Palladium in azaheterocyclic synthesis: α-arylation of sulfones, domino processes and C-H carbene insertion reactions

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PROGRAMA DE DOCTORADO: QUÍMICA ORGÁNICA

PALLADIUM IN AZAHETEROCYCLIC SYNTHESIS: α-ARYLATION OF SULFONES, DOMINO PROCESSES AND C-H CARBENE INSERTION REACTIONS

Memoria presentada por Ferran Pérez Janer

para optar al título de doctor por la Universitat de Barcelona

Director de la Tesis: Doctorando:

Dr. Daniel Solé Arjó Ferran Pérez Janer

Ferran Pérez Janer

Barcelona, mayo 2018

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No me olvido de otros doctorandos del grupo SAN, de los que me acuerdo y con los que he compartido buenos momentos. Quiero acordarme especialmente de Guilhem, Caroline y de la sucesora de éstos, Mar.

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También quiero dar las gracias a Elisa. Aunque llegaste desde Roma a finales del doctorado y te quedaste poco, has sido una compañera de trabajo, alguien en quien confiar y más aún, alguien con quien poder hablar.

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Esta Tesis se presenta como *Compendio de publicaciones*. De acuerdo con la normativa vigente, después del apartado Introducción y objetivos (capítulo 1), en el que se presentan los trabajos publicados y se justifica la temática de la Tesis Doctoral, se incluye un resumen de los resultados obtenidos (capítulos 2 – 6). Después del apartado Resumen y conclusiones (capítulo 7), se presentan como *Anexo I: Publicaciones* (capítulo 8) las copias completas de los trabajos publicados. La parte experimental correspondiente a los resultados que todavía no se han publicado se ha recogido en el *Anexo II: Resultados no publicados. Discusión y parte experimental* (capítulo 9).

1

Introducción y Objetivos

Durante los últimos años, un numeroso grupo de metales de transición han contribuido al gran avance de la síntesis orgánica.[1] Sin embargo, es comúnmente aceptado que, de entre todos ellos, el paladio ha sido el metal que ha cambiado de una manera más significativa la química orgánica sintética. Esto ha sido posible gracias a la eficiencia catalítica y a la gran versatilidad de la química organometálica del paladio.[2] En la actualidad, el número de procesos catalíticos en los que interviene el paladio es extraordinariamente grande e incluye desde reacciones que poseen una utilidad sintética contrastada, como por ejemplo la oxidación de Wacker y las reacciones de Heck, Suzuki y Negishi, a procesos que muchas veces pueden parecer simples curiosidades, pero que con toda seguridad acabarán permitiendo el desarrollo de nuevas aplicaciones sintéticas.

1.1. Reacciones de α-arilación catalizadas por paladio

En este contexto, debe destacarse que los esfuerzos para desarrollar nuevas metodologías para la formación de enlaces C-C mediante reacciones de acoplamiento cruzado catalizadas por paladio han sido particularmente intensos durante las pasadas décadas.[3,4,5] Entre las reacciones de acoplamiento cruzado, las reacciones de α-arilación de compuestos carbonílicos catalizadas por paladio se han convertido en una herramienta extraordinariamente potente para la síntesis orgánica.[6,7] La importancia de estas reacciones radica en que permiten la introducción de un grupo arilo en la posición α de un carbonilo mediante la formación del enlace Csp^3-$C_{Ar}sp^2$, una operación que no puede considerarse trivial desde el punto de vista de la química orgánica clásica.

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[1] Zweig, J. E.; Kim, D. E.; Newhouse, T. R. *Chem. Rev.* **2017**, *117*, 11680.

[2] (a) Negishi, E. Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-VCH: New York, 2002, Vols. I and II. (b) Tsuji, J. Ed. *Palladium in Organic Synthesis*, in *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin; 2005.

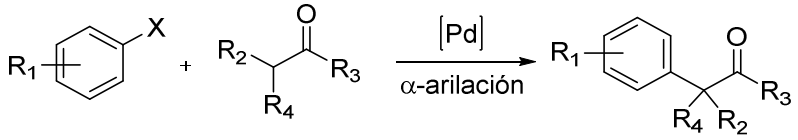
[3] de Meijere, A.; Diederich, F. Ed. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004, Vols. I and II.

[4] Para algunos artículos de revisión, ver: (a) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (c) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486. (d) Negishi, E.; Wang, G.; Rao, H.; Xu, Z. *J. Org. Chem.* **2010**, *75*, 3135. (e) Lipshutz, B. H.; Abela, A. R.; Boskovic, Z. V.; Nishigata, T.; Duplais, C.; Krasovskiy, A. *Top Catal* **2010**, *53*, 985. (f) So, C. M.; Kwong, F. Y. *Chem. Soc. Rev.,* **2011**, *40*, 4963. (g) Kapdi, A. R.; Prajapati, D. *RSC Adv.,* **2014**, *4*, 41245. (h) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587.

[5] Para algunos artículos de revisión, ver: (a) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 3314. (b) Lundgren, R. J.; Stradiotto, M. *Chem. Eur. J.* **2012**, *18*, 9758. (c) Gildner, P. G.; Colacot, T. J. *Organometallics* **2015**, *34*, 5497. (d) Roy, D.; Uozumi, Y. *Adv. Synth. Catal.* **2018**, *360*, 602.

[6] (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (c) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676.

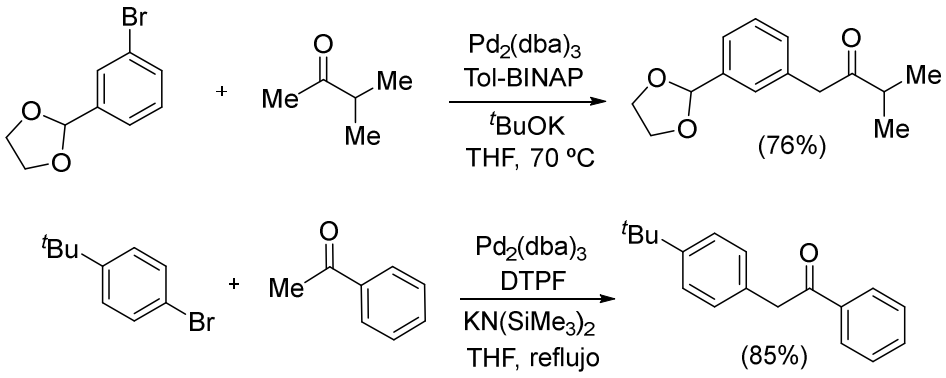
[7] Sivanandan, S. T.; Shaji, A.; Ibnusaud, I.; Johansson-Seechurn, C. C. C.; Colacot, T. J. *Eur. J. Org. Chem.* **2015**, 38.



X: halógeno o equivalente

El primer ejemplo de una reacción de acoplamiento directo entre un haluro de arilo y un enolato promovida por un metal de transición fue descrito por Semmelhack en 1973, en el contexto de la síntesis del alcaloide cefalotaxina.[8] El proceso implicaba una reacción de α-arilación intramolecular de una cetona y requería de la utilización de cantidades estequiométricas de $Ni(COD)_2$. Aunque el rendimiento era moderado, el trabajo de Semmelhack ya anticipaba el potencial sintético que con el tiempo acabarían teniendo este tipo de transformaciones.

A pesar de ello, las reacciones de acoplamiento cruzado entre haluros de arilo y compuestos carbonílicos catalizadas por metales de transición permanecieron prácticamente ignoradas hasta el año 1997, cuando diversos grupos reemprendieron las investigaciones en este campo. Así, de manera prácticamente simultánea Buchwald[9] y Hartwig[10] publicaron sus primeros estudios acerca de la reacción de acoplamiento intermolecular de cetonas y haluros de arilo catalizada por paladio.[11]

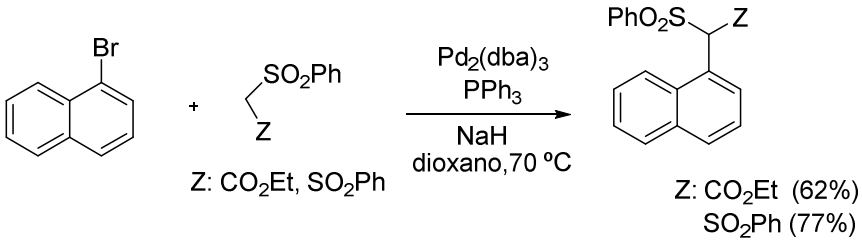


A partir de estos trabajos, las reacciones de acoplamiento entre enolatos y haluros de arilo catalizadas por paladio han sido objeto de una intensa investigación. La reacción se ha estudiado de manera exhaustiva a partir de cetonas, y se ha extrapolado al resto de compuestos carbonílicos: aldehídos, ésteres, amidas, nitrilos y compuestos con metilenos

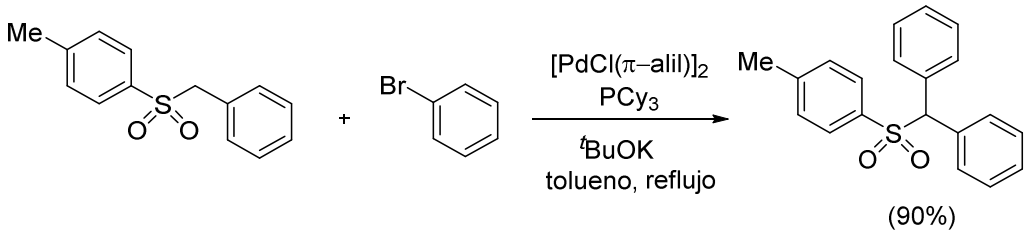
[8] (a) Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, 4519. (b) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.
[9] Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.
[10] Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.
[11] Véase también, Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740.

activos. Adicionalmente, la reacción se ha ampliado a la utilización de nucleófilos no carbonílicos como los nitro alcanos,[12] los sulfóxidos,[13] las sulfonas y las sulfonamidas.

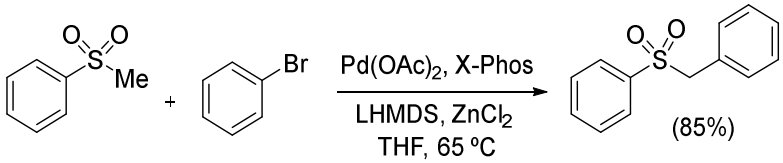
Los primeros estudios para desarrollar un procedimiento efectivo para la α-arilación intermolecular de sulfonas catalizada por paladio fueron realizados por Beletskaya, que en 2002 describió la α-arilación de β-disulfonas y α-sulfonil ésteres.[14] La reacción requería de la utilización de bases fuertes (NaH o BuLi). Sin embargo, todos los intentos para realizar la reacción de arilación a partir de la fenil metil sulfona, cuyos protones en α son considerablemente menos ácidos, resultaron infructuosos.



Posteriormente, Oshima describió la α-arilación intermolecular de benzil sulfonas catalizada por paladio.[15] Las condiciones optimizadas para esta reacción implicaban la utilización como catalizador del $[PdCl(\pi\text{-alil})]_2$ en combinación con una trialquilfosfina voluminosa, y de ^{t}BuOK como base.

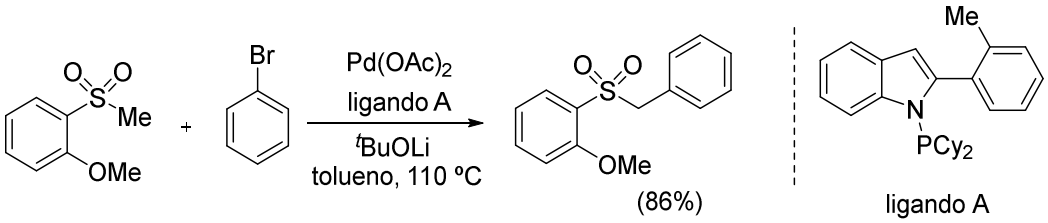


Poco tiempo después, Zhou describió la α-arilación intermolecular de metil sulfonas catalizada por paladio.[16] La reacción utilizaba LHMDS como base, en combinación con $ZnCl_2$. Puesto que el $ZnCl_2$ resultaba crucial para la α-arilación, los autores sugirieron como etapa clave de la reacción, una transmetalación entre el intermedio σ-arilPd(II) y el enolato de zinc.

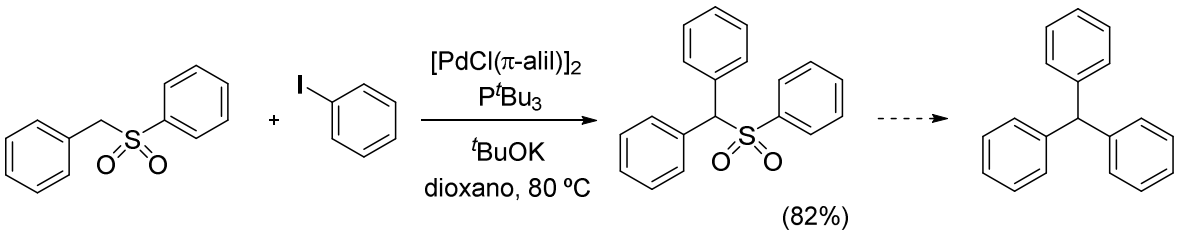


[12] (a) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106. (b) VanGelder K. F.; Kozlowski, M. C. *Org. Lett.* **2015**, *17*, 5748.
[13] (a) Jia, T.; Bellomo, A.; El Baina, K.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc*. **2013,** *135*, 3740. (b) Jia, T.; Bellomo, A.; Montel, S.; Zhang, M.; El Baina, K.; Zheng, B.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 260.
[14] Kashin, A. N.; Mitin, A. V.; Beletskaya, I. P.; Wife, R. *Tetrahedron Lett*. **2002**, *43*, 2539.
[15] Niwa, T.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2009**, *65*, 1971.
[16] Zhou, G.; Ting, P. C.; Aslanian, R. G. *Tetrahedron Lett.* **2010**, *51*, 939.

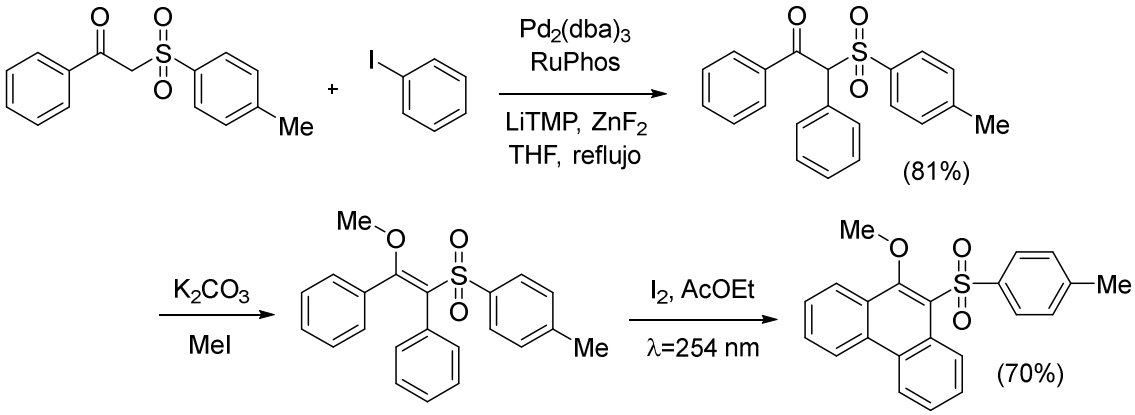
Unos años más tarde, Walsh desarrolló un procedimiento efectivo para la α-arilación intermolecular de metil sulfonas catalizada por paladio utilizando ^{t}BuOLi como base.[17]



Por otro lado, Crudden exploró la α-arilación de metil sulfonas como metodología para la preparación de triarilmetanos.[18]

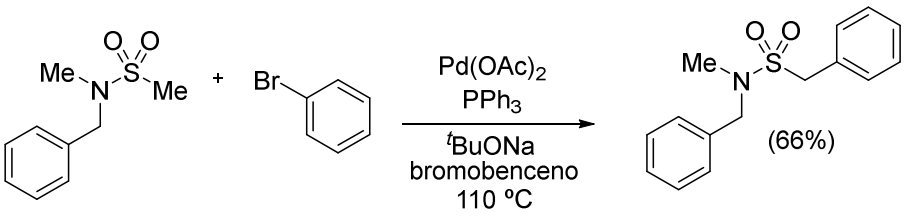


Más recientemente, Chang ha desarrollado un procedimiento efectivo para la α-arilación de β-cetosulfonas, y lo ha aplicado a la síntesis de sulfonilfenantrenos diversamente funcionalizados.[19]

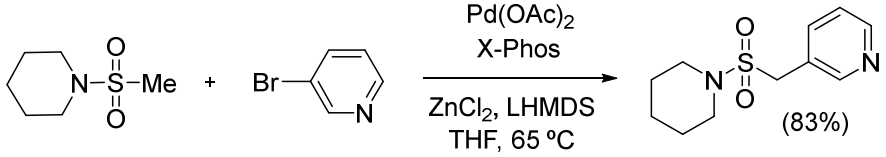


Los ejemplos de reacciones de α-arilación de sulfonamidas que aparecen en la literatura química son también escasos. En 2005, Parkinson describió la α-arilación de metansulfonamidas catalizada por paladio.[20] La reacción, que transcurre con rendimientos moderados, implica la utilización de ^{t}BuONa como base.

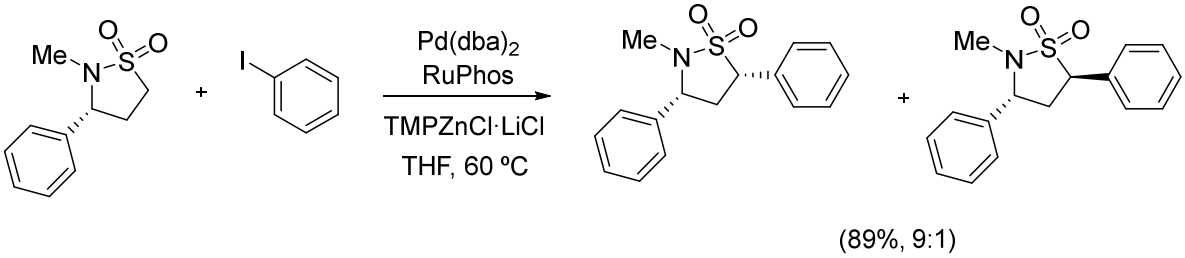
[17] Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 1690.
[18] Nambo, M.; Crudden, C. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 746.
[19] Chang, M.-Y.; Chen, Y.-C.; Chan, C.-K. *Tetrahedron* **2015**, *71*, 782.
[20] Zeevaart, J. G.; Parkinson, C. J.; de Koning, C. B. *Tetrahedron Lett*. **2005**, *46*, 1597.



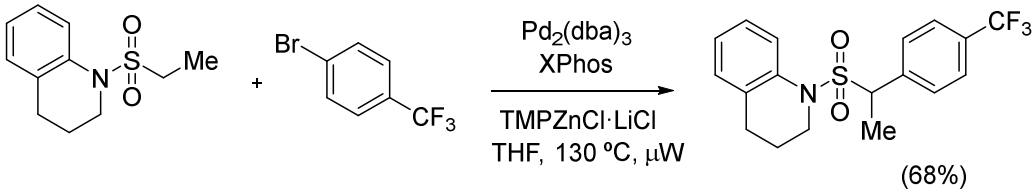
Posteriormente, Zhou describió un procedimiento más efectivo para la α-arilación intermolecular de metansulfonamidas utilizando unas condiciones de reacción similares a las anteriormente descritas por su grupo de investigación para la arilación de metil sulfonas.[16] El proceso implicaría de nuevo una transmetalación del enolato de Zn generado en el medio de reacción.[21]



Unos años más tarde, René utilizó una estrategia similar para la α-arilación intermolecular de sultamas, utilizando como base 2,2,6,6-tetrametilpiperidina en combinación con $ZnCl_2$ y LiCl.[22]

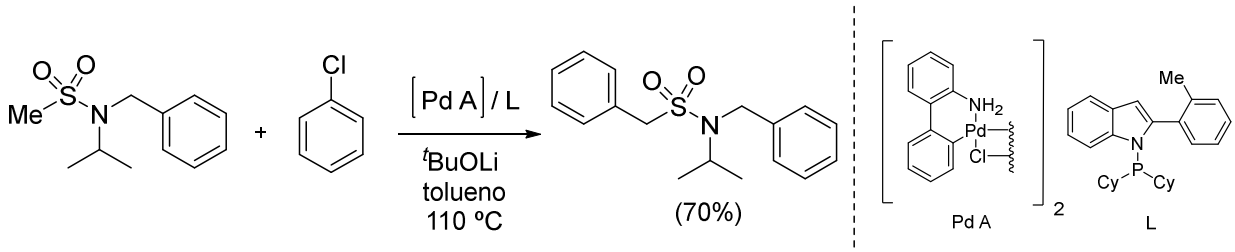


La misma combinación de base y aditivos ha sido utilizada posteriormente por Knauber para la α-arilación intermolecular de sulfonamidas.[23]

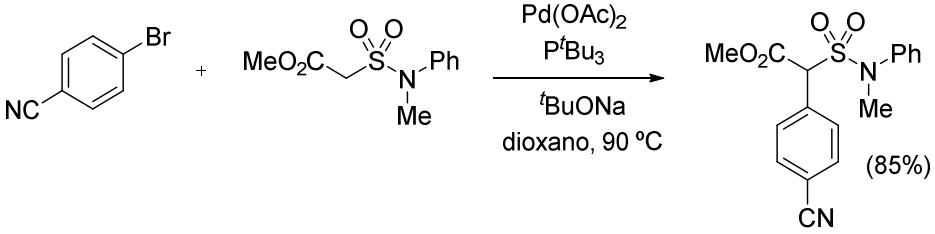


Recientemente, Walsh ha descrito la α-arilación intermolecular de metansulfonamidas utilizando cloruros de arilo como electrófilos.[24]

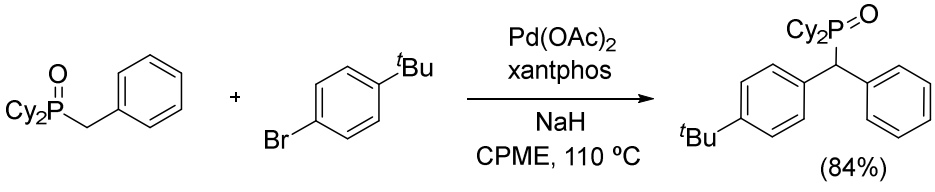
[21] Zhou, G.; Ting, P.; Aslanian, R.; Piwinski, J. J. *Org. Lett*. **2008**, *10*, 2517.
[22] René, O.; Fauber, B. P.; Malhotra, S.; Yajima, H. *Org. Lett*. **2014**, *16*, 3468.
[23] Knauber, T.; Tucker, J. *J. Org. Chem*. **2016**, *81*, 5636.
[24] Zheng, B.; Li, M.; Gao, G.; He, Y.; Walsh, P. J. *Adv. Synth. Catal*. **2016**, *358*, 2156.

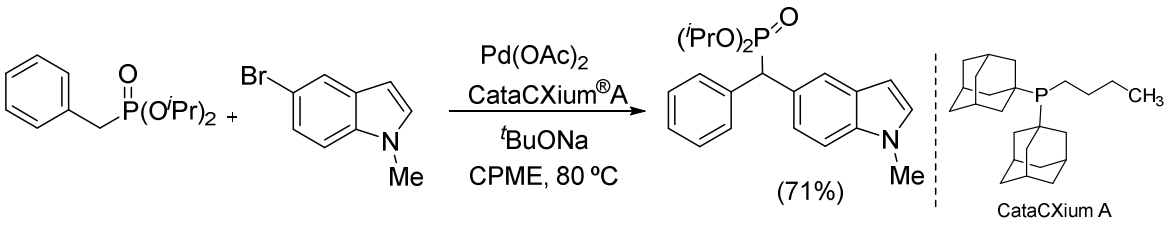


Finalmente, Northrup ha estudiado la α-arilación de sulfonamidas activadas catalizada por paladio.[25]



Para completar el estudio acerca de la utilización de nucleófilos no carbonílicos en la reacción de α-arilación intermolecular, también se han estudiado las reacciones a partir de óxidos de fosfina[26] y de fosfonatos.[27]



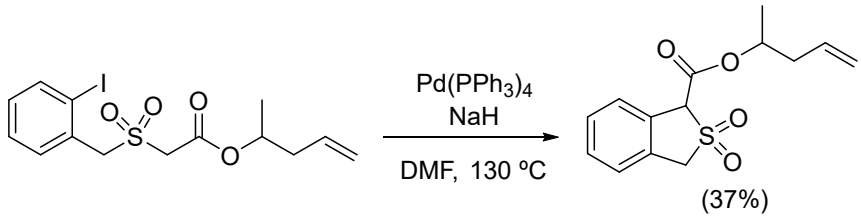


Como puede observarse en los diferentes procesos que se ha comentado hasta el momento, en este tipo de reacciones, además del catalizador y de los ligandos, también es clave la elección de la base que se utiliza para generar el anión en la posición α del grupo atrayente de electrones. Como los hidrógenos en posición α de ésteres, amidas, nitrilos, sulfonas y del resto de grupos atrayentes de electrones son menos ácidos que los de la posición α de aldehídos y cetonas,[28] en la mayoría de los casos es necesaria la utilización de una base fuerte.

[25] Grimm, J. B.; Katcher, M. H.; Witter, D. J.; Northrup, A. B. *J. Org. Chem*. **2007**, *72*, 8135.
[26] Montel, S.; Jia, T.; Walsh, P. J. *Org. Lett.*, **2014**, *16*, 130.
[27] Montel, S.; Raffier, L.; He, Y.; Walsh, P. J. *Org. Lett*. **2014**, *16*, 1446.
[28] (a) Bordwell, F. C. *Acc. Chem. Res*. **1988**, 21, 456. (b) Bordwell, F.G.; Harrelson Jr., J. A.; Zhang, X. *J. Org. Chem*. **1991**, *56*, 4448.

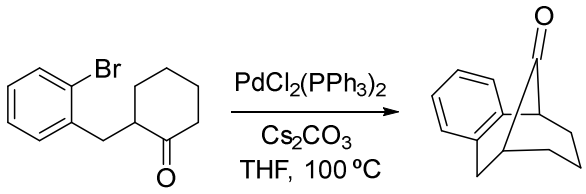
Las versiones intramoleculares de las reacciones de α-arilación, aunque menos exploradas, han seguido un camino paralelo al de los procesos intermoleculares y, en muchos casos, han acabado convirtiéndose en una herramienta de amplia aplicación en la síntesis de productos naturales y de compuestos con actividad farmacológica.

En 1988, casi una década antes de que aparecieran los primeros trabajos de Buchwald y Hartwig, Ciufolini describió la α-arilación intramolecular de α-sulfonil ésteres catalizada por paladio.[29]



(37%)

Por otro lado, en 1997 y de manera prácticamente simultánea a los primeros trabajos de acerca de la α-arilación intermolecular de cetonas catalizada por paladio, Muratake y Natsume describieron la versión intramolecular de la reacción en la serie carbocíclica.[30]

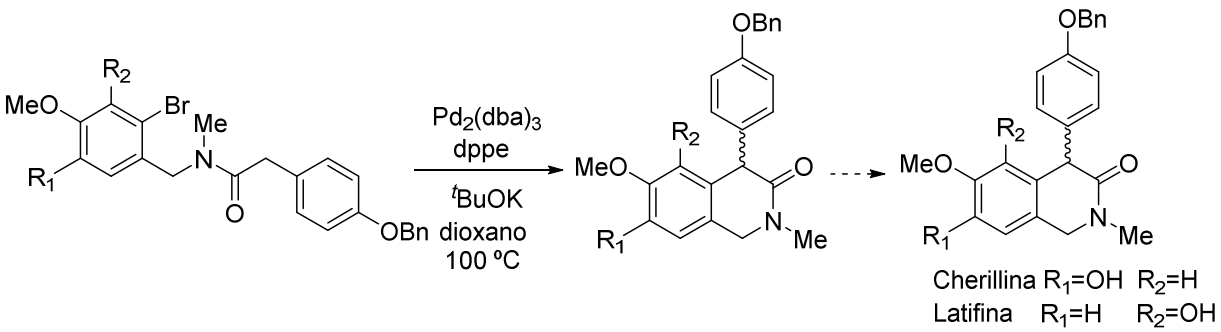


(83%)

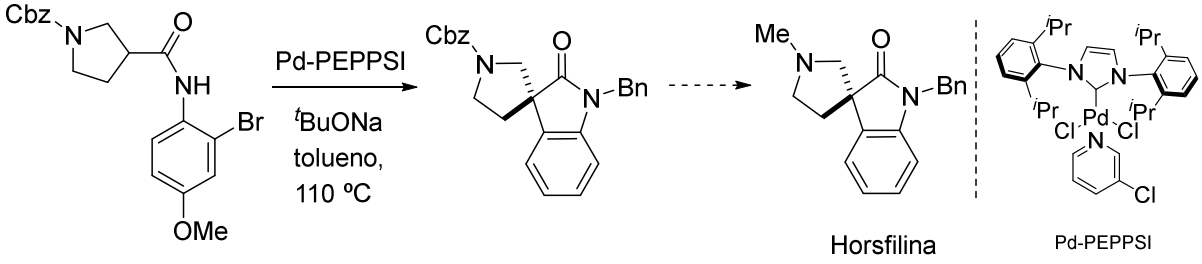
Las reacciones de α-arilación intramolecular de compuestos carbonílicos catalizadas por paladio se han utilizado frecuentemente en la síntesis de heterociclos nitrogenados, especialmente derivados indólicos y tetrahidroisoquinolinas.

En este contexto, sin lugar a dudas, el proceso intramolecular que se ha estudiado de una manera más exhaustiva ha sido la reacción de α-arilación de amidas, que se ha aplicado con éxito en la síntesis de diversos productos naturales. A modo de ejemplo, Honda ha utilizado la reacción de α-arilación intramolecular de amidas catalizada por paladio para la elaboración del sistema de tetrahidroisoquinolina presente en los alcaloides cherillina y latifina.[31]

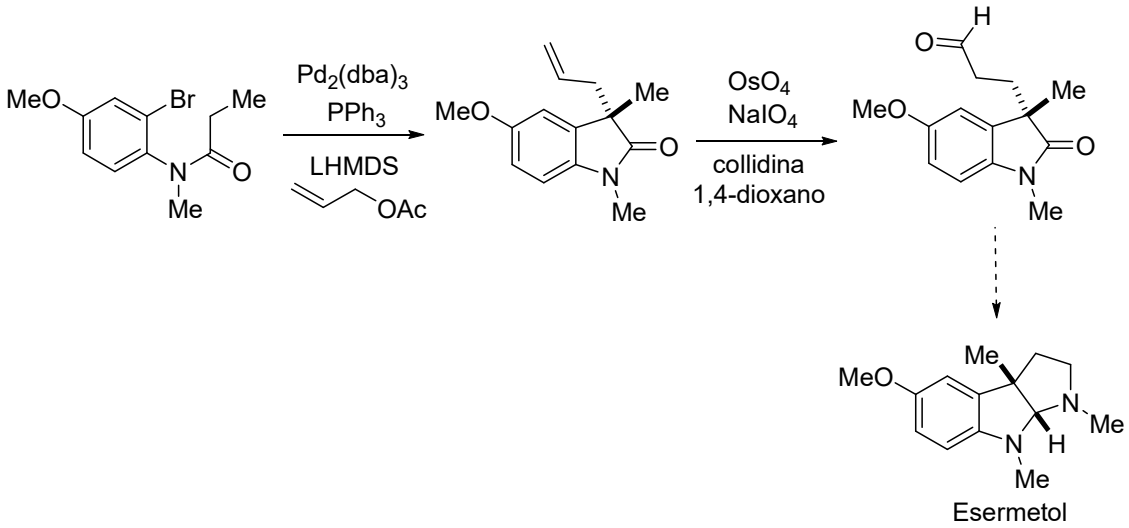
[29] Ciufolini, M. A.; Qi, H-B.; Browne, M. E. *J. Org. Chem*. **1988**, *53*, 4149.
[30] Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581.
[31] Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631.



La α-arilación intramolecular de amidas se ha utilizado también en la síntesis del alcaloide espiro-oxindólico Horsfilina.[32]



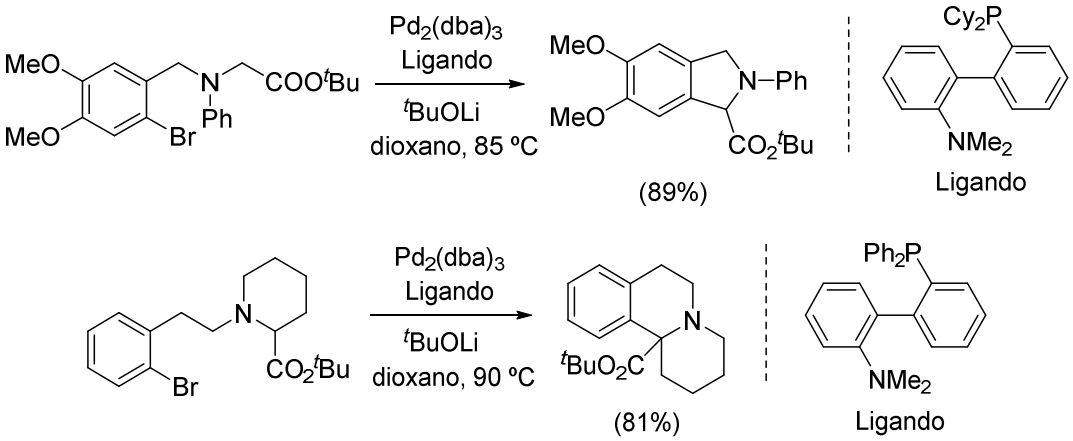
Recientemente, Zhang ha desarrollado un proceso dominó α-arilación/alilación catalizado por paladio para la preparación de un intermedio oxindólico clave en la síntesis del Esermetol, un alcaloide que contiene el sistema de hexahidropirrolo[2,3-*b*]indol.[33]



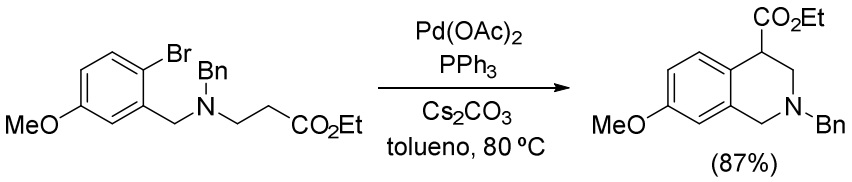
En 2002, Buchwald describió la α-arilación intramolecular de α-amino ésteres catalizada por paladio como metodología para la síntesis de tetrahidroisoquinolinas e isoindolinas. En esta

[32] Depperman, N.; Thomanek, H.; Prenzel, A-H.; Maison, W. *J.Org. Chem*. **2010**, *75*, 5994.
[33] Zhou, Y.; Zhao, Y.; Dai, X.; Liu, J.; Li, L.; Zhang, H. *Org. Biomol. Chem.,* **2011**, *9*, 4091.

reacción se utilizaba como catalizador $Pd_2(dba)_3$ en combinación con una biarilfosfina monodentada, y como base ^{t}BuOLi.[34]



Unos años más tarde, Satyanarayana estudió la α-arilación intramolecular de β-amino ésteres como metodología para la preparación de tetrahidroisoquinolinas.[35]

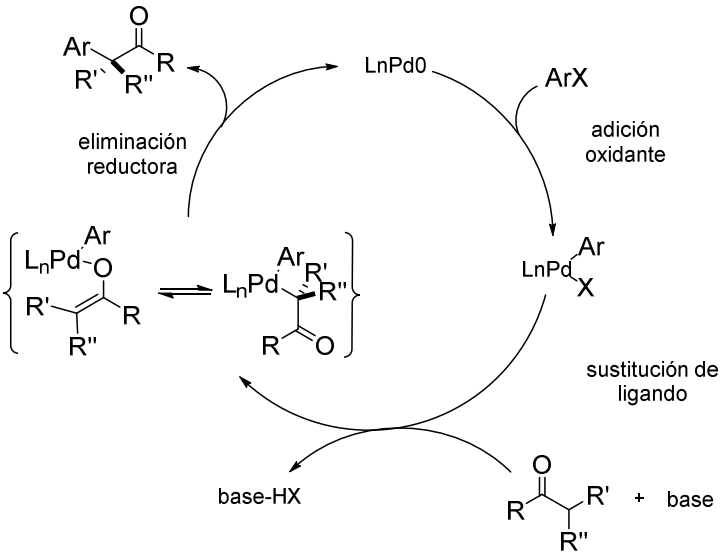


De manera paralela a los estudios metodológicos encaminados a desarrollar procesos catalíticos efectivos para la α-arilación de compuestos carbonílicos, se ha realizado una intensa investigación para establecer el mecanismo de estas reacciones y determinar los parámetros que influyen en las distintas etapas.[36]

Las primeras reacciones de α-arilación catalizadas por paladio que se desarrollaron implicaban la utilización de bases fuertes. La necesidad de este tipo de bases se racionalizó en base al mecanismo propuesto para este tipo de transformaciones. A continuación, se muestra el mecanismo simplificado inicialmente propuesto por Hartwig para la reacción de α-arilación de cetonas.[6a] El proceso se inicia con la adición oxidante del haluro de arilo al catalizador de Pd(0), que proporciona un intermedio σ-arilpaladio(II). A continuación, la reacción aprovecharía el carácter electrófilo del átomo de paladio en este tipo de intermedios. Se produciría la sustitución del ligando haluro del intermedio σ-arilPd(II) por el anión enolato, que se ha generado *in situ* a partir de la cetona. Finalmente, el enolato de

[34] Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465.
[35] Reddy, A. G. K.; Krishna, J.; Satyanarayana, G. *Synlett* **2011**, 1756.
[36] (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Culkin, D. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816. (c) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (d) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330. (e) Wolkowski, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 4289. (f) Liu, X.; Hartwig, J. F. *Org. Lett.* **2003**, *5*, 1915. (g) Katayev, D.; Jia, Y.-X.; Sharma, A. K.; Banerjee, D.; Bernard, C.; Sunoj, R. B.; Kündig, E. P. *Chem. Eur. J.* **2013**, *19*, 11916.

paladio formado en esta etapa experimentaría una reacción de eliminación reductora, que proporcionaría el producto de α-arilación y liberaría la especie de Pd(0) catalítica.



Sin embargo, debe tenerse en cuenta que este mecanismo simplificado no interpreta el papel clave de los ligandos y del disolvente, ni explica tampoco la eficacia que presentan algunas bases débiles en este tipo de reacciones.

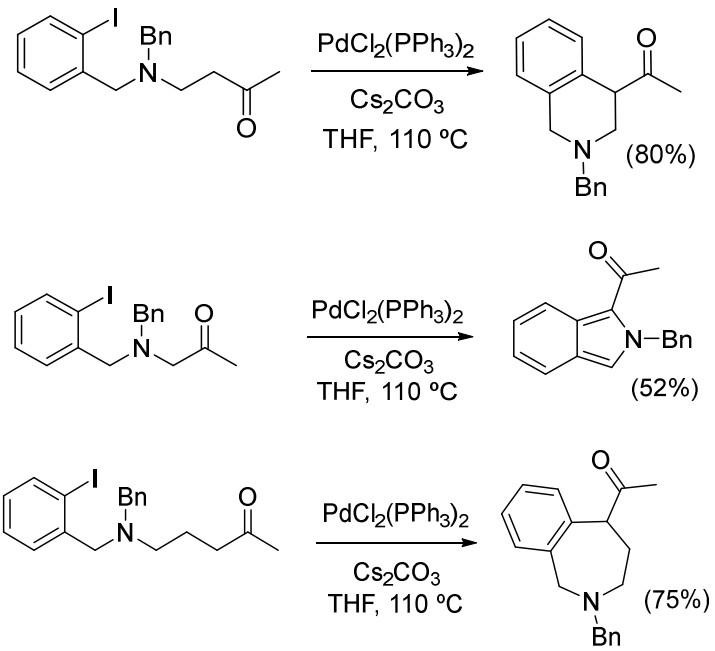
En el contexto de la búsqueda continuada de metodologías sintéticas más respetuosas con el medio ambiente, los procesos dominó se han convertido en una herramienta extraordinariamente potente para la síntesis orgánica.[37] Un proceso dominó se define como una transformación química en la que se producen dos o más reacciones de formación de enlaces en una única operación sintética, de manera que la funcionalización que se genera en una reacción se utiliza en la siguiente, sin que sea necesario modificar las condiciones de reacción.[38] Las reacciones dominó permiten preparar estructuras con una gran complejidad estructural en una única etapa sintética, utilizando productos de partida fácilmente asequibles y minimizando el uso de reactivos, disolventes, tiempo y energía.

El desarrollo de procesos dominó centrados en reacciones de formación de enlaces C-C catalizadas por paladio ha sido objeto de un intenso estudio durante los últimos años.[39] Sorprendentemente, a pesar del gran potencial sintético que poseen las reacciones de α-arilación, el desarrollo de procesos dominó basados en este tipo de reacciones es limitado.

[37] (a) Eppe, G.; Didier, D.; Marek, I. *Chem. Rev.* **2015**, *115*, 9175. (b) Chanda, T.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2018**, *360*, 2.
[38] Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
[39] (a) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (b) Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Adv. Synth. Catal.* **2011**, *353*, 809. (c) Majumdar, K. C.; Sinha, B. *Synthesis* **2013**, *45*, 1271.

Así, considerando que la reacción de α-arilación catalizada por paladio requiere de la presencia de una base y que el producto de reacción puede tener todavía algún hidrógeno en la posición α, el desarrollo de procesos dominó que impliquen una reacción de α-arilación y seguidamente una reacción en la posición α promovida por la base, parecería evidente y relativamente fácil de llevarse a la práctica. Sin embargo, esta posibilidad ha sido muy poco estudiada. A modo de ejemplo, en el apartado anterior ya se ha comentado la síntesis del esermetol de Zhang y colaboradores, que tiene como etapa clave la preparación de un intermedio oxindólico mediante un proceso dominó α-arilación/alilación catalizado por paladio.[33]

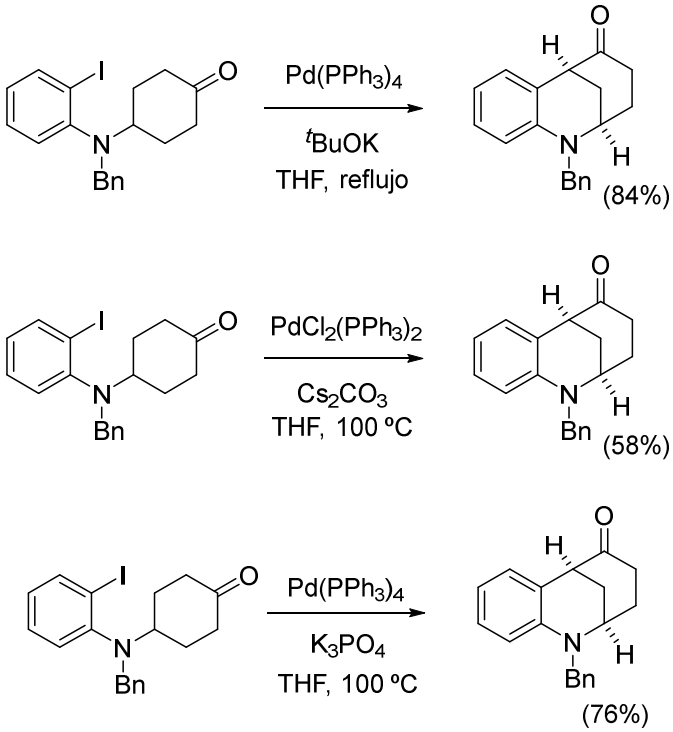
Durante los últimos años, en nuestro grupo de investigación se ha estado trabajando en el desarrollo de una metodología para la síntesis de heterociclos nitrogenados basada en las reacciones de α-arilación intramolecular catalizadas por paladio. Los primeros estudios se realizaron a partir de sustratos de tipo cetona. La reacción de α-arilación a partir de (2-halobencil)amino cetonas permitió la preparación de sistemas heterocíclicos con anillos de 5, 6 y 7 eslabones. La reacción pudo realizarse tanto a partir de yoduros como de bromuros, aunque los bromuros proporcionaron, en general, rendimientos inferiores. Para promover la reacción α-arilación a partir de este tipo de sustratos no fue necesaria la utilización ni de bases fuertes ni de fosfinas elaboradas.[40]



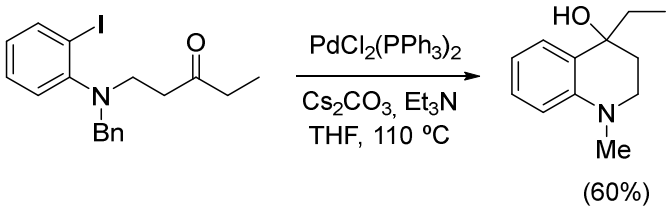
Como continuación del estudio metodológico con cetonas, también se exploró la reacción de α-arilación a partir de sustratos de tipo 2-haloanilina. Durante este estudio, se observó que

[40] Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587.

las γ-anilino cetonas experimentaban la reacción de α-arilación de manera efectiva.[41] La reacción permitió, por ejemplo, la preparación del sistema de 2,6-metanobenzazocina con buenos rendimientos. Para la elaboración de este sistema heterocíclico pudieron utilizarse diversas bases, como ^{t}BuOK, Cs_2CO_3 o K_3PO_4.[42]



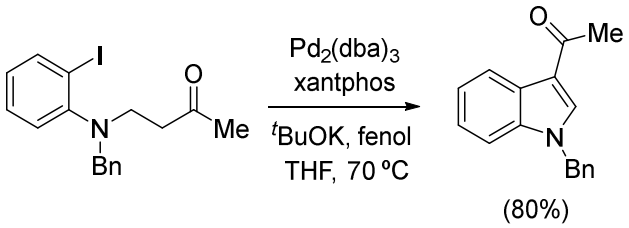
En cambio, cuando los sustratos de tipo α-anilino cetona y β-anilino cetona se sometieron a las mismas condiciones de reacción, utilizando como base Cs_2CO_3 o K_3PO_4, en lugar de formarse de los productos de α-arilación esperados, se obtenían los alcoholes resultantes del ataque del intermedio σ-arilpaladio(II) al carbonilo.[40-41]



En los sustratos de tipo β-anilino cetona, la utilización del ^{t}BuOK como base en presencia de un exceso de fenol, y de xantphos como ligando, permitió modificar la quimioselectividad de la reacción y obtener el producto de α-arilación con buen rendimiento. Debe tenerse en cuenta que al utilizar estas condiciones, en realidad, no existe ^{t}BuOK en el medio de reacción,

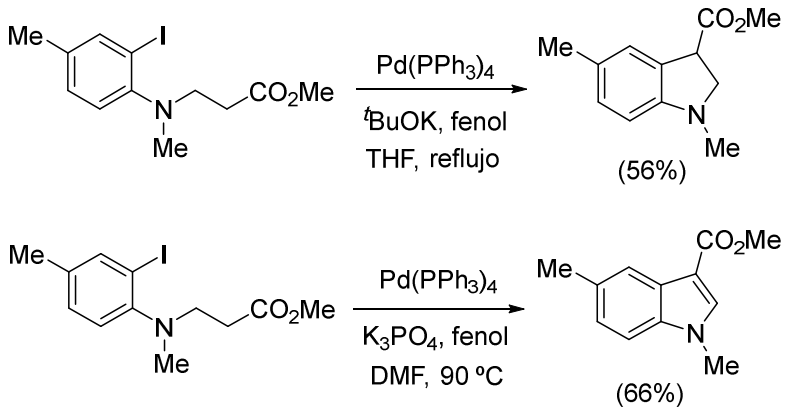
[41] Solé, D.; Vallverdú, L.; Peidró, E.; Bonjoch, J. *Chem. Commun.,* **2001**, 1888.
[42] Solé, D.; Vallverdú, L.; Bonjoch, J. *Adv. Synth. Catal.* **2001**, *343*, 439.

sino que la base es el fenóxido potásico que se genera *in situ* por reacción entre el ^{t}BuOK y el fenol.[43]



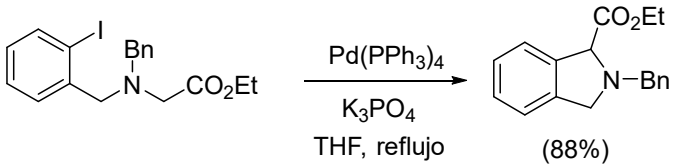
En nuestro grupo también se ha estudiado la reacción de α-arilación utilizando otras agrupaciones carbonílicas como metodología para la síntesis de heterociclos nitrogenados.

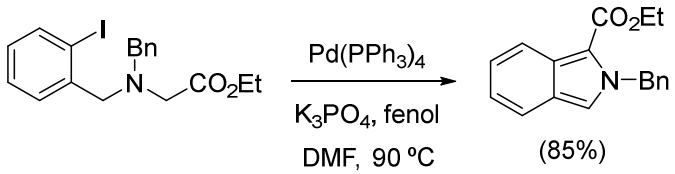
A partir de los sustratos de tipo β-anilino éster se han desarrollado dos procedimientos alternativos para la reacción de α-arilación, que permiten la obtención de manera selectiva ya sea de indolinas o bien de los indoles correspondientes.[44] Así, al tratar los β-anilino ésteres con $Pd(PPh_3)_4$ y en presencia de un exceso de fenóxido potásico, generado *in situ* por reacción del fenol y ^{t}BuOK, en el seno de THF, se obtienen las indolinas. En cambio, cuando la reacción se realiza utilizando K_3PO_4 como base en presencia de cantidades subestequiométricas de fenol, en el seno de DMF, se forma directamente el indol correspondiente.



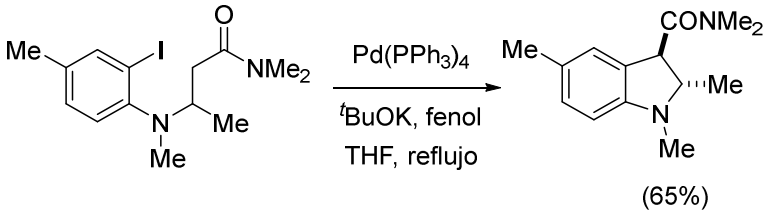
Mediante pequeñas modificaciones de las anteriores condiciones de reacción, también se desarrollaron dos procedimientos alternativos para la α-arilación a partir de α-amino ésteres.[45] Por un lado, a partir de estos sustratos, la utilización de K_3PO_4 como base en el seno de THF proporciona las isoindolinas. Alternativamente, al utilizar K_3PO_4 como base en presencia de cantidades subestequiométricas de fenol, en el seno de DMF, se obtienen directamente los isoindoles correspondientes.

[43] Solé, D.; Fernández, I.; Sierra, M. A. *Chem. Eur. J.* **2012**, *18*, 6950.
[44] Solé, D.; Serrano, O. *J. Org. Chem*. **2008**, *73*, 2476.
[45] Solé, D.; Serrano, O. *J. Org. Chem*. **2010**, *75*, 6267.

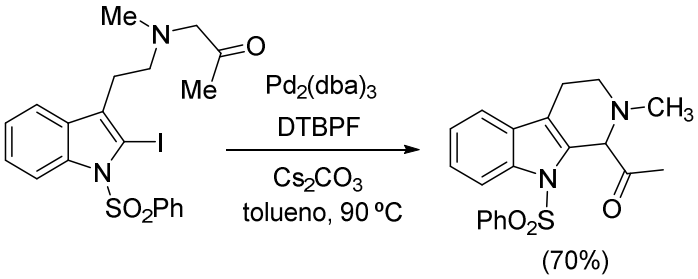




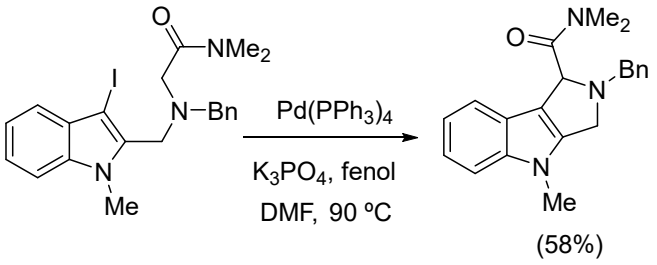
La reacción de α-arilación también se realizó de manera efectiva a partir de los sustratos de tipo amida. El tratamiento de las amidas con las mismas condiciones utilizadas para la α-arilación a partir de los β-anilino ésteres proporcionó las indolinas con rendimientos aceptables.[46]



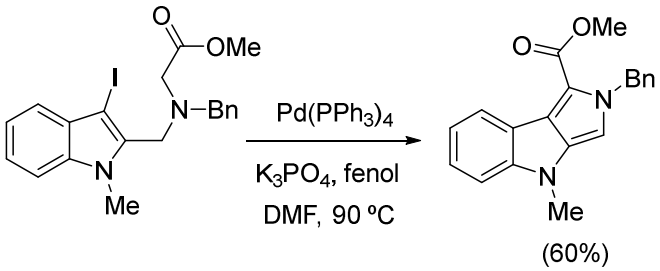
Las reacciones de α-arilación intramolecular a partir de cetonas, ésteres y amidas que se habían desarrollado en nuestro grupo con sustratos de tipo haloarilo sencillos, se utilizaron posteriormente, con pequeñas modificaciones de las condiciones de reacción, para la preparación de sistemas azaheterocíclicos fusionados con el indol.[47] Estos sistemas además de ser frecuentes en la estructura de ciertos productos naturales, forman parte de numerosos compuestos con actividad farmacológica interesante.



[46] Solé, D.; Serrano, O. *J. Org. Chem*. **2008**, *73*, 9372.
[47] Solé, D.; Bennasar, M-L.; Jiménez, I. *Org. Biomol. Chem*. **2011**, *9*, 4535.

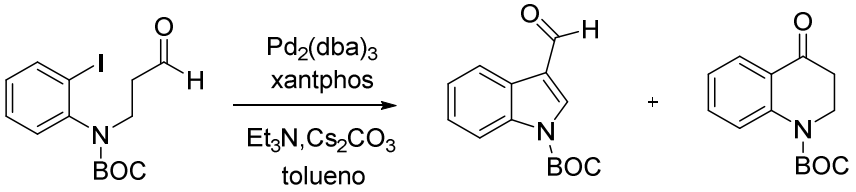


(58%)



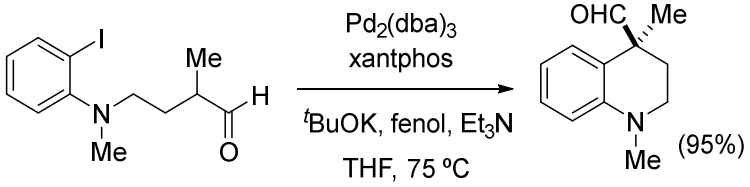
(60%)

El control de la reacción de α-arilación resultó mucho más problemático a partir de los sustratos de tipo aldehído, debido a la mayor tendencia de los aldehídos a experimentar la reacción de acilación a causa del menor impedimento estérico sobre el grupo formilo.[48]



(1:0.9)

A pesar de ello, la reacción de α-arilación pudo realizarse selectivamente y con buen rendimiento a partir de algunos sustratos de tipo aldehído, como por ejemplo el recogido en la figura siguiente. El éxito de esta reacción se debe a la suma de diversos factores. Al tratarse de un sustrato de tipo γ-amino aldehído, mucho más estable, puede utilizarse la combinación de ^{t}BuOK y fenol, que como ya hemos visto anteriormente permite realizar selectivamente las reacciones de α-arilación.



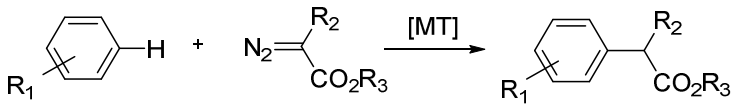
(95%)

[48] Solé, D.; Mariani, F.; Fernández, I.; Sierra, M. A. *J. Org. Chem*. **2012**, *77*, 10272.

1.2. Reacciones de inserción de metalocarbenos en enlaces C-H

Como se ha puesto de manifiesto en las reacciones que se han comentado en el apartado 1.1, los haluros de arilo son los sustratos de elección en las reacciones de α-arilación catalizadas por paladio. Sin embargo, la preparación de los sustratos de partida para estas reacciones no es siempre fácil, ya sea porque los bromuros y los yoduros de arilo no son productos comercialmente asequibles, o bien porque la introducción de un Br o un I en un anillo aromático no es una operación trivial.

Las reacciones de inserción de metalocarbenos, generados por descomposición de compuestos α-diazocarbonílicos, en enlaces C_{Ar}-H constituyen una alternativa a la reacción de α-arilación catalizada por paladio. Formalmente, estas reacciones serían procesos de α-arilación ya que conducen al mismo tipo de productos mediante la formación también del enlace Csp^3-$C_{Ar}sp^2$.[49]



MT: metal de transición

Los complejos de metales de transición que pueden generar metalocarbenos reactivos a partir de diazo derivados son diversos. Entre ellos, los derivados de Rh(II),[50] Cu(I),[51] Au[52] y más recientemente Ru(II)[53] han resultado ser particularmente útiles para el desarrollo de metodologías de inserción sumamente selectivas. Sorprendentemente, el paladio, que sin lugar a dudas es el metal de transición más común en catálisis homogénea y el más utilizado en las reacciones de acoplamiento cruzado entre diazo derivados y haluros orgánicos,[54] ha sido muy poco aplicado para promover ese tipo de procesos de inserción.[55]

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[49] (a) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev*., **2015**, *115*, 9981. (b) Bartuloso, A. C. B.; Dias, R. M. P.; Rafael.; Bernardim, B. *Acc. Chem. Res*., **2015**, *48*, 921.

[50] (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.,* **2010**, *110*, 704. (b) Davies, H. M. L.; Parr, B. T. in *Contemporary Carbene Chemistry*; Wiley: Hoboken, NJ, 2013, pp 363-403.

[51] (a) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.,* **2008**, *108*, 3379. (b) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.,* **2012**, *48*, 10162.

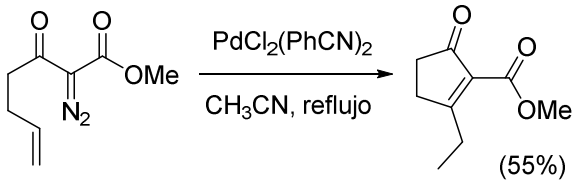
[52] (a) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.,* **2014**, *136*, 6904. (b) Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.,* **2016**, *52*, 7326. (c) Liu, L.; Zhang, J. *Chem. Soc. Rev.,* **2016**, *45*, 506.

[53] (a) Choi, M. K-W.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081. (b) Choi, M. K-W.; Yu, W.-Y.; So, M.-H.; Zhou, C.-Y.; Deng, Q.-H.; Che, C.-M. *Chem. Asian J.,* **2008**, *3*, 1256. (c) Zhou, C. Y.; Huang, J. S.; Che, C. M. *Synlett,* **2010**, 2681. (d) Reddy, A. R.; Zhou, C.-Y.; Guo, Z.; Wei, J.; Che, C.-M. *Angew. Chem. Int. Ed.,* **2014**, *53*, 14175.

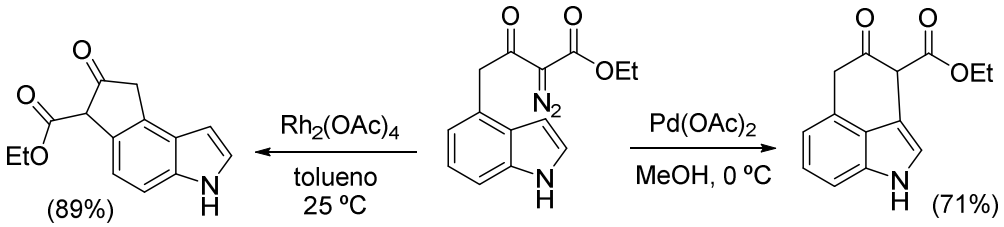
[54] Para artículos de revisión, véase: (a) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015. (b) Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486. (c) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (d) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236.

[55] (a) Taber, D. F.; Amedio Jr., J. C.; Sherill, R. G. *J. Org. Chem.* **1986**, *51*, 3382. (b) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles*, **1987**, *26*, 1479. (c) Rosenberg, M. L.; Aasheim, J. H. F.; Trebbin, M.; Uggerud, E.; Hansen, T. *Tetrahedron Lett.* **2009**, *50*, 6506.

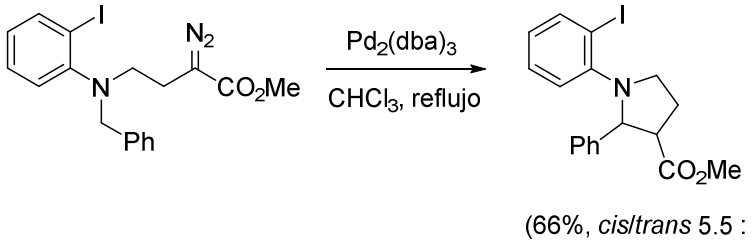
En 1985, Taber describió la descomposición catalizada por paladio de β-ceto-α-diazo ésteres para preparar ciclopentenonas. Esta reacción implica la interacción del carbeno de paladio intermedio con el doble enlace del alqueno.[55a]



Poco tiempo después, Matsumoto estudió la inserción intramolecular de carbenos, generados a partir de β-ceto-α-diazo ésteres por reacción con diversos metales de transición, en enlaces $C_{Ar}sp^2$-H del indol.[55b] En estas reacciones la situselectividad de la inserción varía en función del metal de transición utilizado. Así, al utilizar $Pd(OAc)_2$ como catalizador la inserción se produce en el enlace C(3)-H del indol, mientras que cuando se utilizan catalizadores de cobre o de rodio la inserción tiene lugar en el enlace C(5)-H. En base a los datos experimentales obtenidos, los autores proponen un mecanismo de tipo Friedel-Crafts para la reacción promovida utilizando $Pd(OAc)_2$ como catalizador.



Recientemente, nuestro grupo de investigación ha descrito la inserción intramolecular catalizada por paladio de carbenos generados a partir de α-diazo ésteres como metodología para la preparación de pirrolidinas.[56] Esta reacción supone la formación de un enlace Csp^3-Csp^3.



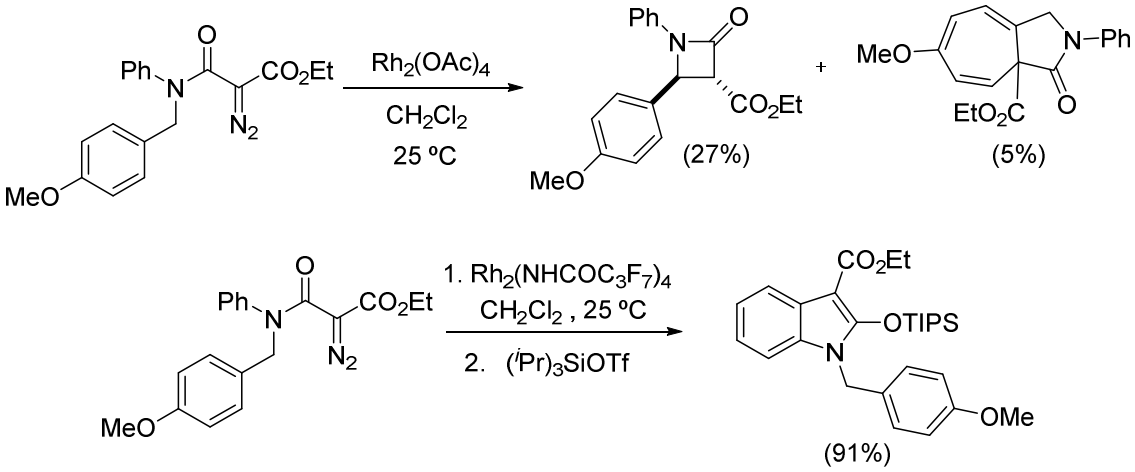
(66%, *cis*/*trans* 5.5 : 1)

Entre las reacciones de inserción intramolecular a partir de diazo derivados catalizadas por metales de transición, uno de los procesos más estudiados es la inserción a partir de α-diazo-α-(alcoxicarbonil)acetamidas. En esta reacción pueden formarse derivados de tipo indólico, si la inserción se produce en el enlace $C_{Ar}sp^2$-H, o β-lactamas si la reacción tiene lugar sobre

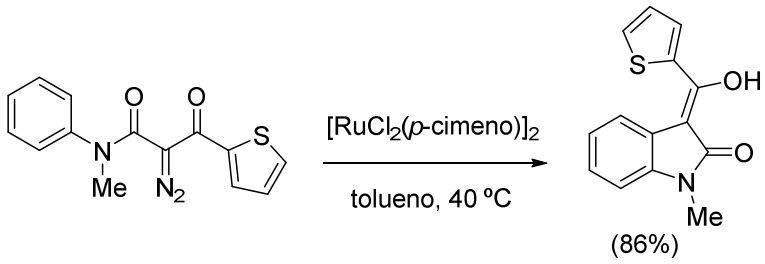
[56] (a) Solé, D.; Mariani, F.; Bennasar, M.-L.; Fernández, I. *Angew. Chem. Int. Ed.* **2016**, *55*, 6467. (b) Solé, D.; Amenta, A.; Mariani, F.; Bennasar, M.-L.; Fernández, I. *Adv. Synth. Catal.* **2017**, *359*, 3654.

el Csp^3-H.[57] La situselectividad de estas reacciones no depende solo del tipo de compuesto carbonílico, sino que también está gobernada por factores conformacionales, estéricos y electrónicos.[58]

Adicionalmente, en estas reacciones se ha demostrado que los ligandos sobre el metal de transición tienen un marcado efecto sobre el curso de la reacción. Así, por ejemplo, la utilización de ligandos de tipo carboxilato o carboxamida en los catalizadores de dirodio(II) ha permitido el desarrollo de transformaciones sumamente selectivas.[59]



Recientemente, también se han utilizado algunos catalizadores de Ru(II) para desarrollar diferentes metodologías para la síntesis de oxindoles mediante procesos de inserción de carbenos en enlaces $C_{Ar}sp^2$-H.[60]

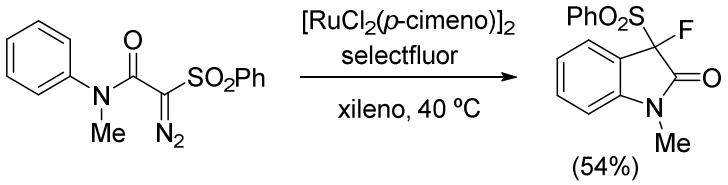


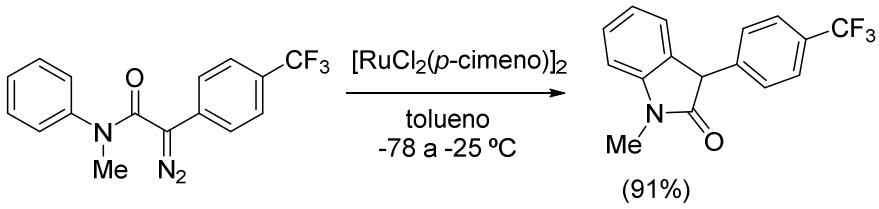
[57] (a) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2004**, 3773. (b) Ring, A.; Ford, A.; Maguire, A. R. *Tetrahedron Lett.,* **2016**, *57*, 5399.

[58] (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.,* **2003**, *103,* 2861. (b) Merlic, C. A.; Zechman, A. L. *Synthesis,* **2003**, 1137. (c) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.,* **2011**, *40*, 1857. (d) Zheng, C.; You, S.-L. *RSC Adv.,* **2014**, *4*, 6173. (e) DeAngelis, A.; Panish, R.; Fox, J. M. *Acc. Chem. Res.,* **2016**, *49*, 115.

[59] Para algunos ejemplos significativos, véase: (a) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.,* **1988**, *53*, 1017. (b) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.,* **1992**, *57*, 4404. (c) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P.; Padwa, A. *J. Org. Chem.,* **1994**, *59*, 2447. (d) Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheedan, S. M.; Marino, J. P.; Semones, M. A.; Padwa, A.; Richards, I. C. *Tetrahedron,* **1996**, *52*, 2489. (e) Qiu, H.; Li, M.; Jiang, L.-Q.; Lv, F.-P.; Zan, l.; Zhai, C.-W.; Doyle, M. P.; Hu, W.-H. *Nat. Chem.,* **2012**, *4*, 733.

[60] (a) Chan, W.-W.; Kwong, T.-L.; Yu, W.-Y. *Org. Biomol. Chem.,* **2012**, *10*, 3749. (b) Liu, N.; Tian, Q.-P.; Yang, Q.; Yang, S.-D. *Synlett*, **2016**, 2621. (c) Yamamoto, K.; Qureshi, Z.; Tsoung, J.; Pisella, G.; Lautens, M. *Org. Lett.,* **2016**, *18*, 4954.



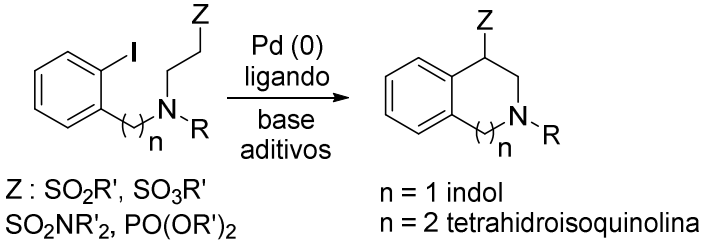


1.3. Objetivos de la Tesis Doctoral

Como continuación de los trabajos realizados durante los últimos años en nuestro grupo de investigación, en la presente tesis doctoral nos propusimos proseguir los estudios para incrementar la versatilidad de las reacciones catalizadas por paladio en la formación de enlaces carbono-carbono y, especialmente, en su utilización para la síntesis de heterociclos nitrogenados.

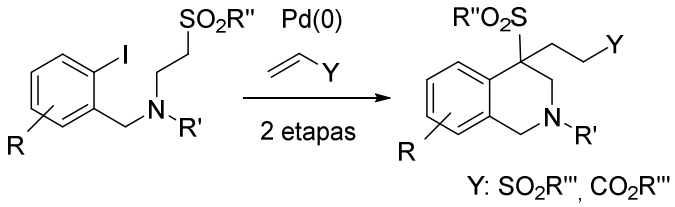
Considerando los precedentes expuestos en los apartados 1.1 y 1.2, en esta tesis doctoral decidimos evaluar la viabilidad de diversas metodologías de α-arilación basadas en reacciones catalizadas por paladio:

1) En la primera parte de la tesis, que abarca los capítulos 2-4, se estudiará la utilización de nucleófilos no carbonílicos en las reacciones de α-arilación intramolecular catalizadas por paladio a partir de sustratos nitrogenados. En concreto, se explorará la utilización de sulfonas, sulfonatos, sulfonamidas y fosfonatos como nucleófilos en las reacciones de acoplamiento intramolecular con haluros de arilo catalizadas por paladio. La utilización de estos nucleófilos se centrará en sistemas que, mediante la reacción de α-arilación, deberían proporcionar tetrahidroisoquinolinas o bien derivados indólicos.

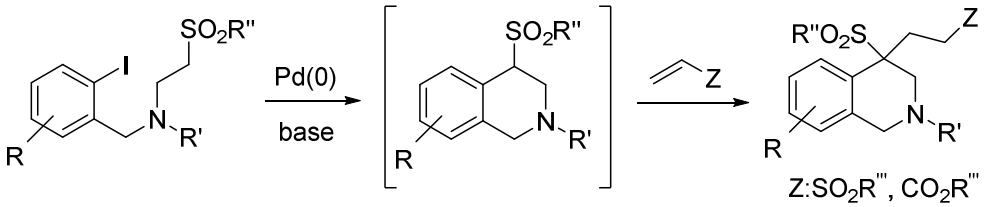


Asimismo, se estudiará la posibilidad de desarrollar procesos dominó combinando las anteriores reacciones de α-arilación con reacciones de adición de Michael. El objetivo último

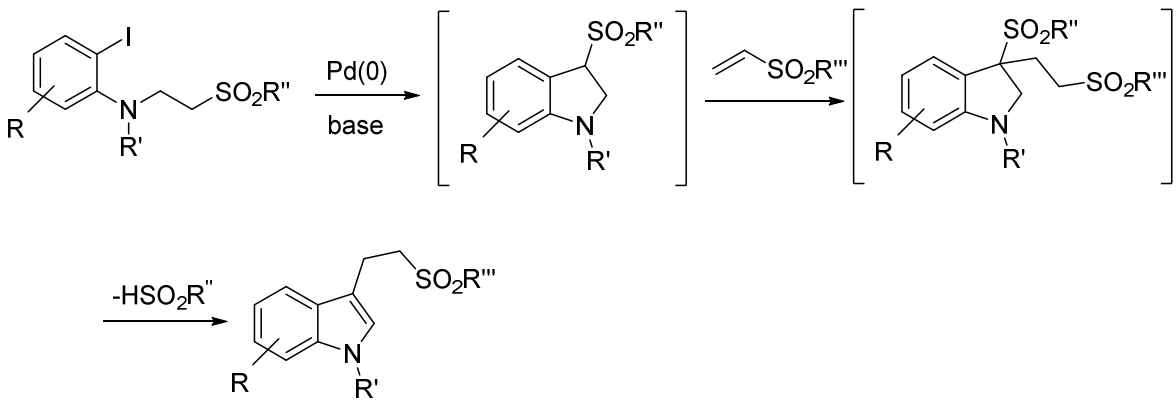
de este estudio es el desarrollo de metodologías de anulación que permitan la preparación de sistemas heterocíclicos complejos y con un elevado grado de funcionalización, a partir de sustratos sencillos y fácilmente accesibles.



En el capítulo 2 se estudiará la reacción de α-arilación intramolecular de β-amino sulfonas catalizada por paladio como metodología para la preparación de tetrahidroisoquinolinas. A continuación se abordará el desarrollo de procesos dominó en dos y tres etapas, mediante la combinación de la reacción de α-arilación con procesos de adición conjugada utilizando como aceptores de Michael vinil sulfonas o acrilatos de alquilo.



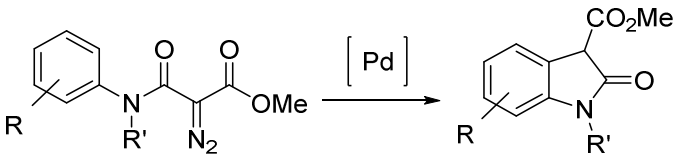
En el capítulo 3 se estudiará la reacción de α-arilación intramolecular de β-amino sulfonas catalizada por paladio como metodología para la preparación de indoles. Se abordará también el desarrollo de procesos dominó que combinan la reacción de α-arilación con la adición conjugada vinil sulfonas, y la posterior eliminación de ácido sulfínico. Adicionalmente, se realizará un estudio computacional (DFT) para intentar desentrañar el mecanismo de este tipo de reacciones.



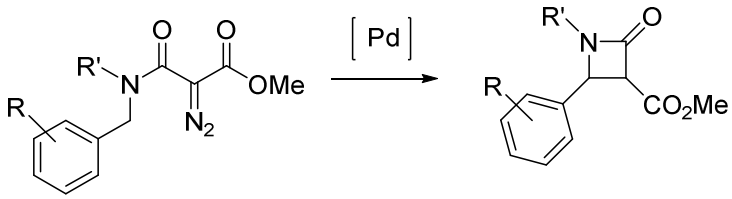
En el capítulo 4 los estudios experimentales y computacionales de las reacciones de α-arilación intramolecular catalizadas por paladio se extenderán a la utilización de sulfonatos, sulfonamidas y fosfonatos como nucleófilos. Se explorará asimismo la viabilidad de estos nucleófilos en el desarrollo de procesos dominó.

2) En la segunda parte de la tesis, que abarca los capítulos 5-6, se estudiará la utilización de complejos de paladio como catalizadores para promover la inserción de carbenos generados por descomposición de α-diazo-α-(metoxicarbonil)acetamidas.

En el capítulo 5 se estudiará la preparación de derivados oxindólicos mediante la reacción de inserción de carbenos generados por la descomposición de α-diazo-α-(metoxicarbonil)acetanilidas catalizada por paladio. Se llevarán a cabo también estudios computacionales para intentar clarificar el mecanismo de la reacción.



En el capítulo 6 se estudiará la reacción de inserción de carbenos generados por la descomposición de α-diazo-α-(metoxicarbonil)acetamidas catalizada por paladio como metodología para la preparación de β-lactamas. De nuevo se combinarán los trabajos experimentales con los estudios computacionales.



2

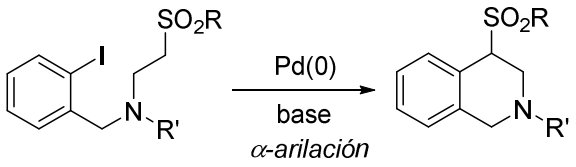
Pd(0)-catalyzed intramolecular α-arylation of sulfones: domino reactions in the synthesis of functionalized tetrahydroisoquinolines

(*Chem. Eur. J.* **2015**, *21*, 4580-4584)

Como continuación de los trabajos realizados en nuestro grupo de investigación acerca de las reacciones de acoplamiento intramolecular catalizadas por paladio entre haluros de arilo y nucleófilos de tipo enolato, en la presente tesis doctoral, nos propusimos extender los estudios de la reacción de α-arilación a la utilización de nucleófilos no carbonílicos.

La sulfona es una agrupación funcional utilizada con frecuencia como auxiliar en una gran variedad de metodologías sintéticas. Entre ellas, deben destacarse las reacciones de formación de enlaces C-C en las que el grupo sulfonilo actúa como grupo atrayente de electrones para favorecer la desprotonación de la posición α y generar un nucleófilo reactivo.[61]

A la vista de los precedentes comentados en el capítulo anterior, como primer objetivo de la tesis doctoral, decidimos explorar la utilización de sulfonas como nucleófilos en la reacción de α-arilación intramolecular catalizada por paladio. Los estudios se centraron inicialmente en la preparación de tetrahidroisoquinolinas ya que el núcleo de tetrahidroisoquinolina forma parte de la estructura de diversos productos con actividad farmacológica y de multitud de productos naturales.[62]



La utilización de las sulfonas como nucleófilos contribuiría a la generalización de la reacción de α-arilación intramolecular como metodología para la síntesis de heterociclos nitrogenados, y además daría acceso a productos con un tipo de funcionalización diferente. En este contexto, debe destacarse que la agrupación sulfona está presente en una gran variedad de productos con actividad biológica[63] y en algunos productos naturales.[64]

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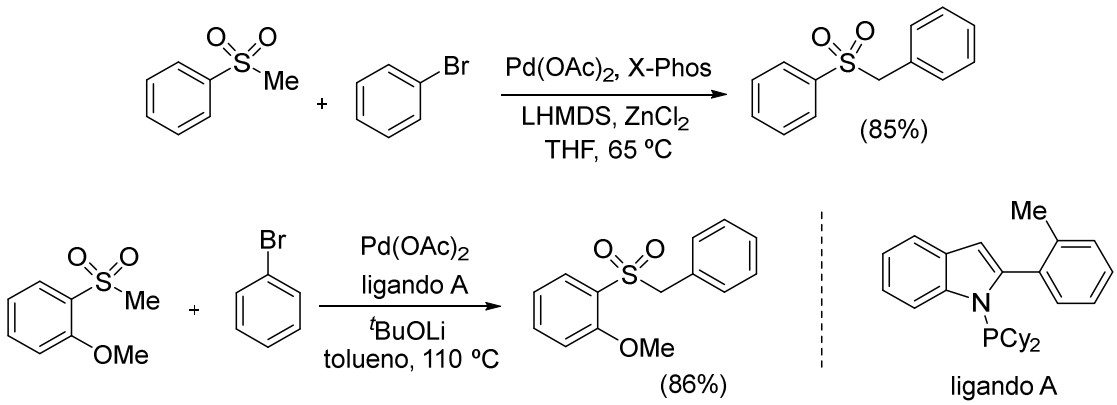
[61] (a) Simpkins, N. S. *Sulphones in Organic Synthesis*, Pergamon Press: Oxford, **1993**. (b) Alonso, D.; Fuensanta, M.; Nájera, C.; Varea, M. *Phosphorus, Sulfur and Silicon Relat. Elem.* **2005**, *180*, 1119. (c) Alba, A.-N. R.; Companyó, X.; Rios, R. *Chem. Soc. Rev.,* **2010**, *39*, 2018. (d) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixao, M. W.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2668.

[62] Para algunos artículos de revision recientes, véase: (a) Bentley, K. W. *Nat. Prod. Rep.,* **2006**, *23*, 444. (b) Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.,* **2008**, *37*, 2676. (c) Bhadra, K.; Kumar, G. S. *Mini-Reviews in Medicinal Chemistry*, **2010**, *10*, 1235. (d) Souto, A. L.; Tavares, J. F.; Sobral da Silva, M.; Diniz, M. F. F. M.; Filgueiras de Athayde-Filho, P.; Barbosa-Filho, J. M. *Molecules*, **2011**, *16*, 8515. (e) Alford, P. E. *Progress in Heterocyclic Chemistry* **2011**, *23*, 329.

[63] Véase por ejemplo: (a) Garuti, L.; Roberti, M.; Pizzirani, D.; Poggi, G. *Curr. Med. Chem.* **2005**, *4*, 167. (b) Sabatini, S.; Kaatz, G. W.; Rossolini, G. M.; Brandini, D.; Fravolini, A. *J. Med. Chem.* **2008**, *51*, 4321. (c) Sasikumar, T. K.; Qiang, L.; Burnett, D. A.; Cole, D.; Xu, R.; Li, H.; Greenlee, W. J.; Clader, J.; Zhang, L.; Hyde, L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3632. (d) Gautam, N.; Dixit, Y.; Dixit, R.; Gupta, S. K.; Gautam, D. C. *Phosphorus, Sulfur and Silicon Relat. Elem.* **2013**, *188*, 1127.

[64] (a) Prinsep, M. R.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **1991**, *54*, 1068. (b) Cao, S.; Foster, C.; Brisson, M.; Lazo, J. S.; Kingston, D. G. I. *Bioorg. Med. Chem.* **2005**, *13*, 999. (c) Yang, F.; Hamann, M. T.; Zou, Y.; Zhang, M.-Y.;

Cuando se inició esta tesis doctoral, la α-arilación intermolecular de sulfonas no activadas catalizada por paladio era ya una reacción conocida. Así, en 2010, Zhou había descrito la α-arilación intermolecular de metilsulfonas catalizada por paladio.[16] Posteriormente, en 2013, Walsh había desarrollado un procedimiento alternativo para la α-arilación intermolecular de metilsulfonas catalizada por paladio.[17] En ambos casos era necesaria la utilización de bases fuertes como LHMDS o ^{t}BuOLi.

