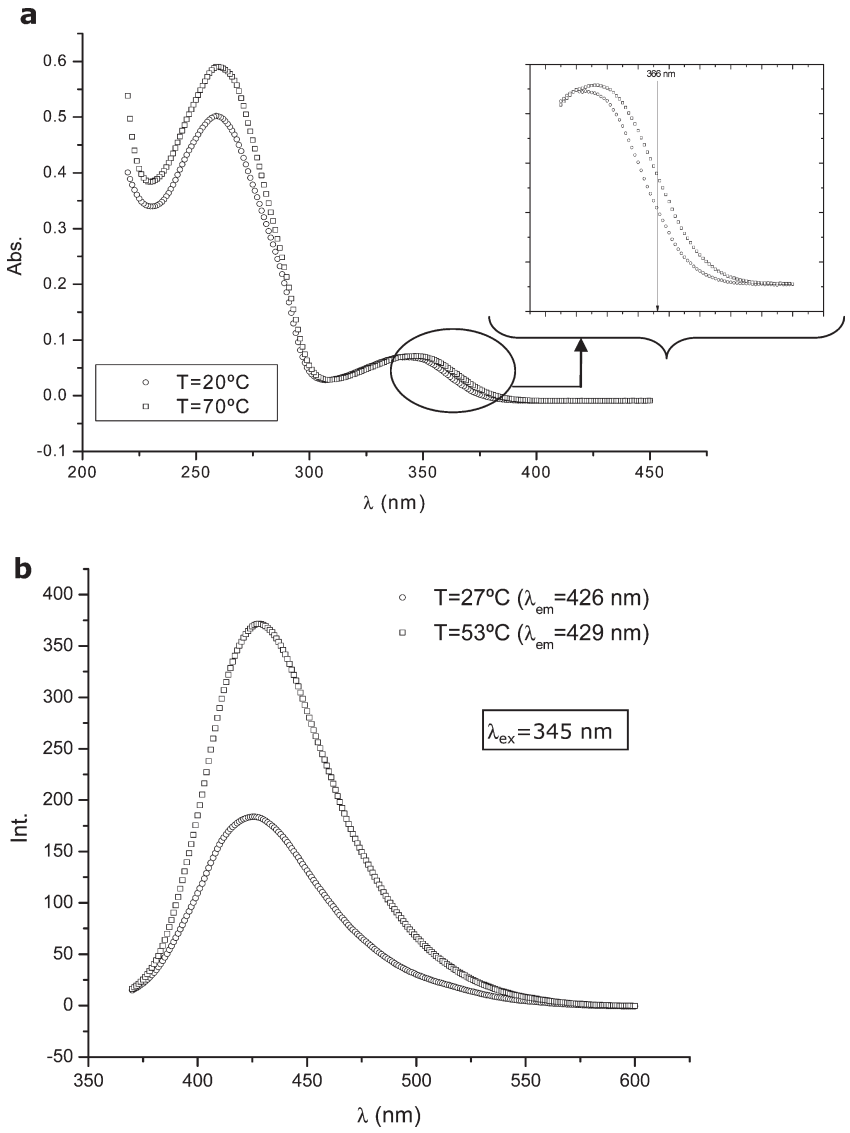


Figure 2. (a) UV and (b) fluorescence spectra of oligonucleotide **2**.

pore glass support carrying the 2-(*N*-{[(9*H*-fluoren-9-yl)methoxy]-carbonyl}-4-aminobutyl)propane-1,3-diol linker (*11*) and following standard protocols. The resulting oligonucleotides were used in the reaction with acyl fluorides (Scheme 1).

Amino-oligonucleotides were reacted with an excess of acyl fluorides **1a** and **1b** in aqueous dimethylformamide (DMF) mixtures at pH 9 and room temperature. In these mild conditions, the desired fluorescent oligonucleotides **2**−**4** and **6** were produced in good yields as shown by the presence of new products with higher retention time, which were characterized by mass spectrometry and UV spectra (Figure 1 and Table 1). In addition, we have prepared the fluoresceine-labeled octamer **5** by reaction of the appropriate amino-octamer with fluoresceine isothiocyanate (**FITC**).

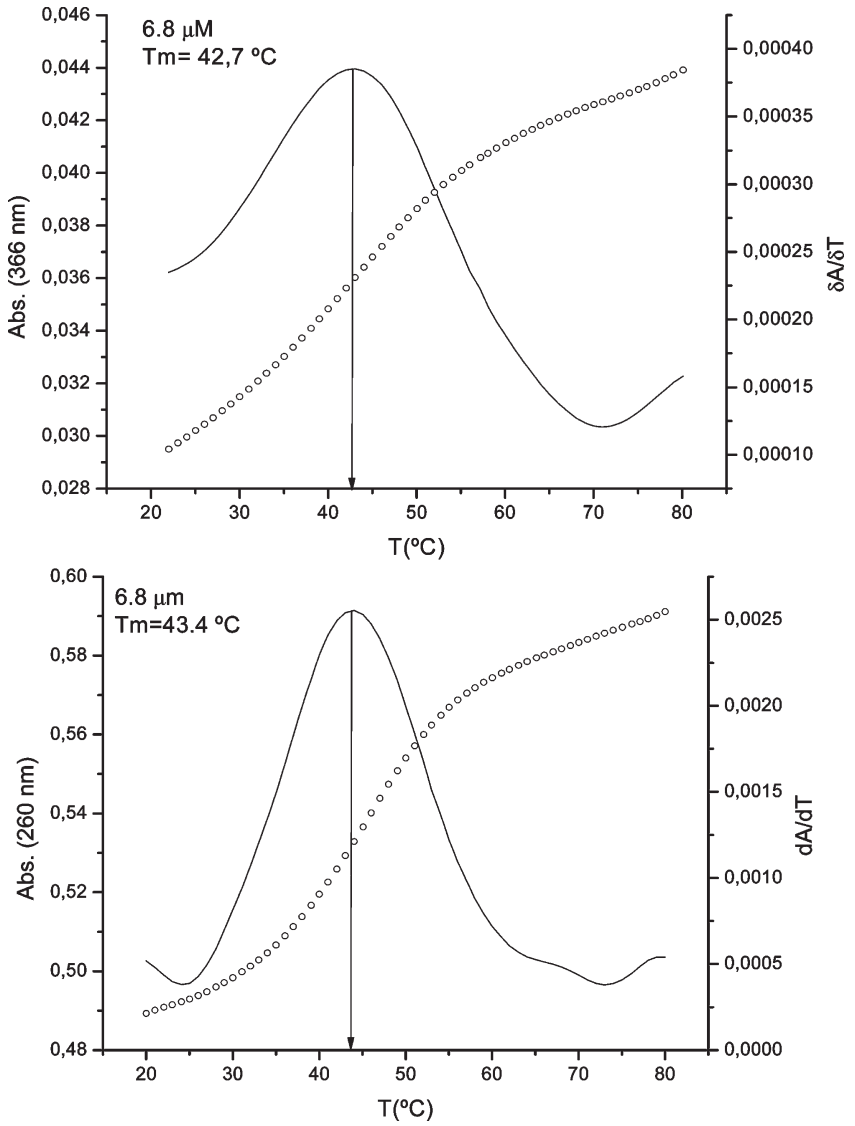


Figure 3. Melting curves of self-complementary oligonucleotide **2** measured at 260 and 366 nm.

The hybridization properties of the oligonucleotides carrying the isoquinoline imidazo[1,2-*a*]azine group were measured spectrophotometrically on the self-complementary octamer duplexes **2**−**4**. Unmodified octamers were included for comparison purposes (Table 2). The duplex formed by sequence **A**, which carried two molecules of compound **1a** (octamer **2**), melted at 41.1 °C (ΔG 20.6 kcal/mol), while the unmodified duplex melted at 33.3 °C (ΔG 18.0 kcal/mol). This observation implies an increase in duplex stability of 3.8 °C ($\Delta\Delta G$ 1.3 kcal/mol) per fluorescent molecule. In contrast, the duplex formed by sequence **A**, carrying two molecules of compound **1b** (octamer **4**), melted at 34 °C (ΔG 17.7 kcal/mol), thereby indicating a small destabilization of the duplex. This effect should reflect the previously mentioned differences between the substituents on the imidazole nitrogen of the dipoles, presumably arising from the distinct interactions at the conformational level of the cyclohexyl and benzyl groups with the oligonucleotide backbone. The stabilizing properties of compound **1a** were slightly increased in octamer **3** ($\Delta\Delta G$ 2.0 kcal/mol), thereby indicating that the stabilizing properties of this compound are not dependent on the DNA sequence at the end as octamer **3** has A.T base pairs, while octamer **2** has G.C base pairs.

Preliminary conformational studies of the linkers containing cyclohexyl or benzyl substituents by means of computer-based molecular modeling (Spartan'04 and Hyperchem'08; molecular mechanics conformational search and geometry optimization) suggest that, in the lower energy conformations, the isoquinoline imidazo[1,2-*a*]azine core containing a cyclohexyl substituent stacks over the terminal guanine nucleobase, at a distance of approximately 3 to 4 Å, whereas the isoquinoline imidazo[1,2-*a*]-azine core containing a benzyl substituent does not interact significantly with the terminal guanine (see Supporting Information Figure S1). These studies were carried out by keeping frozen the duplex of DNA and by allowing the linker to move freely during the calculations. In order to explore the rotational freedom of the cyclohexyl or benzyl-fluorescent isoquinoline imidazo[1,2-*a*]azine in more detail and to determine the dynamic behavior of the conjugates, molecular dynamics simulations and NMR studies on these modified duplexes would be necessary. A comprehensive study is currently under way in our laboratory.

