TESE DE DOUTORAMENTO

# NEW CATALYTIC ROUTES TO BENZOFUSED SEVEN-MEMBERED AZAHETEROCYCLES

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**ESCOLA DE DOUTORAMENTO INTERNACIONAL DA UNIVERSIDADE DE SANTIAGO DE COMPOSTELA**

**PROGRAMA DE DOUTORAMENTO EN CIENCIA E TECNOLOXÍA QUÍMICA**

SANTIAGO DE COMPOSTELA

2021

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**[New Catalytic Routes to Benzofused Seven-Membered Azaheterocycles]**

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# Acknowledgements

En primer lugar, me gustaría agradecer a Carlos por darme la oportunidad de unirme al grupo en el máster y poder realizar mi tesis doctoral. Además de todos los consejos, conversaciones y apoyo dado durante estos 6 años tanto dentro como fuera del laboratorio. También a mi codirector Jesús por su apoyo y ayuda en este trabajo. Además, me gustaría agradecer a Martín Fañanás por todas las conversaciones que hemos mantenido, sus preguntas en los seminarios que siempre ayudaban mucho, por el proyecto de colaboración que hemos compartido y finalmente por todo el apoyo mostrado durante este trabajo.

Me gustaría también agradecer a todas las entidades y proyectos que han subvencionado esta tesis y que sin ellos no habría sido posible realizarla. En especial me gustaría agradecer a la Xunta de Galicia por la beca predoctoral ED481A-2018/34, 2018-2021 que me ha subvencionado la tesis y mi estancia predoctoral.

I would like also to thank Brian for the opportunity to do my predoctoral stay at Caltech and the Stoltz family, in special Harry for all the moments and meals we spent together. I spent three great months with Remi, Eric, Chris, Tyler, Nick, Alex, Fa, Carina, Austin and all the guys from the lab. I would like to thank Sarah Reisman and her group. #StoltzGroupBestGroup

A mis compañeros del laboratorio, a los antiguos: Andrea, por haberme enseñado y acogido cuando llegué al laboratorio; a Damián, por haber sido siempre un apoyo, una pregunta y una respuesta para todo, y por todas nuestras discusiones de cualquier tema que siempre hacían más ameno el trabajo; a Rodri, por haberme dejado en herencia el proyecto y por todos los consejos que me has dado; a José, por ser vecinos de vitrinas, por nuestros momentos madridistas y haber compartido sendas tesis casi enteras; a Jaime Suárez por tu especial ayuda en toda la parte inorgánica desarrollada en la tesis; a Nuria, por ser verdaderamente una amiga que me lo has demostrado durante toda mi tesis, por las tardes de Catán, Dixit y cualquier juego al igual que por todos esos jueves de cervezas post-pandemia. También quería agradecer a los compañeros que llegaron después de mi, como Jesús, siempre elegante, tiene una sonrisa y una pregunta que hacer; a Sergio, por ser tan amable, buen compañero y servicial con los demás; a Álex, que según llegó al laboratorio empezó a demostrar todo su potencial químico con sus preguntas de acoso y derribo y por nuestros cafés. También me gustaría agradecer a otras personas que han pasado por el laboratorio como Jose, Antía, Mauro, Nadesh y Sergio.

A los compañeros del grupo de Fañanás, a Eva, por todos los años de amistad desde el máster; a Nuria, que empezamos vitrina con vitrina y por todas las risas y buenas caras que siempre ayudan; a Andrés, por los momentos pasados en el laboratorio mientras hacía el TFG y TFM; a Isa, Andrea, Víctor, Pol, Balatz, Isaac, Jaime, Edu y Maider por todo lo compartido juntos.

Mención especial requiere el grupo de Granja y Montenegro. Hemos compartido comidas, cafés, cenas, fiestas, viajes, ir a la playa, partidos de tenis y pádel, que me han hecho sentir como uno más del grupo. Agradecimiento especial a Héctor, Iván, Sandra, Evita, Nacho, Alberto, Marisa, Ale, Lamas, Chema, Fede, José, Richard, Geert, Ghibom, Juanillo y Lionel. A Giulia, Alfonso, y Viqui por ser unos verdaderos amigos y estar ahí cuando os he

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necesitado. A Ángel, mi mentor en Salamanca que volvimos a coincidir aquí, siendo una de las mejores personas que conozco y ojalá coincidamos en el futuro.

También me gustaría agradecer a nuestros vecinos "Guitianes", en especial a Jesús, por haber compartido tantos momentos desde el máster y a Iago, por toda la ayuda que me diste cuando la necesité y por los momentos fuera del laboratorio. Admeás agradecer a Ángela todas las comidas y el viaje por California. A Roi, por los momentos compartidos en la SXGQ y las cervezas fuera del laboratorio y a Beni por las cervezas de desconexión.

A mis mejores amigos de Salamanca Marcos, Aitor, Kiko y Garci porque, aunque estemos separados siempre estamos juntos. También Inés, Miguel, Héctor, Rodri, Diego, Villa, Víctor y Jesús por los grandes momentos. A Iván, Yagu, Sergio, Álvaro, Rubén, Monti, Alex, Sando, Feli por todas las vacaciones, barbacoas, partidos de fútbol y fiestas que hemos disfrutado desde pequeños. A mis amigos del pueblo Juan, Rober e Imanol, por todos los veranos, fiestas del pueblo, navidades y semanas santas que siempre que podemos nos juntamos para echar el derbi.

A mis compañeros de la carrera Alex, Recu, Nacho, Pablo, Rachid y Sara, por todos los momentos en clase, en la biblioteca, los trabajos y nuestras noches de fiesta.

A Marta, mi compañera desde el principio de este camino. Has estado en los malos y en los buenos momentos. Por aguantarme cuando estoy de al humor y mis malas contestaciones. Por nuestros viajes a Paris, Málaga, Granada, Asturias, Canadá, California y por los viajes que nos quedan. Porque siempre has estado y estarás ahí.

A mi familia, en especial a mi hermano y mis padres. Me disteis la oportunidad de poder venir a Santiago, habéis estado junto a mí siempre y cuando os he necesitado no os ha importado dejarlo todo por estar junto a mi.

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*A mis padres*

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# Lists of Abbreviations and Acronyms

| | |
|---|---|
| Ac | Acetyl |
| AcOEt | Ethyl acetate |
| ACP | Alkylidenecyclopropane |
| AIBN | Azobisisobutyronitrile |
| Ar | Aryl |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphtalene |
| BINOL | Bi-naphthol |
| Bn | Benzyl |
| BNP | Binaphthyl phosphoric acid |
| Bpin | Bis(pinacolato)diboron |
| Boc | *tert*-Butoxycarbonyl |
| BQ | 1,4-Benzoquinone |
| bs | Broad singlet |
| Bz | Benzoyl |
| BZD | Benzodiazepine |
| BZO | Benzoxazepine |
| CAN | Cerium ammonium nitrate |
| CI | Chemical ionization |
| CMD | Concerted Metalation-Deprotonation |
| CNS | Central Nervous System |
| cod | 1,5-cyclooctadiene |
| Cp* | 1,2,3,4,5-pentamethyl cyclopentadienyl |
| Cy | Cyclohexyl |
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| dba | Dibenzylideneacetone |
| DCC | Dicyclohexylcarbodiimide |
| DCE | Dichloroethane |
| DCM | Dichloromethane |
| DEAD | Diethyl azodicarboxylate |
| DG | Directing group |
| DFT | Density functional theory |
| DHF | Dihydrofuran |
| DIAD | Diisopropyl azadicarboxylate |
| DIBAL-H | Diisobutylaluminium hydride |
| DIPEA | Diisopropylethylamine |
| DKR | Dinamic Kinetic Resolution |
| 2,6-DMBQ | 2,6-Dimethyl-1,4-benzoquinone |
| DMF | *N,N*-Dimethylformamide |
| DMP | Dess-Martin Periodinane |
| DMSO | Dimethyl sulfoxide |
| dppp | 1,3-Bis(diphenylphosphino)propane |
| dppf | 1,1'-Bis(diphenylphosphino) ferrocene |
| d.r. | Diastereomeric ratio |
| 2,5-DtBBQ | 2,5-Di-*tert*-butyl-1-4-benzoquinone |

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| | |
|---|---|
| DTBM | 3,5-Di-*tert*-butyl-4-methoxyphenyl |
| ee | Enantiomeric excess |
| EDG | Electron donating group |
| e.r. | Enantiomeric ratio |
| ESI | ElectroSpray Ionization |
| EWG | Electron Withdrawing Group |
| FDA | U.S. Food and Drug Administration |
| Garphos | (4,4',6,6'-Tetramethoxybiphenyl-2,2'diyl) bis(diphenyl)phosphine |
| GC | Gas Chromatography |
| HIV | Human Immunodeficiency Viruses |
| HFIP | 1,1,1,3,3,3-Hexafluoro-2-propanol |
| HPLC | High Performance Liquid Chromatography |
| HRMS | High Resolution Mass Spectrometry |
| *i*-Pr | Isopropyl |
| L | Ligand |
| L* | Chiral ligand |
| LDA | Lithium diisopropylamide |
| [M] | Metal |
| Me | Methyl |
| MeBQ | Methyl-*p*-benzoquinone |
| MLn | Coordinated metal complex |
| MOMCl | Chloromethyl methyl ether |
| MPAA | Monoprotected amino acid |
| MS | Mass Spectrometry |
| Ms | Mesyl, Methanesulfonyl |
| MW | Microwave |
| Naph | Naphthalene |
| NBS | *N*-bromosuccinimide |
| NHC | *N*-heterocyclic carbene |
| NMR | Nuclear Magnetic Resonance |
| Ns | 4-Nitrobenzenesulfonyl |
| 2-Ns | 2-Nitrobenzeenesulfonyl |
| Nu | Nucleophile |
| OFBA | *ortho*-Fluorobenzoic acid |
| o/n | Overnight |
| PG | Protecting group |
| Ph | Phenyl |
| Phox | [2-(Diphenylphosphino)phenyl]-2-oxazoline |
| PMP | *p*-Methoxyphenyl |
| PPTS | Pyridinium *p*-toluenesulfonate |
| Py | Pyridine |
| quant | Quantitative |
| rac | Racemic |
| RCM | Ring-Closing Metathesis |
| RE | Reductive Elimination |
| Ref. | Reference |
| r.r. | Ratio of regioisomers |

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| | |
|---|---|
| rt | Room temperature |
| Segphos | (4,4'-Bi-1,3-benzodioxole)-5,5'diyl]bis[diphenylphosphine] |
| SFC | Supercritical Fluid Chromatography |
| SPhos | 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl |
| TBAF | Tetrabutylammonium fluoride |
| TBS | *Tert*-butyldimethylsilyl |
| TEMPO | 2,2,6,6-Tetramethyl-1-piperidinyloxy |
| Tf | Trifluoromethanesulfonyl |
| TFA | Trifluoroacetic acid/trifluoroacetate |
| TFE | 2,2,2-Trifluoroethanol |
| THF | Tetrahydrofuran |
| TLC | Thin Layer Chromatography |
| TM | Transition metal |
| TMEDA | *N,N,N',N'*-tetramethyl ethylenediamine |
| TMS | Trimethylsilyl |
| TRIP | 3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate |
| TS | Transition State |
| Ts | Tosyl |
| TsOH | *p*-Toluenesulfonic acid |

**Units/ Symbols**

| | |
|---|---|
| Å | Angstrom |
| Atm | Atmosphere |
| ºC | Degree Celsius |
| Hz | Hertz |
| cal | Calorie |
| g | Gram |
| M | Molar |
| mol | Mole |
| Ppm | Parts per millon |
| Δ | Heat |
| hν | Light |
| m/z | Mass/charge relationship |

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# Resumen

El desarrollo y puesta en acción de nuevas estrategias de síntesis de compuestos orgánicos se configura como uno de los motores necesarios para actualizar y renovar la industria química actual. La preparación de productos de alto valor añadido como fármacos, nuevos polímeros orgánicos degradables y ecoeficientes, materiales inorgánicos de alta eficacia, etc, requiere de métodos sintéticos muy eficientes para transformar materiales de partida no funcionalizados, y de fácil accesibilidad. La utilización de catalizadores activos y selectivos (como enzimas biológicos) en la transformación de compuestos no funcionalizados en productos de alto valor añadido (sin generación de residuos, con alta economía atómica) es sin duda de capital importancia para el progreso mundial (*Green Chemistry, Química Sostenible)* (**Principles of Green Chemistry**).

Es una realidad evidente que la calidad de vida ha mejorado enormemente debido a la gran revolución tecnológica e industrial del mundo actual. En concreto, el mundo occidental en el que nos encuadramos alcanza tasas de longevidad nunca vistas hasta la actualidad. Esta mejora de la calidad de vida conlleva la aparición de nuevas patologías crónicas que antes se desconocían, como distintos tipos de cáncer, enfermedades neurodegenerativas (Alzheimer, Parkinson…), desórdenes metabólicos o bacterias resistentes, que necesitan ser abordadas.

La mayoría de los fármacos utilizados para combatir las enfermedades contienen núcleos heterocíclicos en su estructura y necesitan ser sintetizados en el laboratorio. Para su síntesis, el reto más importante es el desarrollo de nuevas metodologías sostenibles (*Green Chemistry*), frente a las síntesis clásicas de estos farmacóforos generadoras de una gran cantidad de residuos contaminantes y peligrosos para el medioambiente. Las herramientas sintéticas utilizadas para avanzar hacia la sostenibilidad en los métodos de producción están basadas en la catálisis (organometálica, organocatálisis y procesos foto-redox).

Una amplia familia de fármacos ampliamente utilizados para el tratamiento de diversas enfermedades son las benzazepinas, benzodiazepinas y benzoxazepinas. Éstos son heterociclos benzofusionados de siete miembros con una alta actividad biológica. Más en concreto, en esta tesis nos centramos en las 3-benzazepinas, 1,4-benzodiazepinas y 1,4-benzoxazepinas. Estos tres núcleos se muestran como los más activos biológicamente dentro de sus respectivas familias, debido a su interacción con el Sistema Nervioso Central (SNC) humano, una gran variedad de receptores como son el $GABA_A$, los receptores de Dopamina y Serotonina o su facilidad para intercalar en el ADN humano. Estas propiedades les permiten ser utilizados para tratar enfermedades como la obesidad, la ansiedad, el Alzheimer, problemas de insomnio, cáncer, o hasta el VIH. Durante el primer capítulo de tesis se ha recogido la clasificación de los núcleos benzazepínicos, benzodiazepínicos y benzoxazepínicos según la disposición de los heterátomos en el anillo de siete miembros. Además, sus propiedades biológicas e interacciones con el cuerpo humano también se explican. Finalmente, se clasifican los métodos sintéticos de acceso a los núcleos benzazepínicos, benzodiazepínicos y benzoxazepínicos en métodos clásicos y métodos catalíticos durante la última mitad del siglo XX y principios de siglo XXI. Los métodos catalíticos han ayudado a avanzar a la química hacia procesos que respetan más el medioambiente, generando menos cantidades estequiométricas de residuos peligrosos, debido al empleo de cantidades catalíticas de metales de transición.

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La síntesis clásica de estos ciclos de siete miembros benzofusionados se ha basado en síntesis de múltiples etapas consecutivas lo que generan grandes cantidades de residuos tóxicos. Dada la evolución de nuestro mundo actual, se asemeja obligatoria el desarrollo de nuevos procesos químicos que permitan acceder a estos potentes núcleos con actividad biológica mediante reacciones químicas que respeten el medioambiente (química verde) En un intento hacia esta química verde más sostenible, las reacciones catalizadas por metales de transición se han empleado satisfactoriamente para sintetizar dichos heterociclos en las últimas décadas. Así, el empleo de cantidades catalíticas de metales de transición ha ayudado a disminuir en parte la generación de residuos tóxicos. Sin embargo, este tipo de reacciones requiere la funcionalización previa de los sustratos antes de la catálisis, como por ejemplo la introducción regioselectiva de halógenos en las moléculas, los cuáles son claves en las reacciones catalizadas por metales de transición (acoplamientos cruzados, reacciones de tipo Heck, etc) y cuyos residuos halogenados son muy tóxicos para el medioambiente, la capa de ozono y la atmósfera terrestre en general.

Por otro lado, los enlaces C-H son los más abundantes en los compuestos orgánicos. Pese a su baja reactividad, debido a sus altas energías de disociación de enlace (Energía de disociación de enlace $C_{sp^2}$-H = 106-113 Kcal·mol$^{-1}$ y $C_{sp^3}$-H = 90-102 Kcal· mol$^{-1}$), y su alta abundancia se vislumbra difícil una adecuada activación regioselectiva de dichos enlaces. Sin embargo, el empleo de cantidades catalíticas de metales de transición y la utilización de grupos directores, compuestos por heteroátomos capaces de coordinarse a un centro metálico de forma lábil dirigiendo el centro metálico activo a un determinado enlace C-H, ha ayudado a superar dichos problemas. Por esta razón, la activación de enlaces C-H para una posterior funcionalización y formación de nuevos enlaces C-X (X = heteroátomo) se ha convertido en una herramienta sintética muy poderosa en las últimas décadas. Esta metodología ha abierto nuevos caminos de retrosíntesis hacia moléculas de alto valor añadido que antes eran impensables. El uso de la activación C-H junto a un correcto agente de acoplamiento puede permitir la síntesis de heterociclos (cicloadiciones oxidativas). Por ejemplo, esto ha sido frecuentemente utilizado para la síntesis de anillos benzofusionados de 5 y 6 miembros. Sin embargo, su aplicación a anillos de siete miembros no es tan fácil, debido a que primeramente se deben formar metalaciclos de gran tamaño, y que la entropía de la reacción no es favorable para sus síntesis. Durante el capítulo 2 de la presente tesis se explica la síntesis de 3-benzazepinas mediante reacciones de activación C-H catalizada por paladio de sustratos de partida fácilmente sintetizables (una o dos etapas de síntesis). Primero se estudió la importancia del grupo director. El grupo -NHTf se mostró como capital para desarrollar la reacción de cicloadición (5+2), dado que fue el único grupo director con el cuál se observó reacción. Una vez optimizadas las condiciones de reacción se llevo a cabo la exploración del alcance de la reacción entre derivados de la fenetilamina y 1,3-dienos, ambos tipos de sustratos fueron sintetizados en el laboratorio en una o dos etapas de síntesis. La reacción toleró dienos aromáticos con sustitución en cualquier posición del anillo aromático. Además de dienos aromáticos, otro tipo de dienos como son los alifáticos o los electrodeficientes (conjugados con amida de Weinreb) funcionaron en buenos rendimientos. También se analizó la sustitución en el anillo aromático de los derivados de fenetilamina, tolerando desde grupos electrondadores a electronatractores en cualquier posición del anillo. Después se analizó la diastereoselectividad de la reacción, observándose una completa diastereoselectividad cuando la cadena alifática que conectaba el grupo director y el anillo aromático tenía sustitución en la posición alfa al grupo -NHTf. Sin embargo, la sustitución en la posición bencílica mostró una baja diastereoselectividad.

En un intento de obtener más información sobre el mecanismo de la reacción, se realizaron distintos estudios mecanísticos en los que dos paladaciclos fueron aislados y completamente caracterizados por técnicas de RMN, IR y rayos X, las cuáles mostraron la conformación exacta del paladaciclo después de la etapa de activación C-H. Además, se realizó la reacción estequiométrica, dando lugar al producto deseado en rendimientos cuantitativos.

El Prof. Varela realizó estudios mecanísticos con cálculos de DFT lo que mostró que el mecanismo de la reacción tenía las siguientes etapas: una primera activación C-H que se asumió *vía* mecanismo de metalación-desprotonación concertada (CMD). A continuación, una inserción 1,2 del dieno en el paladaciclo previa coordinación (a través de los dos dobles enlaces) al centro metálico dio lugar a un intermedio π-Pd-alilo que, finalmente libera el producto después de un ataque nucleófilo tipo $S_N2$ sobre el alilo de un intermedio Zwiteriónico.

Dado que en el transcurso de la reacción se genera un carbono asimétrico, la reacción enantioselectiva también se estudió. Desafortunadamente no se obtuvieron buenos resultados con ninguno de los ligandos típicamente utilizados en este tipo de reacciones como pueden ser ligandos de tipo aminoácidos monoprotegidos, ligandos tipo bifosfina, NHCs o bidentados de tipo P,N. Por el contrario, dado que la reacción es completamente diastereoselectiva cuando el sustrato de partida tiene sustitución en la posición alfa al NHTf, se llevó a cabo un estudio de desimetrización. Esta técnica, la cuál fue pionero el Prof. J.-Q. Yu, consiste en crear un centro con una esteroquímica determinada a partir de un carbono proquiral, carbono que contiene dos sustituyentes iguales y que tiene potencial de convertirse en un carbono asimétrico mediante la activación enantioselectiva de un C-H. Así, después del estudio de desimetrización observamos que se pudieron obtener de moderadas a altas enantioselectividades de los productos obtenidos, aunque en bajo rendimientos químicos cuando se empleó *L-p*Glu-OH. Esto se puede explicar debido a que existe una competición de activación del enlace C-H entre el acetato (presente en el oxidante y la fuente de paladio) y el ligando quiral *L-p*Glu-OH. Aun así, este ejemplo se muestra como el primero que permite la obtención de 3-benzazepinas quirales mediante la desimetrización de un compuesto proquiral.

En el capítulo 3 de la presente tesis hemos abordado el estudio de obtención de 1,4-benzodiazepinas de forma enantioselectiva. Las 1,4-benzodiazepinas se muestran como uno de los medicamentos de tipo azepínico más utilizados. Su interacción con receptores como el $GABA_A$ o su intercalación en la cadena del ADN humano las hace muy activas biológicamente. Así, han sido empleadas para tratar depresiones, el insomnio, la ansiedad o como relajantes musculares. Este tipo de núcleos son más selectivos que los típicamente utilizados barbitúricos, dado que tienen un control totalmente dirigido sobre el sistema límbico.

Continuando con nuestro programa de síntesis de compuestos activos biológicamente mediante el empleo de técnicas consideradas "verdes", nosotros nos centramos en la catálisis de metal-hidruro. Esta técnica consiste en la generación de un catalizador asimétrico que contenga un hidruro reactivo, a partir de un catalizador metálico, un ligando quiral y un ácido de Brønsted. Este catalizador se inserta regioselectivamente en un alquino o un aleno (intermedio avanzado de la reacción) para finalmente formar un alilo que será atrapado por un nucleófilo y finalmente liberar el producto deseado. La utilización de un ligando quiral adecuado permitirá obtener el producto de forma enantioselectiva. El grupo del Prof. Yamamoto fue pionero en la utilización de dicha herramienta sintética, obteniendo ciclos de

5 y 6 miembros mediante catálisis de paladio a partir de alquinos internos y alenos. Después otros autores han ampliado la técnica y el alcance de ella utilizando otros metales como puede ser el rhodio o el oro. A nuestro conocimiento, esta técnica no ha sido empleada para obtener 1,4-benzodiazepinas.

Con este objetivo sintetizamos dos alquinos internos para estudiar la reacción de ciclación. Comenzamos con un estudio del metal, en el cuál el Rh se mostró como el único que catalizaba la reacción de ciclación. Posteriormente y después de una optimización de las condiciones de reacción, para la reacción racémica, se pudo concluir que ácidos de Brønsted quirales no transferían información quiral al producto, por lo que se comenzó a estudiar la reacción enantioselectiva utilizando ligandos quirales. Una variedad de ligandos quirales fueron utilizados con el primer alquino de partida que contenía un grupo NBoc que conectaba el nucleófilo y el alquino. Dado las bajas enantioselectividades, nos preguntamos si el grupo NBoc dotaba a la molécula de la suficiente rigidez, por lo que decidimos introducir un NTs en su lugar. Con este grupo observamos que la enantioselectividad mejoraba considerablemente, pero no llegamos a altas enantioselectividades. En este punto, nos propusimos la síntesis de dos alenos, en lugar de los alquinos. Los alenos son intermedios en la reacción de isomerización del alquino con protones en alfa. De hecho, son los intermedios anteriores al metal alilo que será posteriormente funcionalizado. Así, comenzamos a estudiar la reactividad de ambos alenos, obteniendo moderadas enantioselectividades para el aleno que contenía el NBoc, aunque mejores que para su respectivo alquino. Sin embargo, al cambiar al aleno con NTs conseguimos elevadas enantioselectividades cuando la reacción se llevó a cabo en presencia de ligandos biarílicos con quiralidad axial de tipo DTBM-Garphos. Con las condiciones de reacción optimizadas, se estudió el alcance de la reacción. La reacción funcionó en buenos a excelentes rendimientos y excelentes enantioselectividades tolerando una amplia gama de sustituciones en el anillo aromático por grupos electrondadores, electronatractores, halógenos o alquilos. Sin embargo, cuando se cambió la naturaleza del nucleófilo por un alcohol, se observó que la correspondiente 1,4-benzoxazepina se obtuvo en bajas enantioselectividades. Además, otro tipo de nucleófilos desafortunadamente no funcionaron (amidas o tosilamidas), tampoco alenos multisustituidos.

Una vez explorado el alcance de la reacción, nos dispusimos a variar químicamente la molécula. Primeramente, para ensalzar la estrategia sintética, pudimos quitar selectivamente ambos grupos protectores de los correspondientes nitrógenos. Además, se realizó una síntesis en 3 etapas desde la 1,4-benzodiazepina obtenida, sin pérdida de la enantioselectividad, de un intermedio avanzado del Lixivaptan®, el cuál se mostró como un antagonista del receptor $V_2$ de la vasopresina para tratar la insuficiencia cardíaca congestiva y la cirrosis hepática.

En el cuarto capítulo de tesis nos propusimos la síntesis de 1,4-benzoxazepinas mediante una activación C-H alílica catalizada por paladio. Las 1,4-Benzoxazepinas fueron descubiertas a mediados de siglo XX como agentes bloqueadores adrenérgicos que poseen la propiedad de impedir las transmisiones de impulsos a lo largo del sistema nervioso simpático. Desde este descubrimiento, una amplia variedad de benzoxazepinas se fueron aislando y descubriendo, encontrándose una alta y potente actividad farmacológica como actividad antihistamínica, propiedades antiinflamatorias, tranquilizadores, psicotrópicos, psiconeuréticos, actividad anticancerígena, analgésicos, inhibición de la escualeno sintasa, antibacterianos, antifúngicos, antiepilépticos, tratamiento contra la enfermedad de Alzheimer o el VIH. Continuando con la temática de la tesis, en la síntesis sostenible de anillos de siete miembros benzofusionados y animados por esta potente actividad biológica

del núcleo benzoxazepínico, estudiamos la síntesis de estos núcleos mediante una reacción de activación C-H alílica, que se ha mostrado como la herramienta más sostenible de formar un complejo electrofílico Pd-π-alilo que puede ser más tarde funcionalizado. Esta herramienta se conoce desde mediados del siglo XX, pero no fue hasta principios de siglo XXI cuando comenzó su verdadera explosión sintética. Consiguiéndose la síntesis selectiva de compuestos lineales o compuestos ramificados con el simple empleo de aditivos tipo sulfóxido o DMSO. Posteriormente, su empleo en la formación de anillos benzofusionados de 6 miembros fue altamente estudiada por el grupo de la Prof. White y el Prof. Gong. También se llevaron a cabo estudios de las variantes enantioselectivas para las cuales, se emplearon ligandos tipo L-SOX (que contiene un sulfóxido y una oxazolina en la molécula), fosforamiditos o ligandos organometálicos complejados a metales como el cobre.

Con estos precedentes comenzamos nuestro estudio, con sustratos de partida fácilmente sintetizables en el laboratorio (dos o tres etapas de síntesis) y observamos rápidamente que la formación de la 1,4-benzoxazepina se podía conseguir en rendimientos cuantitativos cuando empleamos un catalizador de paladio, un acido de fosfórico y ligandos tipo L-SOX. Con el ligando racémico se realizó el estudio de alcance de la reacción. Se observó que el anillo aromático podía ser sustituido en cualquier parte con una variedad de grupos funcionales, como son los grupos electrondadores, electronatractores, alquilos o halógenos dando lugar al producto 1,4-benzoxazepínico correspondiente de moderados a altos rendimientos. Después se realizó el estudio de diastereoselectividad de la reacción introduciendo sustituyentes en la cadena alifática que conectaba el alcohol con el anillo aromático. Se observó que grupos pequeños como el metilo dieron bajas diastereoselectividades y que por el contrario grupos más voluminosos como el fenilo proporcionó el correspondiente producto en altas diastereoselectividades (10:1). Después se evaluó la diastereoselectividad cuando se introdujo un grupo metilo en alfa al NTs que conectaba con el doble enlace. En ese caso se observó una buena diastereoselectividad para el metilo (5:1). Posteriormente se evaluó la necesidad del anillo aromático para el desarrollo de la reacción, observándose la formación de dos tipos de oxazepan en buenos rendimientos con distinto tipo de efecto Thorpe-Ingold. También se valoró el nucleófilo de la reacción, y no solo alcoholes bencílicos fueron tolerados, también otros grupos con distinta nucelofilia como los fenoles, ácidos carboxílicos o tosilamidas dieron lugar a los correspondientes núcleos con disposición 1,4- de los correspondientes heteroátomos.

Una vez estudiado el alcance de la reacción se pasó a estudiar la reacción enantioselectiva. Para ello se sintetizaron distintos ligandos de tipo L-SOX, que desafortunadamente no mostraron una transferencia de la información quiral al producto obtenido. También se sintetizaron unos ligandos organometálicos que fueron descritos por el Prof. Matsunaga recientemente. Estos son ligandos simétricos en tanto en cuanto tienen dos partes orgánicas idénticas, y se forma mediante la condensación de un aldehído con una diamina. Después de sintetizar 4 tipos de ligandos con distinto entorno quiral (antraceno, binaftilo, dibencilo, ciclohexilo) se complejaron a un metal (Cobre) y se estudio su reacción enantioselectiva. Desafortunadamente no mostraron ninguna actividad para la formación de la 1,4-benzoxazepina.

Finalmente, con el objetivo de demostrar la potencia sintética del método se realizó una derivatización de la 1,4-benzoxazepina obtenida. Para nuestro deleite, el grupo tosilo se puede quitar selectivamente en altos rendimientos, al igual que el doble enlace que contiene la molécula se pudo transformar mediante reacciones sencillas en ácido carboxílico, alcohol

o realizarse una reacción de metátesis cruzada con el uso del catalizador de Hoveyda y Grubbs de 2ª generación.

En conclusión, en la presente tesis se ha realizado una aproximación sintética basada en métodos que respetan el medioambiente y recoge el libro de *"Principles of Green Chemistry"*. Se sintetizaron 3-benzazepinas, núcleos muy interesantes debido a su interacción con el Sistema Nervioso Central humano y una amplia variedad de receptores, mediante reacciones de activación C-H catalizadas por complejos de paladio y empleando como oxidante oxígeno molecular en combinación con cantidades subestequiométricas de cobre. Estudios mecanísticos experimentales y en combinación con DFT arrojaron luz sobre el verdadero mecanismo de la reacción. Además, se estudió la reacción enantioselectiva y se exploró una síntesis asimétrica basada en la desimetrización del sustrato de partida. Posteriormente también se realizó la síntesis enantioselectiva de 1,4-benzodiazepinas mediante reacciones catalizadas por complejos asimétricos de rhodio-hidruro. Se toleró una amplia variedad de grupos funcionales en la molécula. También se realizó una aproximación sintética completamente enantioselectiva a un intermedio avanzado del Lixivaptan®, ensalzando la metodología sintética. Finalmente, la síntesis de 1,4-benzoxazepinas a través de reacciones de activación C-H alílica catalizadas por complejos paladio en combinación con ligandos que contiene sulfóxidos fueron realizadas con éxito. Se observó un amplio alcance de la reacción tolerándose una gran variedad de grupos funcionales y también distintos tipos de nucleófilos. Además, se estudió la influencia del efecto de Thorpe-Ingold en la molécula y la diastereoselectividad de la reacción. Desafortunadamente, los intentos hacia la reacción enantioselectiva catalizada por paladio en combinación con ligandos L-SOX de tipo sulfóxido-oxazolina quirales, dieron lugar a bajas enantioselectividades y, por otro lado, los ligandos desarrollados recientemente por el Prof. Matsunaga, que contienen un centro metálico coordinado a una molécula orgánica simétrica con una diimina y dos alcoholes no funcionaron en esta reacción.

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# Resumo

O desenvolvemento e posta en acción de novas estratexias de síntese de compostos orgánicos configúrase como un dos motores necesarios para actualizar e renovar a industria química actual. A preparación de produtos de alto valor engadido como fármacos, novos polímeros orgánicos degradables e ecoeficientes, materiais inorgánicos de alta eficacia, etc, require de métodos sintéticos moi eficientes para transformar materiais de partida non funcionalizados e de fácil accesibilidade. A utilización de catalizadores activos e selectivos (como encimas biolóxicos) na transformación de compostos non funcionalizados en produtos de alto valor engadido (sen xeración de residuos, con alta economía atómica) é sen dúbida de capital importancia para o progreso mundial (Green Chemistry, Química Sostible) ( Principles of Green Chemistry).

É unha realidade evidente que a calidade de vida mellorou enormemente debido á gran revolución tecnolóxica e industrial do mundo actual. En concreto, o mundo occidental no que nos encadramos alcanza taxas de lonxevidade nunca vistas ata a actualidade. Esta mellora da calidade de vida conleva a aparición de novas patoloxías crónicas que antes se descoñecían, como distintos tipos de cancro, enfermidades neurodexenerativas (Alzheimer, Parkinson…), desordes metabólicos ou bacterias resistentes, que necesitan ser abordadas.

A maioría dos fármacos utilizados para combater as enfermidades conteñen núcleos heterocíclicos na súa estrutura e necesitan ser sintetizados no laboratorio. Para a súa síntese, o reto máis importante é o desenvolvemento de novas metodoloxías sostibles (Green Chemistry), fronte ás sínteses clásicas destes farmacóforos xeradoras dunha gran cantidade de residuos contaminantes e perigosos para o medioambiente. As ferramentas sintéticas utilizadas para avanzar cara á sustentabilidade nos métodos de produción están baseadas na catálise ( organometálica, organocatálise e procesos foto- redox).

Unha familia de fármacos amplamente utilizados para o tratamento de diversas enfermidades son as benzazepinas, as benzodiazepinas e as benzoxazepinas. Estes son heterociclos benzofusionados de sete membros cunha alta actividade biolóxica. Máis en concreto, nesta tese centrámonos nas 3- benzazepinas, nas 1,4- benzodiazepinas e nas 1,4-benzoxazepinas. Estes tres núcleos móstranse como os máis activos biolóxicamente dentro das súas respectivas familias, debido á súa interacción co Sistema Nervioso Central (SNC) humano, unha gran variedade de receptores como son o $GABA_A$, os receptores de Dopamina e Serotonina ou a súa facilidade para intercalar no ADN humano. Estas propiedades permítenlles ser utilizados para tratar enfermidades como a obesidade, a ansiedade, o Alzheimer, problemas de insomnio, cancro, ou ata o VIH. Durante o primeiro capítulo de tese recolleuse a clasificación dos núcleos benzazepínicos, benzodiazepínicos e benzoxazepínicos segundo a disposición dos heterátomos no anel de sete membros. Ademais, tamén se explican as súas propiedades biolóxicas e interaccións co corpo humano. Finalmente, clasifícanse os métodos sintéticos de acceso aos núcleos benzazepínicos, benzodiazepínicos e benzoxazepínicos en métodos clásicos e métodos catalíticos durante a última metade do século XX e principios de século XXI. Os métodos catalícos axudaron a avanzar á química cara a procesos que respectan máis o medioambiente, xerando menos cantidades estequiométricas de residuos perigosos, debido ao emprego de cantidades catalíticas de metais de transición.

A síntese clásica destes ciclos de sete membros benzofusionados baseouse en sínteses de múltiples etapas consecutivas o que xeran grandes cantidades de residuos tóxicos. Dada a

evolución do noso mundo actual, aseméllase obrigatoria o desenvolvemento de novos procesos químicos que permitan acceder a estes potentes núcleos con actividade biolóxica mediante reaccións químicas que respecten o medioambiente (química verde) Nun intento cara a esta química verde máis sostible, as reaccións catalizadas por metais de transición empregáronse satisfactoriamente para sintetizar devanditos heterociclos nas últimas décadas. Así, o emprego de cantidades catalíticas de metais de transición axudou a diminuír en parte a xeración de residuos tóxicos. Con todo, este tipo de reaccións require a funcionalización previa dos substratos antes da catálisis, por exemplo a introdución rexioselectiva de halóxenos nas moléculas, os cales son claves nas reaccións catalizadas por metais de transición (axustes cruzados, reaccións de tipo Heck, etc) e cuxos residuos haloxenados son moi tóxicos para o medioambiente, a capa de ozono e a atmosfera terrestre en xeral.