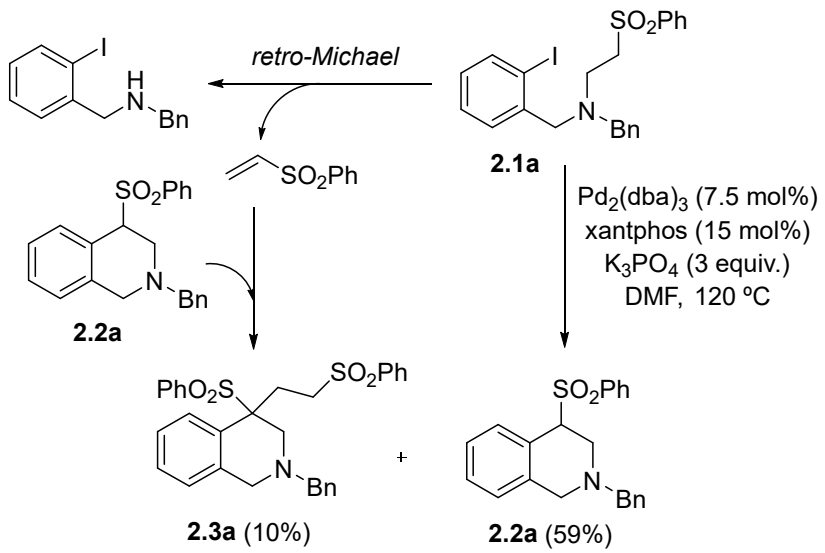


En consecuencia, el primer objetivo de este proyecto consistió en encontrar una combinación de catalizador, base y disolvente adecuada para la reacción de α-arilación intramolecular a partir de β-(2-yodobencilamino) sulfonas. La sulfona **2.1a** se escogió como modelo para la optimización de la reacción de α-arilación. Tal como se ha comentado, las reacciones de α-arilación intermolecular de sulfonas no activadas utilizaban LHMDS o ^{t}BuOLi como base, sin embargo, en nuestro caso la utilización de este tipo de bases quedaba excluida debido a la degradación de la agrupación de β-(2-yodobencilamino) sulfona mediante un proceso de tipo retro-aza-Michael.

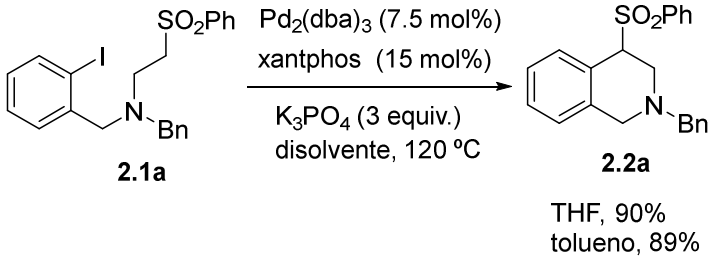
Después de ensayar diferentes combinaciones de fosfina, base y disolvente, encontramos que la utilización de $Pd_2(dba)_3$ en combinación con xantphos como ligando, K_3PO_4 como base y DMF como disolvente permitía llevar a cabo la reacción de α-arilación con un rendimiento aceptable. Sin embargo, en esta reacción también se aislaron cantidades significativas de la disulfona **2.3a**. Esta disulfona proviene de la adición conjugada del producto de α-arilación inicialmente formado a la fenil vinil sulfona,[65] que se forma mediante la fragmentación de tipo retro-aza-Michael del producto de partida en las condiciones básicas de la reacción.

Gong, X.-B.; Xiao, J.-R.; Chen, W.-S.; Lin, H.-W. *J. Nat. Prod.* **2012**, *75*, 774. (d) Stout, E. P.; Yu, L. C.; Molinski, T. F. *Eur. J. Org. Chem.* **2012**, 5131.

[65] Para la adición conjugada de nucleófilos carbonados a vinil sulfonas, véase: Xie, Y.-X.; Song, R.-J.; Liu, Y.; Wang, Z.-Q.; Xiang, J.-N.; Li, J.-H. *Synthesis*, **2014**, *46*, 203.



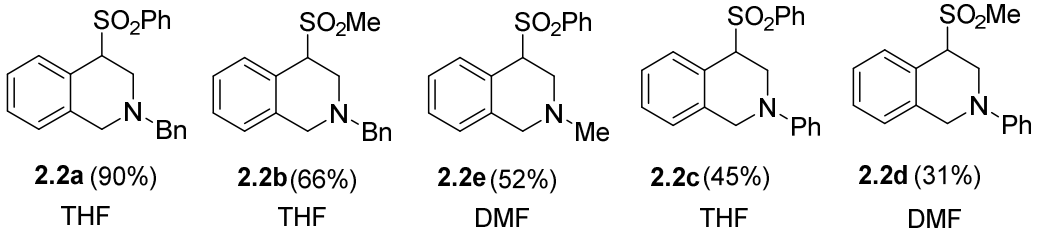
Afortunadamente, el cambio del disolvente por uno menos polar como tolueno o THF evitó la formación de este subproducto y permitió obtener la sulfona **2.2a** con un buen rendimiento.



Una vez disponíamos de unas condiciones adecuadas para la reacción de α-arilación, decidimos estudiar el alcance de esta reacción, extendiéndola a otras β-(2-yodobencilamino) sulfonas, en las que se modificaba el tipo de sulfona (fenil o metil sulfona) y el sustituyente sobre el átomo de nitrógeno (Bn, Me o Ph).

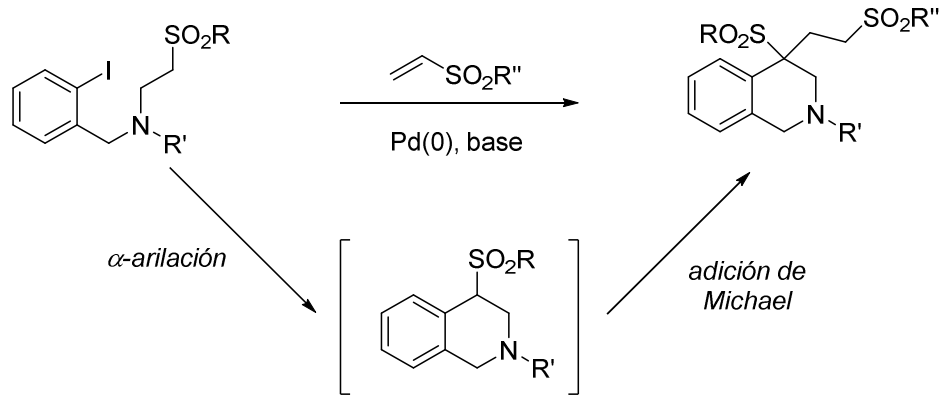
Como puede observarse en la siguiente figura, las metil sulfonas resultaron ser menos eficientes que las fenil sulfonas en la reacción de α-arilación (compárese **2.2a** con **2.2b** y **2.2c** con **2.2d**). Ello es debido, probablemente, a la menor acidez de los α-C-H de las metil sulfonas en relación a los α-C-H de las fenil sulfonas.

Por otro lado, las sulfonas con un grupo metilo o fenilo sobre el átomo de nitrógeno proporcionaron peores rendimientos en la reacción de α-arilación que los sustratos con un grupo bencilo. La peor combinación resultó ser la de una metil sulfona con un sustituyente fenilo sobre el nitrógeno, que proporcionó el producto de ciclación **2.2d** con un rendimiento del 31%. Como puede observarse en los resultados anteriores, la elección del disolvente para esta reacción depende del tipo de sustrato, obteniéndose los mejores resultados al utilizar THF o DMF.

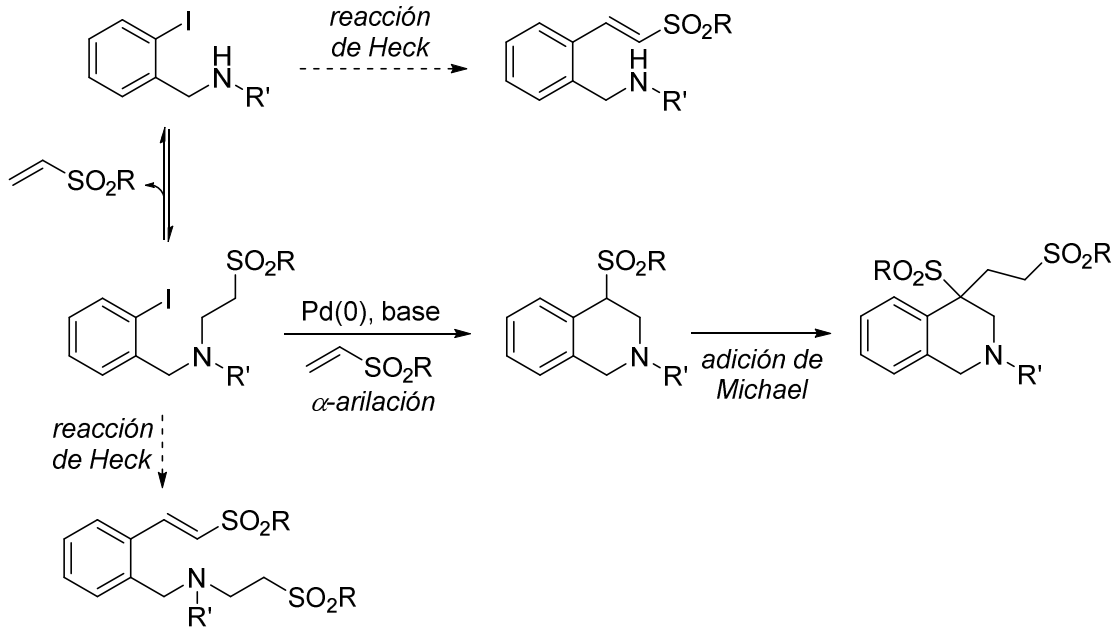


2.2a (90%) THF | **2.2b** (66%) THF | **2.2e** (52%) DMF | **2.2c** (45%) THF | **2.2d** (31%) DMF

Con toda la información que habíamos acumulado hasta el momento, decidimos explorar si era posible ensamblar, en un proceso *one pot*, la reacción de α-arilación con la adición conjugada del producto de ciclación a un aceptor de Michael.



El desarrollo de un proceso dominó de este tipo permitiría acceder a tetrahidroisoquinolinas con un elevado grado de funcionalización. Sin embargo, el desarrollo de un proceso tándem de este tipo no estaba exento de dificultades.



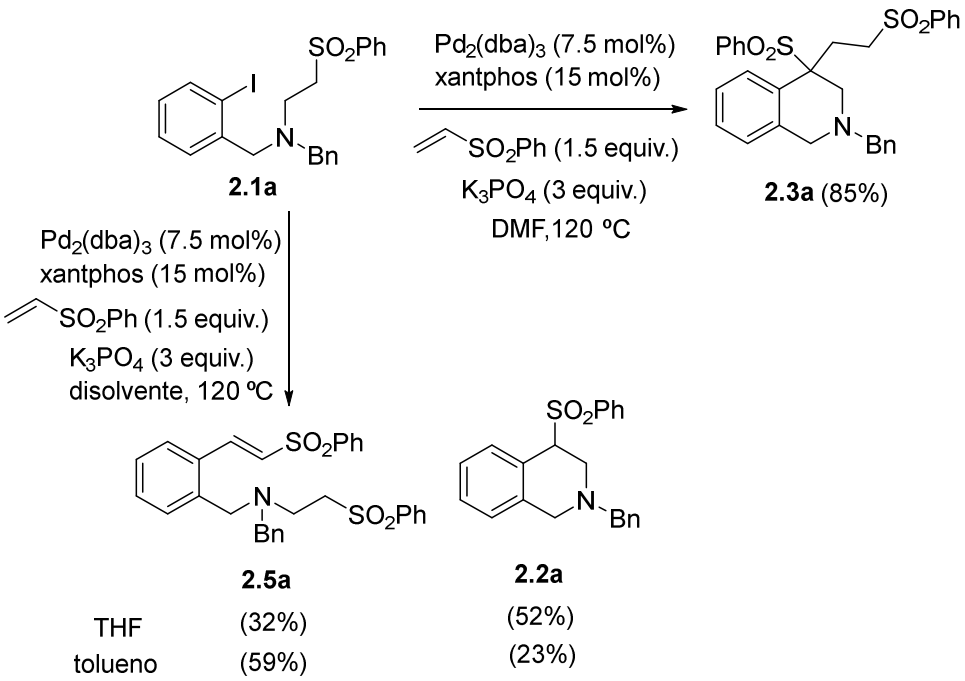
Por un lado, debía evitarse la descomposición de la β-(2-yodobencilamino) sulfona de partida que, tal como ya hemos comentado anteriormente, es relativamente fácil. Además, debían

encontrarse unas condiciones de reacción en las que la reacción de Heck intermolecular competitiva no interfiriera con la α-arilación catalizada por paladio.

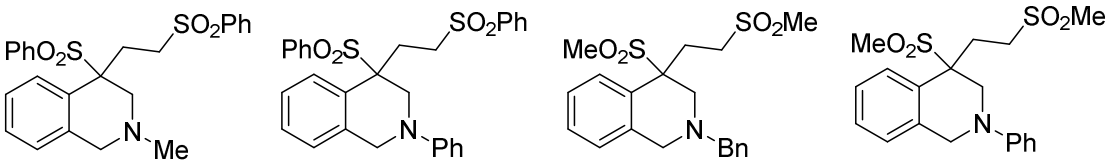
A pesar de todo ello, consideramos que la formación inesperada de cantidades significativas de la disulfona **2.3a** en algunos de los ensayos para la optimización de la reacción de α-arilación a partir de **2.1a** constituía un punto de partida muy prometedor para el desarrollo del proceso tándem deseado.

Desafortunadamente, al tratar la sulfona **2.1a** con $Pd_2(dba)_3$ y xantphos, en presencia de K_3PO_4 como base, fenil vinil sulfona como aceptor de Michael, y utilizando ya sea tolueno o THF como disolvente, el proceso tándem deseado no tuvo lugar. En estas condiciones de reacción se formaban mezclas del producto de α-arilación junto con el producto de la reacción de Heck entre el yoduro arílico y la fenil vinil sulfona.

Por suerte, la utilización de un disolvente más polar como la DMF permitió que el proceso tándem deseado tuviera lugar de manera satisfactoria y sin ninguna interferencia de la reacción de Heck, para proporcionar la disulfona **2.3a** con un buen rendimiento (85%). Utilizando estas mismas condiciones de reacción, pero sustituyendo el ligando xantphos por binap, la disulfona **2.3a** se obtuvo con un rendimiento del 71%.



El proceso tándem α-arilación/adición conjugada a vinil sulfonas permitió la preparación de diversas disulfonas que presentan la misma agrupación sulfona en las dos posiciones con rendimientos aceptables.



2.3e (54%) Xantphos

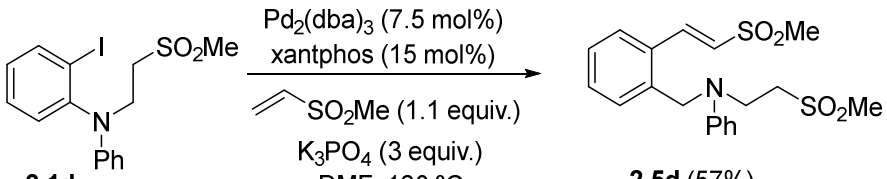
2.3c (68%) Binap

2.3b (56%) Xantphos

2.3d (42%) Binap

Como puede observarse, los procesos tándem que implican la reacción de una metil sulfona como nucleófilo y metil vinil sulfona como aceptor de Michael transcurren con rendimientos inferiores a los que suponen la α-arilación de una fenil sulfona y la adición conjugada a fenil vinil sulfona. Probablemente esto sea debido a la suma de dos factores. Por un lado a la menor acidez de los α-C-H de las metil sulfonas, que dificultaría tanto la reacción de α-arilación como la adición conjugada. Por otro a la menor electrofilia de la metil vinil sulfona que volvería a dificultar la etapa de adición de Michael.

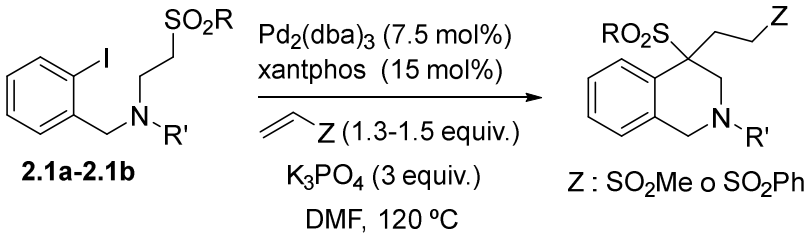
Es importante destacar, por último, que la utilización de xantphos como ligando no permitió la obtención de las disulfonas con un grupo fenilo sobre el átomo de nitrógeno (**2.3c** y **2.3d**) con un rendimiento aceptable. Esto se debe, fundamentalmente, a que al utilizar xantphos en las reacciones a partir de estos sustratos, la reacción de Heck deviene un proceso competitivo. Sin embargo, en ambos casos, el uso de binap como ligando permitió realizar sendos procesos tándem de manera satisfactoria.



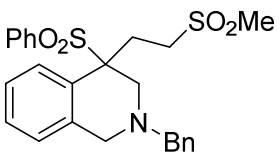
2.1d

2.5d (57%)

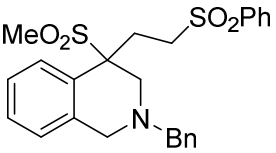
Adicionalmente, a partir de las sulfonas **2.1a** y **2.1b** también se desarrollaron procesos tándem α-arilación/adición conjugada "cruzados" en los que se utiliza un aceptor de Michael que posee un grupo atrayente de electrones distinto del que aparece en la sulfona de partida. En estos procesos tándem "cruzados" pueden utilizarse como aceptores de Michael metil vinil sulfona, fenil vinil sulfona o incluso acrilatos de alquilo.



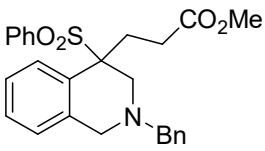
2.1a-2.1b



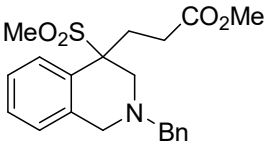
2.6 (65%)



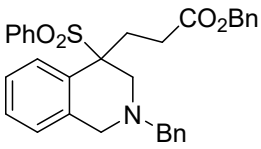
2.7 (62%)



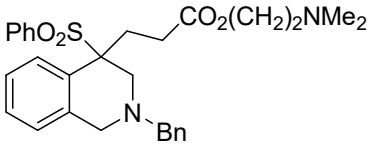
2.8 (63%)



2.11 (45%)

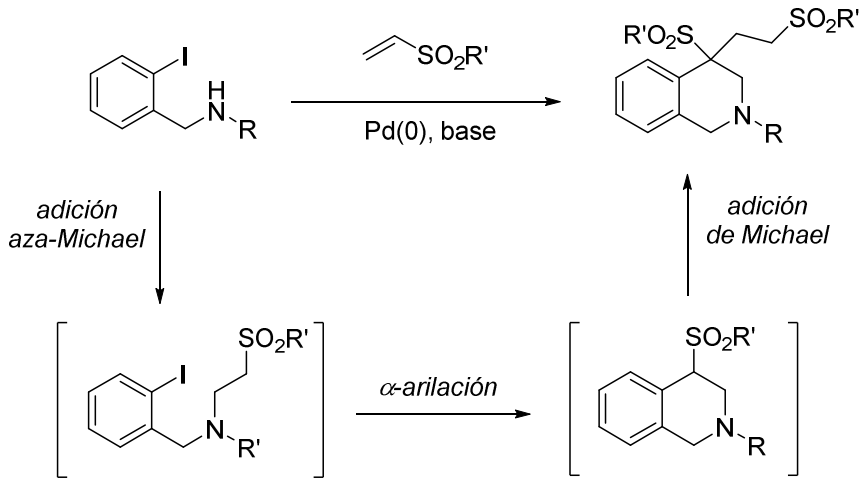


2.9 (40%)

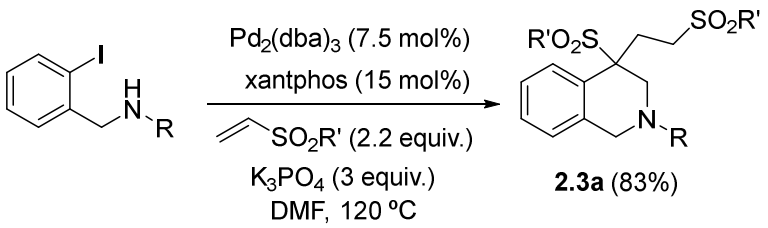


2.10 (35%)

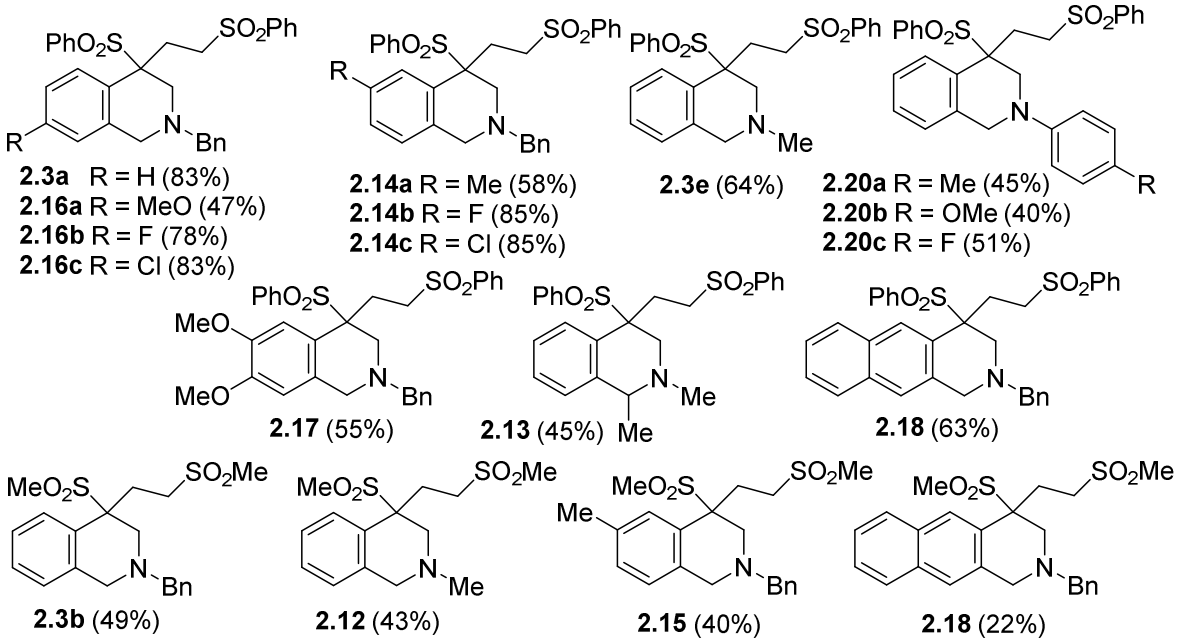
En este punto del trabajo, con el objetivo de simplificar la síntesis de las disulfonas "simétricamente sustituidas" (es decir, aquellas que presentan la misma agrupación sulfona en las dos posiciones) decidimos abordar el desarrollo de un proceso dominó en tres etapas. El proceso consistiría en una adición inicial de tipo aza-Michael de una 2-yodobencilamina a una vinil sulfona, seguida de la reacción de α-arilación catalizada por paladio y de la subsiguiente adición de Michael. El desarrollo de un proceso dominó de este tipo permitiría generar un grado de complejidad molecular considerable en una única operación sintética, minimizando la utilización de reactivos, disolventes, tiempo y energía.



Para nuestra satisfacción, el desarrollo del proceso dominó en tres etapas no requirió modificaciones substanciales de las condiciones de la reacción más allá de un pequeño ajuste en la cantidad del aceptor de Michael utilizado. Así, la reacción de la 2-yodobencilamina con 2,2 equivalentes de fenil vinil sulfona, en presencia de K_3PO_4 y utilizando la pareja $Pd_2(dba)_3$/xantphos como catalizador proporcionó la disulfona **2.3a** con un 83% de rendimiento.



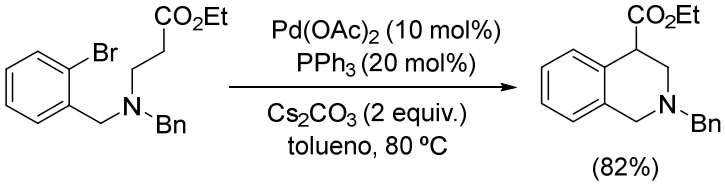
Los resultados recogidos en la siguiente figura ponen de manifiesto la versatilidad de nuestra propuesta. A partir de 2-yodobencilaminas con diferentes sustituyentes en el anillo aromático y utilizando fenil vinil sulfona o metil vinil sulfona como aceptores de Michael pudieron sintetizarse una gran diversidad de tetrahidroisoquinolinas. Los procesos en los que se utilizó fenil vinil sulfona proporcionaron mejores resultados que las reacciones análogas con metil vinil sulfona. Como ya se ha comentado, esto puede deberse a la mayor acidez de los α-C-H de las fenil sulfonas que facilitaría tanto la reacción de α-arilación como la adición de Michael, y a la mayor electrofilia de la fenil vinil sulfona que beneficiaría a las dos etapas de adición conjugada. El proceso dominó en tres etapas transcurre de manera efectiva a partir de 2-yodobencilaminas con sustituyentes donadores de electrones o atrayentes de electrones en el anillo aromático. Los resultados obtenidos parecen indicar que el proceso dominó se ve favorecido cuando hay sustituyentes donadores de electrones sobre el anillo aromático. Finalmente, el proceso dominó también permitió la preparación de sistemas tricíclicos de tipo 1,2,3,4-tetrahidrobenzo[*g*]isoquinolina.



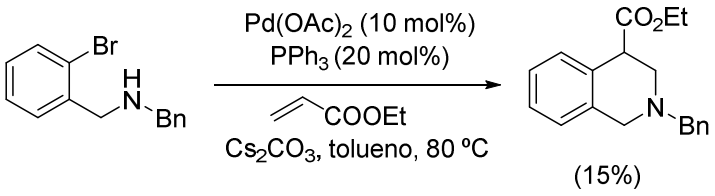
Como puede observarse, los rendimientos obtenidos en los procesos dominó en tres etapas son similares a los que se obtenían en el proceso tándem α-arilación/adición conjugada, lo que indicaría que la etapa inicial de adición de aza-Michael tiene lugar sin que haya una competencia significativa de la reacción de Heck intermolecular.

En este contexto debo destacar que, aunque se han descrito procesos *one pot* aza-Michael/α-arilación utilizando acrilatos como aceptores de Michael, hasta el momento no ha sido posible desarrollar un proceso dominó ya que, en presencia de acrilatos, la reacción de Heck es más rápida que la adición de aza-Michael.

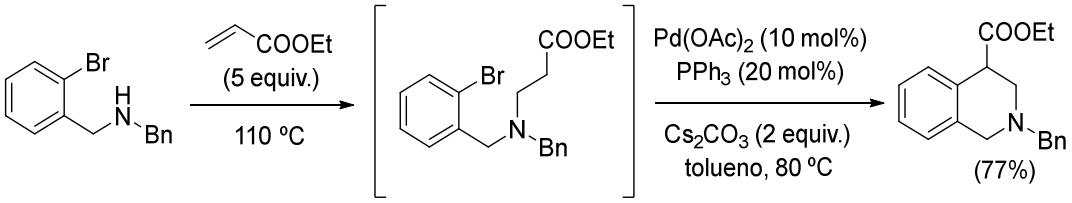
Así, tal y como se ha comentado anteriormente, Satyanarayana ha descrito la α-arilación intramolecular catalizada por paladio de β-amino ésteres como metodología para la síntesis de tetrahidroisoquinolinas.[35]



Sin embargo, todos sus intentos para desarrollar un proceso dominó eficiente acoplando una adición de aza-Michael previa, utilizando como aceptor de Michael un acrilato, con la reacción de α-arilación catalizada por paladio resultaron infructuosos. En las condiciones optimizadas para la reacción de α-arilación, la reacción de Heck intermolecular entre el haluro de arilo y el acrilato competía con la adición de aza-Michael, lo que llevaba a que la isoquinolina se obtuviera con muy bajo rendimiento.



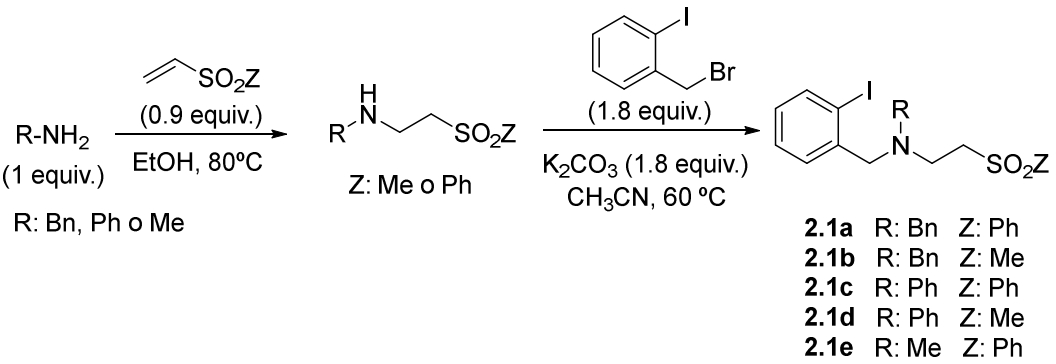
Finalmente, como alternativa al proceso dominó, los autores desarrollaron un proceso *one pot* que implicaba las reacciones de adición de aza-Michael y la α-arilación catalizada por paladio.[66]



[66] Reddy, A. G. K.; Krishna, J.; Satyanarayana, G. *Tetrahedron*. **2012,**68, 8003.

El éxito de los procesos dominó utilizando vinilsulfonas como aceptores de Michael que hemos descrito en este capítulo podría deberse en parte a la conocida dificultad que manifiestan las vinilsulfonas a experimentar la reacción de Heck.[67]

La síntesis de las sulfonas **2.1a-e**, que han sido utilizadas en este estudio, se ilustra en el siguiente esquema. Para una descripción más detallada véase el SI de la publicación *Chem. Eur. J.* **2015**, *21*, 4580-4584 que se adjunta en el anexo I-Publicaciones.



[67] Véase por ejemplo: Bachmann, D. G.; Wittwer, C. C.; Gillingham, D. G. *Adv. Synth. Catal.* **2013**, *355*, 3703.

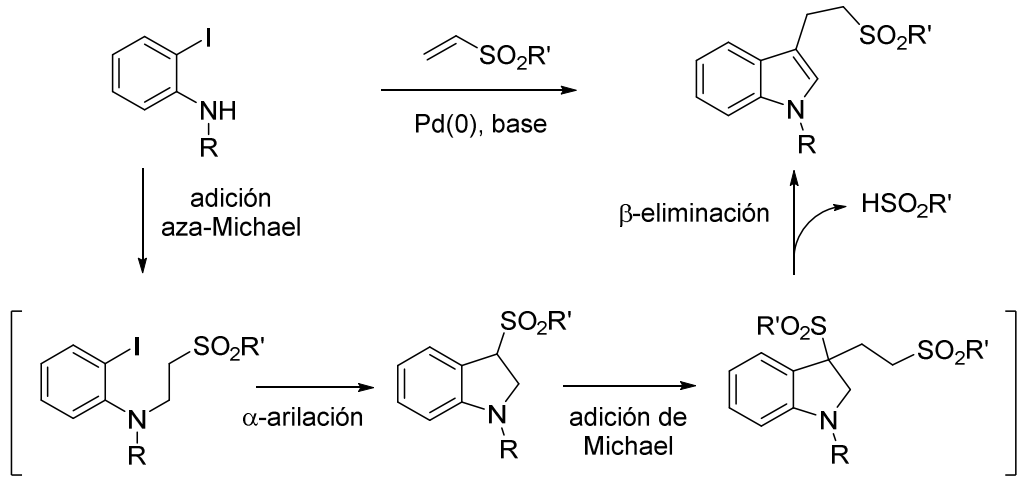
3

Pd-Catalyzed α-arylation of sulfones in a three-component synthesis of 3-[2-(phenyl/methylsulfonyl) ethyl]indoles

(*ACS Catal.* **2016,** *6*, 1691-1700)

En el capítulo anterior se ha estudiado la utilización de la reacción de α-arilación intramolecular catalizada por paladio de β-(2-yodobencilamino) sulfonas como metodología para la síntesis de tetrahidroisoquinolinas. Estos estudios han permitido el desarrollo de diversos procesos dominó en los que se combina la reacción de α-arilación con reacciones de adición conjugada. Estos procesos dominó han resultado ser sumamente eficientes para la síntesis de tetrahidroisoquinolinas con un elevado grado de funcionalización.

Como continuación de estos estudios, en el presente capítulo nos propusimos abordar la preparación de derivados indólicos mediante procesos dominó que se centraran, nuevamente, en la reacción de α-arilación y en la utilización simultánea de las sulfonas como electrófilos y como nucleófilos. Tal como se ilustra en la siguiente figura, la aplicación del proceso dominó en tres etapas que acabamos de comentar (aza-Michael/α-arilación/adición conjugada) a un sustrato de tipo 2-yodoanilina debería proporcionar un producto de tipo 3-sulfonilindolina. Sin embargo, es bien conocido que este tipo de sustratos experimentan fácilmente la eliminación de ácido sulfínico;[68] de manera que nosotros anticipábamos que en este caso tendría lugar un proceso dominó en cuatro etapas que proporcionaría directamente el indol correspondiente.



Este proceso dominó permitiría la preparación de 3-(sulfoniletil)indoles a partir de sustratos fácilmente accesibles.[69] Debe destacarse que entre los diferentes patrones de sustitución del

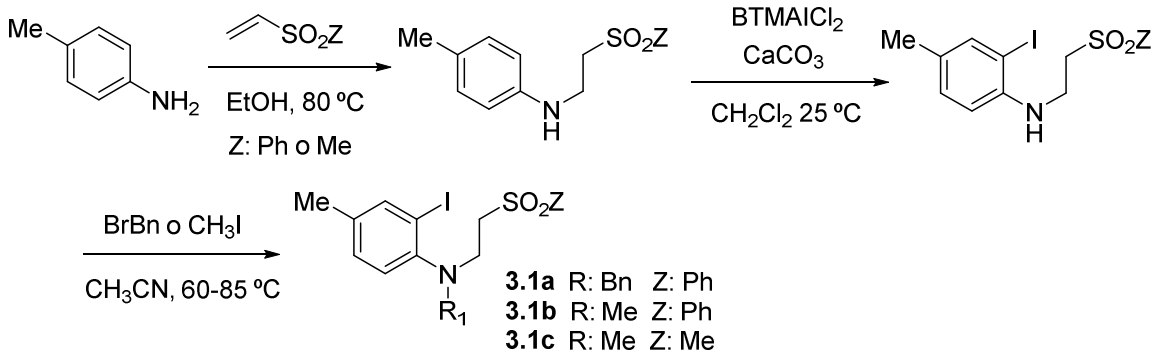
[68] (a) Babu, G.; Orita, A.; Otera, J. *Org. Lett*. **2005**, *7*, 4641. (b) Gray, V. J.; Wilden, J. D. *Tetrahedron Lett.* **2012**, *53*, 41.

[69] Para la síntesis de 3-[2-(fenilsulfonl)etil]indoles, véase: (a) Slätt, J.; Romero, I.; Bergman, J *Synthesis* **2004**, 2760. (b) Ma, S.; Yu, S.; Peng, Z.; Guo, H. *J. Org. Chem.* **2006**, *71*, 9865. (c) Bianchi, L.; Giorgi, G.; Maccagno, M.; Petrillo, G.; Scapolla, C.; Tavani, C. *Tetrahedron Lett.* **2012**, *53*, 752. (d) Nörder, A.; Warren, S. A.; Herdtweck, E.; Huber, S. M.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 13524. (e) Matsuzaki, K.; Furukawa, T.; Tokunaga, E.; Matsumoto, T.; Shiro, M.; Shibata, N. *Org. Lett.* **2013**, *15*, 3282.

núcleo indólico, el sistema de 3-indoliletilo se encuentra presente en numerosos productos con actividad biológica.[70]

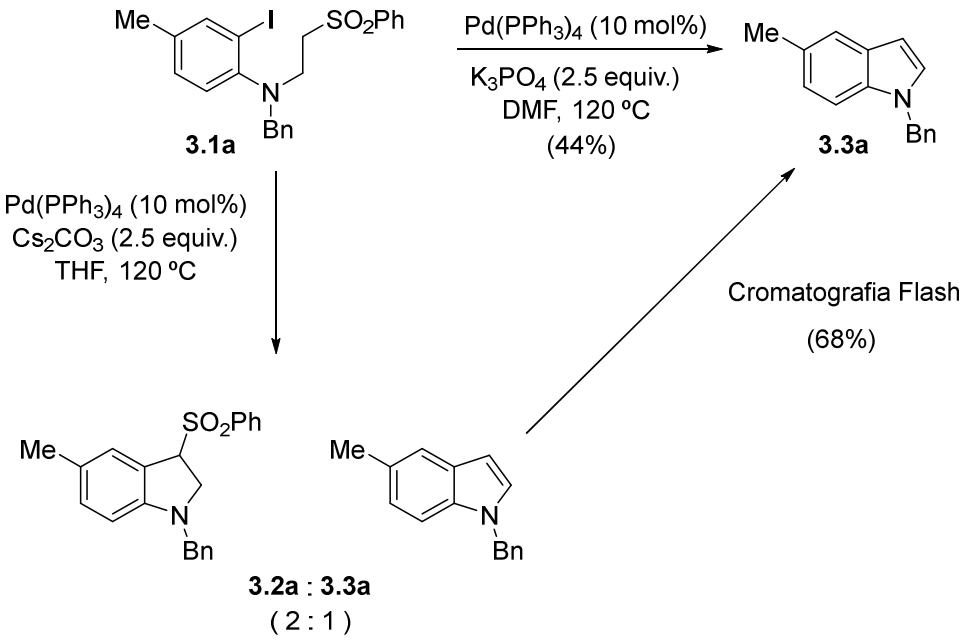
Tal y como se ha comentado anteriormente, durante el proceso de optimización de la secuencia dominó conducente a la formación de tetrahidroisoquinolinas, ya habíamos podido comprobar que el mayor desafío se encontraba en la etapa de α-arilación catalizada por paladio. En consecuencia, antes de abordar el nuevo proceso dominó decidimos realizar algunos estudios acerca de la reacción de α-arilación a partir de sustratos de tipo β-(2-yodoanilino) sulfona.

Para estos estudios de optimización se escogieron las sulfonas **3.1a**, **3.1b** y **3.1c**. La preparación de estas sulfonas se llevó a cabo siguiendo la secuencia de reacciones que se ilustra en la figura siguiente. Para una descripción más detallada véase el SI de la publicación *ACS Catal*. **2016**, *6*, 1691-1700, que se adjunta en el anexo I-Publicaciones.

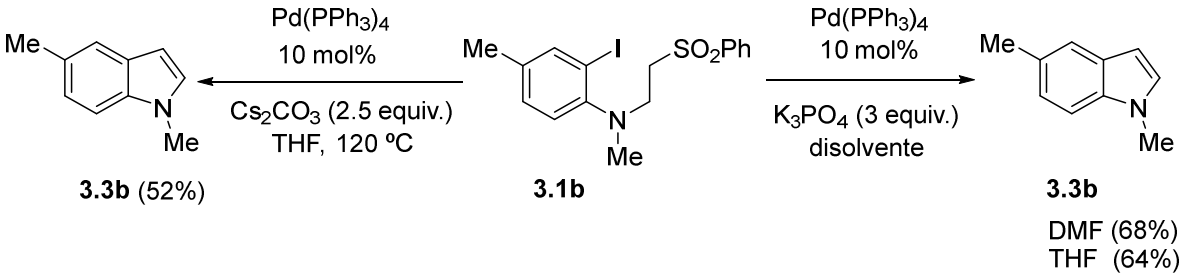


Los estudios acerca de la reacción de α-arilación se iniciaron con la sulfona **3.1a**. La utilización de la pareja $Pd_2(dba)_3$/xantphos, como catalizador, y K_3PO_4 como base en DMF, una combinación que había resultado útil para la α-arilación de los sustratos de tipo β-(2-yodobencilamino) sulfona, provocó la descomposición del producto de partida. En cambio, cuando la reacción se realizó utilizando $Pd(PPh_3)_4$ como catalizador se obtuvo el indol **3.3a** con un 44% de rendimiento. Este indol se forma mediante la β-eliminación de ácido fenilsulfínico a partir de la 3-(fenilsulfonil)indolina generada en la reacción de α-arilación. La utilización de Cs_2CO_3 como base y de un disolvente menos polar, como el THF, proporcionó una mezcla 2:1 de la indolina **3.2a** y del indol **3.3a**. Sin embargo, después de la purificación cromatográfica, sólo se aisló el indol **3.3a** con un rendimiento del 68%.

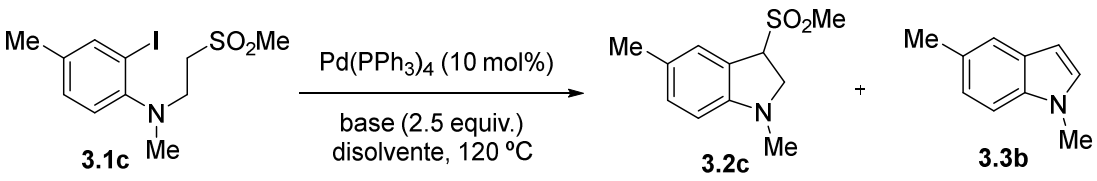
[70] Algunos 3-[2-(sulfonl)etil]indoles han mostrado una actividad antiinflamatoria interesante. Véase por ejemplo: McKew, J. C.; Foley, M. A.; Thakker, P.; Behnke, M. L.; Lovering, F. E.; Sum, F.-W.; Tam, S.; Wu, K.; Shen, M. W. H.; Zhang, W.; Gonzalez, M.; Liu, S.; Mahadevan, A.; Sard, H.; Khor S. P.; Clark, J. D. *J. Med. Chem.* **2006**, *49*, 135.



A partir de la β-aminosulfona **3.1b** y utilizando estas mismas condiciones de reacción se obtuvo el indol **3.3b**, también con un rendimiento moderado. La utilización de K_3PO_4 como base mejoró ligeramente el rendimiento de obtención de **3.3b**. Debo destacar que en ninguno de los ensayos de α-arilación a partir de **3.1b** se pudo observar la 3-(fenilsulfonil)indolina intermedia. Estos resultados indicaban que cuando el sustituyente sobre el átomo de nitrógeno es un metilo, la eliminación de ácido fenilsulfínico era mucho más rápida.



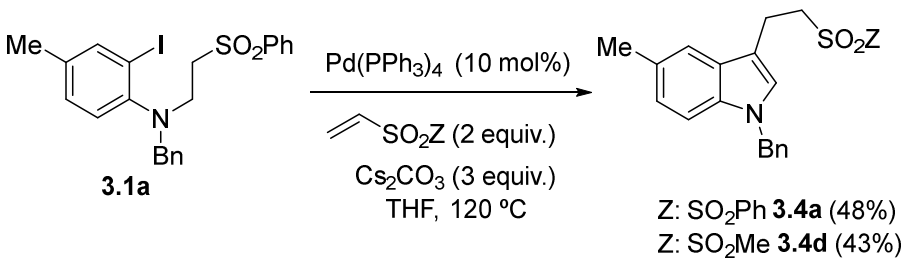
A partir de la β-aminosulfona **3.1c** se obtuvieron resultados similares. Sin embargo, el proceso de eliminación de ácido metilsulfínico resultó ser más lento. La utilización de K_3PO_4 como base y DMF como disolvente condujo a la formación del indol **3.3b** con un rendimiento moderado. El cambio de la DMF por un disolvente menos polar, como THF, resultó en la formación de mezclas de la indolina **3.2c** y del indol **3.3b**. Curiosamente, aunque la indolina **3.2c** también evolucionó en parte al indol **3.3b** durante el proceso de purificación, en este caso la indolina fue suficientemente estable como para poder ser aislada y caracterizada.



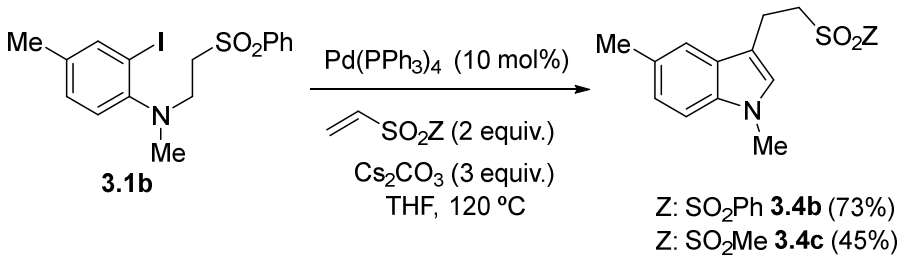
K_3PO_4, DMF	---	42%
K_3PO_4, THF	40%	41%
Cs_2CO_3, THF	7%	76%

Los estudios de optimización realizados con las sulfonas **3.1a**, **3.1b** y **3.1c** habían proporcionado como mejores condiciones para la reacción de α-arilación la utilización de $Pd(PPh_3)_4$ como catalizador, en presencia de K_3PO_4 o Cs_2CO_3 como base en el seno de THF a temperatura elevada. Los resultados obtenidos en estos estudios indicaban que tanto las metil sulfonas como las fenil sulfonas eran, *a priori,* buenos candidatos para desarrollar los procesos dominó, ya que las indolinas **3.2a** y **3.2c** sobrevivían en parte en las condiciones de la reacción de α-arilación. Por otro lado, el hecho de que la eliminación de ácido fenil sulfínico fuera mucho más rápida en las reacciones de la sulfona **3.1b**, que posee un sustituyente metilo sobre el nitrógeno, sugería que el desarrollo de un proceso dominó a partir de los sustratos *N*-metilados podía ser mucho más difícil.

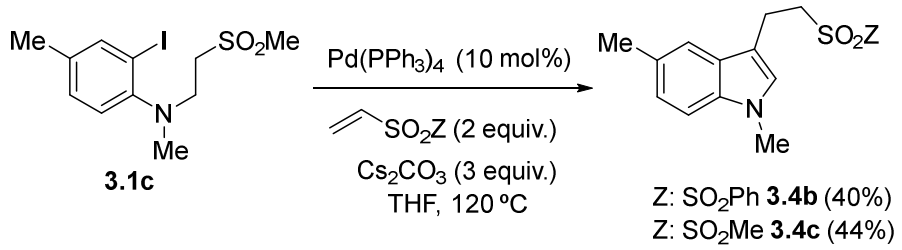
Con esta información, decidimos abordar el desarrollo de un proceso dominó en tres etapas combinando la reacción de α-arilación catalizada por paladio con la subsiguiente adición de Michael y con la eliminación de ácido sulfínico. Los estudios se iniciaron con la fenilsulfona **3.1a**. Utilizando las condiciones optimizadas para la reacción de α-arilación a partir de **3.1a** y en presencia de un exceso de fenil vinil sulfona o de metil vinil sulfona como aceptores de Michael se obtuvieron, respectivamente, los indoles **3.4a** y **3.4d** con rendimientos moderados.



De manera análoga, a partir de la fenilsulfona **3.1b**, que tiene un sustituyente metilo sobre el átomo de nitrógeno, y utilizando fenil vinil sulfona o metil vinil sulfona como aceptores de Michael se obtuvieron los indoles **3.4b** y **3.4c**.



Finalmente, a partir de la metilsulfona **3.1c** también fue posible desarrollar un proceso dominó en tres etapas, obteniéndose los indoles **3.4b** y **3.4c** al utilizar, respectivamente, fenil vinil sulfona y metil vinil sulfona como aceptores de Michael.

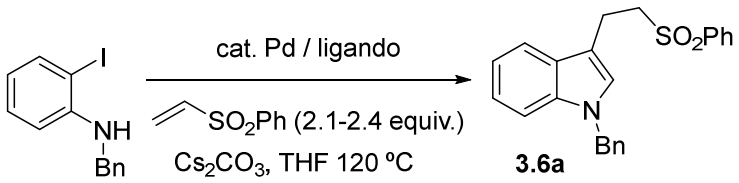


Estos resultados ponían de manifiesto que la reacción de Michael a partir de los intermedios de tipo 3-sulfonilindolina es un proceso más rápido que la β-eliminación del ácido sulfínico.

Los resultados obtenidos en el proceso dominó en 3 etapas constituían un buen punto de partida para abordar el desarrollo del proceso dominó en 4 etapas, inicialmente planteado como metodología para la síntesis de 3-[(sulfonil)etil]indoles a partir de 2-yodoanilinas. Los estudios para el desarrollo de este proceso se iniciaron utilizando la *N*-bencil-2-yodoanilina como producto de partida.

Sin embargo, cuando la *N*-bencil-2-yodoanilina se trató con $Pd(PPh_3)_4$, utilizando Cs_2CO_3 como base y en presencia de un exceso de fenil vinil sulfona, en THF como disolvente, se obtuvo el indol **3.6a** con un rendimiento tan solo del 33%. La utilización de un disolvente más polar, como la DMF, que en principio debería favorecer la reacción de aza-Michael inicial, proporcionó un resultado todavía peor.

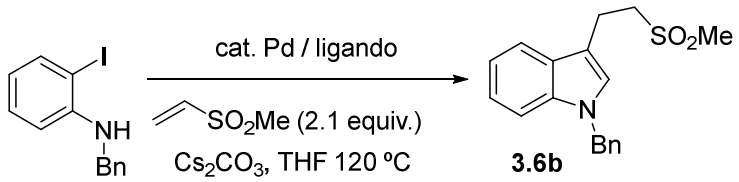
A la vista de estos resultados, se retomaron los estudios para optimizar el proceso dominó en cuatro etapas utilizando diferentes fosfinas como ligandos. Para nuestra satisfacción, al utilizar dppf, manteniendo la misma base y el mismo disolvente, se obtuvo el indol **3.6a** con un 80% de rendimiento.



3.6a

cat. Pd / ligando	
$Pd(PPh_3)_4$ (10 mol%)	33%
$Pd_2(dba)_3$ (7.5 mol%) dppf (15 mol%)	80%

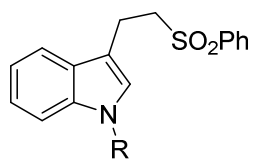
A continuación, se estudió el proceso dominó a partir de *N*-bencil-2-yodoanilina y utilizando metil vinil sulfona como aceptor de Michael. En presencia del ligando dppf, el indol **3.6b** se obtuvo con un modesto rendimiento del 33%. Sin embargo, al cambiar la fosfina por BINAP, el rendimiento de aislamiento de **3.6b** se incrementó hasta el 58%.



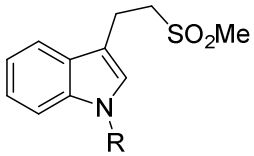
3.6b

cat. Pd / ligando	
$Pd_2(dba)_3$ (7.5 mol%) dppf (15 mol%)	33%
$Pd_2(dba)_3$ (7.5 mol%) BINAP (15 mol%)	58%

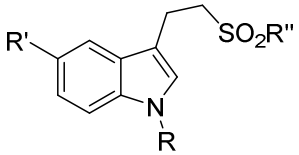
En este punto, decidimos estudiar qué efecto tenían los distintos sustituyentes en el anillo aromático y sobre el átomo de nitrógeno en el curso del proceso dominó. De nuevo se utilizaron tanto la fenil vinil sulfona como la metil vinil sulfona como aceptores de Michael.



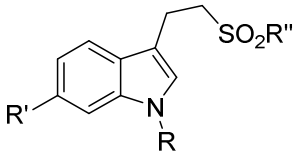
R: Bn (80%)
R: Me (71%)
R: Pr (69%)
R: Et (89%)



R: Bn (58%)
R: Me (45%)
R: Pr (67%)



R: Bn, R': Me, R'': Ph (86%)
R: Bn, R': Me, R'', Me (56%)
R: Bn, R': MeO, R'': Ph (79%)
R: Bn, R': MeO, R'': Me (57%)
R: Pr, R': MeO, R'': Ph (45%)
R: Bn, R', Cl, R'': Ph (85%)
R: Bn, R': Cl, R'': Me (70%)



R: Bn, R': Cl, R'': Ph (65%)
R: Bn, R': Cl, R'': Me (40%)
R: Bn, R': F, R'': Ph (75%)
R: Bn, R': F, R'': Me (73%)
R: Bn, R': CO_2Me, R'': Ph (72%)
R: Bn, R': CO_2Me, R'': Me (56%)
R: Pr, R': CO_2Me, R'': Ph (81%)

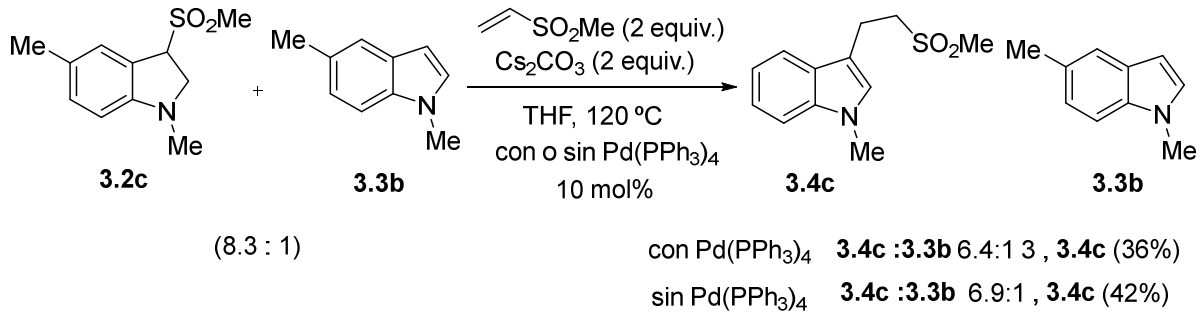
En general, los procesos dominó utilizando fenil vinil sulfona como aceptor de Michael proporcionaron mejores resultados, probablemente debido a la mayor acidez de los α-C-H, que favorece tanto la reacción de α-arilación como la adición de Michael.

El proceso dominó tolera, además de bencilo, la presencia de diferentes sustituyentes alquilo sobre el átomo de nitrógeno, tanto si se utiliza metil vinil sulfona como fenil vinil sulfona como aceptor de Michael.

Finalmente, el proceso dominó tolera la presencia de grupos tanto donadores de electrones como atrayentes de electrones sobre el anillo aromático.

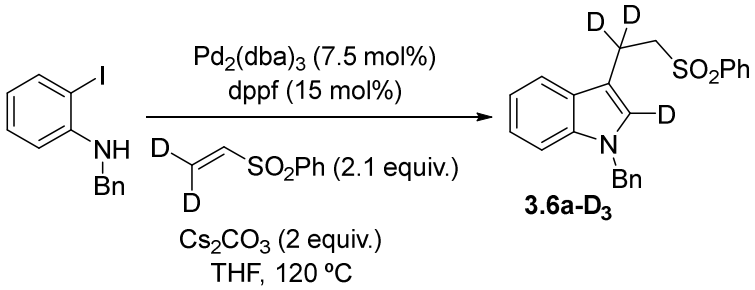
Para confirmar que la secuencia de transformaciones que tienen lugar durante el proceso dominó era la inicialmente propuesta (aza-Michael/α-arilación/adición conjugada/eliminación de ácido sulfínico) y establecer de manera inambigua el mecanismo de reacción, se llevaron a cabo diversos experimentos.

El tratamiento de una mezcla 8.3:1 de la indolina **3.2c** y del indol **3.3b** con metil vinil sulfona y Cs_2CO_3, tanto en presencia del catalizador de paladio como en su ausencia, proporcionó mezclas de los indoles **3.4c** y **3.3b**. Estos ensayos confirman que el indol **3.4c** se obtiene a partir de la indolina **3.2c** mediante un proceso de adición de Michael seguido de β-eliminación de ácido metilsulfínico no catalizado por paladio.



Adicionalmente, el tratamiento del indol **3.3b** con fenil vinil sulfona, utilizando Cs_2CO_3 como base y THF como disolvente, en presencia de $Pd(PPh_3)_4$ resultó en la recuperación del material de partida inalterado, descartando de nuevo una adición nucleófila mediada por paladio del indol a la vinil sulfona.

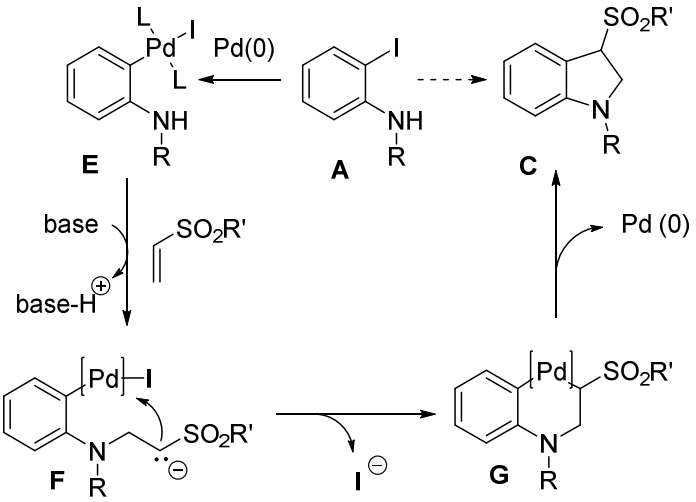
Por otro lado, se sintetizó la fenil vinil sulfona dideuterada en la posición β y se sometió al proceso dominó con la *N*-bencil-2-yodoanilina utilizando las condiciones de reacción optimizadas para el proceso en 4 etapas. En esta reacción se obtuvo el indol **3.6a-D_3**, que posee dos átomos de deuterio en la posición β de la sulfona y también presenta deuterada la posición C-2 del núcleo indólico.



Este resultado confirma de manera definitiva que el 3-(sulfoniletil)indol se forma mediante la secuencia de reacciones inicialmente propuesta: aza-Michael/α-arilación/adición conjugada/eliminación de ácido sulfínico.

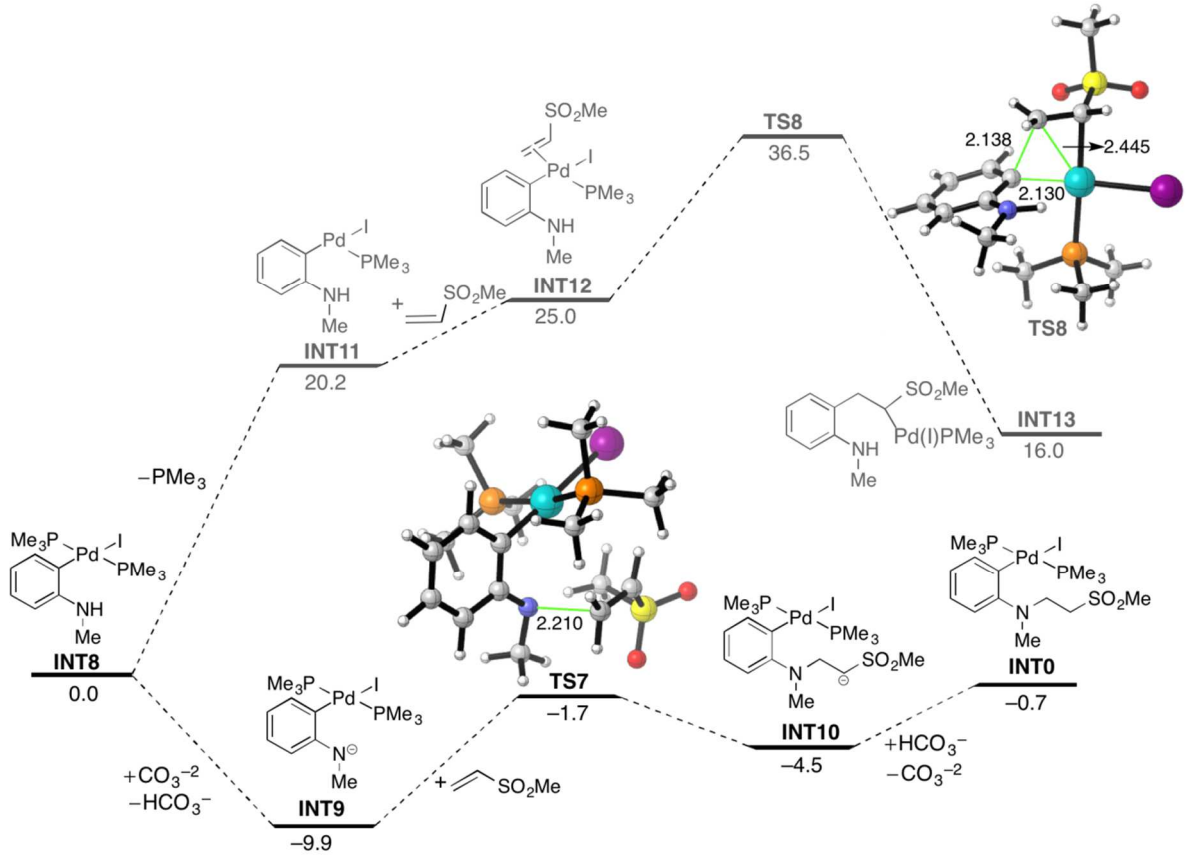
En este punto, creo conveniente realizar algunos comentarios adicionales acerca de los resultados obtenidos en el proceso dominó en cuatro etapas. Los buenos resultados obtenidos en este proceso dominó resultan sorprendentes si se comparan con los modestos resultados obtenidos previamente en la reacción de α-arilación y en el proceso dominó en tres etapas a partir, en ambos casos, de 2-yodoanilinas. Es especialmente sorprendente la no formación de productos resultantes de la posible reacción de Heck competitiva entre la agrupación de yoduro de arilo de los intermedios de reacción y la vinil sulfona. La ausencia de estos productos nos hizo pensar que el proceso dominó en cuatro etapas podía transcurrir a través de una secuencia de eventos ligeramente distinta de la inicialmente propuesta.

En la figura siguiente se resume la nueva propuesta mecanística para el inicio del proceso dominó a partir de las 2-yodoanilinas. Inicialmente tendría lugar la adición oxidante de la 2-yodoanilina al Pd (0). A continuación, se produciría la adición de aza-Michael a la vinil sulfona, que proporcionaría el intermedio **F**. Este intermedio evolucionaría al enolato de Pd(II) **G**. Finalmente, a partir de este intermedio, la formación del enlace carbono-carbono, tendría lugar mediante una reacción de eliminación reductora, que conduciría a la indolina **C** y liberaría el catalizador de paladio (0).



Para obtener más información acerca del mecanismo implicado en este proceso dominó se realizaron cálculos computacionales (DFT) en colaboración con el Dr. Israel Fernández de la Universidad Complutense de Madrid.

En primer lugar, se estudió el nuevo proceso de adición conjugada que se acaba de comentar. Para estos cálculos se utilizó como catalizador de paladio modelo el $Pd(PMe_3)_2$. De acuerdo con nuestros cálculos, después de la adición oxidante inicial, la reacción de aza-Michael tiene lugar de manera extraordinariamente favorable y sin que se produzca ninguna interferencia significativa de la posible reacción de Heck competitiva. En concreto, a partir del intermedio **INT8** y en presencia de CO_3^{-2} se produciría la desprotonación de la anilina, que conduciría a la formación del intermedio **INT9** en un proceso exergónico (ΔG_R = -9.9 Kcal/mol). A continuación, la adición conjugada proporcionaría el intermedio **INT10**. Esta etapa de reacción tendría lugar a través del estado de transición **TS7** que lleva asociado una energía de activación relativamente baja ($\Delta G^{\ddagger}$ = 8.2 Kcal/mol). Finalmente, la protonación del intermedio **INT10** proporcionaría el intermedio σ-arilpaladio(II) **INT0**, a partir del cual tendría lugar la reacción de α-arilación.



Por otro lado, como puede observarse en la figura anterior, el proceso de descomplejación de un ligando fosfina a partir del intermedio **INT8**, que es necesario para crear una vacante de coordinación que pueda ser ocupada por la metil vinil sulfona, y para que se produzca a continuación la reacción de Heck intermolecular, es muy endergónico (ΔG_R = 20.2 Kcal/mol). Esta

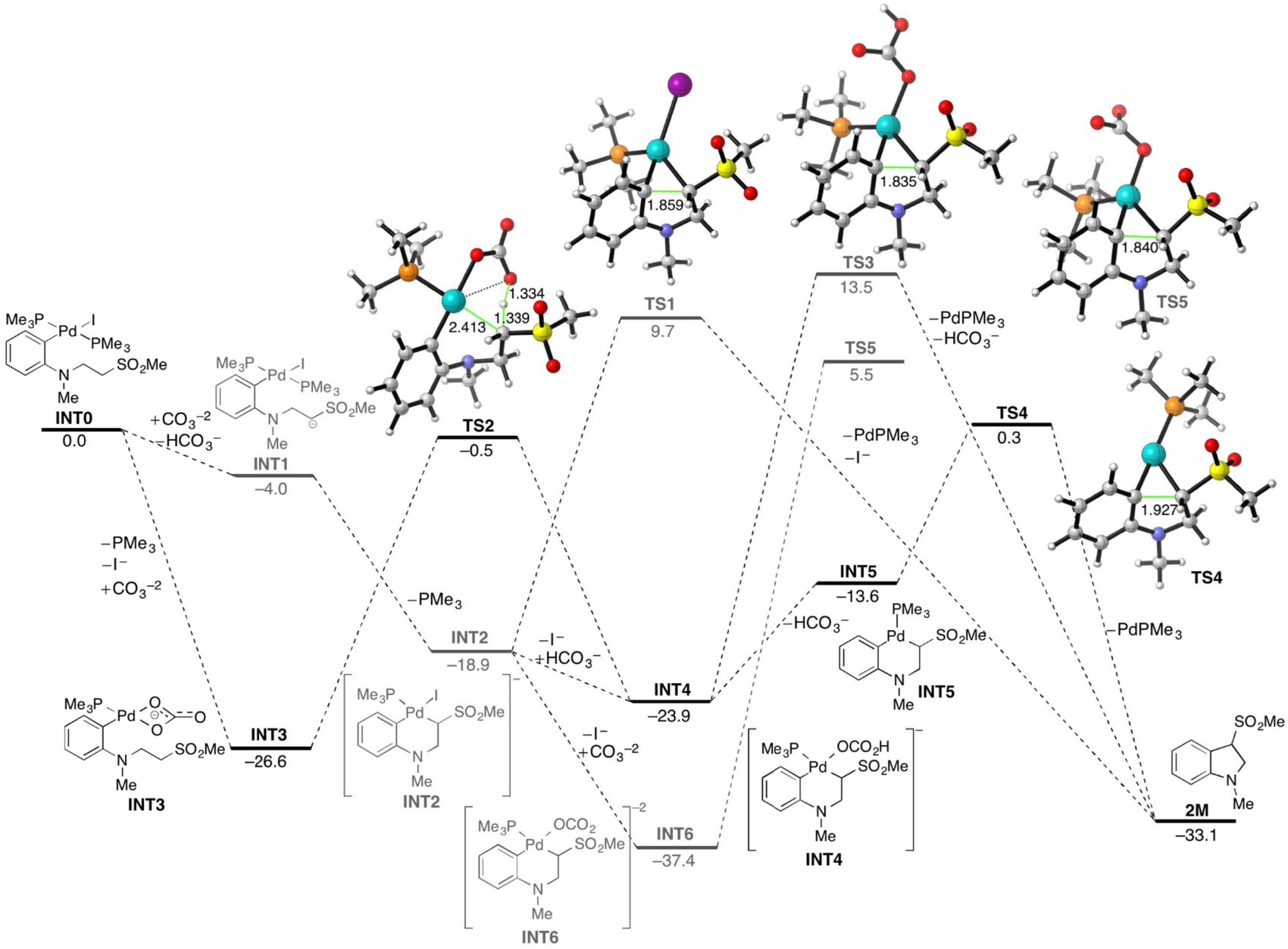
elevada endergonicidad hace que la reacción de Heck no pueda competir con la adición conjugada.

A continuación, se estudió computacionalmente la reacción de α-arilación. Los cálculos computacionales para el mecanismo aniónico mediado por base se iniciaron a partir del intermedio **INT0**. En presencia de CO_3^{-2}, el proceso de desprotonación para dar lugar al intermedio **INT1** es ligeramente exergónico, (ΔG_R = -4.0 Kcal/mol). A continuación tendría lugar la formación del intermedio **INT2** mediante la descomplejación de un ligando fosfina y la coordinación del carbanión al centro metálico. La ΔG_R calculada para este proceso es de -14.9 Kcal/mol. Finalmente, a partir del intermedio **INT2** tendría lugar la formación del enlace carbono-carbono para proporcionar la indolina **2M**. Este proceso, es claramente exergónico (ΔG_R = -14.2 Kcal/mol) y tendría lugar a través del estado de transición **TS1** ($\Delta G^{‡}$ = 28.6 Kcal/mol) que implica una reacción de eliminación reductora. Aunque la $\Delta G^{‡}$ computada para esta última etapa sea elevada, sería perfectamente compatible con una transformación que tiene lugar a una temperatura de 120 °C.

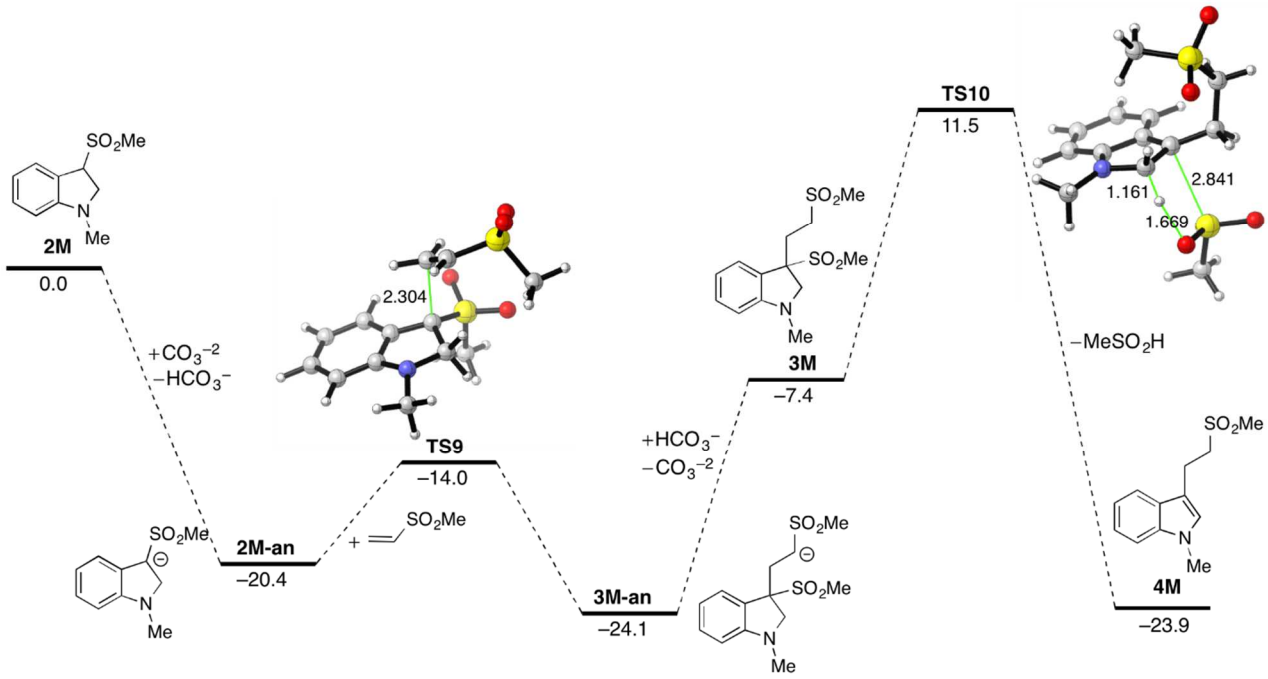
Sin embargo, también se estudió computacionalmente una vía alternativa para la formación de la indolina **2M** a partir del intermedio **INT0**. Según esta vía, la formación de la indolina **2M** tendría lugar mediante un proceso de desprotonación-metalación concertada mediada por CO_3^{-2}. En este caso, el intermedio **INT0** evolucionaria al intermedio **INT3** mediante la sustitución de los ligandos I^- y PPh_3 por parte del anión CO_3^{-2}. La ΔG_R computada para este proceso es de -26.6 Kcal/mol. A continuación, el intermedio **INT3** evolucionaria al intermedio **INT4** (ΔG_R = 2.7 Kcal/mol) a través del estado de transición **TS2** ($\Delta G^{‡}$ = 26.1 Kcal/mol). Esta etapa coincide con la migración concertada del hidrógeno desde la posición α de la sulfona al ligando carbonato y con la formación del enlace Pd-Csp^3. Como puede observarse para los dos mecanismos propuestos $\Delta G^{‡}_{TS1} > \Delta G^{‡}_{TS2}$.

La formación directa de la indolina **2M** a partir del intermedio **INT4** aunque termodinámicamente favorable (ΔG_R = -9.2 Kcal/mol) transcurre mediante el estado de transición **TS3**, que tiene asociada una barrera de activación elevada ($\Delta G^{‡}$ = 37.4 Kcal/mol). Una vía de reacción mucho más plausible implica la pérdida del ligando HCO_3^- para dar lugar al intermedio de paladio no saturado **INT5** (ΔG_R = 10.3 Kcal/mol), a partir del cual se forma finalmente la indolina **2M** (ΔG_R = -19.5 Kcal/mol) través del estado de transición **TS4** ($\Delta G^{‡}$ = 13.9 Kcal/mol desde **INT5**).

Según los ΔG_R i $\Delta G^{‡}$ calculados, aunque los dos mecanismos no son completamente excluyentes, la vía más probable sería **INT0**→**INT3**→**INT4**→**INT5**→**2M**.


INT0
0.0
INT1
–4.0
TS2
–0.5
TS1
9.7
TS3
13.5
TS5
5.5
TS4
0.3
INT5
–13.6
INT2
–18.9
INT4
–23.9
INT3
–26.6
INT6
–37.4
2M
–33.1
+CO3–2
–HCO3–
–PMe3
–I–
–PdPMe3
+HCO3–
1.334
1.339
2.413
1.859
1.835
1.840
1.927
INT2
INT3
INT4
INT5
INT6
TS4
TS5

Finalmente, también se estudió computacionalmente la etapa de adición conjugada de la sulfona a la vinil sulfona. A partir de la indolina **2M**, tendría lugar la desprotonación mediada por CO_3^{-2} de la posición α. La adición de Michael transcurre a través del estado de transición **TS9**. Este proceso es ligeramente exergónico (ΔG_R = -3.7 Kcal/mol) y tiene asociada una barrera de activación baja ($\Delta G^{\ddagger}$ = 6.4 Kcal/mol). La protonación del intermedio **3M-an** daría lugar a la formación del intermedio **3M**. Finalmente, la β-eliminación de ácido sulfínico a partir de **3M**, que implica la ruptura simultánea de los enlaces S-C y C-H, para dar lugar al indol **4M** es un proceso exergónico (ΔG = -16.5 Kcal/mol) que transcurre a través del estado de transición **TS10** ($\Delta G^{\ddagger}$ = 18.1 Kcal/mol).



A modo de resumen, en este capítulo se ha desarrollado un proceso dominó en 4 etapas para la síntesis de 3-[2-(fenil/metilsulfonil)etil]indoles a partir de 2-yodoanilinas. En este proceso la reacción de α-arilación intramolecular de sulfonas catalizada por Pd se combina con reacciones de tipo Michael. Los estudios computaciones DFT y los resultados experimentales obtenidos indican que la reacción aza-Michael inicial transcurre sin interferencia con la reacción de Heck competitiva. Por otro lado, aunque no puede excluirse completamente un mecanismo aniónico mediado por base, la reacción de α-arilación intramolecular catalizada por Pd ocurriría preferentemente mediante un mecanismo CMD mediado por CO_3^{-2}, seguido de una eliminación reductora. Finalmente, a partir de la 3-sulfonilindolina, la formación del 3-[2-(fenil/metilsulfonil)etil]indol tendría lugar mediante una adición de Michael, seguida de la β-eliminación concertada de ácido sulfínico.

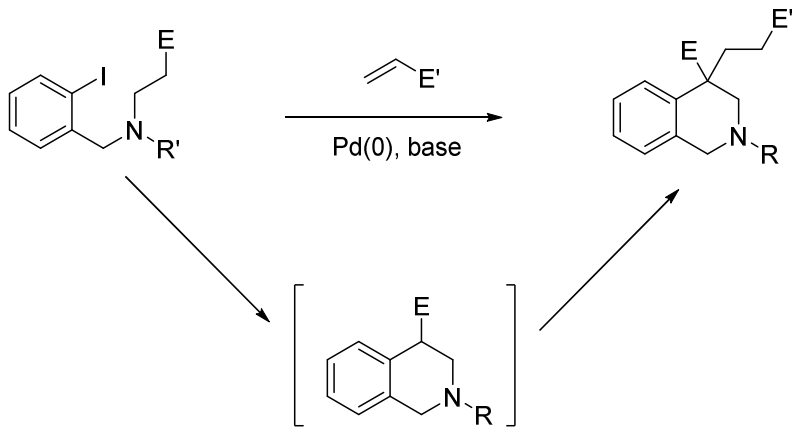
4

Exploring partners for the domino α-arylation/Michael addition reaction leading to tetrahydroisoquinolines

(*Eur. J. Org. Chem.* **2017,** 799-805)

En el presente capítulo, como continuación de los anteriores trabajos acerca de los procesos dominó basados en la combinación de la reacción de α-arilación de sulfonas catalizada por paladio con reacciones de tipo Michael a vinil sulfonas, decidimos explorar la utilización de otros grupos atrayentes de electrones. En concreto, nos propusimos extender los estudios de los procesos dominó a la utilización de ésteres sulfónicos, sulfonamidas y fosfonatos como nucleófilos en la reacción de α-arilación y como electrófilos en las reacciones de adición conjugada, en sistemas conducentes a la preparación de tetrahidroisoquinolinas. La utilización de estos nuevos grupos funcionales permitiría incrementar la versatilidad y el potencial de este tipo de procesos dominó y acceder a sustratos con nuevos grados de funcionalización.

Como primer objetivo, tal como se indica en la siguiente figura, nos propusimos desarrollar procesos dominó en dos etapas que combinara la reacción de α-arilación con la subsiguiente adición de Michael.

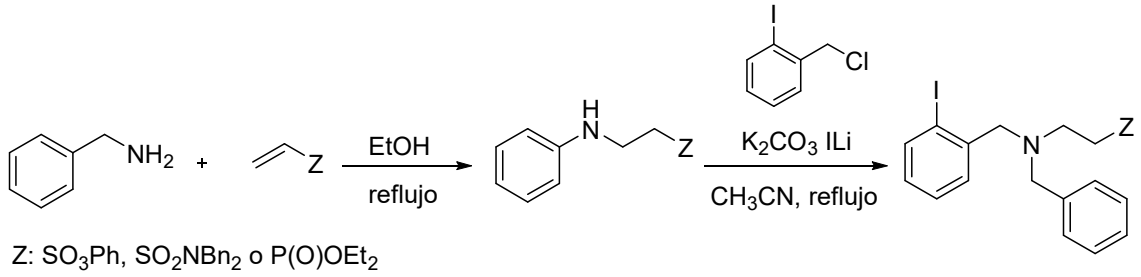


E, E' = SO_3Ph, SO_2NR_2, $PO(OEt)_2$

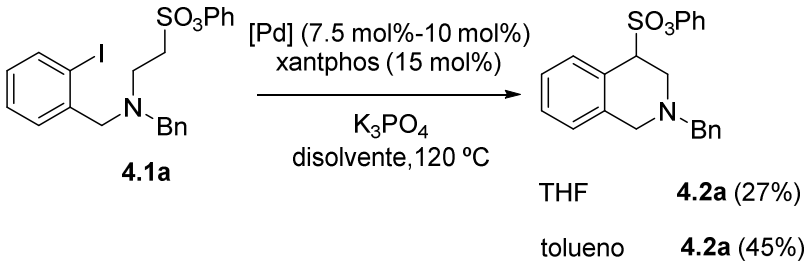
La menor acidez de los α-C-H de ésteres sulfónicos, sulfonamidas y fosfonatos,[28] que a priori podía dificultar tanto la reacción de α-arilación como la adición conjugada, constituía un reto considerable en el desarrollo de este tipo de procesos. En este sentido, se ha de comentar que no había precedentes acerca de la utilización de los ésteres sulfónicos como nucleófilos en las reacciones de α-arilación catalizadas por paladio. Por otro lado, aunque tanto las sulfonamidas[20-25] como los fosfonatos[27] habían sido utilizados en la versión intermolecular de la reacción de α-arilación, en ambos casos era necesaria la utilización de bases fuertes (por ejemplo, ^{t}BuOK o LHMDS). Sin embargo, nuestros anteriores estudios habían puesto de manifiesto que estas bases no eran adecuadas para la reacción de α-arilación intramolecular a partir de los sustratos objeto de nuestro estudio.

Al igual que en el anterior capítulo, en nuestro estudio para establecer el alcance y limitaciones de los nuevos procesos dominó, pretendíamos combinar el trabajo experimental con los cálculos computacionales.

En primer lugar, se estudió la reacción de α-arilación catalizada por paladio de forma aislada utilizando como modelos el éster sulfónico **4.1a**, la sulfonamida **4.1b** y **4.1d**, y el fosfonato **4.1c**. La preparación de estos compuestos se llevó a cabo tal como se indica en la figura siguiente. Para una descripción más detallada véase el SI de la publicación *Eur. J. Org. Chem.* **2017,** 799-805, que se adjunta en el anexo I-Publicaciones.

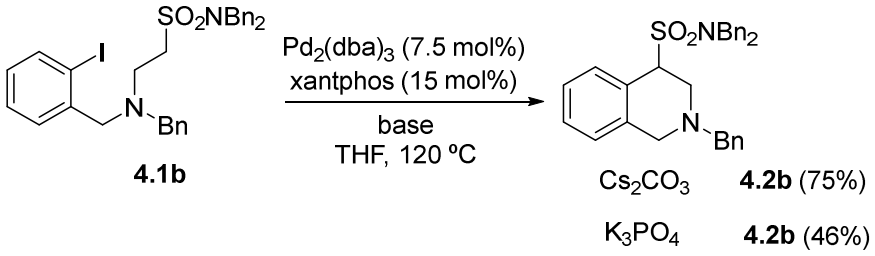


Como punto de partida para el estudio de la reacción de α-arilación, se utilizaron las condiciones optimizadas para la reacción a partir de las β-(2-yodobencilamino) sulfonas, muy relacionadas desde el punto de vista estructural con los nuevos sustratos. Estas condiciones implicaban la utilización de $Pd_2(dba)_3$ como precatalizador, xantphos como ligando, Cs_2CO_3 como base y THF como disolvente. En estas condiciones, a partir del éster sulfónico **4.1a** se obtuvo la tetrahidroisoquinolina **4.2a** con un modesto rendimiento del 27%.