UV spectra of the modified oligonucleotides **2**−**4** at 20 °C (duplex) and 70 °C obtained in a solution containing 1 M NaCl and 100 mM sodium phosphate buffer of pH = 7 at a concentration of 6.8 μM are shown in Figure 2a. The maximum caused by the isoquinoline derivative shows a slight shift depending on the temperature. The hyperchromism in the absorption spectra at 70 °C and the bathochromical shift indicated that the molecule attached to the oligonucleotide is sensitive to the presence of a duplex or a random coil form. The UV spectra indicated a change in hyperchromicity between 340 and 380 nm, the difference being maximum around 366 nm, and so melting curves were recorded at 366 nm. Melting

Table 3. Melting Temperatures of Modified and Unmodified Duplex at Different λ

#	oligonucleotide	Abs. (260 nm, 70 °C)	T_m (°C) (260 nm)	T_m (°C) (λ)[a]
2	5′CCAATGG-**1a**3′	0.59	43.2	42.9
3	5′TTCCGGAA-**1a**3′	0.48	45.9	35.4
4	5′CCAATGG-**1b**3′	0.61	37.2	36.8
5	5′ TTCCGGAA-**FITC**3′	0.63	44.2	44.8

[a] Melting experiments performed at 366 nm for **2** and **4**, 364 nm for **3**, and 493 nm for **5**.

Table 4. Fluorescence Spectral Data for the Modified Oligonucleotides before and after Duplex Denaturation

	temperature (°C)	emission maximum (nm)	fluorescence intensity (I)	F_{RC}/F_D	ΔI (%)
2	27	426	184	2.02	+102
	53	429	371		
3	24	427	322	1.74	+74
	51	430	560		
4	17	418	312	1.34	+34
	39	423	418		
5	20	522	117	0.82	−18
	60	520	96		

curves were recorded simultaneously at 260 and 366 nm for comparison purposes (Figure 3). Melting temperatures at these two wavelengths were similar, although at 366 nm, the duplex showed a lower T_m (see, for example, compound **2** T_m: 42.9 °C at 366 nm and 43.2 °C at 260 nm; Table 3). This indicates that base pair dissociation observed at the end of the oligonucleotide (measured at 366 nm where the fluorescent tag is located) happens at a slightly lower temperature of the global melting of the duplex (measured at 260 nm). A similar behavior has been described for fluorescent compounds attached in the middle a DNA duplex (*15, 16*). The fluoresceine octamer **5** had a melting temperature of the same range than octamers carrying the isoquinoline imidazo[1,2-*a*]azine core with the cyclohexyl group (**1a**) **2** and **3** (Table 3). Surprisingly, at 493 nm it had a slightly higher melting temperature (T_m 44.8 °C at 493 nm, T_m 44.2 °C at 260 nm).

Next, we studied the effects of duplex denaturation in fluorescence. Fluorescent spectra of self-complementary duplex **2** in 1 M NaCl and 100 mM sodium phosphate buffer pH = 7 at a concentration of 2.3 μM at different temperatures were recorded. Figure 2b shows the fluorescent spectra at 27 and 53 °C. Excitation was set at 345 nm. Absorption maxima of oligonucleotides **2**−**4** at high and low temperatures are summarized in Table 4. A strong increase in fluorescence was observed upon duplex denaturation. These results and the slight increase in T_m indicates that the fluorescent label interacts with the DNA duplex most probably as an end-cap and the complex has a lower florescence. Upon duplex denaturation, the fluorescent label changes the environment duplicating the fluorescence emission. These effects were more intense in octamers carrying compound **1a** (oligonucleotides **2** and **3**) than those carrying compound **1b** (oligonucleotide **4**). This effect may be a consequence of the conformational preference of the isoquinoline imidazo[1,2-*a*]azine core containing a cyclohexyl substituent to stack over the terminal nucleobase described above. The fluoresceine octamer **5** does not increase the fluorescence upon heating, but on the contrary, a clear decrease on the fluorescence properties is observed (Table 4).

In summary, dipolar isoquinoline derivatives **1a**−**b** readily prepared by MCR are efficient and inexpensive reagents for introducing of fluorescent labels into synthetic oligonucleotides. Reagent **1a** is particularly useful as it produces fluorescence-labeled oligonucleotides that are sensitive to hybridization and have duplex-stabilizing properties. Next, we studied the capacity of fluorescence-labeled oligonucleotides to monitor cellular uptake.

Cell Uptake Experiments. A 25mer oligonucleotide sequence with an amino group at the 3′-end (Table 1) was also prepared. This sequence corresponds to an antisense oligonucleotide known as GEM91 (*17*), which is complementary to the initiation codon of gag gene of HIV-1 RNA. Reaction of 3′-amino GEM91 with **1a** yielded the expected fluorescence-labeled oligonucleotide (**6**) in excellent yields (85% conversion judged by HPLC, 71% isolated yield). The resulting product was used in the transfection assays without further purification.

We first performed flow cytometry experiments with the model isoquinoline compound **1c** in order to assess the potential toxicity of the dye. HT-29 cells were incubated for 8 h with dipole **1c** and analyzed by flow cytometry. The percentage of living or dead cells remained almost constant at all concentrations of **1c** and was very similar to the control value (see Supporting Information). These results support the notion that this compound has a low toxicity profile.

We then performed confocal microscopy experiments to analyze the distribution of the compound **1c** inside the cells. Compound **1c** was detected in the cytoplasmatic region and formed well-defined aggregates (see Supporting Information). The analogous methyl ester dipole **1d** (*8*) was analyzed under the same conditions and showed a similar distribution pattern (see Supporting Information).

We then performed further confocal microscopy experiments to optimize the conditions in order to evaluate the capacity of conjugate **6** to penetrate HeLa cells in the presence (or absence) of Lipofectamine 2000. When cells were incubated with conjugate **6** (20 μM) for 4 h, no fluorescence was detected, whereas the same product in the presence of Lipofectamine 2000 penetrated the cytoplasmatic region. Longer incubation times (22 h) with conjugate **6** (20 μM) in the presence of Lipofectamine 2000 induced strong cell toxicity and no living cells were found. This result may reflect the toxicity of Lipofectamine under these conditions.

CONCLUSIONS

Here, we describe the use of unexpensive reagents in the synthesis of oligonucleotides carrying highly sensitive fluorophores. The acid fluoride derivative of the fluorophore required for the preparation of the fluorescent-labeled oligonucleotides was synthesized in high yield in a one-pot reaction using an efficient MCR which has been described previously (*8*). The acyl fluorides reacted efficiently in aqueous buffers at pH 9 with amino-oligonucleotides to yield the desired conjugates. The resulting oligonucleotides show intense fluorescent properties in presence of ions, have slightly improved hybridization properties, and are sensitive to denaturation. Flow cytometry and confocal microscopy experiments showed a low toxicity profile and good cell membrane permeability, respectively, for dyes **1c** and **1d**. Oligonucleotide **6** had the capacity to penetrate cells in the presence of Lipofectamine 2000 transfection reagent.

ACKNOWLEDGMENT

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Supporting Information Available: Structure of the most energetically stable conformations of **1a** and **1b** conjugates by molecular mechanics (MM) conformational searches and geometry optimization. Flow cytometry experiments with dipolar

amide **1c**. Confocal microscopy images from cell uptake experiments. Mass spectrometry, HPLC analysis, and melting curves of purified oligonucleotides. This material is available free of charge via the Internet at http://pubs.acs.org.

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BC1000966

Synthesis and properties of oligonucleotides carrying isoquinoline imidazo[1,2-a]azine fluorescent units.

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SUPPORTING INFORMATION:

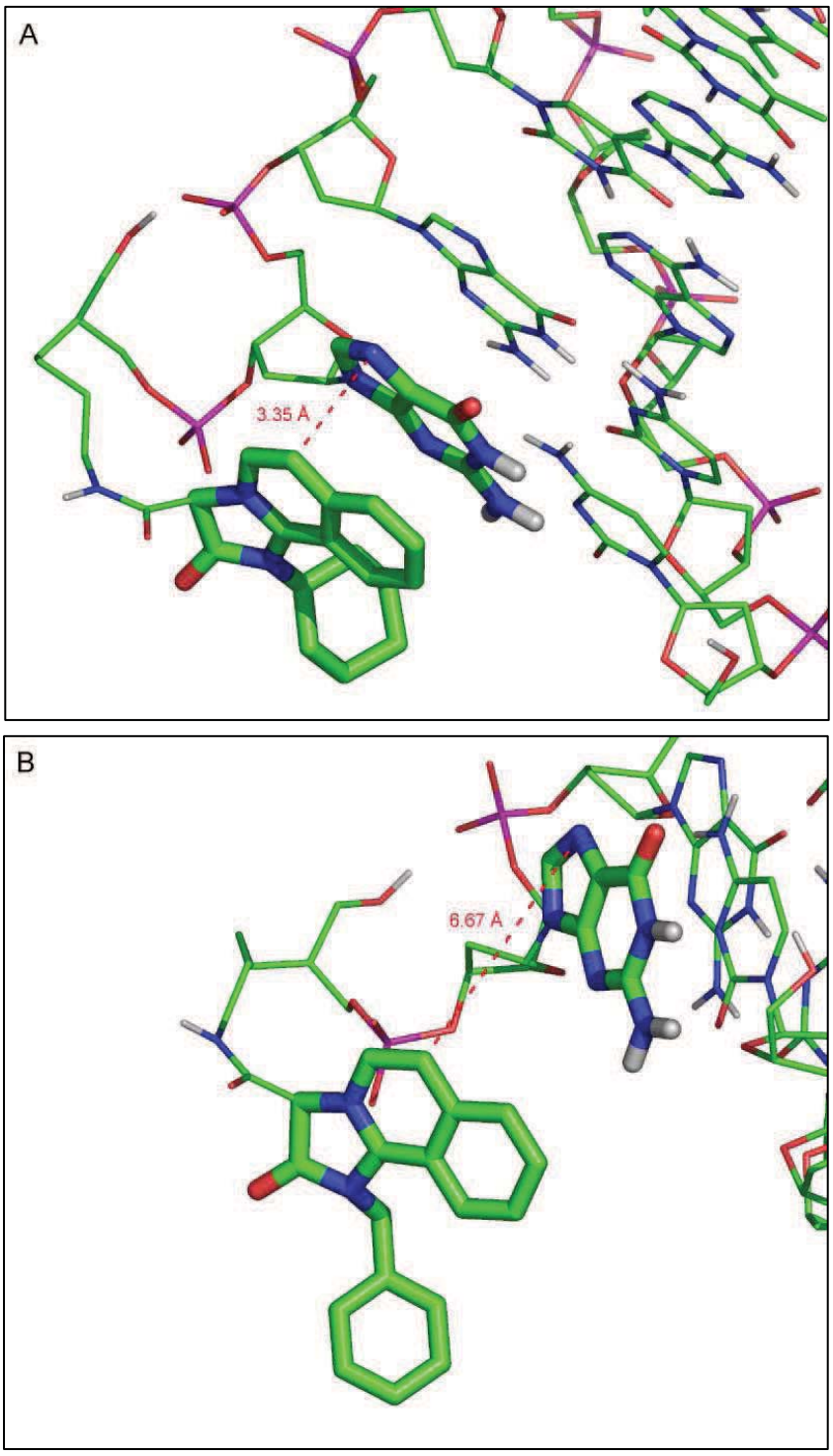

Figure S1. Most energetically stable conformations of **1a** and **1b** conjugates (panels A and B, respectively). The terminal guanine nucleobase and the triazine core are shown as thick lines. Distances between guanine and the isoquinoline imidazo[1,2-a]azine core are indicated. The figures were prepared with PyMOL (http://pymol.sourceforge.net/). Molecular mechanics (MM) conformational searches and geometry optimization of the most energetically stable conformers were carried out with the Amber force field by using the softwares Spartan'04 from Wavefunction and HyperChem'08 and by using water as a solvent. The duplex of DNA was kept frozen and the linker was allowed to move freely during the calculations.

Flow cytometry experimental data:

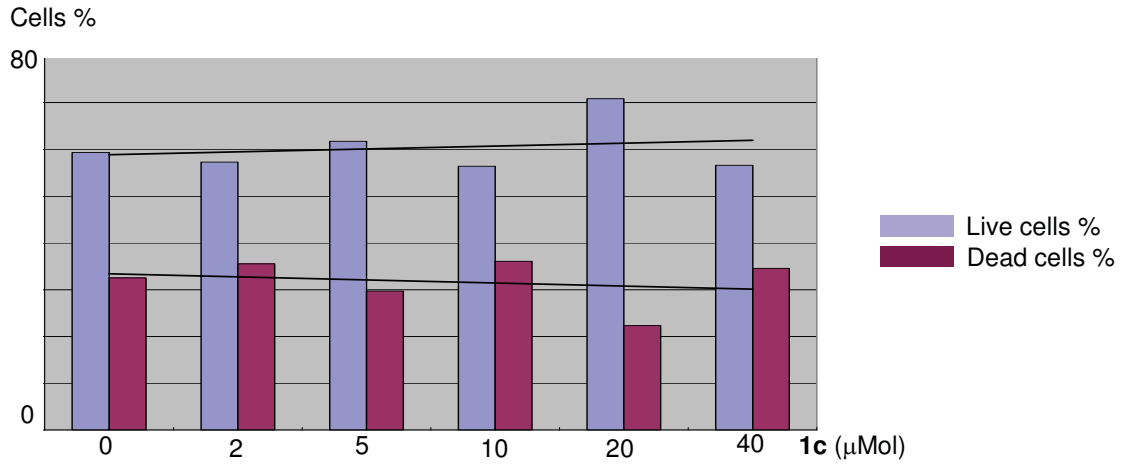

Figure S2: Evaluation of the cytotoxicity profile of **1c** by flow cytometry on HT-29 cells. Incubation time 8h.

Confocal microscopy images:

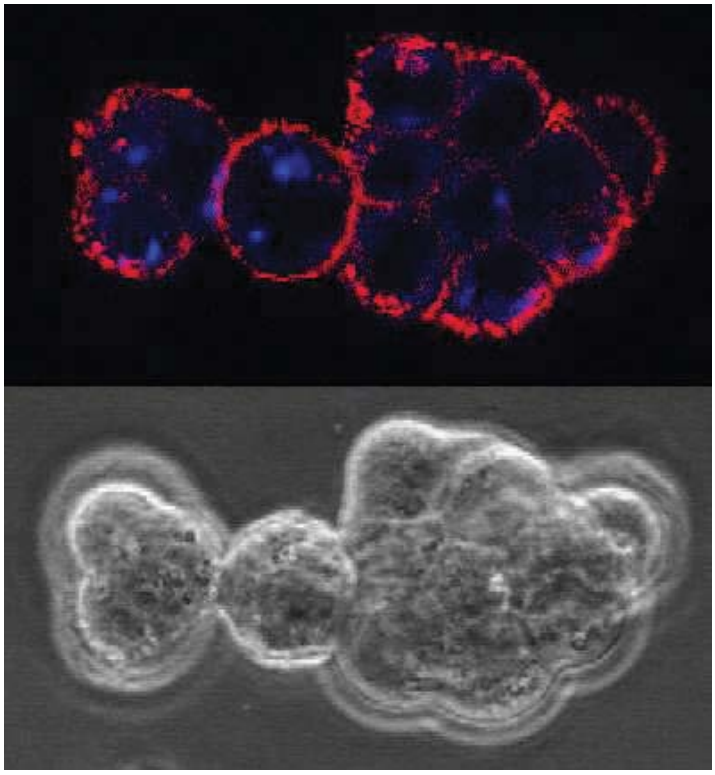

Figure S3: **1c** [20 μM] in HT-29 cells (2h incubation)

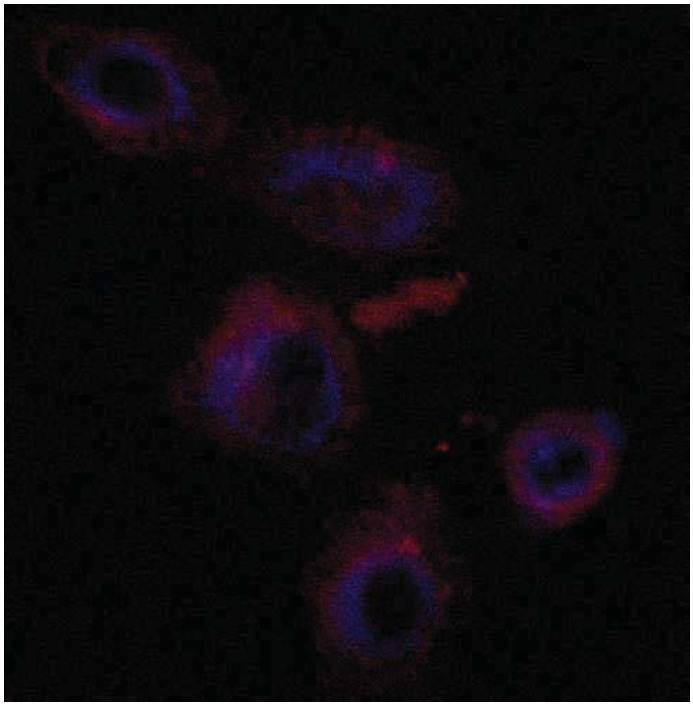

Figure S4.: **1c** [20 μM] in Hela cells (4h incubation)

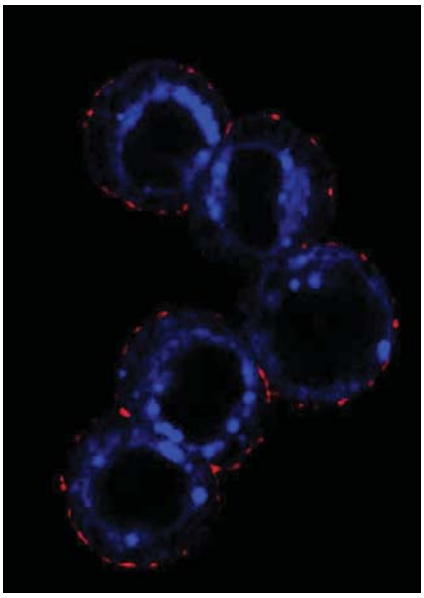

Figure S5: **1d** [20 μM] in HT-29 cells (2h incubation)