Doutra banda, os enlaces C- H son os máis abundantes nos compostos orgánicos. A pesar da súa baixa reactividade, debido ás súas altas enerxías de disociación de enlace (Enerxía de disociación de enlace $C_{sp^2}$- H = 106-113 Kcal· mol-1 e $C_{sp^3}$- H = 90-102 Kcal· mol-1), e a súa alta abundancia albíscase difícil unha adecuada activación rexioselectiva dos devanditos enlaces. Con todo, o emprego de cantidades catalíticas de metais de transición e a utilización de grupos directores, compostos por heteroátomos capaces de coordinarse a un centro metálico de forma lábil dirixindo o centro metálico activo a un determinado enlace C- H, axudou a exceder os devanditos problemas. Por esta razón, a activación de enlaces C-H para unha posterior funcionalización e formación de novos enlaces C-X (X = heteroátomo) converteuse nunha ferramenta sintética moi poderosa nas últimas décadas. Esta metodoloxía abriu novos camiños de retrosíntese cara a moléculas de alto valor engadido que antes eran impensables. O uso da activación C- H xunto a un correcto axente de acoplamento pode permitir a síntese de heterociclos ( cicloadicións oxidantes). Por exemplo, isto foi frecuentemente utilizado para a síntese de aneis benzofusionados de cinco e seis membros. Con todo, a súa aplicación a aneis de sete membros non é tan fácil, debido a que primeiramente se deben formar metalaciclos de gran tamaño, e que a entropía da reacción non é favorable para a súa síntese. No capítulo 2 da presente tese explícase a síntese de 3- benzazepinas mediante reaccións de activación C- H catalizadas por paladio de substratos de partida facilmente accesibles (unha ou dúas etapas de síntese). Primeiro estudouse a importancia do grupo director. O grupo - NHTf mostrouse como capital para desenvolver a reacción de cicloadición (5+2) dado que foi o único grupo director co cal se observou reacción. Unha vez optimizadas as condicións de reacción levouse a cabo a exploración do alcance da reacción entre derivados da fenetilamina e 1,3- dienos, ambos tipos de substratos foron sintetizados no laboratorio nunha ou dúas etapas de síntese. A reacción tolerou dienos aromáticos con substitución en calquera posición do anel aromático. Ademais de dienos aromáticos, outro tipo de dienos como son os alifáticos ou os electrodeficientes (conxugados con amida de Weinreb) acadaron bos rendementos. Tamén se analizou a substitución no anel aromático dos derivados de fenetilamina, tolerando desde grupos doantes de electróns a atractores de electróns en calquera posición do anel. Despois analizouse a diastereoselectividade da reacción, observándose unha completa diastereoselectividade cando a cadea alifática que conecta o grupo director e o anel aromático ten substitución na posición alfa ao grupo -NHTf. Con todo, a substitución na posición bencílica mostrou unha baixa diastereoselectividade.

Nun intento de obter máis información sobre o mecanismo da reacción, realizáronse distintos estudos mecanísticos nos que dous paladaciclos foron illados e completamente caracterizados por técnicas de RMN, IR e raios X, as cales mostraron a conformación exacta

do paladaciclo despois da etapa de activación C- H. Ademais, realizouse a reacción estequiométrica, dando lugar ao produto desexado en rendementos cuantitativos.

O Prof. Varela realizou estudos mecanísticos con cálculos de DFT o que mostrou que o mecanismo da reacción tiña as seguintes etapas: unha primeira activación C- H que se asumiu vía mecanismo de metalación- desprotonación concertada (CMD). A continuación, unha inserción 1,2 do dieno no paladaciclo previa coordinación (a través dos dous dobres enlaces) ao centro metálico deu lugar a un intermedio π- Pd- alilo que, finalmente liberou o produto despois dun ataque nucleófilo tipo $S_N2$ sobre o alilo dun intermedio zwiteriónico.

Dado que no transcurso da reacción xérase un carbono asimétrico, tamén se estudou a reacción enantioselectiva. Desafortunadamente non se obtiveron bos resultados con ningún dos ligandos tipicamente utilizados neste tipo de reaccións como poden ser ligandos de tipo aminoácidos monoprotegidos, ligandos tipo bifosfina, NHCs ou bidentados de tipo P,N. Pola contra, dado que a reacción é completamente diastereoselectiva cando o substrato de partida ten substitución na posición alfa ao NHTf, levouse a cabo un estudo de desimetrización. Esta técnica, na cal foi pioneiro o Prof. J. -Q. Yu, consiste en crear un estereocentro determinado a partir dun carbono proquiral, carbono que contén dous sustituintes iguais e que ten potencial de converterse nun carbono asimétrico mediante a activación enantioselectiva dun C- H. Así, despois do estudo de desimetrización observamos que se puideron obter de moderadas a altas enantioselectividades dos produtos obtidos, aínda que en baixo rendementos químicos cando se empregou L- pGlu-OH. Isto pódese explicar debido a que existe unha competición de activación do enlace C- H entre o acetato (presente no oxidante e a fonte de paladio) e o ligando quiral L- pGlu-OH. Aínda así, este exemplo móstrase como o primeiro que permite a obtención de 3- benzazepinas quirais mediante a desimetrización dun composto proquiral. No capítulo 3 da presente tese abordamos o estudo de obtención de 1,4- benzodiazepinas de forma enantioselectiva. As 1,4- benzodiazepinas móstranse como un dos medicamentos de tipo azepínico máis utilizados. A súa interacción con receptores como o $GABA_A$ ou o seu intercalación na cadea do ADN humano fainas moi activas biolóxicamente. Así, foron empregadas para tratar depresións, o insomnio, a ansiedade ou como relaxantes musculares. Este tipo de núcleos son máis selectivos que os tipicamente utilizados barbitúricos, dado que teñen un control totalmente dirixido sobre o sistema límbico.

Continuando co noso programa de síntese de compostos activos biolóxicamente mediante o emprego de técnicas consideradas "verdes", nós centrámonos na catálisis de metal- hidruro. Esta técnica consiste na xeración dun catalizador asimétrico que contén un hidruro reactivo, a partir dun catalizador metálico, un ligando quiral e un ácido de Brønsted. Este catalizador insérese rexioselectivamente nun alquino ou un aleno (intermedio avanzado da reacción) para finalmente formar un alilo que será atrapado por un nucleófilo e finalmente liberar o produto desexado. A utilización dun ligando quiral adecuado permitirá obter o produto de forma enantioselectiva. O grupo do Prof. Yamamoto foi pioneiro na utilización da devandita ferramenta sintética, obtendo ciclos de cinco e seis membros mediante catálise de paladio a partir de alquinos internos e alenos. Despois outros autores ampliaron a técnica e o alcance dela utilizando outros metais como pode ser o rodio ou o ouro. Ao noso coñecemento, esta técnica non foi empregada para obter 1,4- benzodiazepinas. Con este obxectivo sintetizamos dous alquinos internos para estudar a reacción de ciclación. Comezamos cun estudo do metal, no cal o Rh mostrouse como o único que catalizaba a reacción de ciclación. Posteriormente e despois dunha optimización das condicións de reacción, para a reacción racémica, púidose concluír que ácidos de Brø

nsted quirais non transfiren información quiral ao produto, polo que se comezou a estudar a reacción enantioselectiva utilizando ligandos quirais. Unha variedade de ligandos quirais foron utilizados co primeiro alquino de partida que contiña un grupo NBoc conectando o nucleófilo e o alquino. Dado as baixas enantioselectividades, preguntámonos se o grupo NBoc dotaba á molécula da suficiente rixidez, polo que decidimos introducir un NTs no seu lugar. Con este grupo observamos que a enantioselectividade melloraba considerablemente, pero non chegamos a altas enantioselectividades. Neste punto, propuxémonos a síntese de dous alenos, en lugar dos alquinos. Os alenos son intermedios na reacción de isomerización do alquino con protóns en alfa. De feito, son os intermedios anteriores ao metal alilo que será posteriormente funcionalizado. Así, comezamos a estudar a reactividade de ambos alenos, obtendo moderadas enantioselectividades para o aleno que contiña o NBoc, aínda que mellores que para o seu respectivo alquino. Con todo, ao cambiar ao aleno con NTs conseguimos elevadas enantioselectividades cando a reacción levouse a cabo en presenza de ligandos biarílicos con quiralidade axial de tipo DTBM- Garphos. Coas condicións de reacción optimizadas, estudouse o alcance da reacción. A reacción funcionou en bos a excelentes rendementos e excelentes enantioselectividades tolerando unha ampla gama de substitucións no anel aromático por grupos doantes e atractores de electróns, halóxenos ou alquilos. Con todo, cando se cambiou a natureza do nucleófilo por un alcol, observouse que a correspondente 1,4- benzoxazepina obtívose en baixas enantioselectividades. Ademais, outro tipo de nucleófilos desafortunadamente non funcionaron ( amidas ou tosilamidas), tampouco alenos multisustituidos.
Unha vez explorado o alcance da reacción, dispuxémonos a variar químicamente a molécula. Primeiramente, para resaltar a estratexia sintética, puidemos quitar selectivamente ambos os grupos protectores dos correspondentes nitróxenos. Ademais, realizouse unha síntese en tres etapas desde a 1,4- benzodiazepina obtida, sen perda da enantioselectividade, dun intermedio avanzado do Lixivaptan®, o cal se mostrou como un antagonista do receptor V2 da vasopresina para tratar a insuficiencia cardíaca conxestiva e a cirrose hepática.

No cuarto capítulo de tese propuxémonos a síntese de 1,4- benzoxazepinas mediante unha activación C- H alílica catalizada por paladio. As 1,4- benzoxazepinas foron descubertas a mediados de século XX como axentes bloqueadores adrenérgicos que posúen a propiedade de impedir as transmisións de impulsos ao longo do sistema nervioso simpático. Desde este descubrimento, unha ampla variedade de benzoxazepinas fóronse illando e descubrindo, atopándose unha alta e potente actividade farmacolóxica como actividade antihistamínica, propiedades antiinflamatorias, tranquilizadores, psicotrópicos, psiconeuréticos, actividade anticanceríxena, analxésicos, inhibición da escualeno sintasa, antibacterianos, antifúnxicos, antiepilépticos, tratamento contra a enfermidade de Alzheimer ou o VIH. Continuando coa temática da tese, na síntese sostible de aneis de sete membros benzofusionados e animados por esta potente actividade biolóxica do núcleo benzoxazepínico, estudamos a síntese destes núcleos mediante unha reacción de activación C- H alílica, que se mostrou como a ferramenta máis sostible de formar un complexo electrofílico Pd-π- alilo que pode ser máis tarde funcionalizado. Esta ferramenta coñécese desde mediados do século XX, pero non foi ata principios de século XXI cando comezou a súa verdadeira explosión sintética. Conseguíndose a síntese selectiva de compostos lineais ou compostos ramificados co simple emprego de aditivos tipo sulfóxido ou DMSO. Posteriormente, o seu emprego na formación de aneis benzofusionados de 6 membros foi altamente estudada polo grupo da Prof. White e o Prof. Gong. Tamén levaron a cabo estudos das variantes enantioselectivas para as cales,

empregáronse ligandos tipo L- SOX (que contén un sulfóxido e unha oxazolina na molécula), fosforamiditos ou ligandos organometálicos complexados a metais como o cobre.

Con estes precedentes comezamos o noso estudo, con substratos de partida facilmente sintetizables no laboratorio (dúas ou tres etapas de síntese) e observamos rapidamente que a formación da 1,4- benzoxazepina podíase conseguir en rendementos cuantitativos cando empregamos un catalizador de paladio, un acido de tipo fosfórico e ligandos tipo L- SOX. Co ligando racémico realizouse o estudo de alcance da reacción. Observouse que o anel aromático podía ser substituído en calquera parte cunha variedade de grupos funcionais, como son os grupos doantes e atractores de electróns, alquilos ou halóxenos dando lugar ao produto 1,4- benzoxazepínico correspondente con moderados a altos rendementos. Despois realizouse o estudo de diastereoselectividade da reacción introducindo sustituintes na cadea alifática que conecta o alcol co anel aromático. Observouse que grupos pequenos como o metilo deron baixas diastereoselectividades e que pola contra grupos máis voluminosos como o fenilo proporcionou o correspondente produto en altas diastereoselectividades (10:1). Despois avaliouse a diastereoselectividade cando se introduciu un grupo metilo en alfa ao NTs que conectaba co dobre enlace. Nese caso observouse unha boa diastereoselectividade para o metilo (5:1). Posteriormente avaliouse a necesidade do anel aromático para o desenvolvemento da reacción, observándose a formación de dous tipos de oxazepano en bos rendementos con distinto tipo de efecto Thorpe- Ingold. Tamén se valorou o nucleófilo da reacción, e non só alcois bencílicos foron tolerados, tamén outros grupos con distinta nucelofilia como os fenoles, ácidos carboxílicos ou tosilamidas deron lugar aos correspondentes núcleos con disposición 1,4- dos correspondentes heteroátomos.

Unha vez estudado o alcance da reacción pasouse a estudar a reacción enantioselectiva. Para iso sintetizáronse distintos ligandos de tipo L- SOX, que desafortunadamente non mostraron unha transferencia da información quiral ao produto obtido. Tamén se sintetizaron uns ligandos organometálicos que foron descritos polo Prof. Matsunaga recentemente. Estes son ligandos simétricos sempre que teñen dous partes orgánicas idénticas, e fórmase mediante a condensación dun aldehído cunha diamina. Despois de sintetizar 4 tipos de ligandos con distinta contorna quiral (antraceno, binaftilo, dibencilo, ciclohexilo) complexáronse a un metal (cobre) para estudar a súa reacción enantioselectiva. Desafortunadamente non mostraron ningunha actividade para a formación da 1,4- benzoxazepina.

Finalmente, co obxectivo de demostrar a potencia sintética do método realizouse unha derivatización da 1,4- benzoxazepina obtida. Para a nosa satisfación, o grupo tosilo pódese quitar selectivamente en altos rendementos, do mesmo xeito que o dobre enlace que contén a molécula púidose transformar mediante reaccións sinxelas en ácido carboxílico, alcol ou realizarse unha reacción de metátese cruzada co uso do catalizador de Hoveyda-Grubbs de 2ª xeración. En conclusión, na presente tese realizouse unha aproximación sintética baseada en métodos que respectan o medioambiente e recolle o libro de " Principles of Green Chemistry". Sintetizáronse 3-benzazepinas, núcleos moi interesantes debido á súa interacción co Sistema Nervioso Central humano e unha ampla variedade de receptores, mediante reaccións de activación C- H catalizadas por complexos de paladio e empregando como oxidante osíxeno molecular en combinación con cantidades subestequiométricas de cobre. Estudos mecanísticos experimentais en combinación con cálculos DFT aportaron luz sobre o verdadeiro mecanismo da reacción. Ademais, estudouse a reacción enantioselectiva e explorouse unha síntese asimétrica baseada na desimetrización do substrato de partida. Posteriormente tamén se realizou a síntese enantioselectiva de 1,4- benzodiazepinas mediante reaccións catalizadas por complexos asimétricos Rh-H con unha ampla variedade

de grupos funcionais na molécula. Tamén se realizou unha aproximación sintética completamente enantioselectiva a un intermedio avanzado do Lixivaptan®, enxalzando a metodoloxía sintética. Finalmente, a síntese de 1,4- benzoxazepinas a través de reaccións de activación C- H alílica catalizadas por complexos paladio en combinación con ligandos que contén sulfóxidos foron realizadas con éxito. Observouse un amplo alcance da reacción tolerándose unha gran variedade de grupos funcionais e tamén distintos tipos de nucleófilos. Ademais, estudouse a influencia do efecto de Thorpe-Ingold na molécula e a diastereoselectividade da reacción. Desafortunadamente, os intentos cara á reacción enantioselectiva catalizada por paladio en combinación con ligandos L-SOX, de tipo sulfóxido- oxazolina quirales, deron lugar a baixas enantioselectividades e doutra banda os ligandos desenvolvidos recentemente polo Prof. Matsunaga, que conteñen un centro metálico coordinado a unha molécula orgánica simétrica cunha diimina e dous alcois non funcionaron nesta reacción.

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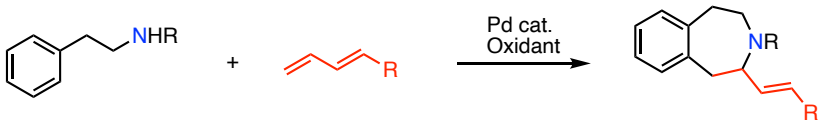
# General Objectives

## Chapter 1

The Chapter 1 contains a general introduction of the main biological properties of the benzofused seven-membered heterocycles like e.g., benzazepines, benzodiazepines and benzoxazepines, as well as the most important classic and transition-metal catalyzed syntheses of benzofused seven-membered heterocycles.

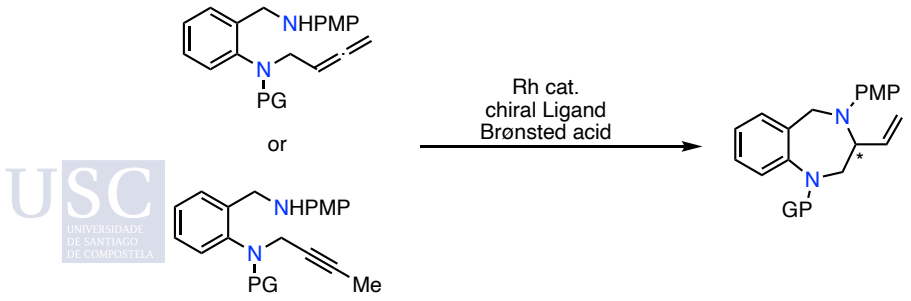
## Chapter 2

3-Benzazepines have been synthesized by a variety of classical and catalytic methods (Chapter 1). Despite the fact that all these methods might be considered very useful, they lack sustainability and atom- and step-economy. The main objective of this chapter would be the development of a more sustainable synthesis of 3-benzazepines, via C-H bond activation/heteroannulation processes (Scheme 20). The main challenge of this [5+2] cycloaddition between phenethylamine derivatives and 1,3-dienes will be the finding of a dual use of a DG linked with a "free" $C_{sp^3}$ chain on the phenethylamine to facilitate the C-H activation that could also act as nucleophile. The enantioselective version of this oxidative annulation will also be explored.




## Chapter 3

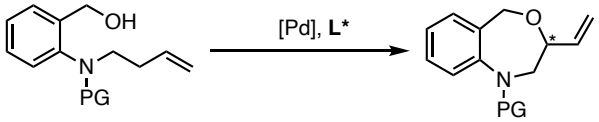
1,4-Benzodiazepines are of capital importance in the pharmaceutical industry since are drugs that interact with a great variety of human receptors key for the treatment of HIV, cancer, or CNS illnesses (See Chapter 1). Furthermore, bioactive 1,4-BZDs usually possess a defined stereogenic center at C3 position in the seven-membered ring. Despite of these properties, to the best of our knowledge, a sustainable and enantioselective route to these biologically active benzofused seven-membered azaheterocycles has not yet been described (see Chapter 1). The main objective of this Chapter would be the development of a sustainable synthesis of 1,4-benzodiazepines based on a Rh-catalyzed enantioselective hydroamination of terminal allenes or methyl-alkynes.




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## Chapter 4

1,4-Benzoxazepines (1,4-BZOs) possess a remarkable biological activity that made them useful as anti-cancer, anti-Alzheimer, antiinflamatory, to treat schizophrenia or as psychotropic substances (See Chapter 1). Continuing with our main thesis goal, the sustainable synthesis of benzofused seven-membered heterocycles, we would like to explore a new synthetic approach to 1,4-benzoxazepines through Pd-catalyzed allylic C-H activation (intramolecular alkoxylation) of arylalkenols (Scheme 64). An enantioselective variant is also disclosed.




## Chapter 5

In this chapter it is recorded the general procedures for the preparation of starting materials and final products. NMR spectra, HPLC spectra, X-ray crystallographic structures and computational details are also included.

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## Chapter 1

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## Chapter 4

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**Author:** Álvaro Velasco-Rubio, Jesús A. Varela, Carlos Saá
**Publication:** Organic Letters
**Publisher:** American Chemical Society
**Date:** May 1, 2020

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| Portions | figures 1 and 2 |
| Requestor Location | Mr. Álvaro Velasco<br>Rua Jenaro de la fuente s/n<br><br>Santiago de Compostela, 15701<br>Spain<br>Attn: Mr. Álvaro Velasco |
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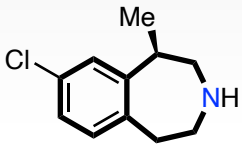
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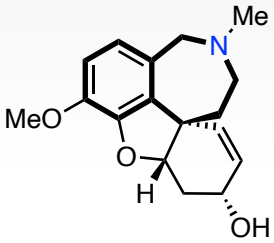
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# Chapter 1

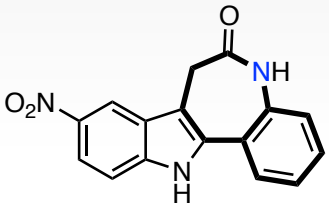
## Benzofused Seven-Membered Heterocycles. Properties and Syntheses. Introduction



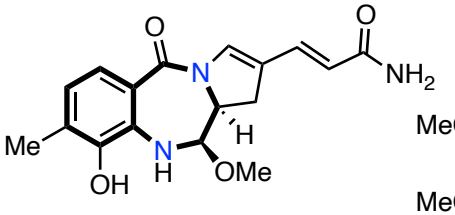

*Lorcaserine*



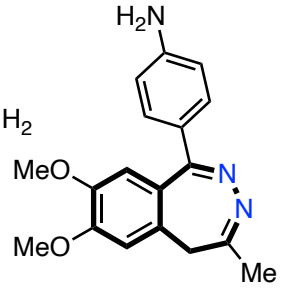

*Galantamine*



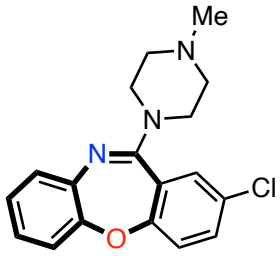

*Alsterpaullone*




*Anthramycin*




*Nerisopam*




*Loxazepine*
*Treatment Schizophrenia*

Benzofused seven-membered heterocycles such as benzazepines, benzodiazepines and benzoxazepines, compose an important family of natural products and pharmaceuticals. In this chapter, the biological properties of these nuclei, as well as their classic syntheses and catalytic methods based on transition metal catalysis are summarized.

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# Chapter 1

## Benzofused Seven-Membered Heterocycles. Properties and Syntheses

## Introduction

### 1. Benzazepines and Benzodiazepines

Benzazepines and benzodiazepines compose a privileged family of benzofused seven-membered azaheterocycles. These nuclei comprise the basic functionalized skeleton of a large number of natural products and pharmaceuticals.[1] Their biological activity is firmly established by their strong interaction with a great variety of human receptors.

The benzazepine family is integrated by three members, 1-benzazepines, 2-benzazepines and 3-benzazepines (Figure 1). This classification comes from the side of the azepine ring benzofused (b, c or d) and, therefore, the position of the nitrogen in the seven-membered ring. 1-Benzazepines have been described as potent antitumoral agents where Alsterpaullone is a remarkable drug.[2] Galantamine is a well-known 2-benzazepine used against Alzheimer's disease.[3] Finally, 3-benzazepines are among the most reliable structures in terms of affinity and selectivity for $D_1$ receptors like dopamine[4] or serotonine,[5] which regulate neuronal growth and development, and mediate other behavioral events. For instance, Lorcaserine was approved by FDA to treat obesity.[6]

[1] Bremner, J. B.; Samosorn, S. Azepines and their Fused-ring Derivatives. In *Comprehensive Heterocyclic Chemistry III*, Katrizky, A. R.; Ramsden, C. A.; Taylor, R. J. K., Eds.; Elsevier, 2008; Vol. 13, pp. 1.

[2] a) Yin, P.; Zheng, N.; Dong, J.; Xu, C.; Zhang, X.; Ding, G. *Oncol. Lett.* **2019**, *17*, 1177. b) Watanabe, T.; Sato, Y.; Masud, H. M. A. A.; Takayama, M.; Matsuda, H.; Hara, Y.; Yanagi, Y.; Yoshida, M.; Goshima, F.; Murata, T.; Kimura, H. *Cancer Sci.* **2020**, *111*, 279.

[3] Simoni, E.; Daniele, S.; Bottegoni, G.; Pizzirani, D.; Trincavelli, M. L.; Goldoni, L.; Tarozzo, G.; Reggiani, A.; Martini, C.; Piomelli, D.; Melchiorre, C.; Rosini, M.; Cavalli, A. *J. Med. Chem.* **2012**, *55*, 9708.

[4] a) Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274. b) Ye, N.; Neumeyer, J. L.; Baldessarini, R. J.; Zhen, X.; Zhang, A. *Chem. Rev.* **2013**, *113*, 123. c) Hall, A.; Provins, L.; Valade, A. *J. Med. Chem.* **2019**, *62*, 128.

[5] a) Zhang, J.; Zhang, H.; Cai, W.; Yu, L.; Zhen, X.; Zhang, A. *Bioorg. Med. Chem.* **2009**, *17*, 4873. b) Higgins, G. A.; Fletcher, P. J. *ACS Chem. Neurosci.* **2015**, *6*, 1071.

[6] a) O'Neil, P. M.; Smith, S. R.; Weissman, N. J.; Fidler, M. C.; Sanchez, M.; Zhang, J.; Raether, B.; Anderson, C. M.; Shanahan, W. R. *Obesity* **2012**, *20*, 1426. b) Yanovski, S. Z.; Yanovski, J. A. *JAMA, J. Am. Med. Assoc.* **2014**, *311*, 74.

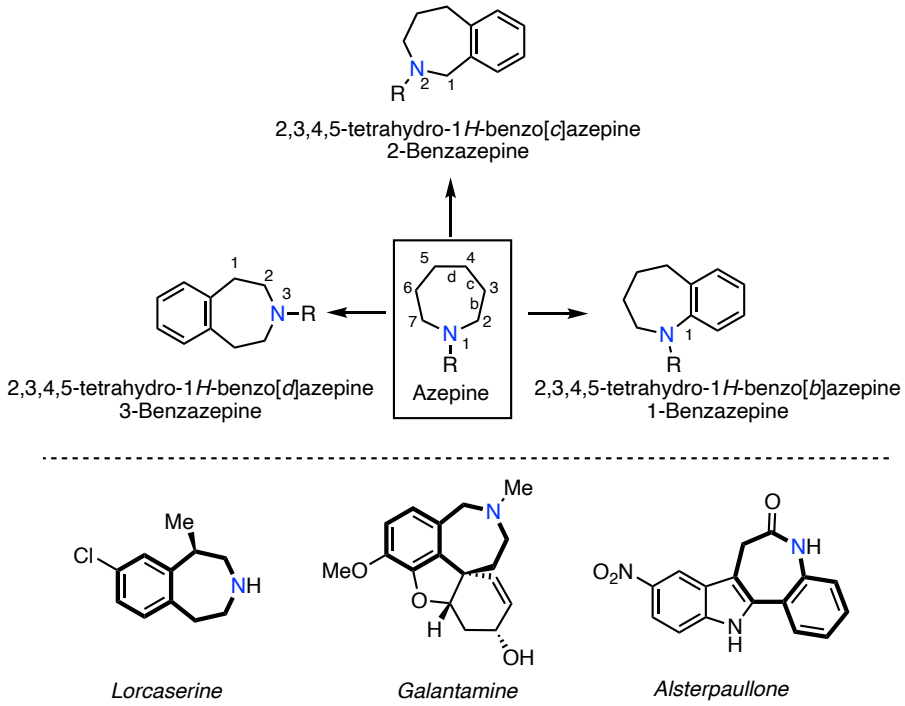



**Figure 1.** Representative benzazepines

Benzodiazepines, dinitrogenated benzofused heterocycles, are classified by the relative position of both nitrogen atoms in the seven-membered ring as 1,2-, 1,3-, 1,4-, 1,5- and 2,3-benzodiazepines (Figure 2). They possess interesting biological properties such as interaction with the human receptors $GABA_A$[7] or AMPA (Nerisopam).[8] Furthermore, they are suitable drugs to interact even with human DNA (Anthramycin)[9] as well as to inhibit bromodomains.[10] In fact, 1,4 benzodiazepines are one of the most common drugs to treat anxiety,[11] insomnia[12] or even cancer.[13] Those kinds of pharmaceuticals are more selective than the typical barbituric due to a direct control over the limbic system.[14] In addition, 1,2-

[7] a) Melancon, B. J.; Hopkins, C. R.; Wood, M. R.; Emmitte, K. A.; Niswender, C. M.; Christopoulos, A.; Conn, P. J.; Lindsley, C. W. *J. Med. Chem.* **2012**, *55*, 1445. b) Lemoine, D.; Jiang, R.; Taly, A.; Chataigneau, T.; Specht, A.; Grutter, T. *Chem. Rev.* **2012**, *112*, 6285. c) Clayton, T.; Poe, M. M.; Rallapalli, S.; Biawat, P.; Savic, M. M.; Rowlett, J. K.; Gallos, G.; Emala, C. W.; Kaczorowski, C. C.; Stafford, D. C.; Arnold, L. A.; Cook, J. M. *Int. J. Med. Chem.* **2015**, 430248. d) Sigel, E.; Ernst, M. *Trends Pharmacol. Sci.* **2018**, *39*, 659.

[8] Solyom, S.; Tarnawa, I. *Curr. Pharm. Des.* **2002**, *8*, 913.

[9] Mantaj, J.; Jackson, P. J. M.; Rahman, K. M.; Thurston, D. E. *Angew. Chem. Int. Ed.* **2017**, *56*, 462.

[10] a) Hewings, D. S.; Rooney, T. P. C.; Jennings, L. E.; Hay, D. A.; Schofield, C. J.; Brennan, P. E.; Knapp, S.; Conway, S. J. *J. Med. Chem.* **2012**, *55*, 9393. b) Zhang, G.; Smith, S. G.; Zhou, M.-M. *Chem. Rev.* **2015**, *115*, 11625.

[11] Calcaterra, N. E.; Barrow, J. C. *ACS Chem. Neurosci.* **2014**, *5*, 253.

[12] Elgarf, A. A.; Steudle, F.; Scholze, P.; Elgarf, A. A.; Siebert, D. C. B.; Steudle, F.; Draxler, A.; Ernst, M.; Li, G.; Huang, S.; Cook, J. M. *ACS Chem. Biol.* **2018**, *13*, 2033.

[13] Benedetti, F.; Perrin, M.-A.; Bosc, S.; Chouteau, F.; Champion, N.; Bigot, A. *Org. Process Res. Dev.* **2020**, *24*, 762.

[14] Batlle, E.; Lizano, E.; Viñas, M.; Pujol, M. 1,4-Benzodiazepines and New Derivatives: Description, Analysis, and Organic Synthesis. 2018.

benzodiazepines also acts as cancer inhibitors (CB-6644)[15] and 1,5-benzodiazepines are potent CNS active agents (Clobazam).[16]

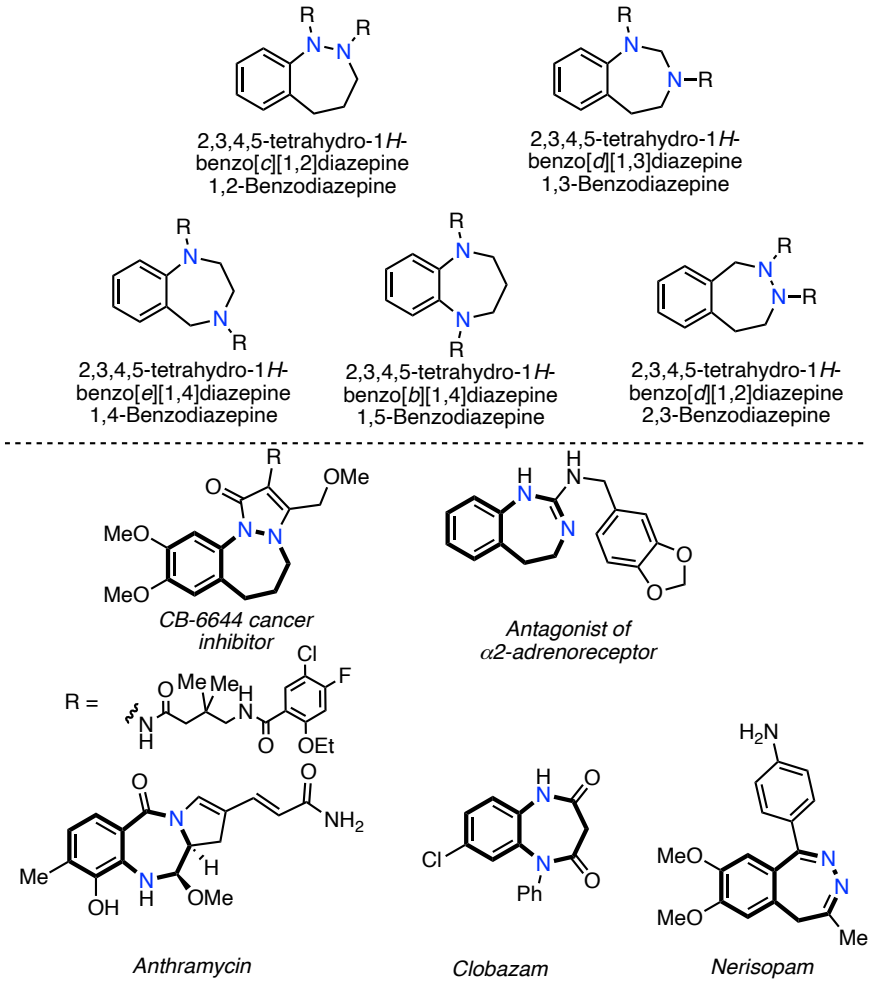



**Figure 2.** Representative benzodiazepines

## 2. Benzoxazepines

Benzoxazepines (BZOs) compose a well-known family of active drugs and natural products (Figure 3).[17] In 1957 the first 1,4-benzoxazepines were discovered, e.g., 2,3,4,5-tetrahydro-4-(β-haloalkyl)-1,4-BZOs, and found that are adrenergic blocking agents which possess the property of preventing impulse transmissions along the sympathetic nerve system pathways.[18] Later on, a number of new, potential pharmacologically useful BZOs

[15] Assimon, V. A.; Tang, Y.; Vargas, J. D.; Lee, G. J.; Wu, Z. Y.; Lou, K.; Yao, B.; Menon, M.-K.; Pios, A.; Perez, K. C.; Madriaga, A.; Buchowiecki, P. K.; Rolfe, M.; Shawver, L.; Jiao, X.; Le Moigne, R.; Zhou, H.-J.; Anderson, D. J. *ACS Chem. Biol.* **2019**, *14*, 236.

[16] Verma, R.; Bhatia, R.; Singh, G.; Kumar, B.; Mehan, S.; Monga, V. *Bioorg. Chem.* **2020**, *101*, 104010.

[17] a) Leval, A., *Heterocycles* **2008**, *75*, 2155. b) Faisca Phillips, A. M. M. M.; Pombeiro, A. J. L. Modern Methods for the Synthesis of 1,4-Oxazepanes and their Benzo- Derivatives. In Synthetic Approaches to Nonaromatic Nitrogen Heterocycles; Wiley, 2020; pp 437−500.