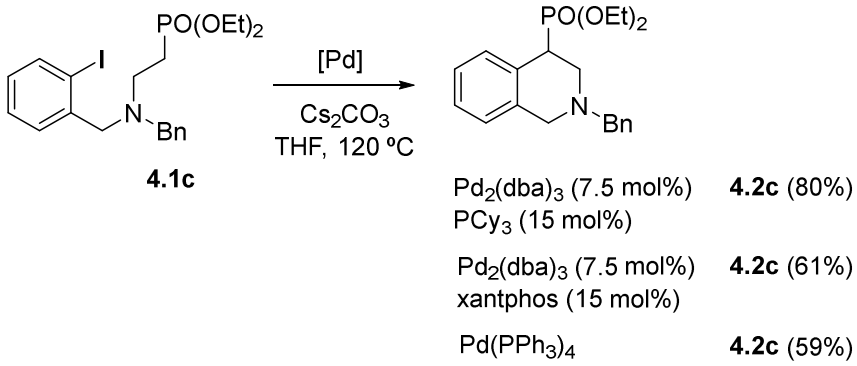


La utilización de $Pd(PPh_3)_4$ como precatalizador, xantphos como ligando y tolueno como disolvente permitió incrementar el rendimiento hasta el 45%. Los bajos rendimientos obtenidos en estas reacciones se deben en parte a la inestabilidad del producto de α-arilación, ya que **4.2a** descompone parcialmente durante la purificación cromatográfica.

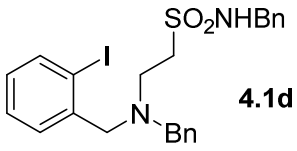
A partir de la sulfonamida **4.1b**, las condiciones optimizadas para la reacción de α-arilación a partir de las β-(2-yodobencilamino) sulfonas, permitieron la obtención de la tetrahidroisoquinolina **4.2b** con un 46% de rendimiento. El cambio de la base de K_3PO_4 a Cs_2CO_3 permitió mejorar el rendimiento de obtención de **4.2b**, incrementándolo hasta el 75%.



A partir del fosfonato **4.1c** las condiciones de reacción optimizadas con las sulfonas proporcionaron el producto de α-arilación **4.2c** con un rendimiento del 61%. Al cambiar el ligando xantphos por PPh_3 se obtuvo un resultado similar. Por el contrario, al utilizar una fosfina monodentada y más voluminosa como la PCy_3, la tetrahidroisoquinolina **4.2c** se obtuvo con un rendimiento del 80%.



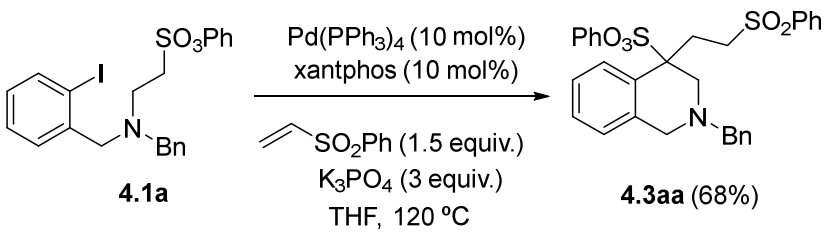
Finalmente, la sulfonamida **4.1d**, que posee un hidrógeno ácido sobre el nitrógeno de amida, resultó completamente no reactiva bajo cualquiera de las combinaciones de catalizador, base y disolvente utilizadas para promover la reacción de α-arilación.



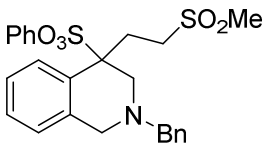
Estos resultados ponían de manifiesto que en la reacción de α-arilación intramolecular catalizada por Pd es posible utilizar nucleófilos derivados de ésteres sulfónicos, sulfonamidas disustituidas y fosfonatos. A continuación, decidimos explorar el desarrollo del proceso dominó en dos etapas inicialmente propuesto, combinando la reacción de α-arilación con la reacción de adición de Michael.

El tratamiento del éster sulfónico **4.1a** con fenil vinil sulfona en presencia de $Pd(PPh_3)_4$, xantphos como ligando, y K_3PO_4 como base en THF proporcionó el sulfonato **4.3aa** con un rendimiento del 68%. Al utilizar metil vinil sulfona como aceptor de Michael se obtuvo un resultado similar.

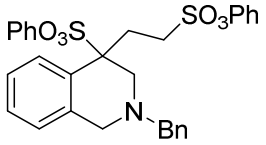
Aplicando las mismas condiciones de reacción, también pudieron realizarse los procesos dominó utilizando como aceptores de Michael un éster sulfónico α,β-insaturado (el etensulfonato de fenilo), acrilato de metilo y una sulfonamida α,β-insaturada (la *N*,*N*-dibenciletensulfonamida). Estas reacciones permitieron la preparación de los sulfonatos **4.3ad**, **4.3ac** y **4.3ae** con rendimientos moderados.



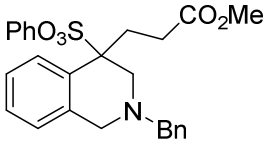
4.1a **4.3aa** (68%)



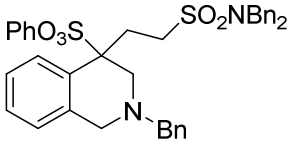
4.3ab (70%)



4.3ad (50%)



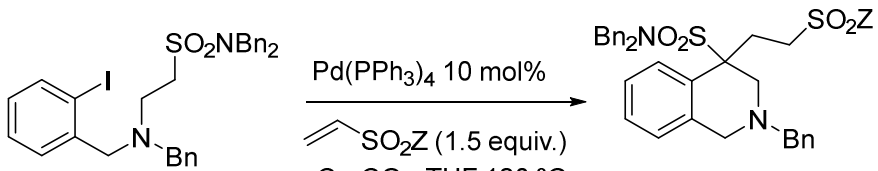
4.3ac (43%)



4.3ae (25%)

Con la excepción de la *N*,*N*-dibenciletensulfonamida, los rendimientos obtenidos en estos procesos dominó en 2 etapas fueron superiores a los rendimientos obtenidos en la reacción de α-arilación. Este hecho confirmaría que la degradación parcial del producto de α-arilación **4.2a** es la principal causa del modesto rendimiento obtenido en esa reacción.

A partir de la sulfonamida **4.1b**, utilizando como aceptores de Michael fenil vinil sulfona o bien metil vinil sulfona, se obtuvieron las sulfonamidas **4.3ba** y **4.3bb** con buenos rendimientos. Sin embargo, en presencia de acrilato de metilo, etensulfonato de fenilo o *N*,*N*-dibenciletensulfonamida no tuvo lugar ningún tipo de proceso dominó, aislándose únicamente el producto de α-arilación **4.2b**.



4.1b

Z: Ph **4.3ba** (74%)
Z: Me **4.3bb** (67%)

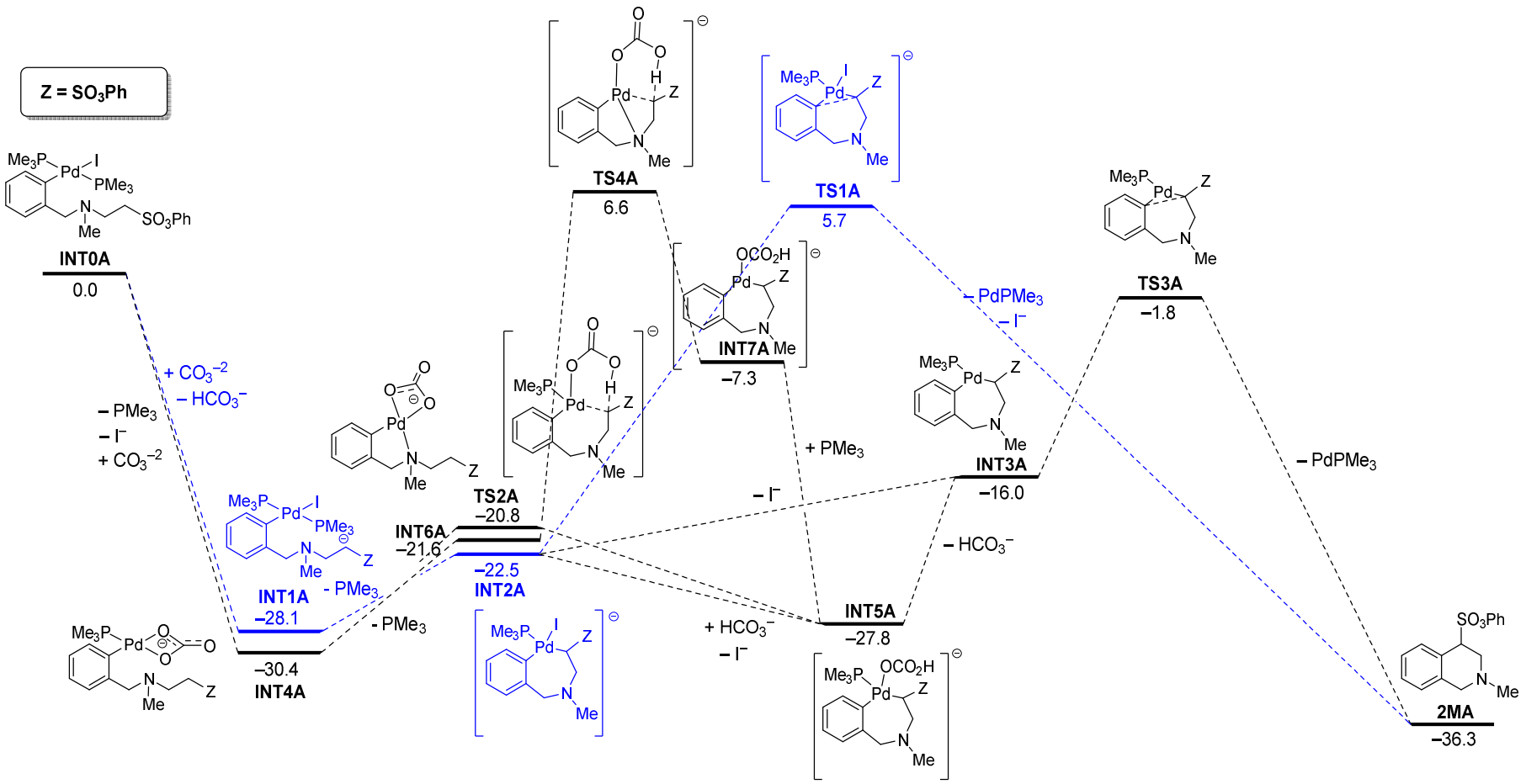
A partir del fosfonato **4.1c** y utilizando los anteriores aceptores de Michael tampoco se pudo desarrollar ningún proceso dominó, aislándose en todos los ensayos realizados el producto de α-arilación **4.2c**.

A la vista de estos resultados, del mismo modo que habíamos hecho en el capítulo anterior, se llevaron a cabo cálculos computacionales (DFT), en colaboración con el Dr. Israel Fernández de la Universidad Complutense de Madrid, con la intención de obtener información adicional acerca del mecanismo implicado en estas reacciones.

Los estudios previos acerca del proceso dominó para la formación de indoles, que he desarrollado en el capítulo 3, habían puesto de manifiesto que eran posibles dos mecanismos alternativos para la reacción de α-arilación de sulfonas catalizada por paladio. El primero de ellos implicaría un mecanismo aniónico mediado por base, el segundo un mecanismo de deprotonación-metalación concertada (CMD) promovido por el ligando CO_3^{2-}.

La competencia entre ambos procesos también se estudió computacionalmente en las reacciones de α-arilación conducentes a la formación de tetrahidroisoquinolinas a partir de ésteres sulfónicos, sulfonamidas y fosfonatos. Para ello, en los tres casos, se utilizaron sustratos modelo en los que el sustituyente bencilo del átomo de nitrógeno se ha sustituido por un metilo, y se utilizó $Pd(PMe_3)_2$ como catalizador modelo.

En la figura siguiente, se incluye el perfil de reacción a partir de **INT0A**, el primer intermedio generado en la reacción a partir del éster sulfónico modelo. La α-arilación aniónica mediada por base (en azul en la figura) se inicia con la deprotonación de **INT0A** para dar el intermedio **INT1A**. Este proceso es altamente exergónico (ΔG_R= -28.1 Kcal/mol). A continuación, este intermedio evolucionaría para dar lugar al intermedio **INT2A**. Este proceso, ligeramente endergónico (ΔG_R= 5.6 Kcal/mol), está asociado a la sustitución de un ligando de tipo fosfina por el carbanión. Esta coordinación intramolecular está asociada a una energía de activación baja ($\Delta G^{\ddagger}$< 10 Kcal/mol) y, en consecuencia, no es la etapa limitante de la transformación. Finalmente, a partir del intermedio **INT2A** tendría lugar la formación del enlace carbono-carbono, a través del estado de transición **TS1A**, para proporcionar el producto de α-arilación **2MA**. Esta transformación es exergónica (ΔG_R= -13.8 Kcal/mol) y está asociada a una energía de activación relativamente alta ($\Delta G^{\ddagger}$= 28.2 Kcal/mol). De manera alternativa, a partir de **INT2A**, la descoordinación del yoduro conduciría a la formación del complejo de paladio no saturado **INT3A** (ΔG_R= 6.5 Kcal/mol). Finalmente, a partir de este intermedio, la formación del producto de α-arilación **2MA** tendría lugar a través del estado de transición **TS3A**, con una energía de activación mucho más baja ($\Delta G^{\ddagger}$= 14.2 Kcal/mol).


Z = SO3Ph
INT0A
0.0
– PMe3
– I–
+ CO3–2
+ CO3–2
– HCO3–
INT1A
–28.1
- PMe3
–30.4
INT4A
- PMe3
TS2A
–20.8
INT6A
–21.6
–22.5
INT2A
TS4A
6.6
TS1A
5.7
INT7A
–7.3
– PdPMe3
– I–
+ PMe3
– I–
INT3A
–16.0
– HCO3–
+ HCO3–
– I–
INT5A
–27.8
TS3A
–1.8
– PdPMe3
2MA
–36.3

El proceso CMD (en negro en la figura) se iniciaría a partir del intermedio **INT0A** por sustitución del yoduro y de una fosfina por el ligando bidentado CO_3^{2-} para dar lugar al intermedio aniónico **INT4A** (ΔG_R= -30.4 Kcal/mol). A continuación, tendría lugar el proceso concertado de migración del átomo de hidrógeno hacia el carbonato y formación simultánea del enlace Pd-carbono (proceso CMD) para dar lugar al intermedio **INT5A**. Este proceso transcurre a través del estado de transición **TS2A**, es ligeramente endergónico (ΔG_R= 2.6 Kcal/mol) y está asociado a una barrera de activación de 9.6 Kcal/mol. A partir de este intermedio, la pérdida de HCO_3^- conduciría a la formación del intermedio **INT3A** (ΔG_R= 11.8 Kcal/mol), que finalmente daría lugar a la formación del compuesto **2MA** a través del estado de transición **TS3A**.

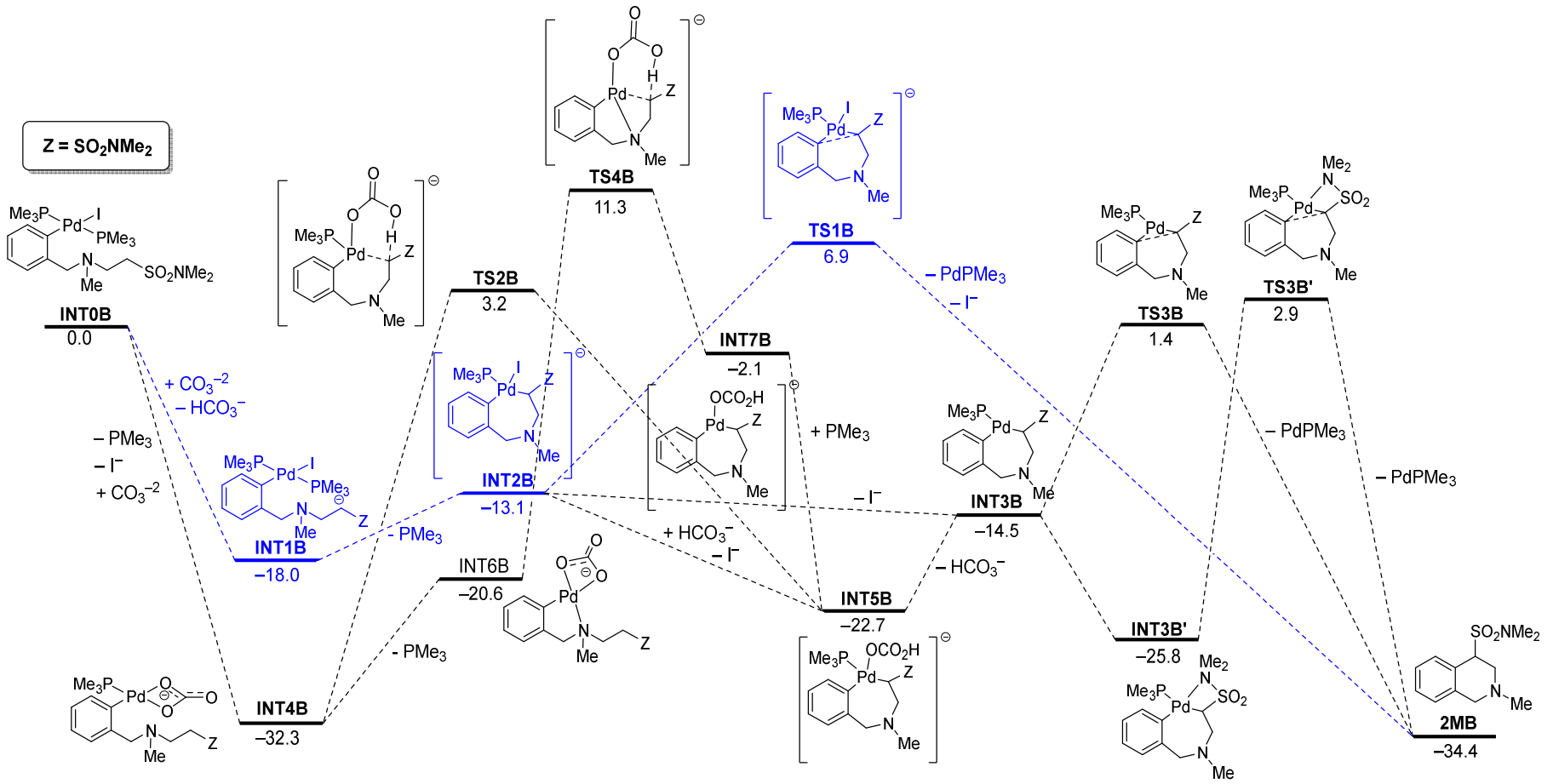
De acuerdo con los perfiles de reacción anteriores y los ΔG_R y $\Delta G^‡$ calculados, el mecanismo más probable en presencia de CO_3^{2-} es el proceso de tipo CMD: **INT0A**→**INT4A**→**INT5A**→**INT3A**→**2MA**. De todos modos, las vías **INT1A**→**INT2A**→**INT5A** y **INT1A**→**INT2A**→**INT3A** no pueden descartarse completamente.

Sin embargo, debo destacar que la formación del producto de α-arilación **4.2a** no se observó experimentalmente cuando se utilizaba Cs_2CO_3 como base y que tan sólo se consiguió obtener **4.2a** cuando se utilizó K_3PO_4 como base. En estas últimas condiciones de reacción el único mecanismo operativo sería el mecanismo aniónico mediado por base a través del intermedio **INT1A**.

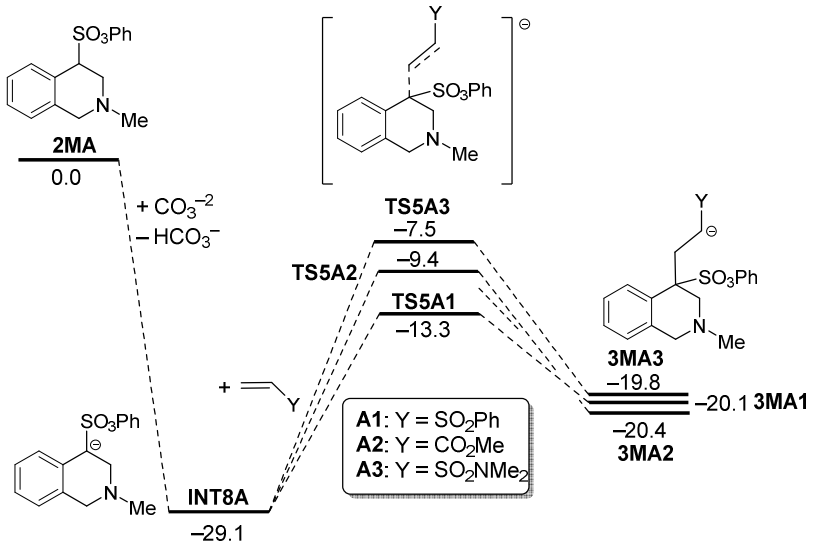
El estudio computacional de la reacción de α-arilación catalizada por Pd a partir de un fosfonato modelo proporcionó resultados similares, es decir, se observa de nuevo la preferencia por un mecanismo de tipo CMD respecto del mecanismo aniónico mediado por base. Sin embargo, la $\Delta G^‡$ de la etapa limitante en la vía CMD calculada para el sustrato de tipo fosfonato fue más alta que la observada para la reacción del éster sulfónico, concretamente de 16 Kcal/mol (Véase la siguiente figura).

Z = PO(OMe)2
INT0C
0.0
+ CO3−2
−HCO3−
INT1C
−9.1
TS1C
5.0
− PdPMe3
−I−
TS2C
−12.8
INT2C
−16.2
INT3C
−12.0
− HCO3−
TS3C
0.4
− PdPMe3
2MC
−36.5
TS4C
12.4
INT7C
−4.4
+ PMe3
INT5C
−17.5
+ HCO3−
−I−
INT6C
−23.2
− PMe3
INT4C
−29.3
− PMe3
−I−
+ CO3−2

En el caso de las sulfonamidas, los cálculos a partir del sustrato modelo proporcionaron el perfil de reacción representado en la figura siguiente. En este caso, para el mecanismo CMD (en negro en la figura), la etapa de migración del átomo de hidrógeno y formación del enlace carbono-paladio, **INT4B→INT5B**, transcurre a través del estado de transición **TS2B** con una barrera energética muy elevada ($\Delta G^{\ddagger}$= 35.5 Kcal/mol). Probablemente, esto sea debido a la mayor fortaleza del enlace C-H en relación con los modelos correspondientes al éster sulfónico y al fosfonato. Sin embargo, para el mecanismo mediado por base (en azul en la figura), la etapa limitante es la formación del enlace carbono-carbono **INT2B→2MB** a través del estado de transición **TS1B**, que transcurre con una barrera energética más baja ($\Delta G^{\ddagger}$= 20.0 Kcal/mol). Alternativamente, el intermedio **INT2B** puede evolucionar hacia la formación de un complejo de paladio no saturado **INT3B**, desde el cuál la formación del enlace carbono-carbono a través del estado de transición **TS3B** tiene lugar con una barrera energética menor ($\Delta G^{\ddagger}$= 15.9 Kcal/mol). A partir del intermedio **INT3B** también se puede sugerir la coordinación del átomo de nitrógeno de la sulfonamida al paladio (ΔG_R= -11.3 Kcal/mol desde **INT3B**). Sin embargo, en este último caso, la etapa de eliminación reductora presenta una barrera energética mucho más elevada ($\Delta G^{\ddagger}$ = 28.7 Kcal/mol) que el proceso vía el estado de transición **TS3B**. En consecuencia, según nuestros cálculos, la vía preferida para la reacción de α-arilación de la sulfonamida sería **INT0B→INT1B→INT2B→INT3B→TS3B→2MB**.


Z = SO2NMe2
INT0B
0.0
INT1B
−18.0
INT2B
−13.1
INT3B
−14.5
INT3B'
−25.8
INT4B
−32.3
INT5B
−22.7
INT6B
−20.6
INT7B
−2.1
TS1B
6.9
TS2B
3.2
TS3B
1.4
TS3B'
2.9
TS4B
11.3
2MB
−34.4
+ CO3−2
− HCO3−
− PMe3
− I−
+ CO3−2
- PMe3
+ PMe3
− I−
+ HCO3−
− I−
− HCO3−
− PdPMe3
− I−
− PdPMe3
− PdPMe3

Tal como se ha comentado en la discusión de los resultados experimentales, el proceso dominó proporciona peores resultados cuando se utiliza acrilato de metilo o *N*,*N*-dibenciletensulfonamida como aceptores de Michael, en lugar de una vinil sulfona. Con la finalidad de obtener alguna información adicional acerca de estas adiciones conjugadas, también se estudió computacionalmente la formación del enlace carbono-carbono por adición del éster sulfónico a los diferentes aceptores de Michael. Los cálculos se realizaron a partir del éster sulfónico modelo **2MA**. Como puede verse a continuación, el proceso de adición conjugada a partir del intermedio **INT8A** transcurre con una barrera energética más elevada con el aceptor de tipo sulfonamida ($\Delta G^{\ddagger}$= 21.6 Kcal/mol) que con el acrilato ($\Delta G^{\ddagger}$= 19.7 Kcal/mol) o la sulfona α,β-insaturada ($\Delta G^{\ddagger}$= 15.8 Kcal/mol). Estos cálculos están de acuerdo con la electrofilia relativa de los tres aceptores de Michael mencionados y concuerdan con nuestros resultados experimentales.



5

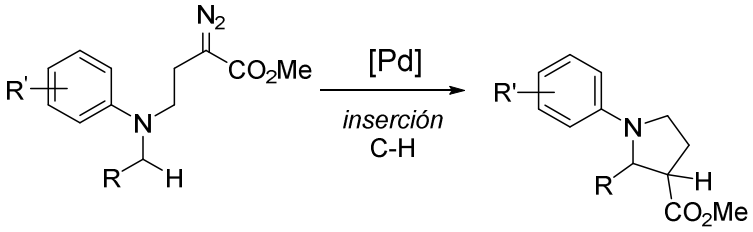
Palladium-catalysed intramolecular carbenoid insertion of α-diazo-α-(methoxycarbonyl) acetanilides for oxindole synthesis

(*Chem. Commun*. **2017,** 53, 3110-3113)

Continuando nuestra búsqueda de metodologías que permitan incrementar el potencial sintético de la química organometálica del paladio, en el presente capítulo se explorará la viabilidad del paladio como catalizador de la inserción intramolecular de carbenos derivados de α-diazoacetanilidas en enlaces C-H para la preparación de oxindoles.

Durante los últimos años, el desarrollo de nuevas metodologías para la funcionalización selectiva de enlaces C-H no activados ha sido un área de investigación muy activa.[71] En este contexto, las reacciones de inserción intramolecular catalizada por metales de transición de carbenos derivados de compuestos α-diazocarbonílicos en enlaces C-H se han convertido en una metodología extraordinariamente versátil para la construcción de sistemas carbocíclicos y heterocíclicos.[49] Los metales de transición capaces de generar metalocarbenos reactivos a partir de compuestos α-diazocarbonílicos son numerosos. Sin embargo, entre todos ellos, los derivados de Rh(II),[50] de Cu(I)[51] y más recientemente los catalizadores de Ru(II)[53] han resultado ser especialmente útiles, permitiendo el desarrollo de metodologías de inserción que en general transcurren con elevada selectividad.

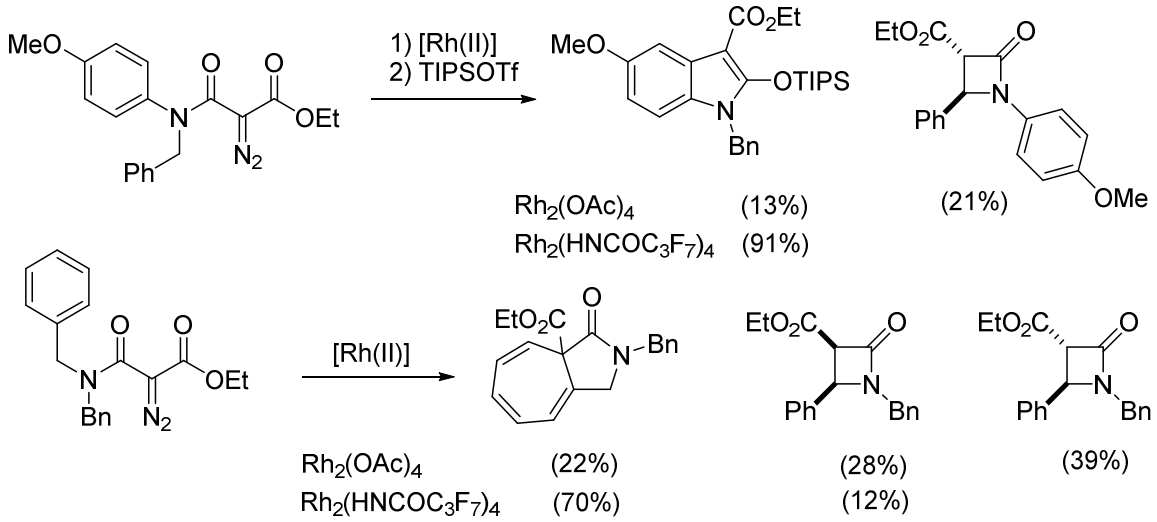
En este contexto, y como parte de un ambicioso proyecto de investigación acerca de la utilización de las reacciones catalizadas por paladio en la síntesis de heterociclos nitrogenados, nuestro grupo describió en 2016 que los catalizadores de paladio eran capaces de promover la inserción de carbenos derivados de α-diazoésteres en enlaces Csp^3-H para proporcionar pirrolidinas mediante la formación del enlace Csp^3-Csp^3.[56]



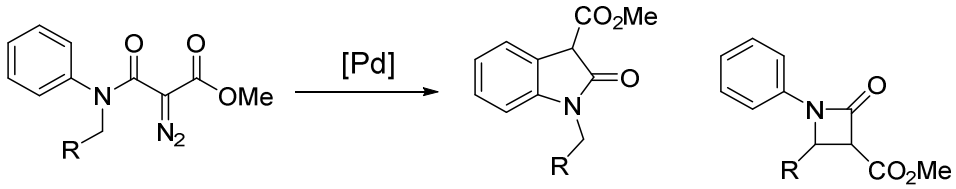
La intensa investigación que se ha realizado durante los últimos años acerca de la inserción intramolecular de carbenos catalizada por metales de transición en enlaces C-H ha generado una extensa bibliografía sobre la utilización de los complejos de dirodio(II) como catalizadores de la inserción de carbenos a partir de α-diazoacetamidas.[57] El gran interés en el desarrollo de estas reacciones se ha debido fundamentalmente a que los productos de inserción, tanto β- y γ-lactamas como oxindoles, son motivos estructurales muy frecuentes entre los productos naturales. La quimioselectividad de este tipo de reacciones de inserción depende de factores

[71] (a) Godula, K.; Sames, D. *Science*, **2006**, *312*, 67. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960.

conformacionales, estéricos y electrónicos inherentes al propio sustrato, pero también del metal de transición empleado y de sus ligandos.[58] Así, por ejemplo, en las reacciones catalizadas por complejos de dirodio(II), la utilización de ligandos de tipo carboxilato y carboxamida ha permitido el desarrollo de reacciones de inserción sumamente quimio-, regio- y estereoselectivas.[59]



A la vista de estos precedentes, en este capítulo se estudiará la descomposición de α-diazo-α-(metoxicarbonil)acetanilidas catalizada por paladio como metodología para la síntesis de heterociclos nitrogenados. De manera análoga a lo que ocurre al utilizar otros metales de transición, en las reacciones de inserción de carbenos catalizadas por paladio a partir de estos sustratos podría esperarse la formación de dos tipos de productos. Por un lado el oxindol, que procede de la inserción en el enlace $C_{Ar}sp^2$-H, y por otro, el derivado β-lactámico resultante de la inserción en el enlace Csp^3-H.

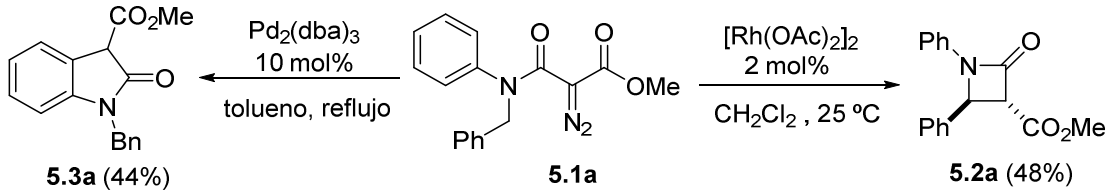


Durante esta investigación pretendíamos identificar las diferencias de reactividad y selectividad de los carbenos de paladio intermedios con los carbenos derivados de otros metales de transición.

Adicionalmente, quiero hacer notar que en el caso de que la inserción se produjera selectivamente en el enlace Csp^3-H para proporcionar el oxindol correspondiente, la reacción de inserción supondría, para estos derivados, una alternativa sintética a la reacción de α-arilación intramolecular catalizada por paladio entre un derivado β-dicarbonílico y un haluro de arilo.

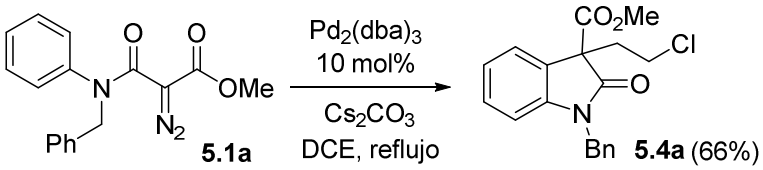
Como sustrato modelo para los estudios iniciales escogimos la α-diazoacetanilida **5.1a**. Tal como esperábamos a la vista de los resultados descritos previamente para sustratos análogos,[59a] el

tratamiento de **5.1a** con $[Rh(OAc)_2]_2$ a temperatura ambiente proporcionó la β-lactama **5.2a**, que procede de la inserción del carbeno de Rh intermedio en el enlace Csp^3-H secundario. Por el contrario, a utilizar de $Pd_2(dba)_3$ como catalizador, en el seno de tolueno a reflujo, se obtuvo el oxindol **5.3a**, un producto que es el resultado de la inserción del carbeno de paladio en el enlace $C_{Ar}sp^2$-H. El rendimiento moderado de esta última reacción se debe, en parte, a la dificultad del aislamiento de **5.3a** de forma pura, debido al equilibrio entre las dos formas tautoméricas: **5.3a** y el enol correspondiente.



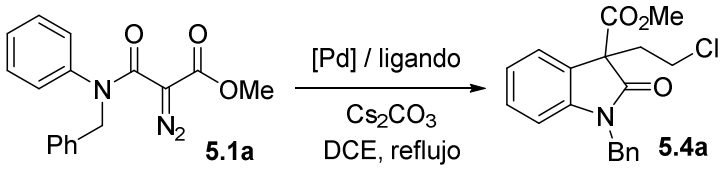
5.3a (44%) **5.1a** **5.2a** (48%)

La utilización de un disolvente más polar como el dioxano proporcionó un resultado similar. Sin embargo, al realizar la reacción en el seno de 1,2-dicloroetano se obtuvo el oxindol **5.4a**, que es el resultado de un proceso dominó inserción $C_{Ar}sp^2$-H/alquilación, con un rendimiento del 66%. La formación de este producto no solo facilitó el aislamiento y purificación de los productos de reacción, sino que también evitó la formación de subproductos de dimerización aeróbica del oxindol que se observaban al utilizar otros disolventes.



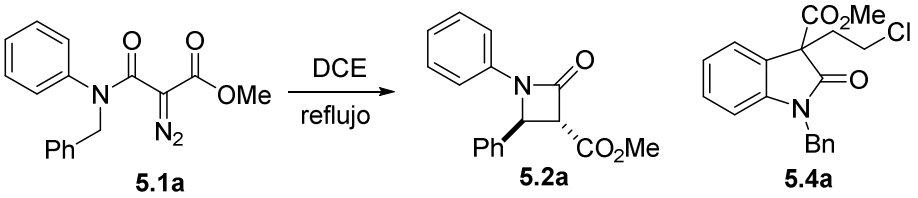
5.1a **5.4a** (66%)

Con la intención de optimizar el proceso tándem inserción/alquilación se ensayaron otros catalizadores de paladio alternativos. La utilización de $Pd(OAc)_2$ y $Pd(PPh_3)_4$ proporcionó peores resultados, obteniéndose mezclas del oxindol **5.4a** y del producto de partida. De la misma manera, todos los intentos para mejorar la eficiencia del proceso utilizando diversas fosfinas comerciales resultaron infructuosos.



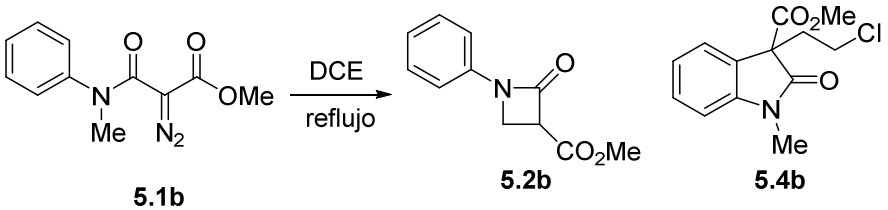
[Pd]/ ligando	Productos
$Pd(OAc)_2$ (20 mol%)	**5.1a**: **5.4a** (1.2 :1)
$Pd(PPh_3)_4$ (20 mol%)	**5.1a**: **5.4a** (1.1 :1)
$Pd_2(dba)_3$ (10 mol%) $(o\text{-Tolyl})_3P$ (40 mol%)	**5.1a: 5.4a** (1:1.6)
$Pd_2(dba)_3$ (10 mol%) dppe (20 mol%)	**5.1a: 5.4e** (1.3:1)
$Pd_2(dba)_3$ (10 mol%) $^tBu_3P{\cdot}HBF_4$	Mezcla compleja de productos

Finalmente, para confirmar el papel del paladio como catalizador en la reacción de inserción, se estudió la descomposición térmica de las α-diazoacetanilidas **5.1a** y **5.1b**. En ausencia de paladio, a iguales tiempos de reacción, la conversión térmica de **5.1a** fue del 32% y proporcionó una mezcla 1:0.2 del oxindol **5.4a** y de la β-lactama **5.2a**.



5.1a: **5.2a**: **5.4a**
2.5 : 0.2 : 1

De manera análoga, la descomposición térmica de **5.1a** resultó en una conversión del 44% y la formación de una mezcla 1:0.6 del oxindol **5.4b** y de la β-lactama **5.2b**.

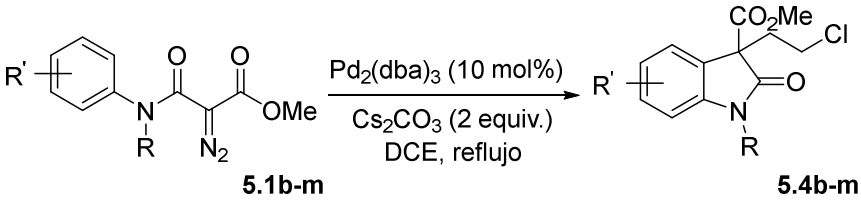


5.1b: **5.2b**: **5.4b**
2 : 0.6 : 1

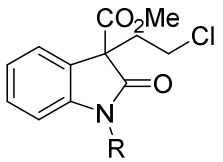
La recuperación de cantidades considerables de producto de partida en estas reacciones y, especialmente, la formación de las β-lactamas **5.2a** y **5.2b** en las reacciones térmicas confirman el papel esencial del paladio como catalizador en los anteriores procesos tándem.

Con la información obtenida hasta el momento, se decidió estudiar el alcance y las limitaciones del proceso dominó inserción $C_{Ar}sp^2$-H/alquilación a partir de diversas α-(metoxicarbonil)-α-diazoacetanilidas.

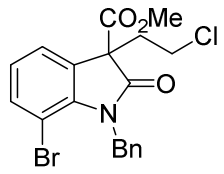
Como puede observarse en la siguiente figura, el proceso tándem tolera distintos sustituyentes sobre el átomo de nitrógeno. La inserción ocurre selectivamente en el enlace Csp^2-H aromático en presencia de enlaces Csp^3-H primarios, secundarios y terciarios. De este modo se sintetizaron los oxindoles **5.4b-d** con rendimientos aceptables. La reacción a partir de las α-(metoxicarbonil)-α-diazoacetanilidas **5.1e** y **5.1f** que presentan, respectivamente, un sustituyente metoxicarboniletilo o fenilo sobre el nitrógeno permitió la preparación de los oxindoles **5.4e** y **5.4f** con rendimientos moderados. Así mismo, el oxindol **5.4g**, que presenta un sustituyente de 2-yodobencilo en el átomo de nitrógeno, se obtuvo también de manera satisfactoria. Debo destacar que, en este caso, no se observaron productos de la posible reacción de acoplamiento competitiva entre el haluro de arilo y la agrupación diazoéster catalizada por paladio.



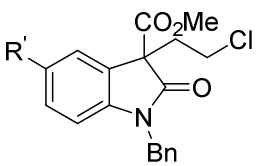
5.1b-m **5.4b-m**



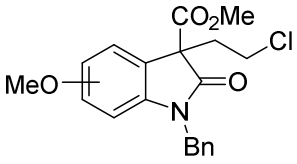
5.4b R= Me (71%)
5.4c R= Et (54%)
5.4d R= *i*Pr (61%)
5.4e R= CH_2CH_2COOMe (45%)
5.4f R= Ph (55%)
5.4g R= CH_2(2-I-Ph) (55%)



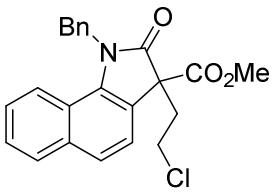
5.4h (23%)



5.4j R'=OMe (36%)
5.4k R'= F (64%)
5.4l R'=CO_2Me (22%)



5.4i (40%, 4-OMe/6-OMe, 1:3)



5.4m (27%)

También estudiamos el efecto que provoca la introducción de sustituyentes sobre el anillo aromático en el curso de la reacción de inserción. Estos estudios pusieron de manifiesto que las propiedades estereoelectrónicas de los sustituyentes afectan de manera considerable el curso de la ciclación. Así por ejemplo, la introducción de un sustituyente bromo en la posición *orto* de la anilina resultó en una reacción mucho más lenta, probablemente por motivos estéricos. A

partir de la acetanilida **5.1h**, a igual tiempo de reacción, se obtuvo una mezcla 1:1 del producto de partida y del oxindol **5.4h**, aislándose el producto de ciclación con un rendimiento del 23%.

Por otro lado, la amida **5.1i**, que presenta un grupo metoxi en la posición *meta*, proporcionó el oxindol **5.4i** con un rendimiento del 40%. El resultado obtenido fue similar a partir de la acetanilida con el sustituyente metoxi en posición *para*. La reacción a partir de **5.1l**, que tiene un sustituyente metoxicarbonilo en posición *para*, proporcionó el oxindol **5.4l** también con un modesto rendimiento del 22%.

Sin embargo, el proceso dominó a partir de la acetanilida **5.1k**, que presenta un sustituyente fluoro en posición *para*, proporcionó el oxindol **5.4k** con un rendimiento del 64%.

Por último, el proceso dominó a partir de la naftilamida **5.1m** proporcionó el oxindol **5.4m** con un rendimiento del 27%.

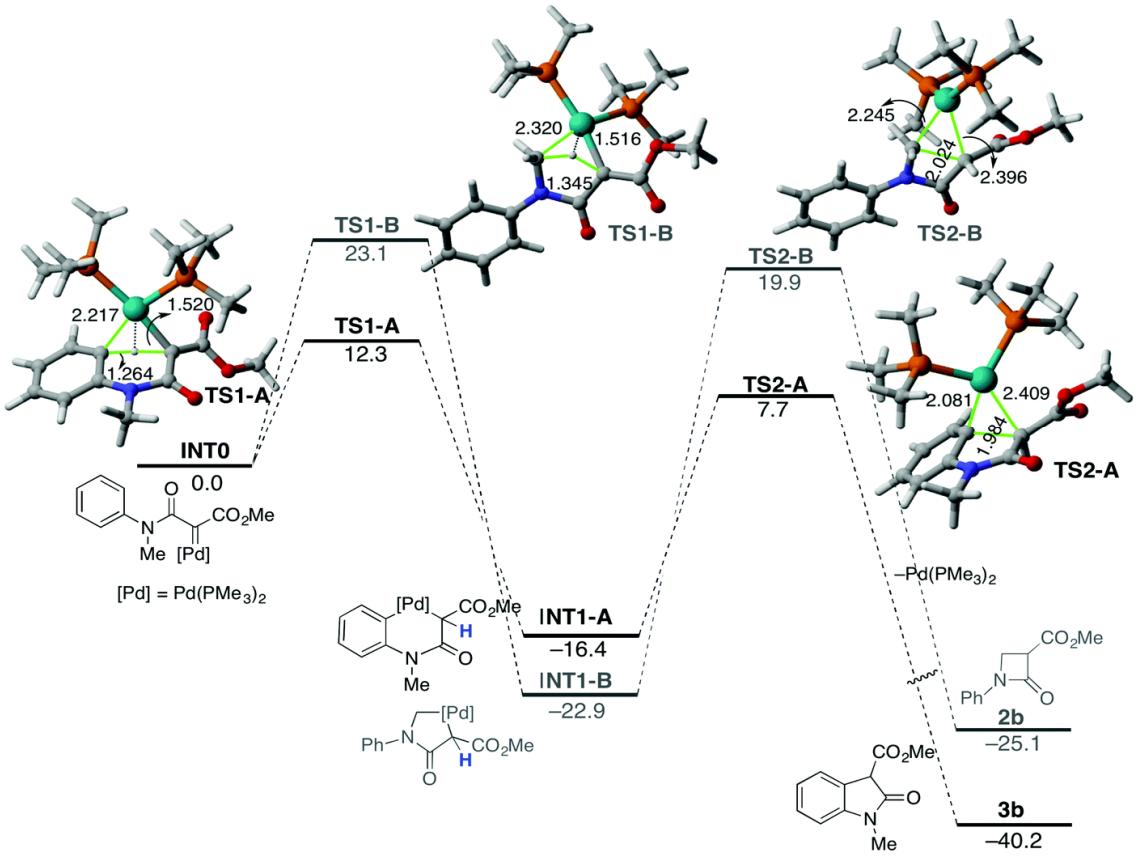
Con la finalidad de obtener alguna información acerca del mecanismo de la presente reacción de inserción catalizada por paladio, se llevaron a cabo estudios computacionales (DFT) en colaboración con el Dr. Israel Fernández de la Universidad Complutense de Madrid.

En estos estudios computacionales se utilizó un sustrato con un sustituyente metilo sobre el átomo de nitrógeno y $Pd(PMe_3)_2$ como catalizador modelo. El perfil de reacción obtenido para la formación del oxindol **3b** se representa en la siguiente figura.

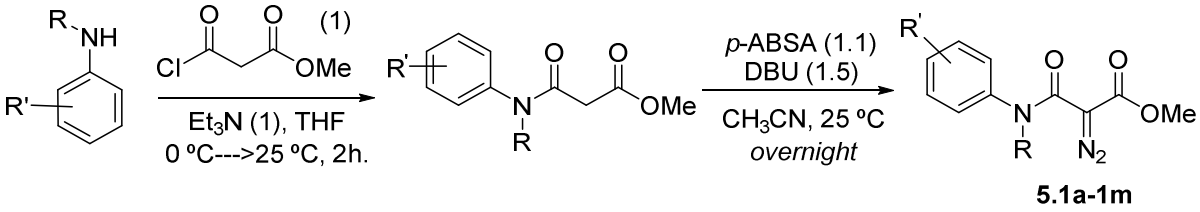
La reacción se iniciaría a partir del intermedio **INT0**, el carbeno de Pd(0) que se forma por reacción del sustrato modelo y el catalizador $Pd(PMe_3)_2$. Este intermedio evolucionaría hacia la formación de **INT1-A** a través del estado de transición **TS1-A**. Esta transformación, que es exergónica (ΔG_R= -16.4 Kcal/mol) y lleva asociada una energía de activación baja ($\Delta G^{\ddagger}$= 12.3 Kcal/mol), implicaría una migración 1,5 de hidrógeno desde el C-H aromático al carbono carbénico y la formación simultánea del enlace C-Pd, lo que supondría un aumento del grado de oxidación formal del metal. A continuación, a partir del intermedio **INT1-A**, el indol **3b** se formaría a través del estado de transición **TS2-A** ($\Delta G^{\ddagger}$= 24.1 Kcal/mol). Este proceso supone una reacción de eliminación reductora, que libera la especie de Pd(0) catalítica y el oxindol, y es fuertemente exergónico (ΔG_R= -23.8 Kcal/mol). A continuación, la alquilación del oxindol **3b** conduciría al oxindol **5.4b**, el producto de reacción experimentalmente observado en esas condiciones de reacción.

Finalmente, también se estudió computacionalmente la formación de la β-lactama **2b**, que se formaría por inserción del carbeno de Pd en el enlace Csp^3-H del metilo. Este proceso implicaría una migración 1,4 de hidrógeno y la posterior eliminación reductora. Como puede verse en los perfiles de reacción obtenidos, los estados de transición **TS1-B** y **TS2-B** llevan asociada una energía de activación mucho mayor que los estados de transición (**TS1-A** y **TS2-A**) del proceso

conducente a la formación del oxindol. En concreto, la energía de activación para el proceso de eliminación reductora **INT1B→2b** es de 42.8 Kcal/mol, lo que hace esta vía muy poco probable.



La preparación de las α-diazo-α-(metoxicarbonil)acetanilidas **5.1a**-**5.1m** se llevó a cabo siguiendo la secuencia de reacciones que se ilustra en la figura siguiente. Para una descripción más detallada véase el SI de la publicación *Chem. Commun*., **2017**, 53, 3110-3113 que se adjunta en el anexo I-Publicaciones.



6

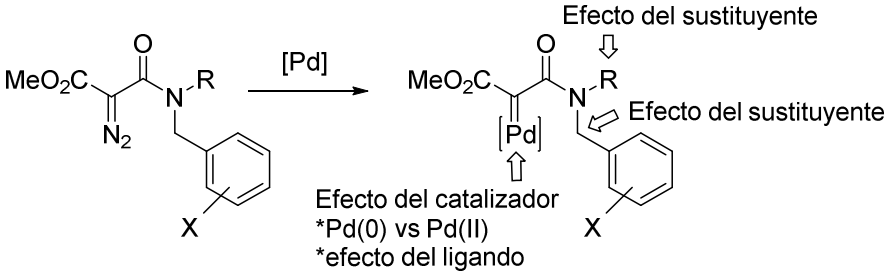
Palladium catalysis in the intramolecular carbene C-H insertion of α-diazo-α-(methoxycarbonyl)acetamides to form β-lactams

(Artículo enviado para su publicación)

Como continuación del trabajo expuesto en el capítulo anterior, en el presente capítulo se procederá al estudio de la reacción de inserción intramolecular, catalizada por paladio, de carbenos derivados de α-diazo-α-(metoxicarbonil)acetamidas en enlaces C-H, como metodología para la preparación de β-lactamas.

Tal como ya he comentado anteriormente, la preparación de β-lactamas mediante reacciones de inserción de carbenos, generados por descomposición de derivados α-diazocarbonílicos, catalizadas por metales de transición ha sido extensamente estudiada. La selectividad de estas reacciones depende tanto del tipo de derivado α-diazocarbonílico como de los factores estereoelectrónicos y conformacionales inherentes al propio sustrato, pero también se ve fuertemente afectada por el tipo de metal de transición del catalizador y sus ligandos.

En este trabajo se evaluará el efecto que tiene la naturaleza estéreo-electrónica del catalizador de paladio en el curso de la reacción. Para ello se utilizarán catalizadores tanto de Pd(0) como de Pd(II), con ligandos de diferente tipo. Adicionalmente, se estudiará de qué manera afecta a la quimioselectividad de la inserción la introducción de sustituyentes en la α-diazo-α-(metoxicarbonil)acetamida.

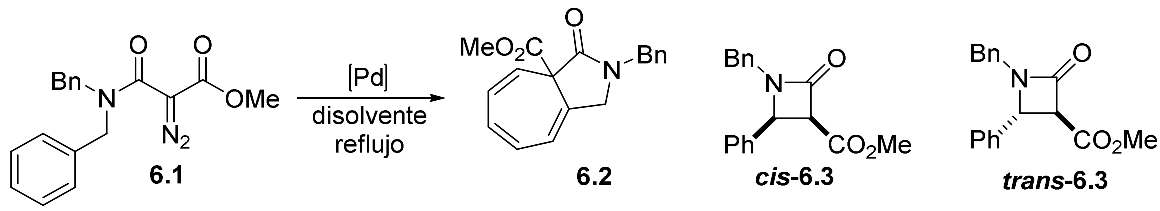


Los primeros estudios acerca de la reacción de inserción catalizada por paladio se realizaron con la *N*,*N*-dibencil α-diazoacetamida **6.1** (véase Tabla 1). El tratamiento de **6.1** con $Pd_2(dba)_3$ en el seno de DCE a la temperatura de reflujo durante 24 horas dio lugar a una conversión del producto de partida del 76%, obteniéndose una mezcla 1:1 de la cicloheptapirrolona **6.2** y de la β-lactama ***trans*-6.3**, junto con una pequeña cantidad de ***cis*-6.3**.

A igual tiempo de reacción, la descomposición térmica, en ausencia de catalizador, de **6.1** dio lugar a una conversión del 40%, obteniéndose una mezcla 1:0.1:1 de la cicloheptapirrolona **6.2** y las β-lactamas ***cis*-6.3** y ***trans*-6.3**.

Aunque el proceso de inserción térmico y la reacción catalizada por $Pd_2(dba)_3$ transcurren con la misma quimioselectividad, la mayor conversión de la última de las reacciones indica que el metal de transición participa en la reacción de inserción.

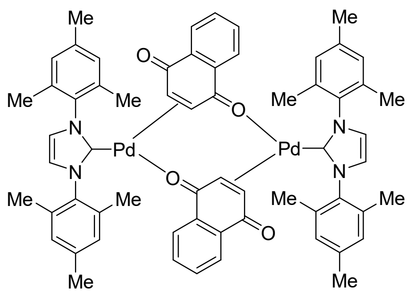
Tabla 1. Reacciones de ciclación de la α-diazoamida **6.1**[a]



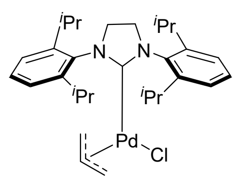
Catalizador (mol%)	Disolvente	^{1}H-RMN[b]	Rendimiento (%)[c]
$Pd_2(dba)_3$ (10)	DCE	**6.1/6.2/*cis*-6.3/*trans*-6.3** (1:1.5:0.15:1.5)	----
----	DCE	**6.1/6.2/*cis*-6.3/*trans*-6.3** (1:0.3:0.04:0.3)	----
$[(IMes)Pd(NQ)]_2$ (2.5)	DCE	**6.2/*cis*-6.3/*trans*-6.3** (1:0.1:0.2)	**6.2** (55), ***trans*-6.3** (5)
$[(IMes)Pd(NQ)]_2$ (2.5)	CH_2Cl_2	**6.1**	----
$[Pd(\pi\text{-alil})Cl]_2$ (5)	DCE	**6.2/*cis*-6.3/*trans*-6.3** (1:1.4:0.5)	**6.2** (20), ***trans*-6.3** (23)
(SiPr)Pd(π-alil)Cl (15)	DCE[d]	**6.2/*cis*-6.3/*trans*-6.3** (1:0.25:1.1)	**6.2** (22), ***trans*-6.3** (20)
$Pd(TFA)_2$ (10)	$CHCl_3$[d]	**6.2/*cis*-6.3/*trans*-6.3** (1:1.2:1)	**6.2** (15), ***trans*-6.3** (24)

[a] Condiciones de reacción: Catalizador en el disolvente indicado a reflujo durante 24h. [b] Relación calculada a partir de la integración de las absorciones en el espectro de ^{1}H-RMN del crudo de reacción. [c] Rendimiento de producto aislado por cromatografía en columna. [d] Tiempo de reacción, 48 h.

Por otro lado, la utilización de $[(IMes)Pd(NQ)]_2$ como catalizador proporcionó la cicloheptapirrolona **6.2** con un rendimiento del 55%, junto a pequeñas cantidades de ***cis*-6.3** y ***trans*-6.3**. La conversión total de la amida **6.1**, así como la diferente selectividad de la reacción cuando se compara con el anterior proceso térmico, confirman el papel catalítico de este complejo de Pd(0). Cuando la reacción se realizó en CH_2Cl_2 a reflujo se recuperó el producto de partida inalterado.



$[(IMes)Pd(NQ)]_2$



(SiPr)Pd(π-alil)Cl

Por otro lado, la utilización de catalizadores de Pd(II) para promover la descomposición de **6.1** dio lugar a la formación de las β-lactamas ***cis*-6.3** y ***trans*-6.3** como productos mayoritarios, a expensas de la cicloheptapirrolona **6.2**. Así por ejemplo, el tratamiento de **6.1** con $[PdCl(\pi\text{-alil})]_2$ proporcionó una mezcla 1:1.4:0.5 de **6.2**, ***cis*-6.3** y ***trans*-6.3**. Sin embargo, después de la

purificación cromatográfica, únicamente se pudo aislar la cicloheptapirrolona **6.2** (20%) y la β-lactama ***trans*-6.3** (23%), debido a la isomerización de ***cis*-6.3** durante el proceso de purificación. La utilización de (SiPr)Pd(π-alil)Cl proporcionó un resultado similar, aunque fue necesaria una mayor carga de catalizador. Finalmente, la utilización de $Pd(TFA)_2$ como catalizador también condujo a la formación de las β-lactamas ***cis*-6.3** y ***trans*-6.3** como productos mayoritarios de reacción. Sin embargo, en este caso, se necesitaron tiempos de reacción más largos para que la reacción fuese completa.

La cicloheptapirrolona **6.2** es el resultado de la reacción de Buchner, un proceso por etapas en el qué en primer lugar se produce una cicloadición intramolecular [2+1] del carbeno con un doble enlace del anillo aromático y, posteriormente, la expansión del anillo. Si bien las reacciones de Buchner mediadas por catalizadores de Rh[59d] y de Ru[72] son frecuentes, los ejemplos de reacciones de Buchner catalizadas por Pd descritos en la bibliografía son escasos.[73]

Por otro lado, las β-lactamas ***cis*-6.3** y ***trans*-6.3** son los productos resultantes de la inserción del carbeno de paladio intermedio en el enlace Csp^3-H del carbono metilénico unido al nitrógeno. Debo destacar que, en ninguna de las reacciones anteriores se observó la formación del producto de inserción en el enlace $C_{Ar}sp^2$-H, el tipo de reacción que se producía precisamente a partir de las α-diazo-α-(metoxicarbonil)acetanilidas estudiadas en el capítulo anterior.

Los estudios mecanísticos realizados acerca de procesos análogos utilizando catalizadores de Rh(II) sugieren que la formación competitiva de β-lactamas y de productos de reacción sobre el anillo aromático se debe a la competencia estereoelectrónica entre las dos conformaciones del metalocarbeno que experimentan la reacción. Estos estudios también han demostrado que la introducción de sustituyente *terc*-butilo sobre el nitrógeno de la amida fuerza al segundo sustituyente a una disposición *syn* con respecto del carbono carbénico, favoreciendo la reacción de inserción.[74]

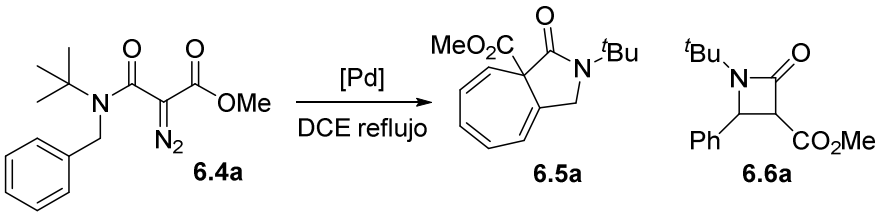
A la vista de estos precedentes y con la intención de mejorar la quimioselectividad de la reacción de inserción catalizada por paladio, se decidió estudiar la reacción a partir de la amida **6.4a**, que presenta un sustituyente *terc*-butilo sobre el nitrógeno.

Los resultados obtenidos en las reacciones de ciclación a partir de **6.4a** se recogen en la tabla siguiente.

[72] Lo, V.K.-Y.; Guo, Z.; Choi, M.K.-W.; Yu, W.-Y.; Huang, J.-S.; Che, C.-M. *J.Am. Chem. Soc.* **2012,**134, 7588.
[73] Deng, Y.; Jing, C.; Arman, H.; Doyle, M.P. *Organometallics.***2016,**35,3413.
[74] (a) Watanabe, N.; Anada, M.; Hashimoto, S-I.; Ikegami, S. *Synlett.***1994,** 1031. (b) Doyle, M.P.; Pieters, R.J.; Taunton, J.; Pho, H.Q.; Padwa, A.; Hertzog, D-L.; Precedo, L. *J.Org. Chem.* **1991,** 56, 820. (c) Yoon, C-H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K-W. *Org. Lett.* **2003,** 5, 2259. (d) Chen, Z.; Chen, Z.; Jiang, H.; Hu, W. *Synlett.* **2004,** 1763. (e) Wee, A-G-H.; Duncan, S-C. *J.Org. Chem.* **2005,**70,8372.

La descomposición de **6.4a** utilizando $Pd_2(dba)_3$ como catalizador en DCE a reflujo proporcionó la cicloheptapirrolona **6.5a** con un rendimiento del 20%, junto con las β-lactamas ***cis*-6.6a** (9%) y ***trans*-6.6a** (42%). La utilización de $[(IMes)Pd(NQ)]_2$ provocó un incremento en la formación de la cicloheptapirrolona **6.5a**. Para nuestra satisfacción, la utilización de los catalizadores de Pd(II), $[PdCl(\pi\text{-alil})]_2$ y (SiPr)Pd(π-alil)Cl, tuvo como consecuencia la inserción exclusiva en el enlace Csp^3-H para proporcionar las β-lactamas ***cis*-6.6a** y ***trans*-6.6a**, que se aislaron con un buen rendimiento global.

Tabla 2. Reacciones de ciclación de la α-diazoamida **6.4a**[a]

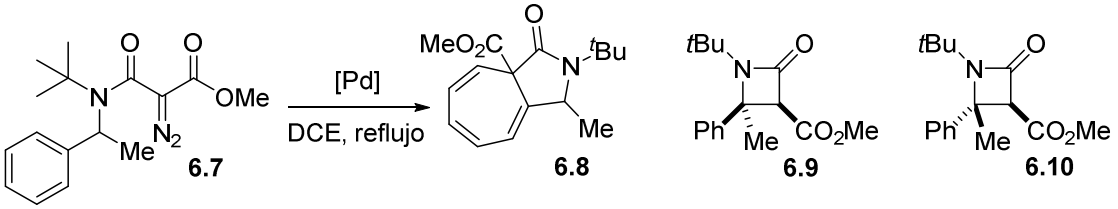


Catalizador (mol%)	6.5a/*cis*-6.6a/*trans*-6.6a[b,c]	Productos (%)[d]
$Pd_2(dba)_3$ (10)	26/48/28	**6.5a** (20), ***cis*-6.6a** (9), ***trans*-6.6a** (42)
[(IMes)Pd(NQ)]2 (2.5)	35/40/25	**6.5a** (28), ***cis*-6.6a** (35), ***trans*-6.6a** (23)
$[Pd(\pi\text{-alilCl})]_2$ (5)	0/47/53	***cis*-6.6a** (25), ***trans*-6.6a** (65)
(SIPr)Pd(π-alil)Cl (15)	0/29/71	***cis*-6.6a** (17), ***trans*-6.6a** (59)

[a] Condiciones de reacción: Catalizador en DCE a reflujo durante 24h. [b] Relación de productos por ^{1}H-NMR. [c] Reacciones por duplicado. La relación de productos **6.5a**/**6.6a** fue similar en los dos ensayos, sin embargo la relación *cis*/*trans* fue ligeramente diferente debido a la isomerización parcial durante el proceso de purificación. [d] Rendimiento en producto aislado por cromatografía en columna.

También se exploró la reacción de inserción catalizada por paladio a partir de la amida **6.7**, que presenta un sustituyente de tipo α-metilbencilo sobre el átomo de nitrógeno. Los resultados obtenidos se recogen en la siguiente tabla.

Tabla 3. Reacciones de ciclación de la α-diazoamida **6.7**[a]



Catalizador (mol%)	8/9/10[b]	Productos (%)[c]
$Pd_2(dba)_3$ (10)	26/37/37	**6.8**[d] (15), **6.9** (18), **6.10** (24)
$[(IMes)Pd(NQ)]_2$ (2.5)	65/20/15	**6.8**[e] (42), **6.9** (7), **6.10** (13)
$[Pd(\pi\text{-alil})Cl]_2$ (5)	0/36/64	**6.9** (23), **6.10** (47)
(SIPr)Pd(π-alil)Cl (15)	0/57/43	**6.9** (24), **6.10** (18)

[a] Condiciones de reacción: Catalizador en DCE a reflujo durante 24h. [b] Relación de productos por ^{1}H-RMN. [c] Rendimiento en producto aislado por cromatografía en columna. [d] Mezcla 1:1.2 de diastereómeros. [e] Mezcla 1:2.2 de diastereómeros.

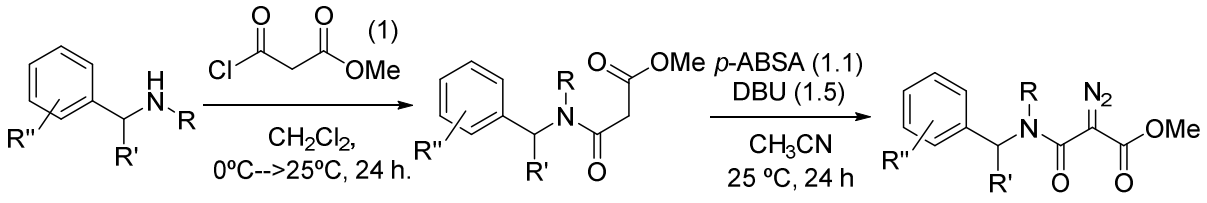
Tal como ya había sucedido con la α-diazoamida **6.4a**, al utilizar catalizadores de Pd(0) para promover la inserción a partir de **6.7** se obtuvieron cantidades significativas de la cicloheptapirrolona **6.8**, junto con las β-lactamas **6.9** y **6.10**. En este sentido, debo destacar que, al utilizar $Pd_2(dba)_3$ como catalizador, tanto **6.4a** como **6.7** proporcionaron una mezcla aproximadamente 1:3 del producto de la reacción de Buchner y de las β-lactamas. En cambio, al utilizar el catalizador estéricamente impedido $[IMes]Pd(NQ)]_2$ con la α-diazoamida **6.7** se obtuvo la cicloheptapirrolona **6.8** como producto mayoritario. Este resultado sugiere que la reacción de inserción en el enlace Csp^3-H es considerablemente sensible al impedimento estérico sobre el punto de inserción.

Al igual que había sucedido con la amida **6.4a**, al utilizar los catalizadores de Pd(II), $[PdCl(\pi\text{-alil})]_2$ y (SiPr)Pd(π-alil)Cl, para promover la descomposición de la α-diazoamida **6.7**, la inserción se produjo exclusivamente en el enlace Csp^3-H para proporcionar las β-lactamas. De nuevo, los mejores resultados se obtuvieron al utilizar $[PdCl(\pi\text{-alil})]_2$ como catalizador.

Como acabamos de ver, la inserción en el enlace Csp^3-H de la posición bencílica se ve enormemente favorecida cuando hay un sustituyente *terc*-butilo sobre el nitrógeno, el efecto es especialmente importante al utilizar catalizadores de Pd (II). Así, en las reacciones a partir de las α-diazoazetamidas **6.4a** y **6.7**, los catalizadores $[PdCl(\pi\text{-alil})]_2$ y (SiPr)Pd(π-alil)Cl promueven quimioselectivamente la inserción en el enlace Csp^3-H, sin que se formen los productos derivados de la reacción de cicloadición aromática competitiva. Estos resultados ponen de manifiesto la importancia de la naturaleza electrónica del catalizador de paladio y de la estructura de la α-diazoacetamida en el curso de la reacción.

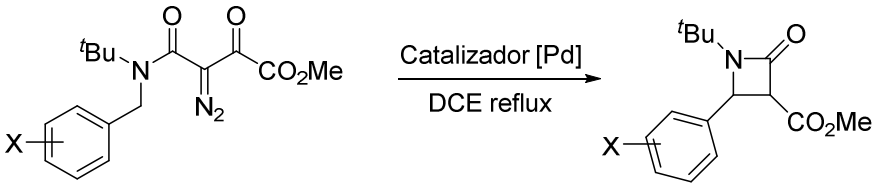
Llegados a este punto, se decidió estudiar qué efecto tenía en el curso de la reacción la introducción de sustituyentes en el anillo aromático. Con esta finalidad, se prepararon las α-diazoacetamidas **6.4b-m**.

La preparación de las α-diazoacetamidas **6.1**, **6.4a-m** y **6.7**, que se han utilizado en el presente estudio, se llevó a cabo siguiendo la secuencia de reacciones que se ilustra en la figura siguiente. Para una descripción más detallada véase el SI de la publicación que se adjunta en el anexo I-Publicaciones.

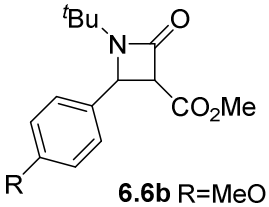


6.1, 6.4a-m, 6.7

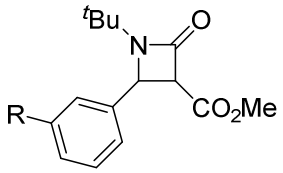
Los resultados obtenidos en las reacciones catalizadas por complejos de Pd(II) a partir de las α-diazoacetamidas **6.4b-m** se recogen en el siguiente esquema.



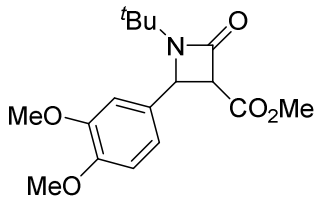
Catalizador [Pd]: método **A**: $[PdCl(\pi\text{-alil})]_2$
método **B**: (SIPr)Pd(π-alil)Cl



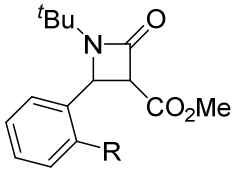
6.6b R=MeO (**A,** 57%, 1:2.2)
(**B,** 60%, 1:6.5)
6.6c R=MeS (**A**, 58%, 1:4.8)
(**B**, 64%. 1:15)
6.6d R=Cl (**A,** 82%, 1.1:1)
(**B**, 69%, 1:1.6)
6.6e R=CN (**A,** 70%, 1:1)
(**B**, 78%, 1:1.9)
6.6f R=NMe_2 (**A**, 14%%, 0:1)
(**B**, 10% 0:1)



6.6g R=Cl (**A**, 80%, 1.2:1)
(**B**, 61%, 1:1)
6.6h R=CN (**A**, 65%, 1:2)
(**B,** 70%, 1:3.7)



6.6m (**A**, 39%, 0:1)
(**B,** 44%, 1:6.3)



6.6l R=MeO (**A**, 54% 1:1.3)
(**B**, 73% 1: 6.3)
6.6j R= F (**A**, 82% 1:2.2)
(**B**, 66%,0:1)
6.6k R=Br (**A**, 65%, 1.1:1)
(**B**, 50%, 1:5.3)
6.6l R=I (**A**, 87%, 1.3:1)
(**B**, 68%, 3.5:1)

El efecto provocado por el sustituyente depende de su posición en el anillo aromático y de su naturaleza estereoelectrónica. Así, por ejemplo, la introducción de sustituyentes donadores de electrones provoca un ligero incremento en la formación de los productos de la reacción de Buchner. Este incremento se acentúa cuando se utiliza el catalizador (SiPr)Pd(π-alil)Cl. Sin embargo, el efecto se minimiza cuando el sustituyente se encuentra en posición *orto*, probablemente debido al impedimento estérico.

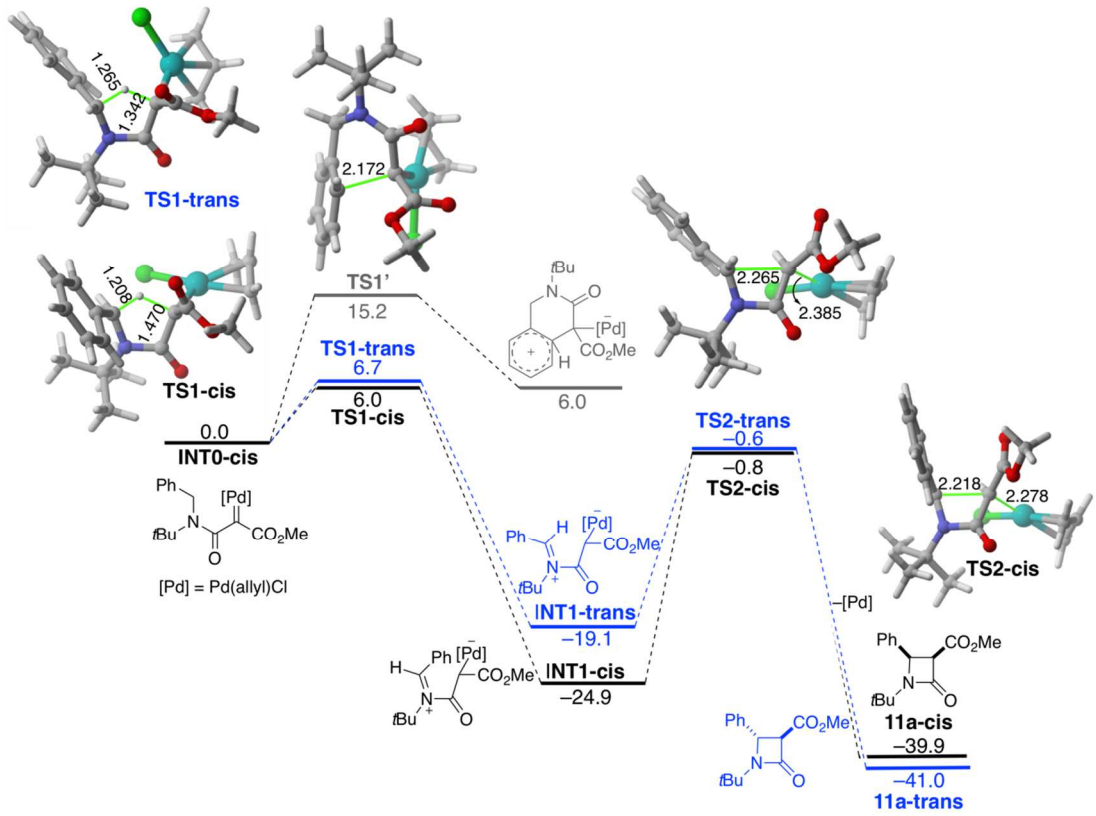
Por otro lado, la introducción de sustituyentes atrayentes de electrones disminuye la formación de los productos de la reacción de Buchner, tanto al utilizar el catalizador (SiPr)Pd(π-alil)Cl como el $[PdCl(\pi\text{-alil})]_2$.

Como puede observarse, en general, la utilización de catalizadores de Pd(II) promueve selectivamente la reacción de inserción en el enlace Csp^3-H. La reacción tolera la presencia de

sustituyentes con diferente carácter electrónico en el anillo aromático y permite obtener las β-lactamas con rendimientos de moderados a buenos, generalmente como mezclas de los isómeros *cis* y *trans*. Como excepción, la reacción de descomposición de la α-diazoacetamida **6.4f**, que presenta un sustituyente dimetilamino sobre el anillo aromático, proporcionó la β-lactama ***trans*-6.6f** con un rendimiento bajo. En esta reacción se obtuvieron cantidades considerables de 4-(dimetilamino)benzaldehído.

Los resultados computacionales obtenidos previamente en nuestro grupo al estudiar las reacciones de inserción catalizadas por paladio sugieren que el mecanismo de estos procesos difiere del comúnmente aceptado para las reacciones catalizadas por derivados de Rh(II). Así, mientras las reacciones catalizadas por Rh(II) tienen lugar a través de un proceso concertado en el que, en una única etapa, se libera directamente el producto de inserción y el catalizador de Rh(II), los catalizadores de paladio implican reacciones por etapas, que se inician mediante una migración de hidrógeno mediada por el metal.[56]

Teniendo en consideración esta información previa, en este caso también se realizaron cálculos computacionales (DFT) para elucidar el mecanismo de la presente reacción de inserción. En la siguiente figura se representa el perfil de reacción obtenido a partir de la α-diazoacetamida **6.4a** utilizando de $[PdCl(\pi\text{-alil})]_2$ como catalizador.



La primera etapa implicaría la generación de los intermedios zwitteriónicos **INT1-*cis*** y **INT1-*trans***. Desde el punto de vista energético, la formación de estos intermedios es claramente favorable

($\Delta G_{R\ INT1\text{-}cis}$= -24.9 Kcal/mol, $\Delta G_{R\ INT1\text{-}TRANS}$= -19.4 Kcal/mol) y transcurre a través de los estados de transición **TS1-*cis*** ($\Delta G^{\ddagger}$= 6.0 Kcal/mol) y **TS1-*trans*** ($\Delta G^{\ddagger}$= 6.7 Kcal/mol), respectivamente. Esta etapa implica una migración 1,4 de hidrógeno no asistida por el metal, similar a la propuesta por nuestro grupo de investigación en ciertas reacciones de inserción catalizadas por Ru.[56b] A continuación, tendría lugar la formación del enlace carbono-carbono, que conduciría a las β-lactamas ***cis*-6.6a** y ***trans*-6.6a**. Esta reacción también es exergónica y ocurriría a través de los estados de transición **TS2-*cis*** y **TS2-*trans***, que suponen unas barreras energéticas de 24.1 Kcal/mol y 18.5 Kcal/mol, respectivamente. Considerando las barreras energéticas calculadas para las dos etapas y la estabilidad relativa de los intermedios **INT0**, **INT1**-***cis*** y **INT1**-***trans***, la etapa de formación del enlace carbono-carbono sería la etapa limitante del proceso.

Por último, también se calculó la formación de la cicloheptapirrolona **6.5a** a partir de **6.4a**, utilizando $[PdCl(\pi\text{-alil})]_2$ como catalizador de Pd(II) modelo. Nuestros cálculos sugieren que la primera etapa en la formación del producto de la reacción de Buchner, implica la formación de un enlace carbono-carbono a través de una reacción de tipo Friedel-Crafts. Este proceso conduce a la formación de un intermedio más inestable (ΔG_R= 6.0 kcal/mol desde **INT0**) a través del estado de transición **TS1'** ($\Delta G^{\ddagger}$= 15.2 Kcal/mol). Considerando $\Delta G^{\ddagger}_{TS1}$ y $\Delta G^{\ddagger}_{TS1}$, así como la estabilidad relativa de los dos intermedios, podemos descartar la vía que conduce a la formación de la cicloheptapirrolona **6.5a**. Por lo tanto la formación exclusiva de las β-lactamas ***cis*-6.6a** y ***trans*-6.6a** confirmada experimentalmente queda perfectamente explicada.

7

Resumen y Conclusiones

Palladium in azaheterocyclic synthesis: α-arylation of sulfones, domino processes and C-H carbene insertion reactions

RESUMEN Y CONCLUSIONES

1) En la presente Tesis Doctoral se ha realizado un extenso estudio de la reacción de α-arilación intramolecular de β-amino sulfonas catalizada por paladio, en el que se combina el trabajo experimental con los cálculos computacionales. Durante este estudio:

1.1) Hemos puesto a punto un procedimiento para la síntesis de tetrahidroisoquinolinas mediante la reacción de α-arilación de sulfonas catalizada per Pd(0). La combinación de la reacción de α-arilación con la subsiguiente adición de Michael a vinil sulfonas o acrilatos ha permitido el desarrollo de un proceso dominó para la síntesis de tetrahidroisoquinolinas diversamente funcionalizadas.

Adicionalmente, el acoplamiento de una reacción de adición de aza-Michael a vinil sulfonas a la secuencia de α-arilación/adición de Michael a vinil sulfonas ha fructificado en el desarrollo de un proceso dominó en tres etapas que permite la síntesis de tetrahidroisoquinolinas con un elevado grado de funcionalización a partir de sustratos de partida sencillos y fácilmente accesibles. En este proceso dominó puede utilizarse como aceptores de Michael tanto la fenil vinil sulfona como la metil vinil sulfona.

1.2) Se ha desarrollado un nuevo proceso dominó para la síntesis de 3-(fenil/metilsulfoniletil)indoles a partir de 2-yodoanilinas, que implica una secuencia de aza-Michael/α-arilación catalizada por Pd(0)/adición de Michael/β-eliminación de ácido sulfínico en la que se utilizan, nuevamente, las sulfonas como electrófilos y como nucleófilos. El proceso dominó transcurre con buenos rendimientos, tolera la presencia de sustituyentes con diferente carácter electrónico sobre la 2-yodoanilina y admite la utilización tanto de la fenil vinil sulfona como de la metil vinil sulfona como aceptores de Michael. Los estudios computacionales realizados acerca de esta secuencia dominó sugieren que la reacción de α-arilación transcurre a través de un proceso de tipo desprotonación-metalación concertado (CMD) seguido de una reacción de eliminación reductora.

1.3) La reacción de α-arilación intramolecular catalizada por paladio se ha extendido a la utilización de sulfonatos, sulfonamidas y fosfonatos. Aunque los tres tipos de nucleófilos pueden utilizarse en la reacción de α-arilación para preparar tetrahidroisoquinolinas, la reacción a partir de estos sustratos transcurre de manera menos eficiente que a partir de las sulfonas.

La reacción de α-arilación de sulfonatos se ha podido combinar de manera efectiva con la adición de Michael a diferentes electrófilos (vinil sulfonas, etensulfonato de fenilo, *N*,*N*-dimetiletensulfonamida y acrilato de metilo) para desarrollar los correspondientes procesos tándem. Por el contrario, las sulfonamidas solo aceptan como aceptor de Michael a las sulfonas α,β-insaturadas, y los fosfonatos han resultado ser completamente inactivos en el proceso tándem.

La reacción de α-arilación de sulfonatos, sulfonamidas y fosfonatos se ha estudiado computacionalmente (DFT). Estos estudios han puesto de manifiesto que la reacción transcurre mediante mecanismos diferentes en función del tipo de nucleófilo y de la base utilizada. Así,

nuestros estudios indican que en la α-arilación de sulfonatos y fosfonatos, utilizando Cs_2CO_3 como a base, pueden competir dos mecanismos alternativos. Por un lado, la α-arilación aniónica a través de la base conjugada y, por otro, un proceso de desprotonación/metalación concertada (CMD). En cambio, en la α-arilación de sulfonamidas la reacción a partir de la base conjugada parece ser mucho más favorable que el proceso de tipo CMD alternativo.