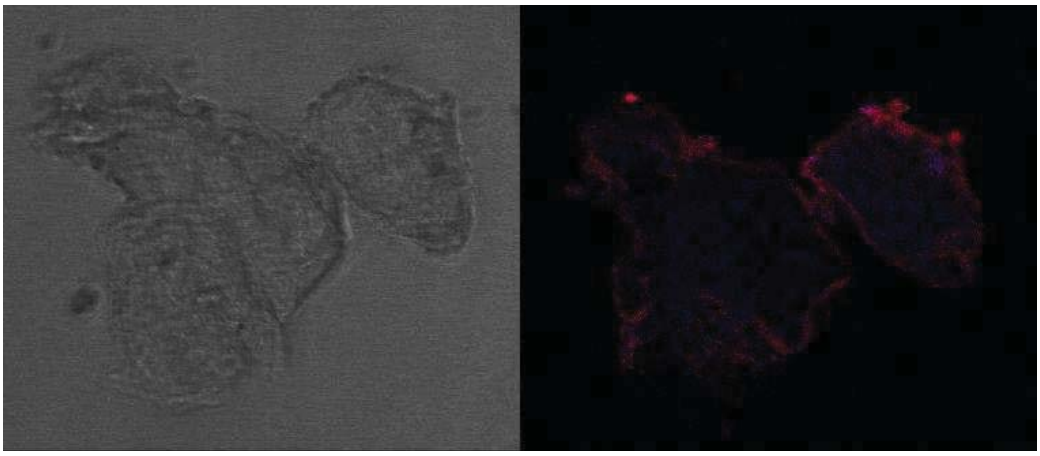

Figure S6.: Oligonucleotide **6** [20 μM] with Lipofectamine in Hela cells (4h incubation)

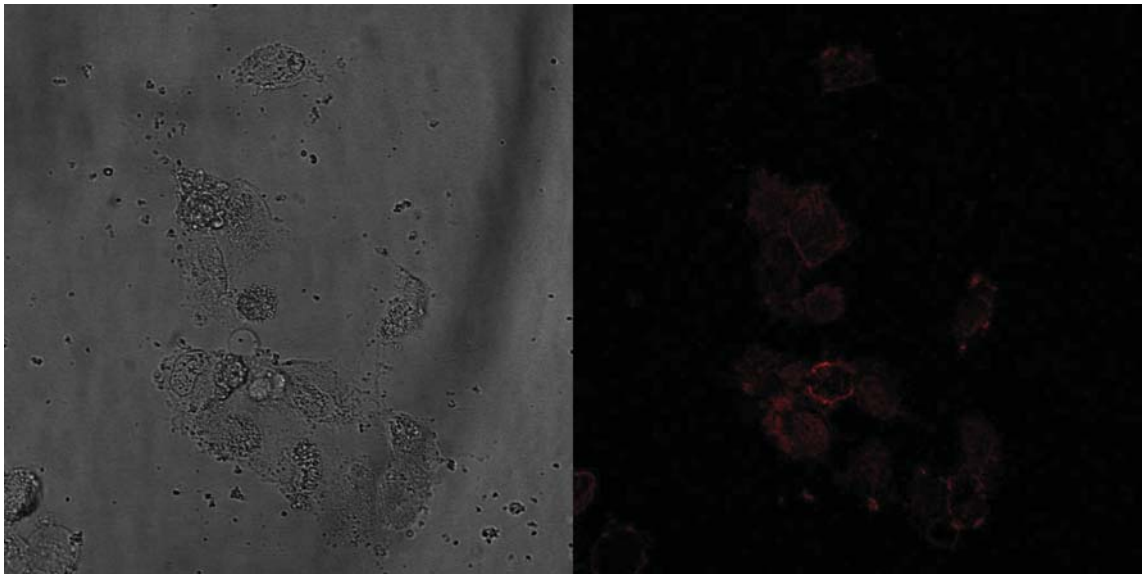

Figure S7. Oligonucleotide **6** [20 mM] with Lipofectamine in Hela cells (22 h incubation).

Mesoionic acid fluorides as biosensors for histamine bioimaging

(Preliminary draft to be sent for publication)

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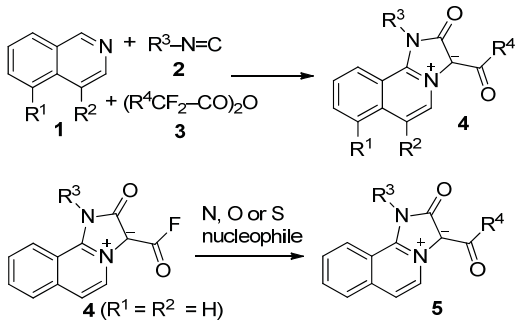
Introduction. The use of small fluorescent molecules as biosensors for species with a key role in biological processes has recently generated a high interest in the scientific community. Histamine is an autacoid having a fundamental biological role similar to hormones; it is synthesized including mast cells, parietal cells of the gastric mucosa and neurons, being released by specific antigen stimulation. His complex function, still not completely understood, is involved in allergic reactions, in inflammation processes;[30] and in the regulation of the secretion of gastric acids. These studies allowed the development of many important drugs that antagonize its effects, and that are effective for the treatment of allergic inflammatory disorders, and gastric hipersecretory disorders. Besides these studies, in recent times this imidazolamine has

been found to have fundamental physiological roles in the nervous system,[31,32] modulating homeostatic functions of the brain, such as behavioural state, biological rhythms, thermoregulation, feeding rhythms and energy metabolism, stress, bone physiology and homeostasis and reproduction. In the same way higher brain functions such as regulation of sensory and motor system, mood and cognition,[33] learning and memory are also regulated. A major challenge in elucidating the function of histamine in these processes is represented by the substantial lack of simple methods for the biological tracking of this species in living cells. Indeed, the most commonly used methods used to quantify histamine such as capillary zone electrophoresis, gas chromatography (GC), high-performance liquid chromatography (HPLC), enzymatic assay, flow immunoassay, and spectrofluorimetry often requires cells lisates or the destruction of the tissues. Imato's group recently described a fluorimetric method based on displacement of calcein (by histamine) in nickel complexes, using suspensions of living cells.[34] However the localization of histamine in cells can only be done by using specific fluorescent antibodies such as the ELISA methods, and the development of in-vivo biosensors based on more simple and direct methods is of primary interest.[35] For this purpose we developed a new histamine biosensor by successfully joining Multicomoponent Reactions (MCRs) strategy with the Diversity-Oriented Fluorescence Library Approach (DOFLA).[26] A small library of twelve fluorescent molecules was synthesized through a recently developed MCR,[36] the library was submitted to a primary screening with 90 chemical species of biological interest using DOFLA technologies, and some compounds showed selective fluorescence increase in presence of histamine. The dye giving the best response in presence of histamine was investigated as possible biosensor. A secondary

screening was made in presence of different neurotransmitters confirming a high selectivity for histamine. A kinetic study and an HPLC experiment were made in order to investigate the nature of the interaction and to optimize the conditions of the following experiments. Subsequently, the most responsive probe was tested in cells, using basophiles (RBL 2H3) and macrophages (RAW 267.3), as a model of cells storing histamine in granules or not, respectively.

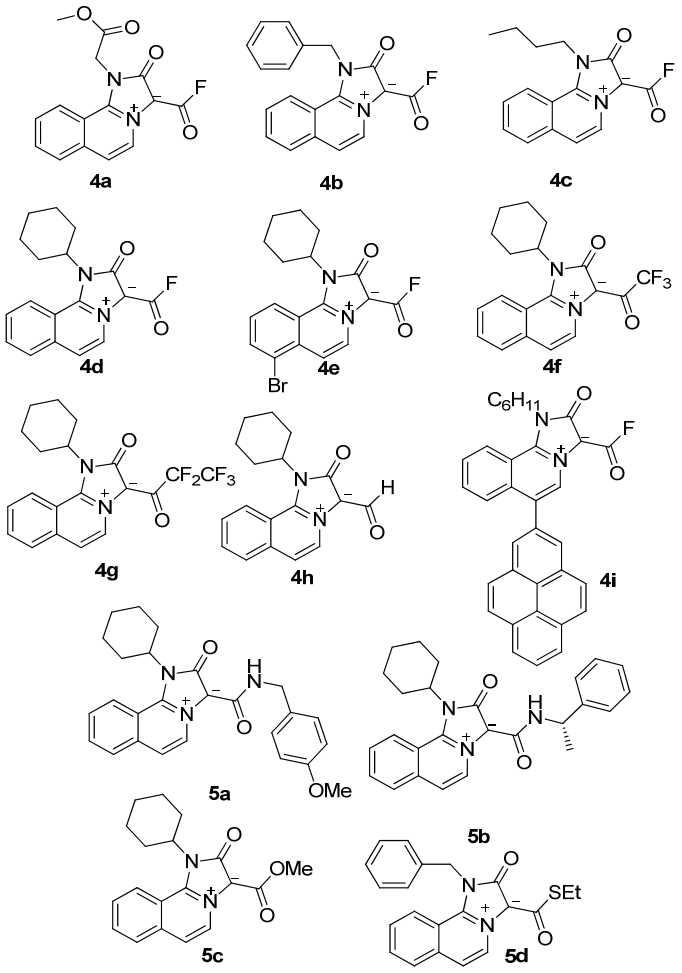
Results and Discussion MCRs are processes in which three or more molecules react to yield a single product bearing the main part of each component, through a single reaction mechanism. We recently described the MCR of, azines **1**, isocyanides **2** and fluorinated anhydrides **3** to yield unprecedented mesoionic adducts including acid fluorides **4a**-**4e**, fluorinated ketones **4f**-**4g**, and aldehydes **4h** (Table 1).[36]

Table 1. Synthesis of fluorescent compounds and spectroscopical features



Entry	Name	R^1	R^2	R^3	R^4	$\lambda_{max\ ABS}$	$\lambda_{max\ emis}$	ϕ
1	**4a**	H	H	-CH_2CO_2Me	F	346	417	1.7×10^{-1}
2	**4b**	H	H	Bn	F	341	418	3.3×10^{-1}
3	**4c**	H	H	*n*-Bu	F	345	418	4.2×10^{-1}
4	**4d**	H	H	*c*-hexyl	F	351	420	1.7×10^{-1}
5	**4e**	Br	H	*c*-hexyl	F	361	443	2.7×10^{-2}
6	**4f**	H	H	*c*-hexyl	CF_3	370	402	8.2×10^{-4}
7	**4g**	H	H	*c*-hexyl	CF_2CF_3	370	419	7.1×10^{-4}
8	**4h**	H	H	*c*-hexyl	H	378	420	5.1×10^{-3}
9	**4i**	H	Pyrene	*c*-hexyl	F	346	470	1.0×10^{-2}

10	**5a**	H	H	*c*-hexyl	NHBn	363	454	4.2×10^{-1}
11	**5b**	H	H	*c*-hexyl	$NHCHPhCH_3$	362	451	4.0×10^{-1}
12	**5c**	H	H	*c*-hexyl	OMe	346	441	3.0×10^{-1}
13	**5d**	H	H	Bn	SEt	371	430	3.3×10^{-1}



Scheme 1: Small library of substrates analyzed as potential biosensors.