[18] Belleau, B. Benzoxazepine compounds and method of producing same. U.S. Patent 2807628, **1957**; *Chem. Abstr.* **1958**, *52*, 16090.

were described with properties, [17b,19] like, e.g., antihistaminic activity,[20] antiinflamatory properties,[21] tranquilizers,[22] antipsychotic,[23] psychoneurotic,[24] anticancer activity,[25] analgesic,[26] squalene synthase inhibitor,[27] antibacterial,[28] antifungal,[29] antiepileptic,[30] treatment of Alzheimer's disease[31] and even activity against HIV.[32]

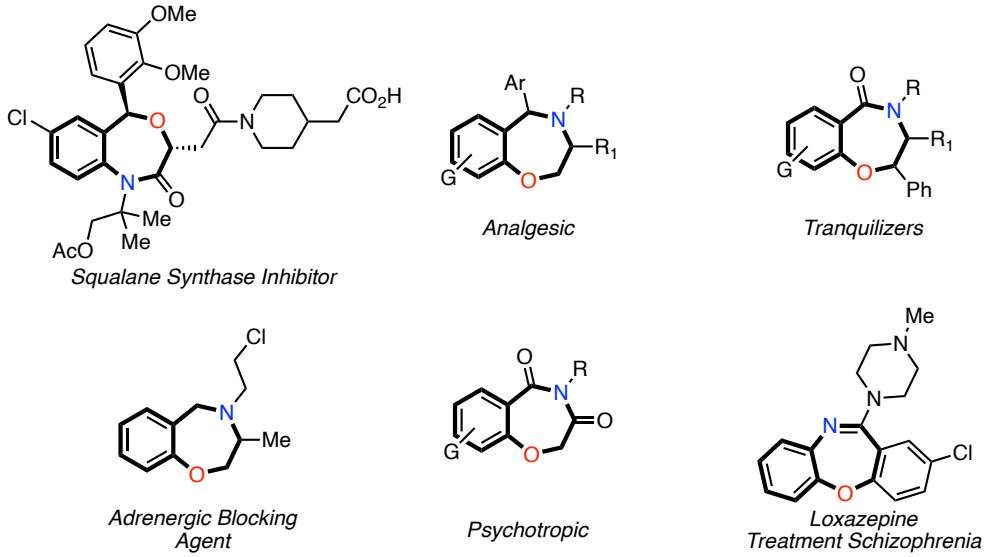



**Figure 3**. Representative 1,4-benzoxazepines

[19] Kwiecien, H.; Smist, M.; Wrzesniewska, A. *Curr. Org. Synth.* **2012**, *9*, 828.

[20] G. Walther, H. Daniel, W. D. Bechtel, K. Brandt, *Arzneim. Forsch.* **1990**, *40*, 440-446. b) Belleau, B. Benzoxazepine compounds. US2807628, 1957.

[21] Swett, R. L., Stein, G. R. , Kimura, T. E. *J. Med. Chem.* **1972**, *15*, 42.

[22] W. E. Coyne, J. W. Cusic, *J. Med. Chem.* **1968**, *11*, 1158.

[23] a) Grove, A. J. S., Zhang, M. U.S. Patent 20040171605 A1, *Chem. Abstr.* **2002**, *138*, 964361. b) Y. Liao, B. J. Venhuis, N. Rodenhuis, W. Timmerman, H. Wikstrom, E. Meire, G. D. Bartoszyk, H. Bottcher, C. A. Seyfried, S. Sundell, *J. Med. Chem.* **1999**, *42*, 2235. c) A. Chakrabarti, A. M. Bagnall, P. Chue, M. Fenton, V. Palaniswamy, W. Wong, J. Xia, *The Cochrane Collaboration*, John Wiley & Sons: New York, **2012**.

[24] Kamei, K.; Maeda, N.; Nomura, K.; Shibata, M.; Katsuragi-Ogino, R.; Koyama, M.; Nakajima, M.; Inoue, T.; Ohno, T.; Tatsuoka, T. *Bioorg. Med. Chem.* **2006**, *14*, 1978.

[25] a) Diaz-Gavilan, M.; Rodriguez-Serrano, F.; Gomez-Vidal, J. A.; Marchal, J. A.; Aranega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2004**, *60*, 11547. b) Binaschi, M.; Boldetti, A.; Gianni, M.; Maggi, C. A.; Gensini, M.; Bigioni, M.; Parlani, M.; Giolitti, A.; Fratelli, M.; Valli, C.; Terao, M.; Garattini, E. *ACS Med. Chemi. Lett.* **2010**, *1*, 411. C) Y. Yin, Y. Q. Zhang, B. Jin, S. Sha, X. Wu, C. B. Sangani, S. F. Wang, F. Qiao, A. M. Lu, P. C. Lv, H. L. Zhu, *Bioorg. Med. Chem.* **2015**, *23*, 1231.

[26] Effland, R. C.; Kapples, K. J. Preparation of 5-aryl-11-substituted-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepines as analgesics and antihypertensives. US4794110, 1988.

[27] Miki, T.; Kori, M.; Mabuchi, H.; Tozawa, R.-i.; Nishimoto, T.; Sugiyama, Y.; Teshima, K.; Yukimasa, H. *J. Med. Chem.* **2002**, *45*, 4571.

[28] Agirbas, H.; Kemal, B.; Budak, F. *Med. Chem. Res.* **2011**, *20*, 1170.

[29] Kaneko, S.; Arai, M.; Uchida, T.; Harasaki, T.; Fukuoka, T.; Konosu, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1705.

[30] a) Bajaj, K.; Srivastava, V. K.; Kumar, A. *Indian J. Chem.* **2003**, *42B*, 1149. b) Garg, N.; Chandra, T.; Archana; Jain, A. B.; Kumar, A. *Eur. J. Med. Chem.* **2010**, *45*, 1529.

[31] a) Galley, G.; Goodnow, R. A.; Peters, J.-U. Preparation of 1,4-benzoxazepin-3-ones as inhibitors of γ-secretase for the treatment of Alzheimer's disease. US20040235819A1, 2004. b) Effland, R.C.; Klein, J.T. Pyrido[3,4-*b*][1,4]benzoxazepines, a process for their preparation and their use as medicaments. EP Patent 0413300 A1, 1990. *Chem. Abstr.* **1990**, *113*,591410.

[32] a) Hargrave, K. D.; Schmidt, G. Preparation of pyrido[2,3-b][1,4]benzoxazepin-6(5H)-ones and sulfur analogs for treatment of HIV-1 infection. EP417534A1, 1991. b) Garofalo, A.; Grande, F.; Brizzi, A. *ChemMedChem* **2008**, *3*, 986.

This family is composed by seven benzoxazepine isomers, which come from the benzofusion of the three oxazepane rings. Thus, depending on the position of *N* and *O* in the seven-membered ring, 1,2-, 1,3-, 1,4-, 1,5- and 2,3-benzoxazepines are considered (Figure 4).

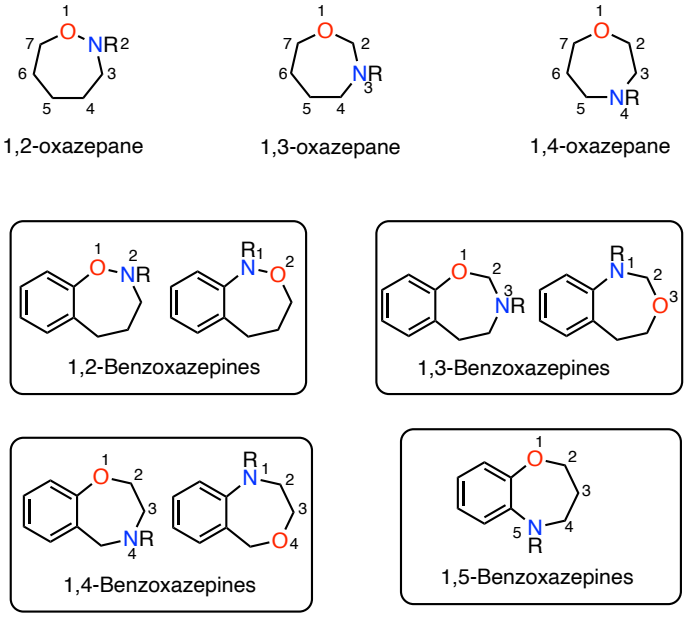



**Figure 4.** Benzoxazepines

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# 3. Synthesis of Benzofused Seven-Membered Heterocycles

## 3.1. Classical Methods

The highly relevant biological properties of benzazepines, benzodiazepines and benzoxazepines triggered the development of a variety of synthetic strategies over the past decades.[33] Despite all these strategies might be considered very useful, they are often based on multistep synthesis with generation of stoichiometric amounts of toxic wastes, that means, with lack of sustainability.

Benzazepines have been synthesized employing condensations,[34] cyclizations,[35] cycloadditions[36] or C-H activation ring expansion reactions.[37] In 1996, our group reported the synthesis of Lennoxamine, a representative isoindolobenzazepine (Scheme 1a),[35e] through a regioselective 7-*endo* radical cyclization of bromo-substituted-methyleneisoindol-1-one **1** to build-up the seven-membered ring **2** in very good yield. In 2015, Chen's group reported the [4+3] cycloaddition of allylic bromide **3** (Morita-Baylis-Hillman adduct) with *o*-(chloromethyl)aryl amide **4** promoted by electron-poor phosphines to afford 1-benzazepine **5** (Scheme 1b).[36a] In 2016, the group of Gu reported a three-component condensation to afford 1-benzazepines (Scheme 1c).[34a] Moderate to excellent yields of 1-benzazepines **8** were obtained when *o*-aminobenzaldehydes **6**, 2-methyl-indol **7** and a variety of ketones/aldehydes reacted in a $BF_3{\cdot}Et_2O$-promoted condensation. In addition, C-H functionalization ring-expansion reaction has also been employed to afford benzazepines. In 2016, the group of Alemán reported the synthesis of 3-benzazepines **10** in moderate to good yields from isoquinolines using trimethylsylildiazomethane as key reagent in the presence of TEMPO as oxidant (Scheme 1d).[37a]

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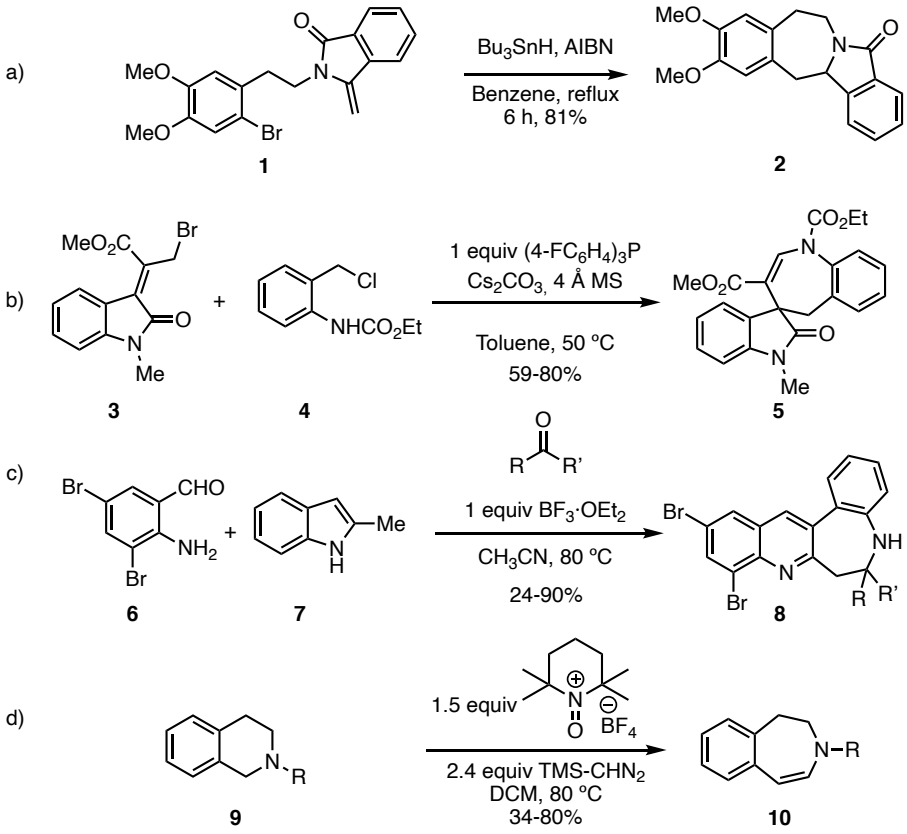
[33] Meyer, A. G.; Bissember, A. C.; Hyland, C. J. T.; Smith, J. A.; Williams, C. C.; Szabo, M.; Pearsal, M. A.; Hyland, I. K.; Olivier, W. J. Seven-Membered Rings. In *Progress in Heterocyclic Chemistry*, Elsevier, 2020; Vol. 31, pp 597.

[34] 1-Benzazepines: a) Min, L.; Pan, B.; Gu, Y. *Org. Lett.* **2016**, *18*, 364.; 2-Benzazepines: b) Vieira, T. O.; Alper, H. *Org. Lett.* **2008**, *10*, 485. c) Hasebein, P.; Aulinger, K.; Schepmann, D.; Wuensch, B. *Tetrahedron* **2013**, *69*, 4552. d) Hasebein, P.; Frehland, B.; Lehmkuhl, K.; Froehlich, R.; Schepmann, D.; Wuensch, B. *Org. Biomol. Chem.* **2014**, *12*, 5407.; 3-Benzazepines: e) Husain, S. M.; Froehlich, R.; Schepmann, D.; Wuensch, B. *J. Org. Chem.* **2009**, *74*, 2788.; 1,4-BDZ: f) Antonow, D.; Thurston, D. E. *Chem. Rev.* **2011**, *111*, 2815. g) Donald, J. R.; Martin, S. F. *Org. Lett.* **2011**, *13*, 852. h) Sharma, U. K.; Sharma, N.; Vachhani, D. D.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2015**, *44*, 1836. 1,5-BDZs: i) Pareek, A.; Kumar, N.; Agarwal, A.; Sharma, P.; Kishore, D. *Res. J. Chem. Sci.* **2013**, *3*, 90. 2,3-BDZs: j) Okuma, K.; Tanabe, Y.; Itoyama, R.; Nagahora, N.; Shioji, K. *Chem. Lett.* **2013**, *42*, 1260.

[35] 1-Benzazepines: a) Cheng, D.-J.; Wu, H.-B.; Tian, S.-K. *Org. Lett.* **2011**, *13*, 5636. b) Suh, C. W.; Kwon, S. J.; Kim, D. Y. *Org. Lett.* **2017**, *19*, 1334. 2-Benzazepines: c) Kamimura, A.; Taguchi, Y.; Omata, Y.; Hagihara, M. *J. Org. Chem.* **2003**, *68*, 4996. d) So, M.; Kotake, T.; Matsuura, K.; Inui, M.; Kamimura, A. *J. Org. Chem.* **2012**, *77*, 4017. 3-Benzazepines: e) Rodríguez, G.; Cid, M. M.; Saá, C.; Castedo, L.; Domínguez, D. *J. Org. Chem.* **1996**, *61*, 2780. f) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, *9*, 1211. g) Mori, K.; Kurihara, K.; Yabe, S.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2014**, *136*, 3744. 1,4-BDZs: h) Yang, J.; Che, X.; Dang, Q.; Wei, Z.; Gao, S.; Bai, X. *Org. Lett.* **2005**, *7*, 1541. i) Wang, J.-Y.; Guo, X.-F.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2008**, *73*, 1979. j) Wang, S.; Shen, Y.-B.; Li, L.-F.; Qiu, B.; Yu, L.; Liu, Q.; Xiao, J. *Org. Lett.* **2019**, *21*, 8904. 2,3-BDZs: k) Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 13072.

[36] a) 3-Benzazepines: a) Zhan, G.; Shi, M.-L.; He, Q.; Du, W.; Chen, Y.-C. *Org. Lett.* **2015**, *17*, 4750. 1,4-BDZs: b) Shin, J.; Lee, J.; Ko, D.; De, N.; Yoo, E. J. *Org. Lett.* **2017**, *19*, 2901.

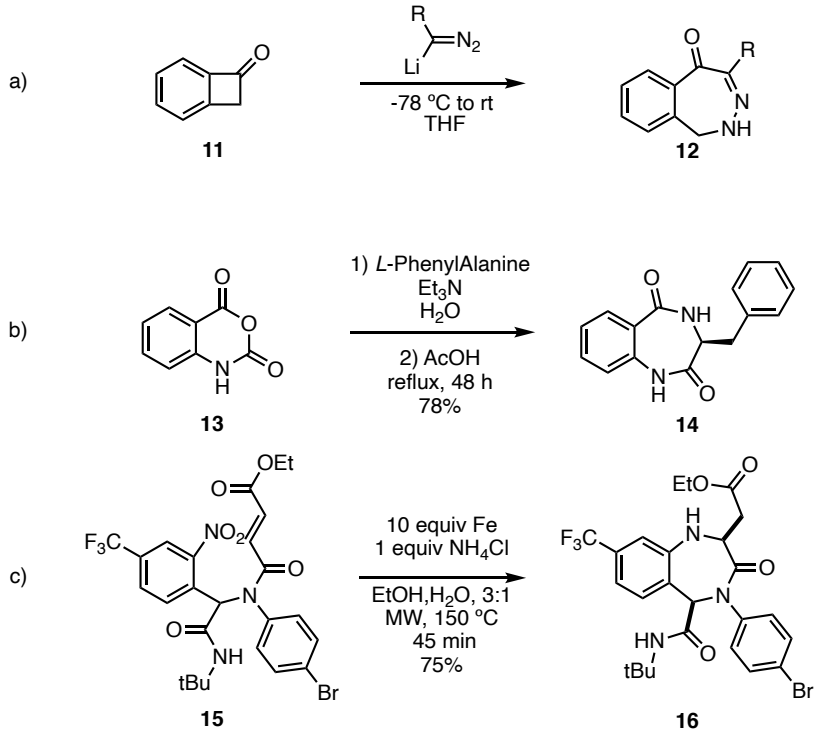
[37] 3-Benzazepines: a) Gini, A.; Bamberger, J.; Luis-Barrera, J.; Zurro, M.; Mas-Balleste, R.; Aleman, J.; Mancheno, O. G. *Adv. Synth. Catal.* **2016**, *358*, 4049. 1,4-BDZs: b) Loudni, L.; Roche, J.; Potiron, V.; Clarhaut, J.; Bachmann, C.; Gesson, J.-P.; Tranoy-Opalinski, I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4819.




**Scheme 1.** Classical methods to benzazepines

Classical methods to obtain benzodiazepines are shown in Scheme 2. In 2006, Nemoto's group reported the synthesis of 2,3-benzodiazepines **12** from benzocyclobutenones **11** in an electrocyclization involving a net insertion of diazocompounds (Scheme 2a).[35k] In 2007, the group of Tranoy-Opalinski reported a ring-expansion of isatoic acid **13** with *L*-phenylalanine that provided chiral 1,4-benzodiazepine **14** in very good yields (Scheme 2b).[37b] In 2011, the group of Martin described the synthesis of 1,4-benzodiazepines **15** in an iron-promoted $NO_2$-reduction/aza-Michael condensation of nitro derivatives **16** (Scheme 2c).[34g]

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**Scheme 2.** Classical methods to benzodiazepines

Since the discovery of the biological properties of 1,4-benzoxazepines, a variety of synthetic approaches have been developed.[38] Typically, the key steps of these processes involve lactonizations,[39] Mitsunobu reactions,[40] Friedel-Crafts reactions,[41] click-chemistry,[42] Pictet-Spengler reactions, Ugi-condensations or ring expansions.[43] Thus, Zhou and coworkers reported a silver-promoted lactonization of ω-bromocarboxylic acids **17** to the desired benzoxazepines **18** in good to excellent yields (Scheme 3a).[39] In 2013, Bell's group described the synthesis of triazolo-fused benzoxazepines **20** through a click reaction of azido alkyne **19** in moderate yield (Scheme 3b).[42] In 2016, Aubé and coworkers described a Schmidt rearrangement (ring expansion) of cyclic ketones **21** with trimethylsilylazide to 1,4-benzoxazepine **22** in moderate to good yields (Scheme 3c).[43]

[38] a) Faisca Phillips, A. M. M. M.; Pombeiro, A. J. L. Modern Methods for the Synthesis of 1,4-Oxazepanes and their Benzo-Derivatives. In *Synthetic Approaches to Nonaromatic Nitrogen Heterocycles*, 2020; pp 437. b) Kwiecien, H.; Smist, M.; Wrzesniewska, A. *Curr. Org. Synth.* **2012**, *9*, 828.

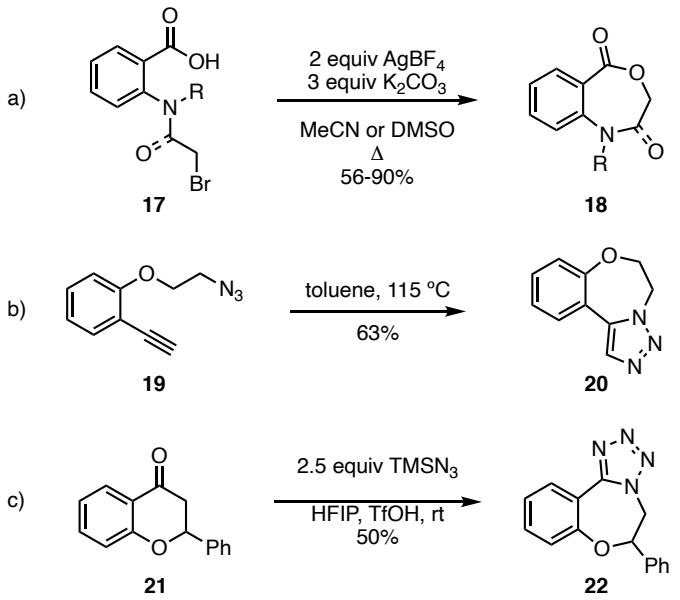
[39] Liu, L.; Xu, S.; Zhou, H. *Tetrahedron* **2013**, *69*, 8386.

[40] Jeong, J. U.; Harris, P. A.; Kang, J.; Leister, L.; Lan, Y.; Romano, J.; Dong, X.; Marquis, R. W. *Tetrahedron Lett.* **2017**, *58*, 2306.

[41] Brindisi, M.; Gemma, S.; Alfano, G.; Kshirsagar, G.; Novellino, E.; Campiani, G.; Butini, S. *Tetrahedron Lett.* **2013**, *54*, 5387.

[42] Ellison, A.; Boyer, R.; Hoogestraat, P.; Bell, M. *Tetrahedron Lett.* **2013**, *54*, 6005.

[43] Motiwala, H. F.; Charaschanya, M.; Day, V. W.; Aube, J. *J. Org. Chem.* **2016**, *81*, 1593.




**Scheme 3.** Classical cyclizations and cycloadditions to 1,4-benzoxazepines

## 3.2. Catalytic Methods

In an attempt to go ahead to sustainability, transition-metal (TM) catalysis has allowed to achieve more versatility and efficiency. Despite the employment of catalytic amounts of TM allows to decrease the waste generation, the regioselective introduction of halogens in the organic molecules or the multistep synthesis required to access to the starting materials prior to catalysis remains as the main drawback in this field.

Over the last decades a variety of methods have been described to synthesize benzazepines, e.g., TM-catalyzed intramolecular Heck-type cyclizations,[44] TM-catalyzed cycloadditions,[45] metathesis,[46] oxidative couplings,[47] tandem reactions[48] or TM catalyzed

[44] Benzazepines: a) Donets, P. A.; Van der Eycken, E. V. *Org. Lett.* **2007**, *9*, 3017. b) Liu, Q.; Ferreira, E. M.; Stoltz, B. M. *J. Org. Chem.* **2007**, *72*, 7352. c) Stewart, S. G.; Heath, C. H.; Ghisalberti, E. L. *Eur. J. Org. Chem.* **2009**, 1934. d) Peshkov, A. A.; Peshkov, V. A.; Pereshivko, O. P.; Kumar, R.; Van, d. E. E. V.; Van, H. K. *J. Org. Chem.* **2015**, *80*, 6598. e) Tabata, H.; Yoneda, T.; Tasaka, T.; Ito, S.; Oshitari, T.; Takahashi, H.; Natsugari, H. *J. Org. Chem.* **2016**, *81*, 3136. BDZs: f) Hayashi, M.; Sai, H.; Horikawa, H. *Heterocycles*, **1998**, *48*, 1331. g) Prasad, B.; Sreenivas, B. Y.; Sushma, A.; Yellanki, S.; Medisetti, R.; Kulkarni, P.; Pal, M. *Org. Biomol. Chem.* **2014**, *12*, 2864.

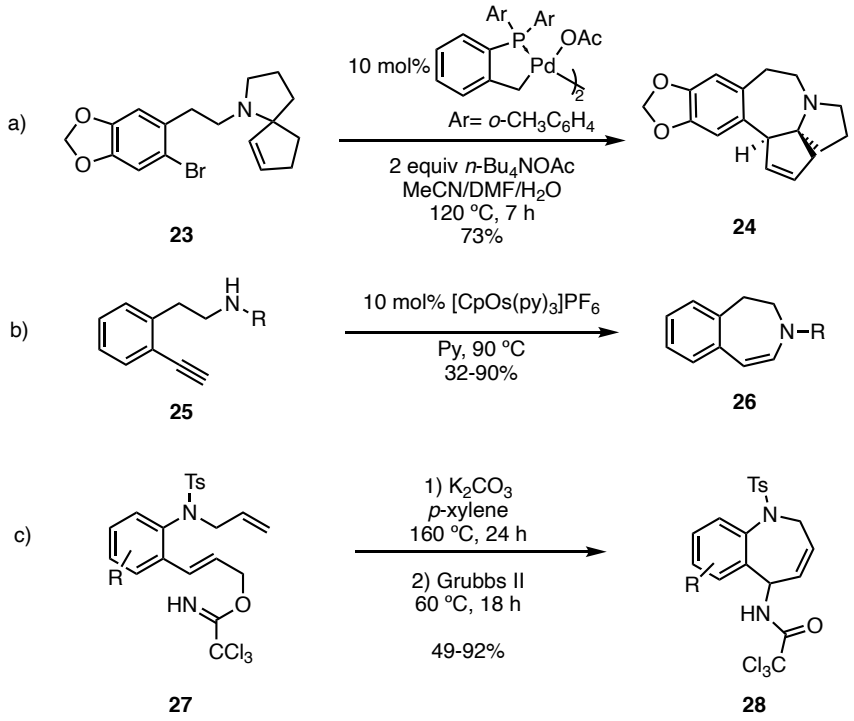
[45] 1-Benzazepines: a) Guo, C.; Fleige, M.; Janssen-Mueller, D.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2016**, *138*, 7840. b) Wang, L.; Li, S.; Bluemel, M.; Philipps, A. R.; Wang, A.; Puttreddy, R.; Rissanen, K.; Enders, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 11110. 2-Benzazepines: c) Iqbal, N.; Fiksdahl, A. *J. Org. Chem.* **2013**, *78*, 7885. 1,4-BDZs: d) Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241. e) Donald, J. R.; Martin, S. F. *Org. Lett.* **2011**, *13*, 852.

[46] 1-Benzazepines: Sharif, S. A. I.; Calder, E. D. D.; Delolo, F. G.; Sutherland, A. *J. Org. Chem.* **2016**, *81*, 6697.

[47] 1-Benzazepines: a) Wang, R.; Jin, R.-X.; Qin, Z.-Y.; Bian, K.-J.; Wang, X.-S. *Chem. Commun.* **2017**, *53*, 12229. b) For a Pd-catalyzed homocoupling of benzamides to dibenzo[*c*,*e*]azepine-5,7-diones, see: Kondapalli, V.; Yu, X.; Yamamoto, Y.; Bao, M. *J. Org. Chem.* **2017**, *82*, 2288.

[48] 1,4-BDZs: a) Jumde, V. R.; Cini, E.; Porcheddu, A.; Taddei, M *Eur. J. Org. Chem.* **2015**, 1068. b) Murugesh, V.; Harish, B.; Adiseshu, M.; Babu Nanubolu, J.; Suresh, S. *Adv. Synth. Catal.* **2016**, *358*, 1309. c) Liu, S.; Zhao, T.; Qu, J.; Wang, B. *Adv. Synth. Catal.* **2018**, *360*, 4094.

intramolecular hydroamin(d)ations of alkynes[49] and alkenes.[50] In 2007, the group of Stoltz reported convergent and divergent strategies to afford Dupracine and Cephalotaxine, where the key tetracyclic intermediate core **24** is achieved upon Pd-catalyzed intramolecular Heck-type cyclization of bromoarenes **23** (Scheme 4a).[44b] In 2015, our group reported the synthesis of 3-benzazepines **26** by the rare Os-catalyzed hydroamination of *o*-alkynyl phenethylamines **25** (Scheme 4b).[49b] Sutherland's group reported in 2016 the synthesis of 1-benzazepines **28** in a one pot reaction that involves a thermal Overman rearrangement of **27** followed by a ring closing metathesis (Scheme 4c).[46]



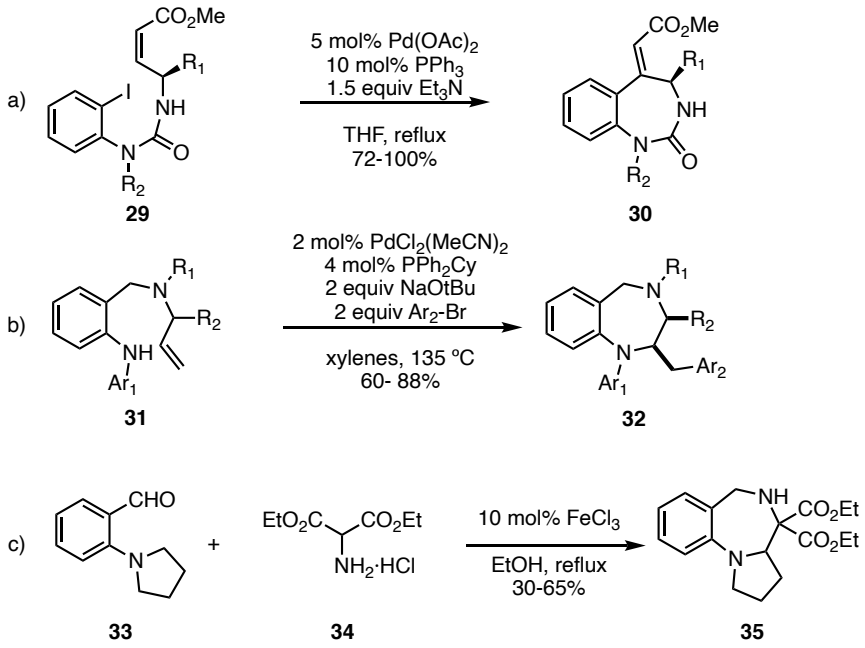

**Scheme 4.** TM-catalyzed cyclizations to benzazepines

Benzodiazepines have also been interesting targets for organometallic catalysis. In 1998, Horikawa reported the synthesis of 1,3-benzodiazepines **30** via Pd-catalyzed Heck-type cyclization from iodoalkenes **29** (Scheme 5a).[44f] In 2011, Wolfe's group published the Pd-catalyzed hydroamination of alkenes **31** to 1,4-benzodiazepines **32** in very good yields (Scheme 5b).[50] In 2018, the group of Wang described the synthesis of pyrrolobenzodiazepines **35** by a Fe-catalyzed cascade that involves an intermolecular condensation/1,5-hydride shift/cyclization of aldehydes **33** with aminomalonate **34** in moderate to good yields (Scheme 5c).[48c]

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[49] 3-Benzazepines: a) Zhang, L.; Ye, D.; Zhou, Y.; Liu, G.; Feng, E.; Jiang, H.; Liu, H. *J. Org. Chem.* **2010**, *75*, 3671.b) Álvarez-Pérez, A.; González-Rodríguez, C.; García-Yebra, C.; Varela, J. A.; Oñate, E.; Esteruelas, M. A.; Saá, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13357.

[50] Neukom, J. D.; Aquino, A. S.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2196.




**Scheme 5.** TM-catalyzed cyclizations to benzodiazepines

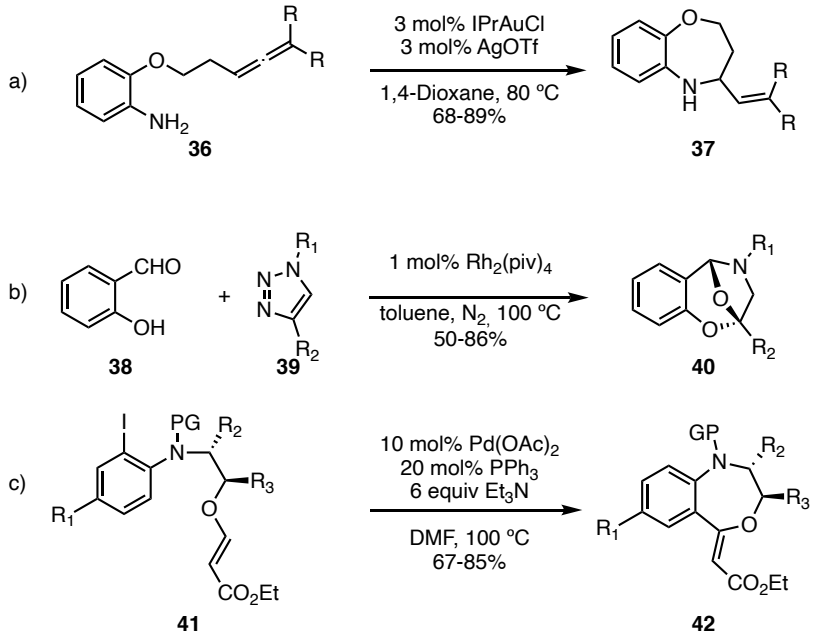
TM-catalysis has been also successfully employed to get the relevant bioactive benzoxazepines. In 2013, Hashmi reported the Au-catalyzed hydroamination of allenes **36** to 1,5-benzoxazepines **37** in very good yields (Scheme 6a).[51] In 2015, Li and coworkers reported the Rh-catalyzed [3+2] cyclization/ring opening/ring-closing cascade reaction between salicylaldehydes **38** and 1,2,3-triazoles **39** to oxabridged 2,5-epoxy-1,4-benzoxazepines **40** in good yields (Scheme 6b).[52] In 2017, Gharpure's group reported an intramolecular Pd-catalyzed Heck cyclization of **41** to 1,4-benzoxazepines **42** in good to excellent yields (Scheme 6c).[53]

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[51] Pflaesterer, D.; Dolbundalchok, P.; Rafique, S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2013**, *355*, 1383.

[52] Shi, Y.; Yu, X.; Li, C.-Y. *Eur. J. Org. Chem.* **2015**, 6429.

[53] Gharpure, S. J.; Anuradha, D. *Org. Lett.* **2017**, *19*, 6136.