2) Se ha estudiado la viabilidad de los complejos de paladio como catalizadores en las reacciones de inserción de carbenos generados a partir de α-diazoacetamidas en enlaces C-H. Con el fin de identificar las diferencias entre la reactividad de los catalizadores de paladio y los basados en otros metales de transición, se ha estudiado de qué manera afectan al curso de la reacción de inserción los sustituyentes en la α-diazoacetamida y el grado de oxidación del paladio en el precatalizador utilizado. Durante este estudio:

2.1) Hemos demostrado que los catalizadores de paladio constituyen una alternativa a otros metales de transición en las reacciones de inserción de carbenos generados a partir de α-diazo-α-(metoxicarbonil)acetanilidas en enlaces C-H. Cuando se utilizan catalizadores de paladio la inserción tiene lugar de manera selectiva en el enlace Csp^2-H del anillo aromático para proporcionar el oxindol correspondiente.

Aunque tanto los catalizadores de Pd(0) como los de Pd(II) pueden promover la reacción de inserción, los mejores resultados se han obtenido al utilizar complejos de Pd(0). Utilizando $Pd_2(dba)_3$ o $[(IMes)Pd(NQ)]_2$ como catalizador, Cs_2CO_3 como base y 1,2-dicloroetano como disolvente hemos podido desarrollar un proceso tándem inserción/alquilación para la síntesis de 3-(cloroetil)oxindoles.

Esta reacción de inserción también se ha estudiado computacionalmente (DFT). Nuestro estudio ha puesto de manifiesto que la inserción tiene lugar mediante un mecanismo por etapas inédito, que implica una migración 1,5 de hidrogeno promovida por Pd desde el Csp^2-H del anillo aromático al carbono carbénico con la formación simultánea del enlace Csp^2-Pd y, seguidamente, una eliminación reductora, que proporciona directamente el producto de inserción y regenera la especie de Pd(0) catalítica.

2.2) Por otro lado, hemos demostrado que los complejos de paladio también pueden utilizarse como catalizadores en la inserción intramolecular de carbenos derivados de α-diazo-α-(metoxicarbonil)acetamidas para generar β-lactamas. Aunque tanto los catalizadores de Pd(0) como los de Pd(II) pueden utilizarse para promover esta reacción de inserción, en general en este proceso los complejos de Pd(II) parecen ser más eficientes y versátiles. Utilizando catalizadores de Pd(II), la reacción de inserción en el enlace Csp^3-H transcurre con una quimioselectividad elevada para proporcionar mezclas de las β-lactamas *cis* y *trans*.

2.3) Se ha estudiado la descomposición catalizada por paladio de α-diazo-α-(metoxicarbonil)acetamidas que poseen agrupaciones heteroaromáticas sobre el nitrógeno de la amida. Aunque todavía preliminares, los resultados obtenidos en este estudio han puesto de manifiesto que el curso de la reacción depende fundamentalmente del tipo de sistema heterocíclico presente en el sustrato de partida.

8

Anexo I: Publicaciones

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Heterocycle Synthesis

Pd^0-Catalyzed Intramolecular α-Arylation of Sulfones: Domino Reactions in the Synthesis of Functionalized Tetrahydroisoquinolines

Daniel Solé,* Ferran Pérez-Janer, and Raffaella Mancuso[a]

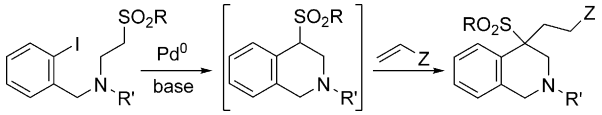
Abstract: A new strategy for the synthesis of tetrahydroisoquinolines based on the Pd^0-catalyzed intramolecular α-arylation of sulfones is reported. The combination of this Pd-catalyzed reaction with intermolecular Michael and aza-Michael reactions allows the development of two- and three-step domino processes to synthesize diversely functionalized scaffolds from readily available starting materials.

The sulfone is a ubiquitous organic structural motif that is often used as an auxiliary group in important synthetic methodologies, especially those devoted to the formation of carbon–carbon bonds, in which the sulfonyl group usually acts as an electron-withdrawing moiety facilitating the deprotonation of a neighboring carbon atom.[1] Moreover, sulfones are also present in a large number of synthetic biologically active compounds,[2] as well as in some natural products.[3] Due to their significance, the development of new and efficient methods for the synthesis of sulfones is today an interesting challenge.

In recent years, palladium-catalyzed arylation of acidic C–H bonds has received a great deal of attention.[4] However, despite the popularity of this type of reaction, examples of palladium-catalyzed α-arylation of sulfones are scarce, probably due to the higher pK_a values of the sulfonyl α-C–H group, and they have been limited to intermolecular processes.[5–7]

As part of our ongoing program on the development of efficient methodologies for the synthesis of nitrogen heterocycles,[8] we have been studying the palladium-catalyzed intramolecular coupling of amino-tethered aryl halides with enolate-type nucleophiles.[9] To further generalize the application of the α-arylation reaction to the synthesis of azaheterocycles, we decided to explore the use of sulfones as the nucleophilic counterpart. Additionally, we envisaged that the potential of this palladium-catalyzed reaction could be dramatically improved if, in one pot, the α-arylation product undergoes further reaction with an electrophile such as a Michael acceptor.

To test our proposal, we focused on the synthesis of tetrahydroisoquinolines, given that this heterocyclic system is a common structural motif in pharmaceuticals and natural products.[10] A general approach to this type of compound, using a tandem palladium-catalyzed α-arylation and Michael addition strategy, would complement existing methodologies and in some cases provide a more attractive option.[11,12] Herein, we report our studies on the intramolecular palladium-catalyzed α-arylation of β-aminosulfones, and present new domino processes based on this reaction, which allow the straightforward synthesis of diversely functionalized tetrahydroisoquinolines (Scheme 1).



Scheme 1. Proposed tandem Pd^0-catalyzed α-arylation/Michael addition of sulfones to access tetrahydroisoquinolines.

The first challenge in developing our project was to identify a suitable combination of base, catalyst, and solvent for the intramolecular α-arylation of β-aminosulfones. The sulfone **1a** was chosen as a model to optimize the reaction conditions for the α-arylation (Table 1). The intermolecular α-arylation of unactivated sulfones usually requires the presence of strong bases, such as $LiN(SiMe_3)_2$ or LiO*t*Bu,[5c–e] but in our case this was precluded by the retro-Michael degradation of the β-aminosulfone moiety (see below). However, treatment of **1a** with $[Pd(PPh_3)_4]$ as the catalyst and K_3PO_4 in DMF at high temperature, an effective combination for the α-arylation of amino acid esters,[9e] resulted only in the recovery of the starting material (Table 1, entry 1). A similar result was obtained when using 1,1′-bis(di-*tert*-butylphosphino)ferrocene (dtpf) as ligand instead of PPh_3 (Table 1, entry 2). The use of the ligand BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; Table 1; Table 1, entry 3) promoted the total consumption of sulfone **1a** to give a complex reaction mixture, from which the major product, disulfone **3a**, was isolated in 22% yield. This compound is generated by the conjugate addition of the initially formed α-arylation product **2a** to phenyl vinyl sulfone, which arises from the partial retro-Michael fragmentation of **1a** under the reaction conditions.

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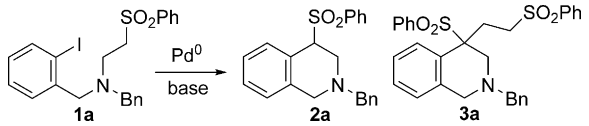
Table 1. Optimization of the α-arylation conditions.[a]

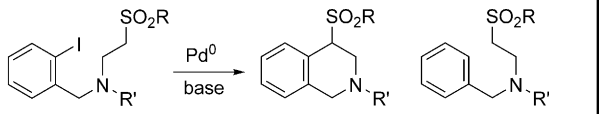


1a 2a 3a

Entry	[Pd] [mol%] ligand [mol%]	Base	Solvent	*t* [h]	Products (yield [%])[b]
1	$[Pd(PPh_3)_4]$ (10)	K_3PO_4	DMF	48	**1a**[c]
2	$[Pd_2(dba)_3]$ (5) dtpf (10)	K_3PO_4	DMF	24	**1a**[c,d]
3	$[Pd_2(dba)_3]$ (5) BINAP (10)	K_3PO_4	DMF	72	**3a** (22)[e]
4	$[Pd_2(dba)_3]$ (5) BINAP (10)	Cs_2CO_3	DMF	72	—[f,g]
5	$[Pd_2(dba)_3]$ (5) BINAP (10)	Et_3N (3)	DMF	72	—[h]
6	$[Pd_2(dba)_3]$ (7.5) xantphos(15)	K_3PO_4	DMF	43	**2a** (59) **3a** (10)
7	$[Pd_2(dba)_3]$ (7.5) xantphos(15)	Cs_2CO_3	DMF	72	**2a** (50) **3a** (9)
8	$[Pd_2(dba)_3]$ (7.5) xantphos(15)	K_3PO_4	THF	68	**2a** (90)[i]
9	$[Pd_2(dba)_3]$ (7.5) xantphos(15)	K_3PO_4	toluene	72	**2a** (89)

[a] Reaction conditions: **1a** (0.2 mmol), [Pd]/ligand (see table), and base (3 equiv) in the indicated solvent at 120 °C in a sealed tube; [b] yield of product isolated by flash chromatography; [c] not quantified; [d] minor amounts of **2a** were detected in the reaction mixture; [e] minor amounts of **2a** and the hydrodehalogenation product were detected in the reaction mixture; [f] complex reaction mixture; [g] the use of K_2CO_3 as the base afforded a similar result; [h] significant amounts of the hydrodehalogenation compound were detected in the reaction mixture; [i] the use of 5 mol% of $[Pd_2(dba)_3]$ resulted in the recovery of 10% of **1a** after 62 h of reaction.

Table 2. Substrate scope in the α-arylation reaction.[a]



1b, R = Me, R' = Bn
1c, R = Ph, R' = Ph
1d, R = Me, R' = Ph
1e, R = Ph, R' = Me

2b **2c** **2d** **2e** **4b** **4d**

Entry	Sulfone	Solvent	Products (yield [%])[b]
1	**1b**	DMF	**2b** (63), **4b** (10)
2	**1b**	THF	**2b** (66), **4b** (11)
3	**1b**	toluene	**2b** (38), **4b** (24)
4	**1c**	DMF	**2c** (14)[c]
5	**1c**	THF	**2c** (45)[d]
6	**1c**	toluene	**2c** (19)[c]
7	**1d**	DMF	**2d** (31), **4d** (10)
8	**1d**	THF	**1d**/**2d**/**4d** (2:1.7:1)[e]
9	**1e**	DMF	**2e** (52)

[a] Reaction conditions: $[Pd_2(dba)_3]$ (7.5 mol%), xantphos (15 mol%), K_3PO_4 (3 equiv), and solvent at 120 °C for 72 h in a sealed tube; [b] yield of product isolated by flash chromatography; [c] complex mixture; [d] traces of the hydrodehalogenation compound ($\leq$5%) were also detected in the crude reaction mixture; [e] ^{1}H NMR ratio, yields not quantified.

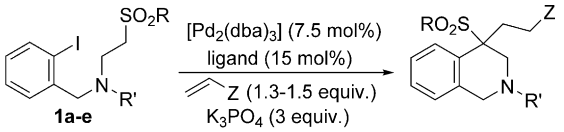
The use of either Cs_2CO_3 or K_2CO_3 as the base instead of K_3PO_4, while retaining the BINAP ligand, mainly resulted in the decomposition of the starting material (Table 1, entry 4), whereas the use of Et_3N exclusively promoted the hydrodehalogenation of the aryl iodide (Table 1, entry 5). Performing the α-arylation of **1a** using xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) as the ligand and K_3PO_4 as the base afforded the desired tetrahydroisoquinoline **2a** in 59% yield, together with a small amount of disulfone **3a** (Table 1, entry 6). Under the same reaction conditions, changing the base to Cs_2CO_3 resulted in a slightly lower yield (Table 1, entry 7), but, gratifyingly, exchanging the solvent for either THF or toluene increased the yield up to 90% (Table 1, entries 8 and 9).

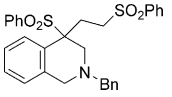
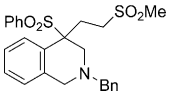
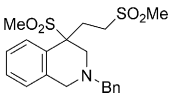
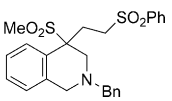
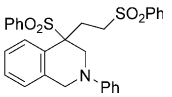
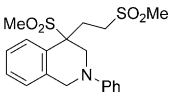
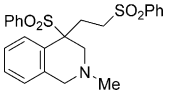
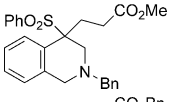
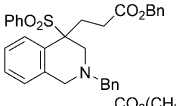
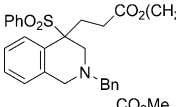
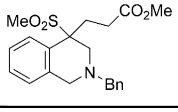
Before embarking on the development of a tandem process, we decided to further explore the scope of α-arylation, extending our studies to methyl sulfones and substrates bearing a phenyl or a methyl group at the nitrogen atom (Table 2).

Methyl sulfone **1b** was less efficient than phenyl sulfone **1a** in the annulation reaction. The lower acidity of the α-C–H bonds of the methyl sulfone made its α-arylation more troublesome and resulted in the formation of significant amounts of the hydrodehalogenation compound **4b** (Table 2, entries 1–3). Nevertheless, the yield of the α-arylation compound **2b** remained reasonably high at 66% when using THF as the solvent. In contrast, sulfones **1c** and **1d**, which bear a phenyl substituent at the nitrogen, were less amenable to undergoing α-arylation. Although compound **2c** was obtained in a reasonable 45% yield starting from phenyl sulfone **1c** (Table 2, entry 5), the annulation reaction from methyl sulfone **1d** leading to **2d** proceeded more slowly and was accompanied by an increase of the hydrodehalogenation reaction (Table 2, entries 7 and 8). Finally, the α-arylation of sulfone **1e**, which bears a methyl group at the nitrogen, afforded isoquinoline **2e** in 52% yield (Table 2, entry 9). As can be seen from Tables 1 and 2, the α-arylation of β-(2-iodobenzylamino)sulfones seems to be somewhat substrate-dependent, the best results being obtained when using phenyl sulfones. Although the reaction tolerates the presence of phenyl and methyl groups at the nitrogen atom, the *N*-benzyl-substituted substrates afforded the highest yields. Finally, the best solvents were the polar THF and DMF.

With this information in hand, without further optimization, we centered our efforts on the development of a tandem intramolecular α-arylation/Michael addition process to give access to more functionalized tetrahydroisoquinolines (Table 3). The unexpected formation of significant amounts of disulfone **3a** in the α-arylation reactions of **1a** when using DMF as the solvent (Table 1, entries 3 and 6), was a promising starting point. Gratifyingly, treatment of **1a** with a catalytic amount of $[Pd_2(dba)_3]$/BINAP and K_3PO_4 in the presence of phenyl vinyl sulfone[13] in DMF afforded disulfone **3a** in 71% yield (Table 3, entry 1). The use of xantphos as the ligand improved the yield to 85% (Table 3, entry 2). However, changing the solvent to either THF or toluene failed to promote the tandem process, and led to the formation of mixtures of the α-arylation com-

Table 3. Tandem α-arylation/Michael addition.[a]

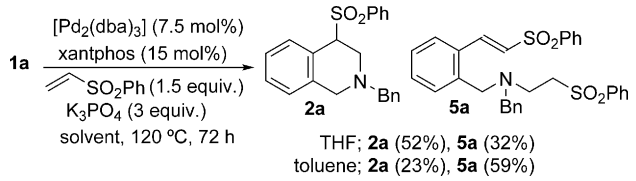


Entry	Sulfone	Michael Acceptor	Ligand	Product (yield [%])[b]	
1	**1a**	SO_2Ph	BINAP		**3a** (71)
2	**1a**	SO_2Ph	Xantphos		**3a** (85)
3	**1a**	SO_2Me	Xantphos		**6** (65)[c]
4	**1b**	SO_2Me	Xantphos		**3b** (56)[d]
5	**1b**	SO_2Me	Xantphos		**3b** (51)[e]
6	**1b**	SO_2Ph	Xantphos		**7** (62)[f]
7	**1c**	SO_2Ph	BINAP		**3c** (68)
8	**1d**	SO_2Me	BINAP		**3d** (42)
9	**1e**	SO_2Ph	Xantphos		**3e** (54)
10	**1a**	CO_2Me	Xantphos		**8** (63)
11	**1a**	CO_2Bn	Xantphos		**9** (40)
12	**1a**	$CO_2(CH_2)_2NMe_2$	Xantphos		**10** (35)
13	**1b**	CO_2Me	Xantphos		**11** (45)

[a] Reaction conditions: $[Pd_2(dba)_3]$ (7.5 mol%), BINAP or xantphos (15 mol%), Michael acceptor (1.3–1.5 equiv), and K_3PO_4 (3 equiv) in DMF at 120 °C for 72 h in a sealed tube; [b] yield of product isolated by flash chromatography; [c] **3b** (7%) was also isolated; [d] trace amounts (< 5%) of **2b** and **4b** were also isolated; [e] Cs_2CO_3 (3 equivalents) was used as the base; [f] 2.5 equivalents of Michael acceptor were used.

pound **2a** and the Heck product **5a** (Scheme 2). Although **2a** (52%) was the major product with THF as solvent, **5a** was isolated in 59% yield when the reaction was run in toluene.

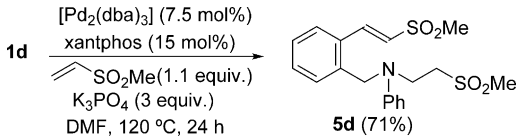
Sulfone **1b** afforded inferior results in the tandem reaction with methyl vinyl sulfone, due to the lower acidity of the methyl sulfone α-C–H bond, as well as the lower electrophilicity of methyl vinyl sulfone as the Michael acceptor (Table 3, entries 4 and 5). Interestingly, "crossed" tandem processes leading



Scheme 2. Formation of Heck-type product **5a**.

to the orthogonally-substituted disulfones **6** and **7** were also promoted when starting from **1a** and **1b**, respectively (Table 3, entries 3 and 6).

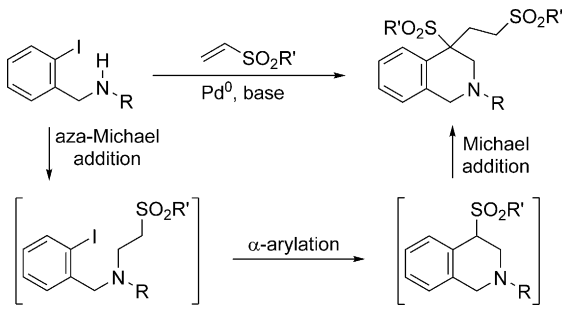
Sulfones **1c** and **1d**, which bear a phenyl substituent at the nitrogen atom, failed to undergo the tandem process when using the ligand xantphos (results not included in the table). Whereas **1c** afforded a complex reaction mixture, due to readily decomposing by retro-Michael fragmentation, the lower acidity of the methyl sulfone **1d** resulted in the exclusive formation of the Heck-type product **5d**, which was isolated in 71% yield (Scheme 3). However, exchanging the ligand for BINAP allowed **1c** and **1d** to readily undergo the tandem processes, leading to **3c** (68%) and **3d** (42%), respectively (Table 3, entries 7 and 8).



Scheme 3. Formation of Heck-type product **5d**.

Finally, the α-arylation/conjugated addition tandem process was also extended to the use of acrylic acid esters as Michael acceptors, which allowed the preparation of γ-sulfonylesters **8**–**11** in acceptable yields when using xantphos as the ligand (Table 3, entries 10–13).

As it was desirable to simplify the synthesis of symmetrically substituted disulfones (**3a–e**), we also attempted a domino aza-Michael addition/α-arylation/Michael addition process starting from the readily available *N*-alkyl-2-iodobenzylamines (Scheme 4). The development of this three-step domino process would generate a high level of molecular complexity in

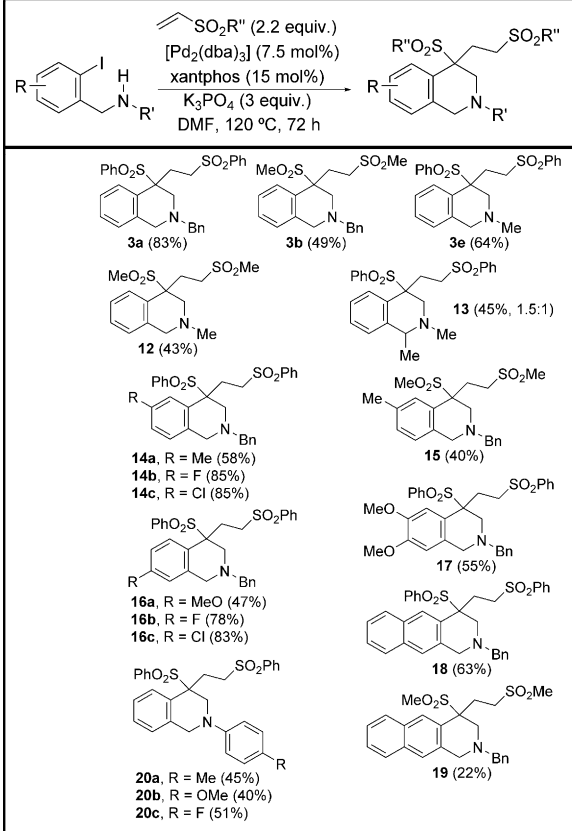


Scheme 4. Proposed domino aza-Michael addition/Pd^0-catalyzed α-arylation/Michael addition to access tetrahydroisoquinolines.

one operation, minimizing the expenditure of solvents, reagents, time, and energy.[14]

The results, shown in Table 4, demonstrate the viability of our proposal. To our delight, the reaction of *N*-benzyl-2-iodobenzylamine with 2.2 equivalents of phenyl vinyl sulfone in the presence of K_3PO_4, and using $[Pd_2(dba)_3]$/xantphos as the catalyst in DMF, afforded disulfone **3a** in 83% yield. When methyl vinyl sulfone was used as the Michael acceptor in the domino process, **3b** was obtained in 49% yield. Under the same reaction conditions and using phenyl vinyl sulfone as the Michael acceptor, *N*-methyl-2-iodobenzylamine afforded disulfone **3e** in 64% yield. The yields of these domino processes are similar to those obtained in the corresponding tandem reactions (Table 3, entries 2, 4, and 9), which indicates that the initial aza-Michael addition takes place without any interference from the competitive Heck reaction.[14] In this context, it should be noted that although one-pot aza-Michael addition/Pd^0-catalyzed α-arylation processes using acrylates have been reported,[11b] it has been impossible to develop a real domino process[15] because, in the presence of the Pd catalyst, the Heck reaction with the acrylate takes precedence over the aza-Michael addition.[12,16] The success of the herein-presented domino process with vinyl sulfones may be due to the poor activity of sulfur-substituted olefins in the Heck reaction.[17]

Table 4. Domino aza-Michael addition/α-arylation/Michael addition process.[a]



[a] Reaction conditions: $[Pd_2(dba)_3]$ (7.5 mol%), xantphos (15 mol%), vinyl sulfone (2.2 equiv), and K_3PO_4 (3 equiv) in DMF at 120 °C for 72 h in a sealed tube.

The scope of the domino aza-Michael addition/α-arylation/Michael addition reaction for the synthesis of diversely functionalized disulfones was then examined. Overall, as also observed in the tandem processes (Table 3), phenyl sulfones afforded better results than methyl sulfones in the three-step domino reaction. The higher acidity of the α-C–H bonds of the phenyl sulfone favors both the α-arylation and the Michael addition, while the higher electrophilicity of phenyl vinyl sulfone benefits the Michael addition reactions.

The domino reaction also proceeded smoothly from 2-iodobenzylamines bearing either electron-donating (Me, OMe) or electron-withdrawing groups (Cl, F) on the aromatic ring, the latter affording higher yields. Considering that the yields of the domino process essentially reflect the yield of the α-arylation reaction, these results seem to indicate that the 2-iodobenzylamines with electron-withdrawing groups show higher reactivity in the palladium-catalyzed reaction than those bearing electron-donating groups. Finally, naphtho-fused heterocycles (**18** and **19**) and tetrahydroisoquinolines bearing aryl groups on the nitrogen atom (**20a–c**) were accessible through the domino reaction.

In summary, we have developed efficient synthetic methods toward diversely functionalized tetrahydroisoquinolines based on the intramolecular Pd^0-catalyzed α-arylation of sulfones. The combination of the Pd-catalyzed reaction with intermolecular Michael and aza-Michael reactions allowed us to develop two- and three-step domino processes to synthesize diversely functionalized scaffolds from readily available starting materials. Further exploration to expand the scope of these domino processes to other heterocyclic systems is underway in our laboratory and will be reported in due course.

Experimental Section

General procedure for the three-step domino reactions

A mixture of *N*-benzyl-2-iodobenzylamine (65 mg, 0.20 mmol), $[Pd_2(dba)_3]$ (14 mg, 0.015 mmol), xantphos (17 mg, 0.03 mmol), phenyl vinyl sulfone (74 mg, 0.44 mmol), and K_3PO_4 (127 mg, 0.60 mmol) in DMF (8 mL) was stirred at 120 °C in a sealed tube for 72 h. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3×30 mL). The organic extracts were washed with brine (3×50 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO_2, from CH_2Cl_2 to 1% MeOH in CH_2Cl_2) to give disulfone **3a** (88 mg, 83%).

Acknowledgements

We gratefully acknowledge financial support for this work from Spanish MINECO-FEDER Project CTQ2012-31391.

Keywords: arylation · domino reactions · nitrogen heterocycles · palladium · sulfones

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Supporting Information

Pd^0-Catalyzed Intramolecular α-Arylation of Sulfones: Domino Reactions in the Synthesis of Functionalized Tetrahydroisoquinolines

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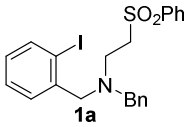
Electronic Supplementary Information

Table of Contents

General Methods. All commercially available reagents were used without further purification. ^{1}H- and ^{13}C-NMR spectra were recorded using Me_4Si as the internal standard, with a Varian Gemini 300 or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si for ^{1}H and ^{13}C NMR. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light, iodoplatinate reagent or 1% aqueous $KMnO_4$. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator.

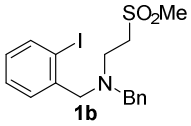
Experimental procedures and characterization data for the starting materials.



1a

***N*-Benzyl-*N*-(2-iodobenzyl)-2-(phenylsulfonyl)ethylamine (1a).** A solution of benzylamine (0.4 mL, 3.66 mmol) and phenyl vinyl sulfone (0.56 g, 3.33 mmol) in absolute EtOH (25 mL) was stirred at 80 ºC for 72 h. The solvent was removed *in vacuo* to give *N*-benzyl-2-(phenylsulfonyl)ethylamine. To a solution of the secondary amine in acetonitrile (25 mL), 2-iodobenzyl bromide (1.09 g, 3.67 mmol) and K_2CO_3 (0.92 g, 6.66 mmol) were added. After stirring at 60 ºC for 24 h, the organic solvent was evaporated. The residue was partitioned between CH_2Cl_2 and water, and the organic extracts were dried and concentrated. The residue was purified by flash chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2-MeOH 98:2) to give *N*-benzyl-*N*-(2-iodobenzyl)-2-(phenylsulfonyl)ethylamine (**1a**, 1.52 g, 93%) as a white solid; M. p. 80-82 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.89 (m, 2H), 3.22 (m, 2H), 3.57 (s, 2H), 3.60 (s, 2H), 6.91 (td, *J* = 7.5 and 1.8 Hz, 1H), 7.18-7.29 (m, 6H), 7.33 (dd, *J* = 7.5 and 1.8 Hz, 1H), 7.48 (m, 2H), 7.60 (tt, *J* = 7.5 and 1.2 Hz, 1H), 7.74-7.80 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 46.8 (CH_2), 53.2 (CH_2), 58.4 (CH_2), 62.8 (CH_2), 100.3 (C), 127.5 (CH), 128.0 (2 CH), 128.3 (CH), 128.5 (2 CH), 128.9 (2 CH), 129.1 (CH), 129.4 (2 CH), 130.4 (CH), 133,7 (CH), 138.2 (C), 139.2 (C), 139.7 (CH), 140.6 (C). HRMS (ESI-TOF) cald for $C_{22}H_{23}INO_2S$: 492.0489 $[M + H]^+$; found: 492.0493.

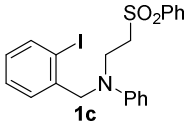
Compounds **1b-e** were prepared according to the preparation of **1a**.



1b

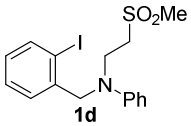
***N*-Benzyl-*N*-(2-iodobenzyl)-2-(methylsulfonyl)ethylamine (1b).** Yellow gum. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71 (s, 3H), 3.04 (m, 4H), 3.68 (s, 2H), 3.70 (s, 2H), 6.96 (td, *J* = 7.8 and 1.8 Hz, 1H), 7.22-7.36 (m, 6H), 7.45 (dd, *J* = 7.8 and 1.8 Hz, 1H), 7.84 (dd, *J* = 7.5 and 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 41.2 (CH_3), 47.1 (CH_2), 52.5 (CH_2), 58.9 (CH_2), 63.2 (CH_2), 100.5 (C), 127.7 (CH), 128.4 (CH), 128.6 (2 CH), 129.1 (2 CH), 129.4 (CH), 130.7

(CH), 138.0 (C), 139.9 (CH), 140.5 (C). HRMS (ESI-TOF) cald for $C_{22}H_{23}INO_2S$: 430.0332 [M + H]$^+$; found: 430.0332.



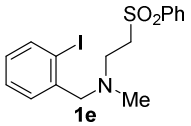
1c

***N*-(2-Iodobenzyl)-*N*-phenyl-2-(phenylsulfonyl)ethylamine (1c).** Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49 (m, 2H), 3.93 (m, 2H), 4.38 (s, 2H), 6.55 (m, 2H), 6.78 (tt, *J* = 7.2 and 1.2 Hz, 1H), 6.99 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.05 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.18-7.28 (m, 3H), 7.62 (m, 2H), 7.72 (tt, *J* = 7.6 and 1.6 Hz, 1H), 7.88 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.96-8.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 44.5 (CH_2), 52.4 (CH_2), 60.1 (CH_2), 97.7 (C), 112.1 (2 CH), 117.7 (CH), 127.3 (CH), 127.7 (2 CH), 128.3 (CH), 128.8 (CH), 129.3 (2 CH), 129.4 (2 CH), 133,8 (CH), 138.6 (C), 139.0 (C), 139.4 (CH), 146.3 (C). HRMS (ESI-TOF) cald for $C_{21}H_{21}INO_2S$: 478.0332 [M + H]$^+$; found: 478.0320.



1d

***N*-(2-Iodobenzyl)-*N*-phenyl-2-(methylsulfonyl)ethylamine (1d).** White solid; M. p. 114-118 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.93 (s, 3H), 3.62 (m, 2H), 3.99 (m, 2H), 4.46 (s, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.97 (ddd, *J* = 8.0, 7.2 and 1.6 Hz, 1H), 7.06 (dd, *J* = 7.4 and 1.6 Hz, 1H), 7.21-8.28 (m, 3H), 7.87 (dd, *J* = 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 41.8 (CH_3), 44.3 (CH_2), 51.4 (CH_2), 60.4 (CH_2), 97.8 (C), 112.7 (2 CH), 118.2 (CH), 127.6 (CH), 128.5 (CH), 129.1 (CH), 129.7 (2 CH), 138.7 (C), 139.7 (CH), 146.6 (C). HRMS (ESI-TOF) cald for $C_{16}H_{19}INO_2S$: 416.0176 [M + H]$^+$; found: 416.0176.



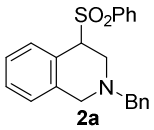
1e

***N*-(2-Iodobenzyl)-*N*-methyl-2-(phenylsulfonyl)ethylamine (1e).** Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H), 2.91 (m, 2H), 3.34 (m, 2H), 3.48 (s, 2H), 6.92 (ddd, *J* = 7.6, 7.2 and 2.0 Hz, 1H), 7.20 (dd, *J* = 7.6 and 2.0 Hz, 1H), 7.25 (ddd, *J* = 7.6, 7.2 and 1.2 Hz, 1H), 7.56 (m, 2H), 7.65 (tt, *J* = 7.5 and 1.2 Hz, 1H), 7.79 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 41.9 (CH_3), 50.6 (CH_2), 53.9 (CH_2), 65.7 (CH_2), 100.4 (C), 128.1 (2 CH), 128.3 (CH), 129.1 (CH), 129.5 (2 CH), 130.4 (CH), 133,9 (CH), 139.5 (C), 139.7 (CH), 140.4 (C). HRMS (ESI-TOF) cald for $C_{16}H_{19}INO_2S$: 416.0176 [M + H]$^+$; found: 416.0163.

Representative procedure for the Pd(0)-catalyzed α-arylation reaction (Table 1, Entry 6). A mixture of sulfone **1a** (75 mg, 0.153 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), xantphos (13 mg, 0.023 mmol), and K_3PO_4 (98 mg, 0.46 mmol) in THF (8 mL) was stirred at 120 ºC in a sealed tube for 72 h. The reaction mixture was partitioned between saturated $NaHCO_3$ aqueous solution and Et_2O. The organic extracts were dried and concentrated. The residue was purified by chromatography (from CH_2Cl_2 to CH_2Cl_2-MeOH 1%) to give sulfone **2a** (50 mg, 90%).

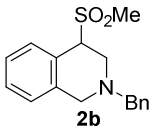
Representative procedure for the domino reactions. A mixture of *N*-benzyl-2-iodobenzylamine (65 mg, 0.20 mmol), $Pd_2(dba)_3$ (14 mg, 0.015 mmol), xantphos (17 mg, 0.03 mmol), phenyl vinyl sulfone (74 mg, 0.44 mmol), and K_3PO_4 (127 mg, 0.60 mmol) in DMF (8 mL) was stirred at 120 ºC in a sealed tube for 72 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2-MeOH 1%) to give disulfone **3a** (88 mg, 83%).

Characterization data for the compounds of Tables 1, 2 and 3, and Scheme 2.



2a

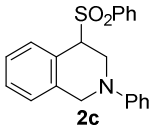
2-Benzyl-4-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (2a). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (dd, *J* = 12.9 and 4.2 Hz, 1H), 3.09 (d, *J* = 15.3 Hz, 1H), 3.35 (d, *J* = 15.3 Hz, 1H), 3.41 (d, *J* = 13.2 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.81 (ddd, *J* = 12.9, 2.4 and 1.2 Hz, 1H), 4.41 (broad t, *J* = 3.0 Hz, 1H), 6.82 (dd, *J* = 6.5 and 2.4 Hz, 1H), 7.09-7.14 (m, 2H), 7.18-7.33 (m, 7H), 7.43-7.51 (m, 3H), 7.70 (dd, *J* = 6.6 and 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 51.5 (CH_2), 53.9 (CH_2), 62.4 (CH_2), 66.1 (CH), 125.6 (C), 126.4 (CH), 126.6 (CH), 127.3 (CH), 128.0 (2 CH), 128.2 (2 CH), 128.6 (CH), 129.2 (2 CH), 129.5 (2 CH), 130.8 (CH), 132.8 (CH), 136.4 (C), 136.6 (C), 138.6 (C). HRMS (ESI-TOF) cald for $C_{22}H_{22}NO_2S$: 364.1366 $[M + H]^+$; found: 364.1362.



2b

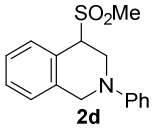
2-Benzyl-4-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (2b). Brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71 (d, *J* = 0.8 Hz, 3H), 2.82 (dd, *J* = 12.8 and 4.0 Hz, 1H), 3.33 (d, *J* = 15.6 Hz, 1H), 3.54 (d, *J* = 12.8 Hz, 1H), 3.86 (d, *J* = 15.6 Hz, 1H), 3.90 (d, *J* = 12.8 Hz, 1H), 3.93 (dt, *J* = 12.8 and 1.2 Hz, 1H), 4.06 (broad d, *J* = 3.2 Hz, 1H), 7.04 (dd, *J* = 6.8 and 2.0 Hz, 1H), 7.22-7.39 (m, H), 7.66 (dd, *J* = 6.8 and 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 40.0

(CH_3), 51.9 (CH_2), 54.6 (CH_2), 62.9 (CH_2), 64.8 (CH), 126.1 (C), 126.9 (CH), 127.0 (CH), 127.6 (CH), 128.5 (2 CH), 128.8 (CH), 129.2 (2 CH), 131.0 (CH), 135.8 (C), 136.8 (C). HRMS (ESI-TOF) cald for $C_{17}H_{20}NO_2S$: 302.1209 $[M + H]^+$; found: 302.1217.



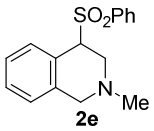
2c

2-Phenyl-4-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (2c). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.37 (dd, *J* = 13.4 and 2.8 Hz, 1H), 3.60 (d, *J* = 16.0 Hz, 1H), 3.90 (d, *J* = 16.0 Hz, 1H), 4.49 (broad t, *J* = 2.4 Hz, 1H), 4.82 (dd, *J* = 13.4 and 2.0 Hz, 1H), 6.87-6.97 (m, 4H), 7.06 (m, 2H), 7.22 (m, 2H), 7.28-7.37 (m, 5H), 7.68 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 46.3 (CH_2), 49.0 (CH_2), 66.5 (CH), 114.8 (2 CH), 119.5 (CH), 126.2 (C), 126.5 (CH), 126.7 (CH), 127.6 (2 CH), 129.0 (CH), 129.3 (4 CH), 130.8 (CH), 132.9 (CH), 135.2 (C), 137.9 (C), 148.8 (C). HRMS (ESI-TOF) cald for $C_{21}H_{20}NO_2S$: 350.1209 $[M + H]^+$; found: 350.1218.



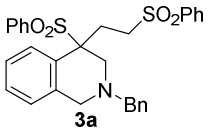
2d

4-(Methylsulfonyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2d). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.60 (d, *J* = 0.6 Hz, 3H), 3.42 (dd, *J* = 13.8 and 3.0 Hz, 1H), 4.19 (broad s, 1H), 4.26 (d, *J* = 15.6 Hz, 1H), 4.52 (d, *J* = 15.6 Hz, 1H), 4.75 (dt, *J* = 13.8 and 1.5 Hz, 1H), 6.98 (tt, *J* = 7.2 and 1.0 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.33-7.44 (m, 4H), 7.71 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 39.6 (CH_3), 49.8 (CH_2), 50.3 (CH_2), 64.9 (CH), 116.6 (2 CH), 121.0 (CH), 126.4 (C), 127.1 (CH), 127.3 (CH), 129.2 (CH), 129.5 (2 CH), 131.2 (CH), 135.0 (C), 149.6 (C). HRMS (ESI-TOF) cald for $C_{16}H_{18}NO_2S$: 288.1053 $[M + H]^+$; found: 288.1056.



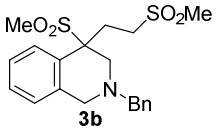
2e

2-Methyl-4-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (2e). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.68 (dd, *J* = 12.8 and 3.6 Hz, 1H), 3.12 (d, *J* = 15.0 Hz, 1H), 3.25 (d, *J* = 15.0 Hz, 1H), 3.64 (d, *J* = 12.8 Hz, 1H), 4.36 (broad s, 1H), 6.84 (m, 1H), 7.20-7.30 (m, 4H), 7.40-7.46 (m, 3H), 7.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 44.9 (CH_3), 52.7 (CH_2), 56.5 (CH_2), 66.4 (CH), 125.9 (C), 126.4 (CH), 126.5 (CH), 127.7 (2 CH), 128.7 (CH), 129.8 (2 CH), 131.0 (CH), 132.9 (CH), 136.7 (C), 138.8 (C). HRMS (ESI-TOF) cald for $C_{16}H_{18}NO_2S$: 288.1053 $[M + H]^+$; found: 288.1051.



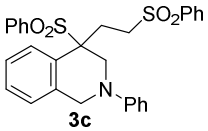
3a

2-Benzyl-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (3a). Yellow foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (m, 1H), 2.75 (dd, *J* = 12.6 and 1.2 Hz, 1H), 2.84-2.95 (m, 2H), 2.87 (d, *J* = 14.6 Hz, 1H), 3.20 (d, *J* = 12.6 Hz, 1H), 3.25 (d, *J* = 14.6 Hz, 1H), 3.37 (d, *J* = 12.6 Hz, 1H), 3.39 (m, 1H), 3.60 (d, *J* = 12.6 Hz, 1H), 6.77 (dd, *J* = 6.8 and 2.0 Hz, 1H), 7.11-7.14 (m, 2H), 7.15-7.24 (m, 4H), 7.27-7.32 (m, 5H), 7.43 (tt, *J* = 7.4 and 1.4 Hz, 1H), 7.53-7.59 (m, 2H), 7.63 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.67 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.81-7.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 27.6 (CH_2), 51.8 (CH_2), 55.2 (CH_2), 56.9 (CH_2), 62.4 (CH_2), 67.8 (C), 126.8 (CH), 127.1 (CH), 127.5 (CH), 127.9 (C), 128.0 (2 CH), 128.1 (2 CH), 128.2 (CH), 128.4 (2 CH), 128.6 (CH), 129.2 (2 CH), 129.3 (2 CH), 130.1 (2 CH), 133.2 (CH), 133.8 (CH), 136.1 (C), 136.8 (C), 137.5 (C), 138.3 (C). HRMS (ESI-TOF) cald for $C_{30}H_{30}NO_4S_2$: 532.1611 $[M + H]^+$; found: 532.1609.



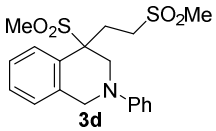
3b

2-Benzyl-4-(methylsulfonyl)-4-[2-(methylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (3b). Golden foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.64-2.89 (m, 3H), 2.70 (d, *J* = 12.6 Hz, 1H), 2.71 (s, 3H), 2.91 (s, 3H), 3.28 (td, *J* = 13.0 and 3.4, 1H), 3.41 (d, *J* = 15.2 Hz, 1H), 3.55 (d, *J* = 12.8 Hz, 1H), 3.73 (dd, *J* = 12.6 and 1.2 Hz, 1H), 3.79 (d, *J* = 15.2 Hz, 1H), 3.89 (d, *J* = 12.8 Hz, 1H), 7.06 (m, 1H), 7.27-7.40 (m, 7H), 7.69 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 25.6 (CH_2), 40.4 (CH_3), 41.0 (CH_3), 50.2 (CH_2), 55.4 (CH_2), 56.8 (CH_2), 62.8 (CH_2), 66.5 (C), 127.4 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.6 (2 CH), 129.1 (CH), 129.2 (C), 129.4 (2 CH), 136.3 (C), 136.4 (C). HRMS (ESI-TOF) cald for $C_{20}H_{26}NO_4S_2$: 408.1298 $[M + H]^+$; found: 408.1306.



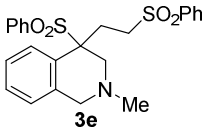
3c

2-Phenyl-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (3c). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.81 (ddd, *J* = 14.4, 12.4 and 5.2 Hz, 1H), 2.99-3.10 (m, 2H), 3.17 (d, *J* = 13.4 Hz, 1H), 3.34 (ddd, *J* = 14.0, 12.8 and 5.2 Hz, 1H), 3.47 (d, *J* = 15.6 Hz, 1H), 3.86 (d, *J* = 15.6 Hz, 1H), 4.48 (d, *J* = 13.4 Hz, 1H), 6.87-7.00 (m, 6H), 7.07 (m, 2H), 7.24-7.35 (m, 5H), 7.53 (m, 1H), 7.63 (m, 2H), 7.73 (tt, *J* = 7.4 and 1.4 Hz, 1H), 7.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 24.9 (CH_2), 50.2 (CH_2), 51.9 (CH_2), 52.2 (CH_2), 68.4 (C), 115.7 (2 CH), 120.5 (CH), 127.0 (CH), 127.5 (CH), 127.6 (2 CH), 128.1 (CH), 128.4 (2 CH), 128.5 (C), 129.3 (CH), 129.5 (2 CH), 129.6 (2 CH), 129.7 (2 CH), 133.0 (CH), 134.2 (CH), 136.3 (C), 138.2 (C), 138.5 (C), 148.6 (C). HRMS (ESI-TOF) cald for $C_{29}H_{28}NO_4S_2$: 518.1454 $[M + H]^+$; found: 518.1453.



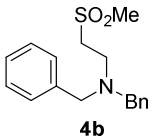
3d

4-(Methylsulfonyl)-4-[2-(methylsulfonyl)ethyl]-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3d). White solid. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 2.55 (m, 1H), 2.58 (s, 3H), 2.72 (ddd, *J* = 13.6, 12.4 and 4.0 Hz, 1H), 2.90 (ddd, *J* = 13.6, 12.4 and 4.0, 1H), 3.01 (s, 3H), 3.30 (td, *J* = 13.6 and 4.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 4.22 (d, *J* = 15.6 Hz, 1H), 4.37 (d, *J* = 13.8 Hz, 1H), 4.62 (d, *J* = 15.6 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.38-7.49 (m, 3H), 7.59 (m, 1H). ^{13}C NMR (d_6-DMSO, 100.5 MHz) δ 22.7 (CH_2), 40.1 (CH_3), 40.4 (CH_3), 48.9 (CH_2), 50.4 (CH_2), 52.9 (CH_2), 66.2 (C), 116.5 (2 CH), 120.4 (CH), 127.3 (CH), 127.6 (CH), 127.9 (CH), 128.7 (C), 129.0 (CH), 129.2 (2 CH), 136.5 (C), 149.6 (C).



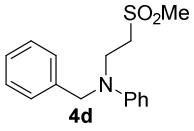
3e

2-Methyl-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (3e). Yellow foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.19 (s, 3H), 2.55 (d, *J* = 12.5 Hz, 1H), 2.65 (ddd, *J* = 13.9, 12.5 and 4.8 Hz, 1H), 2.88 (d, *J* = 15.0 Hz, 1H), 2.83-2.98 (m, 2H), 3.17 (d, *J* = 15.0 Hz, 1H), 3.26 (d, *J* = 12.5 Hz, 1H), 3.40 (ddd, *J* = 14.1, 12.8 and 4.8 Hz, 1H), 6.78 (m, 1H), 7.15-7.29 (m, 6H), 7.39 (tt, *J* = 7.2 and 1.5 Hz, 1H), 7.50-7.64 (m, 3H), 7.71 (tt, *J* = 7.2 and 1.5 Hz, 1H), 7.88-7.93 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 26.6 (CH_2), 44.9 (CH_3), 52.0 (CH_2), 57.2 (CH_2), 58.3 (CH_2), 68.4 (C), 126.8 (CH), 127.2 (CH), 127.7 (2 CH), 128.0 (C), 128.2 (CH), 128.3 (2 CH), 128.9 (CH), 129.6 (2 CH), 130.2 (2 CH), 133.1 (CH), 134.1 (CH), 137.6 (C), 137.9 (C), 138.5 (C). HRMS (ESI-TOF) cald for $C_{24}H_{26}NO_4S_2$: 456.1298 $[M + H]^+$; found: 456.1297.



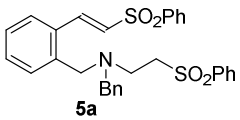
4b

***N*,*N*-Dibenzyl-2-(methylsulfonyl)ethylamine (4b).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (s, 3H), 3.03 (m, 4H), 3.64 (s, 4H), 7.20-7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 41.2 (CH_3), 47.4 (CH_2), 52.8 (CH_2), 58.8 (CH_2), 127.5 (CH), 128.5 (2 CH), 128.9 (2 CH), 138.2 (C). HRMS (ESI-TOF) cald for $C_{17}H_{22}NO_2S$: 304.1366 $[M + H]^+$; found: 304.1359.



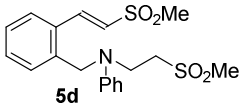
4d

***N*-Benzyl-*N*-phenyl-2-(methylsulfonyl)ethylamine (4d).** White solid; M. p. 118-121 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.89 (s, 3H), 3.28 (t, *J* = 7.2 Hz, 2H), 3.95 (t, *J* = 7.2 Hz, 2H), 4.58 (s, 2H), 6.78-6.82 (m, 3H), 7.19-7.34 (m, 7H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 41.9 (CH_3), 44.4 (CH_2), 51.7 (CH_2), 55.3 (CH_2), 113.4 (2 CH), 118.3 (CH), 127.0 (2 CH), 127.5 (CH), 128.9 (2 CH), 129.8 (2 CH), 138.0 (C), 147.3 (C). HRMS (ESI-TOF) cald for $C_{16}H_{20}NO_2S$: 290.1209 $[M + H]^+$; found: 290.1215.



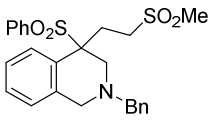
5a

***N*-Benzyl-*N*-{2-[2-(phenylsulfonyl)ethenyl]benzyl}-2-(phenylsulfonyl)ethylamine (5a).** Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82 (m, 2H), 3.26 (m, 2H), 3.50 (s, 2H), 3.69 (s, 2H), 6.75 (d, *J* = 15.3 Hz, 1H), 7.13-7.32 (m, 7H), 7.42-7.64 (m, 8H), 7.33-7.77 (m, 2H), 7.89-7.93 (m, 2H), 8.22 (d, *J* = 15.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 46.2 (CH_2), 53.0 (CH_2), 57.7 (CH_2), 58.5 (CH_2), 127.3 (2 CH), 127.6 (2 CH), 127.7 (CH), 127.8 (2 CH), 128.2 (CH), 128.4 (2 CH), 128.8 (2 CH), 129.2 (2 CH), 129.3 (CH), 129.4 (CH), 130.7 (CH), 131.1 (CH), 132.1 (C), 133.3 (CH), 133.5 (CH), 137.5 (C), 137.9 (C), 138.9 (C), 140.3 (CH), 140.7 (C). HRMS (ESI-TOF) cald for $C_{30}H_{30}NO_4S_2$: 532.1611 $[M + H]^+$; found: 532.1607.



5d

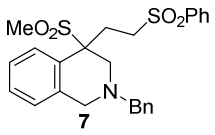
***N*-{2-[2-(Methylsulfonyl)ethenyl]benzyl}-*N*-phenyl-2-(methylsulfonyl)ethylamine (5d).** Brown foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.91 (s, 3H), 3.00 (s, 3H), 3.31 (m, 2H), 3.89 (m, 2H), 4.63 (s, 2H), 6.75 (m, 2H), 6.83 (tt, *J* = 7.2 and 1.2 Hz, 1H), 6.87 (d, *J* = 15.2 Hz, 1H), 7.22-7.27 (m, 3H), 7.28-7.39 (m, 2H), 7.55 (dd, *J* = 7.6 and 1.6 Hz, 2H), 7.93 (d, *J* = 15.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 41.8 (CH_3), 43.0 (CH_3), 43.9 (CH_2), 51.1 (CH_2), 52.9 (CH_2), 113.9 (2 CH), 119.0 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 129.7 (2 CH), 130.7 (C), 131.2 (CH), 137.1 (C), 140.3 (CH), 146.7 (C). HRMS (ESI-TOF) cald for $C_{19}H_{24}NO_4S_2$: 394.1141 $[M + H]^+$; found: 394.1148.



6

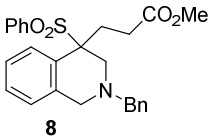
2-Benzyl-4-[2-(methylsulfonyl)ethyl]-4-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (6). Yellow Oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.76-2.86 (m, 2H), 2.83 (s, 3H), 2.88 (d, *J* = 12.6 Hz, 1H), 2.95 (d, *J* = 14.6 Hz, 1H), 3.01 (m, 1H), 3.26 (d, *J* = 12.6 Hz, 1H), 3.33 (d, *J* = 14.6 Hz, 1H), 3.36 (m, 1H), 3.42 (d, *J* = 12.8 Hz, 1H), 3.68 (d, *J* = 12.8 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.17-7.39 (m, 11H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.0 (CH_2), 40.4 (CH_3), 50.7 (CH_2), 55.7 (CH_2), 57.0 (CH_2), 62.6 (CH_2), 68.0

(C), 127.2 (CH), 127.5 (CH), 127.9 (CH), 128.2 (2 CH), 128.4 (CH), 128.5 CH), 128.7 (2 CH), 129.0 (C), 129.6 (2 CH), 130.4 (2 CH), 133.5 (CH), 136.4 (C), 137.0 (C), 137.6 (C). HRMS (ESI-TOF) cald for $C_{25}H_{28}NO_4S_2$: 470.1454 $[M + H]^+$; found: 470.1457.



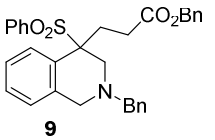
7

2-Benzyl-4-(methylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (7). Pale yellow Oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50 (ddd, *J* = 14.2, 12.6 and 5.2 Hz, 1H), 2.61 (d, *J* = 12.4 Hz, 1H), 2.66 (s, 3H), 2.67 (ddd, *J* = 14.2, 12.6 and 3.8 Hz, 1H), 2.88 (ddd, *J* = 14.2, 12.6 and 3.8 Hz, 1H), 3.26 (ddd, *J* = 14.2, 12.8 and 5.2 Hz, 1H), 3.34 (d, *J* = 15.2 Hz, 1H), 3.49 (d, *J* = 12.6 Hz, 1H), 3.66 (dd, *J* = 12.4 and 1.4 Hz, 1H), 3.74 (d, *J* = 15.2 Hz, 1H), 3.84 (d, *J* = 12.6 Hz, 1H), 7.02 (dd, *J* = 7.4 and 1.2 Hz, 1H), 7.17-7.38 (m, 7H), 7.40 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.56-7.62 (m, 2H), 7.69 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.86-7.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 25.0 (CH_2), 40.8 (CH_3), 51.6 (CH_2), 55.3 (CH_2), 56.8 (CH_2), 62.8 (CH_2), 66.6 (C), 127.3 (CH), 127.7 (CH), 127.8 (CH), 128.1 (CH), 128.2 (2 CH), 128.6 (2 CH), 128.8 (C), 129.0 (CH), 129.3 (2 CH), 129.4 (2 CH), 134.0 (CH), 136.3 (C), 136.4 (C), 138.3 (C). HRMS (ESI-TOF) cald for $C_{25}H_{28}NO_4S_2$: 470.1454 $[M + H]^+$; found: 470.1444.



8

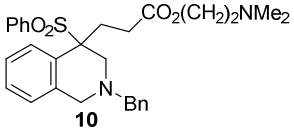
2-Benzyl-4-[2-(methoxycarbonyl)ethyl]-4-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (8). Pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (ddd, *J* = 16.4, 11.2 and 5.2 Hz, 1H), 2.55 (ddd, *J* = 16.4, 11.6 and 5.2 Hz, 1H), 2.65 (ddd, *J* = 14.0, 11.2 and 5.2 Hz, 1H), 2.80 (dd, *J* = 12.6 and 0.8 Hz, 1H), 2.92 (ddd, *J* = 14.0, 11.6 and 5.2 Hz, 1H), 2.96 (d, *J* = 14.4 Hz, 1H), 3.18 (d, *J* = 14.4 Hz, 1H), 3.44 (d, *J* = 13.2 Hz, 1H), 3.45 (d, *J* = 12.6 Hz, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 3.65 (s, 3H), 6.77 (d, *J* = 7.4 Hz, 1H), 7.12-7.37 (m, 11H), 7.42 (tt, *J* = 7.4 and 1.2 Hz, 1H), 7.86 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.8 (CH_2), 29.7 (CH_2), 51.9 (CH_3), 55.0 (CH_2), 57.1 (CH_2), 62.6 (CH_2), 69.2 (C), 126.9 (CH), 127.0 (CH), 127.6 (CH), 128.0 (2 CH), 128.4 (2 CH), 128.6 (CH), 128.9 (CH), 129.0 (C), 129.4 (2 CH), 130.3 (2 CH), 132.9 (CH), 136.4 (C), 137.6 (C), 138.3 (C), 173.2 (C). HRMS (ESI-TOF) cald for $C_{26}H_{28}NO_4S$: 450.1734 $[M + H]^+$; found: 450.1736.



9

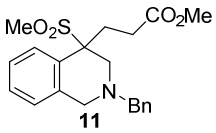
2-Benzyl-4-[2-(benzyloxycarbonyl)ethyl]-4-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (9). Pale yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (ddd, *J* = 16.0, 11.0 and 5.0 Hz, 1H),

2.54-2.70 (m, 2H), 2.79 (d, *J* = 12.8 Hz, 1H), 2.93 (m, 1H), 2.96 (d, *J* = 14.6 Hz, 1H), 3.17 (d, *J* = 14.6 Hz, 1H), 3.41 (d, *J* = 12.8 Hz, 1H), 3.44 (d, *J* = 12.8 Hz, 1H), 3.62 (d, *J* = 12.8 Hz, 1H), 5.08 (s, 2H), 6.76 (dd, *J* = 7.2 and 0.8 Hz, 1H), 7.10-7.44 (m, 17H), 7.85 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.7 (CH_2), 29.9 (CH_2), 55.1 (CH_2), 57.1 (CH_2), 62.6 (CH_2), 66.6 (CH_2), 69.2 (C), 126.9 (CH), 127.1 (CH), 127.6 (CH), 128.0 (2 CH), 128.4 (6 CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 129.0 (C), 129.4 (2 CH), 130.3 (2 CH), 132.9 (CH), 135.9 (C), 136.4 (C), 137.7 (C), 138.3 (C), 172.6 (C). HRMS (ESI-TOF) cald for $C_{32}H_{32}NO_4S$: 526.2047 $[M + H]^+$; found: 526.2042.



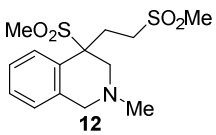
10

2-Benzyl-4-{[2-(dimethylamino)ethoxy]carbonylethyl}-4-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (10). Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (m, 1H), 2.26 (s, 6H), 2.50-2.68 (m, 2H), 2.53 (t, *J* = 5.6 Hz, 2H), 2.78 (d, *J* = 12.8 Hz, 1H), 2.92 (ddd, *J* = 14.0, 11.6 and 4.8 Hz, 1H), 2.98 (d, *J* = 15.0 Hz, 1H), 3.16 (d, *J* = 15.0 Hz, 1H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.48 (d, *J* = 12.8 Hz, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 4.14 (t, *J* = 5.6 Hz, 2H), 6.76 (d, *J* = 7.2 Hz, 1H), 7.10-7.44 (m, 12H), 7.85 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.5 (CH_2), 29.8 (CH_2), 45.9 (2 CH_3), 55.0 (CH_2), 57.1 (CH_2), 57.9 (CH_2), 62.6 (CH_2), 62.7 (CH_2), 69.2 (C), 126.9 (CH), 127.1 (CH), 127.6 (CH), 128.0 (2 CH), 128.4 (2 CH), 128.6 (CH), 128.9 (CH), 129.0 (C), 129.4 (2 CH), 130.3 (2 CH), 132.9 (CH), 136.4 (C), 137.6 (C), 138.4 (C), 172.8 (C). HRMS (ESI-TOF) cald for $C_{29}H_{35}N_2O_4S$: 507.2312 $[M + H]^+$; found: 507.2314.



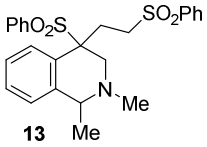
11

2-Benzyl-4-[2-(methoxycarbonyl)ethyl]-4-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (11). Pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (ddd, *J* = 16.2, 11.2 and 5.4 Hz, 1H), 2.44 (ddd, *J* = 16.2, 11.2 and 5.4 Hz, 1H), 2.53 (ddd, *J* = 14.4, 11.2 and 5.4 Hz, 1H), 2.68 (ddd, *J* = 14.4, 11.2 and 5.4 Hz, 1H), 2.68 (d, *J* = 12.6 Hz, 1H), 2.71 (s, 3H), 3.32 (d, *J* = 15.2 Hz, 1H), 3.50 (d, *J* = 12.6 Hz, 1H), 3.64 (s, 3H), 3.76 (dd, *J* = 15.2 and 1.6 Hz, 1H), 3.78 (dd, *J* = 12.6 and 1.6 Hz, 1H), 3.90 (d, *J* = 12.6 Hz, 1H), 7.02 (dd, *J* = 6.4 and 2.4 Hz, 1H), 7.22-7.39 (m, 7H), 7.67 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 26.5 (CH_2), 29.4 (CH_2), 41.3 (CH_3), 52.0 (CH_3), 55.5 (CH_2), 57.0 (CH_2), 63.1 (CH_2), 67.6 (C), 127.3 (CH), 127.7 (CH), 127.8 (CH), 128.7 (2 CH), 128.8 (CH), 128.9 (CH), 129.5 (2 CH), 129.8 (C), 136.6 (C), 136.8 (C), 172.9 (C). HRMS (ESI-TOF) cald for $C_{21}H_{26}NO_4S$: 388.1577 $[M + H]^+$; found: 388.1577.



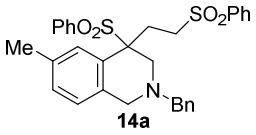
12

2-Methyl-4-(methylsulfonyl)-4-[2-(methylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (12). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 2.54 (d, *J* = 12.8 Hz, 1H), 2.68 (td, *J* = 13.2 and 4.4 Hz, 1H), 2.69 (s, 3H), 2.78 (dd, *J* = 13.2, 12.4 and 4.4, 1H), 2.88 (ddd, *J* = 13.2, 12.4 and 4.4 Hz, 1H), 2.93 (s, 3H), 3.28 (td, *J* = 13.2 and 4.4 Hz, 1H), 3.39 (d, *J* = 14.8 Hz, 1H), 3.61 (dd, *J* = 12.8 and 1.6 Hz, 1H), 3.84 (dd, *J* = 14.8 and 0.8 Hz, 1H), 7.13 (m, 1H), 7.30-7.36 (m, 2H), 7.68 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 25.4 (CH_2), 40.6 (CH_3), 41.2 (CH_3), 45.6 (CH_3), 50.4 (CH_2), 58.0 (CH_2), 58.3 (CH_2), 66.6 (C), 127.3 (CH), 127.9 (CH), 128.5 (CH), 129.0 (C), 129.3 (CH), 136.7 (C). HRMS (ESI-TOF) cald for $C_{14}H_{22}NO_4S_2$: 332.0985 $[M + H]^+$; found: 332.0988.



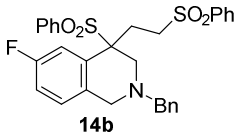
13

2,3-Dimethyl-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (13). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 1.5:1 mixture of diastereomers) δ 0.45 (d, *J* = 6.4 Hz, 3H major diastereomer), 0.99 (d, *J* = 6.8 Hz, 3H minor diastereomer), 2.18 (s, 3H minor diastereomer), 2.20 (s, 3H major diastereomer), 2.54 (d, *J* = 12.4 Hz, 1H major diastereomer), 2.60-2.70 (m, 1H), 2.81-2.91 (m, 2H), 2.98-3.10 (m, 1H), 3.20-3.41 (m, 2H), 6.78 (m, 1H minor diastereomer), 6.93 (m, 1H major diastereomer), 7.09-7.74 (m, 11H), 7.88-7.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz, 1.5:1 mixture of diastereomers) δ 14.3 (CH_3 major), 16.0 (CH_3 minor), 25.1 (CH_2 major), 27.1 (CH_2 minor), 41.1 (CH_3 minor), 42.3 (CH_3 major), 50.7 (CH_2), 51.9 (CH_2), 52.1 (CH_2), 55.5(CH_2), 56.6 (CH minor), 58.9 (CH major), 67.8 (C), 68.9 (C), 126.8 (CH), 126.9 (CH), 127.0 (CH), 127.3 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.8 (CH), 128.9 (CH), 129.5 (CH), 129.6 (CH), 129.7 (CH), 130.5 (CH), 132.7 (CH), 133.1 (CH), 134.1 (CH), 134.2 (CH), 138.5 (C), 138.9 (C), 142.8 (C), 143.2 (C). HRMS (ESI-TOF) cald for $C_{25}H_{28}NO_4S_2$: 470.1454 $[M + H]^+$; found: 470.1452.



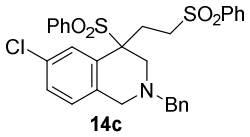
14a

2-Benzyl-6-methyl-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (14a). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 2.56 (m, 1H), 2.72 (d, *J* = 12.4 Hz, 1H), 2.82-2.93 (m, 2H), 2.84 (d, *J* = 14.8 Hz, 1H), 3.18 (d, *J* = 12.4 Hz, 1H), 3.21 (d, *J* = 14.8 Hz, 1H), 3.33-3.42 (m, 1H), 3.37 (d, *J* = 12.8 Hz, 1H), 3.58 (d *J* = 12.8 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.12 (m, 2H), 7.20-7.33 (m, 7H), 7.38 (s, 1H), 7.44 (tt, *J* = 7.4 and 1.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.68 (tt, *J* = 7.4 and 1.2 Hz, 1H), 7.82-7.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 21.5 (CH_3), 27.9 (CH_2), 52.1 (CH_2), 55.3 (CH_2), 57.2 (CH_2), 62.6 (CH_2), 68.1 (C), 126.9 (CH), 127.7 (CH), 127.9 (C), 128.2 (2 CH), 128.3 (2 CH), 128.5 (CH), 128.6 (2 CH), 129.4 (2 CH), 129.5 (2 CH), 129.7 (CH), 130.4 (2 CH), 133.4 (CH), 134.0 (CH), 134.8 (C), 136.4 (C), 136.9 (C), 137.1 (C), 138.6 (C). HRMS (ESI-TOF) cald for $C_{31}H_{32}NO_4S_2$: 546.1767 $[M + H]^+$; found: 546.1769.



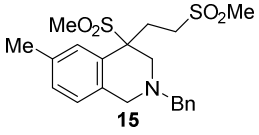
14b

2-Benzyl-6-fluoro-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (14b). Golden foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (ddd, *J* = 13.6, 12.4 and 4.8 Hz, 1H), 2.72-2.90 (m, 2H), 2.76 (d, *J* = 12.8 Hz, 1H), 2.86 (d, *J* = 14.4 Hz, 1H), 3.18 (d, *J* = 12.8 Hz, 1H), 3.24 (d, *J* = 14.4 Hz, 1H), 3.40 (ddd, *J* = 14.0, 12.8 and 4.8 Hz, 1H), 3.40 (d, *J* = 12.8 Hz, 1H), 3.61 (d *J* = 12.8 Hz, 1H), 6.77 (dd, *J* = 8.4 and 5.6 Hz, 1H), 6.91 (td, *J* = 8.4 and 2.4 Hz, 1H), 7.14 (m, 2H), 7.27-7.35 (m, 6H), 7.39 (m, 2H), 7.48 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.59 (m, 2H), 7.70 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.3 (CH_2), 51.9 (CH_2), 54.9 (CH_2), 56.8 (CH_2), 62.5 (CH_2), 67.8 (d, *J* = 1.5 Hz, C), 115.1 (d, *J* = 23.3 Hz, CH), 116.3 (d, *J* = 21.8 Hz, CH), 127.9 (CH), 128.2 (2 CH), 128.4 (2 CH), 128.6 (d, *J* = 7.8 Hz, CH), 128.7 (2 CH), 129.4 (2 CH), 129.6 (2 CH), 130.3 (d, *J* = 7.8 Hz, C), 130.4 (2 CH), 133.5 (d, *J* = 3.1 Hz, C), 133.7 (CH), 134.2 (CH), 136.1 (C), 136.7 (C), 138.3 (C), 161.5 (d, *J* = 246.6 Hz, C). HRMS (ESI-TOF) cald for $C_{30}H_{29}FNO_4S_2$: 550.1117 $[M + H]^+$; found: 550.1119.



14c

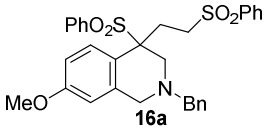
2-Benzyl-6-chloro-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (14c). Golden foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (ddd, *J* = 14.0, 12.2 and 4.8 Hz, 1H), 2.75 (td, *J* = 14.0 and 4.0 Hz, 1H), 2.77 (d, *J* = 12.4 Hz, 1H), 2.88 (ddd, *J* = 14.0, 12.4 and 4.0 Hz, 1H), 2.88 (d, *J* = 15.0 Hz, 1H), 3.21 (d, *J* = 12.4 Hz, 1H), 3.24 (d, *J* = 15.0 Hz, 1H), 3.40 (ddd, *J* = 14.0, 12.4 and 4.8 Hz, 1H), 3.42 (d, *J* = 13.0 Hz, 1H), 3.61 (d *J* = 13.0 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 7.12-7.17 (m, 2H), 7.16 (dd, *J* = 8.4 and 2.0 Hz, 1H), 7.26-7.35 (m, 5H), 7.38 (m, 2H), 7.48 (tt, *J* = 7.4 and 1.2 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.60 (m, 2H), 7.71 (tt, *J* = 7.4 and 1.2 Hz, 1H), 7.83-7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.2 (CH_2), 51.9 (CH_2), 54.9 (CH_2), 56.7 (CH_2), 62.5 (CH_2), 67.7 (C), 127.9 (CH), 128.1 (CH), 128.2 (2 CH), 128.4 (2 CH), 128.5 (CH), 128.7 (2 CH), 129.1 (CH), 129.4 (2 CH), 129.6 (2 CH), 130.3 (C), 130.4 (2 CH), 133.0 (C), 133.7 (CH), 134.2 (CH), 136.0 (C), 136.1 (C), 136.6 (C), 138.3 (C). HRMS (ESI-TOF) cald for $C_{30}H_{29}ClNO_4S_2$: 566.1221 $[M + H]^+$; found: 566.1223.



15

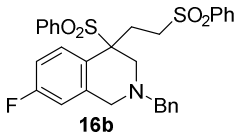
2-Benzyl-6-methyl-4-(methylsulfonyl)-4-[2-(methylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (15). Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.65 (m, 1H), 2.67 (d, *J* = 12.6 Hz, 1H), 2.72 (s, 3H), 2.75-2.92 (m, 2H), 2.92 (s, 3H), 3.30 (m, 1H), 3.35 (d, *J* = 16.0 Hz, 1H), 3.53 (d, *J* = 12.6 Hz, 1H), 3.71 (d, *J* = 12.6 Hz, 1H), 3.75 (d, *J* = 16.0

Hz, 1H), 3.88 (d, *J* = 12.6 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.30-7.39 (m, 5H), 7.47 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 21.5 (CH_3), 25.8 (CH_2), 40.6 (CH_3), 41.2 (CH_3), 50.3 (CH_2), 55.3 (CH_2), 57.1 (CH_2), 63.0 (CH_2), 66.6 (C), 127.4 (CH), 127.9 (CH), 128.5 (CH), 128.8 (2 CH), 129.2 (C), 129.5 (2 CH), 130.2 (CH), 133.4 (C), 136.7 (C), 137.7 (C). HRMS (ESI-TOF) cald for $C_{21}H_{28}NO_4S_2$: 422.1454 $[M + H]^+$; found: 422.1455.



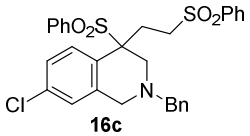
16a

2-Benzyl-7-methoxy-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (16a). Colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (ddd, *J* = 14.4, 12.0 and 4.8 Hz, 1H), 2.71 (dd, *J* = 12.6 and 1.2 Hz, 1H), 2.83 (d, *J* = 15.6 Hz, 1H), 2.82-2.93 (m, 2H), 3.17 (d, *J* = 12.8 Hz, 1H), 3.20 (d, *J* = 14.8 Hz, 1H), 3.35 (ddd, *J* = 14.0, 12.0 and 4.6 Hz, 1H), 3.36 (d, *J* = 12.6 Hz, 1H), 3.57 (d *J* = 12.6 Hz, 1H), 6.30 (d, *J* = 2.8 Hz, 1H), 6.78 (dd, *J* = 8.8 and 2.8 Hz, 1H), 7.10 (m, 2H), 7.23-7.35 (m, 7H), 7.46 (tt, *J* = 7.2 and 1.2 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.54-7.60 (m, 2H), 7.68 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.82-7.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 27.8 (CH_2), 52.1 (CH_2), 55.4 (CH_3), 55.6 (CH_2), 57.3 (CH_2), 62.6 (CH_2), 67.8 (C), 111.6 (CH), 113.7 (CH), 119.9 (C), 127.7 (CH), 128.2 (2 CH), 128.3 (2 CH), 128.6 (2 CH), 129.4 (2 CH), 129.5 (2 CH), 129.8 (CH), 130.3 (2 CH), 133.4 (CH), 134.0 (CH), 136.4 (C), 137.2 (C), 138.6 (C), 139.3 (C), 159.8 (C). HRMS (ESI-TOF) cald for $C_{31}H_{32}NO_5S_2$: 562.1716 $[M + H]^+$; found: 562.1713.



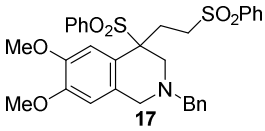
16b

2-Benzyl-7-fluoro-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (16b). Golden foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (m, 1H), 2.74 (dd, *J* = 12.8 and 1.2 Hz, 1H), 2.81-2.89 (m, 2H), 2.87 (d, *J* = 15.6 Hz, 1H), 3.20 (d, *J* = 12.8 Hz, 1H), 3.23 (d, *J* = 15.6 Hz, 1H), 3.36 (m, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 6.51 (dd, *J* = 8.8 and 2.8 Hz, 1H), 6.94 (td, *J* = 8.8 and 2.8 Hz, 1H), 7.11 (m, 2H), 7.25-7.36 (m, 7H), 7.48 (tt, *J* = 7.6 and 1.6 Hz, 1H), 7.58 (m, 2H), 7.63 (dd, *J* = 8.8 and 5.6 Hz, 1H), 7.70 (tt, *J* = 7.6 and 1.6 Hz, 1H), 7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.0 (CH_2), 52.0 (CH_2), 55.3 (CH_2), 56.9 (CH_2), 62.4 (CH_2), 67.6 (C), 113.7 (d, *J* = 21.8 Hz, CH), 114.7 (d, *J* = 21.8 Hz, CH), 124.1 (d, *J* = 3.1 Hz, C), 127.9 (CH), 128.3 (2 CH), 128.4 (2 CH), 128.7 (2 CH), 129.4 (2 CH), 129.6 (2 CH), 130.3 (2 CH), 130.5 (d, *J* = 7.8 Hz, CH), 133.6 (CH), 134.1 (CH), 136.0 (C), 136.9 (C), 138.5 (C), 140.3 (d, *J* = 7.7 Hz, C), 162.5 (d, *J* = 249.6 Hz, C). HRMS (ESI-TOF) cald for $C_{30}H_{29}FNO_4S_2$: 550.1117 $[M + H]^+$; found: 550.1121.



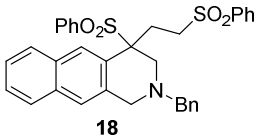
16c

2-Benzyl-7-chloro-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (16c). Golden foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (m, 1H), 2.75 (dd, *J* = 13.2 and 1.2 Hz, 1H), 2.80-2.88 (m, 2H), 2.86 (d, *J* = 15.2 Hz, 1H), 3.19 (d, *J* = 13.2 Hz, 1H), 3.23 (d, *J* = 15.2 Hz, 1H), 3.36 (m, 1H), 3.39 (d, *J* = 12.8 Hz, 1H), 3.59 (d *J* = 12.8 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 7.10-7.12 (m, 2H), 7.21 (dd, *J* = 8.4 and 2.4 Hz, 1H), 7.27-7.38 (m, 7H), 7.50 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.56-7.61 (m, 3H), 7.70 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.82-7.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 27.9 (CH_2), 51.8 (CH_2), 54.9 (CH_2), 56.8 (CH_2), 62.3 (CH_2), 67.4 (C), 126.9 (C), 127.0 (CH), 127.6 (CH), 127.9 (CH), 128.3 (2 CH), 128.4 (2 CH), 128.7 (2 CH), 129.4 (2 CH), 129.6 (2 CH), 129.9 (CH), 130.4 (2 CH), 133.7 (CH), 134.1 (CH), 134.9 (C), 136.0 (C), 136.8 (C), 138.5 (C), 139.6 (C). HRMS (ESI-TOF) cald for $C_{30}H_{29}ClNO_4S_2$: 566.1221 $[M + H]^+$; found: 566.1221.



17

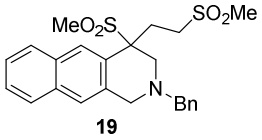
2-Benzyl-6,7-dimethoxy-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (17). Golden foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (ddd, *J* = 13.2, 11.2 and 5.0 Hz, 1H), 2.71 (d, *J* = 12.4 Hz, 1H), 2.81 (d, *J* = 14.4 Hz, 1H), 2.80-2.97 (m, 2H), 3.16 (d, *J* = 13.6 Hz, 2H), 3.36 (d, *J* = 13.0 Hz, 1H), 3.37 (m, 1H), 3.57 (d *J* = 13.0 Hz, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 6.26 (s, 1H), 7.10 (m, 2H), 7.18 (s, 1H), 7.24-7.34 (m, 5H), 7.38 (m, 2H), 7.47 (tt, *J* = 7.2 and 1.2 Hz, 1H), 7.55-7.60 (m, 2H), 7.67 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.83-7.87 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 27.7 (CH_2), 52.1 (CH_2), 55.1 (CH_2), 55.9 (CH_3), 56.3 (CH_3), 57.1 (CH_2), 62.6 (CH_2), 68.0 (C), 109.2 (CH), 110.5 (CH), 119.4 (C), 127.7 (CH), 128.2 (2 CH), 128.3 (2 CH), 128.6 (2 CH), 129.4 (2 CH), 129.5 (2 CH), 130.2 (2 CH), 130.8 (C), 133.4 (CH), 134.0 (CH), 136.4 (C), 137.2 (C), 138.7 (C), 148.3 (C), 149.5 (C). HRMS (ESI-TOF) cald for $C_{32}H_{34}NO_6S_2$: 592.1822 $[M + H]^+$; found: 592.1818.



18

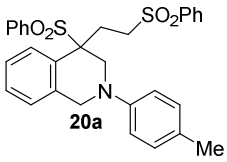
2-Benzyl-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydrobenzo[*g*]isoquinoline (18). Golden foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70 (td, *J* = 12.8 and 4.6 Hz, 1H), 2.86 (dd, *J* = 12.4 and 1.2 Hz, 1H), 2.91 (ddd, *J* = 14.0, 12.8 and 3.6 Hz, 1H), 3.02 (td, *J* = 12.8 and 3.6 Hz, 1H), 3.08 (d, *J* = 14.8 Hz, 1H), 3.31 (d, *J* = 12.4 Hz, 1H), 3.41 (ddd, *J* = 14.0, 12.8 and 4.6 Hz, 1H), 3.45 (d, *J* = 12.8 Hz, 1H), 3.47 (d, *J* = 14.8 Hz, 1H), 3.66 (d, *J* = 12.8 Hz, 1H), 7.12-7.18 (m, 4H), 7.25-7.35 (m, 6H), 7.41 (m, 1H), 7.46-7.51 (m, 2H), 7.52-7.57 (m, 2H), 7.64-7.71 (m, 2H), 7.76 (m, 1H), 7.79-7.83 (m, 2H), 8.06 (s, 1H). ^{13}C

NMR ($CDCl_3$, 100.5 MHz) δ 28.9 (CH_2), 52.0 (CH_2), 56.0 (CH_2), 57.7 (CH_2), 62.8 (CH_2), 68.2 (C), 125.4 (CH), 126.2 (CH), 126.6 (C), 127.1 (CH), 127.4 (CH), 127.8 (CH), 128.2 (2 CH), 128.3 (2 CH), 128.5 (CH), 128.6 (CH), 128.7 (2 CH), 129.4 (2 CH), 129.6 (2 CH), 130.6 (2 CH), 132.2 (C), 132.9 (C), 133.5 (CH), 134.0 (CH), 134.3 (C), 136.4 (C), 136.9 (C), 138.6 (C). HRMS (ESI-TOF) cald for $C_{34}H_{32}NO_4S_2$: 582.1767 $[M + H]^+$; found: 582.1768.



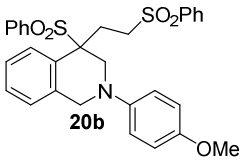
19

2-Benzyl-4-(methylsulfonyl)-4-[2-(methylsulfonyl)ethyl]-1,2,3,4-tetrahydrobenzo[*g*]isoquinoline (19). Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.68 (s, 3H), 2.74-2.96 (m, 3H), 2.79 (d, *J* = 12.8 Hz, 1H), 2.93 (s, 3H), 3.36 (m, 1H), 3.55 (d, *J* = 14.6 Hz, 1H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.83 (dd, *J* = 12.8 and 1.2 Hz, 1H), 3.94 (d, *J* = 12.8 Hz, 1H), 3.99 (d, *J* = 14.6 Hz, 1H), 7.31-7.41 (m, 5H), 7.45-7.53 (m, 2H), 7.55 (s, 1H), 7.71 (m, 1H), 7.87 (m, 1H), 8.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 26.3 (CH_2), 40.7 (CH_3), 41.3 (CH_3), 50.4 (CH_2), 56.0 (CH_2), 57.5 (CH_2), 63.2 (CH_2), 67.0 (C), 126.1 (CH), 126.6 (CH), 127.1 (CH), 127.7 (C), 127.8 (CH), 128.0 (CH), 128.6 (CH), 128.7 (CH), 128.8 (2 CH), 129.6 (2 CH), 132.5 (C), 132.9 (C), 133.2 (C), 136.6 (C). HRMS (ESI-TOF) cald for $C_{24}H_{28}NO_4S_2$: 458.1454 $[M + H]^+$; found: 458.1437.



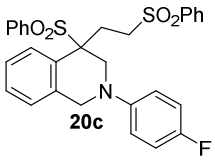
20a

2-(4-Methylphenyl)-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (20a). Orange gum. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 2.79 (ddd, *J* = 14.4, 12.2 and 5.2 Hz, 1H), 2.98-3.10 (m, 2H), 3.12 (d, *J* = 13.2 Hz, 1H), 3.35 (ddd, *J* = 14.0, 12.8 and 5.2 Hz, 1H), 3.45 (d, *J* = 15.4 Hz, 1H), 3.81 (d, *J* = 15.4 Hz, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 6.80 (m, 2H), 6.86 (m, 1H), 6.97-7.02 (m, 2H), 7.07-7.13 (m, 4H), 7.23-7.32 (m, 3H), 7.52 (m, 1H), 7.60-7.65 (m, 2H), 7.72 (tt, *J* = 7.4 and 1.4 Hz, 1H), 7.93-7.96 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 20.6 (CH_3), 25.0 (CH_2), 50.7 (CH_2), 51.9 (CH_2), 52.9 (CH_2), 68.5 (C), 116.1 (2 CH), 127.0 (CH), 127.5 (CH), 127.6 (2 CH), 128.1 (CH), 128.4 (2 CH), 128.5 (C), 129.2 (CH), 129.7 (2 CH), 130.0 (4 CH), 133.0 (CH), 134.2 (CH), 136.5 (C), 138.3 (C), 138.5 (C), 146.6 (C). One C was not observed. HRMS (ESI-TOF) cald for $C_{30}H_{30}NO_4S_2$: 532.1611 $[M + H]^+$; found: 532.1621.