These adducts are obtained in average to good yield in a single step, starting from cheap commercially available substrates, and are characterized by a strong fluorescence in the blue region. Although remarkably stable, even in basic aqueous solutions, the acid fluorides showed the expected reactivity with nucleophiles, therefore a fourth component has been added in a second step by reaction with amines, alcohols or thiols to yield the

corresponding amides **5a-5b**, esther **5c** and thioesther **5d** respectively (Scheme 1). Interestingly acid fluorides have also shown to react with high selectivity with primary amines even when using complex biomolecules such as oligonucleotides bearing a linker.[37] All of the adducts, characterized by a strong fluorescence in the blue region (λ_{max} absorbtion between 340 and 370 nm and λ_{max} emission between 400 and 455 nm) were examined using the DOFLA approach towards a large collections of biomolecules using a high throughput multianalyte screening (Figure 1).

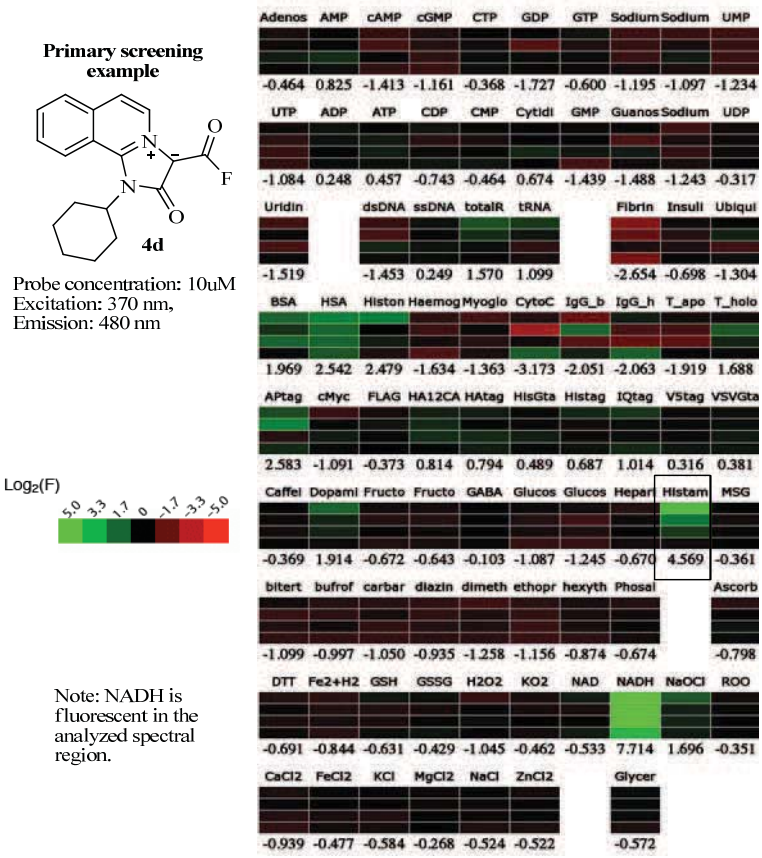


Figure 1. Example of primary screening output using acid fluoride **4d** (DOFLA technologies).

In order to investigate the covalent nature of the interaction between the acid fluoride and histamine an HPLC-MS analysis was made. The formation of the amide bond has been

observed, with complete consumption of the acid fluoride in less than 30 minutes (Figure 2).

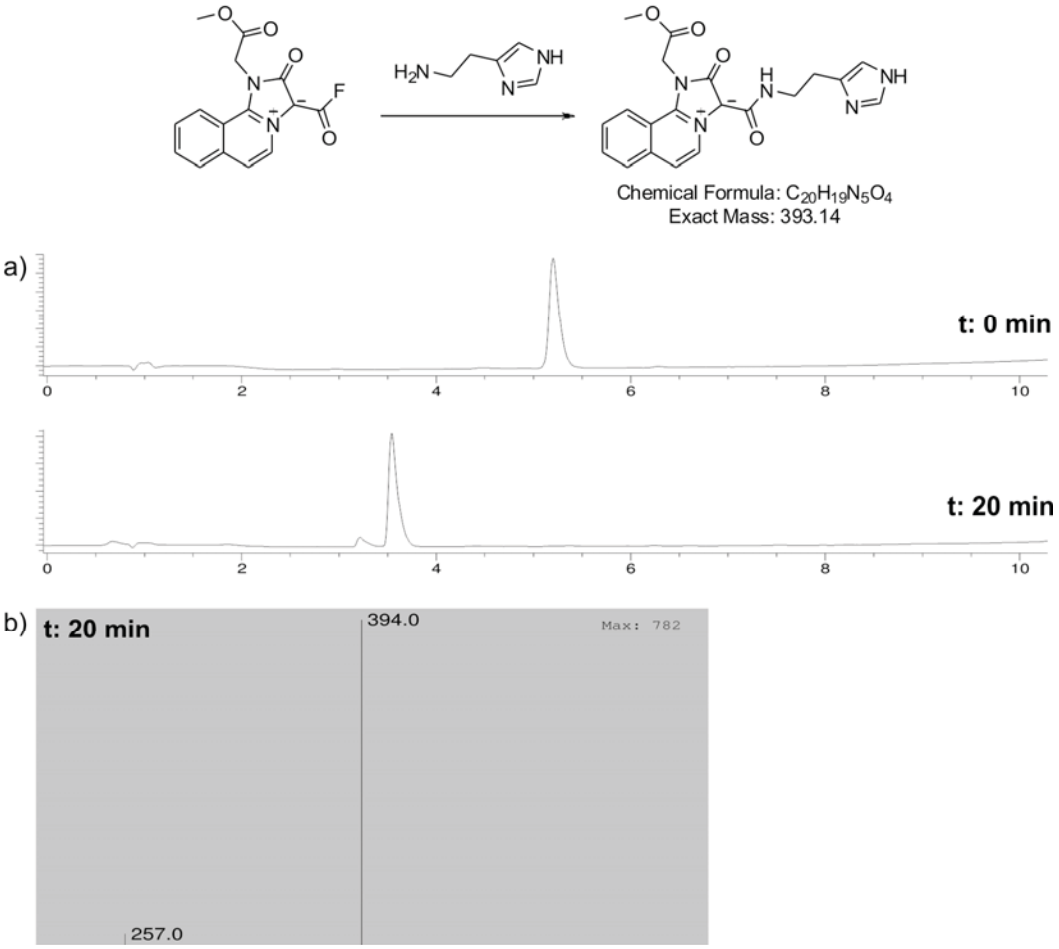
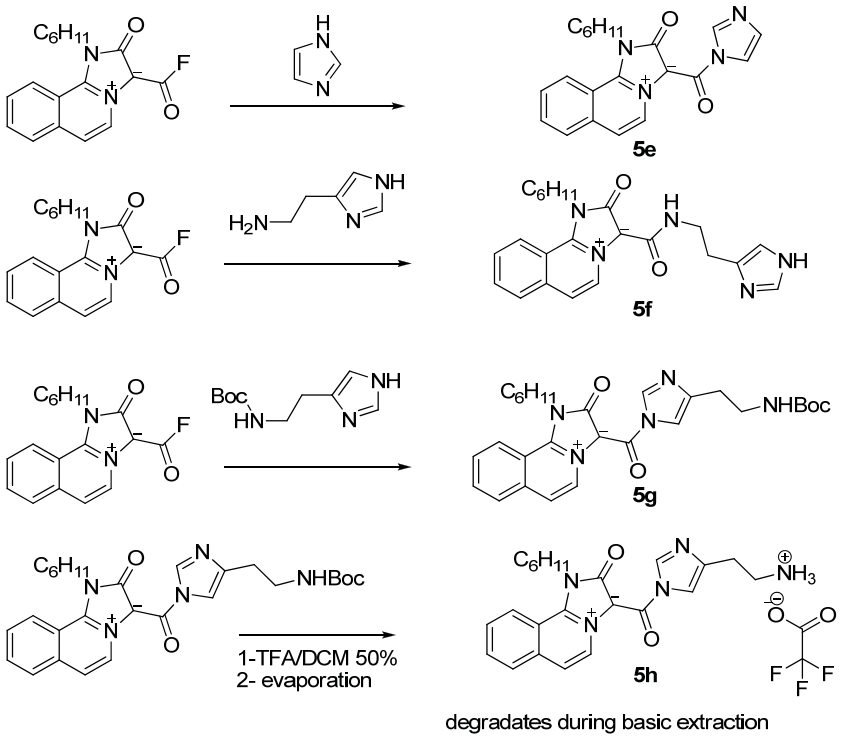


Figure 2 HPLC-MS analysis of the reaction between **4b** and histamine

With the objective of determining which species are in fact responsible for the significant and selective increment of fluorescence detected, all possible adducts coming form this interaction have been independently synthesized in the laboratory. This study was carried out with acid fluoride **4d**, which was available in multigram quantities at that time (Scheme 2). In this way, interaction of the acid fluoride with imidazole, histamine, and *N*-Boc histamine afforded the corresponding adducts **5e**, **5f** and **5g** respectively. The

latter was subjected to deprotection under the usual acid treatment to afford the free amine **5h**, isolated as the trifluoroacetate ammonium salt.