**Scheme 6.** TM-catalyzed cyclizations and cycloadditions to benzoxazepines

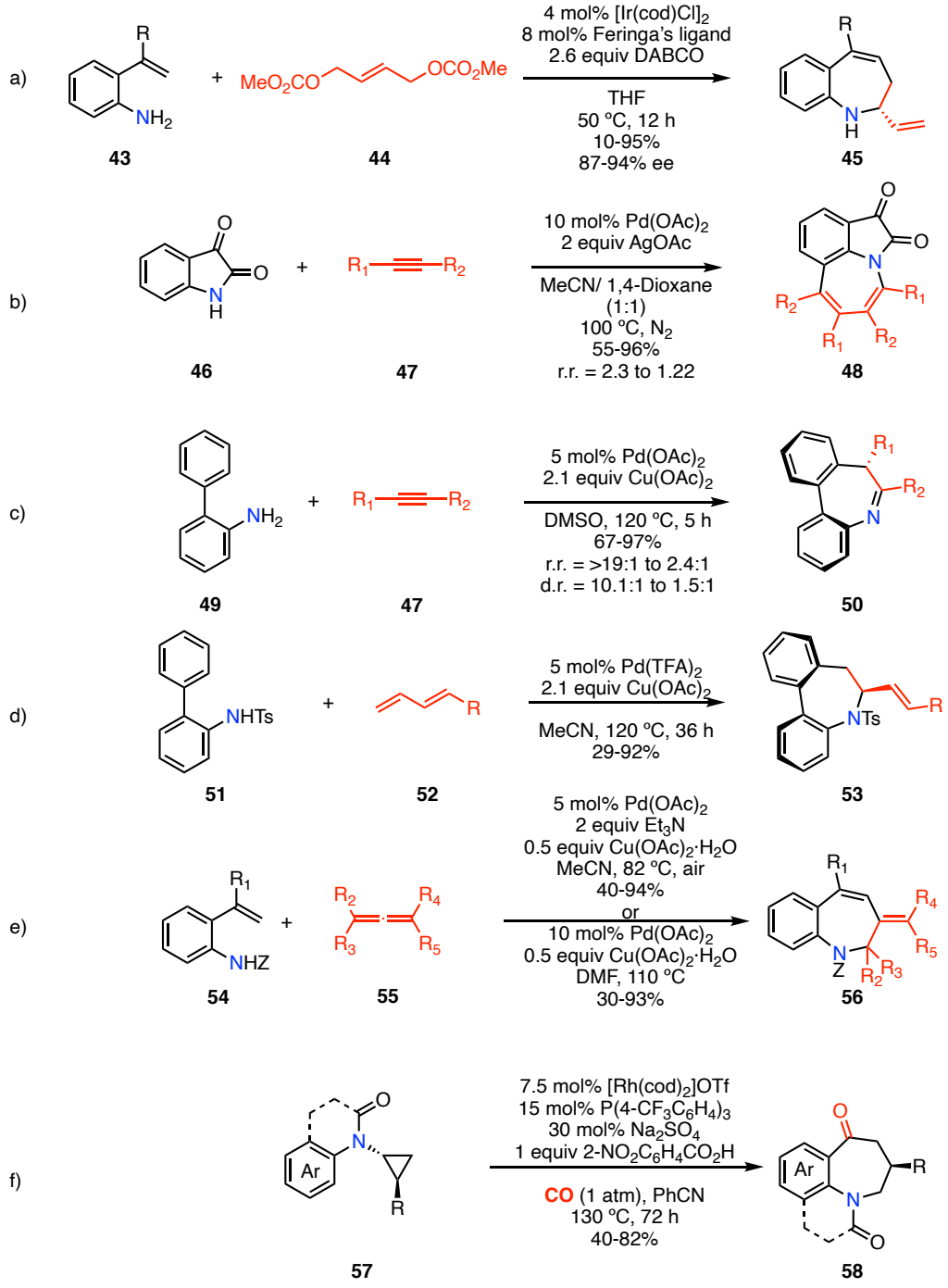
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### 3.2.1. Synthesis of Benzazepines and Benzodiazepines via C-H Bond Activation

Over the last decades, there has been a growing interest in the design of sustainable synthetic approaches to the construction of carbo- and heterocyclic rings. In this regard, dehydrogenative heteroannulation reactions through metal-catalyzed C-H activation provide straightforward access to common heterocyclic scaffolds from easily available substrates, where two new bonds are formed in a single step.[54] Several strategies have been developed to obtain common five- and six-membered heterocycles.[55] Nevertheless, the construction of benzofused seven-membered heterocycles has been less explored due to the high entropy penalty that has to be overcome. In this sense, correct design of the substrate that undergoes the metal-catalyzed cycloaddition with a π rich unsaturated partner (alkynes, alkenes, 1,3-dienes, allenes) and the correct choice of the metal catalyst are crucial to develop the reaction.[56]

The synthesis of 1-benzazepines via metal-catalyzed C-H activation has been extensively studied (Scheme 7). In 2010, You and coworkers described the asymmetric synthesis of 1-benzazepines **45** in an Ir-catalyzed [5+2] heteroannulation of alkenylanilines **43** with allylcarbonates **44** (Scheme 7a).[57] This tandem allylic vinylation/allylic amination yield 1-benzazepines **45** in excellent yields and enantioselectivities. In 2013, Wang and coworkers reported the synthesis of 1-benzazepines **48** in a Pd-catalyzed cycloaddition of isatins **46** with alkynes **47** (Scheme 7b).[58] In 2015, Luan's group reported the synthesis of 1-dibenzoazepines **50** in a Pd-catalyzed heteroannulation of *o*-arylanilines **49** and alkynes **47** (Scheme 7c).[59] Two years later, the same group demonstrated the possibility to access to the same core 1-dibenzoazepines **53** upon changing the substrate design. *o*-Aryltosylanilides **51** successfully underwent a Pd-catalyzed [5+2] cycloaddition with 1,3-dienes **52** (Scheme 7d).[60] Simultaneously, in 2017, Mascareñas/Gulías's[61] and Zeng's[62] groups reported the synthesis of 1-benzazepines **56** in a Pd-catalyzed [5+2] heteroannulation of vinylanilides **54** (Ts, Tf) with allenes **55** (Scheme 7e). In 2018, Bower's group reported the synthesis of 1-benzazepine-5-ones **58** in a Rh-catalyzed [6+1] heteroannulation of *N*-cyclopropylanilides **57** and CO (carbonylative C-C activation) (Scheme 7f).[63]

[54] Wu, X.-F. *Transition Metal-Catalyzed Heterocycle Synthesis via C-H Activation*, Wiley-VCH, Weinheim, 2016.
[55] Gulías, M.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 11000.
[56] Trost, B. M., Zuo, Z.; Schultz, J. E. *Chem. Eur. J.* **2020**, *26*, 15354.
[57] He, H.; Liu, W.-B.; Dai, L.-X.; You, S.-L *Angew. Chem. Int. Ed.* **2010**, *49*, 1496.
[58] Wang, L.; Huang, J.; Peng, S.; Liu, H.; Jiang, X.; Wang, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1768.
[59] Zuo, Z.; Liu, J.; Nan, J.; Fan, L.; Sun, W.; Wang, Y.; Luan, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 15385.
[60] Bai, L.; Wang, Y.; Ge, Y.; Liu, J.; Luan, X. *Org. Lett.* **2017**, *19*, 1734.
[61] Cendón, B.; Casanova, N.; Comanescu, C.; García-Fandiño, R.; Seoane, A.; Gulías, M.; Mascareñas, J. L. *Org. Lett.* **2017**, *19*, 1674.
[62] Wu, L.; Meng, Y.; Ferguson, J.; Wang, L.; Zeng, F. *J. Org. Chem.* **2017**, *82*, 4121.
[63] Wang, G.-W.; Bower, J. F. *J. Am. Chem. Soc.* **2018**, *140*, 2743.

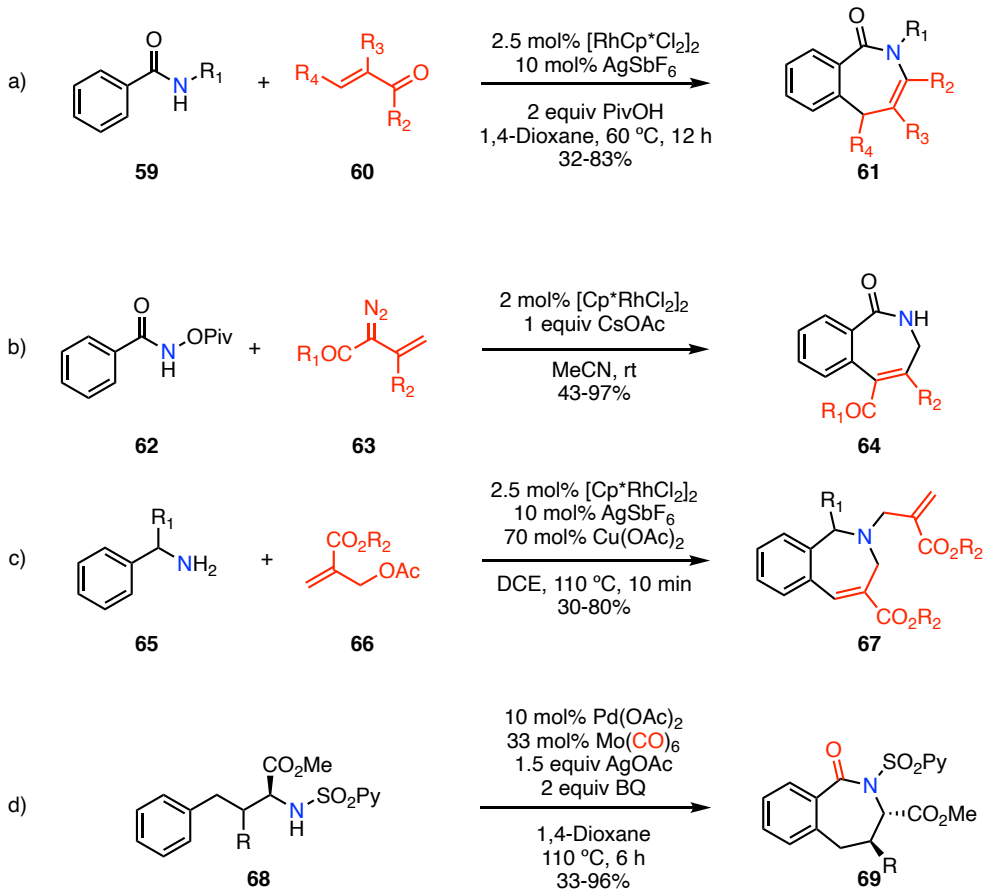



**Scheme 7.** Metal-catalyzed synthesis of 1-benzazepines via C-H activation

By contrast, the synthesis of 2-benzazepines has been less studied (Scheme 8). In 2013, Glorius reported the synthesis of 2-benzazepinones **61** in a Rh-catalyzed cyclization of benzamides **59** and α,β-unsaturated aldehydes and ketones **60** in good yields (Scheme 8a).[64] The same year, Cui's group described the synthesis of 2-benzazepinones **64** in a Rh-catalyzed [4+3] heteroannulation between benzamides **62** and vinylcarbenoids **63** (Scheme 8b).[65] In 2018, Kim reported the synthesis of 2-benzazepines **67** in a Rh-catalyzed cyclization of 2-(benzylamino)methacrylates, prepared *in-situ* from primary benzylamines **65** and allylic

[64] Shi, Z.; Grohmann, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 5393.
[65] Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912.

acetates **66** (Scheme 8c).[66] In 2019, Carretero's group rerported a Pd-catalyzed [6+1] heteroannulation of γ-arylpropylamine **68** derivatives and CO to 2-benzazepinones **69** (Scheme 8d).[67]



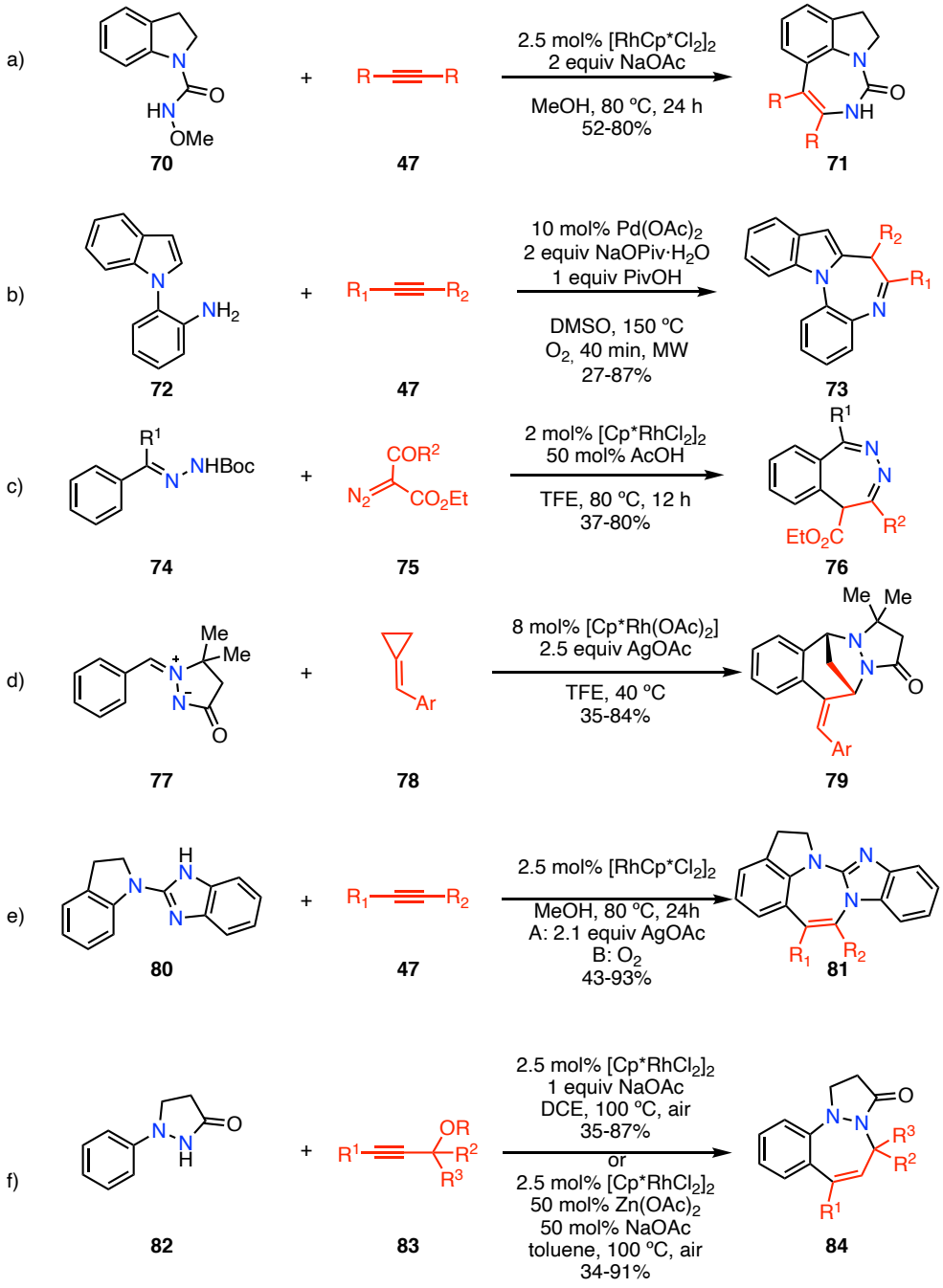

**Scheme 8.** Metal-catalyzed synthesis of 2-benzazepines via C-H activation

A variety of benzodiazepines has also been synthesized through metal-catalyzed C-H activation processes (Scheme 9). In 2015, Zhou described the Rh-catalyzed heteroannulation of *N*-methoxycabamoyl-protected indolines **70** and aryl alkynes **47** to 1,3-benzodiazepines **71** (Scheme 9a).[68] In 2017, Sun reported the Pd-catalyzed annulation of *o*-indoloanilines **72** with alkynes **47** to 1,5-benzodiazepines **73** (Scheme 9b).[69] In the same year, Zhu and coworkers reported the Rh-catalyzed [5+2] annulation between *N*-Boc hydrazones **74** and diazoketoesters **75** to 2,3-benzodiazepines **76** (Scheme 9c).[70] In 2018, Bai and Li's group reported the Rh-catalyzed [5+2] heteroannulation of azomethine imines **77** and alkylidenecyclopropanes (ACP) **78** to bicyclic 2,3-benzodiazepines **79** (Scheme 9d).[71] In 2019, our group described a Rh-catalyzed [5+2] oxidative annulation of cyclic arylguanidines **80**

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[66] Pandey, A. K.; Han, S. H.; Mishra, N. K.; Kang, D.; Lee, S. H.; Chun, R.; Hong, S.; Park, J. S.; Kim, I. S. *ACS Catal.* **2018**, *8*, 742.
[67] Martínez-Mingo, M.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *Org. Lett.* **2019**, *21*, 4345.
[68] Wang, X.; Tang, H.; Feng, H.; Li, Y.; Yang, Y.; Zhou, B. *J. Org. Chem.* **2015**, *80*, 6238.
[69] Thikekar, T. U.; Sun, C.-M. *Adv. Synth. Catal.* **2017**, *359*, 3388.
[70] Wang, J.; Wang, L.; Guo, S.; Zha, S.; Zhu, J. *Org. Lett.* **2017**, *19*, 3640.
[71] Bai, D.; Xu, T.; Ma, C.; Zheng, X.; Liu, B.; Xie, F.; Li, X. *ACS Catal.* **2018**, *8*, 4194.

and alkynes **47** to 1,3-benzodiazepines **81** (Scheme 9e).[72] Very recently, Chauvin/Cui[73]and Zhang/Fan[74] reported the Rh-catalyzed [4+3] annulation of *N*-arylpyrazolidinones **82** and propargyl derivatives **83** to 1,2-benzodiazepines **84** (Scheme 9f).



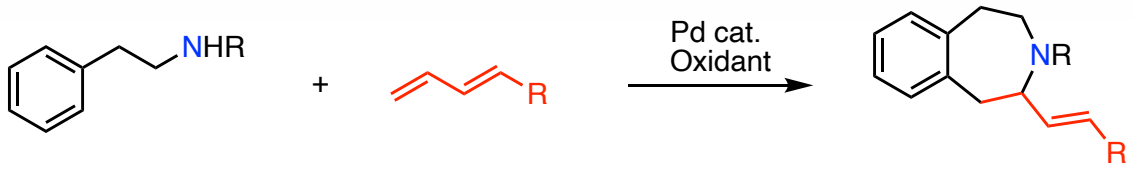

**Scheme 9.** Metal-catalyzed syntheses of benzodiazepines via C-H activation

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[72] Martínez-Yañez, N.; Suárez, J.; Cajaraville, A.; Varela, J. A.; Saá, C. *Org. Lett.* **2019**, *21*, 1779.
[73] Li, T.; Yang, Z.; Song, Z.; Chauvin, R.; Cui, X. *Org. Lett.* **2020**, *22*, 4078.
[74] Zhang, L.; Xu, Y.; Zhang, X.; Zhang, X.; Fan, X. *Org. Chem. Front.* **2020**, *7*, 2284.

# Chapter 2

## 3-Benzazepines *via* C-H Bond Activation/Heteroannulation Processes




Velasco-Rubio, Á.; Varela, J.A.; Saá, C. *Org. Lett.* **2020**, *22*, 3591

Phenethyltriflamides react with 1,3-dienes upon treatment with $Pd(OAc)_2$ and $Cu(OAc)_2/O_2$ as oxidant to afford chemo-, regio- and diastereoselectively 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (3-benzazepine derivatives) in good to excellent yields. A DFT study of the [5+2] heteroannulation suggests a mechanistic pathway starting with formation of six-membered palladacycle *cis*-$PdX_2L_2$ via CMD process followed by $\eta^2$-coordination of 1,3-diene unit in a diastereoselective manner. The enantioselective version of the Pd-catalyzed [5+2] heteroannulation is also studied.

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# Chapter 2

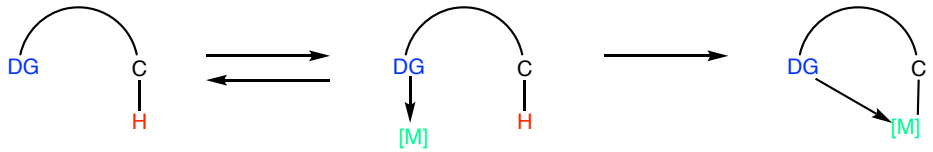
## 3-Benzazepines *via* C-H Bond Activation/Heteroannulation Processes

### 1. C-H Bond Functionalization

Direct functionalization of unactivated C-H bonds, photo-redox and organocatalysis are becoming nowadays the most advanced catalytic methods to reach sustainability and atom-step economy in organic chemistry.[75]

Over the last decades the functionalization of C-H bonds has emerged as a powerful tool to build-up new complex molecules from readily available starting materials which has allowed the development of a plethora of transformations that directly functionalize "inert" C-H bonds.[76] There are some difficulties to overcome such as the low reactivity of C-H bonds (Energy bond dissociation $C_{sp^2}$-H ≈ 106-113 Kcal·mol$^{-1}$ and $C_{sp^3}$-H ≈ 90-102 Kcal·mol$^{-1}$) and the site selectivity, which entails that metal-mediation is often necessary.[77] Undoubtedly, one of the best strategies to overcome these disadvantages and achieve site selectivity would be the employment of directing groups (DGs).

The presence of a DG in the organic molecule locates the C-H bond to be selectively functionalized. Moreover, the basic heteroatoms present in the DGs allow the coordination to the metal center and facilitate the proximity and the selective cleavage of the desired C-H bond (Scheme 10).[78] However, at the same time, DGs became into the main drawback of the C-H bond activation, because they should be removed lately, what contradicts the paradigm of sustainability, atom- and step-economy.[79]

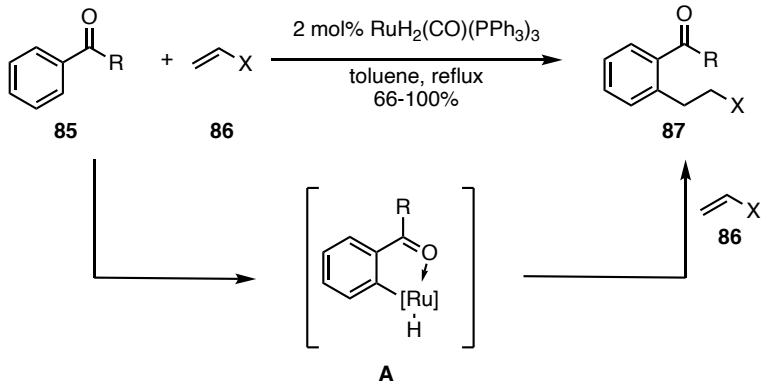



**Scheme 10.** Site selectivity controlled by transition metal catalyzed C-H activation

Transition-metal catalyzed $C_{sp^2}$-H bond functionalization assisted by DG was pioneered by Murai back in 1993. They discovered that complexes of Ru(II) are able to catalyze the *ortho*-alkylation of aromatic ketones **85** with a variety of olefins **86** (Scheme 11).[80] The site selectivity and efficiency of this reaction was attributed to the easier insertion of Ru into *ortho*- $C_{sp^2}$-H bond upon coordination with ketone to provide five-membered metallacyclic intermediate **A**. The olefin **86** then undergoes a 1,2-migratory insertion into the C-Ru bond followed by a reductive elimination to afford the desired *o*-alkyl ketones **87**.

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[75] Anastas, P.; Warner J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, 1998.
[76] a) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. b) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578.
[77] Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651.
[78] Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 1147.
[79] De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461.
[80] Murai, S.; Kakiuchi, F.; Sekini, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.



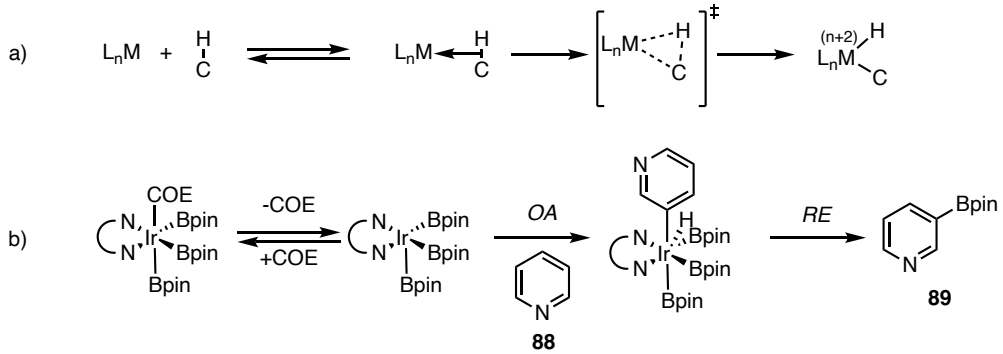

**Scheme 11.** Ru-catalyzed alkylation of aromatic ketones by Murai

## 2. C-H Bond Activation Mechanisms

Following the Shilov definition about C-H bond activation, the metal is directly involved in the C-H bond cleavage and the new σ C-M bond formation.[81] Thus, C-H bond activation mechanism can be classified depending on the C-H bond cleavage and the C-M bond formation, that will depend on the nature of the metal and the employed additives in the reaction.[82]

### 2.1. Oxidative Addition

Once the σ-C-H bond coordinates to the metal complex through an agostic interaction two new bonds are formed, M-C and M-H, and the metal will increment two units its oxidation state (oxidative addition) (Scheme 12a). Electron-rich metal complexes typically follow this mechanism with the low oxidation state of the metal, such as, Fe, Ru, Os, Ir, or Pt. For instance, Hartwig reported in 2005 the Ir-catalyzed C-H bond activation of pyridines **88** to obtain *meta*-borylated pyridines **89** via oxidative addition (Scheme 12b).[83]




**Scheme 12**. C-H bond activation via oxidative addition

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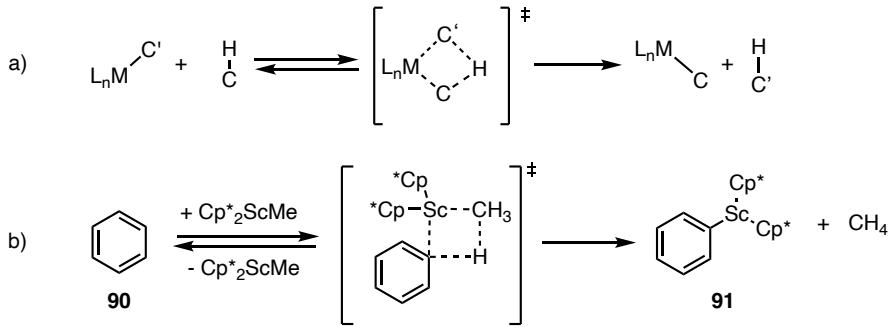
[81] Shilov, A. E.; Shul'pin, G.B *Chem. Rev.* **1997**, *97*, 2879.

[82] Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749.

[83] a) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263. b) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287.

## 2.2. σ-Bond Metathesis

σ-Bond metathesis is characterized by the "*four-spot mechanism*". This concerted mechanism involves the C-H bond cleavage to form the C-M bond while the C'-M bond (C' is the carbon of the ligand, usually alkyl) is broken to form the C'-H bond (Scheme 13a).[84] In this mechanism, the metal does not change the oxidation state, being the metal complex M-H or M-alkyl. Lanthanides and actinides usually follow this mechanism. For example, Bercaw and coworkers proposed this mechanism in 1987 upon development of mechanistic studies in the $C_{sp^2}$-H activation of benzene **90** with [Cp*$_2$ScMe] to obtain the complex **91** (Scheme 13b).[85]



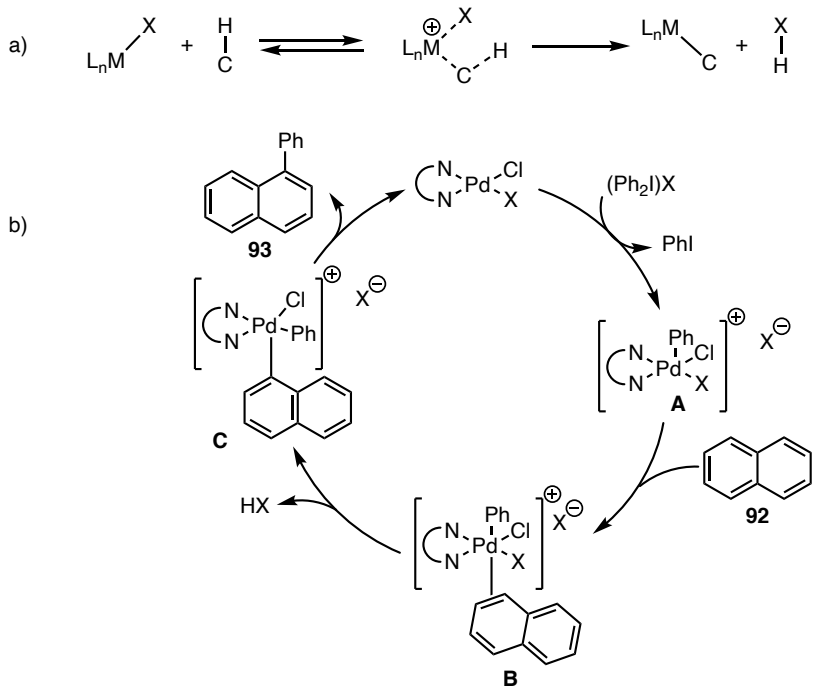

**Scheme 13.** C-H bond activation via σ-bond metathesis

## 2.3. Electrophilic Substitution

Electrophilic substitution takes place when the metal is in the highest oxidation state, the activated substrate is electron-rich, and the media is strongly polarized. The resulting key intermediate comes from the nucleophilic attack of the substrate over the metal center (Lewis acid) (Scheme 14a). The group of Sanford proposed this mechanism in the Pd-catalyzed naphthalene arylation (Scheme 14b).[86] The Pd(II) species undergo an oxidative addition into the aryl iodide to form the Pd(IV) intermediate **A.** Then, the naphthalene **92** coordinates to the metal center (intermediate **B)** and undergoes a palladation to obtain intermediate **C**. Finally, the desired product **93** is released after reductive elimination and the catalytic cycle is restarted.

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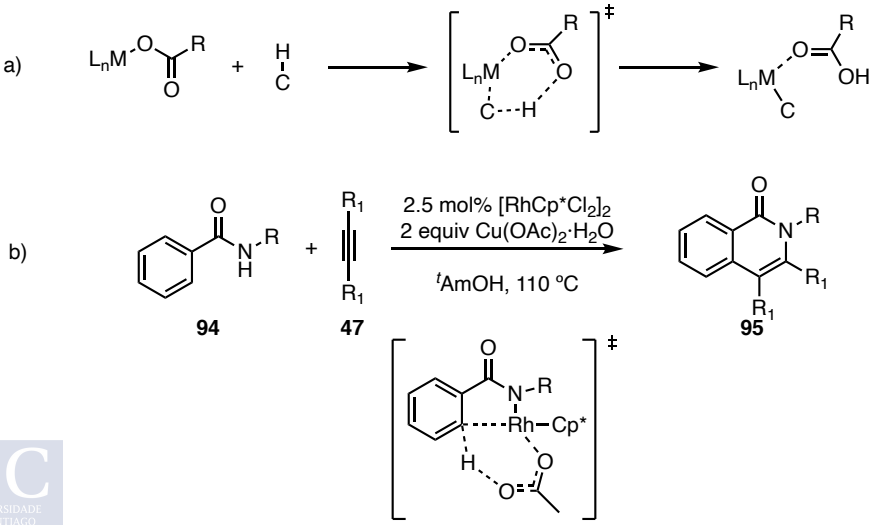
[84] Gandeepan, P.; Müller, T.; Zell, D.; Cero, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192.
[85] Thompson, M. E.; Baxter, S. M.; Bulls, A. R.; Burger, B. J.; Nolan, M. C.; Santarsiero, B. D.; Schaefer, W. P.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 203.
[86] Hickman, A. J. Sanford, M. S. *ACS Catal.* **2011**, *1*, 170.



**Scheme 14.** C-H bond activation via electrophilic substitution

## 2.4. Concerted Metalation-Deprotonation

Concerted metalation-deprotonation (CMD) is a concerted mechanistic pathway in which the C-H bond of the substrate is cleaved and the new C-M bond forms through a single transition state (also called Ambiphilic Metal Ligand Activation (AMLA).[87] This process does not go through a metal species that is bound to the cleaved hydrogen bond. Instead, a carboxylate or carbonate base deprotonates the substrate (Scheme 15a).[88] For example, Rovis proposed in 2010 this kind of mechanism in the Rh-catalyzed (4+2) annulation of benzamides **94** and alkynes **47** to isoquinolones ***95*** (Scheme 15b).[89]

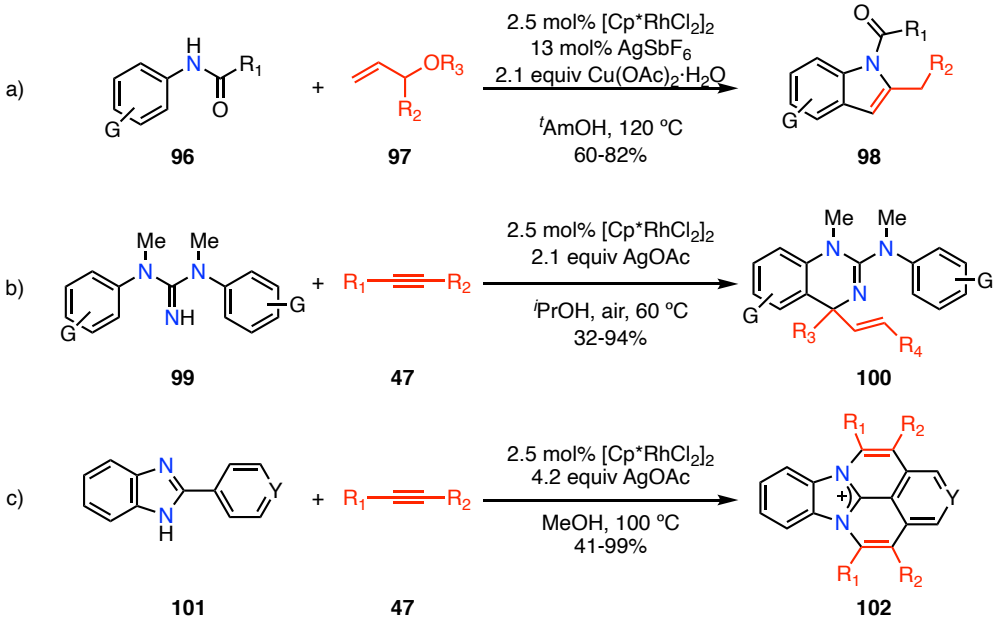


**Scheme 15.** C-H bond activation via CMD

[87] Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820.
[88] Grensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900.
[89] Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565.

## 3. Synthesis of Benzofused Five- and Six-Membered Azaheterocycles via C-H Bond Activation

The benzofused five- and six-membered azaheterocycles have been successfully achieved via C-H activation/heteroannulation processes. Our group has been extensively working in the development of some synthetic strategies over the last years. In 2013, we reported the Rh-catalyzed synthesis of indoles **98** from anilides **96** and allyl carbonates **97** (Scheme 16a).[90] A variety of 2-substituted indoles **98** was successfully synthesized from *ortho*-, *meta*- or *para*-substituted anilides **96**. In 2015, a novel and mild Rh-catalyzed [5+1] oxidative cycloaddition between arylguanidines **99** and aliphatic alkynes **47** to 1,4-dihydroquinazolin-2-amines **100** was discovered (Scheme 16b).[91] Symmetrically substituted arylguanidines **99** were well-tolerated and symmetrical and non-symmetrical alkynes **47** successfully underwent the oxidative cycloaddition. In 2017, we reported a double Rh-catalyzed C-H activation and annulation of 2-arylbenzimidazoles **101** and alkynes **47** to cationic *N*-doped PAHs **102** (Scheme 16c).[92] Symmetrical, non-symmetrical, aliphatic, and aromatic alkynes **47** successfully underwent the double [4+2] cycloaddition.




**Scheme 16.** Synthesis of benzofused five- and six-membered azaheterocycles via Rh-catalyzed C-H bond activation

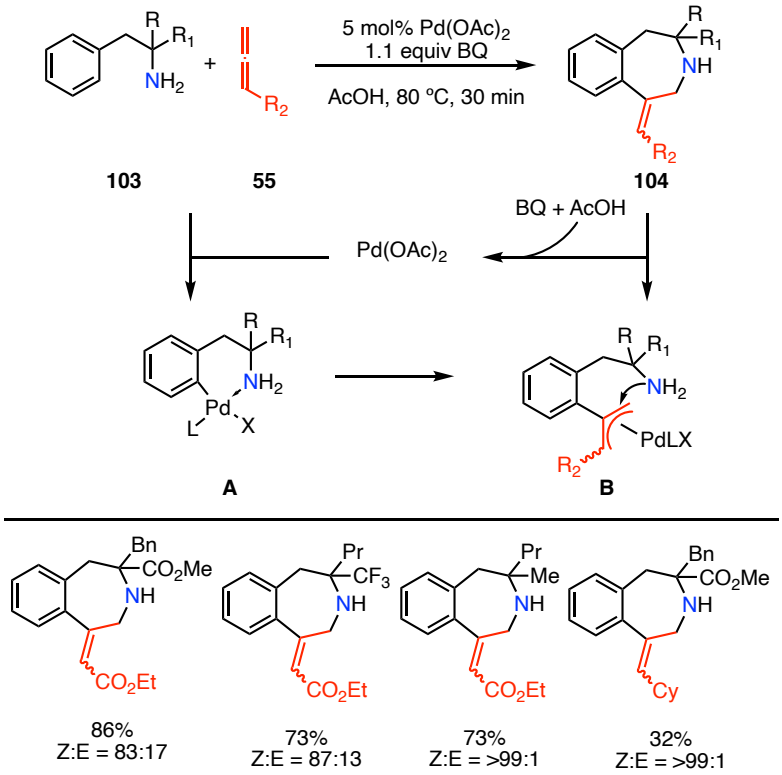
## 4. Synthesis of 3-Benzazepines via Transition Metal Catalyzed C-H Bond Activation/Heteroannulation

In 2014, Ariza and coworkers reported the Pd-catalyzed annulation of phenethylamines **103** with allenes **55** to 3-benzazepines **104** (Scheme 17).[93] The mechanism proposed for this transformation started with the formation of the six-membered palladacycle (*trans*-$PdX_2L_2$) **A**. Then, coordination of the allene and regioselective insertion into C-Pd bond afforded the

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[90] Cajaraville, A.; López, S.; Varela, J. A.; Saá, C. *Org. Lett.* **2013**, *15*, 4576.
[91] Cajaraville, A.; Suárez, J.; López, S.; Varela, J. A.; Saá, C. *Chem. Commun.* **2015**, *51*, 15157.
[92] Villar, J. M.; Suárez, J.; Varela, J. A.; Saá, C. *Org. Lett.* **2017**, *19*, 1702.
[93] Rodriguez, A.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J.; Farras, J.; La Mela, A.; Nicolas, E. *J. Org. Chem.* **2014**, *79*, 9578.