20b

2-(4-Methoxyphenyl)-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (20b). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.79 (ddd, *J* = 14.4, 12.2 and 5.0 Hz, 1H), 2.96-3.10 (m, 2H), 3.11 (d, *J* = 12.8 Hz, 1H), 3.36 (ddd, *J* = 14.4, 12.8 and 4.8 Hz, 1H), 3.44 (d, *J* = 15.2 Hz, 1H), 3.80 (s, 3H), 3.80 (d, *J* = 15.2 Hz, 1H), 4.32 (d, *J* = 12.8 Hz, 1H), 6.82-6.90 (m, 5H), 7.02 (t, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.22-7.33 (m, 3H), 7.53 (m, 1H), 7.62 (t, *J* = 7.6 Hz, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 25.2 (CH_2), 51.7 (CH_2), 52.0 (CH_2), 53.9 (CH_2), 55.8 (CH_3), 68.6 (C), 114.9 (2 CH), 117.9 (2 CH), 127.0 (CH), 127.5 (CH), 127.6 (2 CH), 128.2 (CH), 128.4 (2 CH), 128.5 (C), 129.2 (CH), 129.7 (2 CH), 129.8 (2 CH), 133.0 (CH), 134.3 (CH), 136.6 (C), 138.4 (C), 138.5 (C), 143.0 (C), 154.3 (C). HRMS (ESI-TOF) cald for $C_{30}H_{30}NO_5S_2$: 548.1560 $[M + H]^+$; found: 548.1564.



20c

2-(4-Fluorophenyl)-4-(phenylsulfonyl)-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (20c). Golden foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.79 (ddd, *J* = 14.4, 12.4 and 5.2 Hz, 1H), 2.98-3.09 (m, 2H), 3.14 (d, *J* = 13.2 Hz, 1H), 3.33 (ddd, *J* = 14.4, 12.8 and 4.8 Hz, 1H), 3.43 (d, *J* = 15.4 Hz, 1H), 3.83 (d, *J* = 15.4 Hz, 1H), 4.38 (d, *J* = 13.2 Hz, 1H), 6.83-6.89 (m, 3H), 6.98-7.09 (m, 6H), 7.24-7.33 (m, 3H), 7.52 (m, 1H), 7.62 (t, *J* = 7.6 Hz, 2H), 7.72 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 24.9 (CH_2), 51.0 (CH_2), 51.9 (CH_2), 53.2 (CH_2), 68.5 (C), 116.0 (d, *J* = 22.5 Hz, 2 CH), 117.4 (d, *J* = 7.7 Hz, 2 CH), 127.0 (CH), 127.5 (2 CH), 127.6 (CH), 128.1 (CH), 128.3 (C), 128.4 (2 CH), 129.4 (CH), 129.6 (2 CH), 129.7 (2 CH), 133.0 (CH), 134.3 (CH), 136.1 (C), 138.3 (C), 138.5 (C), 145.2 (d, *J* = 2.3 Hz, C), 157.6 (d, *J* = 239.6 Hz, C). HRMS (ESI-TOF) cald for $C_{29}H_{27}FNO_4S_2$: 536.1360 $[M + H]^+$; found: 536.1360.

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Pd-Catalyzed α-Arylation of Sulfones in a Three-Component Synthesis of 3-[2-(Phenyl/methylsulfonyl)ethyl]indoles

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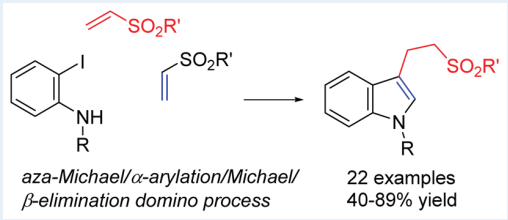
Supporting Information

ABSTRACT: A novel four-step domino process for the synthesis of 3-[2-(aryl/alkylsulfonyl)ethyl]indoles starting from readily available 2-iodoanilines is reported. The domino reaction is based on the intramolecular palladium-catalyzed α-arylation of sulfones, which was combined with both intermolecular aza-Michael and Michael addition reactions using vinyl sulfones as the electrophile. The domino process produced good yields and tolerated the presence of substituents with different electronic properties on the aniline ring. In addition, density functional theory (DFT) calculations were carried out to gain more insight into the formation of the observed indole derivatives.



KEYWORDS: *palladium-catalyzed, arylation, domino reactions, indoles, density functional calculations*

1. INTRODUCTION

Indole is a commonly found heterocycle in biologically active natural products and unnatural pharmaceuticals.[1] For this reason, it is not surprising that since Fischer's pioneering indole synthesis in 1883,[2] numerous methodologies have been reported for the construction and functionalization of the indole skeleton.[3] Besides the vast array of more traditional reactions, recent advances in the area of transition-metal-catalyzed transformations have led to the development of several new reliable methods for the synthesis of indoles from simple starting materials.[4] Among the variety of cross-coupling reactions, the palladium-catalyzed arylation of acidic C−H bonds[5] is of particular interest for the synthesis of this heteroaromatic compound from nonaromatic precursors.[6,7]

In the context of our research on palladium-based methodologies for the synthesis of nitrogen heterocycles,[8] we have reported the palladium-catalyzed intramolecular α-arylation of β-(2-iodoanilino) esters[9] and amides[10] to give indole-3-carboxylic acid derivatives. In parallel with these studies, and in order to create more complex and diverse scaffolds from readily accessible starting materials, we have also explored the integration of the palladium-catalyzed α-arylation reaction into one-pot sequences.[11] This research allowed us to recently achieve an efficient synthesis of highly functionalized tetrahydroisoquinolines by a domino aza-Michael/α-arylation/Michael addition process based on the use of sulfones either as electrophiles or nucleophiles.[12] Continuing these studies, we decided to explore the synthesis of indole derivatives by means of a multistep sequence involving the use of sulfones (Scheme 1). When starting from 2-haloaniline **A**, the aforementioned three-step domino process could be expected to generate a 3-(sulfonyl)indoline intermediate (i.e., **D**), a type of compound known to undergo β-elimination of sulfinic acid to afford indoles.[13,14] We postulated that this additional step would allow us to prepare 3-[2-(aryl/alkylsulfonyl)ethyl]indoles in a new four-step domino process from readily available 2-haloanilines.

Scheme 1. Generic Plan for the Domino Aza-Michael/α-Arylation/Michael Addition/β-Elimination Process Leading to 3-[2-(Aryl/alkylsulfonyl)ethyl]indoles

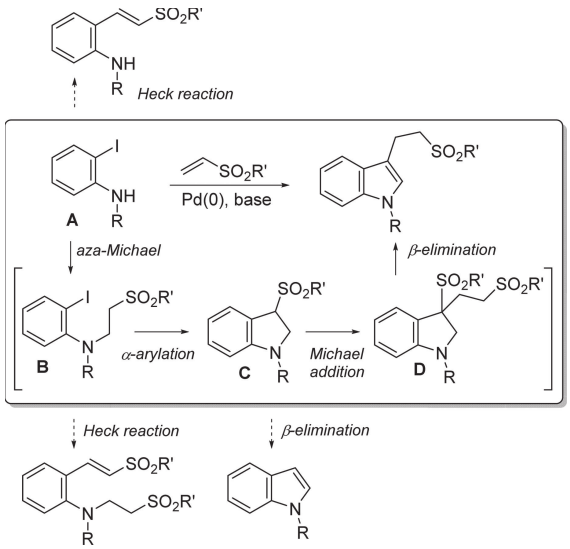


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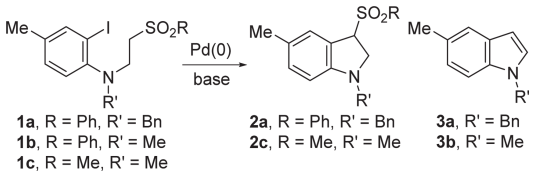
Table 1. Optimization of the α-Arylation Conditions[a]



1a, R = Ph, R' = Bn
1b, R = Ph, R' = Me
1c, R = Me, R' = Me

2a, R = Ph, R' = Bn
2c, R = Me, R' = Me

3a, R' = Bn
3b, R' = Me

entry	sulfone	catalyst (equiv)	base (equiv)	solvent	time	^{1}H NMR ratio	yield (%)[b]
1	**1a**	$Pd_2(dba)_3$ (0.075) xantphos (0.15)	K_3PO_4 (3)	DMF	72 h		---[c]
2	**1a**	$Pd_2(dba)_3$ (0.075) xantphos (0.15)	Cs_2CO_3 (3)	THF	72 h		**1a**[d]
3	**1a**	$Pd_2(dba)_3$ (0.05) BINAP (0.1)	Cs_2CO_3 (3)	THF	72 h		---[c]
4	**1a**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (2.5)	DMF	70 h		**3a** (44%)[e]
5	**1a**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (2.5)	THF	72 h	**2a**:**3a** (1:2)	**3a** (73%)
6	**1a**	$Pd(PPh_3)_4$ (0.05)	Cs_2CO_3 (2.5)	THF	72 h	**2a**:**3a** (2:1)	**3a** (68%)
7	**1b**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3)	DMF	72 h		**3b** (65%)
8	**1b**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3)	THF	72 h		**3b** (64%)
9	**1b**	$Pd(PPh_3)_4$ (0.05)	Cs_2CO_3 (2.5)	THF	72 h		**3b** (52%)
10	**1c**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3)	DMF	120 h		**3b** (42%)[e]
11	**1c**	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (3)	THF	115 h	**2c**:**3b** (5:1)[e]	**2c** (40%) **3b** (41%)
12	**1c**	$Pd(PPh_3)_4$ (0.1)	Cs_2CO_3 (2.5)	THF	120 h	**2c**:**3b** (5:1)[e]	**2c** (7%) **3b** (76%)

[a]The reactions were carried out in a sealed tube at 120 °C. [b]Yields refer to pure products isolated by flash chromatography. [c]Complex mixture. [d]Yield not quantified. [e]Small amounts of the hydrodehalogenation compound (≤10%) were also observed in the crude reaction mixture. $Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium(0). Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. BINAP: 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene.

Among the various substitution patterns of the indole nucleus, compounds bearing the (3-indolyl)ethyl moiety are particularly challenging synthetic targets due to the diversity of biologically active tryptamine analogues.[15,16] Thus, a general approach to this type of compound using the proposed domino aza-Michael/α-arylation/Michael addition/β-elimination strategy would complement existing methodologies and in some instances provide a more attractive option.[17]

A successful domino process should occur under conditions that allow the desired sequence of events to take precedence over any undesired competitive reactions. Thus, in our strategy, the starting iodoaniline **A** would have to be consumed rapidly by the aza-Michael addition[18] to avoid an intramolecular Heck process proceeding as the first step.[19] Similarly, the competitive Heck reaction should not interfere with the palladium-catalyzed α-arylation reaction of intermediate **B**. Finally, the 3-(sulfonyl)-indoline intermediate **C** should be immediately trapped[20] to prevent a premature β-elimination leading to the non-substituted indole.

The work described herein explores the viability of the proposed palladium-catalyzed α-arylation of sulfones in a four-step domino process to obtain 3-[2-(phenyl/methylsulfonyl)-ethyl]indoles from readily available starting materials. To this end, a detailed joint experimental and computational study was carried out to provide insight into the formation of the target indole through this multicomponent domino reaction.

2. RESULTS AND DISCUSSION

During the optimization of the domino process leading to tetrahydroisoquinolines,[12] we realized that the most challenging step of the sequence was the sulfone α-arylation reaction.[21] So, before embarking on the development of a domino process to access 3-substituted indoles, we first examined the palladium-catalyzed α-arylation of β-(2-iodoanilino) sulfones. Sulfones **1a**−**c** were chosen for this purpose (Table 1).

Treatment of **1a** with the $Pd_2(dba)_3$/xantphos couple as the precatalyst and K_3PO_4 as the base in DMF, an effective combination for the domino sequence starting from closely related 2-iodobenzylamines,[12] resulted in the decomposition of the starting material (entry 1, Table 1). When using the same combination of palladium source and ligand, with Cs_2CO_3 as the base in THF, the starting aryl iodide **1a** was recovered unchanged (entry 2, Table 1). Substituting the ligand for BINAP resulted, once again, in the formation of a complex reaction mixture (entry 3, Table 1).

In contrast, the reaction of **1a** with $Pd(PPh_3)_4$ and K_3PO_4 in DMF afforded the product **3a** resulting from the elimination of phenylsulfinic acid from the initially formed α-arylation compound **2a** (entry 4, Table 1). The use of THF as the solvent, maintaining the same combination of reagents and catalyst, led to the formation of a 1:2 mixture of indoline **2a**[22] and indole **3a** (entry 5, Table 1), whereas a ratio of 2:1 was observed when the base was changed from K_3PO_4 to Cs_2CO_3 (entry 6, Table 1). However, after column chromatography of these reaction mixtures, only indole **3a** was isolated, as a result of the SiO_2-promoted elimination of phenylsulfinic acid from **2a**.

Phenyl sulfone **1b**, which bears a methyl group at the aniline nitrogen atom, exclusively afforded indole **3b** when submitted to the reaction conditions optimized for the α-arylation of **1a** (entries 7−9, Table 1). It should be noted that the corresponding indoline intermediate **C** was not observed in any of the crude reaction mixtures of these runs.

Methyl sulfone **1c** was also efficient in the α-arylation reaction, with a similar behavior to phenyl sulfone **1a**, although the process was slower. Although indole **3b** was directly obtained when using DMF as the solvent (entry 10, Table 1), the annulation reaction in THF afforded mixtures of indoline **2c** and the indole **3b** (entries 11 and 12, Table 1). Interestingly, although **2c** partially evolved to indole **3b** during the chromatographic purification, in this case, the indoline was stable enough to be isolated and characterized.

At this point, the best conditions for the α-arylation of β-(2-iodoanilino) sulfones involved the use of $Pd(PPh_3)_4$ as the

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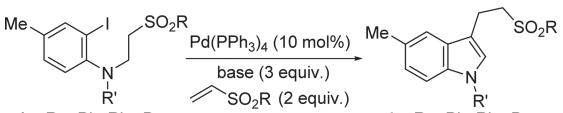
catalyst and either K_3PO_4 or Cs_2CO_3 as the base in THF. On the other hand, the results in Table 1 show that both phenyl and methyl sulfones could *a priori* be useful to develop the proposed reaction cascade, since the corresponding 3-sulfonyl indolines partially survived under the α-arylation conditions. However, in the phenylsulfonyl series, changing the substituent at the nitrogen atom from benzyl to methyl resulted in a fast elimination of phenylsulfinic acid, which could hamper the use of *N*-methyl derivatives in the domino process.

With this information in hand, without any further optimization, we then focused on combining the α-arylation reaction with the next steps of the domino process, namely, the Michael addition of the 3-sulfonyl indoline intermediate **C** and the subsequent β-elimination from the resulting alkylated indoline **D** (Scheme 1 and Table 2).

Table 2. α-Arylation/Michael Addition/β-Elimination Domino Process[a]



1a, R = Ph, R' = Bn
1b, R = Ph, R' = Me
1c, R = Me, R' = Me

4a, R = Ph, R' = Bn
4b, R = Ph, R' = Me
4c, R = Me, R' = Me
4d, R = Me, R' = Bn

entry	sulfone	Michael acceptor	base (equiv.)	solvent	yield (%)[b]
1	**1a**	SO_2Ph	K_3PO_4 (3)	THF	---[c]
2	**1a**	SO_2Ph	Cs_2CO_3 (3)	THF	**4a** (48%)[d]
3	**1a**	SO_2Ph	K_3PO_4 (3)	DMF	**4a** (19%)[c]
4	**1a**	SO_2Ph	Cs_2CO_3 (3)	DMF	**4a** (27%)[c,e]
5	**1a**	SO_2Me	Cs_2CO_3 (3)	THF	**4d** (43%)[f]
6	**1b**	SO_2Ph	Cs_2CO_3 (3)	THF	**4b** (73%)[g]
7	**1b**	SO_2Me	Cs_2CO_3 (3)	THF	**4c** (45%)[g]
8	**1c**	SO_2Me	Cs_2CO_3 (3)	THF	**4c** (44%)[h]
9	**1c**	SO_2Ph	Cs_2CO_3 (3)	THF	**4b** (40%)[i]

[a]Reaction conditions: **1** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), Michael acceptor (2 equiv), and base (3 equiv) in the indicated solvent in a sealed tube at 120 °C for 72 h. [b]Yields refer to pure products isolated by flash chromatography. [c]Complex mixture. [d]*N*-Benzyl-4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (**5a**) was also isolated (17%). [e]Significant amounts of *N*-benzyl-*p*-toluidine were observed in the reaction mixture. [f]**5a** (20%) was also isolated. [g]Small amounts of the corresponding hydrodehalogenation product (<10%) were also observed in the crude reaction mixture. [h]*N*,4-Dimethyl-*N*-[2-(methylsulfonyl)ethyl]aniline (**5c**) was also isolated (20%). [i]**5c** (26%) was also isolated.

Treatment of **1a** with $Pd(PPh_3)_4$ and K_3PO_4 in the presence of phenyl vinyl sulfone in THF afforded a complex mixture in which only trace amounts of the desired indole **4a** were observed, together with the reduction compound **5a** and some products arising from the Heck reaction of the starting aryl iodide (entry 1, Table 2). However, to our delight, changing the base to Cs_2CO_3 resulted in a clean reaction mixture, from which indole **4a** (48%) and the reduction compound **5a** (17%) were isolated (entry 2, Table 2). When the reactions were performed in DMF using either K_3PO_4 or Cs_2CO_3 as the base, indole **4a** was also obtained, although in significantly lower yields (entries 3 and 4, Table 2).

The three-step domino process of **1a** with methyl vinyl sulfone afforded indole **4d** in 43% yield (entry 5, Table 2). Phenyl sulfone **1b**, which bears a methyl group at the nitrogen atom, gave indoles **4b** (73%) and **4c** (45%) when submitted to the domino reaction with phenyl vinyl sulfone (entry 6, Table 2) and methyl vinyl sulfone (entry 7, Table 2), respectively. This indicates that the Michael addition of the 3-sulfonyl indoline intermediate to the vinyl sulfone is faster than the β-elimination of sulfinic acid, even for those substrates having a methyl substituent at the nitrogen atom (*vide supra*).

Finally, methyl sulfone **1c** also underwent the domino reaction, either with methyl vinyl sulfone (entry 8, Table 2) or phenyl vinyl sulfone (entry 9, Table 2), to afford, respectively, indoles **4c** (44%) and **4b** (40%).

The promising results obtained in these three-step domino reactions constituted a good starting point to develop the initially proposed four-step domino process, which would simplify the preparation of 3-[2-(sulfonyl)ethyl]indoles starting from the readily available *N*-alkyl-2-iodoanilines. *N*-Benzyl-2-iodoaniline was chosen to test our proposal (Table 3).

When *N*-benzyl-2-iodoaniline was treated with phenyl vinyl sulfone in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in THF, an effective combination to promote the three-step domino process from **1a**, indole **6a** was obtained in a modest 33% yield, together with *N*-benzylaniline (**7**), which resulted from the reduction of the starting 2-iodoaniline (entry 1, Table 3). Although the use of a more polar solvent should facilitate the initial aza-Michael addition,[18] the yield of indole **6a** was in fact slightly lower when the reaction was performed in DMF (entry 2, Table 3). In view of these poor results, we decided to optimize the four-step domino reaction by using different commercially available phosphines as the ligand. The use of either $(o\text{-tolyl})_3P$ or xantphos resulted in the recovery of the starting material (entries 3 and 4, Table 3). Surprisingly, although BINAP had failed to promote the α-arylation from phenyl sulfone **1a** (see Table 1), its use in the present domino process resulted in the formation of **6a** in an acceptable 54% yield (entry 5, Table 3). Using dppf allowed us to obtain indole **6a** in 69% yield (entry 6, Table 3), while in the presence of the ligand dppp, **6a** was isolated in 65% yield (entry 9, Table 3). We were also able to increase the yield of **6a** up to 80% by using dppf and a slightly higher quantity of the Michael acceptor (entry 7, Table 3). Lower reaction temperatures resulted in the recovery of small amounts of the starting material (entry 8, Table 3). Other bidentate ligands were less amenable to promoting the four-step domino process. For instance, the most hindered dtpf mainly resulted in the formation of the hydrodehalogenation product **7** (entry 10, Table 3), whereas a 1:1 mixture of **6a** and **7** was obtained when using dppe (entry 11, Table 3).

The four-step domino process of *N*-benzyl-2-iodoaniline with methyl vinyl sulfone using dppf as the ligand afforded a complex mixture from which indole **6b** was isolated in 33% (entry 12, Table 3). Interestingly, the replacement of the ligand by BINAP allowed us to obtain **6b** in an acceptable 58% yield (entry 13, Table 3).

As shown in Table 4, a variety of diversely substituted 3-(sulfonylethyl)indoles were prepared through the four-step domino process when using either phenyl vinyl sulfone or methyl vinyl sulfone as the Michael acceptor. The generality and functional group tolerance of the reaction is well illustrated

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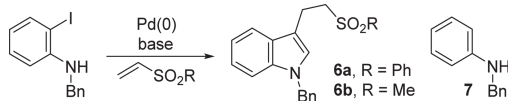
Table 3. Optimization of the Aza-Michael/α-Arylation/Michael Addition/β-Elimination Domino Process[a]



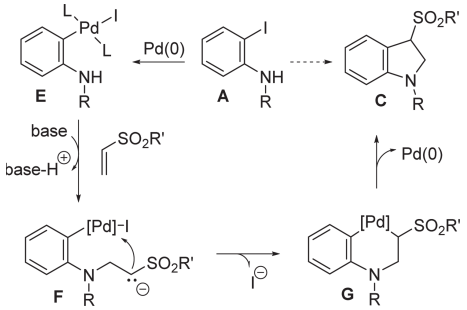
entry	catalyst (equiv.)	Michael acceptor	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$ (0.1)	SO_2Ph	THF	**6a** (33%)[c]
2	$Pd(PPh_3)_4$ (0.1)	SO_2Ph	DMF	**6a** (28%)[d]
3	$Pd_2(dba)_3$ (0.075) (o-tolyl)$_3$P (0.15)	SO_2Ph	THF	SM
4	$Pd_2(dba)_3$ (0.075) xantphos (0.15)	SO_2Ph	THF	SM
5	$Pd_2(dba)_3$ (0.075) BINAP (0.15)	SO_2Ph	THF	**6a** (54%)[c]
6	$Pd_2(dba)_3$ (0.075) dppf (0.15)	SO_2Ph	THF	**6a** (69%)
7	$Pd_2(dba)_3$ (0.075) dppf (0.15)	SO_2Ph[e]	THF	**6a** (80%)
8	$Pd_2(dba)_3$ (0.075) dppf (0.15)	SO_2Ph[e,f]	THF	**6a** (65%)[g]
9	$Pd_2(dba)_3$ (0.075) dppp (0.15)	SO_2Ph[e]	THF	**6a** (65%)
10	$Pd_2(dba)_3$ (0.075) dtpf (0.15)	SO_2Ph	THF	**7**[h]
11	$Pd_2(dba)_3$ (0.075) dppe (0.15)	SO_2Ph[e]	THF	**6a**/**7** (1:1)[i]
12	$Pd_2(dba)_3$ (0.075) dppf (0.15)	SO_2Me	THF	**6b** (33%)[j]
13	$Pd_2(dba)_3$ (0.075) BINAP (0.15)	SO_2Me	THF	**6b** (58%)[k]

[a]Reaction conditions: *N*-Benzyl-2-iodoaniline (0.2 mmol), [Pd] and ligand (see table), Michael acceptor (2.1 equiv), and Cs_2CO_3 (3 equiv) in the indicated solvent in a sealed tube at 120 °C for 72 h. [b]Yields refer to pure products isolated by flash chromatography. [c]*N*-Benzylaniline (**7**) was also isolated (10%). [d]**7** was also isolated (17%). [e]Michael acceptor (2.4 equiv). [f]The reaction was run at 80 °C. [g]*N*-Benzyl-2-iodoaniline (8%) was recovered. [h]Yield not quantified, minor amounts of **6a** (≤10%) were also observed in the reaction mixture. [i]^{1}H NMR ratio, yields not quantified. [j]*E*-*N*-Benzyl-2-[2-(methylsulfonyl)-ethenyl]aniline (**8**) was also isolated (14%). [k]**8** (13%) was also isolated. dppf: 1,1′-Bis(diphenylphosphino)ferrocene. dtpf: 1,1′-Bis-(di-*tert*-butylphosphino)ferrocene. dppp: 1,3-Bis(diphenylphosphino)-propane. dppe: 1,2-Bis(diphenylphosphino)ethane.

by the fact that both electron-donating and electron-withdrawing groups were perfectly accommodated on the aromatic ring. Overall, the phenyl sulfone afforded better results than the methyl sulfone due to its higher electrophilicity as well as the higher acidity of its α−C-H bonds, which favors both the α-arylation and the Michael addition. In this context, it should be noted that the initial aza-Michael addition took place without any appreciable interference from the competitive Heck reaction. The same behavior was also observed in our previously developed three-step domino process leading to tetrahydroisoquinolines.[12] This absence of competition contrasts with what occurred in a related one-pot aza-Michael addition/α-arylation process using acrylates as the Michael acceptor.[23] In this case, it was impossible to develop a real domino reaction[24] because, in the presence of the Pd catalyst, the Heck coupling with the acrylate took place before the aza-Michael addition.[19]

Some additional comments on the four-step domino reactions described above (Tables 3 and 4) are warranted. In these reactions, the expected reduction products of the initially formed intermediates **B** (Scheme 1) were never observed, yet they were a common side-product (i.e., **5a−c**) in the three-step domino processes starting from sulfones **1a−c** (see Table 2). This fact, together with the isolation of significant amounts of *N*-benzylaniline (**7**), as well as the apparently contradictory results obtained with BINAP, suggested that a sequence of events different from those depicted in Scheme 1 could be operating in the four-step domino reaction. Indeed, all these results could be easily accommodated by an alternative sequence of reactions (Scheme 2) in which the formation of

Scheme 2. Alternative Sequence of Events for the Domino Process



indoline **C** begins with the oxidative addition of the iodoaniline to Pd(0). The resulting Pd(II) intermediate **E** would then undergo deprotonation and aza-Michael addition to the vinyl sulfone to give intermediate **F**. The latter would evolve to indoline **C** by means of coordination of the sulfone anion and subsequent reductive elimination.

In search of evidence for the proposed aza-Michael/α-arylation/Michael addition/β-elimination sequence, further experiments were performed. Treatment of indole **3b** with phenyl vinyl sulfone in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in THF at 120 °C resulted in the recovery of the starting material. On the other hand, the treatment of a 8.3:1 mixture of indoline **2c** and indole **3b** with methyl vinyl sulfone and Cs_2CO_3 in THF at 120 °C, both with and without $Pd(PPh_3)_4$, resulted in the formation of a 6.4−6.9:1 mixture of indoles **4c** and **3b** (Scheme 3). These results therefore confirm that indole **4c** was generated by the Michael addition of indoline **2c** to methyl vinyl sulfone followed by β-elimination of sulfinic acid, rather than by the metal-promoted nucleophilic addition of indole **3b** to the vinyl sulfone.[25]

More illustratively, the reactions of *N*-benzyl-2-iodoaniline with the dideuterated phenyl vinyl sulfone **19-D$_2$** under optimized conditions (see for instance Table 3, entry 7) afforded indole **6a-D$_3$**, bearing deuterium labels at C-2 of the indole nucleus as well as at the β position of the 3-(phenylsulfonyl)ethyl chain (Scheme 4). This result provides further experimental evidence for the proposed aza-Michael/α-arylation/Michael addition/β-elimination sequence of events.

Density functional theory (DFT) calculations[26] were carried out to gain more insight into the mechanism of the sulfone α-arylation as well as the other key steps of the domino sequence described above. First, we focused on the α-arylation process involving an analogous compound of **1c** (Table 1), where the methyl group in the aromatic ring was replaced by a hydrogen

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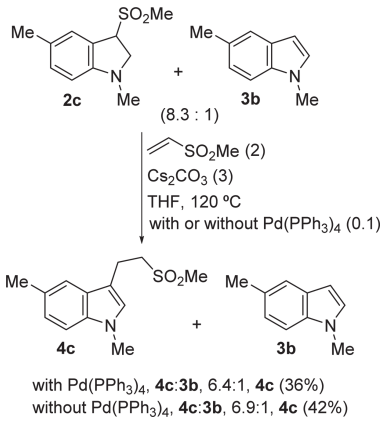
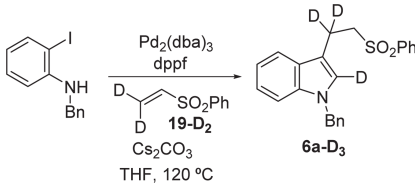
Scheme 3. Reaction of Indoline 2c with Methyl Vinyl Sulfone



Scheme 4. Reaction of *N*-Benzyl-2-iodoaniline with Sulfone 19-D_2



atom. Our calculations started from species **INT0**, the intermediate formed upon the initial oxidative addition of the 2-iodoaniline derivative to the model $Pd(PMe_3)_2$ catalyst (Figure 1). In the presence of CO_3^{-2} as the base, deprotonation of the slightly acidic hydrogen atom attached to a carbon atom linked to the sulfone group may occur, therefore leading to **INT1** species in a slightly exergonic process (ΔG_R = −4.0 kcal/mol). This intermediate would then evolve to complex **INT2** by exergonic coordination of the carbanion to the transition metal (ΔG_R = −14.9 kcal/mol) and release of a phosphine ligand. From this species, the α-arylation would take place directly via **TS1**, a transition state associated with the formation of the new C−C bond. This exergonic step (ΔG_R = −14.2 kcal/mol) occurs with an activation barrier of 28.6 kcal/mol, which is fully compatible with a process occurring at 120 °C. Therefore, this reaction mechanism resembles the one we previously proposed for the α-arylation reaction involving related ketone and ester derivatives.[81]

Nevertheless, an alternative reaction pathway involving a key C−H activation step can be also envisaged. Thus, the initial intermediate **INT0** may be readily transformed into complex **INT3** through a highly exergonic (ΔG_R = −26.6 kcal/mol) iodide and phosphine ligand replacement promoted by bidentate CO_3^{-2}. This complex would be then converted into complex **INT4** via **TS2** with an activation barrier of 26.1 kcal/mol in a slightly endergonic transformation (ΔG_R = +2.7 kcal/mol). As depicted in Figure 1, this saddle point is associated with the concerted hydrogen migration from the sulfone to the carbonate ligand and Pd−C bond formation. In this sense, this transformation is analogous to related concerted metalation-deprotonation (CMD) C−H activations which are assisted by acetate[27] or carbonate.[28] From **INT4**, the final indoline **2M** can be directly produced through **TS3** in a reductive elimination process associated with the formation of the new C−C bond. Although this reaction is exergonic (ΔG_R = −9.2 kcal/mol), it proceeds with a relatively high activation barrier of 37.4 kcal/mol. Therefore, **INT4** may release the HCO_3^- ligand first and be transformed into **INT5**, where the reductive elimination reaction via **TS4** is computed to be kinetically far more favorable ($\Delta G‡$ = 13.9 kcal/mol, from **INT5**). Additionally, due to the excess of CO_3^{-2} in the process, **INT2** may alternatively be converted into **INT6** through a carbonate/iodide ligand exchange. This transformation seems feasible in view of the high exergonicity (ΔG_R = −18.5 kcal/mol) computed for this ligand exchange. However, the corresponding reductive elimination via **TS5** would proceed with a much higher activation barrier ($\Delta G‡$ = 42.9 kcal/mol) than the process involving **TS4**, which renders this alternative pathway very unlikely. Therefore, based on the computed data, it can be concluded that the **INT3** → **INT4** → **INT5** → **2M** pathway, which involves an initial CMD reaction followed by a reductive elimination step, seems to be the most plausible reaction mechanism for the palladium-catalyzed formation of indolines from β-(2-iodoanilino) sulfones.

As indicated in the reaction profile depicted in Figure 1, the preferred pathway involves the formation of the coordinatively unsaturated palladium(II) complex **INT5**. We hypothesize that the involvement of the bidentate phosphine ligands used in the experiments must occur from this intermediate. To find computational evidence for this hypothesis, we explored the feasibility of the final reductive elimination reaction from **INT5′**, the analogous species to **INT5** bearing an additional phosphine ligand (i.e., a model bidentate ligand of the dppp ligand, with phenyl groups replaced by methyl groups). As expected, our calculations (Figure 2) indicate that the coordination of the free phosphine leading to the coordinatively saturated complex **INT7** is highly exergonic (ΔG_R = −18.5 kcal/mol). From this species, the reductive elimination reaction occurs via **TS6**, the corresponding saddle point associated with the formation of the new C−C bond and release of the Pd(dppp) catalyst. From the data in Figure 2, it becomes clear that the process involving the bidentate ligand proceeds with a much higher activation barrier ($\Delta G‡$ = 29.5 kcal/mol) and a lower exergonicity (ΔG_R = −9.7 kcal/mol) than the analogous process involving the monodentate ligand ($\Delta G‡$ = 13.9 kcal/mol and ΔG_R = −19.5 kcal/mol, see Figure 1), which nicely agrees with the experimental findings obtained during the optimization of the α-arylation reaction (see Table 1).

We then focused on understanding the negligible interference from the competitive Heck coupling reaction in the four-step domino process from *N*-alkyl-2-iodoanilines (see above, Tables 3 and 4). To this end, we computed the two possible reaction pathways, namely, aza-Michael reaction vs Heck reaction, starting from **INT8**, the intermediate formed upon the initial oxidative addition of the 2-iodo-*N*-methylaniline to the model $Pd(PMe_3)_2$ catalyst (Figure 3). This species, in the presence of CO_3^{-2} as the base, may deprotonate, leading to the anionic complex **INT9** in an exergonic process (ΔG_R = −9.9 kcal/mol). Then, **INT9** would react with the corresponding vinyl sulfone to produce **INT10** through **TS7**, a saddle point associated with the formation of the N−C bond ($\Delta G‡$ = 8.2 kcal/mol) in an aza-Michael type process. Final protonation of **INT10** leads to the formation of **INT0**, the common intermediate in the processes involving both 2-iodoanilines (Tables 3 and 4) and compounds **1** (Table 1 and 2). As clearly seen in Figure 3, the alternative Heck coupling reaction is not competitive in this transformation. This is mainly due to the

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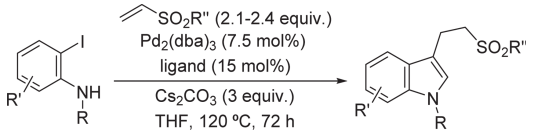
Table 4. Synthesis of 3-[2-(Phenyl/methylsulfonyl)ethyl]indoles[a]



entry	Michael acceptor	ligand	product	yield (%)[b]
1	SO_2Ph	BINAP	**9a**, R = Me, R'' = Ph	(71%)
2	SO_2Ph	dppp	**9a**, R = Me, R'' = Ph	(50%)
3	SO_2Me	BINAP	**9b**, R = Me, R'' = Me	(45%)
4	SO_2Ph	dppf	**10a**, R = Pr, R'' = Ph	(69%)
5	SO_2Me	dppf	**10b**, R = Pr, R'' = Me	(67%)
6	SO_2Me	BINAP	**10b**, R = Pr, R'' = Me	(45%)
7	SO_2Ph	dppf	**11a**, R = Et, R'' = Ph	(89%)
8	SO_2Ph	dppf	**4a**, R = Bn, R' = Me, R''= Ph	(83%)
9	SO_2Me	dppf	**4d**, R = Bn, R' = Me, R'' = Me	(56%)
10	SO_2Me	BINAP	**4d**, R = Bn, R' = Me, R'' = Me	(45%)
11	SO_2Ph	dppf	**12a**, R = Bn, R' = MeO, R'' = Ph	(79%)
12	SO_2Me	dppf	**12b**, R = Bn, R' = MeO, R'' = Me	(57%)
13	SO_2Ph	dppf	**13a**, R = Pr, R' = MeO, R'' = Ph	(45%)
14	SO_2Ph	dppf	**14a**, R = Bn, R' = Cl, R'' = Ph	(85%)
15	SO_2Me	BINAP	**14b**, R = Bn, R' = Cl, R'' = Me	(70%)
16	SO_2Ph	dppf	**15a**, R = Bn, R' = Cl, R'' = Ph	(65%)
17	SO_2Me	BINAP	**15b**, R = Bn, R' = Cl, R'' = Me	(40%)
18	SO_2Ph	dppf	**16a**, R = Bn, R' = F, R'' = Ph	(75%)
19	SO_2Me	dppf	**16b**, R = Bn, R' = F, R'' = Me	(73%)
20	SO_2Ph	dppf	**17a**, R = Bn, R' = CO_2Me, R'' = Ph	(72%)
21	SO_2Me	BINAP	**17b**, R = Bn, R' = CO_2Me, R'' = Me	(56%)
22	SO_2Me	dppf	**17b**, R = Bn, R' = CO_2Me, R'' = Me	(62%)
23	SO_2Ph	dppf	**18a**, R = Pr, R' = CO_2Me, R'' = Ph	(81%)
24	SO_2Me	dppf	**18b**, R = Pr, R' = CO_2Me, R'' = Me	(60%)

[a]Reaction conditions: *N*-Akyl-2-iodoaniline (0.2 mmol), $Pd_2(dba)_3$ (7.5 mol %), ligand (see table, 15 mol %), Michael acceptor (2.1−2.4 equiv), and Cs_2CO_3 (3 equiv) in THF in a sealed tube at 120 °C for 72 h. [b]Yields refer to pure products isolated by flash chromatography.

high endergonicity (ΔG_R = 20.2 kcal/mol) associated with the initial dissociation of a phosphine ligand, which is required to create a vacant coordination to allocate the incoming vinyl sulfone ligand. In addition, the electron-withdrawing effect of the SO_2Me group reduces the coordination ability of the attached double bond, which also renders the coordination of the vinyl sulfone to **INT11** endergonic (ΔG_R = 4.8 kcal/mol).[29] Although the subsequent insertion step via **TS8** proceeds with a relatively low activation barrier ($\Delta G‡$ = 11.5 kcal/mol), this highly unfavorable phosphine/vinyl sulfone ligand interchange makes the alternative Heck reaction very unlikely, which is fully compatible with the experimental observations.

The beneficial effect of bidentate phosphine ligands observed during the optimization of the four-step domino process (see for instance, Table 3) is also in nice agreement with the expected even higher endergonicity associated with the generation of the coordinatively unsaturated species (i.e., **INT 11**), which is required for the Heck coupling when using a chelating phosphine.

Finally, we addressed the last steps of the domino process which involve the transformation of intermediate **C** (Scheme 1)

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ACS Catal. 2016, 6, 1691−1700

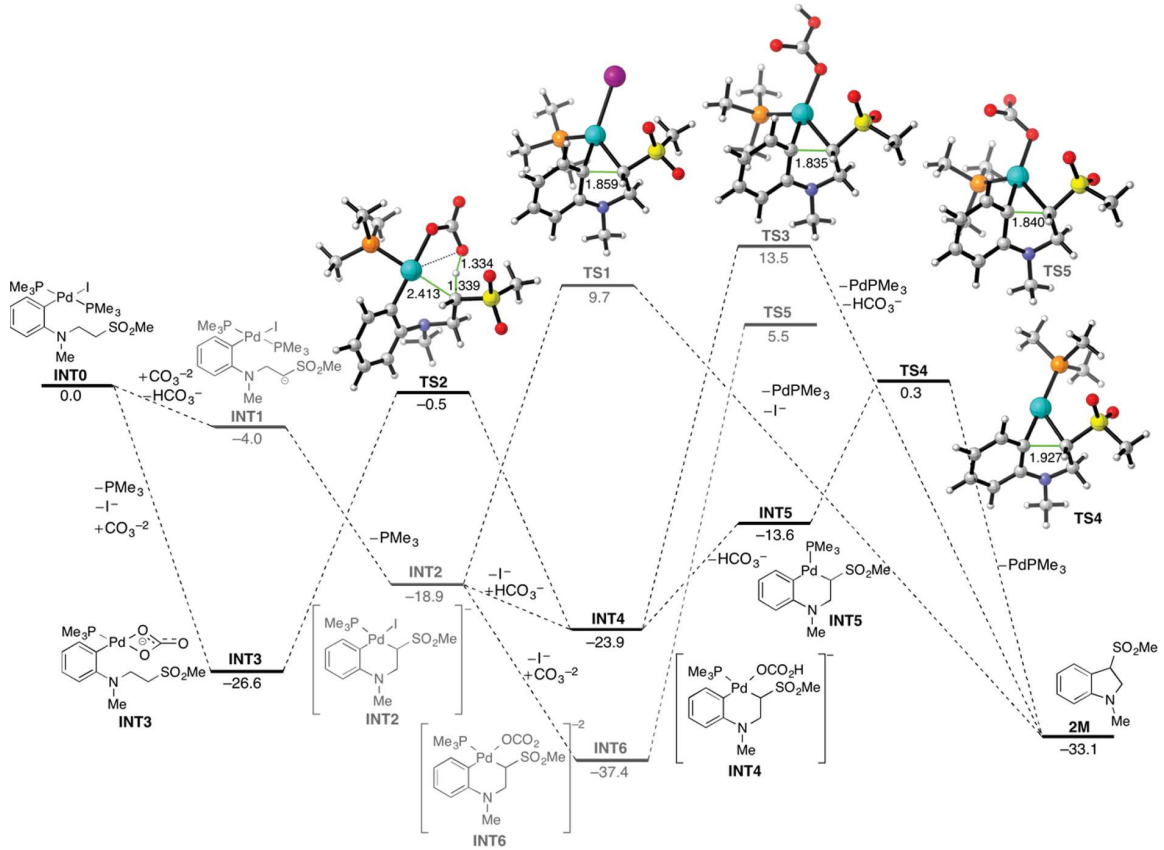

Figure 1. Computed reaction profiles for the palladium catalyzed α-arylation reaction of **INT0**. Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

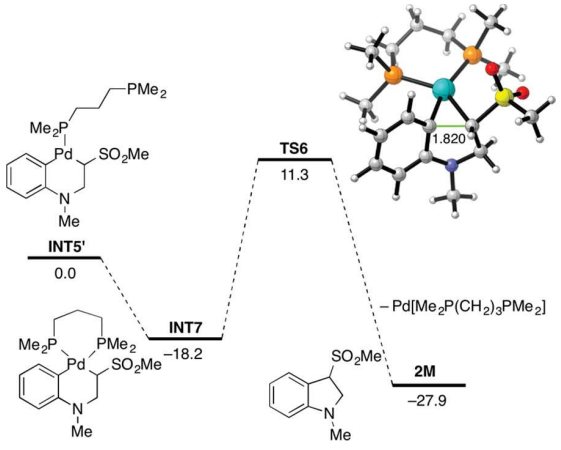

Figure 2. Computed reductive elimination reaction involving **INT5′**. Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM-(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

into the observed 3-[2-(phenyl/methylsulfonyl)ethyl]indoles. Our DFT-calculations began from intermediate **2M**, the indoline formed during the palladium-catalyzed α-arylation (or CMD-reductive elimination) process described above (see Figure 1). Deprotonation of the highly acidic benzylic hydrogen atom by the base would lead to the formation of carbanion **2M-an**, from which a rapid ($\Delta G‡$ = 6.4 kcal/mol) and exergonic (ΔG_R = −3.7 kcal/mol) Michael addition would take place via **TS9**. Protonation of intermediate **3M-an** would then produce the 3-(sulfonyl)indoline intermediate **3M**, which would be transformed into the final indole **4M** through **TS10**.[30] As depicted in Figure 4, this final five-membered ring transition state is associated with a concerted β-elimination reaction of sulfinic acid. Despite the concomitant rupture of both the S−C and C−H bonds, the process was computed to be highly exergonic (ΔG_R = −16.5 kcal/mol) and to proceed with a feasible activation barrier ($\Delta G‡$ = 18.1 kcal/mol). This can be ascribed to the gain in aromaticity in the final indole derivative which therefore constitutes the thermodynamic driving force of the entire transformation.

In summary, we have developed a set of reaction conditions for a new four-step domino process toward 3-[2-(aryl/alkylsulfonyl)ethyl]indoles from readily available 2-iodoanilines. In this three-component domino process, the crucial intramolecular palladium-catalyzed α-arylation of sulfones is combined with intermolecular aza-Michael and Michael additions to vinyl sulfones, as well as a highly selective β-elimination of sulfinic acid, avoiding any undesired competitive reactions. A series of diversely substituted 3-[2-sulfonylethyl]-indoles were easily synthesized in moderate-to-high yields. According to DFT calculations, after the initial oxidative addition to the palladium catalyst, an aza-Michael reaction occurs without any significant interference from the alternative Heck coupling reaction. The α-arylation process would then

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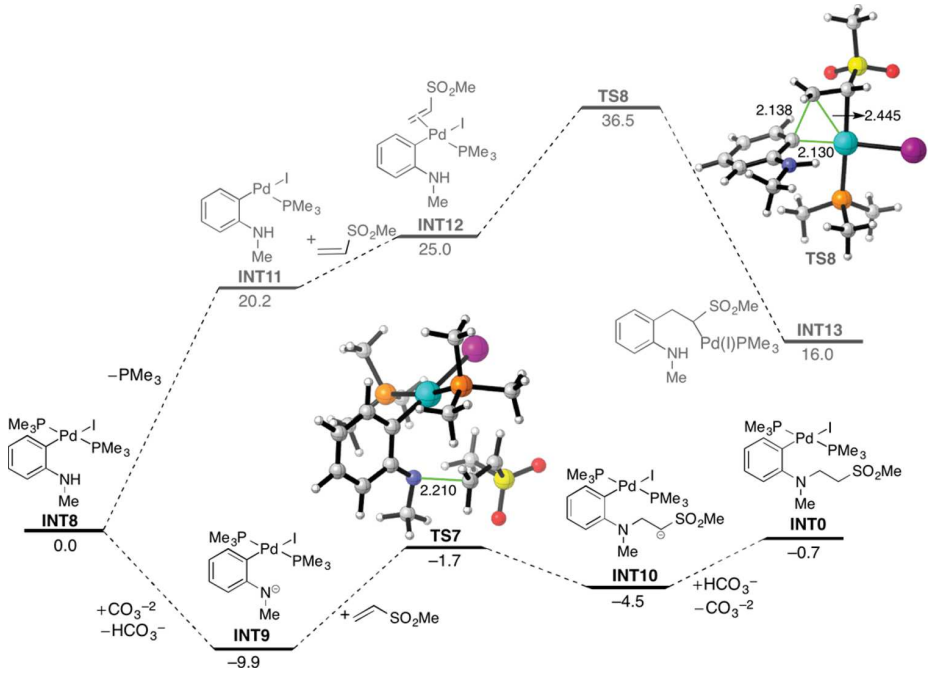

Figure 3. Computed reaction profiles for competitive aza-Michael and Heck coupling reactions from **INT8**. Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

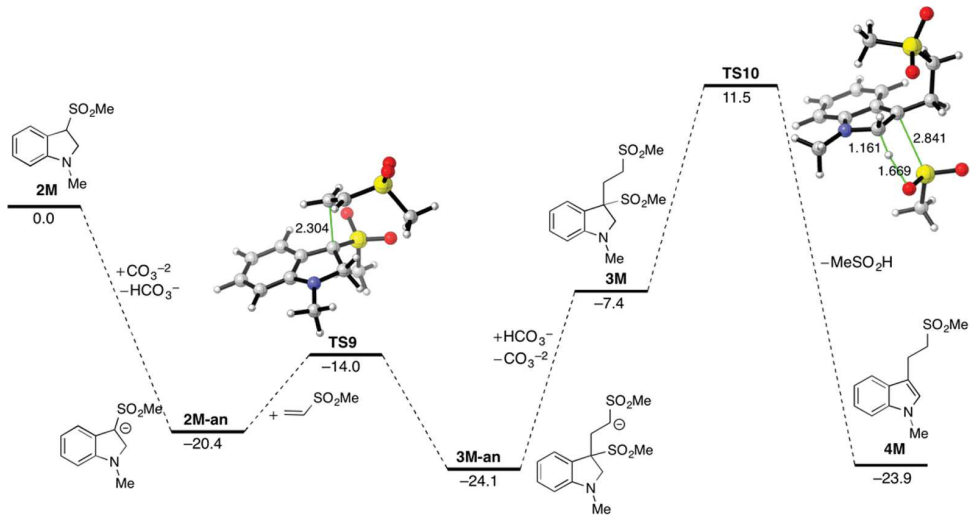

Figure 4. Final transformation of indoline **2M** into indole **4M**. Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

occur through a CMD/reductive elimination process thus leading to indoline derivatives. The latter species are finally converted into the observed 3-[2-(aryl/alkylsulfonyl)ethyl]-indoles through two consecutive reaction steps involving an initial rapid Michael addition followed by an exergonic and concerted β-elimination reaction of sulfinic acid.

3. EXPERIMENTAL SECTION

Representative Procedure for the Domino Reactions (Table 3, Entry 7). A mixture of *N*-benzyl-2-iodobenzylamine (80 mg, 0.26 mmol), $Pd_2(dba)_3$ (18 mg, 0.019 mmol), dppf (21 mg, 0.039 mmol), phenyl vinyl sulfone (104 mg, 0.62 mmol), and Cs_2CO_3 (253 mg, 0.78 mmol) in THF (8 mL) was stirred at 120 °C in a sealed tube for 72 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, from hexanes to hexanes-EtOAc 1:4) to give sulfone **6a** (78 mg, 80%) as an amorphous brown solid.

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ACS Catal. 2016, 6, 1691−1700

4. COMPUTATIONAL DETAILS

All the calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs.[31] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[32] in conjunction with the D3 dispersion correction suggested by Grimme and co-workers[33] using the double-ζ quality plus polarization def2-SVP basis set[34] for all atoms. Reactants and products were characterized by frequency calculations,[35] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[36] Solvents effects were taken into account using the Polarizable Continuum Model (PCM).[37] Single-point calculations on the PCM(THF)-B3LYP-D3/def2-SVP geometries were performed to estimate the change in the Gibbs energies at the B3LYP-D3 level using the triple-ζ quality plus polarization def2-TZVP basis set[34] for all atoms. This level is denoted PCM(THF)-B3LYP-D3/def2-TZVP//PCM(THF)-B3LYP-D3/def2-SVP.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00027.

Detailed experimental procedures, characterization data and copies of NMR spectra for all new compounds, as well as Cartesian coordinates of all species described in the text (PDF)

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Notes

The authors declare no competing financial interest.

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(30) The computed free energy difference between **TS10** and **3M-an** of 35.6 kcal/mol seems unrealistic and can be ascribed to the initial protonation of **3M-an** mediated by HCO_3^-. The high endergonicity computed for the latter transformation (ΔG = 16.7 kcal/mol) seems unreliable and is very likely due to the well-known difficulties associated with the calculations involving either highly polar groups or charged species (such as HCO_3^-, CO_3^{-2} or **3M-an**) using continuum models (such as PCM in our case). For a discussion on this issue, see (a) Harvey, J. N. *Faraday Discuss.* **2010**, *145*, 487−505. (b) Cheng, G.-J.; Zhang, X.; Chung, L. W.; Xu, L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2015**, *137*, 1706−1725. For a related example involving a "computationally intractable" acid−base mechanism, see: (c) Plata, R. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 3811−3826. See also (d) Proutiere, F.; Schoenebeck, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8192−8195.

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Supporting Information

Pd-Catalyzed α-Arylation of Sulfones in a Three-Component Synthesis of 3-[2-(phenyl/methylsulfonyl)ethyl]indoles

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Table of Contents

General Methods. All commercially available reagents were used without further purification. *N*-Methyl-2-iodoaniline,[1] *N*-benzyl-2-iodoaniline, 2-iodo-*N*-propylaniline, *N*-ethyl-2-iodoaniline, *N*-benzyl-2-iodo-4-methylaniline, *N*-benzyl-2-iodo-4-methoxyaniline, 2-iodo-4-methoxy-*N*-propylaniline, *N*-benzyl-4-chloro-2-iodoaniline, *N*-benzyl-5-chloro-2-iodoaniline, *N*-benzyl-5-fluoro-2-iodoaniline, *N*-benzyl-2-iodo-5-(methoxycarbonyl)aniline, 2-iodo-5-(methoxycarbonyl)-*N*-propylaniline, were prepared following previously reported procedures.[2] ^{1}H- and ^{13}C-NMR spectra were recorded using Me_4Si as the internal standard, with a Varian Gemini 300 or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si for ^{1}H and ^{13}C NMR. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light or 1% aqueous $KMnO_4$. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator.

Experimental procedures and characterization data for the starting materials.

4-Methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline. A solution of *p*-toluidine (500 mg, 4.66 mmol) and phenyl vinyl sulfone (713 mg, 4.24 mmol) in absolute EtOH (10 mL) was stirred at 80 ºC for 48 h. The solvent was removed *in vacuo* to give 4-methyl-*N*-2-[(phenylsulfonyl)ethyl]aniline, which was used in the next reaction without purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 3H), 3.34 (t, *J* = 6.3 Hz, 2H), 3.55 (t, *J* = 6.3 Hz, 2H), 4.00 (broad b, 1H), 6.44 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.91 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.3 (CH_3), 38.0 (CH_2), 54.7 (CH_2), 113.3 (2 CH), 127.6 (C), 127.9 (2 CH), 129.4 (2 CH), 129.8 (2 CH), 133.9 (CH), 139.0 (C), 144.1 (C).

2-Iodo-4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline. The crude 4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline was dissolved in a CH_2Cl_2 (14 mL)-MeOH (7 mL) mixture, and $CaCO_3$ (0.61 g, 6.06 mmol) and $BTMAICl_2$[3] (1.7 g, 4.89 mmol) were added. The mixture was stirred at room temperature for 6 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried and concentrated. The residue was purified by flash chromatography (SiO_2, from hexanes to 3:2 hexanes-EtOAc) to give 2-iodo-4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (1.16 g, 62%) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (s, 3H), 3.39 (t, *J* = 6.3 Hz, 2H), 3.59 (q, *J* = 6.3 Hz, 2H), 4.44 (broad t, *J* = 6.3 Hz, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 8.4 and 2.0 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.56 (tt, *J* = 7.5 and 2.0 Hz, 2H), 7.66 (tt, *J* = 7.5 and 2.0 Hz, 1H), 7.91 (dm, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 19.7 (CH_3), 38.0 (CH_2), 54.6 (CH_2), 85.6 (C), 110.1 (CH), 127.8 (2 CH), 128.9 (C), 129.3 (2 CH), 129.9 (CH), 133.9 (CH), 138.8 (C), 139.5 (CH), 143.5 (C).

***N*-Benzyl-2-iodo-4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (1a).** To a solution of 2-iodo-4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (425 mg, 1.06 mmol) in acetonitrile (20 mL), benzyl bromide (0.50 mL, 4.24 mmol) and K_2CO_3 (439 mg, 3.18 mmol) were added. After stirring at 60 ºC for 72 h, the organic solvent was evaporated. The residue was partitioned between CH_2Cl_2 and water, and the organic extracts were dried and concentrated. The residue

was purified by flash chromatography (SiO_2, from hexanes to CH_2Cl_2) to give *N*-benzyl-2-iodo-4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (**1a**, 348 mg, 64%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H), 3.18 (m, 2H), 3.28 (m, 2H), 4.00 (s, 2H), 6.84 (d, *J* = 8.1 Hz, 1H), 7.04 (dd, *J* = 8.1 and 2.1 Hz, 1H), 7.20-7.32 (m, 5H), 7.50 (tm, *J* = 7.5 Hz, 2H), 7.62 (tt, *J* = 7.5 and 1.8 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.78 (dm, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.2 (CH_3), 46.2 (CH_2), 53.4 (CH_2), 59.5 (CH_2), 100.7 (C), 123.7 (CH), 127.4 (CH), 127.8 (2 CH), 128.3 (2 CH), 128.8 (2 CH), 129.2 (2 CH), 129.8 (CH), 133.6 (CH), 136.9 (C), 137.0 (C), 138.9 (C), 140.4 (CH), 147.7 (C). HRMS (ESI-TOF) cald for $C_{22}H_{23}INO_2S$: 492.0489 $[M + H]^+$; found: 492.0486.

2-Iodo-*N*,4-dimethyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (1b). To a solution of 2-iodo-4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (500 mg, 1.25 mmol) in acetonitrile (20 mL), iodomethane (1.47 mL, 12.5 mmol) and K_2CO_3 (518 mg, 3.75 mmol) were added. The mixture was stirred at 85 ºC in a sealed tube for 72 h. The solvent was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to give 2-iodo-*N*,4-dimethyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (**1b**, 470 mg, 90%) as a yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.64 (s, 3H), 3.26-3.36 (m, 4H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.62 (s, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 20.1 (CH_3), 42.6 (CH_3), 49.9 (CH_2), 53.9 (CH_2), 99.0 (C), 121.6 (CH), 127.9 (2 CH), 129.3 (2 CH), 129.9 (CH), 133.7 (CH), 136.2 (C), 139.0 (C), 140.4 (CH), 149.7 (C). HRMS (ESI-TOF) cald for $C_{16}H_{19}INO_2S$: 416.0176 $[M + H]^+$; found: 416.0166.

2-Iodo-*N*,4-dimethyl-*N*-[2-(methylsulfonyl)ethyl]aniline (1c). A solution of *p*-toluidine (500 mg, 4.66 mmol) and methyl vinyl sulfone (0.37 mL, 4.25 mmol) in absolute EtOH (6 mL) was stirred at 80 ºC for 48 h. The solvent was removed *in vacuo* to give 4-methyl-*N*-2-[(methylsulfonyl)ethyl]aniline, which was used in the next reaction without purification. The secondary amine was dissolved in a CH_2Cl_2 (14 mL)-MeOH (7 mL) mixture, and $CaCO_3$ (0.66 g, 6.58 mmol) and $BTMAICl_2$ (1.85 g, 5.32 mmol) were added. The mixture was stirred at room temperature for 6 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried and concentrated. The residue was dissolved in acetonitrile (15 mL), and K_2CO_3 (1.4 g, 10.1 mmol), and iodomethane (2.52 mL, 40.5 mmol) were added. The mixture was stirred at 85 ºC in a sealed tube for 72 h. The solvent was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to give 2-iodo-*N*,4-dimethyl-*N*-[2-(methylsulfonyl)ethyl]aniline (**1c**, 1.5 g, 91%) as a yellow gum. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.70 (s, 3H), 2.98 (s, 3H), 3.18 (t, *J* = 6.9 Hz, 1H), 3.47 (t, *J* = 6.9 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 7.15 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.70 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.1 (CH_3), 41.9 (CH_3), 43.8 (CH_3), 49.8 (CH_2), 52.8 (CH_2), 98.8 (C), 121.5 (CH), 130.0 (CH), 136.5 (C), 140.7 (CH), 149.6 (C). HRMS (ESI-TOF) cald for $C_{11}H_{17}INO_2S$: 354.0019 $[M + H]^+$; found: 354.0023.

Representative procedure for the Pd(0)-catalyzed α-arylation reaction (Table 1, Entry 5). A mixture of sulfone **1a** (75 mg, 0.153 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), and K_3PO_4 (81 mg, 0.38 mmol) in THF (8 mL) was stirred at 120 ºC in a sealed tube for 72 h. The reaction mixture was partitioned between saturated $NaHCO_3$ aqueous solution and Et_2O. The organic

extracts were dried and concentrated. The residue was purified by chromatography (SiO_2, from hexanes to hexanes-CH_2Cl_2 20%) to give indole **3a** (25 mg, 73%) as a pale yellow oil.

Representative procedure for the domino reactions (Table 3, Entry 7). A mixture of *N*-benzyl-2-iodobenzylamine (80 mg, 0.26 mmol), $Pd_2(dba)_3$ (18 mg, 0.019 mmol), dppf (21 mg, 0.039 mmol), phenyl vinyl sulfone (104 mg, 0.62 mmol), and Cs_2CO_3 (253 mg, 0.78 mmol) in THF (8 mL) was stirred at 120 ºC in a sealed tube for 72 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, from hexanes to hexanes-EtOAc 1:4) to give sulfone **6a** (78 mg, 80%) as an amorphous brown solid.

Characterization data for the compounds of Tables 1, 2, 3 and 4.

***N*,5-Dimethyl-3-(methylsulfonyl)indoline (2c).** Brown gum. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 2.58 (d, *J* = 0.9 Hz, 3H), 2.78 (s, 3H), 3.53 (dd, *J* = 11.4 and 9.6 Hz, 1H), 4.03 (dd, *J* = 11.4 and 2.1 Hz, 1H), 4.43 (d, *J* = 9.6 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.29 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.6 (CH_3), 36.2 (CH_3), 36.3 (CH_3), 57.4 (CH_2), 66.5 (CH), 108.8 (CH), 121.6 (C), 127.3 (CH), 129.0 (C), 131.4 (CH), 157.5 (C). HRMS (ESI-TOF) cald for $C_{11}H_{16}NO_2S$: 226.0896 $[M + H]^+$; found: 226.0902.

***N*-Benzyl-5-methylindole (3a).** Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 3H), 5.29 (s, 2H), 6.46 (d, *J* = 3.2 Hz, 1H), 6.98 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.07-7.10 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.21-7.33 (m, 3H), 7.43 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 21.4 (CH_3), 50.1 (CH_2), 101.0 (CH), 109.3 (CH), 120.6 (CH), 123.3 (CH), 126.7 (2 CH), 127.5 (CH), 128.3 (CH), 128.7 (2 CH), 129.0 (C), 134.7 (C), 137.7 (C). One quaternary carbon was not observed. HRMS (ESI-TOF) cald for $C_{16}H_{16}N$: 222.1277 $[M + H]^+$; found: 222.1277.

***N*,5-Dimethylindole (3b).**[4] Pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46 (s, 3H), 3.77 (s, 3H), 6.40 (dd, *J* = 3.3 and 0.9 Hz, 1H), 7.01 (d, *J* = 3.3 Hz, 1H), 7.05 (dd, *J* = 8.4 and 1.5 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 1.5 and 0.9 Hz, 1H). HRMS (ESI-TOF) cald for $C_{10}H_{12}N$: 146.0964 $[M + H]^+$; found: 146.0961.

***N*-Benzyl-3-[2-(phenylsulfonyl)ethyl]-5-methylindole (4a).** Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 3.16 (m, 2H), 3.44 (m, 2H), 5.19 (s, 2H), 6.82 (s, 1H), 6.98 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.05 (dd, *J* = 8.0 and 2.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.18 (s, 1H), 7.22-7.30 (m, 3H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.66 (tt, *J* = 7.5 and 1.2 Hz, 1H), 7.96 (dm, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 21.6 (CH_3), 50.1 (CH_2), 56.9 (CH_2), 109.8 (CH), 110.6 (C), 118.3 (CH), 123.9 (CH), 126.1 (CH), 126.9 (2 CH), 127.6 (C), 127.8 (CH), 128.3 (2 CH), 128.9 (C), 128.9 (2 CH), 129.4 (2 CH), 133.8 (CH), 135.3 (C), 137.6 (C), 139.3 (C). HRMS (ESI-TOF) cald for $C_{24}H_{24}NO_2S$: 390.1522 $[M + H]^+$; found: 390.1529.

***N*,5-Dimethyl-3-[2-(phenylsulfonyl)ethyl]indole (4b).** Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 3.15 (m, 2H), 3.43 (m, 2H), 3.66 (s, 3H), 6.75 (s, 1H), 7.03 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.15 (s, 1H), 7.57 (tm, *J* = 7.5 Hz, 2H), 7.66 (tt, *J* = 7.5 and 1.2 Hz, 1H), 7.96 (dm, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.7 (CH_2), 21.4 (CH_3), 32.6 (CH_3), 56.8 (CH_2), 109.1 (CH), 109.6 (C), 117.9 (CH), 123.5 (CH), 126.6 (CH), 127.2 (C), 128.1 (2 CH), 128.4 (C), 129.2 (2 CH), 133.6 (CH), 135.4 (C), 139.2 (C). HRMS (ESI-TOF) cald for $C_{24}H_{24}NO_2S$: 314.1209 $[M + H]^+$; found: 314.1207.

***N*,5-Dimethyl-3-[2-(methylsulfonyl)ethyl]indole (4c).** Brown gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.47 (s, 3H), 2.80 (s, 3H), 3.28 (m, 2H), 3.36 (m, 2H), 3.72 (s, 3H), 6.89 (s, 1H), 7.07 (dd, *J* = 8.4 and 1.6 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.34 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 21.6 (CH_3), 32.9 (CH_3), 41.2 (CH_3), 55.6 (CH_2), 109.5 (CH), 109.6 (C), 118.2 (CH), 123.9 (CH), 127.1 (CH), 127.3 (C), 128.8 (CH), 135.8 (C). HRMS (ESI-TOF) cald for $C_{13}H_{18}NO_2S$: 252.1053 $[M + H]^+$; found: 252.1047.

***N*-Benzyl-5-methyl-3-[2-(methylsulfonyl)ethyl]indole (4d).** Brown gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 2.78 (s, 3H), 3.30 (m, 2H), 3.37 (m, 2H), 5.24 (s, 2H), 6.96 (s, 1H), 7.03 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.09 (dd, *J* = 8.4 and 2.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.25-7.31 (m, 3H), 7.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 21.6 (CH_3), 41.2 (CH_3), 50.2 (CH_2), 55.5 (CH_2), 109.9 (CH), 110.4 (C), 118.4 (CH), 124.1 (CH), 126.4 (CH), 127.0 (2 CH), 127.6 (C), 127.9 (CH), 129.0 (2 CH), 129.1 (C), 135.4 (C), 137.6 (C). HRMS (ESI-TOF) cald for $C_{19}H_{22}NO_2S$: 328.1366 $[M + H]^+$; found: 328.1354.

***N*-Benzyl-4-methyl-*N*-[2-(phenylsulfonyl)ethyl]aniline (5a).** Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22 (s, 3H), 3.33 (m, 2H), 3.79 (m, 2H), 4.40 (s, 2H), 6.50 (dm, *J* = 8.4 Hz, 2H), 6.96 (dm, *J* = 8.4 Hz, 2H), 7.14 (dm, *J* = 8.4 Hz, 2H), 7.20-7.30 (m, 3H), 7.57 (tm, *J* = 7.5 Hz, 2H), 7.68 (tt, *J* = 7.5 and 1.2 Hz, 1H), 7.88 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 20.3 (CH_3), 44.8 (CH_2), 52.7 (CH_2), 55.2 (CH_2), 113.2 (2 CH), 126.9 (2 CH), 127.3 (CH), 128.1 (2 CH), 128.8 (2 CH), 129.6 (2 CH), 130.2 (2 CH), 134.1 (CH), 138.3 (C), 139.4 (C), 145.1 (C). One quaternary carbon was not observed. HRMS (ESI-TOF) cald for $C_{22}H_{24}NO_2S$: 366.1522 $[M + H]^+$; found: 366.1517.

***N*,4-Dimethyl-*N*-[2-(methylsulfonyl)ethyl]aniline (5c).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H), 2.91 (s, 3H), 2.93 (s, 3H), 3.23 (t, *J* = 6.8 Hz, 2H), 3.84 (t, *J* = 6.8 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 20.4 (CH_3), 39.2 (CH_3), 42.3 (CH_3), 47.3 (CH_2), 51.5 (CH_2), 113.9 (2 CH), 127.9 (C), 130.2 (2 CH), 146.2 (C). HRMS (ESI-TOF) cald for $C_{11}H_{18}NO_2S$: 228.1053 $[M + H]^+$; found: 228.1044.

***N*-Benzyl-3-[2-(phenylsulfonyl)ethyl]indole (6a).** Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.19 (m, 2H), 3.44 (m, 2H), 5.20 (s, 2H), 6.85 (s, 1H), 7.05-7.10 (m, 3H), 7.16 (td, *J* = 7.8 and 1.2 Hz, 1H), 7.22-7.30 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 and 1.2 Hz, 2H), 7.63 (tt, *J* = 8.0 and 1.2 Hz, 1H), 7.94 (dm, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.8 (CH_2), 49.9 (CH_2), 56.6 (CH_2), 109.8 (CH), 110.9 (C), 118.4 (CH), 119.4 (CH), 122.1 (CH), 125.8 (CH), 126.8 (2 CH), 127.2 (C), 127.7 (CH), 128.0 (2 CH), 128.7 (2 CH), 129.2 (2 CH), 133.6 (CH), 136.6 (C), 137.2 (C), 139.0 (C). HRMS (ESI-TOF) cald for $C_{23}H_{22}NO_2S$: 376.1366 $[M + H]^+$; found: 376.1367.

***N*-Benzyl-3-[2-(methylsulfonyl)ethyl]indole (6b).** Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.79 (s, 3H), 3.30-3.41 (m, 4H), 5.28 (s, 2H), 7.00 (s, 1H), 7.09-7.33 (m, 8H), 7.59 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 41.2 (CH_3), 50.2 (CH_2), 55.5 (CH_2), 110.2 (CH), 111.1 (C), 118.7 (CH), 119.8 (CH), 122.5 (CH), 126.3 (CH), 127.0 (2 CH), 127.4 (C), 128.0 (CH), 129.0 (2 CH), 137.0 (C), 137.4 (C). HRMS (ESI-TOF) cald for $C_{18}H_{20}NO_2S$: 314.1209 $[M + H]^+$; found: 314.1220.

***N*-Benzylaniline (7).** Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.03 (broad b, 1H), 4.33 (s, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 6.71 (t, *J* = 7.4 Hz, 1H), 7.15-7.20 (m, 2H), 7.27 (m, 1H), 7.32-7.39 (m, 3H).

***E*-*N*-Benzyl-2-[2-(methylsulfonyl)ethenyl]aniline (8).** Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.02 (s, 3H), 4.41 (d, *J* = 4.8 Hz, 2H), 4.48 (t, *J* = 4.8 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.75 (td, *J* = 8.4 and 1.6 Hz, 1H), 6.84 (d, *J* = 15.2 Hz, 1H), 7.23-7.38 (m, 7H), 7.78 (d, J = 15.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 43.6 (CH_3), 48.2 (CH_2), 112.6 (CH), 117.5 (C), 118.0 (CH), 125.8 (CH), 127.5 (2 CH), 127.7 (CH), 128.8 (CH), 129.0 (2 CH), 132.9 (CH), 138.5 (C), 139.6 (CH), 147.1 (C). HRMS (ESI-TOF) cald for $C_{16}H_{18}NO_2S$: 288.1053 $[M + H]^+$; found: 288.1046.

***N*-Methyl-3-[2-(phenylsulfonyl)ethyl]indole (9a).** Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (m, 2H), 3.43 (m, 2H), 3.69 (s, 3H), 6.80 (s, 1H), 7.07 (ddd, *J* = 8.0, 6.8 and 1.2 Hz, 1H), 7.18-7.27 (m, 2H), 7.39 (dt, *J* = 7.6 and 1.2 Hz, 1H), 7.55 (tm, *J* = 7.6 Hz, 2H), 7.65 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.94 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 32.8 (CH_3), 56.8 (CH_2), 109.6 (CH), 110.3 (C), 118.4 (CH), 119.2 (CH), 122.0 (CH), 126.7 (CH), 127.1 (C), 128.2 (2 CH), 129.4 (2 CH), 133.8 (CH), 137.1 (C), 139.3 (C). HRMS (ESI-TOF) cald for $C_{17}H_{18}NO_2S$: 300.1053 $[M + H]^+$; found: 300.1048.

***N*-Methyl-3-[2-(methylsulfonyl)ethyl]indole (9b).** Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (s, 3H), 3.28-3.39 (m, 4H), 3.75 (s, 3H), 6.94 (s, 1H), 7.14 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.25 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 32.9 (CH_3), 41.1 (CH_3), 55.5 (CH_2), 109.7 (CH), 110.2 (C), 118.5 (CH), 119.5 (CH), 122.2 (CH), 127.0 (CH), 127.1 (C), 137.3 (C). HRMS (ESI-TOF) cald for $C_{12}H_{16}NO_2S$: 238.0896 $[M + H]^+$; found: 238.0898.

3-[2-(Phenylsulfonyl)ethyl]-*N*-propylindole (10a). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.80 (m, 2H), 3.19 (m, 2H), 3.44 (m, 2H), 3.98 (t, *J* = 7.2 Hz, 2H), 6.85 (s, 1H), 7.06 (dd, *J* = 8.0 and 7.6 Hz, 1H), 7.18 (dd, *J* = 8.0 and 7.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.65 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.94 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 11.7 (CH_3), 18.9 (CH_2), 23.7 (CH_2), 48.0 (CH_2), 56.9 (CH_2), 109.8 (CH), 110.3 (C), 118.5 (CH), 119.2 (CH), 121.9 (CH), 125.8 (CH), 127.2 (C), 128.2 (2 CH), 129.4 (2 CH), 133.8 (CH), 136.5 (C), 139.3 (C). HRMS (ESI-TOF) cald for $C_{19}H_{22}NO_2S$: 328.1366 $[M + H]^+$; found: 328.1364.

3-[2-(Methylsulfonyl)ethyl]-*N*-propylindole (10b). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.83 (m, 2H), 2.78 (s, 3H), 3.29-3.40 (m, 4H), 4.03 (t, *J* = 7.2 Hz, 2H), 6.98 (s, 1H), 7.12 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.23 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 11.7 (CH_3), 18.9 (CH_2), 23.7 (CH_2), 41.1 (CH_3), 48.1 (CH_2), 55.5 (CH_2), 109.9 (CH), 110.1 (C), 118.6 (CH), 119.4 (CH), 122.0 (CH), 126.1 (CH), 127.2 (C), 136.6 (C). HRMS (ESI-TOF) cald for $C_{14}H_{20}NO_2S$: 266.1209 $[M + H]^+$; found: 266.1214.

***N*-Ethyl-3-[2-(phenylsulfonyl)ethyl]indole (11a).** Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (t, *J* = 7.2 Hz, 3H), 3.19 (m, 2H), 3.44 (m, 2H), 4.07 (t, *J* = 7.2 Hz, 2H), 6.86 (s, 1H), 7.06 (dd, *J* = 8.0 and 7.6 Hz, 1H), 7.19 (dd, *J* = 8.0 and 7.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.56 (tm, *J* = 7.6 Hz, 2H), 7.65 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.94 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 15.6 (CH_3), 18.9 (CH_2), 40.9 (CH_2), 56.9 (CH_2), 109.6 (CH), 110.4 (C), 118.5 (CH), 119.2 (CH), 121.9 (CH), 124.9 (CH), 127.3 (C), 128.2 (2 CH), 129.4 (2 CH), 133.8 (CH), 136.2 (C), 139.3 (C). HRMS (ESI-TOF) cald for $C_{18}H_{20}NO_2S$: 314.1209 $[M + H]^+$; found: 314.1220.

***N*-Benzyl-5-methoxy-3-[2-(phenylsulfonyl)ethyl]indole (12a).** Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.16 (m, 2H), 3.43 (m, 2H), 3.82 (s, 3H), 5.16 (s, 2H), 6.79-6.86 (m, 3H), 7.04 (dm, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 9.2 Hz, 1H), 7.21-7.30 (m, 3H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.64 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.95 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 50.3 (CH_2), 56.1 (CH_3), 56.7 (CH_2), 100.4 (CH), 110.6 (C), 110.9 (CH), 112.5 (CH), 126.6 (CH), 126.9 (2 CH), 127.7 (C), 127.8 (CH), 128.2 (2 CH), 128.9 (2 CH), 129.4 (2 CH), 132.1 (C), 133.8 (CH), 137.5 (C), 139.3 (C), 154.2 (C). HRMS (ESI-TOF) cald for $C_{24}H_{24}NO_3S$: 406.1471 $[M + H]^+$; found: 406.1468.

***N*-Benzyl-5-methoxy-3-[2-(methylsulfonyl)ethyl]indole (12b).** Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (s, 3H), 3.30 (m, 2H), 3.37 (m, 2H), 3.87 (s, 3H), 5.23 (s, 2H), 6.87 (dd, *J* = 8.8 and 2.4 Hz, 1H), 6.98 (s, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 7.09 (dm, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.25-7.33 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 41.2 (CH_3), 50.3 (CH_2), 55.3 (CH_2), 56.1 (CH_3), 100.5 (CH), 110.5 (C), 111.1 (CH), 112.6 (CH), 126.8 (CH), 126.9 (2 CH), 127.8 (C), 127.9 (CH), 128.9 (2 CH), 132.2 (C), 137.5 (C), 154.4 (C). HRMS (ESI-TOF) cald for $C_{19}H_{22}NO_3S$: 344.1315 $[M + H]^+$; found: 344.1323.

5-Methoxy-*N*-propyl-3-[2-(phenylsulfonyl)ethyl]indole (13a). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, *J* = 7.2 Hz, 3H), 1.78 (m, 2H), 3.15 (m, 2H), 3.43 (m, 2H), 3.82 (s, 3H), 3.94 (t, *J* = 7.2 Hz, 2H), 6.81-6.86 (m, 3H), 7.16 (dd, *J* = 8.4 and 0.8 Hz, 1H), 7.57 (tm, *J* = 7.6 Hz, 2H), 7.65 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.95 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 11.7 (CH_3), 18.9 (CH_2), 23.7 (CH_2), 48.2 (CH_2), 56.2 (CH_3), 56.8 (CH_2), 100.3 (CH), 109.7 (C), 110.6 (CH), 112.1 (CH), 126.3 (CH), 127.5 (C), 128.2 (2 CH), 129.4 (2 CH), 131.8 (C), 133.8 (CH), 139.4 (C), 154.0 (C). HRMS (ESI-TOF) cald for $C_{20}H_{24}NO_3S$: 358.1471 $[M + H]^+$; found: 358.1481.

***N*-Benzyl-5-chloro-3-[2-(phenylsulfonyl)ethyl]indole (14a).** Amorphous pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15 (m, 2H), 3.41 (m, 2H), 5.19 (s, 2H), 6.90 (s, 1H), 7.04 (m, 2H), 7.09 (dd, *J* = 8.4 and 2.0 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.25-7.32 (m, 3H), 7.34 (dd, *J* = 2.0 and 0.8 Hz, 1H), 7.56 (tm, *J* = 7.6 Hz, 2H), 7.66 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.94 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.8 (CH_2), 50.3 (CH_2), 56.7 (CH_2), 110.9 (C), 111.1 (CH), 118.1 (CH), 122.6 (CH), 125.5 (C), 126.9 (2 CH), 127.4 (CH), 128.1 (CH), 128.3 (2 CH), 128.5 (C), 129.0 (2 CH), 129.5 (2 CH), 133.9 (CH), 135.2 (C), 137.0 (C), 139.2 (C). HRMS (ESI-TOF) cald for $C_{23}H_{21}ClNO_2S$: 410.0976 $[M + H]^+$; found: 410.0993.

***N*-Benzyl-5-chloro-3-[2-(methylsulfonyl)ethyl]indole (14b).** Brown gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (s, 3H), 3.30 (m, 2H), 3.37 (m, 2H), 5.24 (s, 2H), 7.03 (s, 1H), 7.08 (dm, *J* = 8.0 Hz, 2H), 7.13 (dd, *J* = 8.8 and 2.0 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.25-7.33 (m, 3H), 7.54 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.6 (CH_2), 41.2 (CH_3), 50.4 (CH_2), 55.3 (CH_2), 110.8 (C), 111.3 (CH), 118.2 (CH), 122.8 (CH), 125.7 (C), 126.9 (2 CH), 127.8 (CH), 128.1 (CH), 128.4 (C), 129.1 (2 CH), 135.3 (C), 137.0 (C). HRMS (ESI-TOF) cald for $C_{18}H_{19}ClNO_2S$: 348.0820 $[M + H]^+$; found: 348.0831.

***N*-Benzyl-6-chloro-3-[2-(phenylsulfonyl)ethyl]indole (15a).** Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.16 (m, 2H), 3.41 (m, 2H), 5.16 (s, 2H), 6.85 (s, 1H), 7.03-7.07 (m, 3H), 7.22 (d, *J* = 1.2 Hz, 1H), 7.25-7.31 (m, 3H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.65 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.93 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.8 (CH_2), 50.2 (CH_2), 56.7 (CH_2), 110.0 (CH), 111.5 (C), 119.5 (CH), 120.3 (CH), 126.0 (C), 126.6 (CH), 126.9 (2 CH), 128.1 (CH), 128.2 (2 CH), 128.5 (C), 129.1 (2 CH), 129.5

(2 CH), 133.9 (CH), 136.9 (C), 137.2 (C), 139.2 (C). HRMS (ESI-TOF) cald for $C_{23}H_{21}ClNO_2S$: 410.0976 $[M + H]^+$; found: 410.0967.

***N*-Benzyl-6-chloro-3-[2-(methylsulfonyl)ethyl]indole (15b).** Amorphous brown solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.80 (s, 3H), 3.27-3.38 (m, 4H), 5.22 (s, 2H), 6.99 (s, 1H), 7.08-7.13 (m, 3H), 7.28-7.33 (m, 4H), 7.49 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.7 (CH_2), 41.2 (CH_3), 50.3 (CH_2), 55.4 (CH_2), 110.2 (CH), 111.4 (C), 119.6 (CH), 120.6 (CH), 126.0 (C), 126.9 (CH), 127.0 (2 CH), 128.1 (CH), 128.7 (C), 129.1 (2 CH), 136.9 (C), 137.3 (C). HRMS (ESI-TOF) cald for $C_{18}H_{19}ClNO_2S$: 348.0820 $[M + H]^+$; found: 348.0813.

***N*-Benzyl-6-fluoro-3-[2-(phenylsulfonyl)ethyl]indole (16a).** Amorphous pale yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.16 (m, 2H), 3.42 (m, 2H), 5.14 (s, 2H), 6.83 (ddd, *J* = 9.6, 8.8 and 2.0 Hz, 1H), 6.84 (s, 1H), 6.89 (dd, *J* = 9.6 and 2.0 Hz, 1H), 7.06 (dm, *J* = 8.0 Hz, 2H), 7.24-7.31 (m, 3H), 7.33 (dd, *J* = 8.8 and 5.2 Hz, 1H), 7.55 (tm, *J* = 7.6 Hz, 2H), 7.64 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.93 (dm, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.9 (CH_2), 50.2 (CH_2), 56.7 (CH_2), 96.5 (d, *J* = 26.0 Hz, CH), 108.4 (d, *J* = 24.5 Hz, CH), 111.5 (C), 119.4 (d, *J* = 10.8 Hz, CH), 124.0 (C), 126.3 (d, *J* = 3.8 Hz, CH), 127.0 (2 CH), 128.0 (CH), 128.2 (2 CH), 129.0 (2 CH), 129.4 (2 CH), 133.9 (CH), 136.9 (d, *J* = 9.1 Hz, C), 139.2 (C), 160.2 (d, *J* = 238.2 Hz, C). One quaternary carbon was not observed. HRMS (ESI-TOF) cald for $C_{23}H_{21}FNO_2S$: 394.1272 $[M + H]^+$; found: 394.1276.