Scheme 2. Synthesis of the possible adducts of the interaction between **4d** and histamine and imidazole.

The analysis of UV and emission spectra of adducts **5e-5h** were compared with the data obtained in the optimized conditions; in conclusion, **5f** is the species responsible for the fluorescence increase. It was also proven the instability of adduct **5h** in neutral or basic aqueous conditions, thus discarding that this species could be present as final products in biological medium.

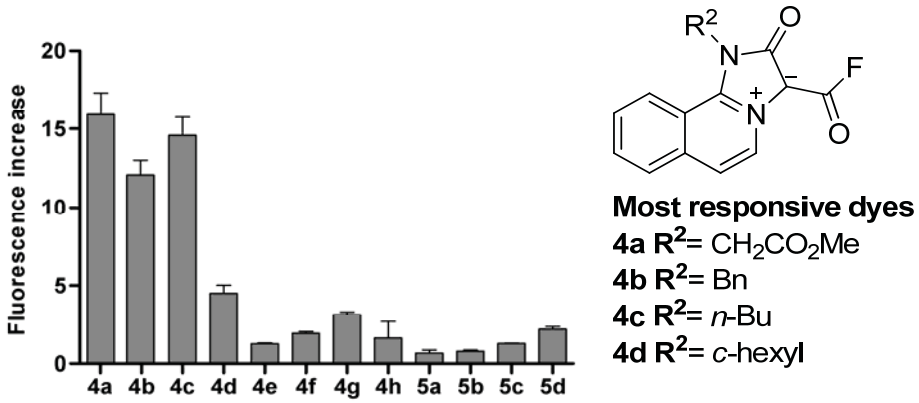


Figure 3. Fluorescence increase of the dyes [10 μM] in presence of Histamine [10 mM] in PBS. Excitation wavelength 370nm, λ emission 430nm.

The preliminary results on fluorescence increase were reproduced in optimized conditions (Figure 3). A relevant florescence increase was observed for the acid fluorides **4a-4d** in presence of histamine, **4a** giving the best results by displaying an increase of fluorescence at 430 nm up to 16 folds when excited at a wavelength 370 nm. Furthermore a consistent ratiometric shift was observed (Figure 4, b).

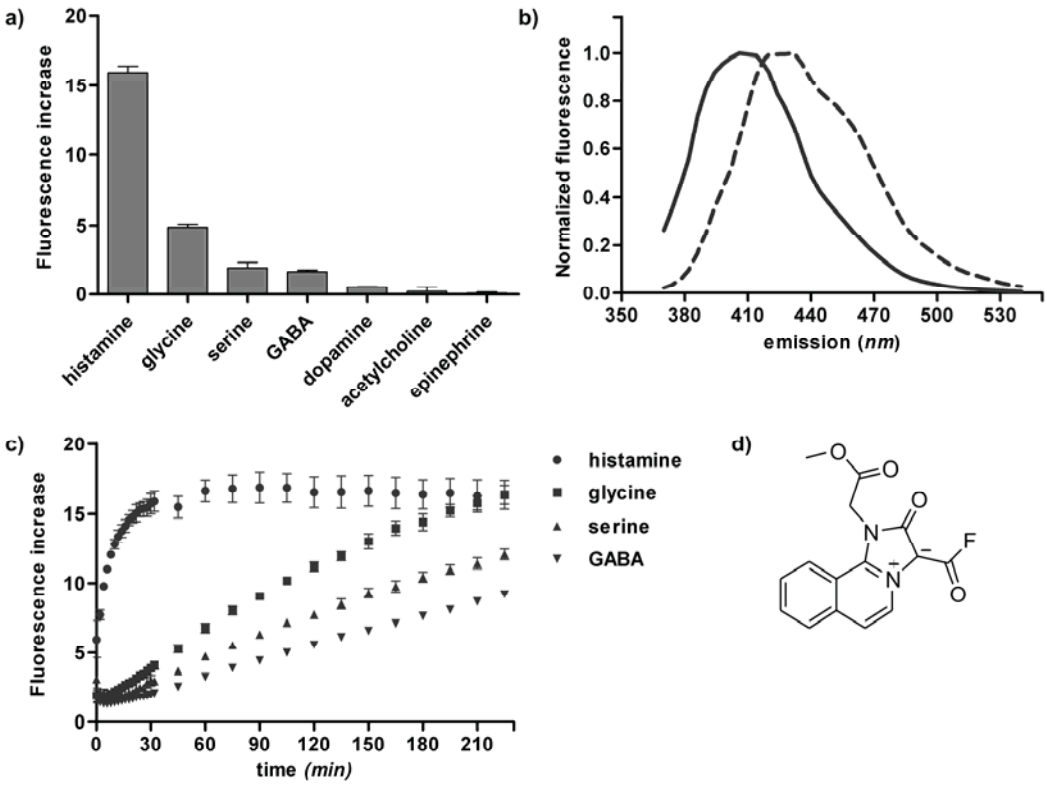


Figure 4. a) Selectivity of compound **4a** for histamine. b) Normalized emission spectra of **4a** 10μM alone (solid line), and after 1h incubation with histamine 5mM in PBS solution (dashed line). c) Kinetics of **4a** 10μM in presence of histamine, glycine, serine or GABA 5mM. d) Structure of mesoionic acid fluoride **4a**.

When acid fluoride **4a** was screened towards seven neurotransmittants, including aminoacids and primary amines, a good selectivity was observed after one hour of incubation. Although histamine response is consistently higher than those coming from other neurotransmitters, a slight fluorescence increase was also noticed in presence of glycine, serine, and GABA, suggesting that other amines may also be able to form an amide with the acid fluoride (Figure 4a). A kinetic study of the reactions evidenced how the reaction rate with histamine is much faster than with the other tested amines (Figure 4c). The kinetic study also demonstrated that even a higher selectivity can be obtained

using shorter reaction times. The maximum response with histamine is then reached after 30 minutes, while glycine reaches the same response level after 4h. In the cases of serine and GABA, analogous levels of response were never reached even after longer reaction times. This preferential reactivity is likely to be due to catalytic properties of the imidazole group, which has been extensively studied in various fields, and plays a fundamental role in biological processes. In order to investigate the role of the sp^2 nitrogen of the heterocyclic residue, the reaction rate of the dye **4a** with 2-(α-piridyl)ethylamine was compared with the equivalent process using 2-phenylethylamine, and both reactions were followed by HPLC (Figure 5).