π-allylic intermediate **B**. The authors proposed a $S_N2$ reaction (Tsuji-Trost allylic alkylation) over the π-allylic intermediate to give rise to the 3-benzazepines **104**. Despite the fact that the reaction was quite fast (30 min), the scope of this transformation was limited to α,α-disubstituted phenethylamines with an electron-withdrawing group, due to the necessity of a clear Thorpe-Ingold effect,[94] and polarized allenes to obtain reasonable yields and good regioselectivities in the Tsuji-Trost allylic alkylation. In this way, $CF_3$, ester and alkyl groups were well-tolerated in the α position of the phenethylamines **103**, and polarized allenes worked in moderate to very good yields.

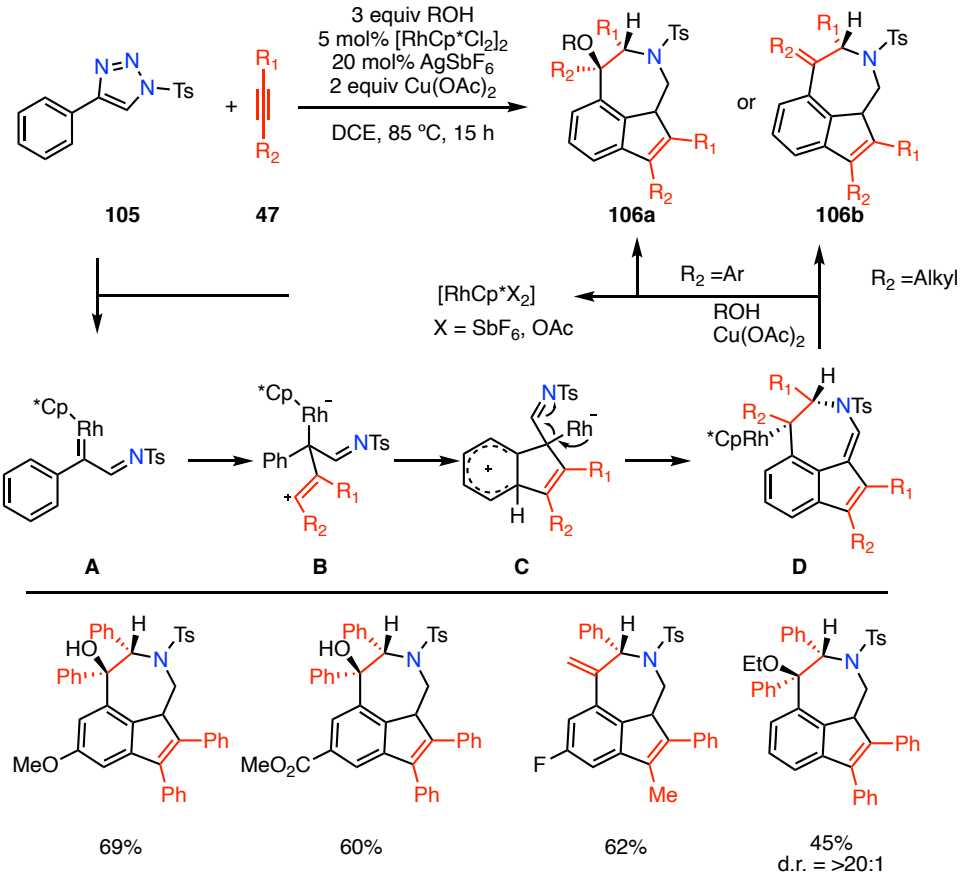



**Scheme 17.** Ariza's synthesis of 3-benzazepines from Pd-catalyzed annulation between α,α-disubstituted phenethylamines and allenes

In 2015, Li's group reported a tandem Rh-catalyzed [3+2]/[5+2] heteroannulation of 2-tosyltriazoles**105** with alkynes **47** to yield 3-benzazepines **106** (Scheme 18).[95] The authors suggested a mechanism which starts with the generation of the Rh-carbenoid intermediate **A**. The addition of the alkyne provides the zwitterionic species **B** which undergoes electrophilic cyclization to give the five-membered ring **C** ([3+2] heteroannulation). Then, a second [5+2] annulation with the alkyne leads to the 3-benzazepine intermediate **D** (*via* transient Rh-H species) that evolves in two different pathways depending on the substituents of the alkyne **47**. When aromatic alkynes are used, cleavage of the C-Rh bond with the aid of $Cu(OAc)_2$ through hydration with water (or ROH) affords the benzylic alcohol **106a** and regenerate the active catalyst. On the other hand, when aliphatic alkynes are used, C-Rh bond is cleaved by $Cu(OAc)_2$ followed by a β-hydride elimination to give the *exo*-methylene 3-benzazepine **106b**. Aromatic and aliphatic alkynes worked in good yields.

[94] a) Beesley, R. M.; Ingold, C, K.; Thorpe, J. F. *J. Chem. Soc., Trans.*, **1915**, *107*, 1080. b) Shaw, B. L. *J. Am. Chem. Soc.* **1975**, *97*, 1080.

[95] Yang, Y.; Zhou, M.-B.; Ouyang, X.-H.; Pi, R.; Song, R.-J.; Li, J.-H., *Angew. Chem. Int. Ed.* **2015**, *54*, 6595.

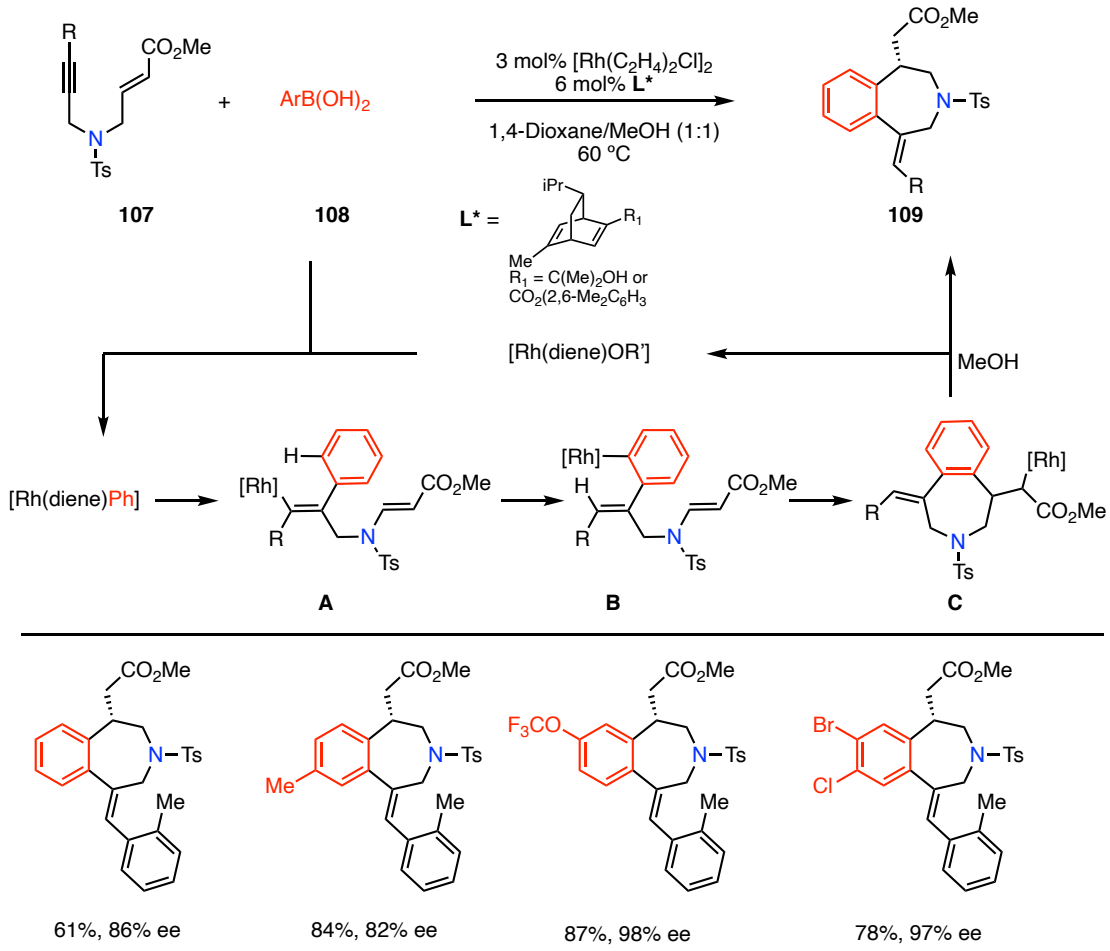



**Scheme 18**. Li's approach to 3-benzazepines by tandem Rh-catalyzed [3+2]/[5+2] heteroannulation of 4-aryltosyltriazoles and alkynes

In 2017, Darses and coworkers reported an enantioselective Rh-catalyzed [5+2] annulation of yne-enoate derivatives **107** with arylboronic acids **108** to yield 3-benzazepines **109** (Scheme 219).[96] The proposed mechanism involves a transmetallation of the arylboron reagent to the hydroxo Rh(I) complex followed by regioselective alkyne insertion to give a vinylrhodium species **A**. Then a 1,4-rearrangement (C-H activation) gives intermediate **B** that undergo a conjugated addition to the enoate to deliver, after hydrolysis, the 3-benzazepine **109**. Halogenated, electron-rich and electron-poor arylboronic acids were well tolerated giving the corresponding 3-benzazepines in fair good yields.

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[96] Claraz, A.; Serpier, F.; Darses, S. *ACS Catal.* **2017**, *7*, 3410.

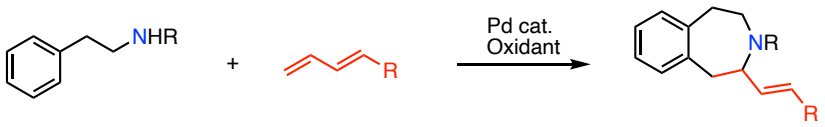



**Scheme 19.** Darses' approach to 3-benzazepines by Rh-catalyzed (5+2) heteroannulation of yne-enoate derivatives and arylboronic acids

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## 5. Objective

3-Benzazepines have been synthesized by a variety of classical and catalytic methods (Chapter 1). Despite the fact that all these methods might be considered very useful, they lack sustainability and atom- and step-economy. The main objective of this chapter would be the development of a more sustainable synthesis of 3-benzazepines, via C-H bond activation/heteroannulation processes (Scheme 20). The main challenge of this [5+2] cycloaddition between phenethylamine derivatives and 1,3-dienes will be the finding of a dual use of a DG linked with a "free" $C_{sp^3}$ chain on the phenethylamine to facilitate the C-H activation that could also act as nucleophile. The enantioselective version of this oxidative annulation will also be explored.




**Scheme 20.** Pd-catalyzed [5+2] cycloaddition of phenethylamines with 1,3-dienes to 3-benzazepines

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# 6. Results and Discussion

## 6.1. Synthesis of Starting Materials

Starting materials were synthesized following methods described in the literature or used as received from commercial sources. Sulfonamides (**110a**,[97] **110m**,[98] **110n**,[99] and **110o**[99]), amides (**110p**[100] and **110q**[44c]) or amines (**110r**[101]) were chosen in order to evaluate the influence of the DG in the reaction, from the N-H acidity to the electronic effects (Figure 5).

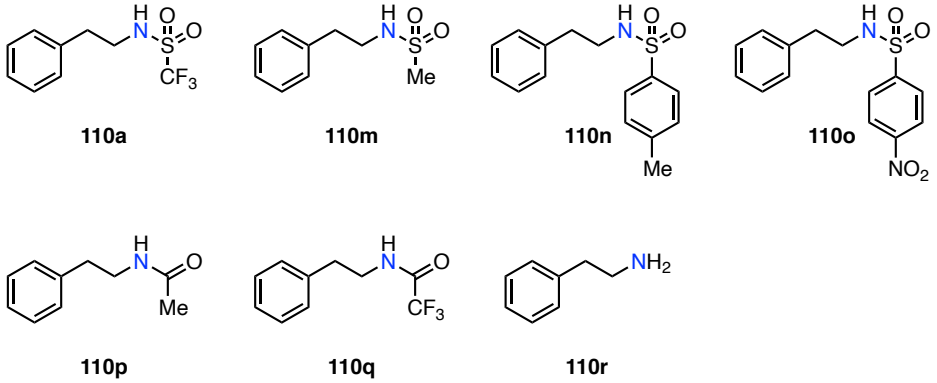



**Figure 5.** Starting materials evaluated

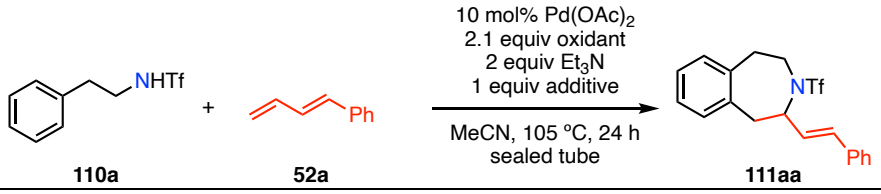
## 6.2. Optimization of Reaction Conditions

We started the evaluation of the reactivity with the triflamide **110a**. This triflamide was previously used by J.-Q. Yu in a Pd-catalyzed C-H bond functionalization.[97,102] that involved a Pd(II)/Pd(IV) catalytic cycle in which the Pd(IV) species facilitate the reductive elimination.[103]

We begin exploring the reaction conditions employing **110a** as starting material, 1,3-diene **52a** as coupling partner and 10 mol% $Pd(OAc)_2$, 2 equiv $Et_3N$ and a variety of oxidants (Table 1). Under typical oxidative conditions using PIFA, PIDA, $H_2O_2$/NaOAc, BQ, 2,5-DtBBQ or Oxone® the reaction failed (Table 1, entries 1-6), recovering **110a** unaltered. Interestingly, in the presence of $Cu(OAc)_2 \cdot H_2O$ as oxidant (Table 1, entry 7), a promising 35% yield of the 3-benzazepine **111aa** was observed.

**Table 1**. Optimization of reaction oxidant

[97] Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.
[98] Madsen, A. S.; Kristensen, H. M. E.; Lanz, G.; Olsen, C. A. *ChemMedChem* **2014**, *9*, 614.
[99] Ramunno, A.; Cosconati, S.; Sartini, S.; Maglio, V.; Angiuoli, S.; La Pietra, V.; Di Maro, S.; Giustiniano, M.; La Motta, C.; Da Settimo, F.; Marinelli, L.; Novellino, E. *Eur. J. Med. Chem.* **2012**, *51*, 216.
[100] Li, H.; Tian, P.; Xu, J.-H.; Zheng, G.-W. *Org. Lett.* **2017**, *19*, 3151.
[101] Commercially available
[102] Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452.
[103] a) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177. b) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936.



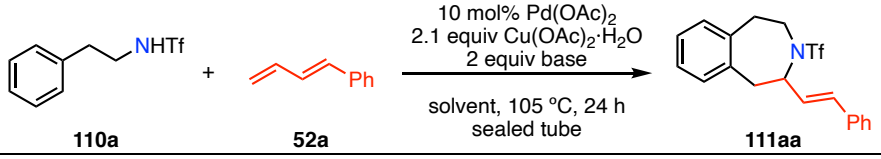

**110a** **52a** **111aa**

| Entry[a] | Oxidant | Additive | NMR % yield[b] |
|---|---|---|---|
| 1 | PIFA | - | - |
| 2 | PIDA | - | - |
| 3 | $H_2O_2$ | NaOAc | - |
| 4 | BQ | NaOAc | - |
| 5 | 2,5-DtBBQ | NaOAc | - |
| 6 | Oxone® | NaOAc | - |
| 7 | $Cu(OAc)_2{\cdot}H_2O$ | - | 35 |

Conditions: a) 0.2 mmol **110a**, 0.4 mmol **52a,** 1 mL MeCN. b) Methyl 3,5-dinitrobenzoate was used as internal standard.

Once $Cu(OAc)_2{\cdot}H_2O$ was found as the best oxidant, we then evaluate other parameters of the reaction such as the base and solvent (Table 2). Inorganic bases, such as, CsOAc, $Cs_2CO_3$, $K_2CO_3$ (Table 2, entries 3-5) gave lower yields than $Et_3N$ (Table 2, entry 1), or similar to DBU (Table 2, entry 2). Regarding the solvent effect, it has been reported that strongly coordinating solvents avoid the polymerization of Pd to ineffective dark palladium.[104] Thus, in the presence of DMF (used in a 4:1 mixture with MeCN) the yield of **111aa** increased to 50% (Table 2, entry 7). However, with other strong coordinating solvents, such as, DMSO or MeOH (Table 2, entries 6-8) gave inferior results. The reaction failed in a mixture 1:1 of DMF and toluene (Table 2, entry 9). When the amount of DMF employed was increased (Table 2, entries 10-11), lower yields of **111aa** were obtained.

**Table 2**. Optimization of base and solvent




**110a** **52a** **111aa**

| Entry[a] | Solvent | Base | NMR % yield[b] |
|---|---|---|---|
| 1 | MeCN | $Et_3N$ | 35 |
| 2 | MeCN | DBU | 20 |
| 3 | MeCN | CsOAc | 25 |
| 4 | MeCN | $Cs_2CO_3$ | 16 |
| 5 | MeCN | $K_2CO_3$ | 15 |
| 6 | MeCN:DMSO (4:1) | $Et_3N$ | 35 |
| 7 | MeCN:DMF (4:1) | $Et_3N$ | 50 |
| 8 | MeCN:MeOH (4:1) | $Et_3N$ | 25 |
| 9 | DMF:Toluene (1:1) | $Et_3N$ | - |
| 10 | MeCN:DMF (1:1) | $Et_3N$ | 10 |
| 11 | DMF | $Et_3N$ | 22 |

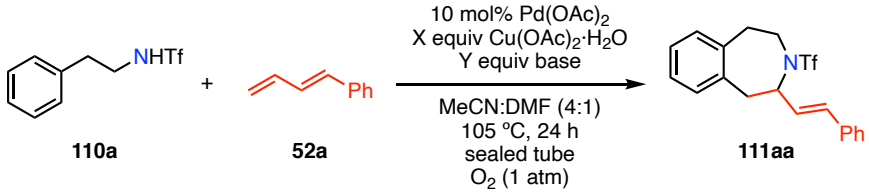
Conditions: a) 0.2 mmol **110a**, 0.4 mmol **52a,** 1 mL solvent. b) Methyl 3,5-dinitrobenzoate was used as internal standard.

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[104] Iwasawa, T.; Tokunaga, M.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2004**, *126*, 6554.

Since the best result was a moderate 50% yield, we wonder if the $Cu(OAc)_2·H_2O$ and $Et_3N$ amounts were in the correct stoichiometries. Hence, we decided to screen the amounts of base and oxidant (Table 3). Indeed, $O_2$ atmosphere in combination with low amounts of $Cu(OAc)_2·H_2O$ has been reported as a good oxidant system.[61] Thus, when the amount of $Cu(OAc)_2·H_2O$ was decreased to 1 equiv a 70% yield of **111aa** was obtained (Table 3, entry 1). With a further decrease of the amount of $Cu(OAc)_2$ to substoichiometric (Table 3, entry 2-3), lower yields were observed; on the contrary, the higher concentration of the reaction, the higher yield was achieved (Table 3, entry 4). The amount of base could also be adjusted. In the presence of 1 equiv or 0.5 equiv of $Et_3N$ (Table 3, entries 5-6) the yield of the reaction was 65% and 60%, respectively. To our delight, when a catalytic amount of $Et_3N$ was used, a quantitative yield of **111aa** was isolated (Table 3, entry 7).

**Table 3**. Optimization of $Et_3N$ and $Cu(OAc)_2·H_2O$ amounts




**110a** **52a** **111aa**

| Entry[a] | X | Y | NMR % yield[b] |
|---|---|---|---|
| 1 | 1 | 2 | 70 |
| 2 | 0.5 | 2 | 65 |
| 3 | 0.25 | 2 | 20 |
| 4[c] | 0.5 | 2 | 75 |
| 5[c] | 0.5 | 1 | 65 |
| 6[c] | 0.5 | 0.5 | 60 |
| **7[c]** | **0.5** | **0.1** | **>95** |
| 8 | 0.5 | 0 | 70 |

a) 0.2 mmol **110a**, 0.4 mmol **52a,** 1 mL solvent mixture. b) Methyl 3,5-dinitrobenzoate was used as internal standard. c) 0.5 mL of solvent mixture.

After these optimization studies, we can conclude:

- In order to avoid the polymerization of palladium into ineffective dark palladium, it is necessary to employ strong coordinating solvents, like DMF (Table 2, entry 7), that might help in the oxidation step of Pd(0) into Pd(II) species.
- The presence of copper complex $Cu(OAc)_2·H_2O$ is crucial for the oxidation steps of the reaction. Furthermore, $O_2$ helps to decrease the amount of $Cu(OAc)_2·H_2O$ to 0.5 equiv, avoiding the employment of stoichiometric amounts of oxidant that deliver undesired side reactions.
- Catalytic amounts of $Et_3N$ are only needed for achieving quantitative yields (Table 3, entry 7). It might also help in the C-H bond activation step. In fact, in the absence of base the yield drops to 70% (Table 3, entry 8).
- The use of -NHTf (triflamide) as directing group is crucial for both the C-H activation and [5+2] oxidative annulation, since other sulfonamides or acetamides

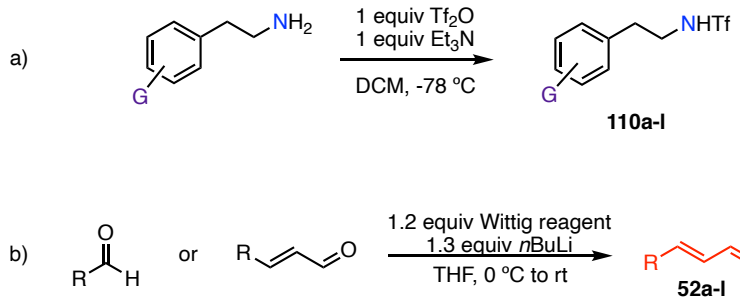
failed to react (**110m-110r**), despite the fact that **110n**,[105] **110o**,[106] **110r**[93] had been reported to undergo C-H bond activation.

- The standard conditions are established as follows: 1 equiv of **110**, 2 equiv of **52**, 10 mol % $Pd(OAc)_2$, 0.5 equiv $Cu(OAc)_2{\cdot}H_2O$, 0.1 equiv $Et_3N$, 0.5 mL of MeCN/DMF (4:1), $O_2$ (1 atm), 105 °C, 24 h, sealed tube.

## 6.3. Scope and Limitations

### 6.3.1. Synthesis of Starting Materials

A variety of phenethyltriflamides **110** were synthesized by treatment of the corresponding phenethylamine with triflic anhydride in DCM at -78°C following the literature procedure (Scheme 21a).[97] In the same manner, 1,3-dienes **52** were synthesized by Wittig reaction of the corresponding phosphonium ylides and the corresponding aldehydes according to the literature (Scheme 21b).[107]




**Scheme 21.** Synthesis of phenethyltriflamides **110a-l** and 1,3-dienes **52a-l**

### 6.3.2. Pd-Catalyzed [5+2] Heteroannulation of Phenethyltriflamides and 1,3-Dienes

Scope and limitations of the [5+2] heteroannulation reaction were then explored (Scheme 22). Phenethyltriflamides **110** and 1,3-dienes **52** reacted under standard conditions: 10 mol % $Pd(OAc)_2$, 0.5 equiv $Cu(OAc)_2{\cdot}H_2O$, 0.1 equiv $Et_3N$, in a mixture of MeCN/DMF (4:1), at 105 °C, under $O_2$ and in a sealed tube.

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[105] Bai, X.-F.; Mu, Q.-C.; Xu, Z.; Yang, K.-F.; Li, L.; Zheng, Z.-J.; Xia, C.-G.; Xu, L.-W. *ACS Catal.* **2019**, *9*, 1431.

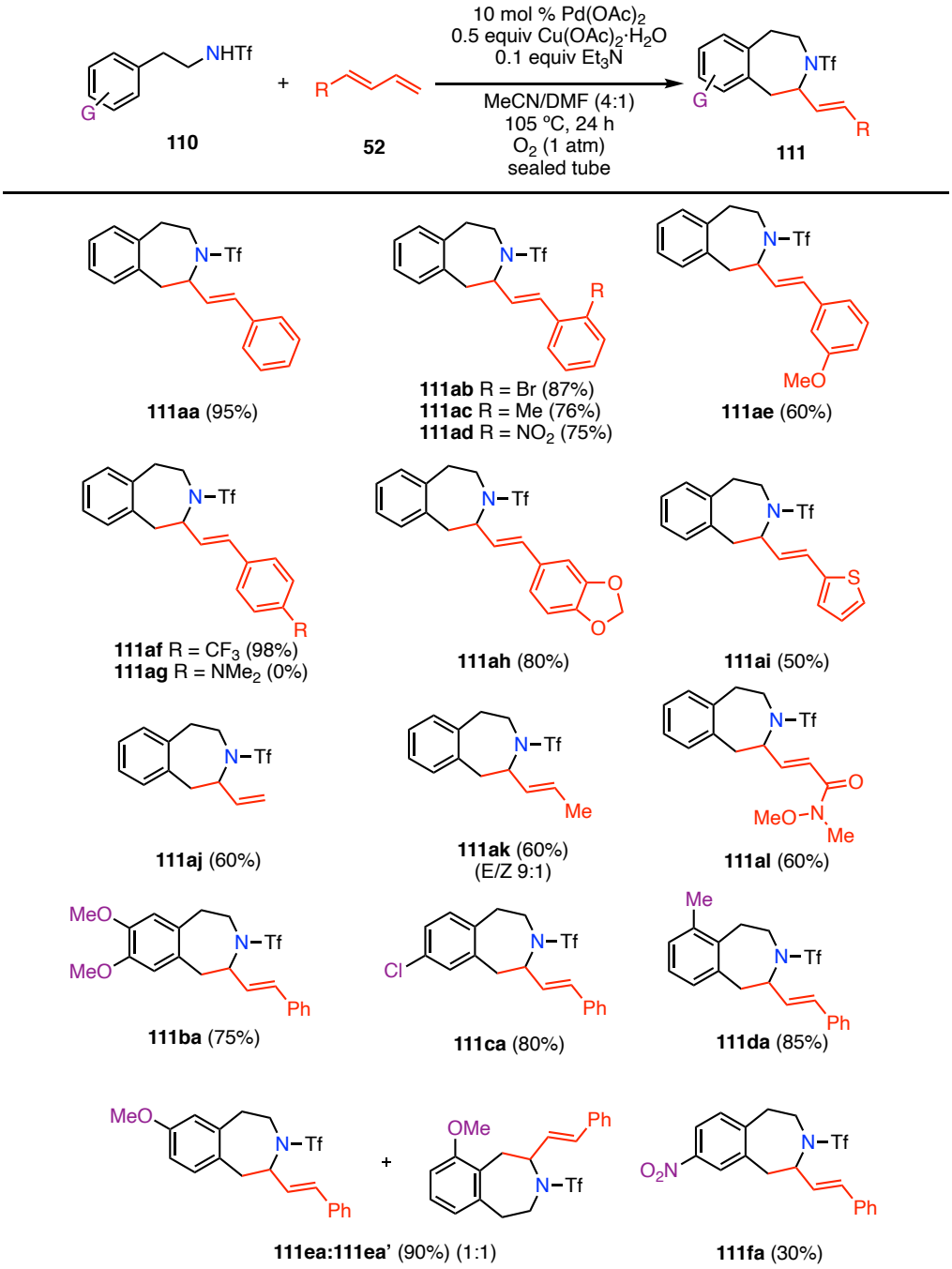
[106] a) Ding, Q.; Ye, S.; Cheng, G.; Wang, P.; Farmer, M. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 417. b) Shi, H.; Herron, A. N.; Shao, Y.; Shao, Q.; Yu, J.-Q. *Nature* **2018**, *558*, 581.

[107] a) Madden, K. S.; David, S.; Knowles, J. P.; Whiting, A. *Chem. Commun.* **2015**, *51*, 11409.; b) Brun, E.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2016**, *81*, 8206.; c) Landesberg, J. M.; Slam, M. A.; Mandel, M. *J. Org. Chem.* **1981**, *46*, 5025.; d) Zhang, M.; Watanabe, K.; Tsukamoto, M.; Shibuya, R.;Morimoto, H.; Ohshima, T. *Chem. Eur. J.* **2015**, *21*, 3937.; e) Bernardi, L.; López-Cantarero, J.; Niess, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5772.; f) Barluenga, S.; Moulin, E.; López, P.; Winssinger, N. *Chem. Eur. J.* **2005**, *11*, 4935.

[61] Cendón, B.; Casanova, N.; Comanescu, C.; García-Fandiño, R.; Seoane, A.; Gulías, M.; Mascareñas, J. L. *Org. Lett.* **2017**, *19*, 1674.

[93] Rodriguez, A.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J.; Farras, J.; La Mela, A.; Nicolas, E. *J. Org. Chem.* **2014**, *79*, 9578.

[97] Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.




Conditions: **110** (0.2 mmol, 1 equiv), **52** (0.4 mmol, 2 equiv), 10 mol % $Pd(OAc)_2$, 0.5 equiv $Cu(OAc)_2 \cdot H_2O$, 0.1 equiv $Et_3N$, 0.5 mL of MeCN/DMF (4:1), 105 °C, $O_2$ (1 atm).

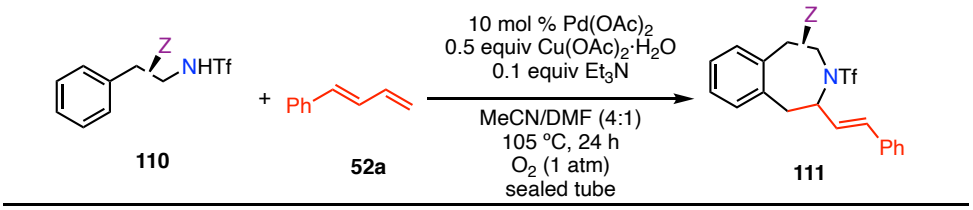
**Scheme 22.** Scope of the reaction

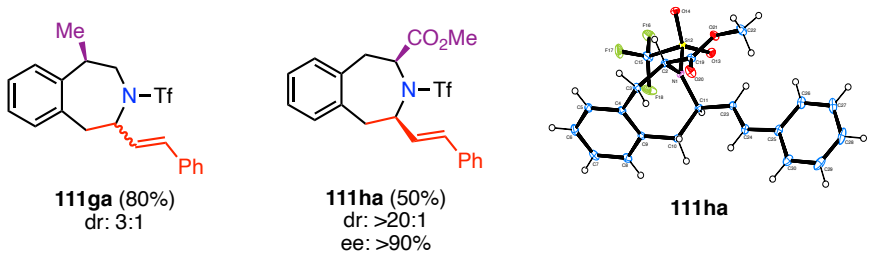
We began our investigation testing a variety of 1,3-dienes **52**. The reaction tolerated terminal monosubstituted 1,3-dienes. *ortho*-Substituted aryl 1,3-dienes reacted in very good yields (**111ab**-**111ad**). Similarly, *meta*- and *para*-substituted aryl 1,3-dienes reacted in good to excellent yields (**111ae**, **111af**, **111ah**), except the electron-enriched **52g**, in which the reaction

gave an extensively polymerization of the 1,3-diene. Heteroaromatic 1,3-diene also reacted in good to very good yields (**111ai**). Interestingly, the unsubstituted parent 1,3-butadiene reacted smoothly in relative good yield, as well as its homolog, 1,3-pentadiene (as a 1:1 mixture of E/Z isomers), that gave the alkenyl derivative **111ak** as a E/Z mixture (9:1). A conjugated 1,3-diene was also well-tolerated to afford the α,β-unsaturated amide **111al** in a fairly good yield, that foresees interesting derivatization of the installed Weinreb-amide. Unfortunately, different location for the substituent, more substituted acyclic and cyclic 1,3-dienes, and other unsaturated coupling partners like 2-substituted, 2,3-disubstituted or 1,4-disubstituted 1,3-dienes, alkenes and alkynes failed in the catalytic transformation.

Electronic effects in the aryl ring of phenethyltriflamides **110** were then analyzed in the reaction with 1,3-diene **52a**. Electron-donating and electron-withdrawing substituents in *ortho*-, *meta*- and *para*-position (**111ba**, **111da**) were tolerated giving the corresponding 3-benzazepines in very good yields (**111ba**-**111da**). When *meta*-OMe substituted phenethyltriflamide **110e** was employed, a mixture of isomers (**111ea**, **111ea'**) was obtained in excellent yield. Activation of the more hindered C-H bond might be occurring upon cooperative C-H bond activation with the methoxy group, otherwise it should be only obtained one isomer (the less hindered one). Unfortunately, the strongly polarized nitro derivative **111fa** was obtained in a poor 30% yield.

We next analyzed the diastereoselectivity of the reaction. To this end, we synthesized the phenethyltriflamides **110g** and **110h** with substituents in α and β positions of the alkyl chain (Scheme 23).



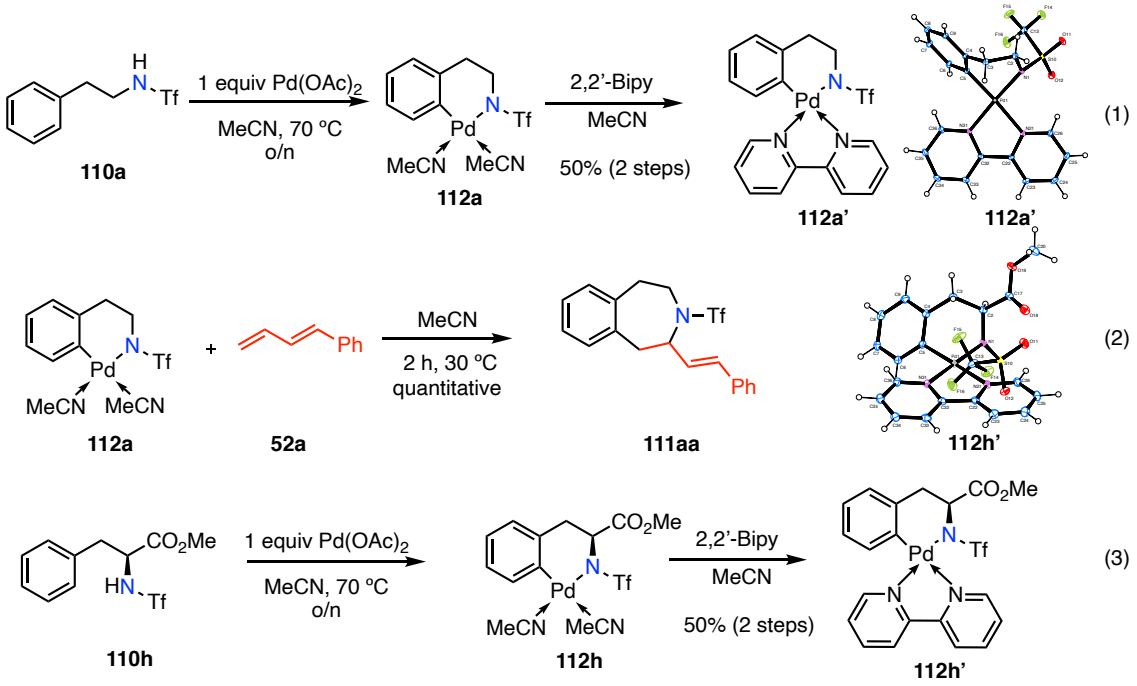

Conditions: **110** (0.2 mmol, 1 equiv), **52a** (0.4 mmol, 2 equiv), 10 mol % $Pd(OAc)_2$, 0.5 equiv $Cu(OAc)_2 \cdot H_2O$, 0.1 equiv $Et_3N$, 0.5 mL of MeCN/DMF (4:1), 105 °C, $O_2$ (1 atm).

**Scheme 23.** Study of the diastereoselectivity of the reaction

When the substituent was in the β-position of the alkyl chain (**110g**), the 3-benzazepine **111ga** was obtained in very good yield but with a low 3:1 diastereoselectivity. By contrast, when the phenylalanine derivative **110h** reacted under standard conditions the 3-benzazepine **111ha** was obtained in a 50% yield as a single diastereoisomer and with a >90% ee. The structure was confirmed by X-ray diffraction analysis and showed that both substituents are in the same face (*syn*-disposition).

## 7. Mechanistic Studies and DFT Calculations

In order to gain further insights into the reaction mechanism, stoichiometric experiments were performed (Scheme 24). The six-membered palladacycle (*cis*-$PdX_2L_2$) **112a** was prepared on heating **110a** in the presence of $Pd(OAc)_2$ in MeCN. Ligand interexchange occurred upon treatment of **112a** with 2,2'-bipy to give **112a'** as off-white crystals, whose structure was confirmed by X-ray diffraction analysis (Scheme 24, eq 1). To our delight, stirring of **112a** at rt in the presence of 1 equiv of **52a** gave rise to **111aa** in quantitative yield (Scheme 24, eq 2). Similarly, to gain further information of the diastereoselectivity of the reaction, complex **112h'**(*cis*-$PdX_2L_2$) was isolated and crystallized upon treatment of **110h** with $Pd(OAc)_2$ at 70 °C, followed by complexation with 2,2'-bipy (Scheme 24, eq 3).