***N*-Benzyl-6-fluoro-3-[2-(methylsulfonyl)ethyl]indole (16b).** Amorphous brown solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.80 (s, 3H), 3.27-3.38 (m, 4H), 5.20 (s, 2H), 6.89 (ddd, *J* = 10.0, 8.8 and 2.0 Hz, 1H), 6.95 (dd, *J* = 10.0 and 2.0 Hz, 1H), 6.98 (s, 1H), 7.10 (dm, *J* = 8.0 Hz, 2H), 7.25-7.33 (m, 3H), 7.49 (dd, *J* = 8.8 and 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.8 (CH_2), 41.2 (CH_3), 50.4 (CH_2), 55.4 (CH_2), 96.7 (d, *J* = 26.0 Hz, CH), 108.6 (d, *J* = 24.5 Hz, CH), 111.4 (C), 119.5 (d, *J* = 9.9 Hz, CH), 124.0 (C), 126.6 (d, *J* = 3.8 Hz, CH), 127.0 (2 CH), 128.1 (CH), 129.1 (2 CH), 136.9 (C), 137.0 (d, *J* = 12.2 Hz, C), 160.3 (d, *J* = 239.0 Hz, C). HRMS (ESI-TOF) cald for $C_{18}H_{19}FNO_2S$: 332.1115 $[M + H]^+$; found: 332.1126.

***N*-Benzyl-6-(methoxycarbonyl)-3-[2-(phenylsulfonyl)ethyl]indole (17a).** Amorphous brown solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.19 (m, 2H), 3.43 (m, 2H), 3.90 (s, 3H), 5.27 (s, 2H), 7.01 (s, 1H), 7.06 (dm, *J* = 7.6 Hz, 2H), 7.25-7.32 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.54 (tm, *J* = 7.6 Hz, 2H), 7.64 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.77 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.93 (dm, *J* = 7.6 Hz, 2H), 8.04 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.8 (CH_2), 50.1 (CH_2), 52.1 (CH_3), 56.6 (CH_2), 111.7 (C), 112.3 (CH), 118.2 (CH), 120.6 (CH), 124.0 (C), 127.0 (2 CH), 128.1 (CH), 128.2 (2 CH), 129.0 (2 CH), 129.2 (CH), 129.4 (2 CH), 130.8 (C), 133.9 (CH), 136.2 (C), 136.9 (C), 139.2 (C), 168.1 (C). HRMS (ESI-TOF) cald for $C_{25}H_{24}NO_4S$: 434.1421 $[M + H]^+$; found: 434.1437.

***N*-Benzyl-6-(methoxycarbonyl)-3-[2-(methylsulfonyl)ethyl]indole (17b).** Amorphous brown solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.81 (s, 3H), 3.30-3.40 (m, 4H), 3.92 (s, 3H), 5.33 (s, 2H), 7.11 (dm, *J* = 7.6 Hz, 2H), 7.15 (s, 1H), 7.26-7.34 (m, 3H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 8.4 and 1.2 Hz, 1H), 8.10 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.7 (CH_2), 41.2 (CH_3), 50.2 (CH_2), 52.2 (CH_3), 55.3 (CH_2), 111.6 (C), 112.4 (CH), 118.4 (CH), 120.8 (CH), 124.3 (C), 127.1 (2 CH), 128.2 (CH), 129.1 (2 CH), 129.5 (CH), 130.8 (C), 136.4 (C), 136.9 (C), 168.1 (C). HRMS (ESI-TOF) cald for $C_{20}H_{22}NO_4S$: 372.1264 $[M + H]^+$; found: 372.1276.

6-(Methoxycarbonyl)-3-[2-(phenylsulfonyl)ethyl]-*N*-propylindole (18a). Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.82 (m, 2H), 3.20 (m, 2H), 3.44 (m, 2H), 3.93 (s, 3H), 4.04 (t, *J* = 7.2 Hz, 2H), 7.03 (s, 1H), 7.41 (dd, *J* = 8.4 and 0.8 Hz, 1H), 7.55 (tm, *J* = 7.6 Hz, 2H), 7.64 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.75 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.93 (dm, *J* = 7.6 Hz, 2H), 8.04 (dd, *J* = 1.2 and 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 11.6 (CH_3), 18.8 (CH_2), 23.8 (CH_2), 48.2 (CH_2), 52.1 (CH_3), 56.7 (CH_2), 110.8 (C), 112.2 (CH), 118.1 (CH), 120.2 (CH), 123.6 (C), 128.2 (2 CH), 129.1 (CH), 129.4 (2 CH), 130.7 (C), 133.8 (CH), 135.8 (C), 139.2 (C), 168.2 (C). HRMS (ESI-TOF) cald for $C_{21}H_{24}NO_4S$: 386.1421 $[M + H]^+$; found: 386.1435.

6-(Methoxycarbonyl)-3-[2-(methylsulfonyl)ethyl]-*N*-propylindole (18b). Amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.87 (m, 2H), 3.30-3.41 (m, 4H), 3.95 (s, 3H), 4.11 (t, *J* = 7.2 Hz, 2H), 7.16 (s, 1H), 7.58 (dd, *J* = 8.6 and 0.8 Hz, 1H), 7.81 (dd, *J* = 8.6 and 1.2 Hz, 1H), 8.10 (dd, *J* = 1.2 and 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 11.6 (CH_3), 18.7 (CH_2), 23.9 (CH_2), 41.2 (CH_3), 48.3 (CH_2), 52.2 (CH_3), 55.4 (CH_2), 110.7 (C), 112.4 (CH), 118.2 (CH), 120.4 (CH), 123.8 (C), 129.4 (CH), 130.7 (C), 136.0 (C), 168.2 (C). HRMS (ESI-TOF) cald for $C_{16}H_{22}NO_4S$: 324.1264 $[M + H]^+$; found: 324.1265.

Synthesis of phenyl 2,2-dideuterovinyl sulfone (19-D_2)

To a cooled (-30 ºC) solution of ethyl phenylthioacetate (3.8 mL, 21.3 mmol) in CH_2Cl_2 (100 mL), DIBAL-D (67 mL of 0.7 M solution in toluene, 46.9 mmol) was added dropwise. After 3 h at room temperature, the reaction mixture was poured into a saturated NH_4Cl aqueous solution and stirring was continued for 10 min. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic extracts were dried and the solvent was removed under vacuum to give 1,1-dideutero-2-phenylthioethanol (3.48 g) as a colourless oil, which was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12 (s, 1H), 3.10 (s, 2H), 3.73 (q, *J* = 5.2 Hz, 0.125 H corresponding to the nondeuterated alcohol), 7.21 (tt, *J* = 7.2 and 1.6 Hz, 1H), 7.29 (tm, *J* = 7.2 Hz, 2H), 7.39 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 37.3 (CH_2), 59.9 (m, CD_2), 126.8 (CH), 129.2 (2 CH), 130.4 (2 CH), 135.0 (C).

To a cooled (0 ºC) solution of crude 1,1-dideutero-2-phenylthioethanol (1.0 g) in CH_2Cl_2 (28 mL), *m*-CPBA (77%, 2.87 g, 12.8 mmol) was added portion wise, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with CH_2Cl_2 (80 mL) and washed with NaOH 2M (2 x 80 mL). The organic extracts were dried and the solvent was removed under vacuum to give 2,2-dideutero-2-hydroxyethyl phenyl sulfone (0.55 g) as a colourless oil, which was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.72 (s, 1H), 3.35 (s, 2H), 4.00 (broad signal, 0.15 H corresponding to the nondeuterated sulfone), 7.61 (tm, *J* = 8.0 Hz, 2H), 7.70 (tt, *J* = 8.0 and 1.6 Hz, 1H), 7.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 55.7 (quintuplet, *J* = 22.2 Hz, CD_2), 58.1 (CH_2), 128.0 (2 CH), 129.5 (2 CH), 134.1 (CH), 139.1 (C).

To a solution of 2,2-dideutero-2-hydroxyethyl phenyl sulfone (0.55 g) and Et_3N (1.0 mL, 7.3 mmol) in CH_2Cl_2 (18 mL), MsCl (0.27 mL, 3.5 mmol) was added dropwise at room temperature. The mixture was stirred for 6 h, treated with saturated ammonium chloride aqueous solution, and extracted with CH_2Cl_2. The organic extracts were washed with water and

brine. The organic phase was dried and the solvent was removed under vacuum. The residue was purified by flash chromatography (from hexanes to hexanes-EtOAc 1:1) to give 2,2-dideuterovinyl phenyl sulfone (**19-D_2**, 0.39 g, 37% from ethyl phenylthioacetate) as an amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.03 (d, *J* = 10.0 Hz, 0.06 H corresponding to the nondeuterated sulfone), 6.45 (d, *J* = 16.4 Hz, 0.06 H corresponding to the nondeuterated sulfone), 6.66 (s, 1H), 7.56 (dm *J* = 7.6 Hz, 2H), 7.65 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 127.4 (quintuplet, *J* = 25.9 Hz, CD_2), 128.0 (2 CH), 129.5 (2 CH), 133.8 (CH), 138.4 (CH), 139.6 (C). HRMS (ESI-TOF) cald for $C_8H_7D_2O_2S$: 171.0443 $[M + H]^+$; found: 171.0439.

Synthesis of 6a-D_3

6a-D_3 was obtained (42 mg, 45%) as an amorphous brown solid following the general procedure for the domino reaction described above. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.43 (s, 2H), 5.22 (s, 2H), 7.06-7.11 (m, 3H), 7.17 (td, *J* = 7.8 and 1.2 Hz, 1H), 7.23-7.30 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 and 1.2 Hz, 2H), 7.65 (tt, *J* = 8.0 and 1.2 Hz, 1H), 7.95 (dm, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.6 (m, CD_2), 50.1 (CH_2), 56.7 (CH_2), 110.1 (CH), 110.9 (C), 118.6 (CH), 119.6 (CH), 122.3 (CH), 127.0 (2 CH), 127.5 (C), 127.9 (CH), 128.3 (2 CH), 129.0 (2 CH), 129.5 (2 CH), 133.8 (CH), 136.8 (C), 137.4 (C), 139.3 (C). The -indole-C_2-D signal was not observed. HRMS (ESI-TOF) cald for $C_{23}H_{19}D_3NO_2S$: 379.1554 $[M + H]^+$; found: 379.1563.

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Domino Reactions

Exploring Partners for the Domino α-Arylation/Michael Addition Reaction Leading to Tetrahydroisoquinolines

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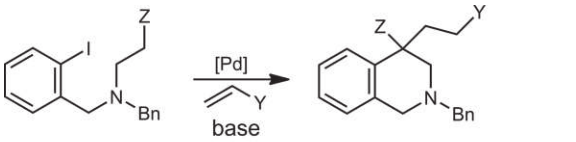
Abstract: Sulfonates, sulfonamides, and phosphonates have proven useful nucleophiles for palladium-catalyzed intramolecular α-arylation reactions leading to tetrahydroisoquinolines. Although the sulfonate α-arylation reaction can be successfully combined in a domino process with a broad range of Michael acceptors, only vinyl sulfones can be used in Michael additions when starting from sulfonamides. No domino process was developed with the phosphonate derivative. DFT calculations were carried out to gain more insights into the experimental differences observed in the reactions involving these substrates.

Introduction

In the continuous search for more environmentally friendly reaction processes, domino reactions have emerged as a powerful tool for synthetic organic chemists.[1] Ideally, a multicomponent domino process would simply involve the mixing of all the reagents, which would then participate chemoselectively in a particular sequence of events leading to the final product without requiring any additional modification of the reaction conditions.[2] The advantages of domino strategies include lower costs, a more expeditious procedure, less purification, and often higher overall reaction yields.

In recent years, different domino processes combining palladium-catalyzed transformations with Michael addition reactions have been developed for the synthesis of a variety of azaheterocycles.[3] In this context, we have recently reported the efficient synthesis of highly functionalized tetrahydroisoquinolines[4] and indoles[5] by domino aza-Michael/Pd-catalyzed α-arylation/Michael addition processes based on the use of sulfones both as electrophiles and nucleophiles. To further generalize the application of these synthetic methodologies and access diversely functionalized heterocycles, we were interested in exploring the feasibility of other electron-withdrawing groups in the domino α-arylation/Michael addition strategy.

In this work we expanded our previous studies towards the use of sulfonates, sulfonamides,[6] and phosphonates[7] as nucleophiles in the α-arylation[8] step of the domino process leading to tetrahydroisoquinolines[9] (Scheme 1). The combined experimental and computational study of these reactions establishes the scope and limitations of these electron-withdrawing groups as alternatives to sulfones.



Z = SO_3Ph, SO_2NBn_2, $PO(OEt)_2$

Y = SO_2Ph, SO_2Me, CO_2Me, SO_3Ph, SO_2NBn_2

Scheme 1. Domino α-arylation/Michael addition process.

Results and Discussion

In our previous work on the α-arylation/Michael addition domino process, we realized that the Pd-catalyzed reaction was the most challenging step of the entire transformation. Thus, we first examined the α-arylation of sulfonate **1a**, sulfonamides **1b** and **1d**, and phosphonate **1c** (Table 1).

Treatment of **1a** with $[Pd_2(dba)_3]$/Xantphos as the catalyst and K_3PO_4 as the base in THF, an effective combination for the intramolecular α-arylation of β-amino sulfones,[4] afforded tetrahydroisoquinoline **2a** in a modest 27 % yield (entry 1). Although exchanging the solvent for toluene increased the yield to 45 % (entry 2), changing the base to Cs_2CO_3 resulted in the complete decomposition of the material. In this context, it should be noted that **2a** was rather unstable and partially decomposed during the chromatographic purification, as evidenced by the isolation of significant amounts of phenol.

The reaction of sulfonamide **1b** with the couple $[Pd_2(dba)_3]$/Xantphos and K_3PO_4 in THF led to the desired tetrahydroisoquinoline **2b** in 46 % yield (entry 3). Interestingly, performing the α-arylation of **1b** with Cs_2CO_3 as the base afforded **2b** in 75 % yield (entry 4). Treatment of phosphonate **1c** under the same reaction conditions gave **2c** in 61 % yield (entry 5). The use of PPh_3 as the ligand instead of Xantphos afforded a similar

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http://www.ucm.es/info/biorgmet/espanol/isra.html
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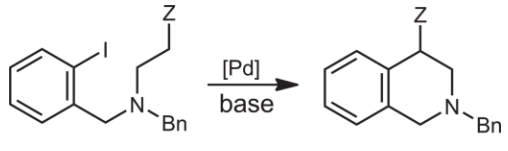
Table 1. Pd-catalyzed α-arylation of **1a**–**c**.[a]



1a, Z = SO_3Ph
1b, Z = SO_2NBn_2
1c, Z = $PO(OEt)_2$
1d, Z = SO_2NHBn

2a
2b
2c

Entry	1	[Pd]/Ligand ([mol-%])	Base	Solvent	Products (Yield [%])[b]
1	**1a**	$[Pd_2(dba)_3]$ (7.5)/ Xantphos (15)	K_3PO_4	THF	**2a** (27)[c]
2	**1a**	$[Pd(PPh_3)_4]$ (10)/ Xantphos (10)	K_3PO_4	Toluene	**2a** (45)[c,d]
3	**1b**	$[Pd_2(dba)_3]$ (7.5)/ Xantphos (15)	K_3PO_4	THF	**2b** (46)[e]
4	**1b**	$[Pd_2(dba)_3]$ (7.5)/ Xantphos (15)	Cs_2CO_3	THF	**2b** (75)
5	**1c**	$[Pd_2(dba)_3]$ (7.5)/ Xantphos (15)	Cs_2CO_3	THF	**2c** (61)[e]
6	**1c**	$[Pd(PPh_3)_4]$ (10)	Cs_2CO_3	THF	**2c** (59)[e]
7	**1c**	$[Pd_2(dba)_3]$ (7.5)/ PCy_3 (15)	Cs_2CO_3	THF	**2c** (80)
8	**1c**	$[Pd_2(dba)_3]$ (7.5)/ PCy_3 (15)	K_3PO_4	THF	**1c**/**2c** (1:2.5)[f]

[a] Reaction conditions: [Pd]/ligand (see Table), base (3 equiv.) in the indicated solvent at 120 °C for 72 h in a sealed tube. [b] Yield refers to products isolated by chromatography. [c] Significant amounts of phenol were observed in the reaction mixture. [d] Similar results were obtained when using $[Pd(PPh_3)_4]$ (15 mol-%) and Xantphos (15 mol-%) as the catalyst; however, the greater amount of the PPh_3 ligand hindered the isolation and purification of **2a**. [e] Significant amounts of the corresponding hydrodehalogenation product were observed in the reaction mixture. [f] ^1H NMR ratio, the yields were not quantified.

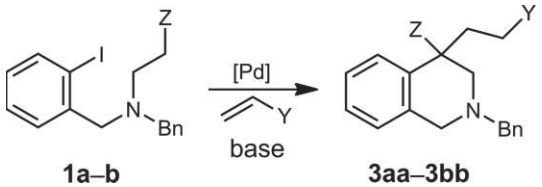
result (entry 6), whereas with PCy_3 the yield increased considerably to 80 % (entry 7). The use of K_3PO_4 as base with the same combination of Pd source and ligand resulted in a slower reaction (entry 8).

Finally, sulfonamide **1d**, which has an acidic H atom at the nitrogen, failed to undergo a similar α-arylation and was recovered unaltered under all explored reaction conditions.

The results in Table 1 show that sulfonates, sulfonamides, and phosphonates can undergo α-arylation and, consequently, they are all potential candidates for the proposed domino cascades. We therefore decided to explore the α-arylation/Michael addition domino process by using these substrates with a variety of Michael acceptors (Table 2).

Gratifyingly, the treatment of sulfonate **1a** with a catalytic amount of $[Pd(PPh_3)_4]$/Xantphos and K_3PO_4 in the presence of phenyl vinyl sulfone in THF afforded sulfonate **3aa** in 68 % yield (entry 1). A similar reaction was observed when using methyl vinyl sulfone as the Michael acceptor, which afforded **3ab** in 70 % yield (entry 2). The α-arylation/conjugated addition tandem process was also possible when using methyl acrylate, phenyl ethenesulfonate, and *N*,*N*-dibenzylethenesulfonamide,

Table 2. Tandem α-arylation/Michael addition reactions.[a]



1a–b **3aa–3bb**

Entry	Z	Y	[Pd]/Ligand	Base	Products (Yield [%])[b]
1	SO_3Ph	SO_2Ph	$[Pd(PPh_3)_4]$/ Xantphos	K_3PO_4	**3aa** (68)
2	SO_3Ph	SO_2Me	$[Pd(PPh_3)_4]$/ Xantphos	K_3PO_4	**3ab** (70)[c]
3	SO_3Ph	CO_2Me	$[Pd(PPh_3)_4]$/ Xantphos	K_3PO_4	**3ac** (43)[c]
4	SO_3Ph	SO_3Ph	$[Pd(PPh_3)_4]$/ Xantphos	K_3PO_4	**3ad** (50)
5	SO_3Ph	SO_2NBn_2	$[Pd(PPh_3)_4]$/ Xantphos	K_3PO_4	**3ae** (25)
6	SO_2NBn_2	SO_2Ph	$[Pd(PPh_3)_4]$	Cs_2CO_3	**3ba** (74)
7	SO_2NBn_2	SO_2Me	$[Pd(PPh_3)_4]$	Cs_2CO_3	**3bb** (67)[c]

[a] Reaction conditions: [Pd] (10 %), ligand (10 %), base (3 equiv.), and Michael acceptor (1.5 equiv.) in THF at 120 °C in a sealed tube for 72 h. [b] Yield refers to products isolated by chromatography. [c] Michael acceptor (3 equiv.).

which allowed us to prepare **3ac**, **3ad**, and **3ae**, respectively, in moderate yields (entries 3–5). It should be noted that, except when using *N*,*N*-dibenzylethenesulfonamide as the Michael acceptor, the domino reactions starting from **1a** proceeded with higher yields than the α-arylation, which confirms that the lower yields observed for the latter are partially due to the degradation of the arylated sulfonate **2a** under the reaction conditions.

In the tandem reactions, sulfonamide **1b** afforded results parallel to those of sulfonate **1a** with phenyl vinyl sulfone and methyl vinyl sulfone (entries 6 and 7), but no product was formed when using methyl acrylate, phenyl ethenesulfonate, or *N*,*N*-dibenzylethenesulfonamide as the Michael acceptor, and only the α-arylation product **2b** was isolated. Similarly, phosphonate **1c** also failed to undergo the α-arylation/conjugated addition tandem process with any of the Michael acceptors explored herein. Once again, the corresponding α-arylation compound **2c** was the only product isolated from the reaction mixtures.

It is noteworthy that in all the domino reactions with **1a** and **1b**, the α-arylation took place without any interference from the competing Heck reaction, which is in agreement with the infeasibility previously observed for this particular pathway when using sulfones in the domino process.[5]

According to our previous study involving 2-iodoanilines and sulfones,[5] two alternative reaction pathways for the above palladium-catalyzed α-arylation reactions leading to the observed tetrahydroisoquinolines **2** can be envisaged: The direct base-mediated α-arylation reaction and a concerted metalation/deprotonation (CMD) C–H activation process. The competition between the two pathways in the reactions involving the new nucleophiles was explored computationally by means of DFT

calculations.[10] To this end, we computed the corresponding reaction profiles starting from **INT0**, the intermediate formed after a model benzylamine derivative (in which the benzyl group attached to the nitrogen atom was replaced by a methyl group) underwent oxidative addition to the model $[Pd(PMe_3)_2]$ catalyst in the presence of carbonate as base.

Figure 1 shows the reaction profiles for the process involving **INT0A** (Z = SO_3Ph). The base-mediated α-arylation pathway (in blue) begins with the base-mediated deprotonation of the acidic hydrogen atom at the carbon atom linked to the sulfonate group, which gives the carbanionic intermediate **INT1A** in a strongly exergonic process (ΔG_R = –28.1 kcal/mol). This species would then evolve to complex **INT2A** by the slightly endergonic (ΔG_R = 5.6 kcal/mol) coordination of the carbanion to the transition metal and concomitant release of a phosphine ligand. This step typically proceeds with the initial endergonic release of the phosphine ligand to produce a vacant coordination site, which is then saturated by the carbanionic ligand. This intramolecular coordination is typically associated with a low barrier (<10 kcal/mol)[11] and therefore it is not the rate-limiting step of the transformation. Reductive elimination would then take place to produce the tetrahydroisoquinoline **2MA**. This exergonic step (ΔG_R = –13.8 kcal/mol) proceeds via **TS1A**, a transition state associated with the direct formation of the new C–C bond, with a relatively high activation barrier of 28.2 kcal/mol. A similar activation barrier of 28.6 kcal/mol was computed for the closely related direct α-arylation reaction involving 2-iodoaniline derivatives with Z = SO_2Me,[5] which indicates that neither the substrate nor the Z group has a significant influence on this step of the reaction. Alternatively, **INT2A** can be transformed into the coordinatively unsaturated complex **INT3A** by releasing the iodide ligand in an endergonic process (ΔG_R = 6.5 kcal/mol). This species would be then converted into the final reaction product **2MA** in a highly exergonic transformation (ΔG_R = –20.3 kcal/mol) via **TS3A** with a much lower activation barrier of 14.2 kcal/mol.

The alternative reaction pathway involving the C–H activation begins with the also highly exergonic (ΔG_R = –30.4 kcal/mol) replacement of the iodide and phosphine ligand in **INT0A** by the bidentate CO_3^{2-} ligand to form the anionic complex **INT4A**. A concerted metalation/deprotonation (CMD) C–H activation reaction assisted by the carbonate ligand then occurs to produce **INT5A** in a slightly endergonic transformation (ΔG_R = 2.6 kcal/mol). Strikingly, this reaction step proceeds with an activation barrier of only 9.6 kcal/mol (via **TS2A**), which is much lower than that computed not only for the direct α-arylation via **TS1A** (see above) but also for the analogous process involving 2-iodoaniline derivatives with Z = SO_2Me ($\Delta G^{\neq}$ = 26.1 kcal/mol).[5] Subsequent release of the HCO_3^- ligand would produce **INT3A**, which, as mentioned above, readily evolves to the final reaction product via **TS3A**. Although, based on the computed relative activation barriers, our calculations suggest that the CMD pathway is strongly favored for the benzylamine derivative with Z = SO_3Ph, the alternative **INT1A** → **INT2A** → **INT5A** or **INT1A** → **INT2A** → **INT3A** pathways cannot be completely discarded.

We also explored the analogous C–H activation/reductive elimination sequence from **INT6A**, the intermediate formed upon coordination of the benzylic nitrogen atom to the transition metal in **INT4A**. However, the CMD reaction pathway from **INT6A** can be considered as noncompetitive in view of the much higher activation barrier ($\Delta G^{\neq}$ = 28.2 kcal/mol) and end-

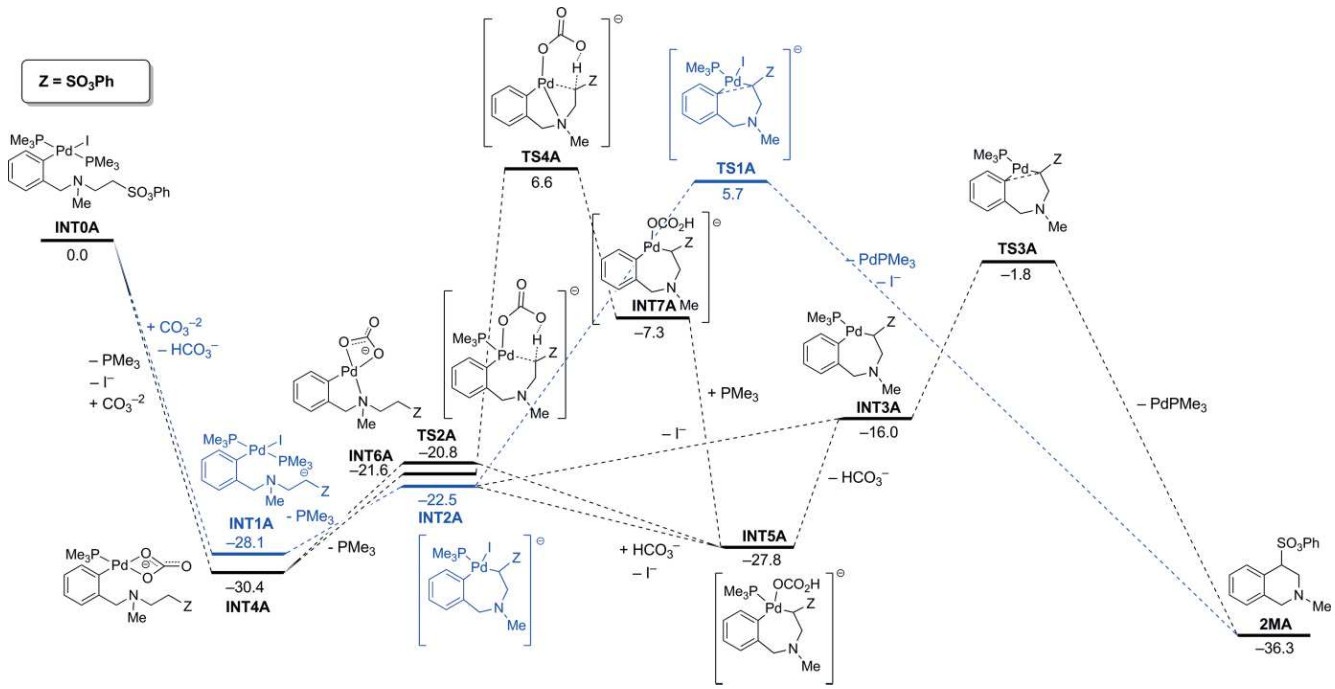


Figure 1. Computed reaction profiles for the palladium-catalyzed α-arylation reaction of **INT0A**. Relative free energies (Δ*G*, at 298 K) and bond lengths are given in kcal/mol and Å, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level of theory.

ergonicity (ΔG_R = 14.3 kcal/mol, from **INT6A**) computed for the CMD reaction via **TS4A** (see Figure 1).

These calculations indicate that the α-arylation of sulfonate **1a** in the presence of Cs_2CO_3 could proceed through the two competing mechanisms sharing the common intermediate **INT3A**, the reductive elimination of which affords the tetrahydroisoquinoline. As no α-arylation product was isolated in the reactions of **1a** when using Cs_2CO_3 as the base, we can conclude that the failure of the transformation has to be due to the instability of the arylated sulfone under the reaction conditions. In contrast, the α-arylation of **1a** did take place when using K_3PO_4 as the base, and in this case the reaction should follow the base-mediated pathway through **INT1A**.

Similar conclusions (i.e., a preference for the C–H activation) can be drawn for the analogous system with the phosphonate substituent [Z = $PO(OMe)_2$ in the calculations, see Figure S1 in the Supporting Information]. In this particular transformation, although the CMD step proceeds with a higher activation barrier of 16.5 kcal/mol, this pathway is still preferred over the direct α-arylation reaction. Indeed, the corresponding transition state for the latter process (**TS1C**) lies 17.8 kcal/mol above that associated with the CMD reaction (**TS2C**, see Figure S1). Thus, by starting from phosphonate **1c** and using Cs_2CO_3, the α-arylated product **2c** could be formed by both competing mechanisms, whereas in the presence of K_3PO_4, only the base-mediated α-arylation pathway would be operative.

The scenario involving the sulfonamide group (Z = SO_2NMe_2 in the calculations) is slightly different to those found for Z = SO_3Ph or $PO(OMe)_2$ (see Figure 2). Indeed, in this case, the corresponding CMD reaction step proceeds with a much higher activation barrier ($\Delta G^{\neq}$ = 35.5 kcal/mol, via **TS2B**), which makes this process unlikely. This is in part due to the stronger C–H bond in **INT4B** compared with in **INT4A**, as confirmed by the corresponding computed Wiberg bond indices (0.89 and 0.86 for **INT4B** and **INT4A**, respectively), and more likely due to the higher pK_a of the R–CH_2–SO_2NMe_2 species compared with R–CH_2–SO_3Ph.[12] Therefore, the preferred α-arylation pathway when Z = SO_2NMe_2 seems to be **INT0B** → **INT1B** → **INT2B** → **INT3B** → **TS3B** → **2MB**. In this particular case, it can also be suggested that the nitrogen atom of the sulfonamide can coordinate to the transition metal in the coordinatively unsaturated complex **INT3B**. However, although such coordination is strongly exergonic (ΔG_R = –11.3 kcal/mol), the corresponding reductive elimination reaction via **TS3B′** proceeds with a much higher activation barrier ($\Delta G^{\neq}$ = 28.7 kcal/mol) than the analogous process involving **TS3B** ($\Delta G^{\neq}$ = 15.9 kcal/mol).

Finally, we investigated the reasons for the observed lower yields in the domino reactions involving methyl acrylate (43 %) and *N*,*N*-dibenzylethenesulfonamide (25 %) compared with in those involving vinyl sulfones (ca. 70 %) as Michael acceptors (see Table 2). As shown in Figure 3, the computed activation barriers for the reactions involving Y = CO_2Me ($\Delta G^{\neq}$ = 19.7 kcal/mol) or Y = SO_2NMe_2 ($\Delta G^{\neq}$ = 21.6 kcal/mol) are clearly higher than that computed for the Michael addition reaction involving the vinyl sulfone (Y = SO_2Ph, $\Delta G^{\neq}$ = 15.8 kcal/mol). This can be ascribed to the relative electrophilicity of the Michael acceptor, which can be estimated from the relative energy of the corresponding LUMO: –1.64 eV (Y = SO_2Ph) > –1.49 eV (Y = CO_2Me) > –1.11 eV (Y = SO_2NMe_2). Therefore, the trend in the experimentally observed reactivity is very likely related to the relative electrophilicity of the Michael acceptor used in the α-arylation/Michael addition domino process.

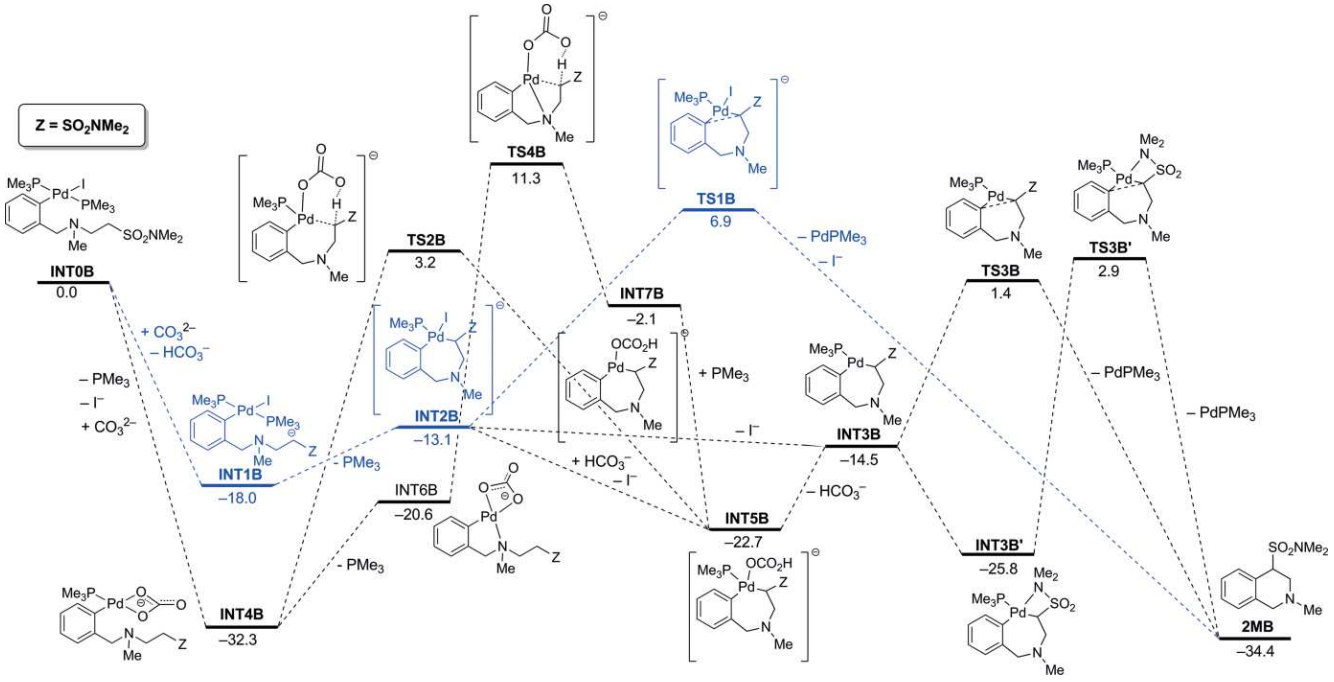


Figure 2. Computed reaction profiles for the palladium-catalyzed α-arylation reaction of **INT0B**. Relative free energies (Δ*G*, at 298 K) and bond lengths are given in kcal/mol and Å, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level of theory.

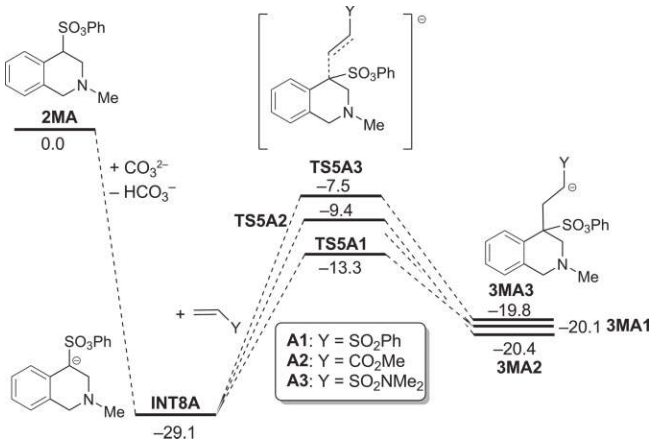


Figure 3. Computed reaction profiles for the Michael addition reaction involving **2MA** and the different Michael acceptors. Relative free energies (ΔG, at 298 K) are given in kcal/mol. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level of theory.

Conclusions

This combined experimental and computational comparative study has established the feasibility of using different nucleophiles and Michael acceptors in the domino α-arylation/Michael addition process leading to tetrahydroisoquinolines. Our calculations indicate that two competing mechanisms, namely the direct base-mediated α-arylation reaction and a concerted metalation/deprotonation (CMD) C–H activation process, are operative in the α-arylation of sulfonates and phosphonates when using Cs_2CO_3 as the base. In contrast, in the reaction with sulfonamides, the base-mediated process seems to be preferred over the concerted metalation/deprotonation pathway. The results of our study also indicate that the success of the two-step domino process is strongly related to the electrophilicity of the Michael acceptor.

Experimental Section

General: All commercially available reagents were used without further purification. All non-aqueous reactions were carried out under argon. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light, 1 % iodoplatinate reagent, or 1 % aqueous $KMnO_4$. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh ASTM). The organic extracts obtained during reaction work-up were dried with anhydrous Na_2SO_4. The solvents were evaporated by using a rotary evaporator. ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 spectrometer by using Me_4Si as internal standard. Chemical shifts (δ) are reported in ppm downfield from Me_4Si for ^1H and ^{13}C NMR spectroscopy. HRMS was performed by using a LC/MSD TOF mass spectrometer.

Typical Method for the Pd^0-Catalyzed α-Arylation Reaction: (Table 1, entry 4) A mixture of sulfonamide **1b** (75 mg, 0.123 mmol), $[Pd_2(dba)_3]$ (8 mg, 0.009 mmol), Xantphos (11 mg, 0.018 mmol), and Cs_2CO_3 (120 mg, 0.37 mmol) in THF (8 mL) was stirred at 120 °C in a sealed tube for 72 h. The reaction mixture was partitioned between a saturated aqueous $NaHCO_3$ solution and Et_2O. The organic extracts were dried and concentrated. The residue was purified by chromatography (CH_2Cl_2) to give sulfonamide **2b** (45 mg, 75 %).

Phenyl 2-Benzyl-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (2a): Chromatography (SiO_2, from hexanes to CH_2Cl_2). Orange oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.03 (dd, J = 13.0, 4.2 Hz, 1 H), 3.50 (d, J = 15.2 Hz, 1 H), 3.71 (d, J = 12.8 Hz, 1 H), 3.73 (ddd, J = 13.0, 4.2, 1.0 Hz, 1 H), 3.79 (d, J = 12.8 Hz, 1 H), 3.94 (d, J = 15.2 Hz, 1 H), 4.72 (t, J = 4.2 Hz, 1 H), 6.99–7.02 (m, 2 H), 7.09 (d, J = 7.4 Hz, 1 H), 7.19–7.34 (m, 8 H), 7.40 (m, 2 H), 7.65 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 51.4 (CH_2), 55.2 (CH_2), 62.3 (CH), 62.3 (CH_2), 122.2 (2 CH), 125.4 (C), 126.8 (CH), 126.9 (CH), 127.3 (CH), 127.5 (CH), 128.5 (2 CH), 129.0 (CH), 129.2 (2 CH), 129.7 (2 CH), 130.5 (CH), 137.1 (C), 137.4 (C), 149.3 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{22}H_{22}NO_3S$ 380.1315 $[M + H]^+$; found 380.1324.

***N,N*,2-Tribenzyl-1,2,3,4-tetrahydroisoquinoline-4-sulfonamide (2b):** Chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 1 %). Brown oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.78 (dd, J = 12.8, 4.4 Hz, 1 H), 3.37 (d, J = 15.2 Hz, 1 H), 3.57 (d, J = 12.8 Hz, 1 H), 3.69 (dd, J = 12.8, 2.4 Hz, 1 H), 3.78 (d, J = 12.8 Hz, 1 H), 3.90 (d, J = 15.2 Hz, 1 H), 4.12 (s, 4 H), 4.50 (dd, J = 4.4, 2.4 Hz, 1 H), 6.95–6.99 (m, 4 H), 7.06–7.31 (m, 14 H), 7.71 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 52.1 (CH_2), 52.3 (CH_2), 55.2 (CH_2), 63.0 (CH_2), 64.9 (CH), 126.6 (C), 126.7 (CH), 127.1 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.7 (CH), 130.8 (CH), 136.4 (C), 136.6 (C), 136.7 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{30}H_{31}N_2O_2S$ 483.2101 $[M + H]^+$; found 483.2103.

Diethyl 2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-ylphosphonate (2c): Chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 4 %). Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (t, J = 7.2 Hz, 3 H), 1.18 (t, J = 7.2 Hz, 3 H), 2.86 (ddd, J = 25.2, 11.6, 4.8 Hz, 1 H), 3.29 (td, J = 11.6, 4.8 Hz, 1 H), 3.42–3.51 (m, 2 H), 3.64 (d, J = 13.2 Hz, 1 H), 3.73 (dd, J = 15.2, 1.6 Hz, 1 H), 3.76 (d, J = 13.2 Hz, 1 H), 3.84–4.09 (m, 4 H), 6.98 (m, 1 H), 7.11–7.19 (m, 2 H), 7.24–7.41 (m, 5 H), 7.54 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 16.4 (d, $J_{C\text{-}P}$ = 6.1 Hz, CH_3), 16.5 (d, $J_{C\text{-}P}$ = 4.5 Hz, CH_3), 38.9 (d, $J_{C\text{-}P}$ = 137.9 Hz, CH), 51.6 (d, $J_{C\text{-}P}$ = 4.6 Hz, CH_2), 55.7 (d, $J_{C\text{-}P}$ = 1.5 Hz, CH_2), 62.1 (d, $J_{C\text{-}P}$ = 6.1 Hz, CH_2), 62.2 (d, $J_{C\text{-}P}$ = 6.9 Hz, CH_2), 62.8 (CH_2), 126.3 (d, $J_{C\text{-}P}$ = 3.0 Hz, CH), 126.7 (d, $J_{C\text{-}P}$ = 3.0 Hz, CH_2), 126.9 (d, $J_{C\text{-}P}$ = 2.3 Hz, CH_2), 127.3 (s, CH), 128.3 (s, 2 CH), 129.4 (s, 2 CH), 129.6 (s, C), 129.7 (d, $J_{C\text{-}P}$ = 4.6 Hz, CH), 135.5 (d, $J_{C\text{-}P}$ = 6.9 Hz, C), 138.0 (s, C) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{27}NO_3P$ 360.1723 $[M + H]^+$; found 360.1724.

Typical Method for the Domino Reactions: (Table 2, entry 1) A mixture of sulfonate **1a** (75 mg, 0.148 mmol), $[Pd(PPh_3)_4]$ (17 mg, 0.015 mmol), Xantphos (8.5 mg, 0.015 mmol), phenyl vinyl sulfone (37 mg, 0.22 mmol), and K_3PO_4 (94 mg, 0.44 mmol) in THF (8 mL) was stirred at 120 °C in a sealed tube for 72 h. The reaction mixture was then poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. Finally, the residue was purified by flash chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 1 %) to give sulfonate **3aa** (55 mg, 68 %).

Phenyl 2-Benzyl-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3aa): Yellow foam. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.62 (td, J = 13.6, 4.4 Hz, 1 H), 2.80–2.91 (m, 2 H), 3.13 (dd, J = 12.4, 2.0 Hz, 1 H), 3.26 (d, J = 12.4 Hz, 1 H), 3.50 (ddd, J = 14.4, 13.2, 4.4 Hz, 1 H), 3.53 (d, J = 15.6 Hz, 1 H), 3.60 (d, J = 12.8 Hz, 1 H), 3.73 (d, J = 15.6 Hz, 1 H), 3.74 (d, J = 12.8 Hz, 1 H), 6.79 (m, 2 H), 7.09 (d, J = 7.6 Hz, 1 H), 7.13–7.38 (m, 10 H), 7.51–7.59 (m, 3 H), 7.66 (tt, J = 7.6, 1.2 Hz, 1 H), 7.79 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 31.2 (CH_2), 52.1 (CH_2), 56.6 (CH_2), 57.0 (CH_2), 62.7 (CH_2), 68.1 (C), 121.9 (2 CH), 127.0 (CH), 127.4 (CH), 127.6

(CH), 127.9 (CH), 128.0 (CH), 128.1 (C), 128.2 (2 CH), 128.8 (2 CH), 129.1 (CH), 129.4 (2 CH), 129.5 (2 CH), 129.7 (2 CH), 134.0 (CH), 136.9 (C), 137.3 (C), 138.6 (C), 149.1 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{30}H_{30}NO_5S_2$ 548.1560 $[M + H]^+$; found 548.1567.

Phenyl 2-Benzyl-4-[2-(methylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3ab): Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.67–2.78 (m, 2 H), 2.75 (s, 3 H), 2.90–3.01 (m, 1 H), 3.22 (dd, *J* = 12.4, 1.6 Hz, 1 H), 3.27 (d, *J* = 12.4 Hz, 1 H), 3.37–3.47 (m, 1 H), 3.60 (d, *J* = 12.8 Hz, 1 H), 3.61 (d, *J* = 14.8 Hz, 1 H), 3.82 (d, *J* = 12.8 Hz, 1 H), 3.83 (d, *J* = 14.8 Hz, 1 H), 6.85 (m, 2 H), 7.14 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.18–7.40 (m, 10 H), 7.79 (dd, *J* = 8.0, 1.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 31.1 (CH_2), 40.5 (CH_3), 50.7 (CH_2), 56.5 (CH_2), 56.9 (CH_2), 62.6 (CH_2), 68.1 (C), 122.0 (2 CH), 127.1 (CH), 127.5 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.5 (C), 128.9 (2 CH), 129.2 (CH), 129.6 (2 CH), 129.8 (2 CH), 137.0 (C), 137.2 (C), 149.1 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{28}NO_5S_2$ 486.1403 $[M + H]^+$; found 486.1403.

Phenyl 2-Benzyl-4-[2-(methoxycarbonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3ac): Pale-yellow solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.22 (ddd, *J* = 16.2, 11.2, 5.2 Hz, 1 H), 2.65 (ddd, *J* = 11.2, 8.0, 5.2 Hz, 1 H), 2.69 (ddd, *J* = 11.2, 8.0, 5.2 Hz, 1 H), 2.84 (ddd, *J* = 16.2, 11.2, 5.2 Hz, 1 H), 3.18 (dd, *J* = 12.4, 1.6 Hz, 1 H), 3.38 (d, *J* = 12.4 Hz, 1 H), 3.58 (d, *J* = 14.8 Hz, 1 H), 3.63 (s, 3 H), 3.69 (d, *J* = 13.2 Hz, 1 H), 3.70 (d, *J* = 14.8 Hz, 1 H), 3.74 (d, *J* = 13.2 Hz, 1 H), 6.84 (m, 2 H), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.16–7.38 (m, 10 H), 7.77 (dd, *J* = 7.6, 1.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 29.7 (CH_2), 32.5 (CH_2), 51.9 (CH_3), 56.3 (CH_2), 57.0 (CH_2), 62.6 (CH_2), 69.2 (C), 122.1 (2 CH), 126.8 (CH), 127.2 (CH), 127.3 (CH), 127.7 (CH), 128.4 (CH), 128.6 (2 CH), 128.7 (CH), 129.1 (C), 129.2 (2 CH), 129.6 (2 CH), 137.2 (C), 137.3 (C), 149.3 (C), 173.0 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{28}NO_5S$ 466.1683 $[M + H]^+$; found 466.1683.

Phenyl 2-Benzyl-4-[2-(phenoxysulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3ad): Yellow foam. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.93 (td, *J* = 12.4, 3.2 Hz, 1 H), 2.99 (td, *J* = 12.4, 3.2 Hz, 1 H), 3.11 (td, *J* = 12.4, 3.2 Hz, 1 H), 3.27 (s, 2 H), 3.56 (d, *J* = 15.2 Hz, 1 H), 3.63 (d, *J* = 12.8 Hz, 1 H), 3.72 (td, *J* = 12.4, 3.2 Hz, 1 H), 3.78 (d, *J* = 12.8 Hz, 1 H), 3.82 (d, *J* = 15.2 Hz, 1 H), 6.87 (m, 2 H), 7.13 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.17–7.38 (m, 15 H), 7.82 (dd, *J* = 8.0, 1.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 32.3 (CH_2), 46.7 (CH_2), 56.6 (CH_2), 56.8 (CH_2), 62.6 (CH_2), 68.0 (C), 122.0 (2 CH), 122.1 (2 CH), 127.1 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.3 (C), 128.9 (2 CH), 129.2 (CH), 129.3 (2 CH), 129.8 (2 CH), 130.1 (2 CH), 136.7 (C), 137.1 (C), 149.0 (C), 149.1 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{30}H_{30}NO_6S_2$ 564.1509 $[M + H]^+$; found 564.1518.

Phenyl 2-Benzyl-4-[2-(*N*,*N*-dibenzylaminosulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3ae): Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.68–2.79 (m, 2 H), 2.88–2.99 (m, 1 H), 3.07 (dd, *J* = 12.4, 1.2 Hz, 1 H), 3.26 (d, *J* = 12.4 Hz, 1 H), 3.20–3.33 (m, 1 H), 3.54 (d, *J* = 14.8 Hz, 1 H), 3.61 (d, *J* = 13.2 Hz, 1 H), 3.69 (d, *J* = 14.8 Hz, 1 H), 3.71 (d, *J* = 13.2 Hz, 1 H), 4.22 (d, *J* = 15.2 Hz, 2 H), 4.30 (d, *J* = 15.2 Hz, 2 H), 6.85 (m, 2 H), 7.09 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.17–7.35 (m, 20 H), 7.71 (dd, *J* = 8.0, 0.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 31.7 (CH_2), 49.7 (CH_2), 50.3 (2 CH_2), 56.5 (CH_2), 57.0 (CH_2), 62.6 (CH_2), 68.4 (C), 122.0 (2 CH), 127.0 (CH), 127.4 (CH), 127.5 (CH), 127.8 (CH), 128.1 (2 CH), 128.3 (CH), 128.4 (C), 128.7 (2 CH), 128.8 (4 CH), 128.9 (4 CH), 129.0 (CH), 129.2 (2 CH), 129.7 (2 CH), 135.7 (2 C), 137.0 (C), 137.2 (C), 149.2 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{38}H_{39}N_2O_5S_2$ 667.2295 $[M + H]^+$; found 667.2289.

2,*N*,*N*-Tribenzyl-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonamide (3ba): Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.63 (ddd, *J* = 13.6, 12.8, 4.8 Hz, 1 H), 2.79 (ddd, *J* = 13.6, 12.8, 3.6 Hz, 1 H), 2.86 (d, *J* = 12.4 Hz, 1 H), 2.89 (ddd, *J* = 13.6, 12.8, 3.6 Hz, 1 H), 3.16 (d, *J* = 12.4 Hz, 1 H), 3.44 (d, *J* = 12.8 Hz, 1 H), 3.49 (ddd, *J* = 13.6, 12.8, 4.8 Hz, 1 H), 3.49 (d, *J* = 14.8 Hz, 1 H), 3.57 (d, *J* = 14.8 Hz, 1 H), 3.70 (d, *J* = 12.8 Hz, 1 H), 4.01 (br. s, 4 H), 6.77 (d, *J* = 6.8 Hz, 4 H), 7.06–7.35 (m, 14 H), 7.55 (tt, *J* = 7.6, 1.2 Hz, 2 H), 7.65 (tt, *J* = 7.6, 1.2 Hz, 1 H), 7.76 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.83 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 31.6 (CH_2), 52.4 (CH_2), 52.5 (2 CH_2), 56.4 (CH_2), 57.1 (CH_2), 63.0 (CH_2), 69.7 (C), 127.4 (CH), 127.5 (CH), 127.6 (2 CH), 127.9 (CH), 128.2 (2 CH), 128.3 (4 CH), 128.5 (4 CH), 128.6 (CH), 128.8 (2 CH), 128.9 (CH), 129.5 (2 CH), 129.6 (C), 129.7 (2 CH), 133.9 (CH), 135.7 (2 C), 136.5 (C), 137.2 (C), 138.7 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{38}H_{39}N_2O_4S_2$ 651.2346 $[M + H]^+$; found 651.2349.

2,*N*,*N*-Tribenzyl-4-[2-(methylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonamide (3bb): Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.73–2.91 (m, 3 H), 2.81 (s, 3 H), 2.94 (dd, *J* = 12.4, 1.2 Hz, 1 H), 3.18 (d, *J* = 12.4 Hz, 1 H), 3.42–3.51 (m, 1 H), 3.45 (d, *J* = 12.8 Hz, 1 H), 3.55 (d, *J* = 14.8 Hz, 1 H), 3.66 (d, *J* = 14.8 Hz, 1 H), 3.77 (d, *J* = 12.8 Hz, 1 H), 4.08 (br. s, 4 H), 6.80 (d, *J* = 6.4 Hz, 4 H), 7.09–7.17 (m, 7 H), 7.24–7.36 (m, 7 H), 7.99 (dd, *J* = 7.6, 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 31.7 (CH_2), 40.4 (CH_3), 50.9 (CH_2), 52.4 (2 CH_2), 56.6 (2 CH_2), 62.9 (CH_2), 69.7 (C), 127.4 (CH), 127.5 (CH), 127.6 (2 CH), 127.9 (CH), 128.3 (4 CH), 128.5 (4 CH), 128.6 (CH), 128.8 (2 CH), 129.0 (CH), 129.7 (2 CH), 130.0 (C), 135.7 (2 C), 136.5 (C), 137.1 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{33}H_{37}N_2O_4S_2$ 589.2189 $[M + H]^+$; found 589.2199.

Computational Details: All the calculations reported in this paper were carried out with the Gaussian 09 suite of programs.[13] Electron correlation was partially taken into account by using the hybrid functional usually denoted as B3LYP[14] in conjunction with the D3 dispersion correction suggested by Grimme et al.[15] with the double-ζ quality plus polarization def2-SVP basis set[16] for all atoms. Reactants and products were characterized by frequency calculations[17] and have positive definite Hessian matrices. The transition-state structures (TSs) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration by using the intrinsic reaction coordinate (IRC) method.[18] Solvent effects were taken into account by using the polarizable continuum model (PCM).[19] Single-point calculations on the PCM(THF)-B3LYP-D3/def2-SVP geometries were performed to estimate the change in the Gibbs energies at the B3LYP-D3 level of theory by using the triple-ζ quality plus polarization def2-TZVP basis set[16] for all atoms. This level is denoted PCM(THF)-B3LYP-D3/def2-TZVP//PCM(THF)-B3LYP-D3/def2-SVP.

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Keywords: Arylation · Palladium · Domino reactions · Nitrogen heterocycles · Density functional calculations

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SUPPORTING INFORMATION

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Title: Exploring Partners for the Domino α-Arylation/Michael Addition Reaction Leading to Tetrahydroisoquinolines
Author(s): Daniel Solé,* Ferran Pérez-Janer, Yago García-Rodeja, Israel Fernández*

Table of Contents

Experimental procedures and characterization data for the starting materials.

Phenyl ethenesulfonate. A solution of phenol (1.04 g, 11.04 mmol) and triethylamine (3 mL, 22.08 mmol) in CH_2Cl_2 (8 mL) was added dropwise to a stirred solution of 2-chloroethanesulfonyl chloride (1.0 mL, 9.2 mmol) in CH_2Cl_2 (8 mL) at -78 ºC. The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with 2M NaOH aqueous solution and brine. The organic layer was dried, filtered, and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2-MeOH 0.5%) to give phenyl ethenesulfonate (1.41 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.15 (dd, *J* = 10.4 and 0.8 Hz, 1H), 6.36 (dd, *J* = 16.8 and 0.8 Hz, 1H), 6.67 (dd, *J* = 16.8 and 10.4 Hz, 1H), 7.21-7.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 122.4 (2 CH), 127.5 (CH), 130.0 (2 CH), 131.8 (CH_2), 132.2 (CH), 149.6 (C).

***N,N*-Dibenzylethenesulfonamide.** A solution of dibenzylamine (0.25 mL, 1.31 mmol), DMAP (16 mg, 0.13 mmol), and Et_3N (0.55 mL, 3.94 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature under argon for 10 minutes. The mixture was cooled to 0 ºC and 2-chloroethanesulfonyl chloride (0.2 mL, 1.84 mmol) was added. The resulting solution was stirred at 0 ºC for 5 minutes and at room temperature for 4 hours. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried, filtered, and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2-MeOH 0.75%) to give *N,N*-dibenzylethenesulfonamide (254 mg, 67%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (s, 4H), 5.86 (d, *J* = 10.0 Hz, 1H), 6.22 (d, *J* = 16.4 Hz, 1H), 6.34 (dd, *J* = 16.4 and 10.0 Hz, 1H), 7.25-7.37 (m, 10H).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 49.8 (CH_2), 126.5 (CH_2), 128.1 (CH), 128.8 (2 CH), 128.9 (2 CH), 135.7 (C), 136,2 (CH).

***N*-Benzylethenesulfonamide.** Operating as above, *N*-benzylethenesulfonamide was prepared (555 mg, 64%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.22 (d, *J* = 6.0 Hz, 2H), 4.58 (broad signal, 1H), 5.92 (d, *J* = 10.0 Hz, 1H), 6.26 (d, *J* = 16.4 Hz, 1H), 6.48 (dd, *J* = 16.4 and 10.0 Hz, 1H), 7.28-7.38 (m, 5H).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 47.2 (CH_2), 127.0 (CH_2), 128.1 (2 CH), 128.3 (CH), 129.0 (2 CH), 136.2 (CH), 136.6 (C).

Phenyl 2-[*N*-benzyl-*N*-(2-iodobenzyl)amino]ethanesulfonate (1a).

A solution of phenyl ethenesulfonate (250 mg, 1.36 mmol) and benzylamine (160 mg, 1.49 mmol) in EtOH (10 mL) was stirred at reflux for 24 hours. The solvent was evaporated and the residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2-MeOH 1%) to give phenyl 2-[*N*-benzylamino]ethanesulfonate (289 mg, 73%) as

a yellow oil. ^{1}H NMR ($CDCl_3$. 400 MHz) δ 1.60-1.80 (broad s, 1H), 3.22 (t, *J* = 6.4 Hz, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 3.84 (s, 2H), 7.23-7.41 (m, 10H).

A mixture of phenyl 2-[*N*-benzylamino]ethanesulfonate (289 mg, 1.0 mmol), K_2CO_3 (274 mg, 2.0 mmol), a catalytic amount of LiI, and 2-iodobenzyl chloride (0.2 mL, 1.04 mmol) in acetonitrile (5 mL) was stirred at reflux for 24 hours. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 and water. The organic extracts were washed with brine, dried, filtered, and concentrated. The residue was purified by chromatography (SiO_2, from hexanes to hexanes-CH_2Cl_2 1:4) to give **1a** (373 mg, 99%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.16 (m, 2H), 3.31 (m, 2H), 3.68 (s, 2H), 3.73 (s, 2H), 6.94-7.01 (m, 3H), 7.25-7.38 (m, 9H), 7.48 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.84 (dd, *J* = 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 47.6 (CH_2), 47.9 (CH_2), 58.7 (CH_2), 63.2 (CH_2), 100.4 (C), 122.0 (2 CH), 127.3 (CH), 127.7 (CH), 128.5 (CH), 128.7 (2 CH), 129.0 (2 CH), 129.4 (CH), 130.1 (2 CH), 130.7 (CH), 138.3 (C), 139.9 (CH), 140.5 (C), 149.2 (C). HRMS (ESI-TOF) calcd. for $C_{22}H_{23}INO_3S$: 508.0438 $[M+H]^+$; found: 508.0435.

***N,N*-Dibenzyl-2-[*N*-benzyl-*N*-(2-iodobenzyl)amino]ethanesulfonamide (1b).** Operating as in the preparation of **1a**, starting from *N,N*-dibenzylethenesulfonamide (100 mg, 0.35 mmol), sulfonamide **1b** was obtained (319 mg, 72% for two steps) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.94-2.99 (m, 2H), 3.01-3.06 (m, 2H), 3.56 (s, 2H), 3.59 (s, 2H), 4.21 (s, 4H), 6.95 (td, *J* = 8.0 Hz and 2.0 Hz, 1H), 7.18-7.34 (m, 16H), 7.44 (dd, *J* = 8.0 Hz and 1.6 Hz, 1H), 7.83 (dd, *J* = 8.0 and 1.6 Hz, 1H).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 47.6 (CH_2), 50.3 (CH_2), 51.2 (CH_2), 58.4 (CH_2), 62.9 (CH_2), 100.3 (C), 127.4 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.8 (CH), 128.9 (CH), 129.1 (CH), 130.6 (CH), 135.8 (C), 138.6 (C), 139.7 (CH), 140.8 (C). One CH was no observed. HRMS (ESI-TOF) calcd. for $C_{30}H_{32}IN_2O_2S$: 611.1224 $[M+H]^+$; found: 611.1231.

Diethyl 2-[*N*-benzyl-(*N*-iodobenzyl)amino]ethylphosphonate (1c).

Diethyl vinylphosphonate (766 mg, 4.66 mmol) was added under argon to a solution of benzylamine (0.5 g, 4.66 mmol) in degasified water (2 mL). The mixture was stirred at reflux for 45 minutes, cooled to room temperature, and partitioned between CH_2Cl_2 and water. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 8%) to give diethyl 2-(*N*-benzylamino)ethylphosphonate (891 mg, 70%) as a yellow oil. ^{1}H NMR ($CDCl_3$,

400 MHz) δ 1.30 (t, *J* = 7.0 Hz, 6H), 2.00 (dt, *J* = 18.4 and 7.2 Hz, 2H), 2.92 (dt, *J* = 15.6 and 7.2 Hz, 2H), 3.80 (s, 2H), 4.08 (m, 2H), 7.22-7.35 (m, 5H).

K_2CO_3 (908 mg, 6.57 mmol) and 2-iodobenzyl chloride (912 mg, 3.61 mmol) were added to a solution of diethyl 2-(*N*-benzylamino)ethylphosphonate (891 mg, 3.28 mmol) in CH_3CN (12 mL). The mixture was stirred at reflux overnight. The solvent was removed under vacuum, the residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried and concentrated. The residue was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 5%) to give phosphonate **1c** (1.15 g, 73%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.0 Hz, 6H), 1.99 (m, 2H), 2.81 (m, 2H), 3.63 (s, 2H), 3.64 (s, 2H), 3.98 (m, 4H), 6.93 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.20-7.37 (m, 6H), 7.52 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.81 (dd, *J* = 8.0 and 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 16.4 (d, $J_{C\text{-}P}$ = 6.1 Hz, CH_3), 22.9 (d, $J_{C\text{-}P}$ = 135.7 Hz, CH_2), 46.5 (CH_2), 57.6 (CH_2), 61.5 (d, $J_{C\text{-}P}$ = 6.1 Hz, CH_2), 62.2 (CH_2), 100.2 (C), 127.1 (CH), 128.1 (CH), 128.3 (2 CH), 128.8 (3 CH), 130.3 (CH), 138.8 (C), 139.5 (CH), 141.1 (C). HRMS (ESI-TOF) calcd. for $C_{20}H_{28}INO_3P$: 488.0846 $[M+H]^+$; found: 488.0848.

***N*-Benzyl-2-[*N*-benzyl-*N*-(2-iodobenzyl)amino]ethanesulfonamide (1d).** Operating as in the preparation of **1a**, starting from *N*-benzylethenesulfonamide (467 mg, 2.37 mmol), sulfonamide **1d** was obtained (860 mg, 69% for two steps) as a yellow oil, after chromatographic purification (SiO_2, from CH_2Cl_2 to CH_2Cl_2-MeOH 4%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (m, 2H), 3.11 (m, 2H), 3.60 (s, 2H), 3.62 (s, 2H), 4.09 (d, *J* = 6.4 Hz, 2H), 4.49 (t, *J* = 6.4 Hz, 1H), 6.95 (td, *J* = 7.2 and 1.6 Hz, 1H), 7.19-7.34 (m, 11H), 7.43 (dd, *J* = 7.6 and 2.0 Hz, 1H), 7.82 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100.6 MHz) δ 47.1 (CH_2), 47.8 (CH_2), 50.3 (CH_2), 58.5 (CH_2), 62.9 (CH_2), 100.5 (C), 127.6 (CH), 128.1 (2 CH), 128.2 (CH), 128.4 (CH), 128.6 (2 CH), 128.9 (2 CH), 129.1 (2 CH), 129.3 (CH), 130.6 (CH), 136.8 (C), 138.2 (C), 139.8 (CH), 140.7 (C). HRMS (ESI-TOF) calcd. for $C_{23}H_{26}IN_2O_2S$: 521.0754 $[M+H]^+$; found: 521.0757.

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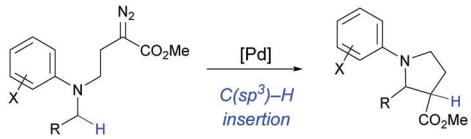
Palladium-catalysed intramolecular carbenoid insertion of α-diazo-α-(methoxycarbonyl)acetanilides for oxindole synthesis†

Daniel Solé,*[a] Ferran Pérez-Janer[a] and Israel Fernández*[b]

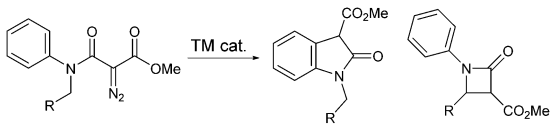
A novel, selective palladium-catalysed carbenoid C(aryl)–H insertion of α-diazo-α-(methoxycarbonyl)acetanilides leading to oxindoles is described.

The transition metal-catalysed intramolecular C–H insertion of diazo compounds constitutes a powerful methodology for the construction of carbocyclic and heterocyclic frameworks.[1] Although the use of dirhodium(II)[2] and copper[3] catalysts has traditionally monopolized this area of research, in recent years different transition metals, including gold,[4] nickel,[5] ruthenium,[6] cobalt,[7] iron and manganese,[8] have emerged as useful alternatives. Surprisingly, palladium, one of the most commonly employed metals in homogeneous catalysis, has been scarcely applied to these processes, its use being restricted to a couple of examples of α-diazo-β-ketoester insertion into Csp^2–H bonds.[9,10] In this context, we recently reported that palladium catalysts are also able to promote Csp^3–H insertion of carbenoids derived from α-diazoesters to form pyrrolidines through intramolecular $C(sp^3)$–$C(sp^3)$ bond formation (Scheme 1).[11]

Among the reported transition metal-catalysed intramolecular C–H insertions of diazo compounds, the reaction of *N*-alkyl-*N*-aryl α-diazoamides has been extensively explored,[12] since the insertion products, namely β- and γ-lactams as well as 2-oxindoles, are common scaffolds found in numerous natural products. The selectivity of these reactions depends not only on the carbenoid and substrate substitution, but is also governed by the catalyst.[13] Thus, for instance, the use of Rh(II) carboxylate and, in particular, carboxamide catalysts has resulted in the development of highly chemo-, regio- and stereoselective transformations with a variety of reaction modes.[14] On the other hand, more recently,



Scheme 1 Previously reported Pd-catalysed Csp^3–H insertion of carbenoids derived from α-diazoesters (see ref. 11).



Scheme 2 Transition metal (TM) catalysed carbenoid C–H insertion of α-diazo-α-(methoxycarbonyl)acetanilides.

the commercially available $[Ru(p\text{-cymene})Cl_2]_2$ has been used as a catalyst to develop diverse methodologies for oxindole synthesis based on the α-diazoamide carbenoid insertion.[15]

Encouraged by the results of our previous work, we decided to explore the feasibility of palladium as a catalyst to promote the carbenoid C–H insertion from α-diazo-α-(methoxycarbonyl)-acetanilides (Scheme 2). In this investigation, we sought to identify differences in the reactivities and selectivities between the palladium catalyst and the transition-metal catalysts mentioned above.[16]

α-Diazoamide **1a** was chosen as a model substrate for our initial studies (Table 1). In line with the results previously reported for related substrates,[14b–d] the Rh(II) acetate-catalysed decomposition of **1a** resulted in the intramolecular carbenoid insertion into the benzylic C–H bond to give mainly *trans*-β-lactam **2a** (entry 1). In contrast, treatment of **1a** with a catalytic amount of $Pd_2(dba)_3$ in toluene at reflux for 72 h afforded oxindole **3a**, arising from the arylic C–H bond insertion, in 42% yield (entry 2). While a similar result was obtained when the reaction was carried out in dioxane for 31 h (entry 3), the use of either the more polar CH_3CN or the high boiling chlorobenzene as the solvent led to the complete decomposition of the material (results not shown in the table). Note that oxindole **3a** was

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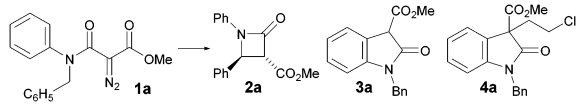
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds, copies of NMR spectra and computational details and Cartesian coordinates of all species. See DOI: 10.1039/c7cc00718c

Table 1 Transition metal-catalysed cyclisation reactions of α-diazoamide **1a**[a]



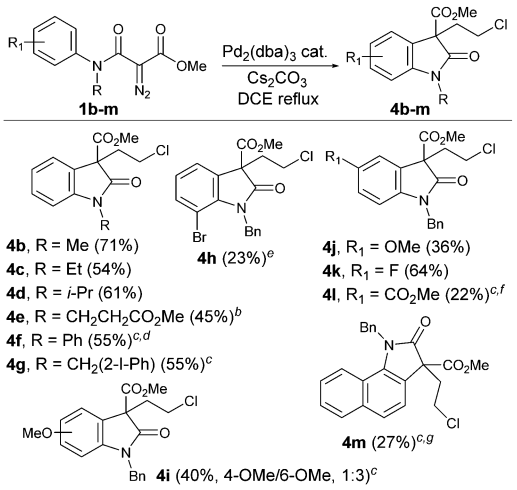
Entry	Catalyst (mol%)	Additives (equiv.)	Solvent	Temp.	Time (h)	Products[b] (%)
1	$[Rh(OAc)_2]_2$ (2)	—	CH_2Cl_2	rt	33	**2a** (48%)[c]
2	$Pd_2(dba)_3$ (7.5)	Cs_2CO_3 (2)	Toluene	Reflux	72	**3a** (42%)[d]
3	$Pd_2(dba)_3$ (10)	Cs_2CO_3 (2)	Dioxane	Reflux	31	**3a** (44%)[d]
4	$Pd_2(dba)_3$ (10)	Cs_2CO_3 (2)	DCE	Reflux	96	**4a** (66%)
5	$Pd(OAc)_2$ (20)	Cs_2CO_3 (2)	DCE	Reflux	72	**1a** : **4a** (1.2 : 1)[e]
6	$Pd(PPh_3)_4$ (20)	Cs_2CO_3 (2)	DCE	Reflux	72	**1a** : **4a** (1.1 : 1)[e]
7	$Pd_2(dba)_3$ (10) (o-Tolyl)$_3$P (40)	Cs_2CO_3 (2)	DCE	Reflux	72	**1a** : **4a** (1 : 1.6)[e]
8	$Pd_2(dba)_3$ (10) dppe (20)	Cs_2CO_3 (2)	DCE	Reflux	72	**1a** : **4a** (1.3 : 1)[e]
9	$Pd_2(dba)_3$ (10) $^tBu_3P{\cdot}HBF_4$ (40)	Cs_2CO_3 (2)	DCE	Reflux	72	CM[f]
10	—	Cs_2CO_3 (2)	DCE	Reflux	96	**1a** : **2a** : **4a** (2.5 : 0.2 : 1)[e]

[a] All reactions were conducted with **1a** (0.2 mmol, 0.2 M). [b] Isolated yield. [c] Minor amounts of the *cis*-β-lactam (<10%) were also formed. [d] Small amounts of the bisoxindole dimer (≈5%) were also formed, see the ESI. [e] ^{1}H NMR ratio, yields were not quantified. [f] Complex mixture with less than 10% of **4a**.

difficult to isolate in pure form due to its well-known tautomeric equilibrium.[14c–d]

Pleasingly, we found that when using dichloroethane as the solvent, oxindole **4a** was directly obtained (66% yield) from a sequential carbenoid insertion/alkylation process (entry 4). The formation of **4a** not only facilitated the isolation of the cyclization product, but also avoided the generation of minor amounts of bisoxindole by-products,[17] which were also observed when using solvents other than DCE. The use of other palladium precatalysts such as $Pd(OAc)_2$ and $Pd(PPh_3)_4$ resulted in slower reaction rates (entries 5 and 6). Similarly, all our attempts to increase the efficiency of the Pd-catalysed reaction by adding different phosphine ligands met with no success (entries 7–9). Finally, *ca.* 30% of conversion was observed in the absence of the palladium catalyst, giving a 0.2 : 1 mixture of *trans*-β-lactam **2a** and oxindole **4a**, together with unreacted starting material (entry 10).[18] These results therefore indicate that $Pd_2(dba)_3$ can catalyse the carbenoid C–H insertion of α-diazo-α-(methoxycarbonyl)acetanilides, which chemoselectively proceeds into the arylic C–H bond to give the oxindole **3a**.[19] The selectivity of the insertion is the opposite of that observed in our previous work with α-diazoesters.[11] Moreover, when using dichloroethane as the solvent, the initially formed oxindole undergoes *in situ* alkylation[20] to afford **4a**. Interestingly, when the reaction was carried out with the base DBU [$Pd_2(dba)_3$ (0.1), DBU (1.2) in DCE at reflux], *N*-benzyl-2-oxindole was obtained (69%) from the demethoxycarbonylation[21] of the initially formed oxindole **3a**.[22] This result confirms that Cs_2CO_3 is not necessary for the Pd-catalysed insertion, but is needed for the alkylation process.

In order to assess the scope of this novel Pd-catalysed reaction, we then explored the sequential C–H insertion/alkylation process starting from a variety of α-diazoacetanilides (Scheme 3). Firstly, we investigated the effect of changing the *N*-alkyl substituent on the course of the two-step sequential process. All the tested *N*-alkyl substrates were well tolerated under the conditions



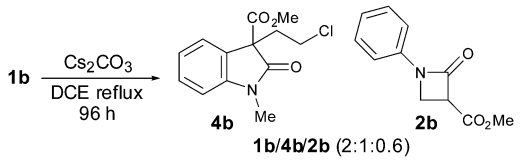
Scheme 3 Scope of the Pd-catalysed reaction. [a] See Table 1 for representative procedure. [b] 18% of unreacted starting material was recovered. [c] Catalyst loading: 15%. [d] 20% of unreacted starting material was recovered. [e] ^{1}H NMR analysis of the reaction mixture showed a 1 : 1 mixture of **1h** and **4h**. [f] The *O*-alkylation product **4l′** was also obtained (**4l**/**4l′**, 3 : 1), see the ESI.† [g] The *O*-alkylation product **4m′** was also obtained (**4m**/**4m′**, 2 : 1), see the ESI.†

of the Pd-catalysed reaction. As can be seen in Scheme 3, the insertion occurs selectively into the arylic C–H bond, in the presence of primary, secondary as well as tertiary Csp^3–H bonds. Oxindoles **4e** and **4f**, bearing a (methoxycarbonyl)ethyl and a phenyl group, respectively, were also obtained in acceptable yields. Under the optimized reaction conditions, amide **1g**, bearing a 2-iodobenzyl substituent at the nitrogen atom, selectively afforded oxindole **4g**. Strikingly, no product resulting from the competitive Pd-catalysed coupling of the aryl iodide with the diazo moiety[23] was observed in the reaction mixture.[11]

It was also found that the stereoelectronic properties of the substituents on the aniline ring considerably affect the course of the cyclisation reaction. The presence of an *ortho*-bromo

substituent on the arylic ring resulted in a very slow reaction, probably due to steric interactions. Thus, starting from **1h** and after 4 days under the usual reaction conditions, a 1 : 1 mixture of the starting amide and oxindole **4h** (23%) was obtained. Amide **1i**, which bears a good electron-donating *meta*-methoxy group, underwent complete reaction to give oxindole **4i** (40%), which was isolated as a 1 : 3 mixture of regioisomers. On the other hand, amides **1j** and **1l**, which bear the electron-donating methoxy and electron-withdrawing (methoxycarbonyl) groups, respectively, at the *para* position afforded oxindoles **4j** and **4l** also in modest yields, despite complete consumption of the starting material. In contrast, oxindole **4k**, which has a fluoro substituent, was obtained in 64% yield. Finally, the *N*-naphthyl amide **1m** underwent selective C–H insertion to give **4m**, which was isolated together with the corresponding *O*-alkylation product.

To further confirm the catalytic role of palladium in the insertion reaction, the thermal decomposition of α-diazoamides **1b** (R_1 = H, R = Me) and **1f** (R_1 = H, R = Ph) was also evaluated. In the absence of $Pd_2(dba)_3$ and under otherwise the same reaction conditions, **1b** afforded a 2 : 1 : 0.6 mixture of **1b**, **4b** and β-lactam **2b** (Scheme 4).[24] When the thermal reaction was run starting from **1f**, a 4 : 1 mixture of the starting material and oxindole **4f** was obtained. The recovery of a considerable amount of starting material and, especially, the formation of β-lactams **2a** and **2b** in the thermal reactions clearly support the essential role of palladium as a catalyst for the oxindole formation.



Scheme 4 Thermal decomposition of amide **1b**.

To shed light on the reaction mechanism and selectivity of the Pd-catalysed C–H insertion reaction described above, density functional theory (DFT) calculations were carried out.[25] To this end, the reaction profile involving the simplest substrate **1b** and the model palladium(0) catalyst $Pd(PMe_3)_2$ (thus resembling the reaction conditions gathered in Table 1, entry 6) was explored (Fig. 1).

As previously reported for the process involving the strongly related α-diazoesters,[11] the reaction begins with intermediate **INT0**, the initial Pd(0)–carbene complex formed upon reaction of $Pd(PMe_3)_2$ with **1b**. This species evolves to the Pd(II)-complex **INT1-A** through **TS1-A** with a low activation barrier of 12.3 kcal mol^{-1} in a highly exergonic transformation (ΔG_R = −16.4 kcal mol^{-1}). As clearly depicted in Fig. 1, this step can be viewed as a Pd-mediated 1,5-*H* migration from the C(aryl)–H moiety to the carbenoid carbon atom, thus resulting in the formal oxidation of the transition metal. This transformation strongly resembles the one we recently described for the Pd(0)-catalysed Csp^3–H insertion reactions of carbenoids derived from α-diazoesters,[11] therefore suggesting a general reaction mechanism that does not depend upon the nature of the initial substrate. The process ends up with the conversion of the readily formed Pd(II)-complex **INT1-A** into oxindole **3b** (which in the presence of DCE and Cs_2CO_3 evolves into the observed alkylated oxindole **4b**). This highly exergonic **INT1-A** → **3b** transformation (ΔG_R = −23.8 kcal mol^{-1}) can be viewed as a reductive elimination reaction (*via* **TS2-A**, $\Delta G^{\ddagger}$ = 24.1 kcal mol^{-1}) which releases the active catalyst $Pd(PMe_3)_2$.

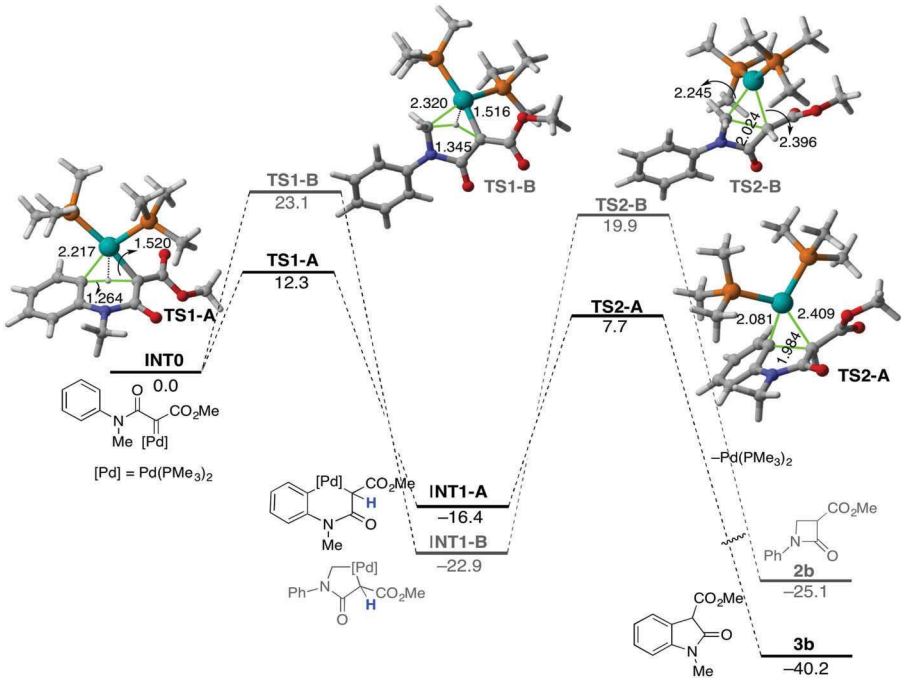


Fig. 1 Computed reaction profiles for the Pd-catalysed formation of oxindoles over β-lactams. Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal mol^{-1} and angstroms, respectively. All data were computed at the PCM(dichloroethane)-M06L/def2-TZVPP//PCM(dichloroethane)-B3LYP-D3/def2-SVP level.

To understand the selectivity of the insertion, the formation of the possible β-lactam **2b** was also computed. As shown in Fig. 1, the corresponding pathway leading to β-lactam **2b** is rather similar to that computed for oxindole **3b**, *i.e.* Pd-mediated 1,4-*H* migration *via* **TS1-B** followed by reductive elimination through **TS2-B**. From the data in Fig. 1, it becomes evident that both reaction steps are associated with much higher activation barriers than those computed for the pathway involving **TS1-A** and **TS1-B**. In particular, the rather high barrier computed for the reductive elimination *via* **TS2-B** ($\Delta G^{\ddagger}$ = 42.8 kcal mol^{-1}) makes this step unfeasible. Therefore, it can be concluded that the complete selectivity of the process, which exclusively produces oxindoles over β-lactams, takes place mainly under kinetic control.

In summary, we have shown that palladium catalysis constitutes a useful alternative to promote the carbenoid C–H insertion of α-diazo-α-(methoxycarbonyl)acetanilides, which selectively occurs into the arylic C(sp^2)–H bond rather than the C(sp^3)–H bonds. Moreover, when using DCE as the solvent, the insertion is followed by alkylation to give 3-(chloroethyl)oxindoles. Although the carbenoid insertion into the arylic C–H bond starting from α-diazo-α-(alkoxycarbonyl)acetanilides can also be promoted by rhodium(II) perfluorocarboxamides,[14c,d] these catalysts are not commercially produced. Thus, considering the ready availability of $Pd_2(dba)_3$ in particular, the present process would complement the existing methodologies based on the use of Rh as well as Ru catalysts.