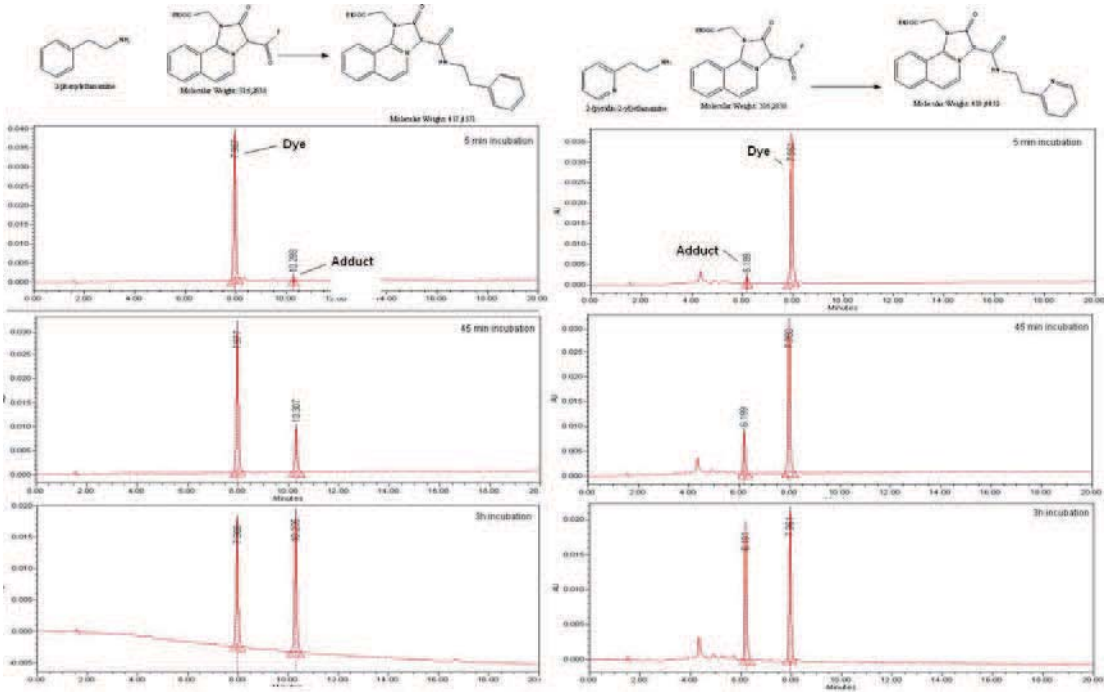
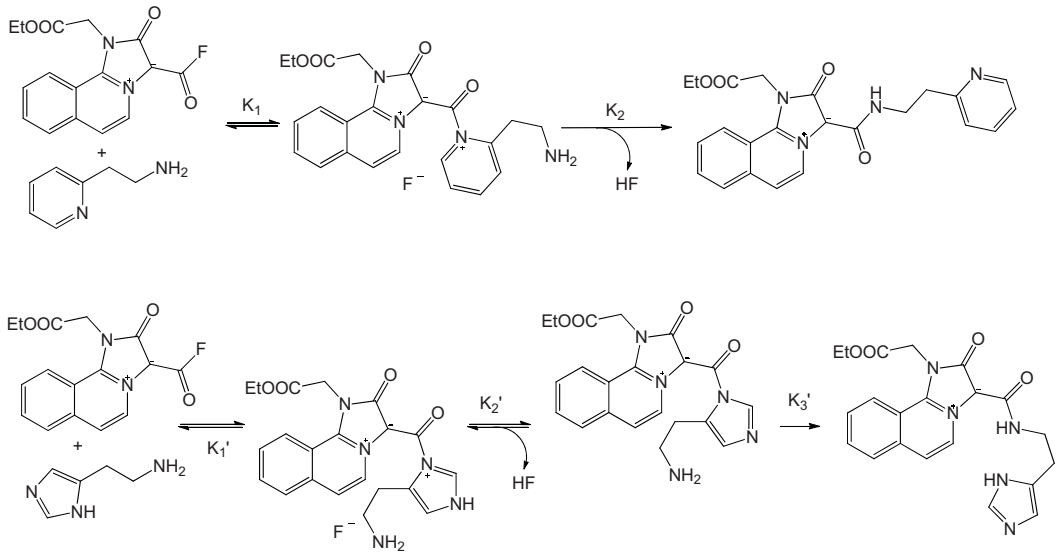


Figure 5. Comparison between the reaction rates between the dye **4a** and 2-(α-piridyl)ethylamine or 2-phenylethylamine,

Interestingly the reaction rate of both processes is approximately equal. The result suggests that the nucleophilic sp^2 heterocyclic nitrogen is not involved in the enhancement of the reaction rate (it does not work as a nucleophilic catalyst, in the way DMAP does). Therefore the higher rate observed with histamine may be the result of a different process. Probably the concomitant participation of the NH group (acting as self-buffering moiety) allows the rapid neutralization of the cationic intermediate, leading to a neutral acyl-imidazole species, which may be the reactive intermediates en route to the adduct (Scheme 3). Some reports in the literature point in this direction.[38]



Scheme 3. Mechanistic hypothesis on the imidazole participation in the amide formation process

Therefore **4a** was used in a staining experiments using basophyl cells (RBL 2H3 cells) and macrophages (RAW 267.3 cells). Basophyl cells are known to store histamine in granules, and to be able to release it when immunogenically stimulated. RAW cells do not contain significant levels of histamine at their natural state, but they are able to generate histamine when treated with thapsigargin.[39] First staining of RBL 2H3 and

RAW 267.3 cells were incubated with **4a** 20 μM for 15 min. In these conditions, fluorescence of RBL cells (naturally storing histamine in granules) was found to be consistently higher than in RAW cells (not containing histamine). (Figure 4)

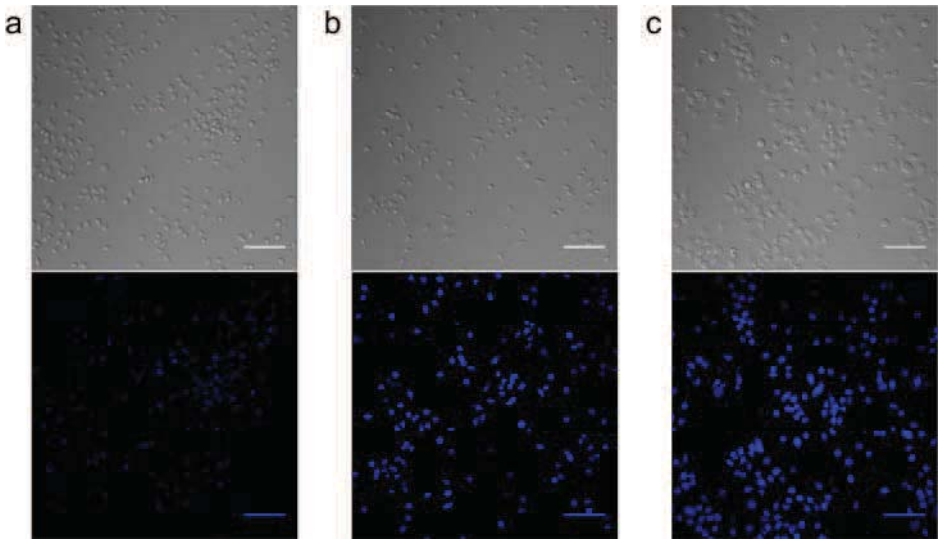


Figure 4. a) RAW 267.3 cells treated with **4a** 20 μM 15 min, then washed with KR-HEPES buffer b) RAW 267.3 cells incubated with external histamine 5mM for 2h. Cells were washed with KR-HEPES, then treated with **4a** 20 μM 15 min, then washed again with KR-HEPES buffer. c) RBL 2H3 cells treated with **4a** 20 μM 15 min, then washed with Krebs-Ringer HEPES buffer (KR-HEPES)

In the following experiment, histamine production was induced in RAW 267.3 cells by incubating thapsigargin 300nM for 24h, as reported by Ohuchi.[39] Cells were then treated with **4a** 20μM for 15 minutes, and subsequently washed with Krebs-Ringer HEPES buffer, and compared with the not treated cells (Figure 5). In these conditions macrophages treated with thapsigargin are qualitatively more stained than not treated cells. As a control experiment, RAW 267.3 cells were incubated with histamine 5mM for 2h before staining with **4a**. In these conditions, this cell line is described to adsorb relevant amounts of histamine. Washed cells were then incubated with **4a** (20μM) for 15

minutes to detect a fluorescence increase comparable with the one described treating the same cell line with thapsigargin.

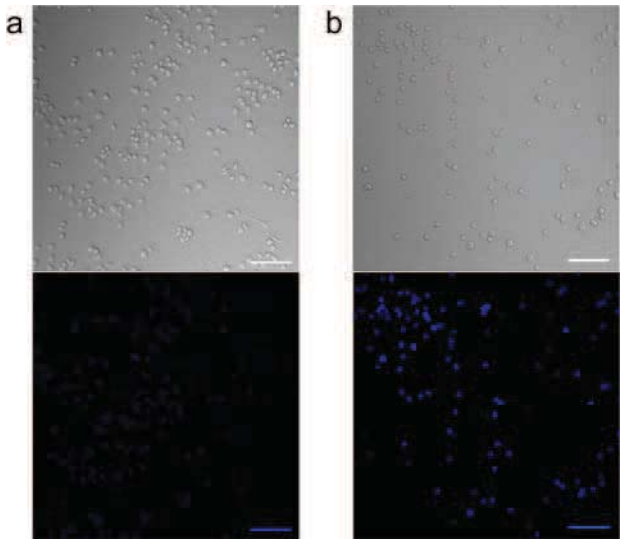


Figure 5. RAW 267.3 cells incubated were incubated with (b) or without (a) thapsigargin 300nM for 24h, then treated with **4a** 20 μM 15 min, and washed with KR-HEPES buffer.

Furthermore, RBL cells were pretreated with IgE-anti DNP (dinitrophenyl) overnight, and stimulated with albumin-DNP to induce histamine release. Cells were then washed and incubated with **4a** in the optimized conditions, and it was possible to detect a relevant decrease of fluorescence when compared with not treated cells. In this case a clear change is more much difficult to be detected as histamine is reported to be released in just 40% of the total amount stored in the granules (Figure 5).

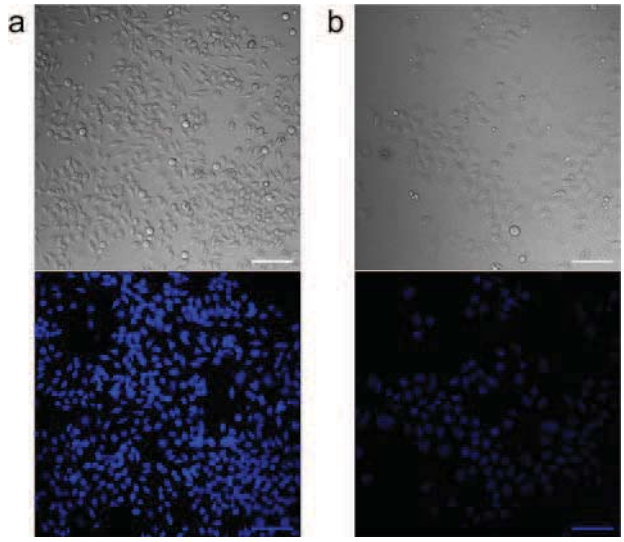


Figure 5. a) RBL 2H3 cells treated with **4a** 20 μM 15 min, then washed with Krebs-Ringer HEPES buffer (KR-HEPES) b) RBL 2H3 cells were pretereated with IgE for 24h (DMEM, 2%FBS), then with BSA-DNP 50ug/mL for 30min, then with **4a** 20 μM 15 min. Cells were washed after every treatment.