**Scheme 24.** Isolation of palladacycles **112a'** and **112h'** and mechanistic probes

Diastereoselectivity of the reaction was then analyzed by DFT calculations,[108] startingfrom palladacycle **112h** (*cis*-$PdX_2L_2$) (Scheme 24). Based on the literature precedents,[109] this intermediate should be generated via a CMD mechanism. There are four possible perpendicular $\eta^2$-coordination modes of the less substituted olefin of the 1,3-diene to the palladacycle (substituent left/right and up/down).[110] It was only possible to find the transition states for the 1,2-migratory insertion of the two shown, **I** (left-down)[111] and **I'** (left-up).[112] Even though **I'** was more stable than **I** ($\Delta G^\circ$ = 2.6 Kcal $mol^{-1}$), 1,2- migratory insertion

[108] DFT calculations were performed by Dr. Jesús Varela Carrete

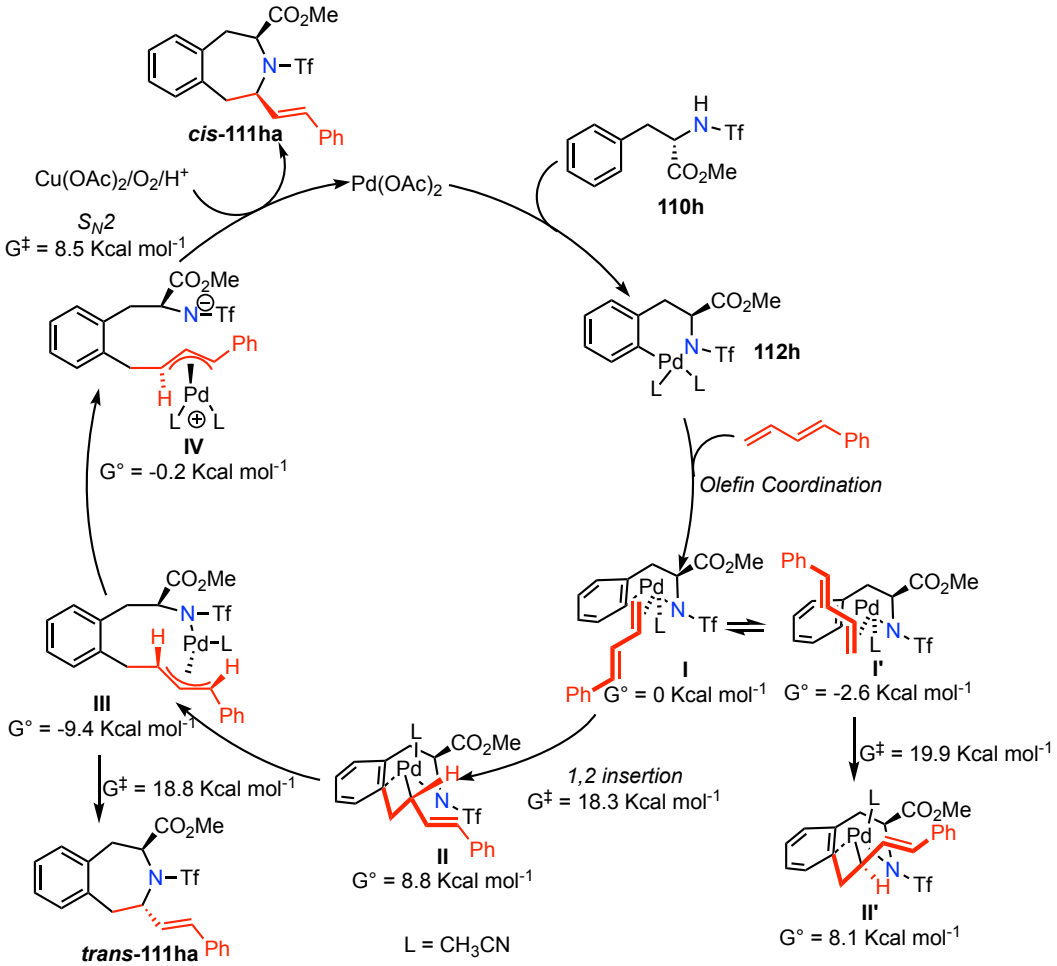
[109] Abada, E.; Zavalij, P. Y.; Vedernikov, A. N. *J. Am. Chem. Soc.* **2017**, *139*, 643.

[110] For the sake of simplicity, the six-membered palladacycle has been considered plane although its two boat-like conformers have been computed. See Chapter 5 for details

[111] We have not observed any coordinating effect by the -$CO_2Me$ group and, therefore, we assume that the steric effect is predominant to locate it at the more stable equatorial position, as shown in X-Ray structure **112h'** and calculated structure **I**, that dictates the regioselectivity found.

[112] The $\eta^4$-s-cis coordination mode of the 1,3-diene to the palladacycle was also considered but lead to the corresponding intermediates through higher energy transition states. See Chapter 5 for details.

of the coordinated double bond of the diene into the C-Pd bond from **I** to afford the eight-membered palladacycle **II** resulted kinetically more favorable than the same elemental step to afford **II'** from **I'** ($\Delta\Delta G^{\ddagger}$ = 1.6 Kcal mol$^{-1}$). A direct route involving a conformational change from **II** to the more stable π-allyl complex **III** followed by reductive elimination affords the ***trans*-111ha** through a high energetic barrier $\Delta G^{\ddagger}$ = 28.2 Kcal mol$^{-1}$ (this diastereomer was not observed experimentally). However, decoordination of the nitrogen from **III** to a zwitterionic species **IV** followed by a favorable $S_N2$-type reaction afforded the observed *cis* 3-benzazepine ***cis*-111ha** with a relative low barrier ($\Delta G^{\ddagger}$ = 8.7 Kcal mol$^{-1}$).[113] Final Pd reoxidation of Pd(0) to Pd(II) would regenerate the catalytic species.




**Scheme 25.** Proposed catalytic cycle and DFT calculations

## 8. Asymmetric Pd-Catalyzed Reaction

The generation of a new stereogenic center in the 3-benzazepine upon Pd-catalyzed C-H bond activation/heteroannulation process, encouraged us to investigate the asymmetric reaction. A variety of chiral N,O-, N,P-, N,N-, P,P-, monodentate NHC- and phosphoramidites, and N,-S(O)- ligands were tested to get an enantioenriched product (Figure 6). Typical chiral N,O- ligands used are based on aminoacid derivatives (**L1**-**L5**).[114]

[113] See Chapter 5 for the energetic profiles of the reductive elimination and $S_N2$-type reaction of all the other analyzed isomers.

[114] Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882.

Other chiral ligands used were N,N- ligands (**L7**, **L11**), P-N ligands (**L6**), monodentate ligands (phosphoramidite **L8**, NHC **L9**), biphosphine (**L10**) or SOX-family (**L1-SOX**). This SOX-family was developed by White[115] and it has been successfully employed in a Pd-catalyzed [3+2] cycloaddition reported by Han.[116]

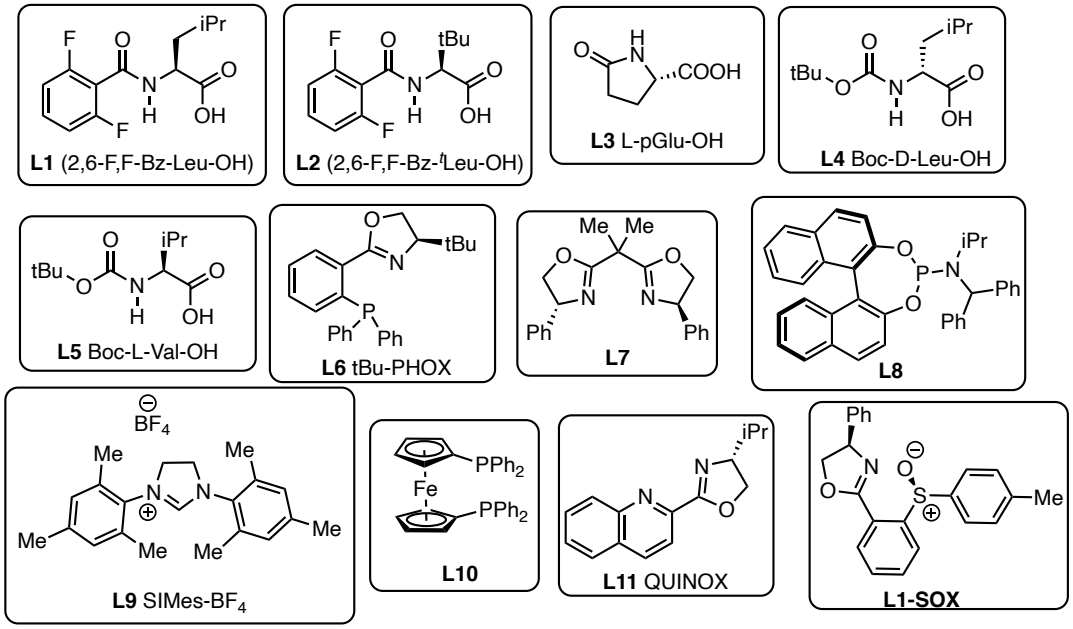
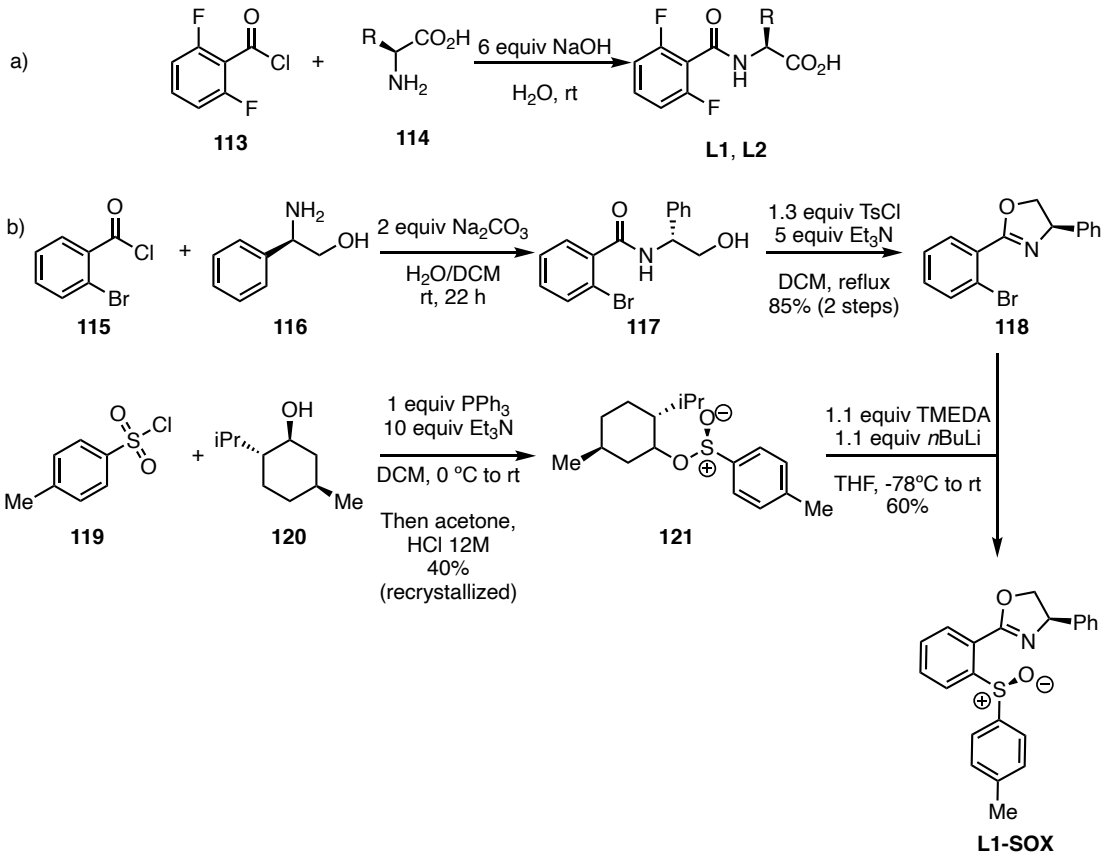



**Figure 6.** Chiral ligands used for the Pd-catalyzed enantioselective C-H bond activation

Most of them are commercially available, but in the case of **L1** and **L2** had to be synthesized by condensation of the amino acid **114** and 2,6-F,F-benzoyl chloride **113** (Scheme 26a).[117] In the case of **L1-SOX** had to be synthesized according to the procedure described by White in a multistep synthesis. First, condensation between the corresponding aminoalcohol **115** and the benzoyl chloride **116** yield the amide **117** in quantitative yield. Second, the intramolecular condensation of the amide **117** in the presence of tosyl chloride furnished the oxazoline **118** in very good yield. On the other hand, tosyl chloride **119** reacted with (-)-menthol **120** to obtain a mixture of sulfinates, that after recrystallization in hot acetone and HCl yield the enantioenriched sulfinate **121** ($[\alpha]_D^{25}$ = -197.0, c = 1, acetone).[118] Sulfinate **121** and lithiated oxazoline **118** reacted to afford **L1-SOX** in 60% yield ($[\alpha]_D^{25}$ = -200.0, c = 1, $CH_2Cl_2$)[115] (Scheme 26b).[119]

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[115] Ammann, S. E.; Liu, W.; White, M. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 9571.
[116] Chen, S.-S.; Wu, M.-S.; Han, Z.-Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 6641.
[117] Plata, R. E.; Hill, D. E.; Haines, B. E.; Musaev, D. G.; Chu, L.; Hickey, D. P.; Sigman, M. S.; Yu, J.-Q.; Blackmond, D. G. *J. Am. Chem. Soc.* **2017**, *139*, 9238.
[118] Trost, B. M.; Rao, M.; Dieskau, A. P., *J. Am. Chem. Soc.* **2013,** *135*, 18697.
[119] Liu, W.; Ali, S. Z.; Ammann, S. E.; White, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 10658.

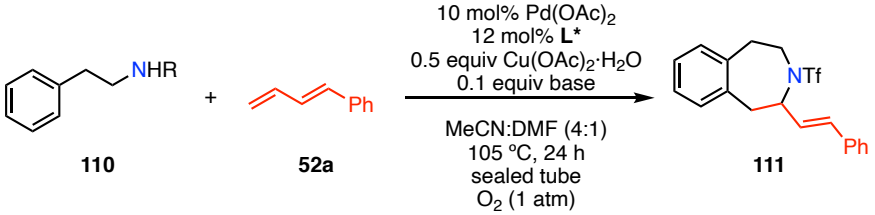



**Scheme 26.** Synthesis of **L1**, **L2** and **L1-SOX**

We started testing all the chiral ligands under the optimized conditions (Table 4). The amino acid type ligands afforded the product in good (Table 4, entries 1-2) to poor yields (Table 4, entry 3), but in all cases in the racemic form. On the other hand, **L7** gave the best result regarding the enantioselectivity (Table 4, entry 5), however only one catalytic cycle turnover was achieved meaning that the oxidant was not able to be reoxidized to the active catalyst. Unfortunately, **L8**-**L11** failed in the Pd-catalyzed enantioselective reaction (Table 4, entries 6-9). Interestingly, in the presence of **L1**-**SOX** the desired 3-benzazepine was obtained in moderate chemical yield with some chiral information transferred (Table 4, entry 10). This ligand family had been already used in other Pd-catalyzed enantioselective heteroannulation processes involving 1,3-dienes and ureas.[116] In these examples, the cationic Pd catalyst was crucial to transfer the chiral information and to develop the reaction. So, new conditions were tried avoiding the use of acetate either in the oxidant as in the palladium source (Table 4, entries 11-13). Unfruitful results were obtained when the reaction was performed in the absence of acetate, which might be explained because the C-H activation follows a CMD mechanism, and therefore, the base (acetate) is crucial to afford the desired product.

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**Table 4**. Enantioselective Pd-catalyzed [5+2] cycloaddition of **110a** with **52a**




**110** **52a** **111**

| Entry[a] | Pd source | L* | oxidant | %yield[b] | %ee[c] |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | **L1** | [Cu] | 70 | - |
| 2 | $Pd(OAc)_2$ | **L2** | [Cu] | 75 | - |
| 3 | $Pd(OAc)_2$ | **L4** | [Cu] | 30 | - |
| 4 | $Pd(OAc)_2$ | **L6** | [Cu] | - | - |
| 5 | $Pd(OAc)_2$ | **L7** | [Cu] | 10 | 20 |
| 6 | $Pd(OAc)_2$ | **L8** | [Cu] | - | - |
| 7[d] | $Pd(OAc)_2$ | **L9** | [Cu] | - | - |
| 8 | $Pd(OAc)_2$ | **L10** | [Cu] | - | - |
| 9 | $Pd(OAc)_2$ | **L11** | [Cu] | - | - |
| 10 | $Pd(OAc)_2$ | **L1-SOX** | [Cu] | 50 | 10 |
| 11 | $Pd(OTs)_2(MeCN)_2$ | **L1-SOX** | BQ | - | - |
| 12 | $Pd(OTs)_2(MeCN)_2$ | **L1-SOX** | 2,5-DtBBQ | - | - |
| 13 | $Pd(OTs)_2(MeCN)_2$ | **L1-SOX** | $Cu(OTf)_2$ | - | - |

Conditions: a) 10 mol% Pd source., 12 mol% **L***, 0.5 equiv oxidant, 0.1 equiv $Et_3N$, 0.5 mL MeCN/DMF, $O_2$ (1 atm) 105 °C, 24 h, sealed tube; b) Isolated yield; c) % ee was determined by chiral SFC; d) 0.12 equiv of KO*t*Bu was used to deprotonate the NHC. [Cu] = $Cu(OAc)_2·H_2O$

After this enantioselective Pd-catalyzed analysis, we can conclude:

- Amino acid chiral ligands are appropriate for the chemical reaction, but they do not transfer chiral information to the formation of 3-benzazepine (Table 4, entries 1-3). It might be explained according to the mechanism (Scheme 25), after the C-H bond activation step the chiral ligand would be released from the coordination sphere of the Pd, and a L-type ligand (MeCN) could enter in the coordination sphere to continue the catalytic cycle.
- The hemilabile N,N-type ligand gave the best enantiomeric excess 20% but in a low 10% yield (Table 4, entry 4). Probably, the $Cu(OAc)_2$ was not able to reoxidize the Pd-catalyst and only one turnover of the catalytic cycle is obtained.
- Other type of chiral ligands P,P- (Table 4, entries 4 and 8), monodentate (Table 4, entries 6-7) or N,N- (Table 4, entry 9) failed in the cyclization.
- Hemilabile N,S(O) type ligand (**L1-SOX**) gave rise to moderate yields and low ee of 3-benzazepine (Table 4, entry 10). Unfortunately, Pd cationic species in combination with **L-SOX** failed to give the [5+2] heteroannulation (Table 4, entries 11-13). A more extensive study of the enantioselective reaction would be needed to improve the results obtained.

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## 9. Pd-Catalyzed Enantioselective C-H Activation via Substrate Desymmetrization

Generation of a new stereogenic center via asymmetric catalysis still remains as a challenge as we have seen in the previous point. A potential strategy to accomplish this goal could be the C-H bond activation of prochiral substrates (Figure 7a). This methodology is

based on the enantioselective C-H bond activation via combination of Pd catalyst and mono-protected amino acids ligands (MPAAs). The resulting catalyst possess a different structure and reactivity, that might lower the activation energy of one elementary step. In addition, it could also improve the site selectivity and stereoselectivity of the catalyst.[120] This catalyst should be able to distinguish among the possible C-H bonds, and only activate selectively one creating in this step the chirality to be transferred to the substrate. Lastly, the final derivatization (e.g., cross-coupling) would afford the enantioenriched desired product.[121] MPAAs are the ligands who enable the enantioselective C-H bond activation and are composed by a carboxylic acid and an amide. The carboxylate binds as a X-type ligand to palladium. Furthermore, the N-H of the amide promotes bidentate coordination to the palladium, and the *N*-acyl group participates in the C-H deprotonation. Besides, MPAAs also possess two R groups, $R_2$ group is the responsible of the chirality information and can affect to the bite angle of the ligand. Additionally, $R_1$ group tunes the electronic properties to the ligand (Figure 7b).

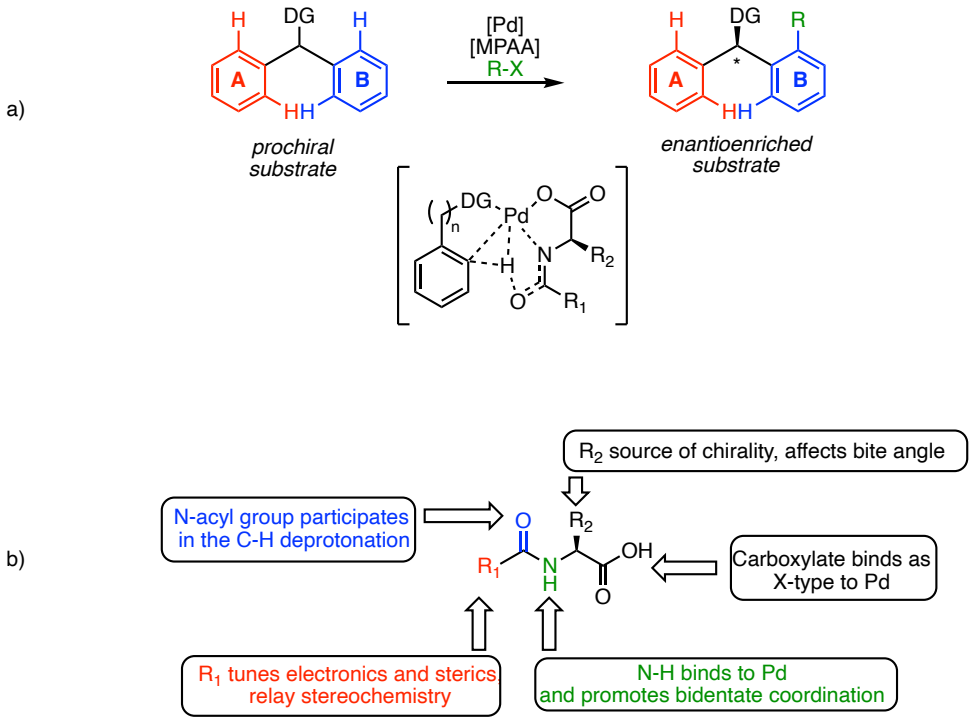



**Figure 7.** MPAAs in Pd-catalyzed enantioselective C-H bond activation

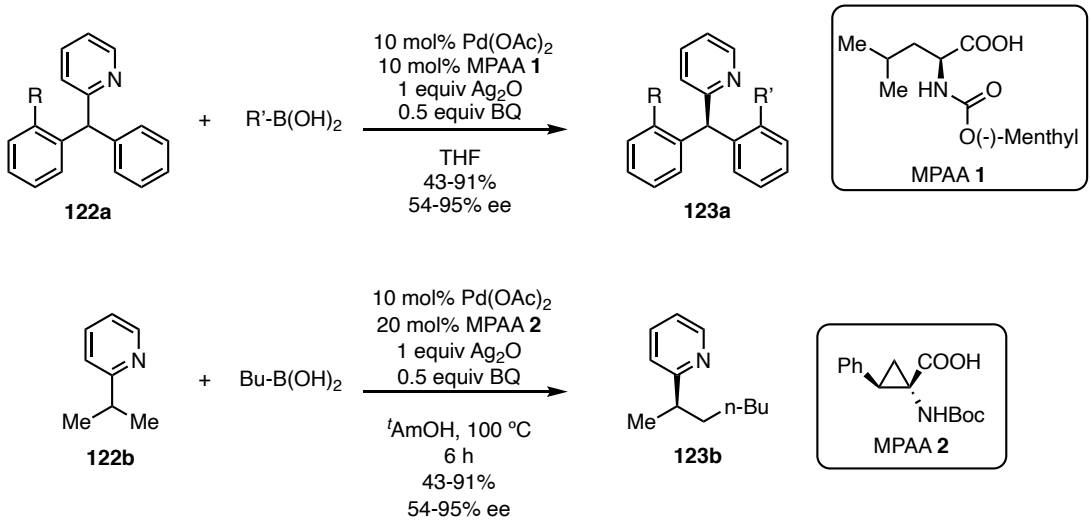
The group of J.-Q. Yu pioneered this methodology in 2008 when a Pd-catalyzed enantioselective activation of $C_{sp^2}$-H and $C_{sp^3}$-H bonds using MPAAs as ligand was described. The DG was a pyridine, and a lastly cross-coupling with boronic acids afforded the enantioenriched products **123** (Scheme 27). Since then, several examples of enantioselective

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[120] a) Cheng, G.-J.; Chen, P.; Sun, T.-Y.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D. *Chem. Eur. J.* **2015**, *21*, 11180. b) Haines, B. E.; Yu, J.-Q.; Musaev, D. G. *ACS Catalysis* **2017**, *7*, 4344.

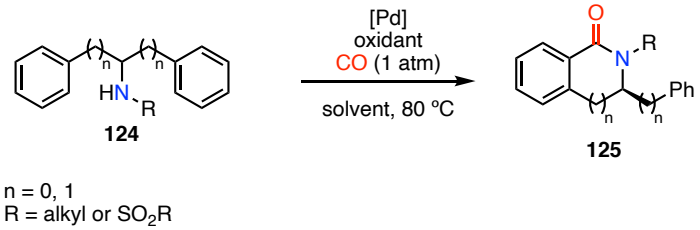
[121] Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. *Acc. Chem. Res.* **2020**, *53*, 833.

C-H bond activation via desymmetrization of prochiral substrates have been described, using as DG carboxylic acids,[122] sulfonamides[123] or amides.[124]




**Scheme 27.** Pd-catalyzed enantioselective C-H bond activation of pyridine derivatives

Based on this methodology, other groups have reported the Pd-catalyzed enantioselective five- and six-membered ring heteroannulation. In 2019, the group of Xia[125] and Xu[105] reported concurrently the Pd-catalyzed C-H amin(d)ocarbonylation (Scheme 28). The group of Xia used amines as DGs, whereas the group of Xu used sulfonamides. Both five- and six- membered lactams **125** were synthesized in high yields and enantioselectivities.




**Scheme 28.** Pd-catalyzed enantioselective C-H amin(d)ocarbonylation

[122] a) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. b) Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 1236. c) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927. d) Xiao, K.-J.; Chu, L.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 2856. e) Hu, L.; Shen, P.-X.; Shao, Q.; Hong, K.; Qiao, J. X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 2134.

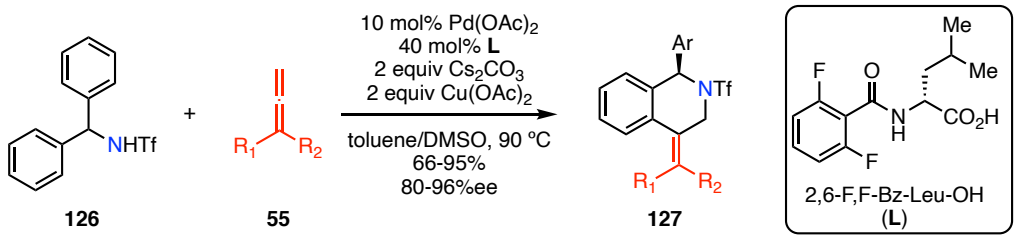
[123] a) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344. b) Chu, L.; Xiao, K.-J.; Yu, J.-Q. *Science* **2014**, *346*, 451. c) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042. d) Laforteza, B. N.; Chan, K. S. L.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 11143. d) Xiao, K.-J.; Chu, L.; Chen, G.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 7796.

[124] a) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. b) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138. c) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. *Science* **2016**, *353*, 1023. d) Wu, Q.-F.; Shen, P.-X.; He, J.; Wang, X.-B.; Zhang, F.; Shao, Q.; Zhu, R.-Y.; Mapelli, C.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *Science* **2017**, *355*, 499. e) Yang, Y.-F.; Chen, G.; Hong, X.; Yu, J.-Q.; Houk, K. N. *J. Am. Chem. Soc.* **2017**, *139*, 8514. f) Wu, Q.-F.; Wang, X.-B.; Shen, P.-X.; Yu, J.-Q. *ACS Catalysis* **2018**, *8*, 2577.

[125] Han, H.; Zhang, T.; Yang, S.-D.; Lan, Y.; Xia, J.-B. *Org. Lett.* **2019**, *21*, 1749.

[105] Bai, X.-F.; Mu, Q.-C.; Xu, Z.; Yang, K.-F.; Li, L.; Zheng, Z.-J.; Xia, C.-G.; Xu, L.-W. *ACS Catal.* **2019**, *9*, 1431.

Interestingly, the group of Mascareñas reported the enantioselective Pd-catalyzed [4+2] cycloaddition of benzyltriflamides **126** and allenes **55** to isoquinolines **127** in fairly good yields and enantioselectivities (Scheme 29).[126] This work was the first Pd-catalyzed enantioselective cycloaddition, involving a C-H bond desymmetrization step to afford heterocycles.

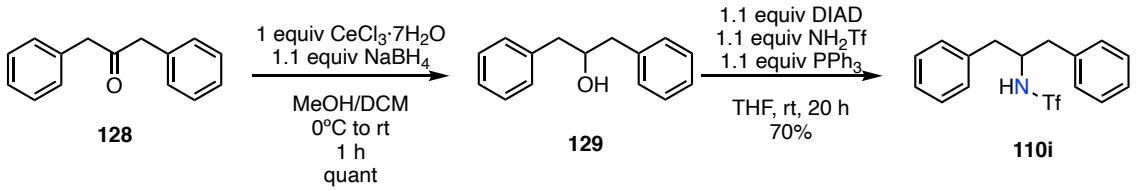



**Scheme 29.** Pd-catalyzed enantioselective synthesis of isoquinolines from benzyltriflamides and allenes by Mascareñas / Gulías

## 9.1. Synthesis of Starting Materials

Inspired by the Pd-catalyzed enantioselective C-H activation via substrate desymmetrization and the diastereoselectivity observed in our Pd-catalyzed [5+2] heteroannulation, we envisioned that substrate **110i** might undergo a Pd-catalyzed enantioselective C-H activation to afford enantioenriched 3-benzazepines.

For this purpose, we synthesized **110i** in two steps, starting with the reduction of commercially available ketone **128** with $NaBH_4$ and $CeCl_3$ to the corresponding alcohol **129** followed by a Mitsunobu reaction with triflamide (Scheme 30).




**Scheme 30.** Synthesis of **110i**

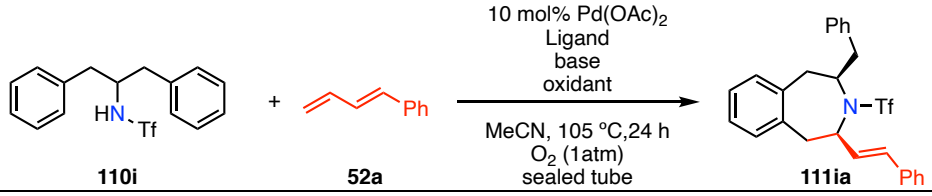
## 9.2. Optimization of the Reaction Conditions

We then explored the Pd-catalyzed [5+2] cycloaddition between **110i** and 1,3-diene **52a** under a variety of conditions (Table 5). Unfortunately, only *rac*-**111ia** could be isolated in a 40% yield under our standard conditions previously established (Table 5, entry 1). Interestingly, under Mascareñas´ conditions for [4+2] cycloadditions, the 3-benzazepine **111ia** was obtained in a low 25% yield with a poor 68:32 er (Table 5, entry 2). The yield could be increased to 40% when the amount of base was reduced to 0.4 equiv (enough amount of base to deprotonate the ligand), however, erosion of enantiomeric ratio to 60:40 was observed (Table 5, entry 3). A series of chiral amino acid ligands (see Figure 6) was then tested (Table 5, entries 4-8). The best reactivity was found for the *p*-Glu-OH (**L3**), with a 40% yield and 25:75 er (Table 5, entry 6,). In an attempt to improve both yield and enantioselectivity, *rac*-BINOL was used as an additive, with a slight increase in the

[126] Vidal, X.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2019**, *141*, 1862.

enantioselectivity (Table 5, entry 9).[125] Unfortunately, other attempts to increase concurrently yield and enantioselectivity failed. Nevertheless, enantioselectivity was increased when lower amounts of $Cu(OAc)_2 \cdot H_2O$ were used (Table 5, entries 10-11), albeit with lower chemical yield. Thus, **111ia** was isolated in an excellent 95:05 er when 0.2 equiv of $Cu(OAc)_2 \cdot H_2O$ was used, however only a 25% yield could be obtained (Table 5, entry 11). The use of base proved to be mandatory, because in its absence, both yield and enantioselectivity dropped (Table 5, entry 12). Other Pd catalysts and copper salts were tested. $Pd(OAc)_2$ showed better yields and enantioselectivities than $Pd_2(dba)_3$ (Table 5, entry 13). Finally, other copper oxidants failed in the oxidation step of the enantioselective Pd-catalyzed [5+2] cycloaddition (Table 5, entries 14-16).

**Table 5**. Optimization of desymmetrization conditions




| Entry[a] | Ligand (equiv) | Base (equiv) | Additive (equiv) | Oxidant (equiv) | % yield | er |
|---|---|---|---|---|---|---|
| 1 | - | 0.1 $Et_3N$ | 10 DMF | 0.5 [Cu] | 40 | - |
| 2 | 0.4 **L1** | 1.5 $Cs_2CO_3$ | 10 DMF | 0.5 [Cu] | 25 | 68:32 |
| 3 | 0.4 **L1** | 0.4 $Cs_2CO_3$ | 10 DMF | 0.5 [Cu] | 40 | 60:40 |
| 4 | 0.4 **L1** | 0.4 $Et_3N$ | 10 DMF | 0.5 [Cu] | 50 | 62.5:37.5 |
| 5 | 0.4 **L2** | 0.4 $Et_3N$ | 10 DMF | 0.5 [Cu] | 45 | 53.5:46.5 |
| 6 | 0.4 **L3** | 0.4 $Et_3N$ | 10 DMF | 0.5 [Cu] | 40 | 25:75 |
| 7 | 0.4 **L4** | 0.4 $Et_3N$ | 10 DMF | 0.5 [Cu] | 37 | 43.5:56.5 |
| 8 | 0.4 **L5** | 0.4 $Et_3N$ | 10 DMF | 0.5 [Cu] | 43 | 57.5:42.5 |
| **9** | **0.4 L3** | **0.4 $Et_3N$** | **0.1 *rac*-BINOL** | **0.5** [Cu] | **45** | **20:80** |
| 10 | 0.4 **L3** | 0.4 $Et_3N$ | 0.1 rac-BINOL | 0.3 [Cu] | 32 | 10:90 |
| **11** | **0.4 L3** | **0.4 $Et_3N$** | **0.1 *rac*-BINOL** | **0.2** [Cu] | **25** | **5:95** |
| 12 | 0.4 **L3** | - | 0.1 *rac-BINOL* | 0.5 [Cu] | 20 | 25:75 |
| 13[b] | 0.4 **L3** | 0.4 $Et_3N$ | 0.1 *rac-BINOL* | 0.5 [Cu] | 22 | 20:80 |
| 14 | 0.4 **L3** | 0.4 $Et_3N$ | 0.1 *rac-BINOL* | 0.5 $CuCl_2$ | - | - |

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| | | | | | | |
|---|---|---|---|---|---|---|
| 15 | 0.4 **L3** | 0.4 $Et_3N$ | 0.1 *rac*-*BINOL* | 0.5 $Cu(OTf)_2$ | <5 | - |
| 16 | 0.4 **L3** | 0.4 $Et_3N$ | 0.1 *rac*-*BINOL* | 0.5 Cu(*p*Glu)$_2$ | - | - |

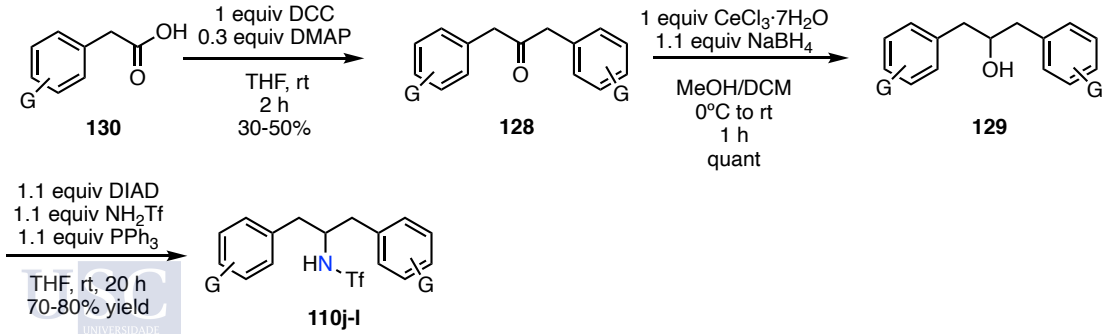
Conditions. a) **110i** (0.2 mmol, 1 equiv), **67a** (0.4 mmol, 2 equiv), 10 mol % $Pd(OAc)_2$, 0.5 mL of MeCN, 105 °C, $O_2$ (1 atm). b) $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$. [Cu] = $Cu(OAc)_2 \cdot H_2O$

After this optimization study of desymmetrization, the main conclusions are:

- The minimal amount of base needed is 0.4 equiv. Organic bases like $Et_3N$ showed better results than inorganic bases like $Cs_2CO_3$.
- The chiral amino acid ligand *L*-*p*Glu-OH (**L3**) gave the best enantiomeric ratio for this transformation.
- For the C-H activation step, the optimization studies would suggest that there is a competition between two bases, the acetate of the copper salt and the chiral ligand used.
- $Cu(OAc)_2$ was the only oxidant able to reoxidize Pd(0) species in this catalytic transformation.
- The best reaction conditions (conditions A) to get the better chemical yield are: 0.4 equiv $Et_3N$, 0.4 **L3**, 0.1 equiv *rac*-BINOL, 0.5 equiv $Cu(OAc)_2 \cdot H_2O$, 0.5 mL MeCN, $O_2$ (1 atm), 105 °C, sealed tube (Table 5, entry 9).
- The best reaction conditions (conditions B) to get the better enantiomeric ratio are: 0.4 equiv $Et_3N$, 0.4 **L3**, 0.1 equiv *rac*-BINOL, 0.2 equiv $Cu(OAc)_2 \cdot H_2O$, 0.5 mL MeCN, $O_2$ (1 atm), 105 °C, sealed tube (Table 5, entry 11).