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Palladium-catalysed intramolecular carbenoid insertion of α-diazo-α-(methoxycarbonyl)acetanilides for oxindole synthesis

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Electronic Supplementary Information

Table of Contents

General Methods. All commercially available reagents were used without further purification. ^{1}H- and ^{13}C NMR spectra were recorded using Me_4Si as the internal standard, with a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si for ^{1}H and ^{13}C NMR. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light or 1% aqueous $KMnO_4$. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator.

General Procedure for the Preparation of Diazoacetamides 1a-m.

To a solution of methyl malonyl chloride (1.18 mL, 10.9 mmol) and Et_3N (1.5 mL, 10.9 mmol) in THF (50 mL), cooled at 0 °C, was added slowly a solution of *N*-benzylaniline (2.0 g, 10.9 mmol) in THF (20 mL). The mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, filtered and concentrated to give *N*-benzyl-*N*-phenyl-α-(methoxycarbonyl)acetamide (3.1 g, quantitative), which was used in the next step without purification.

To a solution of *N*-benzyl-*N*-phenyl-α-(methoxycarbonyl)acetamide (650 mg, 2.29 mmols) and DBU (0.52 mL, 3.44 mmols) in dry acetonitrile (20 mL), was added dropwise a solution of *p*-ABSA (625 mg, 2.6 mmols) in dry acetonitrile (5 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 and 10% NaOH aqueous solution. The organic extracts were dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give *N*-benzyl-*N*-phenyl-α-(methoxycarbonyl)-α-diazoacetamide (**1a**, 610 mg; 86%) as a yellow oil.

Characterization data for Diazoacetamides 1a-m.

***N*-Benzyl-*N*-phenyl-α-(methoxycarbonyl)-α-diazoacetamide (1a).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 (s, 3H), 5.00 (s, 2H), 7.08-7.12 (m, 2H), 7.20-7.34 (m, 8H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.4 (CH_3), 54.5 (CH_2), 66.8 (C), 126.6 (2 CH), 127.3 (CH), 127.6 (CH), 128.5 (2 CH), 128.6 (2 CH), 129.5 (2 CH), 137.0 (C), 142.6 (C), 160.9 (C), 162.6 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{16}N_3O_3$: 310.1186 $[M+H]^+$; found: 310.1184.

***N*-Methyl-*N*-phenyl-α-(methoxycarbonyl)-α-diazoacetamide (1b).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.39 (s, 3H), 3.58 (s, 3H), 7.19-7.23 (m, 2H), 7.27 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.39 (tt, *J* = 7.6 and 1.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 38.8 (CH_3), 52.4 (CH_3), 125.7 (2 CH), 127.0 (CH), 129.5 (2 CH), 143.8 (C), 160.8 (C), 162.6 (C). One C was no observed. HRMS (ESI-TOF) calcd. for $C_{11}H_{12}N_3O_3$: 234.0873 $[M+H]^+$; found: 234.0874.

***N*-Ethyl-*N*-phenyl-α-(methoxycarbonyl)-α-diazoacetamide (1c).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (t, *J* = 7.2 Hz, 3H), 3.56 (s, 3H), 3.83 (q, *J* = 7.2 Hz, 2H), 7.14-7.19 (m, 2H), 7.26 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.37 (tt, *J* = 7.6 and 1.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.0 (CH_3), 46.1 (CH_2), 52.3 (CH_3), 66.4 (C), 126.8 (2 CH), 127.3 (CH), 129.6 (2

CH), 142.0 (C), 160.3 (C), 162.8 (C). HRMS (ESI-TOF) calcd. for $C_{12}H_{14}N_3O_3$: 248.1030 $[M+H]^+$; found: 248.1032.

***N*-Isopropyl-*N*-phenyl-α-(methoxycarbonyl)-α-diazoacetamide (1d).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (d, *J* = 6.8 Hz, 6H), 3.62 (s, 3H), 4.84 (heptuplet, *J* = 6.8 Hz, 1H), 7.12-7.16 (m, 2H), 7.32-7.42 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.0 (CH_3), 49.4 (CH), 52.4 (CH_3), 128.2 (CH), 129.2 (2 CH), 129.9 (2 CH), 138.6 (C), 160.3 (C), 163.3 (C). One C was no observed. HRMS (ESI-TOF) calcd. for $C_{13}H_{16}N_3O_3$: 262.1186 $[M+H]^+$; found: 262.1188.

***N*-(2-Methoxycarbonylethyl)-*N*-phenyl-α-(methoxycarbonyl)-α-diazoacetamide (1e).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.66 (t, *J* = 7.2 Hz, 3H), 3.58 (s, 6H), 4.08 (t, *J* = 7.2 Hz, 2H), 7.18-7.22 (m, 2H), 7.28 (tt, *J* = 7.6 and 1.2 Hz, 1H), 7.39 (tt, *J* = 7.6 and 1.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 32.5 (CH_2), 47.2 (CH_2), 51.8 (CH_3), 52.4 (CH_3), 66.8 (C), 126.8 (2 CH), 127.6 (CH), 129.7 (2 CH), 141.9 (C), 161.0 (C), 162.5 (C), 171.9 (C).

***N*,*N*-Diphenyl-α-(methoxycarbonyl)-α-diazoacetamide (1f).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.56 (s, 3H), 7.15-7.20 (m, 4H), 7.23 (tt, *J* = 7.6 and 1.2 Hz, 2H), 7.35 (tt, *J* = 7.6 and 1.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.4 (CH_3), 68.6 (C), 126.8 (2 CH), 126.9 (4 CH), 129.4 (4 CH), 143.3 (2 C), 161.8 (C), 162.2 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{14}N_3O_3$: 296.1030 $[M+H]^+$; found: 296.1027.

***N*-(2-Iodobenzyl)-*N*-phenyl-α-(methoxycarbonyl)-α-diazoacetamide (1g).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 (s, 3H), 5.05 (s, 2H), 6.95 (ddd, *J* = 8.0, 7.2 and 1.6 Hz, 1H), 7.12-7.15 (m, 2H), 7.22 (tt, *J* = 8.0 and 1.2 Hz, 1H), 7.27-7.35 (m, 3H), 7.42 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.79 (dd, *J* = 8.0 and 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.4 (CH_3), 59.2 (CH_2), 67.2 (C), 98.5 (C), 126.1 (2 CH), 127.3 (CH), 128.6 (CH), 128.7 (CH), 129.2 (CH), 129.5 (2 CH), 139.0 (C), 139.6 (CH) 142.7 (C), 161.4 (C), 162.4 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{15}IN_3O_3$: 436.1053 $[M+H]^+$; found: 436.0146.

***N*-Benzyl-*N*-(2-bromophenyl)-α-(methoxycarbonyl)-α-diazoacetamide (1h).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.61 (s, 3H), 4.48 (d, *J* = 14.4 Hz, 1H), 5.38 (d, *J* = 14.4 Hz, 1H), 6.95 (dd, *J* = 7.6 and 2.0 Hz, 1H),7.14 (td, *J* = 7.6 and 2.0 Hz, 1H), 7.19 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.20-7.27 (m, 5H), 7.60 (dd, *J* = 7.6 and 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.4 (CH_3), 53.2 (CH_2), 66.4 (C), 123.5 (C), 127.8 (CH), 128.2 (CH), 128.5 (2 CH), 129.5 (2 CH), 129.6 (CH), 131.5 (CH), 133.9 (CH), 136.1 (C), 140.0 (C), 161.1 (C), 162.6 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{15}IN_3O_3$: 388.0291 $[M+H]^+$; found: 388.0291.

***N*-Benzyl-*N*-(3-methoxyphenyl)-α-(methoxycarbonyl)-α-diazoacetamide (1i).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.61 (s, 3H), 3.72 (s, 3H), 4.97 (s, 2H), 6.61 (t, *J* = 2.4 Hz, 1H), 6.69 (ddd, *J* = 8.0, 2.4 and 0.8 Hz, 1H), 6.77 (ddd, *J* = 8.0, 2.4 and 0.8 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.22-7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.4 (CH_3), 54.5 (CH_2), 55.6 (CH_3), 66.7 (C), 112.6 (CH), 112.7 (CH), 118.9 (CH), 127.6 (CH), 128.5 (2 CH), 128.6 (2 CH), 130.2 (CH), 137.1 (C), 143.6 (C), 160.4 (C), 160.8 (C), 162.8 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}N_3O_4$: 340.1292 $[M+H]^+$; found: 340.1294.

***N*-Benzyl-*N*-(4-methoxyphenyl)-α-(methoxycarbonyl)-α-diazoacetamide (1j).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.63 (s, 3H), 3.77 (s, 3H), 4.93 (s, 2H), 6.78-6.83 (m, 2H), 6.95-6.99 (m, 2H), 7.20-7.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.4 (CH_3), 54.5 (CH_2), 55.5

(CH_3), 65.9 (C), 114.6 (2 CH), 127.6 (CH), 128.3 (2 CH), 128.5 (2 CH), 128.8 (2 CH), 134.8 (C), 137.0 (C), 158.7 (C), 160.8 (C), 162.9 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}N_3O_4$: 340.1292 $[M+H]^+$; found: 340.1295.

***N*-Benzyl-*N*-(4-fluorophenyl)-α-(methoxycarbonyl)-α-diazoacetamide (1k).** Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.59 (s, 3H), 4.95 (s, 2H), 6.96-7.07 (m, 4H), 7.21-7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.4 (CH_3), 54.7 (CH_2), 66.7 (C), 116.3 (d, J = 22.7 Hz, 2 CH), 127.8 (CH), 128.6 (2 CH), 128.7 (2 CH), 128.7 (d, J = 8.5 Hz, 2 CH), 136.7 (C), 138.4 (d, J = 3.2 Hz, C), 160.9 (C), 161.2 (d, J = 248.0 Hz, C), 162.1 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{15}FN_3O_3$: 328.1092 $[M+H]^+$; found: 328.1089.

***N*-Benzyl-*N*-[4-(methoxycarbonyl)phenyl]-α-(methoxycarbonyl)-α-diazoacetamide (1l).** Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.52 (s, 3H), 3.90 (s, 3H), 5.04 (s, 2H), 7.17-7.30 (m, 7H), 7.95-7.99 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.3 (CH_3), 52.4 (CH_3), 54.3 (CH_2), 68.1(C), 125.7 (2 CH), 127.8 (CH), 128.2 (2 CH), 128.3 (C), 128.7 (2 CH), 130.8 (2 CH), 136.6 (C), 147.2 (C), 161.5 (C), 161.8 (C), 166.3 (C). HRMS (ESI-TOF) calcd. for $C_{19}H_{18}N_3O_5$: 368.1241 $[M+H]^+$; found: 368.1236.

***N*-Benzyl-*N*-(1-naphthyl)-α-(methoxycarbonyl)-α-diazoacetamide (1m).** Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.46 (s, 3H), 4.50 (d, J = 14.0 Hz, 1H), 5.57 (d, J = 14.0 Hz, 1H), 6.99 (dd, J = 7.6 and 1.2 Hz, 1H), 7.15-7.23 (m, 5H), 7.32 (dd, J = 8.0 and 7.6 Hz, 1H), 7.51-7.58 (m, 2H), 7.80-7.85 (m, 2H), 7.87-7.92 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.3 (CH_3), 54.2 (CH_2), 122.5 (CH), 125.4 (CH), 126.8 (CH), 127.2 (CH), 127.6 (CH), 127.8 (CH), 128.4 (2 CH), 128.9 (CH), 129.2 (CH), 129.6 (2 CH), 130.1 (C), 134.7 (C), 136.7 (C), 137.3 (C), 161.5 (C), 163.2 (C). One C was not observed. HRMS (ESI-TOF) calcd. for $C_{21}H_{18}N_3O_3$: 360.1343 $[M+H]^+$; found: 360.1337.

Rh(II)-Catalysed Cyclisation Reactions.

Methyl *trans*-2-oxo-1,4-diphenylazetidine-3-carboxylate (2a). A mixture of diazoamide **1a** (60 mg, 0.19 mmol), $Rh_2(OAc)_4$ (1.8 mg, 0.004 mmol) in dichloromethane (2 mL) was stirred at room temperature under Argon atmosphere for 33 h. The reaction mixture was concentrated and the residue was purified by chromatography (SiO_2, CH_2Cl_2) to give β-lactam **2a** (25 mg, 48%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H), 3.98 (d, J = 2.4 Hz, 1H), 5.33 (d, J = 2.4 Hz, 1H), 7.07 (tt, J = 7.2 and 1.2 Hz, 1H), 7.22-7.30 (m, 4H), 7.34-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 53.1 (CH_3), 57.7 (CH), 63.5 (CH), 117.4 (2 CH), 124.6 (CH), 126.3 (2 CH), 129.2 (CH), 129.3 (2 CH), 129.5 (2 CH), 136.4 (C), 137.3 (C), 159.3 (C), 166.9 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{16}NO_3$: 282.1125 $[M+H]^+$; found: 282.1122.

Methyl 2-oxo-1-phenylazetidine-3-carboxylate (2b). A mixture of diazoamide **1b** (60 mg, 0.26 mmol), $Rh_2(OAc)_4$ (2.2 mg, 0.005mmol) in dichloromethane (2 mL) was stirred at room temperature under Argon atmosphere for 33 h. The reaction mixture was concentrated and the residue was purified by chromatography (SiO_2, hexanes to hexanes/EtOAc 1:1) to give β-lactam **2b** (21 mg, 40%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.79 (t, J = 6.0 Hz, 1H), 3.82 (s, 3H), 3.97 (dd, J = 6.0 and 3.2 Hz, 1H), 4.21 (dd, J = 6.0 and 3.2 Hz, 1H), 7.10-7.16 (m, 1H), 7.33-7.37 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 41.5 (CH_2), 53.0 (CH), 53.1 (CH_3), 116.6 (2 CH), 124.7 (CH), 129.4 (2 CH), 137.9 (C), 158.9 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{11}H_{15}N_2O_3$: 223.1077 $[M+NH_4]^+$; found: 223.1077.

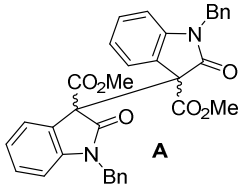
Representative Procedure for the Pd(0)-Catalysed Cyclisation Reactions (Table 1, Entry 4). A mixture of diazoamide **1a** (65 mg, 0.21 mmol), $Pd_2(dba)_3$ (19 mg, 0.021 mmol), and Cs_2CO_3 (137 mg, 0.42 mmol) in dichloroethane (10 mL) was stirred at reflux under Argon atmosphere for 96 h. The reaction mixture was partitioned water and CH_2Cl_2. The organic extracts were dried and concentrated. The residue was purified by chromatography (SiO_2, from hexanes to CH_2Cl_2) to give oxindoline **4a** (48 mg, 66%) as an amorphous orange solid.

Pd(0)-Catalysed Reaction of 1a with DBU. A mixture of diazoamide **1a** (30 mg, 0.1 mmol), $Pd_2(dba)_3$ (8.8 mg, 0.01 mmol), and DBU (18 μl, 0.12 mmol) in dichloroethane (6 mL) was stirred at reflux under Argon atmosphere for 96 h. The reaction mixture was partitioned water and CH_2Cl_2. The organic extracts were dried and concentrated. The residue was purified by chromatography (SiO_2, from hexanes to CH_2Cl_2) to give *N*-benzyl-2-oxindole (15.5 mg, 69%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.62 (s, 2H), 4.92 (s, 2H), 6.72 (d, *J* = 7.6 Hz, 1H), 7.00 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.16 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.23-7.34 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 35.9 (CH_2), 43.9 (CH_2), 109.2 (CH), 122.5 (CH), 124.6 (CH), 124.7 (C), 127.6 (2 CH), 127.8 (CH), 128.0 (CH), 128.9 (2 CH), 136.0 (C), 144.5 (C), 175.3 (C).

Characterization data for the oxindole derivatives

Methyl 1-benzyl-2-oxoindoline-3-carboxylate (3a). 26 mg (44%, Table 1, Entry 3). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.78 (s, 3H), 4.32 (s, 1H), 4.78 (d, *J* = 15.8 Hz, 1H), 5.08 (d, *J* = 15.8 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 7.06 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.23-7.35 (m, 7H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 44.2 (CH_2), 54.1 (CH_3), 110.2 (CH), 123.6 (CH), 124.1 (CH), 126.9 (C), 127.2 (2 CH), 128.0 (CH), 129.0 (2 CH), 130.9 (CH), 135.2 (C), 143.9 (C), 170.6 (C), 173.3 (C). One CH was not observed.

Bisoxindole dimer A.[1]



A

Significant signals from a 3:1 mixture of **3a** and **A** obtained from the crude reaction mixture corresponding to entry 2 of Table 1: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.75 (s, 3H), 4.68 (d, *J* = 15.8 Hz, 1H), 4.98 (d, *J* = 15.8 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 6.85 (td, *J* = 7.6 and 0.8 Hz, 1H), 7.12 (td, *J* = 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 44.3 (CH_2), 53.5 (CH_3), 109.2 (CH), 122.6 (CH), 126.9 (CH), 127.6 (CH), 128.8 (CH), 129.7 (CH), 143.6 (C), 167.2 (C). HRMS (ESI-TOF) calcd. for $C_{34}H_{29}N_2O_6$: 561.2020 $[M+H]^+$; found: 561.2018.

Methyl 1-benzyl-3-(2-chloroethyl)-2-oxoindoline-3-carboxylate (4a). 48 mg (66%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.69 (ddd, *J* = 14.0, 9.2 and 5.6 Hz, 1H), 2.85 (ddd, *J* = 14.0, 9.6 and 6.8 Hz, 1H), 3.35-3.46 (m, 2H), 3.69 (s, 3H), 4.82 (d, *J* = 15.8 Hz, 1H), 5.08 (d, *J* = 15.8

[1] S. Ghosh, S. Chaudhuri and A. Bisai, *Org. Lett.* **2015**, *17*, 1373.

Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.20-7.34 (m, 7H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.6 (CH_2), 39.4 (CH_2), 44.2 (CH_2), 53.4 (CH_3), 58.3 (C), 109.9 (CH), 123.3 (CH), 123.6 (CH), 126.9 (C), 127.4 (2 CH), 127.9 (CH), 129.0 (2 CH), 129.7 (CH), 135.4 (C), 143.3 (C), 169.2 (C), 173.7 (C). HRMS (ESI-TOF) calcd. for $C_{19}H_{19}ClNO_3$: 344.1048 $[M+H]^+$; found: 344.1041.

Methyl 3-(2-chloroethyl)-1-methyl-2-oxoindoline-3-carboxylate (4b). 41 mg (71%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.63 (ddd, *J* = 14.0, 9.6 and 5.2 Hz, 1H), 2.80 (ddd, *J* = 14.0, 9.6 and 6.4 Hz, 1H), 3.25 (s, 3H), 3.30-3.44 (m, 2H), 3.67 (s, 3H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.10 (td, *J* = 7.6 and 0.8 Hz, 1H), 7.25 (dd, *J* = 7.6 and 0.8 Hz, 1H), 7.36 (td, *J* = 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.8 (CH_3), 36.8 (CH_2), 39.4 (CH_2), 53.4 (CH_3), 58.2 (C), 108.9 (CH), 123.3 (CH), 123.6 (CH), 126.9 (C), 129.8 (CH), 144.2 (C), 169.3 (C), 173.5 (C). HRMS (ESI-TOF) calcd. for $C_{13}H_{15}ClNO_3$: 268.0735 $[M+H]^+$; found: 268.0737.

Methyl 3-(2-chloroethyl)-1-ethyl-2-oxoindoline-3-carboxylate (4c). 31 mg (54%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.64 (ddd, *J* = 14.0, 9.2 and 5.6 Hz, 1H), 2.79 (ddd, *J* = 14.0, 9.6 and 6.8 Hz, 1H), 3.29-3.40 (m, 2H), 3.66 (s, 3H), 3.70-3.88 (m, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.08 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.25 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.34 (td, *J* = 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.5 (CH_3), 35.2 (CH_2), 36.6 (CH_2), 39.4 (CH_2), 53.4 (CH_3), 58.2 (C), 109.0 (CH), 123.0 (CH), 123.8 (CH), 127.1 (C), 129.7 (CH), 143.3 (C), 169.3 (C), 173.1 (C). HRMS (ESI-TOF) calcd. for $C_{14}H_{17}ClNO_3$: 282.0891 $[M+H]^+$; found: 282.0889.

Methyl 3-(2-chloroethyl)-1-isopropyl-2-oxoindoline-3-carboxylate (4d). 38 mg (61%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (d, *J* = 6.8 Hz, 3H), 1.51 (d, *J* = 6.8 Hz, 3H), 2.65 (ddd, *J* = 14.0, 8.8 and 6.0 Hz, 1H), 2.79 (ddd, *J* = 14.0, 9.6 and 6.8 Hz, 1H), 3.27-3.38 (m, 2H), 3.66 (s, 3H), 4.63 (heptuplet, *J* = 6.8 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.07 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.24 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.32 (td, *J* = 7.6 and 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.3 (CH_3), 19.4 (CH_3), 36.6 (CH_2), 39.4 (CH_2), 44.5 (CH), 53.4 (CH_3), 58.1 (C), 110.5 (CH), 122.7 (CH), 123.8 (CH), 127.2 (C), 129.4 (CH), 143.0 (C), 169.4 (C), 173.1 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1045.

Methyl 3-(2-chloroethyl)-1-(methoxycarbonylethyl)-2-oxoindoline-3-carboxylate (4e). 30 mg (45%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60-2.85 (4H), 3.29-3.42 (m, 2H), 3.66 (s, 3H), 3.67 (s, 3H), 3.97-4.13 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 7.08 (td, *J* = 7.6 and 0.8 Hz, 1H), 7.25 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.36 (ddd, *J* = 8.0, 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 32.0 (CH_2), 36.5 (2 CH_2), 39.4 (CH_2), 52.1 (CH_3), 53.5 (CH_3), 58.1 (C), 109.1 (CH), 123.3 (CH), 123.8 (CH), 126.9 (C), 129.8 (CH), 143.1 (C), 169.2 (C), 171.6 (C), 173.5 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}ClNO_5$: 340.0946 $[M+H]^+$; found: 340.0951.

Methyl 3-(2-chloroethyl)-2-oxo-1-phenylindoline-3-carboxylate (4f). 37 mg (55%). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.79 (ddd, *J* = 14.0, 9.2 and 5.2 Hz, 1H), 2.91 (ddd, *J* = 14.0, 9.2 and 7.2 Hz, 1H), 3.45 (ddd, *J* = 10.8, 9.2 and 7.2 Hz, 1H), 3.53 (ddd, *J* = 10.8, 9.2 and 5.2 Hz, 1H), 3.72 (s, 3H), 6.85 (dd, *J* = 7.6 and 0.8 Hz, 1H), 7.13 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.26-7.32 (m, 2H), 7.41-7.46 (m, 3H), 7.51-7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.7 (CH_2), 39.6 (CH_2), 53.6 (CH_3), 58.4 (C), 110.2 (CH), 123.7 (CH), 123.8 (CH), 126.6 (C), 126.7 (2 CH), 128.6 (CH), 129.7 (CH), 129.9 (2 CH), 134.2 (C), 144.4 (C), 169.3 (C), 173.0 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{17}ClNO_3$: 330.0891 $[M+H]^+$; found: 330.0888.

Methyl 3-(2-chloroethyl)-1-(2-iodobenzyl)-2-oxoindoline-3-carboxylate (4g). 50 mg (55%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.72 (ddd, *J* = 14.0, 9.6 and 5.6 Hz, 1H), 2.89 (ddd, *J* = 14.0, 9.6 and 6.4 Hz, 1H), 3.41-3.53 (m, 2H), 3.73 (s, 3H), 4.83 (d, *J* = 16.6 Hz, 1H), 5.10 (d, *J* = 16.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.98 (ddd, *J* = 7.6, 7.2 and 1.6 Hz, 1H), 7.06 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.09 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.22-7.31 (m, 4H), 7.90 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.5 (CH_2), 39.4 (CH_2), 49.4 (CH_2), 53.6 (CH_3), 58.5 (C), 97.8 (C), 110.1 (CH), 123.6 (CH), 123.7 (CH), 126.8 (C), 127.1 (CH), 128.8 (CH), 129.5 (CH), 129.9 (CH), 137.0 (C), 139.8 (CH), 143.1 (C), 169.2 (C), 173.8 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}ClINO_3$: 470.0014 $[M+H]^+$; found: 470.0006.

Methyl 1-benzyl-7-bromo-3-(2-chloroethyl)-2-oxoindoline-3-carboxylate (4h). Oxoindoline **4i** could not be isolarted in pure form and was obtained together with minor amounts of dba. 25 mg (23%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.64 (ddd, *J* = 14.0, 9.2 and 6.0 Hz, 1H), 2.82 (ddd, *J* = 14.0, 9.6 and 6.4 Hz, 1H), 3.34-3.45 (m, 2H), 3.70 (s, 3H), 5.38 (d, *J* = 16.4 Hz, 1H), 5.48 (d, *J* = 16.4 Hz, 1H), 6.96 (dd, *J* = 8.0 and 7.6 Hz, 1H), 7.22 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.24-7.38 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.9 (CH_2), 39.1 (CH_2), 45.1 (CH_2), 53.6 (CH_3), 57.9 (C), 103.1 (C), 122.7 (CH), 124.5 (CH), 126.5(2 CH), 127.4 (CH), 128.7 (2 CH), 130.0 (C), 135.7 (C), 137.2 (C), 141.0 (C), 168.7 (C), 174.3 (C). HRMS (ESI-TOF) calcd. for $C_{19}H_{18}BrClNO_3$: 422.0153 $[M+H]^+$; found: 422.0153.

Methyl 1-benzyl-3-(2-chloroethyl)-6-methoxy-2-oxoindoline-3-carboxylate (4i). Oxindoline **4i** was obtained together with methyl 1-benzyl-3-(2-chloroethyl)-4-methoxy-2-oxoindoline-3-carboxylate (3:1 ratio, 36 mg, 40%). **Methyl 1-benzyl-3-(2-chloroethyl)-6-methoxy-2-oxoindoline-3-carboxylate**: Signals from the 3:1 mixture. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.66 (ddd, *J* = 14.0, 10.0 and 5.6 Hz, 1H), 2.81 (ddd, *J* = 14.0, 10.0 and 6.4 Hz, 1H), 3.33-3.46 (m, 2H), 3.68 (s, 3H), 3.73 (s, 3H), 4.79 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 8.0 and 2.4 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.25-7-35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.6 (CH_2), 39.5 (CH_2), 44.3 (CH_2), 53.4 (CH_3), 55.6 (CH_3), 57.8 (C), 98.1 (CH), 106.9 (CH), 118.7 (C), 124.3 (CH), 127.4 (2 CH), 128.0 (CH), 129.0 (2 CH), 135.5 (C), 144.6 (C), 161.2 (C), 169.5 (C), 174.2 (C). **Methyl 1-benzyl-3-(2-chloroethyl)-4-methoxy-2-oxoindoline-3-carboxylate**: Signals from the 3:1 mixture. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.77-2.87 (m, 1H), 2.96 (ddd, *J* = 14.0, 8.8 and 5.2 Hz, 1H), 3.25-3.40 (m, 2H), 3.68 (s, 3H), 3.82 (s, 3H), 4.79 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 6.41 (dd, *J* = 8.4 and 2.4 Hz, 1H), 6.60 (dd, *J* = 8.4 and 0.8 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 7.25-7-35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 34.3 (CH_2), 40.3 (CH_2), 44.5 (CH_2), 53.3 (CH_3), 55.8 (CH_3), 57.9 (C), 103.2 (CH), 106.2 (CH), 113.2 (C), 127.3 (2 CH), 127.9 (CH), 128.9 (2 CH), 130.8 (CH), 135.7 (C), 145.0 (C), 155.9 (C), 168.5 (C), 174.0 (C). HRMS (ESI-TOF) calcd. for $C_{20}H_{21}ClNO_4$: 374.1154 $[M+H]^+$; found: 374.1150.

Methyl 1-benzyl-3-(2-chloroethyl)-5-methoxy-2-oxoindoline-3-carboxylate (4j). 26 mg (36%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.66 (ddd, *J* = 14.0, 9.2 and 6.0 Hz, 1H), 2.85 (ddd, *J* = 14.0, 9.6 and 6.8 Hz, 1H), 3.35-3.45 (m, 2H), 3.70 (s, 3H), 3.76 (s, 3H), 4.79 (d, *J* = 16.0 Hz, 1H), 5.05 (d, *J* = 16.0 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 6.74 (dd, *J* = 8.8 and 2.4 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 7.25-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.7 (CH_2), 39.4 (CH_2), 44.3 (CH_2), 53.5 (CH_3), 56.0 (CH_3), 58.7 (C), 110.4 (CH), 110.7 (CH), 114.1 (CH), 127.4 (2 CH), 127.9 (CH), 128.1 (C), 129.0 (2 CH), 135.5 (C), 136.6 (C), 156.4 (C), 169.2 (C), 173.4 (C). HRMS (ESI-TOF) calcd. for $C_{20}H_{21}ClNO_4$: 374.1154 $[M+H]^+$; found: 374.1154.

Methyl 1-benzyl-3-(2-chloroethyl)-5-fluoro-2-oxoindoline-3-carboxylate (4k). 46 mg (64%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (ddd, *J* = 14.0, 9.2 and 6.0 Hz, 1H), 2.86 (ddd, *J* = 14.0, 9.2 and 6.8 Hz, 1H), 3.37-3.48 (m, 2H), 3.72 (s, 3H), 4.80 (d, *J* = 15.6 Hz, 1H), 5.07 (d, *J* = 15.6 Hz, 1H), 6.66 (dd, *J* = 8.8 and 4.0 Hz, 1H), 6.93 (ddd, *J* = 8.8, 8.4 and 2.4 Hz, 1H), 7.02 (dd, *J* = 7.2 and 2.4 Hz, 1H), 7.26-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.6 (CH_2), 39.2 (CH_2), 44.4 (CH_2), 53.7 (CH_3), 58.6 (C), 110.6 (d, *J* = 8.1 Hz, CH), 111.9 (d, *J* = 25.3 Hz, CH), 116.1 (d, *J* = 23.4 Hz, CH), 127.4 (2 CH), 128.1 (CH), 128.3 (d, *J* = 8.3 Hz, C), 129.1 (2 CH), 135.2 (C), 139.3 (d, *J* = 2.2 Hz, C), 159.4 (d, *J* = 242.5 Hz, C), 168.7 (C), 173.4 (C). HRMS (ESI-TOF) calcd. for $C_{19}H_{18}ClFNO_3$: 362.0954 $[M+H]^+$; found: 362.0949.

Methyl 1-benzyl-3-(2-chloroethyl)-5-(methoxycarbonyl)-2-oxoindoline-3-carboxylate (4l). Oxindoline **4l** was obtained together with the O-alkylation product **4l'** (3:1 ratio, 29 mg, 30%). **4l:** Signals from the 3:1 mixture of **4l** and **4l'**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.74 (ddd, *J* = 14.4, 9.2 and 5.2 Hz, 1H), 2.89 (ddd, *J* = 14.4, 9.6 and 6.8 Hz, 1H), 3.34-3.48 (m, 2H), 3.70 (s, 3H), 3.89 (s, 3H), 4.84 (d, *J* = 15.2 Hz, 1H), 5.11 (d, *J* = 15.2 Hz, 1H), 6.79 (dd, *J* = 8.4 and 0.4 Hz, 1H), 7.92 (dd, *J* = 1.6 and 0.4 Hz, 1H), 7.98 (dd, *J* = 8.4 and 1.6 Hz, 1H), 7.20-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.3 (CH_2), 39.3 (CH_2), 44.5 (CH_2), 52.4 (CH_3), 54.4 (CH_3), 58.1 (C), 109.5 (CH), 124.9 (CH), 125.8 (C), 126.9 (C), 127.4 (2 CH), 128.2 (CH), 129.1 (2 CH), 132,2 (CH), 134.9 (C), 147.4 (C), 166.4 (C), 168.6 (C), 174.0 (C). **Methyl 1-benzyl-2-(2-chloroethoxy)-5-(methoxycarbonyl)indole-3-carboxylate (4l').** Significant signals from the 3:1 mixture of **4l** and the O-alkylated product **4l'**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79-3.82 (m, 2H), 3.93 (s, 3H), 3.97 (s, 3H), 4.75-4.78 (m, 2H), 5.40 (s, 2H), 7.89 (dd, *J* = 8.4 and 1.6 Hz, 1H), 8.76 (dd, *J* = 1.6 and 0.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 43.1(CH_2), 45.8 (CH_2), 51.4 (CH_3), 52.2 (CH_3), 76.1 (CH_2), 92.1 (C), 125.9 (CH), 126.8 (CH), 128.3 (CH), 128.7 (CH), 130.8 (CH), 147.2 (C), 164.6 (C), 168.0 (C). HRMS (ESI-TOF) calcd. for $C_{21}H_{21}ClNO_5$: 402.1103 $[M+H]^+$; found: 402.1099.

Methyl 1-benzyl-3-(2-chloroethyl)-2-oxo-2,3-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (4m) and **methyl 1-benzyl-2-(2-chloroethoxy)-1*H*-benzo[*g*]indole-3-carboxylate (4m').** A 2:1 mixture of **4m** and the O-alkylated product **4m'** was obtained: 34 mg (2:1, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz, assignment aided by HSQC) δ 2.80 (ddd, *J* = 14.0, 8.8 and 6.4 Hz, 1H, **4m**), 2.97 (ddd, *J* = 14.0, 9.2 and 7.2 Hz, 1H, **4m**), 3.38-3.48 (m, 2H, **4m**), 3.71 (s, 3H, **4m**), 3.77-3.80 (m, 2H, **4m'**), 3.99 (s, 3H, **4m'**), 4.62-4.65 (m, 2H, **4m'**), 5.39 (d, *J* = 17.2 Hz, 1H, **4m**), 5.65 (d, *J* = 17.2 Hz, 1H, **4m**), 5.92 (s, 2H, **4m'**), 7.12 (dd, *J* = 7.6 and 1.2 Hz, 1H, **4m**), 7.22-7.42 (m, 6H from **4m** and 8H from **4m'**), 7.64 (d, *J* = 8.4 Hz, 1H, **4m**), 7.69 (dd, *J* = 8.4 and 0.8 Hz, 1H, **4m'**), 7.83 (dd, *J* = 8.4 and 0.8 Hz, 1H, **4m**), 7.92 (dd, *J* = 8.4 and 1.6 Hz, 1H, **4m'**), 7.99 (dd, *J* = 8.4 and 0.8 Hz, 1H, **4m**), 8.03 (dd, *J* = 8.4 and 1.2 Hz, 1H, **4m'**), 8.32 (d, *J* = 8.4 Hz, 1H, **4m**). ^{13}C NMR ($CDCl_3$, 100.6 MHz, assignment aided by HSQC) δ 36.6 (CH_2, **4m**), 39.4 (CH_2, **4m**), 42.9 (CH_2, **4m'**), 46.5 (CH_2, **4m**), 47.8 (CH_2, **4m'**), 51.3 (CH_3, **4m'**), 53.5 (CH_3, **4m**), 58.4 (C, **4m**), 76.2 (CH_2, **4m'**), 93.3 (C, **4m'**), 120.2 (CH), 120.6 (CH), 120.7 (C), 120.8 (CH), 121.8 (C), 122.2 (CH), 122.3 (C), 122.6 (C), 123.6 (CH), 123.8 (CH), 124.4 (CH), 124.6 (C), 125.9 (CH), 126.0 (CH), 126.1 (CH), 126.3 (CH), 126.6 (CH), 127.6 (CH), 127.7 (CH), 129.2 (CH), 129.5 (CH), 129.6 (CH), 131.5 (C), 135.3 (C), 136.7 (C), 137.0 (C), 139.4 (C), 154.1 (C), 165.0 (C), 169.2 (C), 175.6 (C). HRMS (ESI-TOF) calcd. for $C_{23}H_{21}ClNO_3$: 394.1204 $[M+H]^+$; found: 394.1201.

Palladium Catalysis in the Intramolecular Carbene C–H Insertion of α-Diazo-α-(methoxycarbonyl)acetamides to Form β-Lactams

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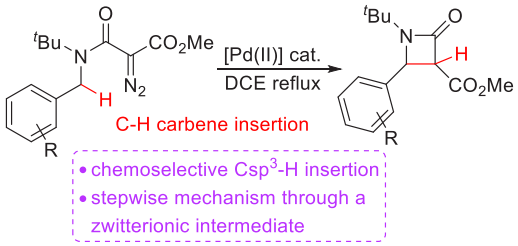
Table of Contents



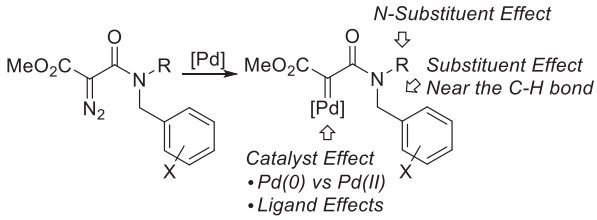
Abstract: The intramolecular carbene C–H insertion of α-diazo-α-(methoxycarbonyl)acetamides leading to β-lactams is effectively catalyzed by Pd(II)-complexes. According to DFT calculations, this insertion reaction occurs stepwise through a metallacarbene-induced zwitterionic intermediate.

The transition metal-catalyzed intramolecular carbene C–H insertion by decomposition of diazo compounds is a well-established powerful carbon-carbon bond-forming methodology for the construction of carbocyclic and heterocyclic frameworks.[1] Many transition metal complexes have been used as effective catalysts to generate reactive metallacarbenes starting from diazo derivatives.[2] Among them, rhodium(II),[3] copper(I),[4] and more recently ruthenium(II) catalysts[5] have proven especially useful for the development of highly selective carbene C–H insertion methodologies via a variety of reaction modes.

Surprisingly, palladium, though one of the most commonly employed metals in homogeneous catalysis, has been scarcely applied to promote carbene C–H insertion processes.[6] In this context, we recently reported that palladium catalysts are able to promote Csp^3–H insertion of carbenes derived from α-diazoesters to form pyrrolidines through intramolecular Csp^3–Csp^3 bond formation.[7] We also explored the palladium-catalyzed carbene C–H insertion of α-diazo-α-(methoxycarbonyl)acetanilides. We found that when using palladium catalysts the C–H insertion of such amides occurs selectively into the arylic Csp^2–H to give the oxindole.[8]

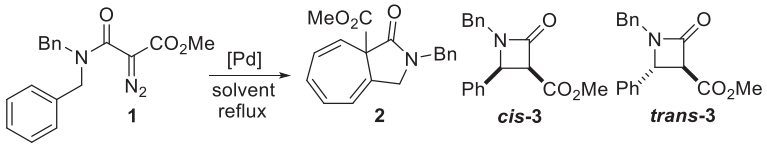
The aim of the current work was to explore the palladium-catalyzed intramolecular carbene insertion of α-diazo-α-(methoxycarbonyl)acetamides for β-lactam elaboration. The β-lactam system has attracted considerable attention due to its ubiquitous presence in the molecular structure of natural products and biologically active compounds.[9] We studied how the selectivity of the process[10] is affected by the type of catalyst, using two oxidation states of palladium, and the substituents on the α-diazoacetamide (Scheme 1).

Scheme 1. Substituent and catalyst effects on Pd-catalyzed reactions of α-diazoacetamides



We commenced our investigation by studying the palladium-catalyzed reactions of *N*,*N*-dibenzyl-α-diazoacetamide **1** (Table 1).[11]

Table 1. Pd-catalyzed cyclisation reactions of α-diazoamide 1[a]



entry	catalyst (mol%)	solvent	^{1}H NMR ratio[b]	Yield (%)[c]
1	$Pd_2(dba)_3$ (10)	DCE	**1**/**2**/***cis*-3**/***trans*-3** (1:1.5:0.15:1.5)	---
2	---	DCE	**1**/**2**/***cis*-3**/***trans*-3** (1:0.3:0.04:0.3)	---
3	$Pd_2(dba)_3$ (10)	toluene	**2**/***cis*-3**/***trans*-3** (1:0.1:1)	**2** (42), ***trans*-3** (42)
4	---	toluene	**2**/***cis*-3**/***trans*-3** (1:0.25:1)	**2** (43), ***trans*-3** (45)
5	$[(IMes)Pd(NQ)]_2$ (2.5)	DCE	**2**/***cis*-3**/***trans*-3** (1:0.1:0.2)	**2** (55), ***trans*-3** (5)
6	$[(IMes)Pd(NQ)]_2$ (2.5)	CH_2Cl_2	**1**	---
7	$[Pd(allyl)Cl]_2$ (5)	DCE	**2**/***cis*-3**/***trans*-3** (1:1.4:0.5)	**2** (20), ***trans*-3** (23)[d]
8	(SIPr)Pd(allyl)Cl (15)	DCE[e]	**2**/***cis*-3**/***trans*-3** (1:0.25:1.1)	**2** (22), ***trans*-3** (20)[d]
9	(SIPr)Pd(allyl)Cl (10)	DCE[e]	**1**/**2**/***cis*-3**/***trans*-3** (1:1.1:0.3:1.4)	---
10	$Pd(TFA)_2$ (10)	$CHCl_3$[e]	**2**/***cis*-3**/***trans*-3** (1:1.2:1)	**2** (15), ***trans*-3** (24)[d]

[a] Reaction conditions: Catalyst (see table) in the indicated solvent at reflux for 24 h. [b] Ratio determined by ^{1}H NMR (400 MHz) from the reaction mixture. [c] Yields refer to products isolated by chromatography. [d] Small amounts (≤10%) of *N*,*N*-dibenzyl-α-chloro-α-(methoxycarbonyl)acetamide were also obtained. [e] Reaction time: 48 h. $Pd_2(dba)_3$ = Tris(dibenzylideneacetone)dipalladium(0). $[(IMes)Pd(NQ)]_2$ = 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer. (SIPr)Pd(allyl)Cl = Allyl-chloro-[1,3-bis-(2,6-diisopropylphenyl)-2-imidazolidinylidene]palladium(II).

Treatment of **1** with $Pd_2(dba)_3$ in 1,2-dichloroethane at reflux for 24 h resulted in 76% conversion to give a 1:1 mixture of cycloheptapyrrolone **2** and β-lactam ***trans*-3**, together with some β-lactam ***cis*-3** and the recovery of significant amounts of unreacted

starting material (entry 1). When the reaction was performed in the absence of the palladium catalyst, ca. 40% of conversion was observed, giving a 1:0.1:1 mixture of **2**, ***cis*-3** and ***trans*-3**, together with the unreacted material (entry 2). The complete consumption of the starting material was achieved when reactions were run in refluxing toluene (entries 3-4).

On the other hand, the $[(IMes)Pd(NQ)]_2$-catalyzed decomposition of **1** in DCE at reflux gave cycloheptapyrrolone **2** as the major product (55%), together with small amounts of β-lactams ***cis*-3** and ***trans*-3** (entry 5). The complete consumption of the starting material and the notably different selectivity of the latter reaction compared with the thermal process in DCE (entry 2) clearly supports the role of $[(IMes)Pd(NQ)]_2$ as a catalyst in the decomposition of α-diazoacetamide **1**.

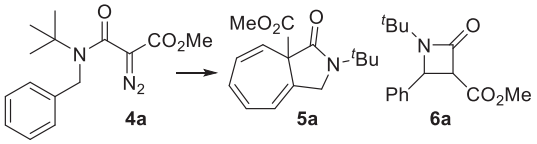
Pd(II)-catalysts were also able to promote the carbene reactions of **1**, which resulted in the major formation of β-lactams ***cis*-3** and ***trans*-3** at the expense of the Buchner product **2**. Thus, the $[Pd(allyl)Cl]_2$-catalyzed decomposition of **1** afforded a 1:1.4:0.5 mixture of cycloheptapyrrolone **2** and β-lactams ***cis*-3** and ***trans*-3** (entry 7). However, after flash chromatography, only **2** (20%) and ***trans*-3** (23%) were isolated because β-lactam ***cis*-3** underwent isomerization to the more stable *trans* isomer during the purification process. When using (SIPr)Pd(allyl)Cl as the catalyst, products **2** and ***trans*-3** were isolated in comparable yields (entry 8). Finally, $Pd(TFA)_2$ also led to the formation of the β-lactams as the main products, although a longer reaction time was required and ***trans*-3** was still isolated in poor yield (entry 10).

The competition between Csp^3–H insertion leading to β-lactams and intramolecular aromatic cycloaddition to give the corresponding cycloheptapyrrolone is also common in reactions of α-diazoacetamides catalyzed by Rh(II)[11a] and Ru(II)-

catalysts.[11b,12] According to previous mechanistic studies on related Rh(II)-catalyzed transformations, the competitive formation of β-lactams and aromatic ring reaction products is probably due to the stereoelectronic competition between the two conformational isomers of the metallacarbene undergoing the intramolecular reactions.[13] A strategy to improve site-selectivity in the transition metal-catalyzed carbene reactions of α-diazoacetamides involves replacing one of the *N*-substituents at the amide moiety with a bulky group,[14] which sterically biases the conformational preference around the amide N–C(O) bond and makes the metallacarbene reaction at the remaining substituent more feasible.

In search of higher site-selectivity in the palladium-catalyzed insertion leading to β-lactams, we decided to replace one of the benzyl groups in **1** with a ^{t}butyl substituent. Table 2 shows the results of the palladium-catalyzed reactions with *N*-benzyl-*N*-^{t}butyl-α-diazoacetamide **4a**.[15]

Table 2. Pd-catalyzed cyclisation reactions of α-diazoamide 4a[a]



4a **5a** **6a**

entry	catalyst (mol%)	**5a**/***cis*-6a**/***trans*-6a**[b,c]	products (%)[d]
1	$Pd_2(dba)_3$ (10)	26/46/28	**5a** (20) ***cis*-6a** (9) ***trans*-6a** (42)
2	$[(IMes)Pd(NQ)]_2$ (2.5)	35/40/25	**5a** (28) ***cis*-6a** (35) ***trans*-6a** (23)
3	$[Pd(allyl)Cl]_2$ (5)	0/47/53	***cis*-6a** (25) ***trans*-6a** (65)
4	(SIPr)Pd(allyl)Cl (15)	0/29/71	***cis*-6a** (17) ***trans*-6a** (59)

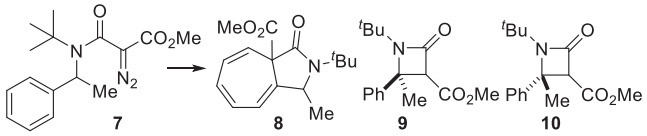
[a] Reaction conditions: Catalyst in DCE at reflux for 24 h. [b] ^{1}H NMR ratio. [c] All reactions were performed twice. While the **5a**/**6a** ratio was essentially the same in the two runs, the *cis*/*trans* ratio was quite different

due to the partial isomerization of *cis* β-lactam to the more stable *trans* isomer during the work-up. [d] Isolated yields.

When α-diazoamide **4a** was decomposed in the presence of $Pd_2(dba)_3$ (entry 1), cycloheptapyrrolone **5a** (20%) was isolated together with β-lactams ***cis*-6a** (9%) and ***trans*-6a** (42%).[16] On changing the catalyst to $[(IMes)Pd(NQ)]_2$, a slight increase in the formation of the Buchner product was observed (entry 2). To our delight, the more electrophilic $[Pd(allyl)Cl]_2$ or (SIPr)Pd(allyl)Cl catalysts exclusively promoted the Csp^3–H insertion to give the β-lactams, which were isolated in good overall yields (entries 3-4).

The palladium-catalyzed carbene insertion was also explored from α-diazoamide **7**, which bears the α-methylbenzyl substituent at the nitrogen (Table 3).

Table 3. Pd-catalyzed cyclisation reactions of α-diazoamide 7[a]



entry	catalyst (mol%)	8/9/10[b]	products (%)[c]
1	$Pd_2(dba)_3$ (10)	26/37/37	**8**[d] (15), **9** (18), **10** (24)
2	$[(IMes)Pd(NQ)]_2$ (2.5)	65/20/15	**8**[e] (42), **9** (7), **10** (13)
3	$[Pd(allyl)Cl]_2$ (5)	0/36/64	**9** (23), **10** (47)
4	(SIPr)Pd(allyl)Cl (15)	0/57/43	**9** (24), **10** (18)

[a] Reaction conditions: Catalyst in DCE at reflux for 24 h. [b] ^1H NMR ratio. [c] Isolated yields. [d] 1:1.2 mixture of stereoisomers. [e] 1:2.2 mixture of stereoisomers.

Similarly to the reactions of *N*-benzylamide **4a**, when Pd(0)-catalysts were used to promote the decomposition of **7** a significant amount of the Buchner product **8** was

obtained (entries 1 and 2). Interestingly, when the reaction was catalyzed by $Pd_2(dba)_3$, both **4a** and **7** gave a ca. 1:3 Buchner/β-lactam ratio. On the contrary, when the reaction of **7** was promoted by the sterically encumbered $[(IMes)Pd(NQ)]_2$ catalyst, cycloheptapyrrolone **8** was obtained as the major product, suggesting that the Pd(0)-catalyzed reaction is highly sensitive to the steric hindrance on the reactive Csp^3–H bond. At variance, similar to the reactions of **4a**, the use of Pd(II)-catalysts with **7** resulted in the chemoselective insertion into the Csp^3–H bond (entries 3 and 4), $[Pd(allyl)Cl]_2$ once again affording the best result.

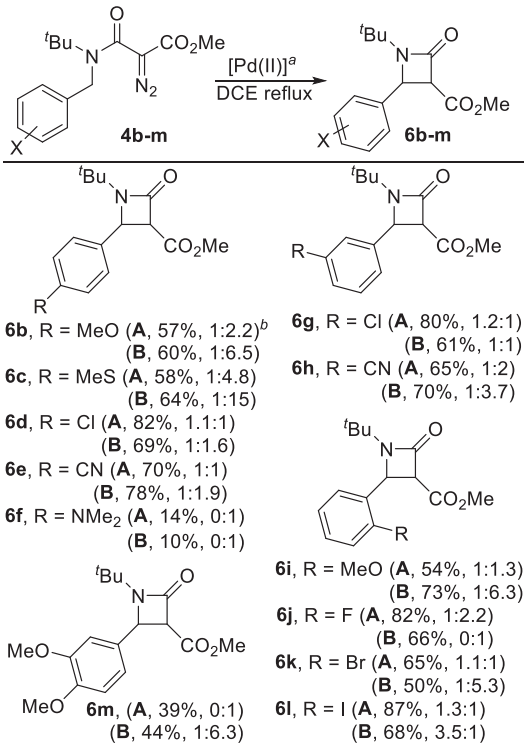
The studies with α-diazoacetamides **4a** and **7** gave us two experimental procedures for the insertion reaction based on the use of either $[Pd(allyl)Cl]_2$ (Method A) or (SIPr)Pd(allyl)Cl (Method B) as the catalyst. To explore how the introduction of substituents at the benzylic group might influence the insertion process leading to β-lactams, these catalytic systems were studied with α-diazoacetamides **4b-m** (Scheme 2, see Table S1 in the SI for additional details).

The effect of the substituent varied according to its electronic nature as well as its position on the aromatic ring. The introduction of electron-releasing groups at the benzyl substituent led to an increased formation of the cycloheptapyrrolone product, especially when using (SIPr)Pd(allyl)Cl as the catalyst. The increase was lower when the substituent was located at the *ortho*-position, probably due to steric interactions. In contrast, electron-withdrawing groups generally diverted the palladacarbene away from the Buchner reaction in favor of the Csp^3–H insertion. Similar electronic effects have been observed in related Rh(II)-catalyzed transformations.[11a]

The examples in Tables 2-3 and Scheme 2 confirm the generality and functional group tolerance of this novel Pd(II)-catalyzed insertion. The resulting β-lactams were

obtained in moderate to good overall yields (44-90%), usually as mixtures of *cis* and *trans* isomers, in transformations proceeding with high site-selectivity. As an exception, the Pd(II)-catalyzed decomposition of **4f** gave ***trans*-6f** in poor yield together with major amounts of 4-(dimethylamino)benzaldehyde.

Scheme 2. Synthesis of β-lactams by Pd(II)-catalyzed cyclisation of α-diazoamides



[a] Method **A**: $[Pd(allyl)Cl]_2$ or Method **B**: (SIPr)Pd(allyl)Cl. [b] (Method, Isolated yield (%), *cis*/*trans* ratio after chromatography).

The above results also confirm the significant impact of the electronic nature of the palladium catalyst and ensuing electrophilicity of the carbene intermediate in the reaction pathway. Thus, whereas benzylic Csp^3–H insertion is strongly favored over the Buchner reaction when using Pd(II)-catalysts, an increased cycloheptapyrrolone product formation is usually observed with the more electron-rich Pd(0)-catalysts.

Our previous work has shown that the mechanism involved in palladium-catalyzed insertion reactions[7,8] differs considerably from that accepted for Rh(II)-catalyzed transformations. Whereas Rh(II)-catalysts typically proceed in a concerted process that directly releases the insertion product and metal catalyst in a single step,[17] palladium catalysts involve stepwise reaction mechanisms initiated by a metal-mediated hydrogen migration. To shed light on the reaction mechanism and the influence of the Pd(II)-catalyst on the selectivity of the C–H insertion described herein, density functional theory (DFT) calculations were carried out.[18] To this end, the process involving **4a** in the presence of the $[Pd(allyl)Cl]_2$ catalyst (see Table 2, entry 3) was explored.

The data in Figure 1, which gathers the computed reaction profile starting from the initial Pd(II)-carbene intermediate **INT0**, indicate that the formation of the corresponding β-lactams **6a** occurs stepwise. Thus, **INT0** is first transformed into the zwitterionic intermediate **INT1**[19] in a highly exergonic process via the transition state **TS1**. This step can be viewed as a 1,4-hydrogen migration that is not directly assisted by the metal, therefore resembling the mechanism involved in related Ru(II)-C–H activation processes previously studied by us.[7b] The transformation ends with the formation of the new C–C bond via the transition state **TS2**, again in a strongly exergonic transformation that releases the β-lactam with concomitant regeneration of the active Pd(II)-catalyst. According to the rather similar relative energies computed for the *cis*/*trans* transition states **TS1** and **TS2**, a ca. 50:50 mixture of ***cis*-6a** and ***trans*-6a** can be expected, which is fully consistent with the experimental findings (Table 2, entry 3).

Finally, we also investigated the reasons for the non-formation of cycloheptapyrrolone **5a** when using these reaction conditions (i.e. **4a** in the presence of $[Pd(allyl)Cl]_2$). Our calculations suggest that the first step of the alternative Buchner reaction, which involves a palladium-promoted C–C bond formation, is not competitive in view of the much higher activation barrier required to reach the corresponding transition state **TS1'** as compared to **TS1-trans** ($\Delta\Delta G^{\neq}$= 8.5 kcal/mol) as well as the endergonicity ($\Delta\Delta G$ = +6.0 kcal/mol) associated with this step. Therefore, no Buchner reaction product should be expected, which agrees nicely with the complete selectivity observed experimentally (Table 2, entry 3).

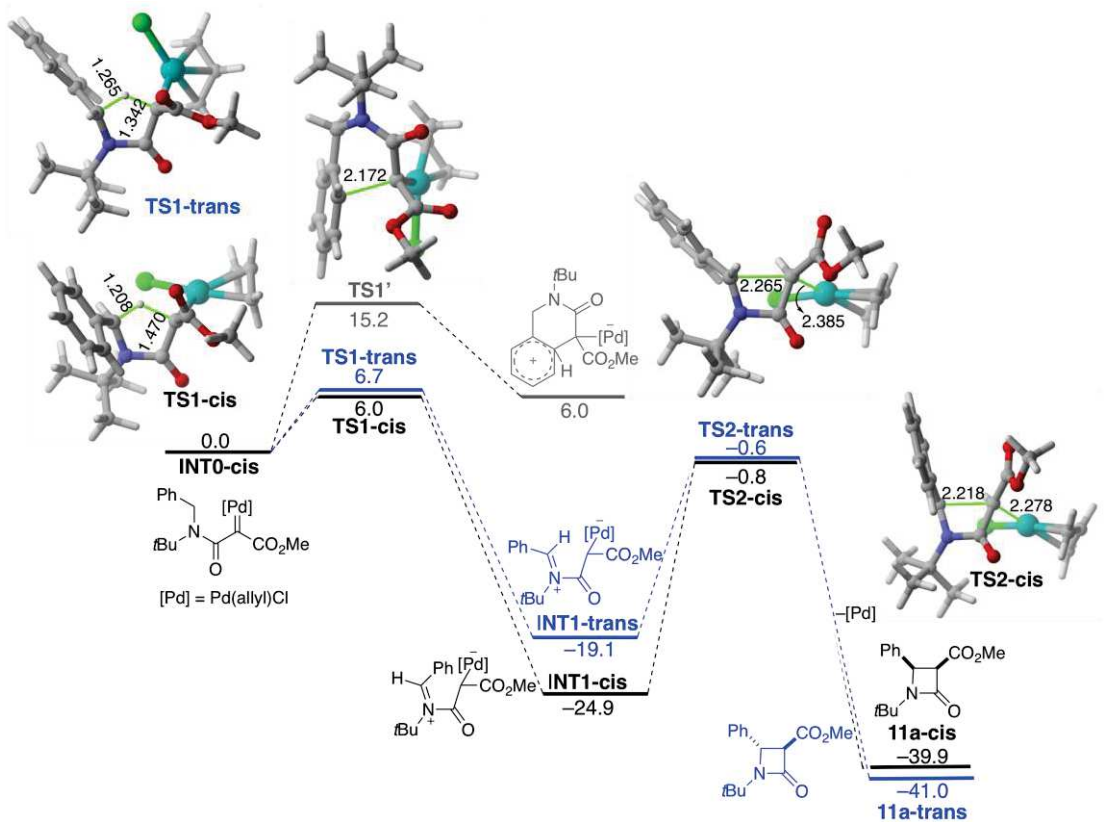


Figure 1. Computed reaction profiles for the formation of β-lactams 6a. Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and angstroms (Å), respectively.

In summary, we have shown that palladium can be used to promote the carbene Csp^3–H insertion of α-diazoacetamides to form β-lactams, Pd(II)-catalysts giving the best chemoselectivities. DFT calculations suggest that this transformation involves an unprecedented Pd(II)-promoted Mannich-type reaction through a metallacarbene-induced zwitterionic intermediate.

Experimental Section

General Methods. All commercially available reagents were used without further purification. ^{1}H- and ^{13}C NMR spectra were recorded using Me_4Si as the internal standard, with a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si for ^{1}H and ^{13}C NMR. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light or 1% aqueous $KMnO_4$. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator.

Representative Procedure for the Preparation of Diazoacetamides 1, 4a-m and 7. To a solution of dibenzylamine (0.6 mL, 3.04 mmol) and Et_3N (0.86 mL, 6.1 mmol) in CH_2Cl_2 (18 mL), cooled at 0 °C, was added slowly methyl malonyl chloride (0.67 mL, 6.1 mmol). The mixture was stirred at room temperature for 24 h. After the reaction was completed, the mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$ aqueous solution, dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from hexanes to hexanes/EtOAc 3:2) to give *N*,*N*-dibenzyl-α-(methoxycarbonyl)acetamide (0.88 g, 97%).

To a solution of *N*,*N*-dibenzyl-α-(methoxycarbonyl)acetamide (678 mg, 2.28 mmols) and DBU (0.52 mL, 3.43 mmols) in dry acetonitrile (16 mL) was added dropwise a solution of *p*-ABSA (602 mg, 2.5 mmols) in dry acetonitrile (6 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 and 10% NaOH aqueous solution. The organic extracts were dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give *N*,*N*-dibenzyl-α-(methoxycarbonyl)-α-diazoacetamide (**1**, 554 mg; 75%).

***N*,*N*-Dibenzyl-α-(methoxycarbonyl)-α-diazoacetamide (1).** Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 4.51 (s, 4H), 7.15-7.19 (m, 4H), 7.25-7.36 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 50.5 (broad signal, 2 CH_2), 52.5 (CH_3), 67.0 (C), 127.8 (CH), 127.9 (2 CH), 128.8 (2 CH), 136.4 (C), 162.4 (C), 163.0 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}N_3O_3$: 324.1343 $[M+H]^+$; found: 324.1347.

***N*-Benzyl-*N*-*tert*-butyl-α-(methoxycarbonyl)-α-diazoacetamide (4a). 4a** was obtained as a yellow oil that solidified on refrigeration (433 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1 equiv.), Et_3N (1 equiv.); (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 75% two steps]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 9H), 3.77 (s, 3H), 4.62 (s, 2H), 7.18-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.7 (CH_2), 52.3 (CH_3), 59.1 (C), 68.2 (C), 126.9 (2 CH), 127.5 (CH), 128.8 (2 CH), 139.7 (C), 163.1 (C), 163.2 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}N_3\ NaO_3$: 312.1319 $[M+H]^+$; found: 312.1327.

***N*-*tert*-Butyl-*N*-(4-methoxybenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4b). 4b** was obtained as a yellow oil that solidified on refrigeration (600 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.2 equiv.), Et_3N (1.2 equiv.),

61%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 98%]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 9H), 3.76 (s, 3H), 3.78 (s, 3H), 4.54 (s, 2H), 6.84 (d, *J* = 8.4 Hz, 2H) 7.09 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.2 (CH_2), 52.3 (CH_3), 55.4 (CH_3), 59.0 (C), 68.2 (C), 114.1 (2 CH), 128.1 (2 CH), 131.5 (C), 159.0 (C), 163.1 (C), 163.2 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{21}N_3$ NaO_4: 342.1424 $[M+H]^+$; found: 342.1423.

***N*-*tert*-Butyl-*N*-[4-(methylthio)benzyl]-α-(methoxycarbonyl)-α-diazoacetamide (4c). 4c** was obtained as a yellow oil that solidified on refrigeration (555 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.2 equiv.), Et_3N (1.2 equiv.), 68%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 94%]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (s, 9H), 2.47 (s, 3H), 3.76 (s, 3H), 4.56 (s, 2H), 7.10 (d, *J* = 8.0 Hz, 2H) 7.20 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.0 (CH_3), 28.9 (3 CH_3), 51.3 (CH_2), 52.3 (CH_3), 59.1 (C), 68.2 (C), 126.9 (2 CH), 127.4 (2 CH), 136.5 (C), 137.6 (C), 163.0 (C), 163.2 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}N_3O_3S$: 336.1376 $[M+H]^+$; found: 336.1378.

***N*-*tert*-Butyl-*N*-[4-chlorobenzyl]-α-(methoxycarbonyl)-α-diazoacetamide (4d). 4d** was obtained as a yellow oil that solidified on refrigeration (514 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 54%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 83%]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 3.77 (s, 3H), 4.58 (s, 2H), 7.14 (d, *J* = 8.4 Hz, 2H) 7.30 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.1 (CH_2), 52.4 (CH_3), 59.2 (C), 68.4 (C), 128.3 (2 CH), 129.0 (2 CH), 133.2 (C), 138.3 (C), 163.0 (C), 163.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}ClN_3NaO_3$: 346.0929 $[M+H]^+$; found: 346.0937.

***N-tert*-Butyl-*N*-(4-cyanobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4e). 4e** was obtained as a red oil that solidified on refrigeration (155 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 52%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 33%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 3.77 (s, 3H), 4.67 (s, 2H), 7.33 (d, *J* = 8.0 Hz, 2H) 7.63 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 51.2 (CH_2), 52.4 (CH_3), 59.5 (C), 68.8 (C), 111.5 (C), 118.7 (C), 127.6 (2 CH), 132.6 (2 CH), 145.7 (C), 162.8 (C), 163.6 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{18}N_4NaO_3$: 337.1271 $[M+H]^+$; found: 337.1279.

***N-tert*-Butyl-*N*-[4-(dimethylamino)benzyl]-α-(methoxycarbonyl)-α-diazoacetamide (4f). 4f** was obtained as a yellow oil that solidified on refrigeration (190 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 58%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 85%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 2.93 (s, 6H), 3.77 (s, 3H), 4.52 (s, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 40.8 (2 CH_3), 51.3 (CH_2), 52.3 (CH_3), 58.9 (C), 68.0 (C), 112.7 (2 CH), 126.9 (C), 127.9 (2 CH), 150.0 (C), 163.0 (C), 163.3 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{25}N_4O_3$: 333.1921 $[M+H]^+$; found: 333.1925.

***N-tert*-Butyl-*N*-(3-chlorobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4g). 4g** was obtained as a yellow oil that solidified on refrigeration (505 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.2 equiv.), Et_3N (1.2 equiv.), 82%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 85%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 9H), 3.77 (s, 3H), 4.59 (s, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.18 (broad s, 1H), 7.22-7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 51.2 (CH_2), 52.4 (CH_3), 59.3 (C), 68.4 (C), 125.0 (CH), 127.1 (CH), 127.7 (CH), 130.1 (CH), 134.8 (C),

142.0 (C), 163.0 (C), 163.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}ClN_3NaO_3$: 346.0929 $[M+H]^+$; found: 346.0933.

***N-tert*-Butyl-*N*-(3-cyanobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4h). 4h** was obtained as a yellow oil that solidified on refrigeration (330 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.); (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 63% two steps]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 3.78 (s, 3H), 4.65 (s, 2H), 7.45-7.51 (m, 3H), 7.55-7.59 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 51.0 (CH_2), 52.4 (CH_3), 59.4 (C), 68.8 (C), 113.0 (C), 118.6 (C), 129.7 (CH), 130.4 (CH), 131.3 (CH), 131.4 (CH), 141.7 (C), 162.8 (C), 163.6 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{18}N_4NaO_3$: 337.1271 $[M+H]^+$; found: 337.1278.

***N-tert*-Butyl-*N*-(2-methoxybenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4i). 4i** was obtained as a yellow oil that solidified on refrigeration (384 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1 equiv.), Et_3N (1 equiv.); (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 70% two steps]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 9H), 3.77 (s, 3H), 3.80 (s, 3H), 4.60 (s, 2H), 6.85 (dd, J = 8.0, and 1.2 Hz, 1H), 6.92 (td, J = 7.6 and 1.2 Hz, 1H), 7.18 (dd, J = 7.6 and 1.2 Hz, 1H), 7.25 (ddd, J = 8.0, 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.6 (3 CH_3), 48.5 (CH_2), 52.2 (CH_3), 55.6 (CH_3), 58.6 (C), 68.0 (C), 110.7 (CH), 120.5 (CH), 127.1 (C), 128.8 (CH), 129.3 (CH), 157.9 (C), 163.5 (C), 163.7 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}N_3O_4$: 320.1605 $[M+H]^+$; found: 320.1601.

***N-tert*-Butyl-*N*-(2-fluorobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4j). 4j** was obtained as a yellow oil that solidified on refrigeration (563 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1 equiv.), Et_3N (1 equiv.), 84%;

(b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 56%]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (s, 9H), 3.78 (s, 3H), 4.67 (s, 2H), 7.00-7.14 (m, 2H) 7.22-7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.8 (3 CH_3), 46.2 (d, *J* = 3.4 Hz, CH_2), 52.3 (CH_3), 58.9 (C), 68.2 (C), 116.0 (d, *J* = 21.7 Hz, CH), 124.3 (d, *J* = 3.7 Hz, CH), 126.4 (d, *J* = 13.4 Hz, C), 129.3 (d, *J* = 8.2 Hz, CH), 129.5 (d, *J* = 4.3 Hz, CH), 160.8 (d, *J* = 246.5 Hz, C), 163.1 (C), 163.6 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}FN_3NaO_3$: 330.1224 $[M+H]^+$; found: 330.1225.

***N*-(2-Bromobenzyl)-*N*-*tert*-butyl-α-(methoxycarbonyl)-α-diazoacetamide (4k). 4k** was obtained as a yellow oil that solidified on refrigeration (417 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1 equiv.), Et_3N (1 equiv.); (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 83% two steps]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.76 (s, 3H), 4.72 (s, 2H), 7.13 (ddd, *J* = 8.0, 7.6 and 2.4 Hz, 1H), 7.26-7.34 (m, 2H), 7.54 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.6 (CH_2), 52.4 (CH_3), 59.4 (C), 67.6 (C), 122.1 (C), 127.5 (CH), 128.6 (CH), 128.9 (CH), 133.4 (CH), 138.5 (C), 163.2 (C), 163.6 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}BrN_3NaO_3$: 390.0424 $[M+H]^+$; found: 390.0432.

***N*-*tert*-Butyl-*N*-(2-iodobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4l). 4l** was obtained as a yellow oil that solidified on refrigeration (260 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 64%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 89%]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.76 (s, 3H), 4.63 (s, 2H), 6.97 (ddd, *J* = 8.0, 7.6 and 1.6 Hz, 1H), 7.24 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.35 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.83 (dd, *J* = 8.0 and 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 52.4 (CH_3), 56.7 (CH_2), 59.6 (C), 67.6 (C), 97.1 (C), 127.9 (CH), 128.4 (CH), 129.1 (CH), 140.0 (CH), 141.2 (C), 163.2

(C), 163.5 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}IN_3NaO_3$: 438.0258 $[M+H]^+$; found: 438.0283.

***N-tert*-Butyl-*N*-(3,4-dimethoxybenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4m). 4m** was obtained as a yellow oil that solidified on refrigeration (570 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.2 equiv.), Et_3N (1.2 equiv.), 68%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 80%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 3.78 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.56 (s, 2H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.74 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.3 (CH_2), 52.3 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 59.1 (C), 67.9 (C), 110.0 (CH), 111.4 (CH), 119.0 (CH), 132.1 (C), 148.4 (C), 149.2 (C), 163.2 (2 C). HRMS (ESI-TOF) calcd. for $C_{17}H_{24}N_3O_5$: 350.1710 $[M+H]^+$; found: 350.1713.

***N-tert*-Butyl-*N*-(1-phenylethyl)-α-(methoxycarbonyl)-α-diazoacetamide (7). 7** was obtained as a yellow oil (210 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 35%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 63%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 1.80 (d, *J* = 7.2 Hz, 3H), 3.70 (s, 3H), 5.19 (q, *J* = 7.2 Hz, 1H), 7.22-7.28 (m, 1H), 7.32-7.37 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.2 (CH_3), 29.5 (3 CH_3), 52.3 (CH_3), 56.3 (CH), 60.1 (C), 66.8 (C), 126.9 (2 CH), 127.2 (CH), 128.6 (2 CH), 142.3 (C), 163.2 (C), 164.2 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{21}N_3NaO_3$: 326.1475 $[M+H]^+$; found: 326.1471.

Representative Procedure for the Pd-Catalyzed Cyclisation Reactions (Table 2, Entry 3). A mixture of diazoamide **4a** (50 mg, 0.17 mmol), $[Pd(allyl)Cl]_2$ (3 mg, 0.008 mmol) in dichloroethane (10 mL) was stirred at reflux under Argon atmosphere for 24 h. The solvent was removed in vacuo, and the residue was purified

by chromatography (SiO_2, from hexanes to hexanes-EtOAc 2:3) to give β-lactam ***trans*-6a** (29.5 mg, 65%) and β-lactam ***cis*-6a** (11 mg, 25%).

Methyl 2-benzyl-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (2). 25 mg (55%, Table 1, Entry 5). Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.61 (s, 3H), 4.01 (dd, *J* = 14.8 and 1.6 Hz, 1H), 4.27 (dd, *J* = 14.8 and 2.4 Hz, 1H), 4.53 (d, *J* = 14.8 Hz, 1H), 4.69 (d, *J* = 14.8 Hz, 1H), 5.65 (d, *J* = 9.6 Hz, 1H), 6.24 (m, 1H), 6.42-6.54 (m, 3H), 7.23-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 47.0 (CH_2), 50.3 (CH_2), 53.0 (CH_3), 60.0 (C), 120.9 (CH), 122.4 (CH), 128.0 (CH), 128.1 (2 CH), 128.3 (CH), 128.7 (CH), 129.0 (2 CH), 130.0 (CH), 130.4 (C), 135.6 (C), 168.6 (C), 171.1 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}NO_3$: 296.1281 $[M+H]^+$; found: 296.1281.

Methyl *cis*-1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate (*cis*-3). This compound could not be isolated and characterized. ^{1}H NMR ($CDCl_3$, 400 MHz, significant signals from the crude reaction mixture) δ 3.33 (s, 3H), 3.93 (d, *J* = 14.8 Hz, 1H), 4.34 (d, *J* = 6.0 Hz, 1H), 4.71 (dd, *J* = 6.0 and 1.2 Hz, 1H), 4.94 (d, *J* = 14.8 Hz, 1H).

Methyl *trans*-1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate (*trans*-3). 10.5 mg (23%, Table 1, Entry 7). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 3.84 (d, *J* = 15.2 Hz, 1H), 3.93 (dd, *J* = 2.0 and 0.8 Hz, 1H), 4.71 (d, *J* = 2.0 Hz, 1H), 4.85 (d, *J* = 15.2 Hz, 1H), 7.14-7.17 (m, 2H), 7.23-7.40 (m, 8H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 45.1 (CH_2), 52.9 (CH_3), 57.2 (CH), 63.4 (CH), 126.9 (2 CH), 128.0 (CH), 128.5 (2 CH), 129.0 (2 CH), 129.2 (CH), 129.3 (2 CH), 134.8 (C), 136.0 (C), 162.4 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}NO_3$: 296.1281 $[M+H]^+$; found: 296.1275.

***N*,*N*-Dibenzyl-α-chloro-α-(methoxycarbonyl)acetamide.** Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 3H), 4.34 (d, *J* = 14.8 Hz, 1H), 4.45 (d, *J* = 17.2 Hz, 1H), 4.62 (d, *J* = 17.2 Hz, 1H), 4.88 (d, *J* = 14.8 Hz, 1H), 5.13 (s, 1H), 7.18-7.23 (m, 4H), 7.28-7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 48.9 (CH_2), 50.6 (CH_2), 54.0 (CH), 54.5 (CH_3), 126.7 (2 CH), 128.0 (CH), 128.3 (CH), 128.4 (2 CH), 129.0 (2 CH), 129.3 (2 CH), 132.3 (C), 136.2 (C), 165.5 (C), 165.6 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{19}ClNO_3$: 332.1048 $[M+H]^+$; found: 332.1049.

Methyl 2-*tert*-butyl-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5a). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 8:1 mixture of **5a** and ***trans*-6a**) δ 1.46 (s, 9H), 3.59 (s, 3H), 4.24 (dd, *J* = 15.2 and 1.6 Hz, 1H), 4.47 (dd, *J* = 15.2 and 2.0 Hz, 1H), 5.59 (dd, *J* = 9.2 and 0.8 Hz, 1H), 6.28 (m, 1H), 6.38-6.46 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 8:1 mixture of **5a** and ***trans*-6a**) δ 27.6 (3 CH_3), 49.6 (CH_2), 52.8 (CH_3), 55.0 (C), 61.3 (C), 120.5 (CH), 123.2 (CH), 127.8 (CH), 128.9 (CH), 129.9 (CH), 131.3 (C), 169.0 (C), 170.8 (C).

Methyl *cis*-1-*tert*-butyl-2-oxo-4-phenylazetidine-3-carboxylate (*cis*-6a). 11 mg (25%, Table 2, Entry 3). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.32 (s, 3H), 4.23 (d, *J* = 6.4 Hz, 1H), 4.91 (d, *J* = 6.4 Hz, 1H), 7.28-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.0 (CH_3), 55.2 (C), 56.8 (CH), 59.3 (CH), 127.2 (CH), 128.6 (2 CH), 128.9 (2 CH), 136.7 (C), 163.0 (C), 166.6 (C).). HRMS (ESI-TOF) calcd. for $C_{15}H_{20}NO_3$: 262.1438 $[M+H]^+$; found: 262.1439.

Methyl *trans*-1-*tert*-butyl-2-oxo-4-phenylazetidine-3-carboxylate (*trans*-6a). 29 mg (65%, Table 2, Entry 3). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 3.72 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 4.86 (d, *J* = 2.0 Hz, 1H), 7.31-7.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.8 (CH_3), 55.4 (C), 56.6

(CH), 62.5 (CH), 126.8 (2 CH), 128.9 (CH), 129.2 (2 CH), 139.2 (C), 162.1 (C), 167.7 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{20}NO_3$: 262.1438 $[M+H]^+$; found: 262.1439.

Methyl 2-*tert*-butyl-6-methoxy-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5b). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 10:1 mixture of **5b** and ***trans*-6b**) δ 1.45 (s, 9H), 3.60 (s, 3H), 3.61 (s, 3H), 4.18 (ddd, *J* = 14.4, 2.0 and 0.8 Hz, 1H), 4.42 (ddd, *J* = 14.4, 2.4 and 1.2 Hz, 1H), 5.63 (dd, *J* = 7.2 and 1.6 Hz, 1H), 5.73 (d, *J* = 10.8 Hz, 1H), 6.15 (dt, *J* = 7.2 and 2.0 Hz, 1H), 6.26 (dd, *J* = 10.8 and 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 10:1 mixture of **5b** and ***trans*-6b**) δ 27.6 (3 CH_3), 49.5 (CH_2), 52.9 (CH_3), 54.9 (C), 55.0 (CH_3), 60.8 (C), 101.8 (CH), 118.8 (CH), 124.9 (CH), 125.1 (C), 126.2 (CH), 159.0 (C), 169.3 (C), 170.7 (C).

Methyl *cis*-1-*tert*-butyl-4-(4-methoxyphenyl)-2-oxoazetidine-3-carboxylate (*cis*-6b). 8 mg (18%, Table S1, Entry 1). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 3.38 (s, 3H), 3.80 (s, 3H), 4.20 (d, *J* = 6.4 Hz, 1H), 4.87 (d, *J* = 6.4 Hz, 1H), 6.86 (d, *J*= 8.4 Hz, 2H), 7.29 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.0 (CH_3), 55.1 (C), 55.4 (CH_3), 56.4 (CH), 59.3 (CH), 113.9 (2 CH), 128.4 (2 CH), 128.5 (C), 160.0 (C), 163.1 (C), 166.8 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_4$: 292.1543 $[M+H]^+$; found: 292.1549.

Methyl *trans*-1-*tert*-butyl-4-(4-methoxyphenyl)-2-oxoazetidine-3-carboxylate (*trans*-6b). 18 mg (39%, Table S1, Entry 1). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 3.69 (d, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 4.81 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J*= 8.4 Hz, 2H), 7.30 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.8 (CH_3), 55.3 (C), 55.5 (CH_3), 56.3 (CH), 62.5 (CH), 114.5 (2 CH), 128.1 (2 CH), 131.0 (C), 160.1 (C), 162.2 (C), 167.9 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_4$: 292.1543 $[M+H]^+$; found: 292.1547.

Methyl 2-*tert*-butyl-6-(methylthio)-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5c). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 3.3:1 mixture of ***trans*-6c** and **5c**) δ 1.45 (s, 9H), 2.32 (s, 3H), 3.61 (s, 3H), 4.21 (d, *J* = 14.8 Hz, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 5.64 (d, *J* = 10.4 Hz, 1H), 6.14 (d, *J* = 6.8 Hz, 1H), 6.38 (d, *J* = 10.8 Hz, 1H), 6.39 (d, *J* = 6.8 Hz, 1H).

Methyl *cis*-1-*tert*-butyl-4-[4-(methylthio)phenyl]-2-oxoazetidine-3-carboxylate (*cis*-6c). 4.5 mg (10%, Table S1, Entry 3). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 2.48 (s, 3H), 3.37 (s, 3H), 4.22 (d, *J* = 6.4 Hz, 1H), 4.87 (d, *J* = 6.4 Hz, 1H), 7.20 (d, *J*= 8.4 Hz, 2H), 7.29 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.6 (CH_3), 28.3 (3 CH_3), 52.1 (CH_3), 55.2 (C), 56.4 (CH), 59.2 (CH), 126.1 (2 CH), 127.7 (2 CH), 133.2 (C), 139.6 (C), 163.0 (C), 166.6 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_3S$: 308.1315 $[M+H]^+$; found: 308.1319.

Methyl *trans*-1-*tert*-butyl-4-[4-(methylthio)phenyl]-2-oxoazetidine-3-carboxylate (*trans*-6c). 22 mg (48%, Table S1, Entry 3). Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 2.49 (s, 3H), 3.68 (d, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 4.82 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J*= 8.0 Hz, 2H), 7.30 (d, *J*= 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.7 (CH_3), 28.3 (3 CH_3), 52.8 (CH_3), 55.4 (C), 56.3 (CH), 62.4 (CH), 126.8 (2 CH), 127.3 (2 CH), 135.8 (C), 139.7 (C), 162.1 (C), 167.7 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_3S$: 308.1315 $[M+H]^+$; found: 308.1318.

Methyl *cis*-1-*tert*-butyl-4-(4-chlorophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6d). 19 mg (42%, Table S1, Entry 5). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 3.38 (s, 3H), 4.23 (d, *J* = 6.4 Hz, 1H), 4.89 (d, *J* = 6.4 Hz, 1H), 7.33 (s, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.2 (CH_3), 55.3 (C), 56.1 (CH), 59.2 (CH), 128.6 (2 CH), 128.8 (2 CH), 134.8 (C), 135.4 (C), 162.8 (C),

166.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1050.

Methyl *trans*-1-*tert*-butyl-4-(4-chlorophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6d). 18 mg (40%, Table S1, Entry 5). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 3.67 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 4.84 (d, *J* = 2.0 Hz, 1H), 7.32-7-38 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.9 (CH_3), 55.5 (C), 55.9 (CH), 62.5 (CH), 128.1 (2 CH), 129.4 (2 CH), 134.8 (C), 137.9 (C), 162.0 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1051.

Methyl *cis*-1-*tert*-butyl-4-(4-cyanophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6e). 12 mg (27%, Table S1, Entry 8). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 3.34 (s, 3H), 4.28 (d, *J* = 6.4 Hz, 1H), 4.94 (d, *J* = 6.4 Hz, 1H), 7.52 (d, *J*= 8.4 Hz, 2H), 7.65 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.2 (CH_3), 55.5 (C), 56.0 (CH), 59.2 (CH), 112.9 (C), 118.4 (C), 128.0 (2 CH), 132.4 (2 CH), 142.5 (C), 162.5 (C), 166.0 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}N_2O_3$: 287.1390 $[M+H]^+$; found: 287.1389.

Methyl *trans*-1-*tert*-butyl-4-(4-cyanophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6e). 23 mg (51%, Table S1, Entry 8). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 3.67 (d, *J* = 2.4 Hz, 1H), 3.79 (s, 3H), 4.92 (d, *J* = 2.4 Hz, 1H), 7.53 (d, *J*= 8.4 Hz, 2H), 7.69 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 53.1 (CH_3), 55.7 (C), 55.8 (CH), 62.5 (CH), 113.0 (C), 118.3 (C), 127.5 (2 CH), 133.1 (2 CH), 144.9 (C), 161.7 (C), 167.0 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}N_2O_3$: 287.1390 $[M+H]^+$; found: 287.1393.