Conclusions A new histamine sensor has been discovered through a novel approach combining MCRs and DOFLA. The fluorescent library is characterized by a strong fluorescence in the blue region and is based on an unprecedented dipolar isoquinolinium scaffold. The new histamine biosensor exploits the nucleophilic catalysis of the imidazole group to selectively generate an amide between the histamine analyte and the water stable mesoionic acid fluorides. Acid fluoride **4a** was then used to detect changes in histamine levels in cells using basophiles (RBL 2H3 cell line) storing histamine, or macrophages (RAW 267.3) capable of generating histamine when properly stimulated by thapsigargin. The new probe is the first example of biosensor for in vivo imaging of histamine, not based on recognition by antibodies provided with fluorescent tags, such as ELISA methods, furthermore it is non toxic at concentration up to 40 μM.[37]

Further studies dealing with semiquantitative analysis, drug discovery, cell profiling and compartimentalization are being evaluated for the future work.

Acknowledgements We warmly thank all the members of our research groups involved in this project for their enthusiasm and dedication. Financial support from the DGICYT (Spain, project BQUCTQ2009-07758), Generalitat de Catalunya (project 2009SGR 1024), A*STAR (Agency for Science, Technology and Research, Singapore), Biomedical Research Council and A*STAR SSCC Grant (SSCC10/024) and the Barcelona Science Park is acknowledged. N. K. thanks the Spanish Ministry of Science and Education for a grant.

Conclusiones

Capítulo 1. Recent progress in non-classical isocyanide- based MCRs.

En este capítulo se ha estudiado la reactividad de los isonitrilos en MCRs recientemente descritas, excluyendo procesos clásicos como variantes de reacciones de Ugi, Passerini o Van Leusen. Los procesos se han ordenado en base a criterios de mecanismos de reacción. La primera parte describe procesos en los cuales dos componentes reaccionan entre si para dar un intermedio que será atrapado por un isonitrilo. La segunda sección trata de la activación directa del isonitrilo por electrófilos, seguida de la interacción con una tercera especie. La tercera parte incluye procesos de inserción en enlaces débiles y reacciones con especies organometálicas, que no se pueden clasificar en las clases precedentes. El estudio ha evidenciado un gran número de reacciones pertenecientes al primer tipo, que en consecuencia se halla muy explorado. Por el contrario la activación directa de isonitrilos se perfila como un campo de estudio relativamente virgen y prometedor de cara a desarrollar nuevos procesos multicomponente. Destacar, finalmente, que existen pocos ejemplos de MCRs asignadas al tercer tipo de reactividad.

Capítulo 2. Boron-Based Dipolar Multicomponent Reactions: Simple Generation of Substituted Aziridines, Oxazolidines and Pyrrolidines.

La síntesis de oxazolidinas de Hesse, descrita en 1965 y olvidada durante más de cuarenta años, ha sido evaluada y rediseñada en esta tesis. Se ha validado el proceso original y se ha demostrado su utilidad sintética. Se ha conseguido transformar el proceso de tres componentes en una nueva familia de reacciones de cuatro componentes por sustitución de un equivalente de aldehído por otros dipolarófilos. Adicionalmente en algunos casos se han obtenido aziridinas sustituidas de forma directa y sencilla. Se ha explorado el rango de cada componente y se han establecido las limitaciones en la combinación de reactantes. El desarrollo de versiones de estas reacciones en fase sólida no solamente ha proporcionado una purificación eficaz de los aductos, sino que ha permitido la síntesis de productos que no se pueden obtener de forma tradicional (en fase solución), como la síntesis de una oxazolidina mixta.

Capítulo 3. Recent Developments in Reissert-Type Multicomponent Reactions.

En este capítulo se analizan los descubrimientos más relevantes sobre la participación de azinas en procesos multicomponente de tipo Reissert, en presencia de agentes activantes y nucleófilos. La primera parte abarca los procesos clásicos, en los cuales un nucleófilo ataca en posición α una azina activada por un electrófilo, para generar dihidroazinas sustituidas. La segunda sección describe la activación de azinas para generar especies dipolares, las cuales participan en procesos de cicloadiciones (o similares) con un tercer componente. La tercera tipología trata de las MCRs con azinas en

presencia de isonitrilos. Esta combinación de reactivos es capaz de generar aductos de gran complejidad de forma sencilla, y en muchos casos se originan largas secuencias mecanísticas difícilmente previsibles (reacciones de tipo dominó). Las reacciones de tipo Reissert permiten un acceso sencillo y rápido a estructuras heterocíclicas de interés farmacéutico y es razonable presumir que los estudios en este tema conducirán a avances relevantes en química biomédica.

Capítulo 4. Multicomponent Access to Functionalized Mesoionic Structures Based on TFAA Activation of Isocyanides: Novel Domino Reactions

En este capítulo se describe una nueva reacción multicomponente entre isoquinolinas, isonitrilos y TFAA para originar fluoruros de ácido mesoiónicos. El uso de TFAA como agente activante en procesos de tipo Reissert es capaz de alterar totalmente el proceso dominó con respecto a la reacción original con coloroformiatos desarrollada en nuestro laboratorio. Se sugieren dos mecanismos razonables: el primero se iniciaría con la activación del isonitrilo por el TFAA, descrito en la química de El Kaïm; en el segundo caso, el TFAA acilaría la isoquinolina y, posteriormente, el isonitrilo atacaría al carbonilo del intermedio activado. Se ha determinado el rango de reactividad útil para azinas e isonitrilos, y la reacción resulta tener un carácter general. Se ha logrado sustituir el TFAA por diversos anhídridos fluorados. El empleo del anhídrido tricloroacético dió lugar a una cascada aún más compleja que implicaba la formación del cloruro de ácido mesoiónico esperado. Se ha explorado la reactividad de los fluoruros de ácido, introduciendo en un segundo paso un nucleófilo como cuarto componente formal. De esta forma se han obtenido amidas, esteres y tioesteres.

Capítulo 5. Synthesis and Properties of Oligonucleotides Carrying Isoquinoline Imidazo[1,2-a]azine Fluorescent Units

En este capítulo se emplean dos fluoruros de ácido mesoiónicos como marcadores fluorescentes de oligonucleótidos. Se han preparado los bioconjugados de oligonucleótidos mediante síntesis en solución, ligando el fluoróforo al extremo 3' o 5' del oligonucleótido por medio de un espaciador lineal de tipo amina. Se han acoplado los fluoruros de ácido a oligonucleótidos de hasta 20 bases. Se ha llevado a cabo la reacción en un tampón acuoso básico en presencia de dimetilformamida, y se han aislado los aductos esperados con excelentes rendimientos y selectividad. Adicionalmente se ha sintetizado un oligonucleótido autocomplementario de 8 bases, conjugado con un fluoruro de ácido mesoiónico. De esta forma se han podido realizar estudios sobre los efectos de estabilización del marcador sobre estabilidad de la doble hélice (*temperatura de fusión*). En este aspecto, diferentes sustituyentes (procedentes del residuo del isonitrilo) son capaces de estabilizar la formación de la doble hélice con mayor o menor eficacia. Cálculos computacionales preliminares sugieren que las diferentes interacciones que se producen entre el marcador y la última base en la secuencia sean los factores determinantes en la estabilidad del conjugado. Finalmente se han hecho experimentos de microscopia confocal para internalizar el bioconjugado en células HeLa con ayuda de un agente de transfección.

Adenda: Mesoionic acid fluorides as biosensors for histamine bioimaging

En este capítulo se ha descrito un nuevo biosensor de histamina por s*creening* de una pequeña librería de aductos multicomponente (elegidos entre los que se prepararon

en el Capítulo 4) con tecnología DOFLA. Este trabajo se ha desarrollado en colaboración con el prof. Chang (Universidad de Singapur), durante una estancia breve en el Singapore Bioimaging Consortium (SBIC, Biopolis). En un *screening* primario se ha analizado una librería de 12 compuestos fluorescentes en presencia de 90 analitos, y se ha observado un incremento de fluorescencia selectivo para algunos compuestos en presencia de histamina. Un segundo *screening* con neurotransmisores ha confirmado la selectividad del proceso y el rango de respuesta de los fluoruros de ácido mesoiónicos. Se ha demostrado el mecanismo de respuesta del nuevo sensor con experimentos cinéticos y análisis con HPLC. Se han conducido experimentos de microscopia con basófilos (RBL-2H3) y macrófagos (RAW 264.7) como modelo de células capaces de almacenar histamina. Se han marcado selectivamente los basófilos (que almacenan histamina en gránulos) frente a los macrófagos (sin histamina). En un otro experimento se ha logrado inducir una disminución de contenido en histamina en células RBL-2H3 con un tratamiento imunogénico (IgE anti DNP/ BSA-DNP[i]) y se ha detectado esta variación con el sensor. De manera análoga, se ha podido inducir la formación de histamina en células RAW 264.7 con thapsigargina (tal como se halla descrito en la literatura), y se ha detectado un incremento de fluorescencia con el nuevo biosensor, comparando células tratadas con células sin tratar.

[i] DNP: dinitrofenil; BSA: Albumina di siero bovino.

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Índice

Publicaciones