## 9.3. Scope of Desymmetrization: Synthesis of Starting Materials

A variety of α-substituted phenethyltriflamides (**110j-l**) were synthesized in three steps from the commercially available arylacetic acids (Scheme 31). Firstly, the ketone **128** was obtained from condensation of two units of the corresponding arylacetic acid **130**.[127] Secondly, ketone **128** was reduced with $NaBH_4$ and $CeCl_3$ followed by a last Mitsunobu reaction to give the phenehtyltriflamides **110j-l** in good overall yields.[126]

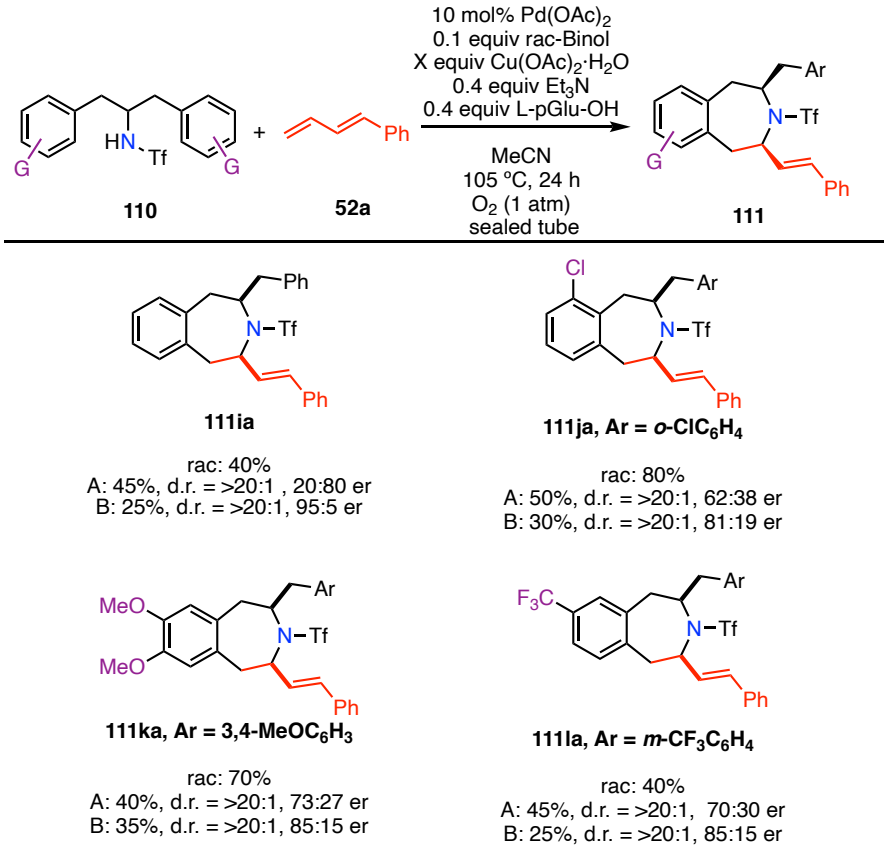



**Scheme 31.** Synthesis of phenethyltriflamides **110j-l**

[127] Vanos, C. M.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 12222.

## 9.4. Scope and Limitations of Desymmetrization Reaction

We next explored the scope and limitations of the desymmetrization. Reactions were performed between phenethyltriflamides **110i-l** and 1,3-diene **52a** under standard conditions for the chemical yield (Conditions A) and for the enantiomeric ratio (Conditions B).




Conditions (racemic): **110** (0.2 mmol, 1 equiv), **52a** (0.4 mmol, 2 equiv), 10 mol % $Pd(OAc)_2$, 0.5 equiv $Cu(OAc)_2{\cdot}H_2O$, 0.1 equiv $Et_3N$, 0.5 mL of MeCN/DMF (4:1), 105 °C, $O_2$ (1 atm), sealed tube
Conditions (chiral): **110** (0.2 mmol), **52a** (0.4 mmol), 10 mol% $Pd(OAc)_2$,, 0.4 **L3**, 0.1 equiv *rac*-BINOL, $Cu(OAc)_2{\cdot}H_2O$: 0.5 equiv (Conditions A) or 0.2 equiv (Conditions B), 0.4 equiv $Et_3N$, 0.5 mL MeCN, 105 °C, $O_2$ (1 atm), sealed tube.

**Scheme 32.** Scope of desymmetrization reaction

The reaction tolerated EDG and EWG substituents in the aryl ring. The amounts of $Et_3N$ and $Cu(OAc)_2$ used affected dramatically to the course of the reaction. While *ortho*-Cl phenethyltriflamide **111ja** was obtained as racemic in a very good 80% yield (0.1 equiv $Et_3N$ and 0.5 equiv $Cu(OAc)_2$), on using chiral conditions the yield decreased to 50% yield, 62:38 er (0,4 equiv $Et_3N$, 0.5 equiv $Cu(OAc)_2$, conditions A) or to 30% yield, 81:19 er (0.4 equiv $Et_3N$ and 0.2 equiv $Cu(OAc)_2$, conditions B). The 3,4-dimethoxyphenethyltriflamide **111ka** was obtained as racemic in a good 70% yield (0.1 equiv $Et_3N$ and 0.5 equiv $Cu(OAc)_2$), on using chiral conditions the yield decreased to 40% yield, 73:27 er (0,4 equiv $Et_3N$, 0.5 equiv $Cu(OAc)_2$, conditions A) or to 35% yield, 85:15 er (0.4 equiv $Et_3N$ and 0.2 equiv $Cu(OAc)_2$, conditions B). Finally, *meta*-$CF_3$ substituted phenethyltriflamide **111la** was obtained as racemic in a moderate 40% yield (0.1 equiv $Et_3N$ and 0.5 equiv $Cu(OAc)_2$) but, to our surprise, on using chiral conditions the yield increased to 45% yield, 70:30 er (0,4 equiv $Et_3N$,

0.5 equiv $Cu(OAc)_2$, conditions A) or decreased to a low 25% yield, 85:15 er (0.4 equiv $Et_3N$ and 0.2 equiv $Cu(OAc)_2$, conditions B).

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# 10. Conclusions[128]

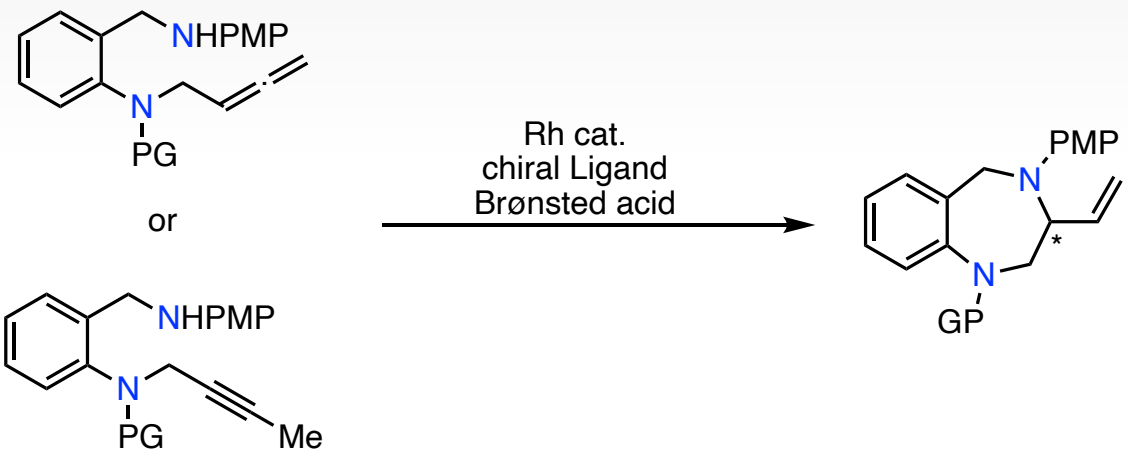
- A sustainable, ecofriendly, atom- and step-economy methodology has been described to afford 3-benzazepines. The Pd-catalyzed [5+2] heteroannulation that requires a C-H activation step allowed the obtention of 2-substituted 3-benzazepines in moderate to good yields from commercially available starting materials.
- The use of $O_2$ allowed a reduction of the amount of metal oxidant needed and, therefore, the generation of waste amount.
- The diastereoselectivity of the reaction showed a high ratio when a substituent is located in the α-position (>20:1), whereas only gave a mixture 3:1 of diastereoisomers in β-position.
- Mechanistic studies suggested the key *cis*-$PdL_2X_2$ intermediates that were corroborated by the isolation and X-ray structural determination of **112a'** and **112h'**.
- DFT calculations shed light on the mechanism and the diastereoselectivity of the reaction. The 1,2-migratory insertion starts with a coordination of the less substituted olefin of the 1,3-diene. The key C-N bond formation occurs by an intramolecular $S_N2$-type reaction of the zwitterionic Pd-π-allyl intermediate **IV**.
- Unfortunately, despite the fact that a variety of chiral ligands were tested for the enantioselective Pd-catalyzed reaction, all of them failed either in the chemical yield or in the enantiomeric excess.
- An enantioselective Pd-catalyzed reaction of prochiral α-substituted phenethyltriflamides (desymmetrization reaction) using *L-p*Glu-OH (**L3**) was successfully developed. However, only moderate enantioselectivities were observed.
- In the enantioselective reaction, for the C-H activation step, a competition between two bases, the chiral ligand *L-p*Glu-OH (**L3**) and the acetate of the copper salt, was observed. As a rule of thumb, the higher enantioselectivities the lower yields were obtained.

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[128] a) Velasco-Rubio, Á.; Varela, J. A.; Saá, C. *Org. Lett.* **2020**, *22*, 3591. b) Velasco-Rubio, Á.; Varela, J. A.; Saá, C. *Adv. Synth. Catal.* **2020**, *362*, 4861.

# Chapter 3

## 1,4-Benzodiazepines *via* Rh-Catalyzed Intramolecular Hydroamination




Velasco-Rubio, Á.; Bernárdez, R.; Varela, J.A.; Saá, C. *J. Org. Chem.* **2021**, *86*, 10889

Benzofused seven-membered heterocycles such as 1,4-benzo[*e*]diazepines (1,4-BZDs) and 1,4-Benzo[*e*]oxazepines (1,4-BZOs) were efficiently synthesized by Rh-catalyzed hydrofunctionalization of internal alkynes and allenes in good to excellent yields. The asymmetric hydroamination of (aminomethyl)anilines gave rise to 3-vinyl-1,4-BZDs with excellent enantioselectivities. Orthogonal *N*-deprotection of 1,4-BZDs allowed an easy entry to an advanced pyrrolobenzodiazepine metabolite of the $V_2$-repecptor antagonist Lixivaptan.

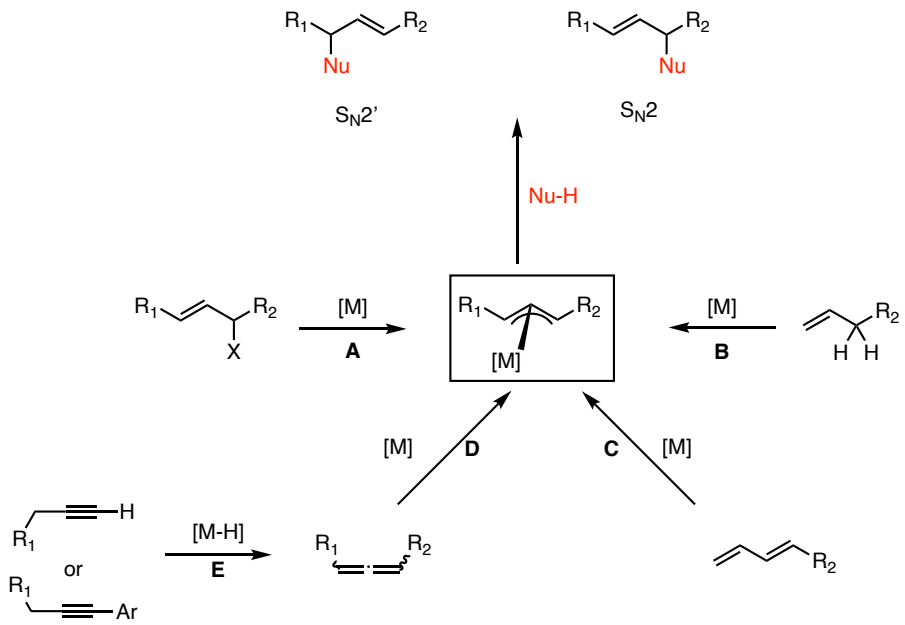
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# Chapter 3

## 1,4-Benzodiazepines *via* Rh-Catalyzed Intramolecular Hydroamination

### 1. TM-Catalyzed Allylic Alkylation

Allylic alkylation reaction occurs when a nucleophile attacks over a π-allylic electrophile. Despite this reaction occurs in absence of catalyst, the use of catalytic amounts of TM accelerates the reaction allowing the use of milder conditions. The reaction can follow $S_N2$ selectivity, the nucleophilic attack is over the carbon where the leaving group is, or $S_N2'$ selectivity, the nucleophilic attack is over the carbon where the leaving group is not. The key π-metal-allylic intermediate can be generated by a variety of methods (Scheme 33), such as, the classic allylic alkylation of allylic halides or allylic alcohol derivatives (more accessible than halides) (method **A**),[129] C-H bond allylic activation (method **B**) (Chapter 4), allylic functionalization of 1,3-diene (method **C**) (Chapter 2) or functionalization of 1,2-dienes (allenes) (method **D**) (Chapter 3). Alternatively, allene can be generated from an isomerization of alkynes (method **E**) (Chapter 3).




**Scheme 33.** Generation of M-π-allylic intermediate

### 1.1. Trapping of the π-Allyl Complex

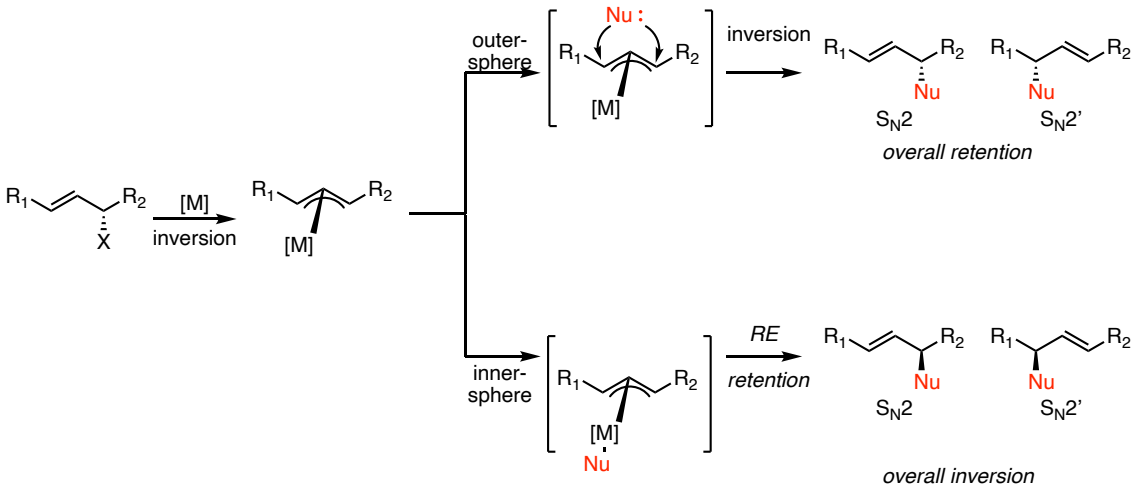
The π-allyl intermediates can be trapped by a carbo- or heteronucleophiles that would form a new C-C or C-heteroatom bond at one allylic terminus. The mechanism of the

[129] Hartwig, J. F. Allylic Substitution. In *Organotransition Metal Chemistry from Bonding to Catalysis*, University Science Books, **2010**, 967.

nucleophilic substitution mainly depends on the nature of the incoming nucleophile, "soft" nucleophiles, and "hard" nucleophiles (Scheme 34).[130]

On the one hand, "soft" nucleophiles are characterized by a pKa <25 of the conjugate acid. The nucleophilic attack occurs outside the coordination sphere of the metal with inversion of configuration of the π-allyl intermediate (outer-sphere mechanism). Indeed, the nucleophile approaches the electrophilic π-allyl ligand on the face opposite to metal center and directly attacks the allylic carbon. Hence, most nucleophiles are "soft" nucleophiles like e.g., carbanions, amines, amides, sulfonamides, phenols, alcohols, thiols or even phosphines.[130]

On the other hand, "hard" nucleophiles are characterized by a pKa > 25 of the conjugate acids. The nucleophilic attack occurs inside the coordination sphere of the metal (inner-sphere mechanism), reductive elimination, with retention in the configuration of the π-allyl intermediate. Thus, the typical nucleophiles are aryl- and alkenylmetals involving Al, B, Mg, Si, Sn, Zn and Zr.[130]

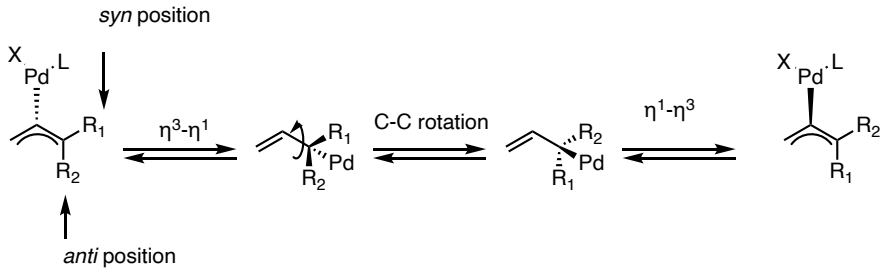



**Scheme 34.** Outer-/inner-sphere mechanism

Regarding the general mechanism described in the Scheme 34, the enantioselectivity of the reaction would have to be determined by the face of the olefin where the metal binds and the sort of nucleophile. However, the η³-allyl intermediate is in dynamic equilibrium that undergo its isomerization. This step is a process where the coordination mode changes from $\eta^3 \rightarrow \eta^1 \rightarrow \eta^3$. This process leads to a global *syn-anti* exchange of the substituent pair concerned in the rotation, with concomitant exchange of the complexed allyl face (Scheme 35). The barrier to C-C bond rotation within the resulting η¹ intermediate was found to be 7.3 kcal·mol$^{-1}$, whereas restoration of the η³ coordination is almost barrierless.[131] However, there are present more processes that can trigger exchange of the allyl face complex by the metal or the formal rotation of the allyl moiety with respect to the ligand, e.g., ligand association, ligand dissociation or allyl transfer to another metal center. As conclusion, the selectivity of the reaction is only determined by the coordinated ligands that enable to distinguish both possible η³-allyl intermediates.[132]

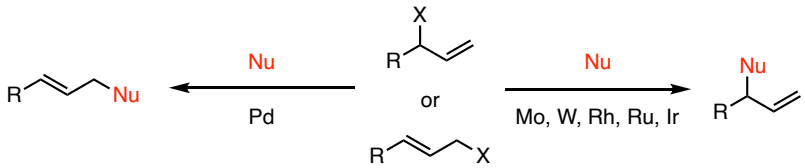
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[130] Bruneau, C.; Dixneuf, P. H. *Top. Organomet. Chem.* **2016**, *55*, 260.
[131] Solin, N.; Szabó, K. J. *Organometallics* **2001**, *20*, 5464.
[132] Poli, G.; Prestat, G.; Liron, F.; Kammerer-Pentier, C. Selectivity in Palladium-Catalyzed Allylic Substitution. In *Top. Organomet. Chem.* **2012**, *34*, 1.




**Scheme 35.** *Syn-anti* isomerization of a generic π-allylpalladium complex

The functionalization of monosubstituted allylic compounds give rise to a mixture of products (branched/linear). The regioselectivity is determined by the nucleophilic attack over η³-allyl complex. Curiously, TM-complex of Molybdenum,[133] Tungsten,[133b] Rhodium,[134] Ruthenium[135] or Iridium[136] favor the nucleophilic attack over the more substituted C to yield branched product, whereas Palladium complex usually favors the nucleophilic attack over the less hindered carbon to yield the linear product (Scheme 36).[132] However, in this last example, the regioselectivity of the reaction will also depend on the structure of the η³-allyl intermediate, nucleophile and also the bite angle and electronics effects of the ligand, such as, *trans*-effect induced by P-N ligands owing to the square-planar geometry of the Pd(II) complexes.[132,137]




**Scheme 36.** Regioselectivity of allylic alkylation with different metals

## 2. TM-Catalyzed Hydrometallation of Allenes and Alkynes

One of the most ecofriendly allylic formation is the hydrometallation of dienes. 1,3-Dienes[138] and allenes (1,2-dienes)[139] provide completely atom-efficient access to π-allyl-metal intermediates.[140] In addition, it has been documented the stoichiometric transformation of

[133] a) Moberg, C. *Org. React.* **2014**, *84*, 1. b) Moberg, C. Molybdenum-Catalyzed and Tungsten-Catalyzed Enantioselective Allylic Substitutions. In *Top. Organomet. Chem.* **2012**, *34*, 209.

[134] Leahy, D. K.; Evans, P. A. Rhodium(I)-Catalyzed Allylic Substitution Reactions and Their Applications to Target Directed Synthesis. In Modern *Rhodium-Catalyzed Organic Reactions*, Wiley-VCH, **2005**, 191.

[135] Bruneau, C.; Achard, M. *Coord. Chem. Rev.* **2012**, *256*, 525.

[136] a) Hartwig, J. F.; Pouy, M. J. Iridium Catalyzed Allylic Substitution. In *Top. Organomet. Chem.* **2011**, *34*, 169. b) Qu, J.; Helmchen, G. *Acc. Chem. Res.* **2017**, *50*, 2539.

[137] a) van Haaren, R. J.; Goubitz, K.; Fraanje, J.; van Strijdonck, G. P. F.; Oevering, H.; Coussens, B.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Inorg. Chem.* **2001**, *40*, 3363. b) van Haaren, R. J.; Keeven, P. H.; van der Veen, L. A.; Goubitz, K.; van Strijdonck, G. P. F.; Oevering, H.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Inorg. Chim. Acta.* **2002**, *327*, 108.

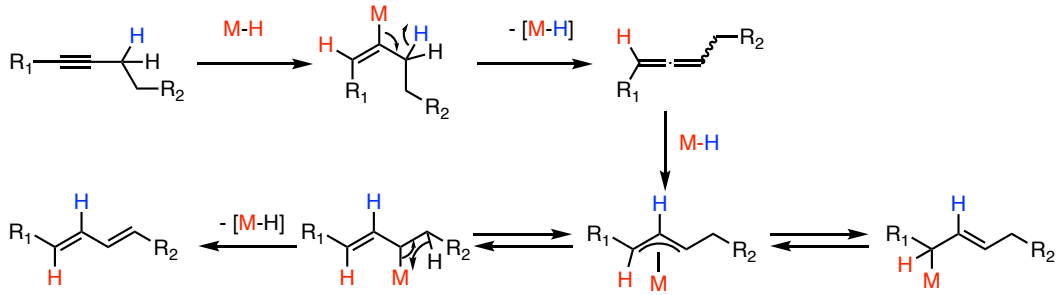
[138] a) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324. b) Chen, Q.-A.; Chen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 8392. c) McNeill, E.; Ritter, T. *Acc. Chem. Res.* **2015**, *48*, 2330. d) Yang, X.-H.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1774.

[139] a) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916. b) Thieme, N.; Breit, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 1520.

[140] Haydl, A.; Breit, B.; Liang, T.; Krische, M. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 11312.

alkynes into allenes[141] to generate π-allyl species.[142] This process is in accordance with the "*Principles of Green Chemistry*",[75] neither stoichiometric amounts of waste are generated, e.g., inorganic salts, nor oxidants are needed.

As mentioned above, alkynes are precursors of allenes.[140] Metal-hydride catalyzed isomerization of alkynes, with protons in the α position, into the corresponding allenes.[142a] In turn, allenes can isomerize into the corresponding 1,3-dienes by metal-hydride insertion.[143] In sum, 1,3-dienes, allenes and alkynes are readily available starting materials for the allylic alkylation via hydrometallation (Scheme 37).




**Scheme 37.** M-H catalyzed alkyne isomerization

The allylic functionalization via hydrometallation has been well studied for a variety of transition metals. In this work, we are going to focus on new applications of Rh- and Pd-catalyzed hydrometallation.

## 2.1. Hydropalladation of Allenes and Alkynes

Hydropalladation of 1,3-dienes has scarcely been explored due to the ability to undergo Pd-catalyzed telomerization. In fact, allylic functionalized products are obtained in relative low yields.[144] Despite the fact that side-products are favored *vs* allylic functionalization, attempts to synthesize allylic amines in acid conditions,[145] and using bidentate phosphorous ligands have been developed.[146]

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[141] a) Franck-Neumann, M.; Brion, F. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 688. b) Casey, C. P.; Brady, J. T. *Organometallics* **1998**, *17*, 4620. c) Phadke, N.; Findlater, M. *Organometallics* **2014**, *33*, 16.

[142] a) Wolf, J.; Werner, H. *Organometallics* **1987**, *6*, 1164. b) Casey, C. P.; Brady, J. T.; Boller, T. M.; Weinhold, F.; Hayashi, R. K. *J. Am. Chem. Soc.* **1998**, *120*, 12500.

[143] a) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301. b) Guo, C.; Lu, X. *Tetrahedron Lett.* **1991**, *32*, 7549.

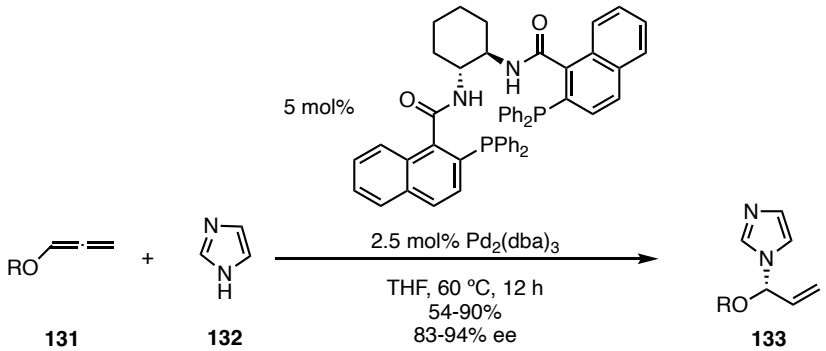
[144] a) Tsuji, J. *Acc. Chem. Res.* **1973**, *6*, 8. b) Dzhemilev, U. M.; Tolstikov, G. A.; Khusnutdinov, R. I. Russ. *J. Org. Chem.* **2009**, *45*, 957.

[145] a) Keim, W.; Röper, M.; Schieren, M. *J. Mol. Catal.* **1983**, *20*, 139. b) Armbruster, R. W.; Morgan, M. M.; Schmidt, J. L.; Lau, C. M.; Riley, R. M.; Zabrowski, D. L.; Dieck, H. A. *Organometallics* **1986**, *5*, 234. c) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.

[146] a) Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4501. b) Johns, A. M.; Liu, Z.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7259. c) Jahromi, B. T.; Kharat, A. N.; Zamanian, S.; Bakhoda, A.; Mashhayekh, K.; Khazaeli, S. *Appl. Catal. A.* **2012**, *433- 434*, 188. d) Banerjee, D.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 1630. e) Banerjee, D.; Junge, K.; Beller, M. *Org. Chem. Front.* **2014**, *1*, 368.

[75] Anastas, P.; Warner J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, 1998.

Yamamoto pioneered the study of nucleophilic attack to a Pd-π-allyl intermediate generated upon hydropalladation of allenes and alkynes.[147] A variety of nucleophiles have been employed, e.g., malonate derivatives,[148] oxygenated nucleophiles[149] and nitrogenated nucleophiles.[150] The best results were achieved by combination of a catalytic amount of Pd(0) and carboxylic acids. Despite the fact that Brønsted acid was not necessary, its presence facilitates the Pd-H formation. In addition, hydropalladation of alkynes or allenes usually affords linear products due to steric restrictions, however, this rule can be switched based on the electronics of the substituents. This is the case of the allylation of imidazole **132** with alkoxyallenes **131**, the *O* atom stabilized the positive charge in α-position, therefore, the nucleophilic attack over this carbon was favored. Enantioselective variants that use Trost-family ligands have been described to create a new stereogenic center of enantioenriched products **133** (Scheme 38).[151]




**Scheme 38.** Pd-catalyzed asymmetric allylic alkylation of imidazole with alkoxy allenes reported by Rutjes

[147] Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199.

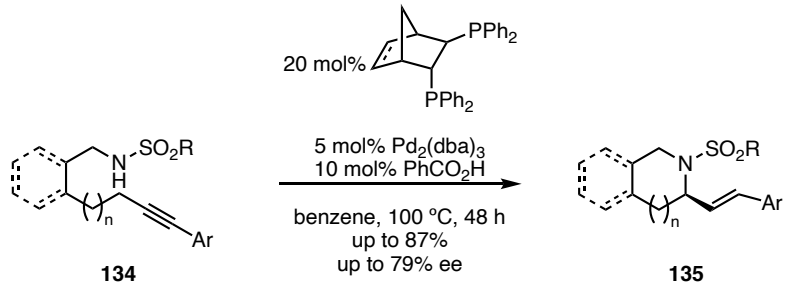
[148] Allylation of allenes: a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. b) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N.; Asao, N. *Tetrahedron Lett.* **1995**, *36*, 2811. c) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. d) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853. e) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. S*ynthesis* **2004**, 2186. Allylation of alkynes: f) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262. g) Patil, N. T.; Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *Adv. Synth. Catal.* **2004**, *346*, 800. h) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 6478. i) Ni, C.; Hu, J. *Tetrahedron Lett.* **2009**, *50*, 7252. j) Yao, S.; Liu, J.; Yang, Z.; Gui, Q.; Chen, X.; Tan, Z.; Li, P. *Synth. Commun.* **2014**, *44*, 3165. k) Gao, S.; Liu, H.; Wu, Z.; Yao, H.; Lin, A. *Green Chem.* **2017**, *19*, 1861.

[149] Allylation of allenes: a) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809. b) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Can. J. Chem.* **2005**, *83*, 569. Allylation of alkynes: c) Trost, B. M.; Brieden, W.; Baringhaus, K. H. *Angew. Chem. Int. Ed.* **1992**, *31*, 1335. d) Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207. e) Zhang, W.; Haight, A. R.; Hsu, M. C. *Tetrahedron Lett.* **2002**, *43*, 6575.

[150] Allylation of allenes: a) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett. 1995*, *36*, 3857. b) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071. c) Tafazolian, H.; Samblanet, D. C.; Schmidt, J. A. R. *Organometallics* **2015**, *34*, 1809. Allylation of alkynes: d) Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570. e) Lutete, L. M.; Kadota, I.; Shibuya, A.; Yamamoto, Y. *Heterocycles* **2002**, *58*, 347. f) Patil, N. T.; Wu, H.; Kadota, I.; Yamamoto, Y. *J. Org. Chem. 2004*, *69*, 8745. g) Lu, C.-J.; Chen, D.-K.; Chen, H.; Wang, H.; Jin, H.; Huang, X.; Gao, J. *Org. Biomol. Chem.* **2017**, *15*, 5756.

[151] a) Trost, B. M.; Jäkel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438. b) Trost, B. M.; Simas, A. B. C.; Plietker, B.; Jäkel, C.; Xie, J. *Chem. Eur. J.* **2005**, *11*, 7075. c) Trost, B. M.; Xie, J.; Sieber, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 20611. d) Bernar, I.; Fiser, B.; Blanco-Ania, D.; Gómez-Bengoa, E.; Rutjes, F. P. J. T. *Org. Lett.* **2017**, *19*, 42.

Branched products are typically obtained in intramolecular allylic functionalization.[152] Yamamoto firstly described the five-membered ring formation in a Pd-catalyzed hydroamidation of allenes with sulfonamides.[150b] Later he reported the successful asymmetric formation of five- and six-membered rings **135** in a Pd-catalyzed hydroamidation of internal alkynes **134**. Chiral NORPHOS-type ligand was used to obtain the heterocycles in moderate to good enantioselectivities (Scheme 39).[153]




**Scheme 39.** Pd-catalyzed asymmetric heterocycles formation via hydroamidation of alkynes by Yamamoto

## 2.2. Hydrorhodation of Allenes and Alkynes

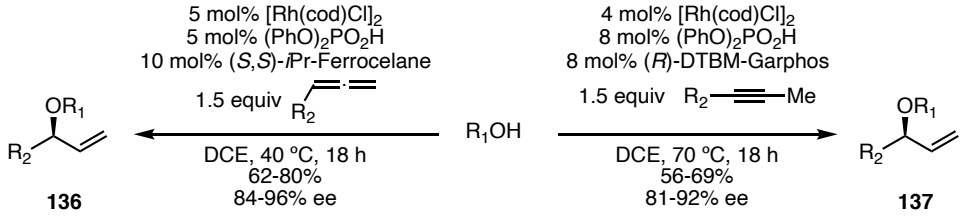
Hydrorhodation of dienes and alkynes has been more explored than the hydropalladation due to the typical branched selectivity obtained. Breit has profoundly studied the hydrofunctionalization of alkynes and allenes to get enantioenriched branched allyl -esters, -ethers, -amines, -thioethers or -diketones.[154] In situ generation of a chiral Rh(III) species is key for this successful methodology. The Rh(III) catalytic species is achieved after Rh(I) oxidative addition into the Brønsted acid or Nu-H employhed. In addition, the in situ Rh-H complex formed enables isomerization of alkynes into allenes that finally affords the Rh-π-allyl complex. Thus, Breit reported the Rh-catalyzed allylic alkylation of alcohols with allenes or alkynes to allylic ethers **136** and **137**. High enantioselectivities using Ferrocelane type ligand were obtained for the allylic alkylation with allenes, whereas (*R*)-DTBM-Garphos was the most effective ligand to develop the allylic alkylation with alkynes (Scheme 40).[155]

[152] a) Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453. b) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421. c) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 2101. d) Patil, N. T.; Huo, Z.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 3612. e) Huo, Z.; Patil, N. T.; Jin, T.; Pahadi, N. K.; Yamamoto, Y. *Adv. Synth. Catal.* **2007**, *349*, 680. f) Ogiwara, Y.; Sato, K.; Sakai, N. *Org. Lett.* **2017**, *19*, 5296.

[153] a) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622. b) Bajracharya, G. B.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4883. c) Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270. d) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 6577. e) Narsireddy, M.; Yamamoto, Y. *J. Org. Chem.* **2008**, *73*, 9698.

[154] Koschker, P.; Breit, B. *Acc. Chem. Res.* **2016**, *49*, 1524.