Methyl *trans*-1-*tert*-butyl-4-[4-(dimethylamino)phenyl]-2-oxoazetidine-3-carboxylate (*trans*-6f). 6 mg (14%, Table S1, Entry 9). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 2.96 (s, 6H), 3.70 (d, *J* = 2.0 Hz, 1H), 3.76 (s, 3H), 4.77 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J*= 8.8 Hz, 2H), 7.23 (d, *J*= 8.8 Hz, 2H). HRMS (ESI-TOF) calcd. for $C_{17}H_{25}N_2O_3$: 305.1860 $[M+H]^+$; found: 305.1860.

Methyl *cis*-1-*tert*-butyl-4-(3-chlorophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6g). 20 mg (44%, Table S1, Entry 11). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.40 (s, 3H), 4.24 (d, *J* = 6.4 Hz, 1H), 4.87 (d, *J* = 6.4 Hz, 1H), 7.26-7.32 (m, 3H), 7.39 (d, *J*= 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.1 (CH_3), 55.4 (C), 56.1 (CH), 59.3 (CH), 125.4 (broad CH), 127.4 (broad CH), 129.1 (CH), 129.9 (CH), 134.6 (C), 139.0 (C), 162.8 (C), 166.3 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1057.

Methyl *trans*-1-*tert*-butyl-4-(3-chlorophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6g). 16.5 mg (36%, Table S1, Entry 11). Brown gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 3.68 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 4.83 (d, *J* = 2.0 Hz, 1H), 7.27-7.34 (m, 3H), 7.39 (broad singlet, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.9 (CH_3), 55.6 (C), 55.9 (CH), 62.5 (CH), 124.8 (CH), 127.0 (CH), 129.2 (CH), 130.5 (CH), 135.2 (C), 141.5 (C), 161.9 (C), 167.3 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1050.

Methyl *cis*-1-*tert*-butyl-4-(3-cyanophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6h). 10 mg (22%, Table S1, Entry 13). Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.38 (s, 3H), 4.28 (d, *J* = 6.4 Hz, 1H), 4.93 (d, *J* = 6.4 Hz, 1H), 7.50 (dd, *J*= 8.4 and 7.6 Hz, 1H), 7.64 (dt, *J*= 7.6 and 1.6 Hz, 1H), 7.65-7.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.3 (CH_3), 55.5 (C), 55.7 (CH), 59.3 (CH), 112.9

(C), 118.4 (C), 129.5 (CH), 130.9 (broad, CH), 131.5 (broad, CH), 132.6 (CH), 138.8 (C), 162.5 (C), 166.1 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}N_2O_3$: 287.1390 $[M+H]^+$; found: 287.1399.

Methyl *trans*-1-*tert*-butyl-4-(3-cyanophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6h). 19.5 mg (43%, Table S1, Entry 13). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 3.68 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 4.91 (d, *J* = 2.4 Hz, 1H), 7.54 (td, *J*= 7.6 and 0.4 Hz, 1H), 7.64-7.71 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 53.0 (CH_3), 55.5 (CH), 55.7 (C), 62.5 (CH), 113.5 (C), 118.3 (C), 130.2 (CH), 130.4 (CH), 130.8 (CH), 132.6 (CH), 141.2 (C), 161.7 (C), 167.0 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}N_2O_3$: 287.1390 $[M+H]^+$; found: 287.1387.

Methyl *cis*-1-*tert*-butyl-4-(2-methoxyphenyl)-2-oxoazetidine-3-carboxylate (*cis*-6i). 5 mg (10%, Table S1, Entry 16). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 9H), 3.29 (s, 3H), 3.85 (s, 3H), 4.22 (d, *J* = 6.4 Hz, 1H), 5.43 (d, *J* = 6.4 Hz, 1H), 6.85 (d, *J*= 8.0 Hz, 1H), 6.94 (ddd, *J*= 8.0, 7.6 and 0.8 Hz, 1H), 7.26 (dd, *J* = 8.0 and 7.6 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 1:8 mixture of **5i** and ***cis*-6i**) δ 28.1 (3 CH_3), 50.0 (CH), 51.8 (CH_3), 54.9 (C), 55.8 (CH_3), 58.7 (CH), 110.6 (CH), 120.2 (CH), 124.8 (C), 127.5 (CH), 129.6 (CH), 157.3 (C), 163.8 (C), 166.8 (C).

Methyl *trans*-1-*tert*-butyl-4-(2-methoxyphenyl)-2-oxoazetidine-3-carboxylate (*trans*-6i). 29 mg (63%, Table S1, Entry 16). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 3.78 (s, 3H), 3.84 (s, 3H), 3.86 (broad, 1H), 5.17 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J*= 8.0 and 1.2 Hz, 1H), 6.96 (td, *J*= 7.6 and 1.2 Hz, 1H), 7.30 (ddd, *J*= 8.0, 7.6 and 2.0 Hz, 1H), 7.35 (dd, *J*= 7.6 and 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.0 (3 CH_3), 52.2 (broad, CH), 52.7 (CH_3), 55.0 (C), 55.5 (CH_3), 60.4

(CH), 111.0 (CH), 120.9 (CH), 126.5 (C), 128.5 (broad, CH), 129.9 (CH), 157.7 (C), 162.5 (C), 168.4 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_4$: 292.1543 $[M+H]^+$; found: 292.1539.

Methyl *cis*-1-*tert*-butyl-4-(2-fluorophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6j). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 8:1 mixture of ***cis*-6j** and ***trans*-6j**) δ 1.32 (s, 9H), 3.36 (broad s, 3H), 4.28 (d, *J* = 6.4 Hz, 1H), 5.30 (broad, 1H), 7.05 (ddd, *J*= 10.4, 8.0 and 1.2 Hz, 1H), 7.15 (td, *J*= 7.6 and 1.2 Hz, 1H), 7.27-7.33 (m, 1H), 7.49 (ddd, *J*= 8.0, 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 8:1 mixture of ***cis*-6j** and ***trans*-6j**) δ 28.1 (3 CH_3), 52.1 (CH_3), 55.2 (C), 58.5 (broad, CH), 61.1 (broad, CH), 115.7 (d, *J* = 21.5 Hz, CH), 124.0 (d, *J* = 12.0 Hz, CH), 124.0 (d, *J*= 3.6 Hz, CH), 128.0 (broad, C), 130.4 (d, *J* = 8.3 Hz, CH), 163.0 (C), 166.4 (C). One C was not observed.

Methyl *trans*-1-*tert*-butyl-4-(2-fluorophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6j). 30 mg (66%, Table S1, Entry 18). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 3.79 (s, 3H), 3.84 (d, *J* = 2.4 Hz, 1H), 5.16 (d, *J* = 2.4 Hz, 1H), 7.08 (ddd, *J*= 10.4, 8.0 and 1.2 Hz, 1H), 7.18 (td, *J*= 7.6 and 1.2 Hz, 1H), 7.30-7.36 (m, 1H), 7.43 (td, *J*= 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.0 (3 CH_3), 50.3 (d, *J* = 3.8 Hz, CH), 52.9 (CH_3), 55.3 (C), 61.1 (d, *J* = 1.8 Hz, CH), 116.3 (d, *J* = 21.5 Hz, CH), 124.8 (d, *J* = 3.6 Hz, CH), 126.0 (d, *J* = 11.9 Hz, C), 128.5 (d, *J*= 3.6 Hz, CH), 130.6 (d, *J* = 8.4 Hz, CH), 160.9 (d, *J* = 248.7 Hz, C), 161.9 (C), 167.6 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}FNO_3$: 280.1343 $[M+H]^+$; found: 280.1345.

Methyl 2-*tert*-butyl-8-bromo-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5k). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1:2 mixture of **5k** and

***trans*-6k**) δ 1.48 (s, 9H), 3.61 (s, 3H), 4.15 (d, *J* = 16.0 Hz, 1H), 4.28 (d, *J* = 16.0 Hz, 1H), 5.65-5.69 (m, 1H), 6.36-6.43 (m, 2H), 6.50-6.57 (m, 1H).

Methyl *cis*-4-(2-bromophenyl)-1-*tert*-butyl-2-oxoazetidine-3-carboxylate (*cis*-6k). 16 mg (34%, Table S1, Entry 19). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 9H), 3.31 (s, 3H), 4.31 (d, *J* = 6.4 Hz, 1H), 5.39 (d, *J* = 6.4 Hz, 1H), 7.18 (ddd, *J*= 8.0, 7.2 and 1.6 Hz, 1H), 7.33 (ddd, *J*= 7.6, 7.2 and 1.2 Hz, 1H), 7.53-7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.1 (3 CH_3), 52.0 (CH_3), 55.2 (C), 55.5 (CH), 58.4 (CH), 123.4 (C), 127.2 (CH), 128.5 (CH), 130.0 (CH), 133.0 (CH), 135.7 (C), 163.3 (C), 166.2 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}BrNO_3$: 340.0543 $[M+H]^+$; found: 340.0542.

Methyl *trans*-4-(2-bromophenyl)-1-*tert*-butyl-2-oxoazetidine-3-carboxylate (*trans*-6k). 14 mg (31%, Table S1, Entry 19). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.59 (broad, 1H), 3.80 (s, 3H), 5.38 (broad, 1H), 7.19 (ddd, *J*= 8.0, 7.6 and 1.2 Hz, 1H), 7.37 (ddd, *J*= 8.0, 7.6 and 1.2 Hz, 1H), 7.50 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.57 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.1 (3 CH_3), 52.9 (CH_3), 55.2 (broad, CH), 55.4 (C), 62.1 (broad, CH), 127.2 (broad, CH), 128.1 (CH), 128.5 (C), 130.1 (CH), 133.0 (C), 133.4 (broad, CH), 162.5 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}BrNO_3$: 340.0543 $[M+H]^+$; found: 340.0552.

Methyl 2-*tert*-butyl-8-iodo-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5l). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1:3.3 mixture of **5l** and ***trans*-6l**) δ 1.49 (s, 9H), 3.60 (s, 3H), 4.04 (d, *J* = 16.4 Hz, 1H), 4.22 (d, *J* = 16.4 Hz, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 6.23 (dd, *J* = 11.6 and 6.0 Hz, 1H), 6.43 (dd, *J* = 10.0 and 6.0 Hz, 1H), 6.72 (d, *J* = 11.6 Hz, 1H).

Methyl *cis*-4-(2-iodophenyl)-1-*tert*-butyl-2-oxoazetidine-3-carboxylate (*cis*-6l). 23 mg (49%, Table S1, Entry 21). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 9H), 3.30 (s, 3H), 4.31 (d, *J* = 6.4 Hz, 1H), 5.22 (d, *J* = 6.4 Hz, 1H), 7.02 (ddd, *J*= 8.0, 7.2 and 1.6 Hz, 1H), 7.36 (ddd, *J*= 8.0, 7.2 and 1.6 Hz, 1H), 7.52 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.83 (dd, *J* = 8.0 and 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.2 (3 CH_3), 52.0 (CH_3), 55.3 (C), 58.4 (CH), 60.6 (CH), 98.7 (C), 128.0 (CH), 128.2 (CH), 130.4 (CH), 138.5 (C), 139.7 (CH), 163.2 (C), 166.1 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}INO_3$: 388.0404 $[M+H]^+$; found: 388.0405.

Methyl *trans*-4-(2-iodophenyl)-1-*tert*-butyl-2-oxoazetidine-3-carboxylate (*trans*-6l). 18 mg (38%, Table S1, Entry 21). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.55 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 3H), 5.24 (d, *J* = 2.0 Hz, 1H), 7.03 (ddd, *J*= 8.0, 7.2 and 2.0 Hz, 1H), 7.40 (ddd, *J*= 8.0, 7.2 and 1.2 Hz, 1H), 7.46 (dd, *J* = 8.0 and 2.0 Hz, 1H), 7.85 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.2 (3 CH_3), 52.9 (CH_3), 55.5 (C), 60.3 (CH), 62.4 (CH), 98.4 (C), 126.9 (broad, CH), 128.9 (CH), 130.4 (CH), 140.0 (broad, CH), 141.4 (C), 162.5 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}INO_3$: 388.0404 $[M+H]^+$; found: 388.0404.

Methyl 2-*tert*-butyl-5,6-dimethoxy-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5m). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1.5:1 mixture of **5m** and ***trans*-6m**) δ 1.46 (s, 9H), 3.61 (s, 3H), 3.67 (s, 3H), 3.73 (s, 3H), 4.21 (ddd, *J* = 14.4, 1.6 and 0.8 Hz, 1H), 4.40 (ddd, *J* = 14.4, 2.4 and 1.2 Hz, 1H), 5.01 (s, 1H), 5.67 (d, *J* = 7.2 Hz, 1H), 6.00 (ddd, *J* = 7.2, 2.4 and 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 1.5:1 mixture of **5m** and ***trans*-6m**) δ 27.6 (3 CH_3), 49.2 (CH_2), 52.9 (CH_3), 55.0 (C), 55.9 (CH_3), 56.2 (CH_3), 57.9 (C), 99.8 (CH), 103.5 (CH), 117.3 (CH), 131.1 (C), 152.3 (C), 154.9 (C), 169.9 (C), 171.1 (C).

Methyl *cis*-1-*tert*-butyl-4-(3,4-dimethoxyphenyl)-2-oxoazetidine-3-carboxylate (*cis*-6m). 3 mg (6%, Table S1, Entry 24). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.40 (s, 3H), 3.88 (s, 6H), 4.21 (d, *J* = 6.4 Hz, 1H), 4.86 (d, *J* = 6.4 Hz, 1H), 6.82 (d, *J*= 8.4 Hz, 1H), 6.91-6.93 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.2 (CH_3), 55.1 (C), 56.0 (CH_3), 56.1 (CH_3), 56.8 (CH), 59.3 (CH), 109.8 (broad, CH), 110.9 (CH), 120.1 (broad, CH), 129.0 (C), 149.0 (C), 149.4 (C), 163.0 (C), 166.8 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{24}NO_5$: 322.1654 $[M+H]^+$; found: 322.1656.

Methyl *trans*-1-*tert*-butyl-4-(3,4-dimethoxyphenyl)-2-oxoazetidine-3-carboxylate (*trans*-6m). 17.5 mg (38%, Table S1, Entry 24). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 3.71 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 3.89 (s, 6H), 4.82 (d, *J* = 2.4 Hz, 1H), 6.85 (d, *J*= 8.0 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.0 and 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.2 (3 CH_3), 52.8 (CH_3), 55.3 (C), 56.1 (CH_3), 56.2 (CH_3), 56.6 (CH), 62.5 (CH), 109.1 (CH), 111.4 (CH), 119.6 (CH), 131.4 (C), 149.5 (C), 149.6 (C), 162.2 (C), 167.8 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{24}NO_5$: 322.1654 $[M+H]^+$; found: 322.1655.

Methyl 2-*tert*-butyl-1-methyl-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (8). 7 mg (15%, Table 3, Entry 1). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1:1.2 mixture of stereoisomers) δ 1.37 (d, *J* = 6.0 Hz, 3H minor isomer), 1.50 (s, 9H major isomer), 1.51 (s, 9H minor isomer), 1.72 (d, *J* = 6.0 Hz, 3H major isomer), 3.55 (s, 3H minor isomer), 3.60 (s, 3H major isomer), 4.53 (qd, *J* = 6.0 and 1.6 Hz, 1H major isomer), 4.75 (qd, *J* = 6.0 and 1.6 Hz, 1H minor isomer), 5.57 (d, *J* = 9.6 Hz, 1H major isomer), 5.65 (d, *J* = 9.6 Hz, 1H minor isomer), 6.23-6.28 (m, 1H major and 1H minor isomer), 6.35-6.53 (m, 3H major and 3H minor isomer). ^{13}C NMR ($CDCl_3$, 100.6

MHz, signals from a 1:1.2 mixture of stereoisomers) δ 25.7 (CH_3), 28.3 (CH_3), 28.4 (3 CH_3), 29.4 (3 CH_3), 52.8 (CH_3), 52.9 (CH_3), 55.3 (C), 55.4 (C), 57.5 (CH), 57.6 (CH), 60.7 (C), 61.0 (C), 118.8 (CH), 119.8 (CH), 122.8 (CH), 124.0 (CH), 127.7 (2 CH), 128.6 (CH), 128.9 (CH), 129.4 (CH), 130.0 (CH), 138.4 (C), 138.6 (C), 168.9 (C), 169.0 (C), 170.1 (C), 170.7 (C).

Methyl (2RS,3RS)-1-(*tert*-butyl)-2-methyl-4-oxo-2-phenylazetidine-3-carboxylate (9). 10.5 mg (23%, Table 3, Entry 3). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 2.11 (s, 3H), 3.23 (s, 3H), 3.84 (s, 1H), 7.29-7.38 (m, 3H), 7.46-7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.2 (CH_3), 28.6 (3 CH_3), 51.8 (CH_3), 55.8 (C), 64.9 (C), 66.8 (CH), 126.6 (2 CH), 128.3 (2 CH), 139.9 (C), 162.8 (C), 166.7 (C). One CH was not observed. HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_3$: 276.1594 $[M+H]^+$; found: 276.1595.

Methyl (2RS,3SR)-1-(*tert*-butyl)-2-methyl-4-oxo-2-phenylazetidine-3-carboxylate (10). 21 mg (47%, Table 3, Entry 3). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 1.96 (s, 3H), 3.75 (s, 3H), 3.86 (s, 1H), 7.32 (ddd, J = 7.2, 6.0 and 1.2 Hz, 1H), 7.37-7.42 (m, 2H), 7.47-7.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7 (CH_3), 28.6 (3 CH_3), 52.4 (CH_3), 56.0 (C), 62.6 (C), 67.0 (CH), 125.5 (2 CH), 128.3 (CH), 128.9 (2 CH), 143.3 (C), 162.9 (C), 167.3 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_3$: 276.1594 $[M+H]^+$; found: 276.1596.

Computational Details. All the calculations reported in this paper were performed with the Gaussian 09 suite of programs.[20] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[21] in conjunction with the D3 dispersion correction suggested by Grimme et al.[22] using the double-ζ quality plus polarization def2-SVP[23] basis set for all atoms. Reactants and

products were characterized by frequency calculations,[24] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[25] Solvents effects were also taken into account using the Polarizable Continuum Model (PCM)[26] during the geometry optimizations. This level is denoted PCM-(dichloroethane)-B3LYP-D3/def2-SVP. Single-point energy refinements were carried out at the M06L[27]/def2-TZVPP[24] level of theory employing the PCM model to account for solvation. This level is denoted PCM(dichloroethane)-M06L/def2-TZVP//PCM-(dichloroethane)-B3LYP-D3/def2-SVP.

Supporting Information: Table S1, ^{1}H and ^{13}C NMR spectra of new compounds, and Cartesian coordinates and free energies of all species discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org/.

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(19) The intermediacy of a zwitterionic species in these Pd-catalysed insertions is experimentally supported by the isolation of 4-(dimethylamino)benzaldehyde in the reactions of **4f**. This aldehyde would be formed by hydrolysis of the corresponding zwitterionic intermediate.

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Palladium Catalysis in the Intramolecular Carbene C–H insertion of α-Diazo-α-(methoxycarbonyl)acetamides to Form β-Lactams

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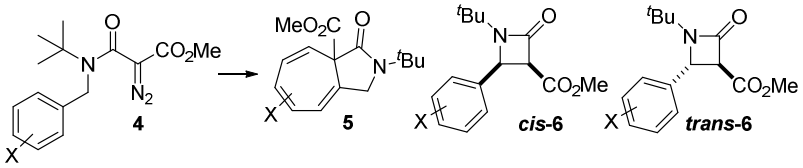
Electronic Supplementary Information

Table of Contents

Table S1. Pd(II)-catalyzed cyclisation reactions of α-diazoamides **4b-m**[a]



entry	**4** (X)	catalyst (mol%)	**5**/**6**[b,c]	***cis*-6**/***trans*-6**[b,c]	yield (%)[d]
1	**4b** (4-MeO)	$[Pd(allyl)Cl]_2$ (5)	14/86	29/57	**5b** (8) ***cis*-6b** (18), ***trans*-6b** (39)
2	**4b** (4-MeO)	(SIPr)Pd(allyl)Cl (15)	16/84	42/42	**5b** (10) ***cis*-6b** (8), ***trans*-6b** (52)
3	**4c** (4-MeS)	$[Pd(allyl)Cl]_2$ (5)	5/95	42/53	***cis*-6c** (10), ***trans*-6c** (48)
4	**4c** (4-MeS)	(SIPr)Pd(allyl)Cl (15)	12/88	48/40	**5c** (7) ***cis*-6c** (4), ***trans*-6c** (60)
5	**4d** (4-Cl)	$[Pd(allyl)Cl]_2$ (5)	0/100	52/48	***cis*-6d** (42), ***trans*-6d** (40)
6	**4d** (4-Cl)	(SIPr)Pd(allyl)Cl (15)	0/100	62/38	***cis*-6d** (27), ***trans*-6d** (42)
7	**4e** (4-CN)	$[Pd(allyl)Cl]_2$ (5)	0/100	71/29	***cis*-6e** (34), ***trans*-6e** (36)
8	**4e** (4-CN)	(SIPr)Pd(allyl)Cl (15)	0/100	38/62	***cis*-6e** (27), ***trans*-6e** (51)
9	**4f** (4-NMe_2)	$[Pd(allyl)Cl]_2$ (5)	CM[e]	---	***trans*-6f** (14)[f]
10	**4f** (4-NMe_2)	(SIPr)Pd(allyl)Cl (15)	CM[e]	---	***trans*-6f** (10)[g]
11	**4g** (3-Cl)	$[Pd(allyl)Cl]_2$ (5)	0/100	64/36	***cis*-6g** (44), ***trans*-6g** (36)
12	**4g** (3-Cl)	(SIPr)Pd(allyl)Cl (15)	0/100	50/50	***cis*-6g** (30), ***trans*-6g** (31)
13	**4h** (3-CN)	$[Pd(allyl)Cl]_2$ (5)	0/100	47/53	***cis*-6h** (22), ***trans*-6h** (43)
14	**4h** (3-CN)	(SIPr)Pd(allyl)Cl (15)	0/100	29/71	***cis*-6h** (15), ***trans*-6h** (55)
15	**4i** (2-MeO)	$[Pd(allyl)Cl]_2$ (5)	5/95	42/53	***cis*-6i** (23), ***trans*-6i** (31)
16	**4i** (2-MeO)	(SIPr)Pd(allyl)Cl (15)	6/94	39/55	***cis*-6i** (10), ***trans*-6i** (63)
17	**4j** (2-F)	$[Pd(allyl)Cl]_2$ (5)	0/100	69/31	***cis*-6j** (26), ***trans*-6j** (56)
18	**4j** (2-F)	(SIPr)Pd(allyl)Cl (15)	0/100	0/100	***trans*-6j** (66)
19	**4k** (2-Br)	$[Pd(allyl)Cl]_2$ (5)	14/86	52/34	**5k**(9) ***cis*-6k**(34), ***trans*-6k** (31)
20	**4k** (2-Br)	(SIPr)Pd(allyl)Cl (15)	8/92	21/71	**5k** (4) ***cis*-6k** (8), ***trans*-6k** (42)
21	**4l** (2-I)	$[Pd(allyl)Cl]_2$ (5)	8/92	50/42	**5l** (9) ***cis*-6l** (49), ***trans*-6l** (38)
22	**4l** (2-I)	(SIPr)Pd(allyl)Cl (15)	0/100	77/23	***cis*-6l** (53), ***trans*-6l** (15)
23	**4m** (3-MeO, 4-MeO)	$[Pd(allyl)Cl]_2$ (5)	15/85	8/77	**5m** (6) ***trans*-6m** (39)
24	**4m** (3-MeO, 4-MeO)	(SIPr)Pd(allyl)Cl (15)	24/76	43/33	**5m** (9) ***cis*-6m** (6), ***trans*-6m** (38)

[a] Reaction conditions: Catalyst (see table) in DCE at reflux for 24 h. [b] Ratio determined by integration of characteristic ^{1}H NMR absorptions from the spectrum of the reaction mixture. [c] The majority of reactions were performed twice. While the Buchner/β-lactam ratio was essentially the same in the two runs, the *cis*:*trans* ratio was quite different due to the partial isomerization of *cis* β-lactams to the more stable *trans* isomer during the work-up or even when recording the ^{1}H NMR spectra. [d] Yields refer to products isolated by chromatography. [e] Complex mixture. [f] 4-(*N*,*N*-dimethylamino)benzaldehyde (36%) was also obtained. [g] 4-(*N*,*N*-dimethylamino)benzaldehyde (45%) was also obtained.

9

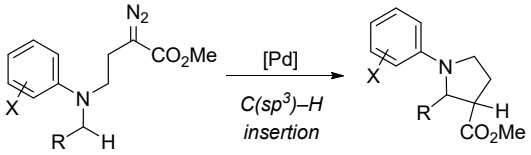
Anexo II: Resultados no publicados

Discusión y parte experimental

Site selectivity in Pd-catalyzed reactions of α-diazo-α-(methoxycarbonyl)acetamides: Effects of catalysts and substrate substitution

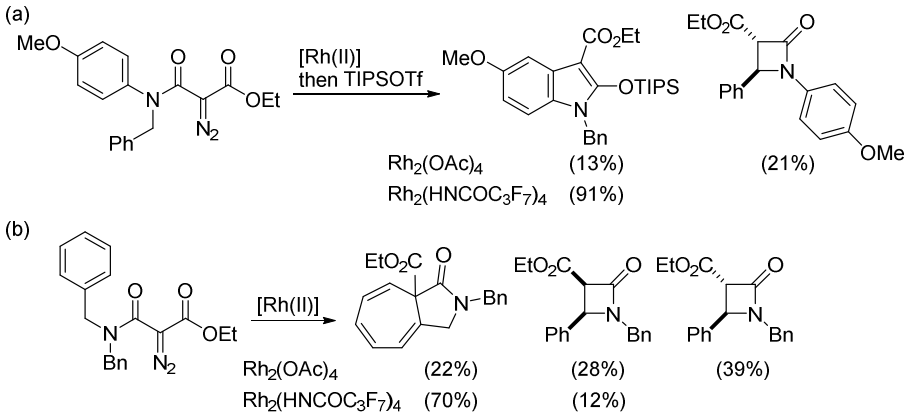
In recent years, the development of new methodologies for the selective functionalization of unactivated C–H bonds has become a very active area of research.[1] As part of this exciting field, the transition metal-catalyzed intramolecular carbene C–H insertion by decomposition of α-diazocarbonyl compounds has emerged as a powerful methodology for the construction of carbocyclic and heterocyclic frameworks.[2] A number of transition metal complexes have been used as effective catalysts to generate reactive metallacarbenes starting from α-diazocarbonyl compounds.[3] Among them, rhodium(II),[4] copper(I),[5] and more recently ruthenium(II) catalysts[6] have proved to be especially useful for the development of highly selective carbene C–H insertion methodologies via a variety of reaction modes. However, the use of palladium catalysis in this type of carbene C–H insertion processes remains underexploited.[7,8] This fact is highly surprising if we take into account the great success of palladium catalysis in cross-coupling reactions of diazo compounds with either organic halides, pseudohalides or arylboronic acids.[9]

As part of our research program on the synthesis of nitrogen heterocycles, we have been exploring different ways to increase the versatility of palladium catalysis in C–C bond-forming reactions,[10] for example, by controlling the ambiphilic character of the organopalladium intermediates in the intramolecular coupling reactions with carbonyl derivatives.[11] Continuing our search for methodologies to increase the synthetic potential of organopalladium chemistry, we have also investigated the feasibility of palladium as a catalyst for the carbene C-H insertion from α-diazoesters. In this context, we recently reported that palladium catalysts are able to promote Csp^3–H insertion of carbenes derived from such esters to form pyrrolidines through intramolecular Csp^3–Csp^3 bond formation (Scheme 1).[12]



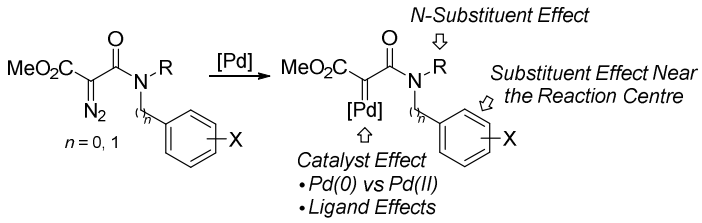
Scheme 1. Pd-Catalyzed Csp^3–H insertion of α-diazoesters

The research on transition metal-catalyzed carbene C–H insertion has generated an extensive literature on the use of dirhodium(II)-catalysts to promote the intramolecular C–H insertion of α-diazoacetamides,[13] since the insertion products, namely β- and -lactams as well as 2-oxindoles, are common scaffolds found in numerous natural products. It has been shown that the site selectivity of these reactions not only depends on the type of diazocarbonyl compound, but is also governed by conformational, steric, as well as electronic factors.[14] Moreover, some dramatic ligand effects have also been observed in these reactions. Thus, for example, the use of carboxylate and, in particular, carboxamide ligands in dirhodium(II)-catalysts has resulted in the development of highly chemo-, regio- and stereoselective transformations[15] despite a variety of potentially competitive carbene processes (Scheme 2).



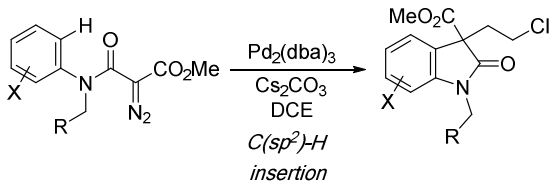
Scheme 2. Typical Rh(II)-catalyzed reactions of α-diazoamides[15d]

The aim of the current work was to explore the feasibility of palladium as a catalyst for the carbene C–H insertion from α-diazoacetamides. In this investigation we sought to identify differences in the reactivities and selectivities between the palladium catalysts and the abovementioned transition metals. Presented here is a full account of our studies on the palladium-catalyzed intramolecular carbene insertion of α-diazoacetamides, and how the reaction is affected by the substituents on the α-diazoacetamide and the type of catalyst, using complexes with two oxidation states of Pd and a variety of ligands (Scheme 3).



Scheme 3. Substituent and catalyst effects on Pd-catalyzed reactions of α-diazoacetamides

The palladium-catalyzed reaction of α-diazo-α-(methoxycarbonyl)acetanilides was studied first. We found that when using palladium catalysts the C–H insertion from these substrates occurs selectively into the arylic Csp^2–H rather than the Csp^3–H bonds. This allowed us to develop a one-pot methodology to prepare 3-(chloroethyl)oxindoles by means of a sequential C–H insertion/alkylation process (Scheme 4).[16]

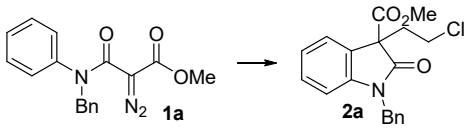


Scheme 4. Pd-catalyzed Csp^2–H insertion of α-diazo-α-(methoxycarbonyl)acetanilides

Our previous studies with α-diazoacetanilide **1a** revealed that the carbene $C_{Ar}sp^2$–H insertion can be selectively promoted by both Pd(0) and Pd(II)-catalysts. The best result was obtained when using $Pd_2(dba)_3$ in the presence of Cs_2CO_3 in dichloroethane at reflux for 96 h, which afforded oxindole **2a**, arising from the sequential carbene insertion/alkylation reaction, in 66%

yield (Table 1, entry 1). All attempts to increase the efficiency of the Pd(0)-catalyzed reaction by adding different phosphine ligands failed, always resulting in a slower reaction rate.[16]

Table 1. Palladium-catalyzed reactions of α-diazoamide **1a**[a]



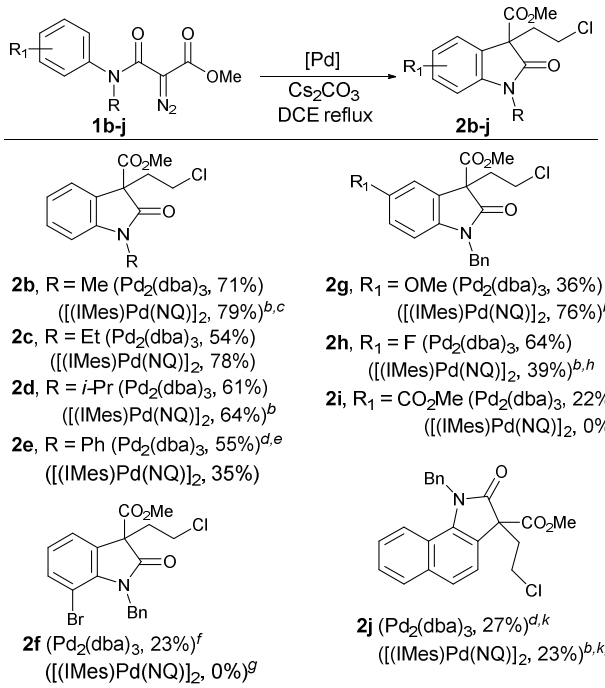
entry	catalyst (mol%)	additives (equiv.)	solvent	temp.	time	products (%)[b]
1	$Pd_2(dba)_3$ (10)	Cs_2CO_3 (2)	DCE	reflux	96 h	**2a** (66%)
2	$[Pd(allyl)Cl]_2$ (5)	Cs_2CO_3 (1)	DCE	reflux	24 h	**1a**:**2a** (1:2.2)[c]
3	$[Pd(allyl)Cl]_2$ (5)	Cs_2CO_3 (1)	DCE	reflux	60 h	**1a**:**2a** (1:5.5)[c]
4	$[(IMes)Pd(NQ)]_2$ (4)	Cs_2CO_3 (1)	DCE	reflux	24 h	**2a** (65%)

[a] All reactions were conducted with **1a** (0.2 mmol, 0.2 M). [b] Isolated yield. [c] ^{1}H NMR ratio, yields were not quantified. $Pd_2(dba)_3$ = Tris(dibenzylideneacetone)dipalladium(0). $[(IMes)Pd(NQ)]_2$ = 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer.

In order to increase the efficiency of the carbene insertion of α-diazoacetanilide **1a**, we have decided to test some palladium precatalysts bearing non-phosphine ligands. $[Pd(allyl)Cl]_2$ was first explored as the catalyst for the insertion/alkylation sequential process, but unfortunately, as previously observed with $Pd(OAc)_2$,[16] the reaction was slower (entries 2-3). In contrast, we found that the use of $[(IMes)Pd(NQ)]_2$ required a notably shorter reaction time and lower catalyst loading (entry 4). It should be noted that this NHC-Pd(0) catalyst also proved to be highly efficient in the carbene Csp^3–H insertion reaction leading to *N*-arylpyrrolidines.[12b]

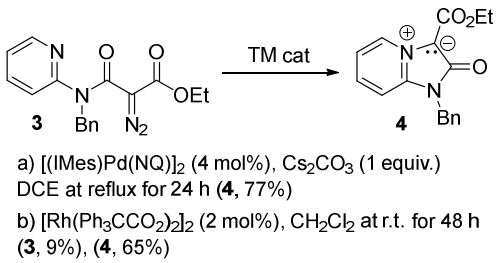
With these data in hand, we then explored the generality of the NHC-Pd(0)-catalyst by applying it for the synthesis of diversely substituted 3-(chloroethyl)-3-(methoxycarbonyl)oxindoles.[17] Scheme 5 gathers the results obtained in the reactions of different α-diazoacetanilides (**1b-j**) when using $[(IMes)Pd(NQ)]_2$ as the catalyst, and, for the sake of comparison, those previously obtained with $Pd_2(dba)_3$.[16]

As can be seen in Scheme 5, like $Pd_2(dba)_3$, $[(IMes)Pd(NQ)]_2$ also selectively promotes the carbene insertion into the arylic C–H bond in the presence of primary, secondary as well as tertiary Csp^3–H bonds. Notably, $[(IMes)Pd(NQ)]_2$ was more efficient than $Pd_2(dba)_3$ in promoting the insertion of *N*-alkylacetanilides lacking substituents on the arylic ring (**1b-d**) or bearing electron-donating substituents (**1g**). In contrast, the introduction of electron-withdrawing groups dramatically diminished the catalytic efficiency of $[(IMes)Pd(NQ)]_2$. Thus, for example, acetanilide **1f**, bearing an *ortho*-bromo substituent, was recovered unchanged when using $[(IMes)Pd(NQ)]_2$ as the catalyst, while in the presence of $Pd_2(dba)_3$ it afforded oxindole **2f** in 23% yield. Oxindole **2h**, with a fluoro group, was isolated in a modest 39% yield when using $[(IMes)Pd(NQ)]_2$, but obtained in an acceptable 64% yield in the presence of $Pd_2(dba)_3$. No insertion product was formed in the $[(IMes)Pd(NQ)]_2$-catalyzed reaction of acetanilide **1i**, which bears a methoxycarbonyl substituent, while oxindole **2i** was isolated in 22% yield when using $Pd_2(dba)_3$. $[(IMes)Pd(NQ)]_2$ also gave worse results than $Pd_2(dba)_3$ in the sequential insertion/alkylation sequence from *N*,*N*-diphenylacetamide **1e** and *N*-naphthylacetamide **1j**.



Scheme 5. Scope of the Pd-catalyzed reaction. [a] See Table 1 for representative procedures. [b] Catalyst loading: 5%, reaction time: 48h. [c] A small amount of the *O*-alkylation product was also observed in the crude reaction mixture. [d] Catalyst loading: 15%. [e] 20% of unreacted starting material was recovered. [f] ^{1}H NMR analysis of the reaction mixture showed a 1:1 mixture of **1f** and **2f**. [g] **2f** was recovered. [h] ^{1}H NMR analysis of the reaction mixture showed a 1:4.8 mixture of **1h** and **2h**. [i] The *O*-alkylation product **2i'** was also obtained (**2i**/**2i'**, 3:1). [j] Complex reaction mixture. [k] The *O*-alkylation product **2j'** was also obtained (**2j**/**2j'**, 2:1). [l] ^{1}H NMR analysis of the reaction mixture showed a 1:1.5 mixture of **1j** and **2j**.

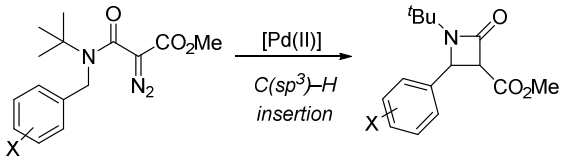
Finally, we explored the transition metal-catalyzed decomposition of α-diazo-*N*-pyridinylacetamide **3** (Scheme 6). Treatment of **3** with a catalytic amount of $[(IMes)Pd(NQ)]_2$ under the optimized reaction conditions afforded mesoionic compound **4** (77%),[18] resulting from the interception of the transient metallacarbene by the pyridine nitrogen. The same product was obtained in slightly lower yield when $[Rh(Ph_3CCO_2)_2]_2$ was used as the catalyst.[19]



Scheme 6. Transition metal-catalyzed cyclization reactions of α-diazoamide **3**

It should be noted that no β-lactam product, resulting from the possible competitive carbene Csp^3–H insertion, was observed in any of the palladium-catalyzed reactions shown in Table 1 and Schemes 5 and 6. This fact contrasts with the competition between carbene $C_{Ar}sp^2$–H and Csp^3–H insertions observed in Rh(II)-catalyzed processes (see, for instance, Scheme 2a),[15d] and prompted us to explore whether palladium complexes can be used to catalyze intramolecular carbene Csp^3–H insertion of α-diazo-α-(methoxycarbonyl)acetamides to form β-lactams.

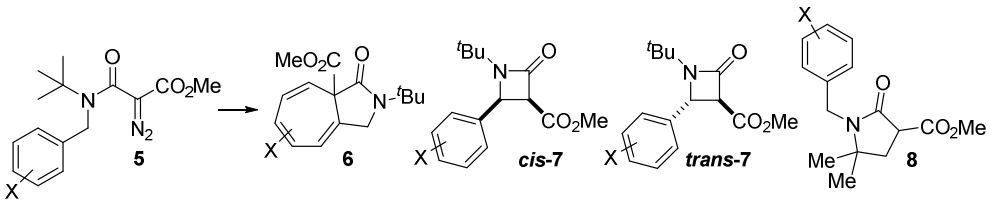
In a preliminary study, we described that the intramolecular carbene C–H insertion of α-diazo-α-(methoxycarbonyl)acetamides to form β-lactams can be effectively catalyzed by Pd(II)-complexes (Scheme 7).[20]



Scheme 7. Pd-catalyzed Csp^3–H insertion of α-diazo-α-(methoxycarbonyl)acetamides

To gain more insight into the impact of the electronic nature of the catalyst in the insertion reaction leading to β-lactams, we also explored the use of some Pd(0)-precatalysts. Table 2 shows the results obtained in the reactions of diversely substituted *N*-benzyl-*N*-^{t}butyl-α-diazoacetamides (**5a-m**) when using either $Pd_2(dba)_3$ or $[(IMes)Pd(NQ)]_2$ as the catalyst, and, for the sake of comparison, those previously obtained in the Pd(II)-catalyzed reactions.

Table 2. Palladium-catalyzed cyclisation reactions of α-diazoamides **5a-m**[a]



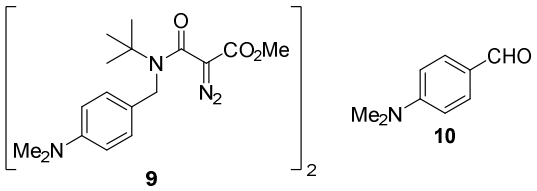
entry	5 (X)	catalyst (mol%)	6/7/8[b,c]	*cis*-7/*trans*-7[b,c]	yield (%)[d]
1	**5a** (H)	$Pd_2(dba)_3$ (10)	26/74/0	46/28	**6a** (20) ***cis*-7a** (9), ***trans*-7a** (42)
2	**5a** (H)	$[(IMes)Pd(NQ)]_2$ (2.5)	35/65/0	40/25	**6a** (28) ***cis*-7a** (35), ***trans*-7a** (23)
3	**5a** (H)	$[Pd(allyl)Cl]_2$ (5)	0/100/0	47/53	***cis*-7a** (25), ***trans*-7a** (65)
4	**5a** (H)	(SIPr)Pd(allyl)Cl (15)	0/100/0	29/71	***cis*-7a** (17), ***trans*-7a** (59)
5	**5b** (4-MeO)	$Pd_2(dba)_3$ (10)	50/50/0	21/29	**6b** (24) ***cis*-7b** (9), ***trans*-7b** (20)
6	**5b** (4-MeO)	$[(IMes)Pd(NQ)]_2$ (2.5)	34/66/0	46/20	**6b** (22) ***cis*-7b** (21), ***trans*-7b** (24)
7	**5b** (4-MeO)	$[Pd(allyl)Cl]_2$ (5)	14/86/0	29/57	**6b** (8) ***cis*-7b** (18), ***trans*-7b** (39)
8	**5b** (4-MeO)	(SIPr)Pd(allyl)Cl (15)	16/84/0	42/42	**6b** (10) ***cis*-7b** (8), ***trans*-7b** (52)
9	**5c** (4-MeS)	$Pd_2(dba)_3$ (10)	18/82/0	36/46	**6c** (6) ***cis*-7c** (4), ***trans*-7c** (30)
10	**5c** (4-MeS)	$[(IMes)Pd(NQ)]_2$ (2.5)	11/89/0	68/21	**6c** (7) ***cis*-7c** (30), ***trans*-7c** (50)
11	**5c** (4-MeS)	$[Pd(allyl)Cl]_2$ (5)	5/95/0	42/53	***cis*-7c** (10), ***trans*-7c** (48)
12	**5c** (4-MeS)	(SIPr)Pd(allyl)Cl (15)	12/88/0	48/40	**6c** (7) ***cis*-7c** (4), ***trans*-7c** (60)
13	**5d** (4-Cl)	$Pd_2(dba)_3$ (10)	15/85/0	8/77	**6d** (9) ***cis*-7d** (5), ***trans*-7d** (50)
14	**5d** (4-Cl)	$[(IMes)Pd(NQ)]_2$ (2.5)	5/95/0	69/26	**6d** (5) ***cis*-7d** (53), ***trans*-7d** (19)
15	**5d** (4-Cl)	$[Pd(allyl)Cl]_2$ (5)	0/100/0	52/48	***cis*-7d** (42), ***trans*-7d** (40)
16	**5d** (4-Cl)	(SIPr)Pd(allyl)Cl (15)	0/100/0	62/38	***cis*-7d** (27), ***trans*-7d** (42)
17	**5e** (4-CN)	$Pd_2(dba)_3$ (10)	3/97/0	67/30	***cis*-7e** (22), ***trans*-7e** (38)
18	**5e** (4-CN)	$[(IMes)Pd(NQ)]_2$ (2.5)	5/75/20	25/50	***cis*-7e** (15), ***trans*-7e** (33) **8e** (15)

19	**5e** (4-CN)	$[Pd(allyl)Cl]_2$ (5)	0/100/0	71/29	***cis*-7e** (34), ***trans*-7e** (36)
20	**5e** (4-CN)	(SIPr)Pd(allyl)Cl (15)	0/100/0	38/62	***cis*-7e** (27), ***trans*-7e** (51)
21	**5f** (4-NMe_2)	$Pd_2(dba)_3$ (10)	---	---	**DIMER 9** (84)
22	**5f** (4-NMe_2)	$[(IMes)Pd(NQ)]_2$ (2.5)	CM	---	***cis*-7f** (9), ***trans*-7f** (10) **DIMER 9** (20) **10** (15)
23	**5f** (4-NMe_2)	$[Pd(allyl)Cl]_2$ (5)	CM	---	***trans*-7f** (14) **10** (36)
24	**5f** (4-NMe_2)	(SIPr)Pd(allyl)Cl (15)	CM	---	***trans*-7f** (10) **10** (45)
25	**5g** (3-Cl)	$Pd_2(dba)_3$ (10)	8/92/0	54/38	**6g**[e] (7) ***cis*-7g** (30), ***trans*-7g** (43)
26	**5g** (3-Cl)	$[(IMes)Pd(NQ)]_2$ (2.5)	6/94/0	73/21	**6g**[e] (5) ***cis*-7g** (50), ***trans*-7g** (20)
27	**5g** (3-Cl)	$[Pd(allyl)Cl]_2$ (5)	0/100/0	64/36	***cis*-7g** (44), ***trans*-7g** (36)
28	**5g** (3-Cl)	(SIPr)Pd(allyl)Cl (15)	0/100/0	50/50	***cis*-7g** (30), ***trans*-7g** (31)
29	**5h** (3-CN)	$Pd_2(dba)_3$ (10)	0/100/0	33/67	***cis*-7h** (25), ***trans*-7h** (48)
30	**5h** (3-CN)	$[(IMes)Pd(NQ)]_2$ (2.5)	4/74/22	30/44	***cis*-7h** (15), ***trans*-7h** (37) **8h** (6)
31	**5h** (3-CN)	$[Pd(allyl)Cl]_2$ (5)	0/100/0	47/53	***cis*-7h** (22), ***trans*-7h** (43)
32	**5h** (3-CN)	(SIPr)Pd(allyl)Cl (15)	0/100/0	29/71	***cis*-7h** (15), ***trans*-7h** (55)
33	**5i** (2-MeO)	$Pd_2(dba)_3$ (10)	14/86/0	43/43	**6i** (8) ***cis*-7i** (12), ***trans*-7i** (19)
34	**5i** (2-MeO)	$[(IMes)Pd(NQ)]_2$ (2.5)	20/80/0	57/23	**6i** (10) ***cis*-7i** (45), ***trans*-7i** (24)
35	**5i** (2-MeO)	$[Pd(allyl)Cl]_2$ (5)	5/95/0	42/53	***cis*-7i** (23), ***trans*-7i** (31)
36	**5i** (2-MeO)	(SIPr)Pd(allyl)Cl (15)	6/94/0	39/55	***cis*-7i** (10), ***trans*-7i** (63)
37	**5j** (2-F)	$Pd_2(dba)_3$ (10)	8/92/0	8/84	***cis*-7j** (5), ***trans*-7j** (66)
38	**5j** (2-F)	$[(IMes)Pd(NQ)]_2$ (2.5)	5/83/12	24/59	***cis*-7j** (10), ***trans*-7j** (62) **8j** (11)
39	**5j** (2-F)	$[Pd(allyl)Cl]_2$ (5)	0/100/0	69/31	***cis*-7j** (26), ***trans*-7j** (56)
40	**5j** (2-F)	(SIPr)Pd(allyl)Cl (15)	0/100/0	0/100	***trans*-7j** (66)
41	**5k** (2-Br)	$Pd_2(dba)_3$ (10)	7/93/0	70/23	**6k** (6) ***cis*-7k** (46), ***trans*-7k** (15)
42	**5k** (2-Br)	$[(IMes)Pd(NQ)]_2$ (2.5)	0/85/15	66/19	***cis*-7k** (43), ***trans*-7k** (20) **8k** (12)
43	**5k** (2-Br)	$[Pd(allyl)Cl]_2$ (5)	14/86/0	52/34	**6k**(9) ***cis*-7k**(34), ***trans*-7k** (31)
44	**5k** (2-Br)	(SIPr)Pd(allyl)Cl (15)	8/92/0	21/71	**6k** (4) ***cis*-7k** (8), ***trans*-7k** (42)
45	**5l** (2-I)	$Pd_2(dba)_3$ (10)	0/100/0	9/91	***cis*-7l** (5), ***trans*-7l** (45)
46	**5l** (2-I)	$[(IMes)Pd(NQ)]_2$ (2.5)	0/78/22	66/12	***cis*-7l** (64), ***trans*-7l** (12) **8l** (15)
47	**5l** (2-I)	$[Pd(allyl)Cl]_2$ (5)	8/92/0	50/42	**6l** (9) ***cis*-7l** (49), ***trans*-7l** (38)
48	**5l** (2-I)	(SIPr)Pd(allyl)Cl (15)	0/100/0	77/23	***cis*-7l** (53), ***trans*-7l** (15)
49	**5m** (3-MeO, 4-MeO)	$Pd_2(dba)_3$ (10)	50/50/0	21/29	**6m** (25) ***cis*-7m** (11), ***trans*-7m** (20)
50	**5m** (3-MeO, 4-MeO)	$[(IMes)Pd(NQ)]_2$ (2.5)	32/68/0	44/24	**6m** (13) ***cis*-7m** (23), ***trans*-7m** (30)
51	**5m** (3-MeO, 4-MeO)	$[Pd(allyl)Cl]_2$ (5)	15/85/0	8/77	**6m** (6) ***trans*-7m** (39)
52	**5m** (3-MeO, 4-MeO)	(SIPr)Pd(allyl)Cl (15)	24/76/0	43/33	**6m** (9) ***cis*-7m** (6), ***trans*-7m** (38)

[a] Reaction conditions: Catalyst (see table) in DCE at reflux for 24 h. [b] Ratio determined by integration of characteristic ^{1}H NMR absorptions from the spectrum of the reaction mixture. [c] The majority of reactions were performed twice. While the Buchner/β-lactam/ -lactam ratio was essentially the same in the two runs, the *cis*:*trans* ratio was quite different due to the partial isomerization of *cis* β-lactams to the more stable *trans* isomer during the work-up or even when recording the ^{1}H NMR spectra. [d] Yields refer to products isolated by chromatography. [e] Mixture of regioisomers.

The examples in Table 2 confirm the generality and functional group tolerance of these palladium-catalyzed insertion processes. Either Pd(0)- and Pd(II)-catalysts can be used to

promote Csp^3–H insertion.[21] On the whole, the Pd(II)-complexes proved to be the most versatile catalysts for β-lactam formation, despite not always giving the highest yield. In general, the resulting β-lactams were obtained in moderate to good overall yields (53-90%), usually as mixtures of *cis* and *trans* isomers,[22] in transformations proceeding with high site selectivity. Among the explored α-diazoamides, **5f** was the only exception. Thus, the use of Pd(II)-catalysts to promote the decomposition of **5f** (entries 23-24) resulted in the formation of ***trans*-7f** (10-14%), together with major amounts of 4-(dimethylamino)benzaldehyde **10** (Figure 1), which results from the hydrolysis of the transient zwitterionic intermediate.[20] On the other hand, when $[(IMes)Pd(NQ)]_2$ was used as the catalyst, a complex reaction mixture was obtained, from which ***cis*-7f** (9%), ***trans*-7f** (10%), dimer **9** (20%) and aldehyde **10** (15%) were isolated (entry 22). Finally, the $Pd_2(dba)_3$-catalyzed decomposition of **5f** exclusively afforded dimer **9** (entry 21).[23]



9 **10**

Figure 1. Dimer **9** and aldehyde **10**

It is worth noting that no product from the potentially competitive palladium-catalyzed cross-coupling of the aryl halide with the α-diazoamide moiety[9] was observed in the reactions of **5k** and **5l**, which bear an *ortho*-bromo and *ortho*-iodo substituent, respectively.

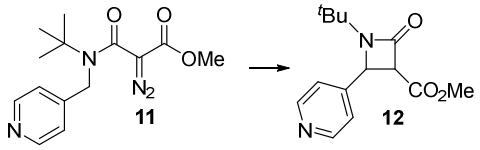
As can be seen in Table 2, the effect of the substituent at the benzyl group on the course of the process varied according to its electronic nature as well as its position on the aromatic ring. The introduction of electron-releasing groups led to an increased formation of the cycloheptapyrrolone product, especially when using Pd(0)-catalysts. The increase was lower when the substituent was located at the *ortho*-position, probably due to steric interactions. In contrast, the electron-withdrawing groups generally diverted the palladacarbene away from the Buchner reaction in favor of the Csp^3–H insertion. Similar electronic effects have been observed in related Rh(II)-catalyzed transformations.[15d] On the other hand, the use of $[(IMes)Pd(NQ)]_2$ as the catalyst in the reaction of the substrates bearing electron-withdrawing groups resulted in the formation of minor amounts of the corresponding -lactam (**8**), which arises from the ^{t}butyl Csp^3–H insertion. Interestingly, the -lactams were not observed when using Pd(II)-catalysts.

The above results also confirm the significant impact of the electronic nature of the Pd-catalyst and ensuing electrophilicity of the carbene intermediate in the reaction pathway. Thus, whereas benzylic Csp^3–H insertion is strongly favored over the Buchner reaction when using Pd(II)-catalysts, an increased cycloheptapyrrolone product formation is usually observed with the more electron-rich Pd(0)-catalysts. Interestingly, Rh(II)-catalyzed transformations show opposite reactivity trends, in which highly electrophilic Rh(II)-complexes favor Buchner reactions over benzylic Csp^3–H insertion.[14]

At this point, we also explored the transition metal-catalyzed decomposition of α-diazoacetamide **11**, which bears a (4-pyridinyl)methyl group instead of the *N*-benzyl substituent (Table 3). Treatment of **11** with a catalytic amount of $[(IMes)Pd(NQ)]_2$ under the optimized

reaction conditions resulted in the complete decomposition of the material (entry 1). When the reaction was performed at lower temperature (refluxing dichloromethane), **11** was recovered unchanged (entry 2). In contrast, the use of Pd(II)-catalysts (entries 3-4) resulted in the formation of β-lactam **12** (*cis*/*trans* mixture), (SIPr)Pd(allyl)Cl affording the highest yield. Interestingly, α-diazoacetamide **11** was recovered unchanged when using the well-known $[Rh(OAc)_2]_2$ catalyst (entry 5).

Table 3. Transition metal-catalyzed cyclisation reactions of α-diazoamide **11**

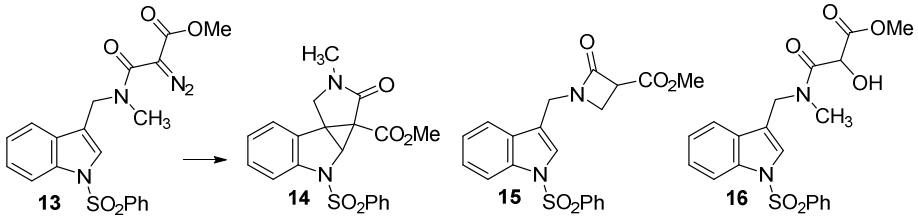


entry	catalyst (mol%)	solvent	temp.	time	yield (%)[a]
1	$[(IMes)Pd(NQ)]_2$ (2.5)	DCE	reflux	24h	**decomposition**
2	$[(IMes)Pd(NQ)]_2$ (2.5)	CH_2Cl_2	reflux	24 h	**11**
3	$[Pd(allyl)Cl]_2$ (5)	DCE	reflux	24 h	***cis*-12**/***trans*-12** (1:10, 30)
4	(SIPr)Pd(allyl)Cl (15)	DCE	reflux	48 h	***cis*-12**/***trans*-12** (1:2.2, 54)
5	$[Rh(OAc)_2]_2$ (3)	CH_2Cl_2	rt	24 h	**11**

[a] Yields refer to products isolated by chromatography.

Finally, we also explored the transition metal-catalyzed decomposition of some α-diazo-α-(methoxycarbonyl)acetamides bearing an *N*-(3-indolylmethyl) moiety. The studies began with indole **13** (Table 4), from which the metallacarbene can, in principle, be involved in a variety of reaction modes.[24]

Table 4. Transition metal-catalyzed cyclisation reactions of α-diazoamide **13**



entry	catalyst (mol%)	solvent	temp.	time	yield (%)[b]
1	$Pd_2(dba)_3$ (5)	toluene	reflux[a]	24 h	**14** (30%)[c]
2	$Pd_2(dba)_3$ (10)	DCE	reflux[a]	96 h	**14** (24%), **15** (18%)
3	$Pd_2(dba)_3$ (7.5)	dioxane	reflux[a]	24 h	**14** (10%)
4	$Pd_2(dba)_3$ (5) BINAP (10)	toluene	reflux[a]	24 h	**14** (10%)
5	$Pd(PPh_3)_4$ (5)	toluene	reflux[a]	24 h	**CM**[d]
6	$Pd(OAc)_2$ (20)	toluene	reflux[a]	24 h	**14** (13%)
7	$[Rh(OAc)_2]_2$ (2)	CH_2Cl_2	rt	5 h	**14** (25%), **16** (45%)

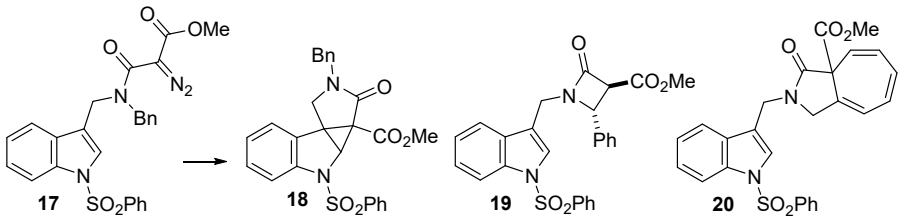
[a] Reaction conditions: Catalyst (see table) and Cs_2CO_3 (2 equiv.) in the indicated solvent at reflux. [b] Yields refer to products isolated by chromatography. [c] **14** is a rather unstable compound that decomposes during the purification by flash chromatography. In fact, ^1H NMR analysis of the crude reaction mixture gave c.a. 70% yield of **14**. [d] Trace amounts of **14** were observed in the crude complex reaction mixture.

However, treatment of **13** with $Pd_2(dba)_3$ in refluxing toluene gave tetracyclic compound **14**, resulting from the metallacarbene addition to the indole C(2)-C(3) double bond,[24] as the only reaction product (entry 1). When the reaction was performed in the low boiling dichloroethane, **14** (24%) and β-lactam **15** (18%) were obtained (entry 2). The use of dioxane as the solvent (entry

3) or the addition of BINAP (entry 4) also resulted in the formation of **14**, albeit in worse yield. A complex mixture was obtained when the reaction was performed with $Pd(PPh_3)_4$ (entry 5), while **14** was obtained again when using $Pd(OAc)_2$ as the catalyst (entry 6). Finally, exposure of **13** to $[Rh(OAc)_2]_2$ gave **14** (25%) together with major amounts of alcohol **16** (entry 7).[25]

The palladium-catalyzed decomposition of α-diazoacetamide **17** was also explored (Table 5). When $Pd_2(dba)_3$ was used as the catalyst, mixtures of tetracyclic compound **18**, β-lactam **19** and the Buchner product **20** were obtained, the product ratio depending on the reaction solvent.

Table 5. Palladium-catalyzed cyclisation reactions of α-diazoamide **17**



entry	catalyst (mol%)	solvent	temp.	time	yield (%)[a]
1	$Pd_2(dba)_3$ (5)	toluene	reflux	26 h	**18** (30%), **19** (20%), **20** (18%)
2	$Pd_2(dba)_3$ (10)	DCE	reflux	72 h	**18** (38%), **19** (9%), **20** (13%)

[a] Yields refer to products isolated by chromatography.

Experimental Section

General Methods. All commercially available reagents were used without further purification. ^{1}H- and ^{13}C NMR spectra were recorded using Me_4Si as the internal standard, with a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si for ^{1}H and ^{13}C NMR. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light or 1% aqueous $KMnO_4$. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator.

Synthesis and characterization data of diazoacetamides 3, 11, 13 and 17

***N*-Benzyl-*N*-(2-pyridinyl)-α-(ethoxycarbonyl)-α-diazoacetamide (3).**

To a solution of 2-benzylaminopyridine (0.5 g, 2.71 mmol) and Et_3N (0.39 mL, 2.71 mmol) in CH_2Cl_2 (10 mL), cooled at 0 °C, was added slowly ethyl malonyl chloride (0.38 mL, 2.71 mmol). The mixture was stirred at room temperature for 24 h. After the reaction was completed, the mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$ aqueous solution, dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 97:3) to give *N*-benzyl-*N*-(2-pyridinyl)-α-(ethoxycarbonyl)acetamide (0.77 g, 95%).

To a solution of *N*-benzyl-*N*-(2-pyridinyl)-α-(ethoxycarbonyl)acetamide (0.25 g, 0.84 mmol) and Et_3N (0.14 mL, 1.0 mmol) in dry acetonitrile (15 mL), was added dropwise *p*-toluenesulfonylazide (2.6 mL of a 11% solution in toluene, 1.45 mmol). The mixture was stirred at room temperature for 90 h. The solvent was removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 and 10% NaOH aqueous solution. The organic extracts were dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 99:1) to give *N*-benzyl-*N*-(2-pyridinyl)-α-(ethoxycarbonyl)-α-diazoacetamide (**3**, 150 mg; 55%) as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, *J* = 7.2 Hz, 3H), 3.92 (q, *J* = 7.2 Hz, 2H), 5.22 (s, 2H), 7.04 (ddd, *J* = 7.4, 4.8 and 0.8 Hz, 1H), 7.10 (dt,

J = 8.4 and 0.8 Hz, 1H), 7.20 (tt, *J* = 7.2 and 1.2 Hz, 1H), 7.23-7.29 (m, 2H), 7.32-7.36 (m, 2H), 7.60 (ddd, *J* = 8.4, 7.4 and 2.0 Hz, 1H), 8.40 (ddd, *J* = 4.8, 2.0 and 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.3 (CH_3), 52.3 (CH_2), 61.4 (CH_2), 70.2 (C), 118.3 (CH), 120.8 (CH), 127.4 (CH), 127.9 (2 CH), 128.6 (2 CH), 137.5 (C), 138.0 (CH), 148.6 (CH), 156.1 (C), 161.4 (C), 162.3 (C).

***N*-*tert*-Butyl-*N*-(4-pyridinylmethyl)-α-(methoxycarbonyl)-α-diazoacetamide (11).**

To a solution of *N*-*tert*-butyl-*N*-(4-pyridinylmethyl)amine (0.67 g, 4.1 mmol) and Et_3N (0.58 mL, 4.1 mmol) in CH_2Cl_2 (20 mL), cooled at 0 °C, was added slowly methyl malonyl chloride (0.57 mL, 5.3 mmol). The mixture was stirred at room temperature for 24 h. After the reaction was completed, the mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$ aqueous solution, dried, filtered and concentrated to give *N*-*tert*-butyl-*N*-(4-pyridinylmethyl)-α-(methoxycarbonyl)acetamide as an orange oil (0.98 g, 90%), which was used in the next reaction without purification.

To a solution of *N*-*tert*-butyl-*N*-(4-pyridinylmethyl)-α-(methoxycarbonyl)acetamide (0.5 g, 1.89 mmol) and DBU (0.45 mL, 2.85 mmol) in dry acetonitrile (6 mL), was added dropwise a solution of *p*-ABSA (515 mg, 2.1 mmol) in dry acetonitrile (2 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 and 10% NaOH aqueous solution. The organic extracts were dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give *N*-*tert*-butyl-*N*-(4-pyridinylmethyl)-α-(methoxycarbonyl)-α-diazoacetamide (**11**, 145 mg; 26%) as an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 3.77 (s, 3H), 4.63 (s, 2H), 7.15 (d, *J* = 6.0 Hz, 2H), 7.57 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 50.6 (CH_2), 52.4 (CH_3), 59.5 (C), 68.7 (C), 121.9 (2 CH), 149.3 (C), 150.2 (2 CH), 162.8 (C), 163.5 (C).

***N*-Methyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-(methoxycarbonyl)-α-diazoacetamide (13).**

To a solution of *N*-methyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]amine (0.75 g, 2.49 mmol) and Et_3N (1.0 mL, 7.47 mmol) in CH_2Cl_2 (14 mL), cooled at 0 °C, was added slowly methyl malonyl chloride (0.8 mL, 7.47 mmol). The mixture was stirred at room temperature for 24 h. After the reaction was completed, the mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$ aqueous solution, dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 99:1) to give *N*-methyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-(methoxycarbonyl)acetamide (0.97 g, 97%) as a yellow oil.

To a solution of *N*-methyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-(methoxycarbonyl)acetamide (0.54 g, 1.35 mmol) and DBU (0.3 mL, 2.03 mmol) in dry acetonitrile (8 mL), was added dropwise a solution of *p*-ABSA (420 mg, 1.76 mmol) in dry acetonitrile (4 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 and 10% NaOH aqueous solution. The organic extracts were dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 96:4) to give *N*-methyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-(methoxycarbonyl)-α-diazoacetamide (**13**, 350 mg; 61%) as a yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.87 (s, 3H), 3.78 (s, 3H), 4.69 (s, 2H), 7.25 (td, *J* = 7.6 and 0.8 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.6 and 1.2 Hz, 1H), 7.41-7.46 (m, 2H), 7.51-7.60 (m, 3H), 7.86-7.89 (m, 2H), 7.98 (dd, *J* = 8.4 and 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.0 (broad, CH_3), 43.9 (broad, CH_2), 52.4 (CH_3), 66.6 (C), 113.8 (CH), 118.2 (C), 120.2 (CH), 123.8 (CH), 125.4 (CH), 125.5 (CH), 126.9 (2 CH), 129.5 (2 CH), 129.8 (C), 134.1 (CH), 135.5 (C), 138.2 (C), 161.9 (C), 162.7 (C).

***N*-Benzyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-(methoxycarbonyl)-α-diazoacetamide (17).**

To a solution of *N*-benzyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]amine (0.74 g, 1.97 mmol) and Et_3N (0.3 mL, 2.17 mmol) in CH_2Cl_2 (15 mL), cooled at 0 °C, was added slowly methyl malonyl chloride (0.24 mL, 2.17 mmol). The mixture was stirred at room temperature for 24 h. After the reaction was completed,

the mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$ aqueous solution, dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 99:1) to give *N*-benzyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-(methoxycarbonyl)acetamide (0.65 g, 69%) as a yellow oil.

To a solution of *N*-benzyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-(methoxycarbonyl)acetamide (0.65 g, 1.36 mmol) and DBU (0.3 mL, 2.05 mmol) in dry acetonitrile (12 mL), was added dropwise a solution of *p*-ABSA (360 mg, 1.5 mmol) in dry acetonitrile (6 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 and 10% NaOH aqueous solution. The organic extracts were dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give *N*-benzyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-(methoxycarbonyl)-α-diazoacetamide (**17**, 670 mg; 97%) as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H), 4.44 (s, 2H), 4.60 (s, 2H), 7.10 (m, 2H), 7.17 (dd, *J* = 8.0 and 2.0 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.2 and 0.8 Hz, 2H), 7.27-7.36 (m, 2H), 7.37 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.44 (tt, *J* = 8.0 and 0.8 Hz, 2H), 7.55 (tt, *J* = 7.6 and 0.8 Hz, 1H), 7.85-7.88 (m, 2H), 8.00 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 41.5 (broad, CH_2), 50.5 (broad, CH_2), 52.6 (CH_3), 67.1 (C), 113.9 (CH), 117.9 (C), 120.0 (CH), 123.7 (CH), 125.4 (CH), 125.5 (CH), 126.9 (2 CH), 127.7 (2 CH), 127.9 (CH), 128.9 (2 CH), 129.5 (2 CH), 129.8 (C), 134.1 (CH), 135.5 (C), 136.2 (C), 138.3 (C), 162.4 (C), 162.8 (C).

Characterization data for new compounds of Scheme 6 and Tables 2-5

1-Benzyl-3-(ethoxycarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-4-ium-3-ide (4). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45(t, *J* = 7.2 Hz, 3H), 4.43 (q, *J* = 7.2 Hz, 2H), 5.20 (s, 2H), 6.99 (ddd, *J*= 8.8, 1.6 and 0.8 Hz, 1H), 7.08 (ddd, *J*= 7.6, 6.8 and 1.2 Hz, 1H), 7.25-7.37 (m, 5H), 7.40 (ddd, *J* = 8.8, 7.6 and 1.2 Hz, 1H), 9.65 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.9 (CH_3), 43.3 (CH_2), 60.0 (CH_2), 94.0 (C), 106.4 (CH), 115.7 (CH), 127.8 (2 CH), 128.2 (CH), 129.0 (CH), 129.1 (2 CH), 129.9 (CH), 135.4 (C), 135.6 (C), 157.0 (C), 162.6 (C).

Methyl 2-*tert*-butyl-6-chloro-3-oxo-1*H*-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (6d). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 4.5:1 mixture of ***trans*-7d** and **6d**) δ 1.45 (s, 9H), 3.64 (s, 3H), 4.21 (dd, *J* = 14.8 and 1.2 Hz, 1H), 4.44 (d, *J* = 14.8 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 6.17 (d, *J* = 6.8 Hz, 1H), 6.39 (d, *J* = 10.2 Hz, 1H), 6.62 (d, *J* = 6.8 Hz, 1H).

Methyl 1-(4-cyanobenzyl)-5,5-dimethyl-2-oxopyrrolidine-3-carboxylate (8e). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 3H), 1.22 (s, 3H), 2.19 (dd, *J* = 13.2 and 9.2 Hz, 1H), 2.33 (dd, *J* = 13.2 and 9.2 Hz, 1H), 3.62 (t, *J* = 9.2 Hz, 1H), 3.82 (s, 3H), 4.33 (d, *J* = 16.0 Hz, 1H), 4.60 (d, *J* = 16.0 Hz, 1H), 7.39 (d, *J*= 8.4 Hz, 2H), 7.60 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.1 (CH_3), 28.1 (s, CH_3), 38.3 (CH_2), 43.2 (CH_2), 47.4 (CH), 53.0 (CH_3), 60.0 (C), 111.5 (C), 118.8 (C), 128.3 (2 CH), 132.6 (2 CH), 143.9 (C), 170.2 (C), 170.9 (C).

Methyl *cis*-1-*tert*-butyl-4-[4-(dimethylamino)phenyl]-2-oxoazetidine-3-carboxylate (*cis*-7f). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 2.95 (s, 6H), 3.40 (s, 3H), 4.18 (d, *J* = 6.0 Hz, 1H), 4.83 (d, *J* = 6.0 Hz, 1H), 6.65 (d, *J*= 8.8 Hz, 2H), 7.21 (d, *J*= 8.8 Hz, 2H).

Dimer 9. Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 18H), 2.94 (s, 12H), 3.87 (s, 6H), 5.65 (s, 4H), 6.65 (d, *J* = 8.8 Hz, 4H), 7.25 (d, *J* = 8.8 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.7 (6 CH_3), 40.5 (4 CH_3), 51.8 (2 CH_3), 56.4 (2 CH_2), 61.0 (2 C), 109.0 (C), 112.3 (4 CH), 121.2 (2 C), 129.8 (4 CH), 150.9 (2 C), 157.2 (2 C), 160.4 (2 C). HRMS (ESI-TOF) calcd. for $C_{34}H_{48}N_8NaO_6$: 687.3589 $[M+Na]^+$; found: 687.3581.

Methyl 2-*tert*-butyl-7-chloro-3-oxo-1*H*-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (6g). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 11:1 mixture of ***trans*-7g** and **6g**) δ 1.45 (s, 9H), 3.64 (s, 3H), 4.22

(dd, *J* = 15.6 and 2.0 Hz, 1H), 4.47 (dd, *J* = 15.6 and 2.4 Hz, 1H), 5.60 (d, *J* = 9.6 Hz, 1H), 6.27-6.30 (m, 1H), 6.32 (dd, *J* = 9.6 and 7.2 Hz, 1H), 6.61 (dd, *J* = 7.2 and 1.2 Hz, 1H).

Methyl 2-*tert*-butyl-5-chloro-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (6g'). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 12:4:1 mixture of ***trans*-7g**, **6g** and **6g'**) δ 1.46 (s, 9H), 3.64 (s, 3H), 4.23 (dd, *J* = 15.2 and 2.0 Hz, 1H), 4.42 (dd, *J* = 15.2 and 2.4 Hz, 1H), 5.76 (t, *J* = 1.2 Hz, 1H), 6.18-6.21 (m, 1H), 6.38-6.40 (m, 2H).

Methyl 1-(3-cyanobenzyl)-5,5-dimethyl-2-oxopyrrolidine-3-carboxylate (8h). ^{1}H NMR ($CDCl_3$, 400 MHz, significant signals from a 2:1 mixture of **8h** and ***cis*-7h**) δ 1.16 (s, 3H), 1.24 (s, 3H), 2.19 (dd, *J* = 12.8 and 9.2 Hz, 1H), 2.33 (dd, *J* = 12.8 and 9.2 Hz, 1H), 3.62 (t, *J* = 9.2 Hz, 1H), 3.80 (s, 3H), 4.33 (d, *J* = 16.0 Hz, 1H), 4.55 (d, *J* = 16.0 Hz, 1H).

Methyl 2-*tert*-butyl-8-methoxy-3-oxo-1*H*-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (6i). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1.5:1 mixture of **6i** and ***cis*-7i**) δ 1.47 (s, 9H), 3.55 (s, 3H), 3.69 (s, 3H), 4.23 (dd, *J* = 14.4 and 1.6 Hz, 1H), 4.48 (dd, *J* = 14.4 and 1.6 Hz, 1H), 5.65 (d, *J* = 7.2 Hz, 1H), 6.29-6.33 (m, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 6.38-6.45 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, significant signals from a 1:8 mixture of **6i** and ***cis*-7i**) δ 27.6 (3 CH_3), 49.4 (CH_2), 52.8 (CH_3), 55.1 (C), 57.5 (CH_3), 99.8 (CH), 120.6 (CH), 122.5 (CH), 126.9 (CH).

Methyl 1-(2-fluorobenzyl)-5,5-dimethyl-2-oxopyrrolidine-3-carboxylate (8j). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 8:1 mixture of **8j** and ***cis*-7j**) δ 1.14 (s, 3H), 1.25 (s, 3H), 2.15 (dd, *J* = 12.8 and 9.2 Hz, 1H), 2.31 (dd, *J* = 12.8 and 9.2 Hz, 1H), 3.61 (t, *J* = 9.2 Hz, 1H), 3.82 (s, 3H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.55 (d, *J* = 16.0 Hz, 1H), 7.00 (ddd, *J*= 10.4, 8.4 and 1.2 Hz, 1H), 7.09 (td, *J*= 7.6 and 1.2 Hz, 1H), 7.19-7.25 (m, 1H), 7.39 (td, *J*= 7.6 and 1.2 Hz, 1H).

Methyl 1-(2-bromobenzyl)-5,5-dimethyl-2-oxopyrrolidine-3-carboxylate (8k). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (s, 3H), 1.23 (s, 3H), 2.20 (dd, *J* = 12.8 and 9.2 Hz, 1H), 2.35 (dd, *J* = 12.8 and 9.2 Hz, 1H), 3.65 (t, *J* = 9.2 Hz, 1H), 3.83 (s, 3H), 4.45 (d, *J* = 16.4 Hz, 1H), 4.64 (d, *J* = 16.4 Hz, 1H), 7.10 (ddd, *J*= 8.0, 6.8 and 2.4 Hz, 1H), 7.24-7.30 (m, 2H), 7.51 (dd, *J*= 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.9 (s, CH_3), 27.8 (s, CH_3), 38.3 (CH_2), 43.1 (CH_2), 47.6 (CH), 52.9 (CH_3), 60.0 (C), 122.6 (C), 128.0 (CH), 128.9 (CH), 129.2 (CH), 132.7 (CH), 137.1 (C), 170.1 (C), 171.1 (C).

Methyl 1-(2-iodobenzyl)-5,5-dimethyl-2-oxopyrrolidine-3-carboxylate (8l). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (s, 3H), 1.22 (s, 3H), 2.20 (dd, *J* = 13.2 and 9.2 Hz, 1H), 2.35 (dd, *J* = 13.2 and 9.2 Hz, 1H), 3.65 (t, *J* = 9.2 Hz, 1H), 3.83 (s, 3H), 4.35 (d, *J* = 16.4 Hz, 1H), 4.59 (d, *J* = 16.4 Hz, 1H), 6.93 (td, *J*= 8.0 and 1.6 Hz, 1H), 7.23 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.30 (td, *J*= 8.0 and 1.2 Hz, 1H), 7.79 (dd, *J* = 8.0 and 1.2 Hz, 1H).

Methyl *cis*-1-*tert*-butyl-2-oxo-4-(pyridin-4-yl)azetidine-3-carboxylate (*cis*-12). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 2.6:1 mixture of ***trans*-12** and ***cis*-12**) δ 1.32 (s, 9H), 3.36 (s, 3H), 4.28 (d, *J* = 6.4 Hz, 1H), 4.88 (d, *J* = 6.4 Hz, 1H), 7.32-7.35 (m, 2H), 8.61-8.65 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 2.6:1 mixture of ***trans*-12** and ***cis*-12**) δ 28.2 (3 CH_3), 52.2 (CH_3), 55.4 (CH), 55.5 (C), 59.0 (CH), 121.1 (2 CH), 146.2 (C), 150.2 (2 CH), 162.5 (C), 165.9 (C).

Methyl *trans*-1-*tert*-butyl-2-oxo-4-(pyridin-4-yl)azetidine-3-carboxylate (*trans*-12). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 3.67 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 4.84 (d, *J* = 2.4 Hz, 1H), 7.33 (dd, *J* = 4.4 and 1.6 Hz, 2H), 8.64 (dd, *J* = 4.4 and 1.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.2 (3 CH_3), 53.0 (CH_3), 55.2 (CH), 55.7 (C), 62.1 (CH), 121.6 (2 CH), 148.5 (C), 150.7 (2 CH), 161.7 (C), 167.0 (C).

Tetracyclic ester 14. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (s, 3H), 3.11 (s, 3H), 3.61 (d, *J* = 10.4 Hz, 1H), 4.16 (d, *J* = 10.4 Hz, 1H), 4.66 (s, 1H), 7.07 (td, *J* = 8.0 and 0.8 Hz, 1H), 7.29 (dd, *J* = 7.6 and 0.8 Hz, 1H), 7.34 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.50-7.54 (m, 2H), 7.57-7.62 (m, 2H), 7.98-8.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 30.2 (CH_3), 30.3 (C), 40.4 (C), 48.6 (CH_2), 52.0 (CH_3), 53.6 (CH), 113.3

(CH), 123.3 (CH), 123.5 (C), 124.0 (CH), 127.4 (2 CH), 129.4 (2 CH), 129.6 (CH), 133.6 (CH), 139.0 (C), 143.3 (C), 163.2 (C), 166.9 (C). HRMS (ESI-TOF) calcd. for $C_{20}H_{19}N_2O_5S$: 399.1009 $[M+H]^+$; found: 399.1017.

Methyl 2-oxo-1-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]azetidine-3-carboxylate (15). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (t, *J* = 5.6 Hz, 1H), 3.39 (dd, *J* = 5.6 and 2.8 Hz, 1H), 3.75 (s, 3H), 3.99 (dd, *J* = 5.6 and 2.8 Hz, 1H), 4.47 (d, *J* = 15.6 Hz, 1H), 4.56 (d, *J* = 15.6 Hz, 1H), 7.27 (td, *J* = 8.4 and 1.2 Hz, 1H), 7.37 (td, *J* = 8.4 and 0.8 Hz, 1H), 7.43-7.48 (m, 2H), 7.53-7.58 (m, 3H), 7.87-7.90 (m, 2H), 7.98-8.01 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 37.3 (CH_2), 41.9 (CH_2), 52.9 (CH_3), 53.9 (CH), 113.9 (CH), 116.6 (C), 119.8 (CH), 123.9 (CH), 125.2 (CH), 125.6 (CH), 127.0 (2 CH), 129.4 (C), 129.5 (2 CH), 134.2 (CH), 135.5 (C), 138.2 (C), 162.3 (C), 167.7 (C).

***N*-Methyl-*N*-[(1-phenylsulfonyl-1*H*-indol-3-yl)methyl]-α-hydroxy-α-(methoxycarbonyl) acetamide (16).** Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.96 (s, 3H), 3.68 (s, 3H), 4.31 (d, *J* = 8.4 Hz, 1H), 4.64 (d, *J* = 14.8 Hz, 1H), 4.86 (d, *J* = 14.8 Hz, 1H), 4.95 (d, *J* = 8.4 Hz, 1H), 7.20-7.57 (m, 7H), 7.86-7.89 (m, 2H), 7.97 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 34.0 (CH_3), 43.2 (CH_2), 53.0 (CH_3), 69.7 (CH), 113.8 (CH), 117.6 (C), 120.2 (CH), 123.8 (CH), 125.5 (CH), 125.6 (CH), 126.9 (2 CH), 129.5 (2 CH), 129.6 (C), 134.2 (CH), 135.6 (C), 138.1 (C), 168.0 (C), 169.3 (C).

Tetracyclic ester 18. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.12 (s, 3H), 3.47 (d, *J* = 10.6 Hz, 1H), 3.99 (d, *J* = 10.6 Hz, 1H), 4.46 (d, *J* = 14.4 Hz, 1H), 4.59 (d, *J* = 14.4 Hz, 1H), 4.63 (s, 1H), 7.03 (td, *J* = 8.0 and 0.8 Hz, 1H), 7.21 (dd, *J* = 8.0 and 0.8 Hz, 1H), 7.26-7.40 (m, 6H), 7.49-7.54 (m, 2H), 7.57-7.61 (m, 2H), 7.97-8.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 30.4 (C), 40.3 (C), 45.9 (CH_2), 47.1 (CH_2), 52.0 (CH_3), 53.6 (CH), 113.3 (CH), 123.3 (CH), 123.4 (C), 124.0 (CH), 127.4 (2 CH), 128.3 (CH), 128.5 (2 CH), 129.2 (2 CH), 129.4 (2 CH), 129.6 (CH), 133.6 (CH), 135.8 (C), 138.9 (C), 143.2 (C), 163.2 (C), 166.8 (C).

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