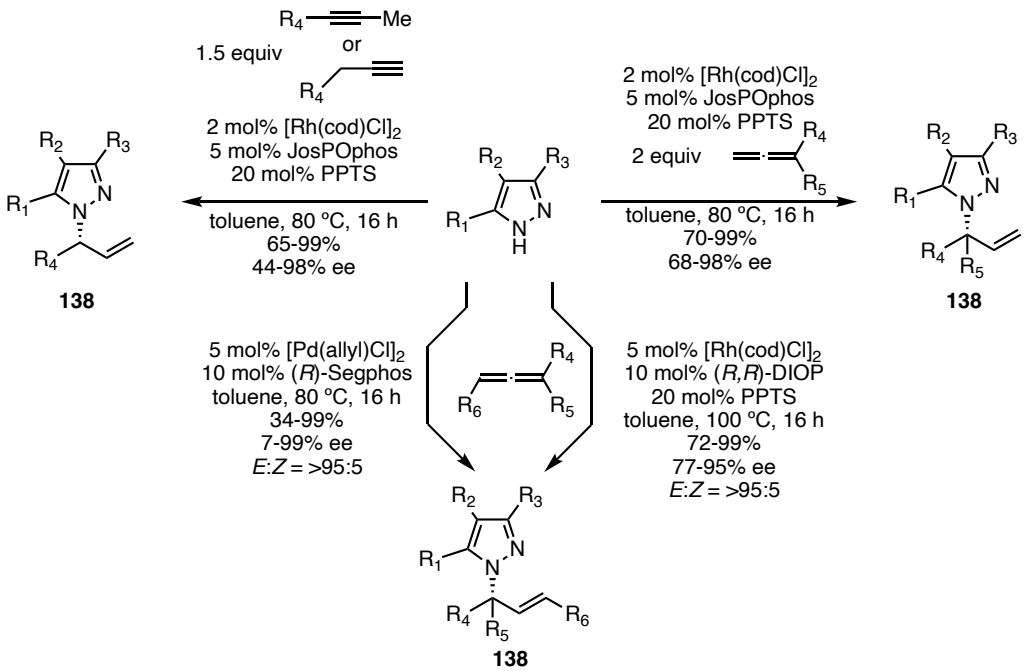
[155] Liu, Z.; Breit, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 8440.




**Scheme 40.** Rh-catalyzed synthesis of allylic ethers reported by Breit

Allenes usually give rise to better enantioselectivities and yields than alkynes. Furthermore, the employment of allenes typically needs milder conditions than alkynes. It is explained because allenes afford directly the Rh-π-allyl complex upon Rh-H migratory insertion, whereas alkynes require an extra-step to isomerize them. These advantages allowed the use of a greater variety of nucleophiles with allenes as substrates. Breit has reported an extensive study of the synthesis of allylamines using as nucleophiles anilines,[156] imidazoles,[157] 2-[158] and 4-pyridones,[159] benzotriazoles,[160] pyrazoles,[161] tetrazoles,[162] arylhydrazines,[163] imines,[164] pyridazinones,[165] purines,[166] quinazolines,[167] triazoles,[168] 2-aminothiazoles,[169] and oximes.[170] Pyrazoles as nucleophiles are the most studied examples. In 2015, Breit reported the *N*-selective coupling of pyrazole derivatives with terminal allenes.[161a] One year later, Breit described the *N*-selective coupling of pyrazoles with terminal-alkynes and methyl-alkynes,[161c] and finally in 2019, Breit reported a Pd- and Rh-catalyzed dynamic kinetic resolution (DKR) of racemic allenes (Scheme 41).[161b] In this case, a complementary methodology with both metals allowed to obtain a great variety of allylated products.

[156] a) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 10876. b) Berthold, D.; Breit, B. *Org. Lett.* **2020**, *22*, 565.
[157] Xu, K.; Thieme, N.; Breit, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 2162.
[158] Li, C.; Kähny, M.; Breit, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 13780.
[159] Schmidt, J. P.; Li, C.; Breit, B. *Chem. Eur. J.* **2017**, *23*, 6531.
[160] Xu, K.; Thieme, N.; Breit, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 7268.
[161] Allylation of allenes: a) Haydl, A. M.; Xu, K.; Breit, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 7149. b) Zheng, J.; Wörl, B.; Breit, B. *Eur. J. Org. Chem.* **2019**, *2019*, 5180. Allylation of alkynes: c) Haydl, A. M.; Hilpert, L. J.; Breit, B. *Chem. Eur. J.* **2016**, *22*, 6547.
[162] Xu, K.; Raimondi, W.; Bury, T.; Breit, B. *Chem. Commun.* **2015**, *51*, 10861.
[163] Xu, K.; Gilles, T.; Breit, B. *Nat. Commun.* **2015**, *6*, 7616.
[164] Xu, K.; Wang, Y.-H.; Khakyzadeh, V.; Breit, B. *Chem. Sci.* **2016**, *7*, 3313.
[165] Parveen, S.; Li, C.; Hassan, A.; Breit, B. *Org. Lett.* **2017**, *19*, 2326.
[166] Thieme, N.; Breit. B.; *Angew. Chem. Int. Ed.* **2017**, *56*, 1520.
[167] Zhou, Y.; Breit, B. *Chem. Eur. J.* **2017**, *23*, 18156.
[168] Berthold, D.; Breit, B. *Org. Lett.* **2018**, *20*, 598.
[169] Zheng, J.; Wörl, B.; Breit, B. *Eur. J. Org. Chem.* **2019**, *2019*, 5180.
[170] Wang, Y.-H.; Breit, B. *Chem. Commun.* **2019**, *55*, 7619.




**Scheme 41.** Rh- and Pd-catalyzed hydroamination of allenes and alkynes with pyrazoles reported by Breit

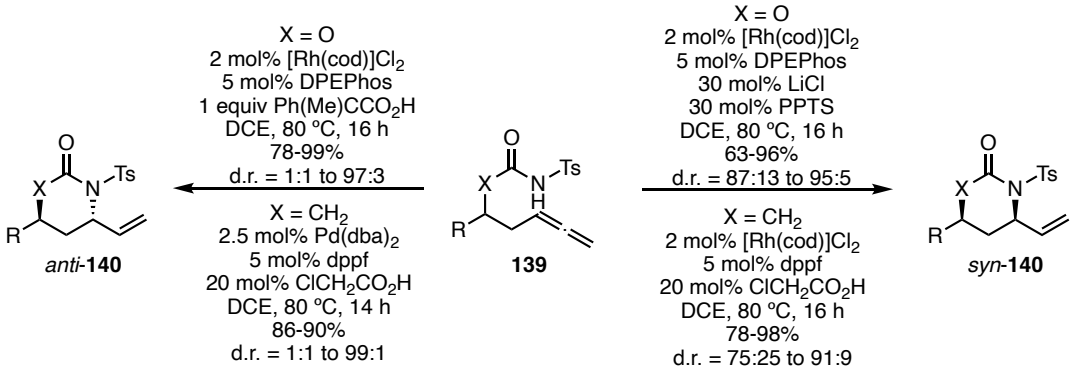
Other goals of Breit's research were the synthesis of heterocycles. Despite macrocycles were obtained under Rh(III) catalysis, using carboxylic acids as nucleophiles in a intramolecular macrolactonization[171] or by dimerization of ω-allenyl carboxylic acids,[172] medium-sized azaheterocycles have been the main goal.[173] Firstly, Breit described the six-membered ring formation in an Rh-catalyzed a diastereoselective intramolecular cyclization of tosylcarbamates **139**.[173a] Depending on the additives added to the reaction, the *syn*- or *anti*- diastereoisomer could be obtained. The employment of LiCl yield the *syn*-**140** due to an increase of acidity of tosylamide by lithium coordination to the carbonyl group and, therefore the Rh(I) insertion into the N-H bond was more facile followed by the C-N bond formation by a reductive elimination pathway. By contrast, the use of a carboxylic acid facilitated the oxidative addition into the carboxylic acid to form the Rh-H species and, therefore the C-N bond formation occurred via an outer-sphere mechanism. In 2019, Breit reported a similar cyclization with tosylamides. The diastereoselectivity was achieved by the employment of different metals. Hence, Pd-catalyzed cyclization afforded *anti*-**140**, meanwhile Rh-catalyzed cyclization provided *syn*-**140** (Scheme 42).[173b] DFT calculations and mechanistic experiments showed that *anti*-**140** was 1.4 kcal·mol$^{-1}$ more stable than *syn*-**140**. Therefore, the selectivity was achieved in the presence of rhodium by kinetic control, whereas in presence of palladium the reaction towards *syn*-**140** was reversible and the formation of the more stable *anti*-**140** occurred under thermodynamic control.

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[171] Ganss, S.; Breit, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 9738.

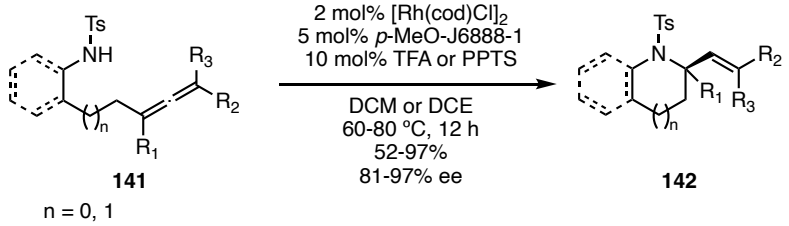
[172] Steib, P.; Breit, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 6572.

[173] a) Spreider, P. A.; Haydl, A. M.; Heinrich, M.; Breit, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 15569. b) Schmidt, J. P.; Breit, B. *Chem. Sci.* **2019**, *10*, 3074. c) Berthold, D.; Geissler, A. G. A.; Giofre, S.; Breit, B. *Angew. Chem. Int. Ed.* **2019**, *58*, 9994.



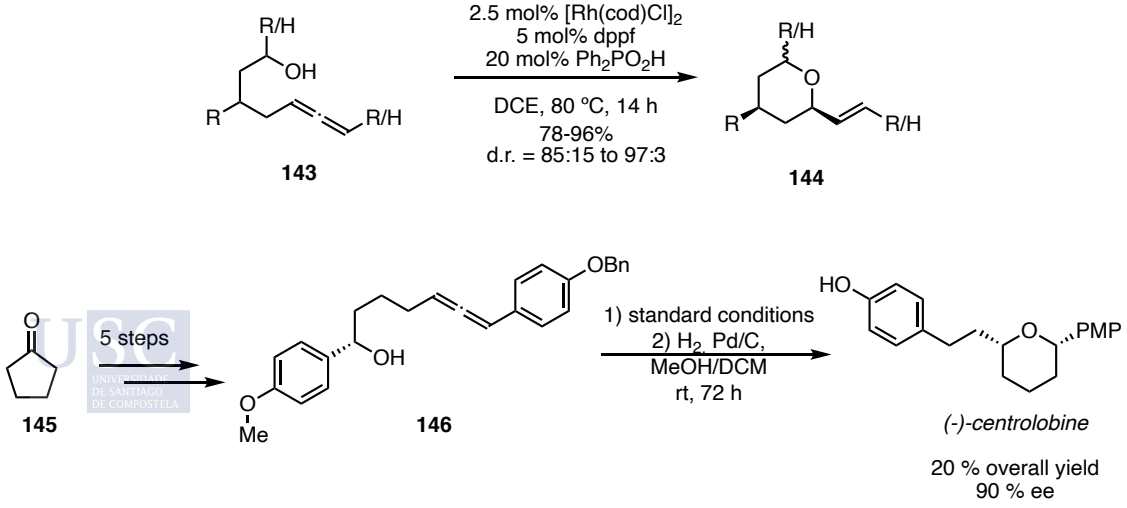

**Scheme 42.** Diastereoselective synthesis of six-membered azaheterocycles reported by Breit

Interestingly, in 2019 Breit described the enantioselective Rh-catalyzed hydroamidation of internal allenes to five- and six-membered azaheterocycles (Scheme 43).[173c] Under typical conditions, Rh(I) catalyst, Brønsted acid (TFA or PPTS), chiral ligand (*p*-MeO-J688-1) and tosylamides **141**, a variety of five- and six-membered azaheterocycles **142** were successfully obtained.




**Scheme 43.** Rh-catalyzed synthesis of five- and six-membered azaheterocycles reported by Breit

Very recently, Breit reported the synthesis of tetrahydropyrans **144** in an Rh-catalyzed cyclization of terminal and internal allenols **143** (Scheme 44).[174] The diastereoselective reaction worked in the presence of dppf as ligand and PPTS as Brønsted acid. A variety of *syn*-1,3-disubstituted tetrahydropyrans are obtained in good to excellent yields and in good diastereoselectivities. In order to highlight the synthetic utility of the method, the enantioselective synthesis of the (-)-centrolobine was accomplished in 6 steps with an overall yield of 20% from the commercially available cyclopentanone **145**.

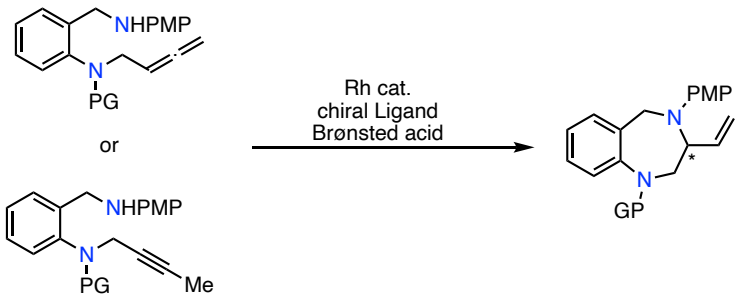



**Scheme 44.** Rh-catalyzed diastereoselective synthesis of tetrahydropyrans by Breit

[174] Schmidt, J. P.; Breit, B. *Angew. Chem. Int. Ed.* **2020**; *59*, 23485.

## 3. Objective

1,4-Benzodiazepines are of capital importance in the pharmaceutical industry since are drugs that interact with a great variety of human receptors key for the treatment of HIV, cancer, or CNS illnesses (See Chapter 1). Furthermore, bioactive 1,4-BZDs usually possess a defined stereogenic center at C3 position in the seven-membered ring. Despite of these properties, to the best of our knowledge, a sustainable and enantioselective route to these biologically active benzofused seven-membered azaheterocycles has not yet been described (see Chapter 1). The main objective of this Chapter would be the development of a sustainable synthesis of 1,4-benzodiazepines based on a Rh-catalyzed enantioselective hydroamination of terminal allenes or methyl-alkynes (Scheme 45).




**Scheme 45.** Rh-catalyzed enantioselective hydroamination of allenes and methyl-alkynes to 1,4-benzodiazepines (1,4-BZDs)

.

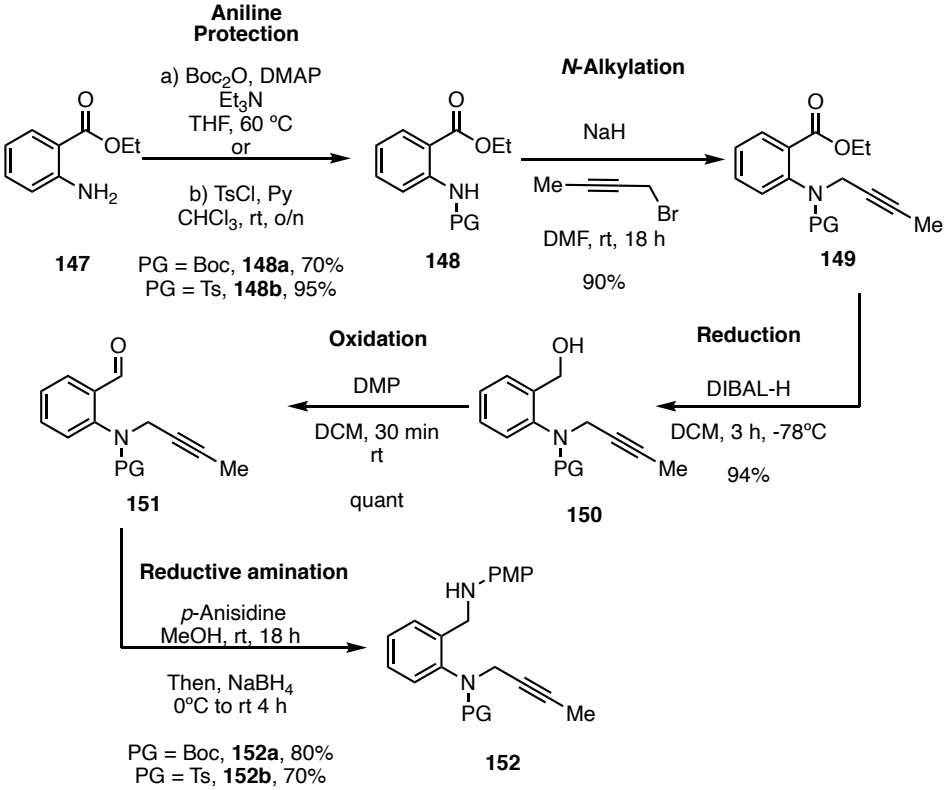
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Carried out in collaboration with Dr. Bernárdez

# 4. Results and Discussion

## 4.1. Synthesis of Alkynes 152

The two propargylated alkynes **152a** (PG = Boc) and **152b** (PG = Ts) were synthesized in five steps from commercially available ethyl 2-aminobenzoate **147** with a good overall yield. These two protecting groups (Boc, Ts) would allow the evaluation of the Thorpe-Ingold effect in the Rh-catalyzed hydroamination and would also facilitate a later derivatization of the final product. Thus, the protection of the commercially available aniline **147** gave excellent yields of *N*-Boc- (**148a**) and *N*-Ts (**148b**) derivatives. Then, alkylation with 1-bromobut-2-yne to *N*-propargyl derivatives **149**, reduction with DIBAL-H to the alcohols **150,** oxidation with DMP to the aldehydes **151** and final, without further purification, reductive amination provided the desired alkynes **152a** and **152b** in good overall yields (Scheme 46).

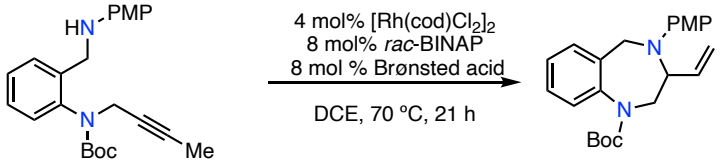



**Scheme 46.** Synthesis of alkynes **152**

## 4.2. Rh-catalyzed Intramolecular Asymmetric Hydroamination of Alkynes 152

We begin with the Rh-catalyzed hydroamination of **152a**. Firstly, we evaluate the nature of the Brønsted acid needed for the Rh-catalyzed hydroamination under Breit's conditions (Table 6). As it was mentioned in the introduction, the Brønsted acid possess a capital importance in the development of hydrorhodation of alkynes and allenes, since triggers the formation of a Rh-H active catalyst that would isomerize the alkyne into the allene, and then the allene into the key Rh-π-alyll intermediate. We started using 4 mol% $[Rh(cod)Cl_2]_2$, 8 mol% *rac*-BINAP, 8 mol% Brønsted acid, DCE, 70 °C as initial conditions.

**Table 6**. Optimization of the Brønsted acid




**152a** **153a**

| entry[a] | Brønsted acid | % yield[b] | er[c] |
|---|---|---|---|
| 1 | 8 mol% *rac*-BNP acid | 61 | - |
| 2 | 8 mol% $(PhO)_2PO_2H$ | 52 | - |
| 3 | 8 mol% $PhCO_2H$ | -[d] | - |
| 4 | 8 mol% (*R*)-TRIP | 69 | - |

Conditions: a) **152a** (0.2 mmol), 0.4 M in DCE, 70 °C, 21 h b) Isolated yields; c) er were determined by HPLC; d) All **152a** was recovered.

To our delight, *rac*-BNP acid showed the best reactivity and gave the desired product **153a** in a good 61% yield (Table 6, entry 1). The yield decreased to 52% when $(PhO)_2PO_2H$ acted as Brønsted acid (Table 6, entry 2), and no reaction was observed when phenylacetic acid was used (Table 6, entry 3). When a chiral phosphoric acid (*R*)-TRIP was used, a good 69% yield of **153a** was achieved, but as a racemic mixture (Table 6, entry 4). This result indicates that the chiral information is not transferred by the acid and, therefore, chiral ligands should be used to transfer the chiral information to the final product.

A series of most common chiral ligands were then screened (Figure 8). Thus, (*R*)-BINAP ligands (Table 7, entries 1-2) and (*R*)-DTBM-Segphos (Table 7, entry 3) afforded the product **153a** in good yields at 70°C, but almost as racemic mixture. In the case of Josiphos ligand, used by Breit for the preparation of five- and six-membered azaheterocycles,[174] the yield of **153a** was low (26%) but in a promising 61:39 er (Table 7, entry 4). Reaction performed at 50 °C gave similar er but a low chemical yield (19%) of **153a** (Table 7, entry 5). Interestingly, the yield of **153a** could be improved to 58% without erosion of the enantioselectivity after 120 h (Table 7, entry 6). (*R*)-*xyl*-BINAP gave good yields of **153a** but as racemic mixture (Table 7, entry 7). Interestingly, the electron-rich biaryl phosphines (*R*)-DTBM-Segphos provided **153a** in a good 73% yield with 62:38 er (Table 7, entry 8), and even better yields and enantioselectivities were found for (*S*)-DTBM-Garphos (Table 7, entry 9). Unfortunately, the reaction failed at lower temperatures (Table 7, entries 14-16) as well as with other family type of ligands (Table 7, entries 10-13)

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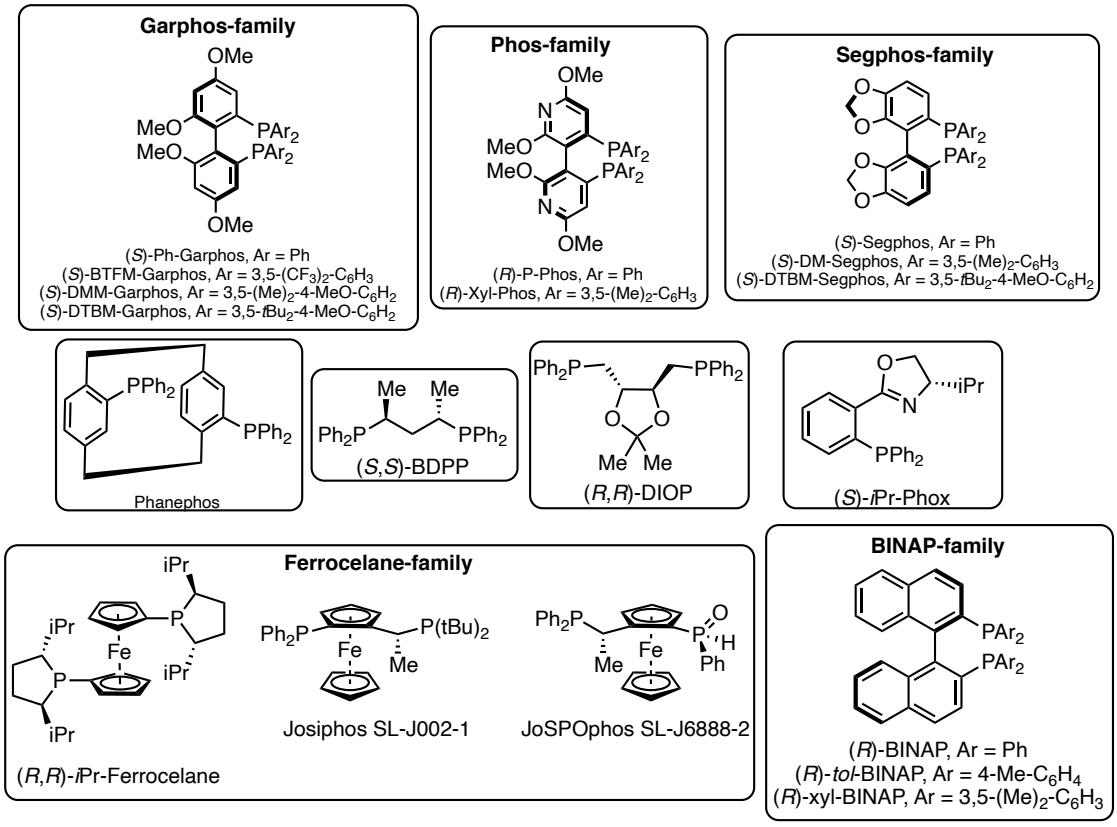
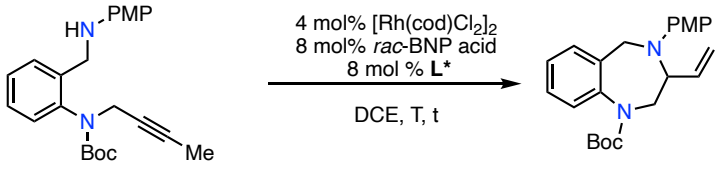



**Figure 8.** Chiral ligands used in the Rh-catalyzed asymmetric hydroamination

**Table 7**. Screening of chiral ligands




**152a** **153a**

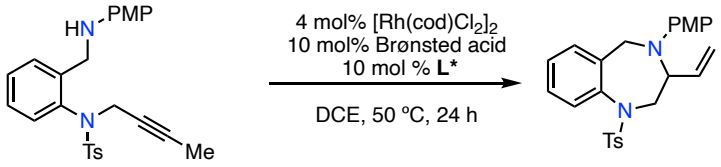
| Entry[a] | Ligand | T/°C | t/h | %Yield[b] | er[c] |
|---|---|---|---|---|---|
| 1 | (*R*)-BINAP | 70 | 20 | 65 | 57:43 |
| 2 | (*R*)-*tol*-BINAP | 70 | 20 | 77 | 49:51 |
| 3 | (*R*)-DTBM-Segphos | 70 | 20 | 78 | 53:46 |
| 4 | Josiphos-SL-J002-1 | 70 | 20 | 26 | 61:39 |
| 5 | (*R*)-BINAP | 50 | 24 | 19 | 62:38 |
| 6 | (*R*)-BINAP | 50 | 5d | 58 | 62:38 |
| 7 | (*R*)-*xyl*-BINAP | 50 | 24 | 69 | 49:51 |
| 8 | (*R*)-DTBM-Segphos | 50 | 24 | 73 | 62:38 |
| 9 | (*S*)-DTBM-Garphos | 50 | 24 | 81 | 33:67 |
| 10 | (*S*, *S*)-BDPP | 50 | 24 | 0[d] | - |
| 11 | (*R*, *R*)-DIOP | 50 | 24 | >5 | - |
| 12 | (*R*, *R*)-*i*Pr-Ferrocelane | 50 | 24 | 0[d] | - |
| 13 | Josiphos-SL-J002-1 | 50 | 24 | >5 | - |
| 14 | (*R*)-DTBM-Segphos | 30 | 24 | 0[d] | - |
| 15 | (*S*)-DTBM-Garphos | 30 | 24 | 0[d] | - |
| 16 | (*R*)-DTBM-Segphos | 40 | 24 | 0[d] | - |

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Conditions: **152a** (0.2 mmol), 0.4 M in DCE; b) Isolated yields; c) er were determined by HPLC; d) SM was recovered

These unfruitful results with *N*-Boc-protected alkyne **152a**, led us to explore the reactivity with the other protected alkyne **152b**. This new EWG protecting group, sulfonamide NTs, is less conjugated with the nitrogen that might help with a higher Thorpe-Ingold effect during cyclization. Once again, we started screening the Brønsted acids to promote the cyclization (Table 8). Neither PPTS (Table 8, entry 1) nor *rac*-BNP acid (Table 8, entry 3) gave the cyclization, even at higher temperature (Table 8, entry 2). However, at 70 °C, *rac*-BNP acid gave a low 30% yield of **153b** (Table 8, entry 4). Interestingly, when the acidity of the Brønsted acid was higher, TFA (pka=0.52) the yield of **153b** increased to 62% yield (Table 8, entry 5). Unexpectedly, with the more acidic TfOH (pka=-14.9) a lower 40% yield of **153b** was obtained (Table 8, entry 6). Finally, the reaction of alkyne **152b** with TFA as Brønsted acid and (*R*)-DTBM-Garphos gave a 50% of **153b** with a promising to 80:20 er (Table 8, entry 7). Unfortunately, the reaction heated at 70 °C gave a better 60% yield, but almost as a racemic mixture (Table 8, entry 8).

**Table 8**. Optimization of conditions to cyclize **152b**




**152b** **153b**

| Entry[a] | Ligand | Brønsted acid | % Yield[b] | er[c] |
|---|---|---|---|---|
| 1 | *rac*-BINAP | PPTS | traces | - |
| 2[d] | *rac*-BINAP | PPTS | traces | - |
| 3 | *rac*-BINAP | *rac*-BNP acid | - | - |
| 4[d] | *rac*-BINAP | *rac*-BNP acid | 30 | - |
| 5 | *rac*-BINAP | TFA | 62 | - |
| 6 | *rac*-BINAP | TfOH | 40 | |
| 7 | (*R*)-DTBM-Garphos | TFA | 50 | 80:20 |
| 8[d] | (*R*)-DTBM-Garphos | TFA | 60 | 60:40 |

Conditions: **152b** (0.15 mmol), 0.4 M in DCE; b) Isolated yields; c) er were determined by chiral SFC; d) 70 °C instead of 50 °C

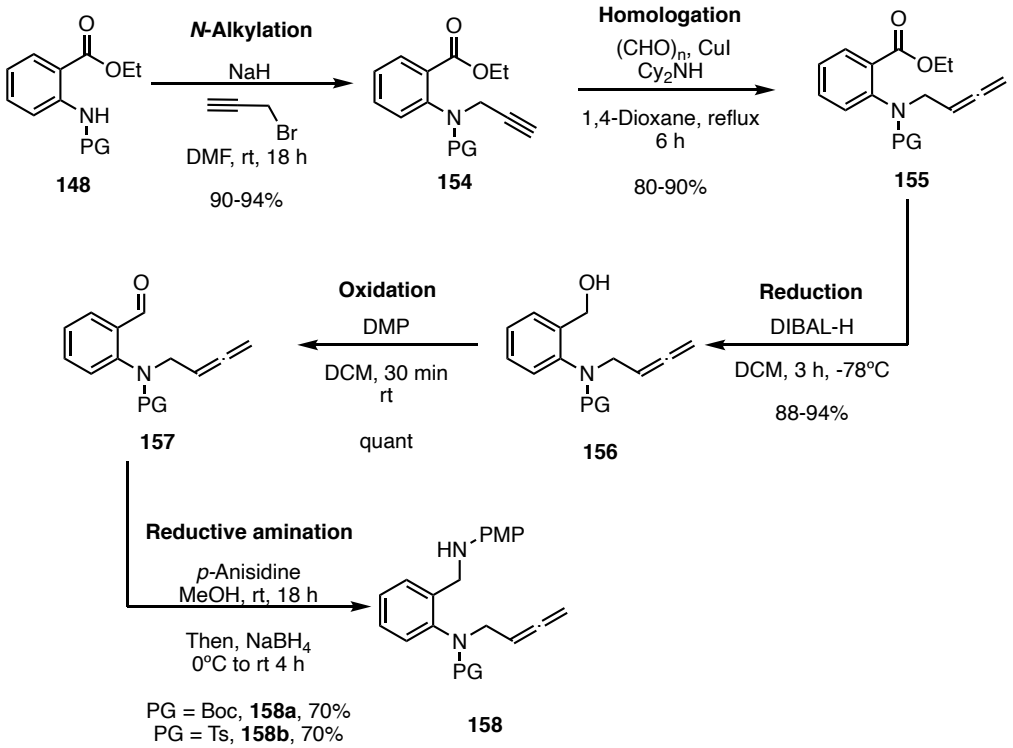
After the screening of conditions for the cyclizations of alkynes **152**, we can conclude:

- -The Brønsted acid plays a capital role in the hydrorhodation of alkynes. *Rac*-BNP acid is the best acid to cyclize **152a** while TFA is the best acid to cyclize **152b**.
- (*R*)-DTBM-Garphos is the best ligand for the asymmetric cyclization, yielding **153a** in an 81% yield with 33:67 er (Table 7, entry 9), and **153b** is afforded in a 50% yield with 80:20 er (Table 8, entry 7).
- The N-Ts protecting group leads to better enantiomeric ratio than the N-Boc, probably due to a more efficient Thorpe-Ingold effect.

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## 4.3. Synthesis of Allenes 159

With the best result of 60% ee (Table 8, entry 7) the influence of the Brønsted acid in the isomerization of internal alkyne to terminal allene was analyzed. In addition, the Rh-catalyzed functionalization of allenes usually provides better results than the functionalization of alkynes. Therefore, we decided to directly synthesize allenes **158a** (PG = Boc) and **158b** (PG = Ts). A similar synthetic procedure than alkynes **152a** and **152b** was followed to prepare the corresponding allenes **158a** and **158b**. Firstly, *N*-alkylation with propargyl bromide yields the propargylated compounds **154a** and **154b** in excellent yields. Secondly, homologation of terminal alkynes **154** to the corresponding allenes **155a** and **155b** under typical conditions gave excellent yields. The last steps comprising reduction of the esters **156** to the alcohols **156,** their oxidation to the aldehydes **157** and final reductive amination provided the desired allenes **158a** and **158b** in good overall yields (Scheme 47).



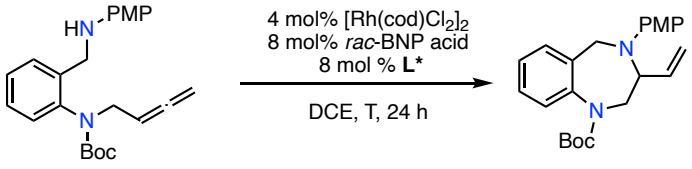

**Scheme 47.** Synthesis of allenes **158**

## 4.4. Rh-Catalyzed Intramolecular Asymmetric Hydroamination of Allenes 158

We started examining those ligands that possessed any activity in the cyclization of alkyne **152a**. (*R*)-BINAP showed similar activity with the allene **158a**, giving a 36% yield of **153a** with a 59:41 er (Table 9, entry 1). Better yields were obtained with (*R*)-*tol*-BINAP and (*R*)-*xyl*-BINAP and also with $^{i}$Pr-Ferrocelane but almost as a racemic mixture (Table 9, entries 2-4). Other members of the ferrocene family like Josiphos-SL-J002-1 provided **153a** in a low 25% yield with 25:75 er (Table 9, entry 5), while JoSPOphos gave rise to **153a** (45%) almost as a racemic mixture (Table 9, entry 6). In the case of chiral biaryl phosphine ligands, the simple (*R*)-Segphos provided **153a** in a 47% yield as a racemic mixture (Table 9, entry 7), whereas (*R*)-DTBM-Segphos gave better enantiomeric ratio (Table9, entry 8). The best ligand for the hydroamination of **158a** was (*R*)-DTBM-Garphos that gave rise to **153a** in a

76% yield with 74:26 er (concentration **[158a]** = 0.4 M) (Table 9, entry 9) and 70% yield with 77:23 er (concentration **[158a]** = 0.2 M) (Table 9, entry 10).

**Table 9**. Optimization of reaction conditions for Rh-catalyzed hydroamination of allene **158a**




**158a** **153a**

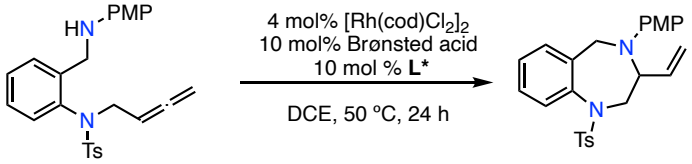
| Entry[a] | Ligand | T/°C | [M] | %Yield[b] | er[c] |
|---|---|---|---|---|---|
| 1 | (*R*)-BINAP | 50 | 0.4 | 36 | 59:41 |
| 2 | (*R*)-*tol*-BINAP | 50 | 0.4 | 51 | 54:46 |
| 3 | (*R*)-*xyl*-BINAP | 50 | 0.4 | 72 | 51:49 |
| 4 | (*R*, *R*)-$^{i}$Pr-Ferrocelane | 50 | 0.4 | 48 | 47:53 |
| 5 | Josiphos-SL-J002-1 | 50 | 0.4 | 14 | 75:25 |
| 6 | JoSPOphos-SL-J688-2 | 50 | 0.4 | 45 | 55:45 |
| 7 | (*R*)- Segphos | 50 | 0.4 | 47 | 52:48 |
| 8 | (*R*)-DTBM-Segphos | 50 | 0.4 | 50 | 74:26 |
| 9 | (*R*)-DTBM-Garphos | 50 | 0.4 | 76 | 74:26 |
| 10 | (*R*)-DTBM-Garphos | 50 | 0.2 | 70 | 77:23 |

Conditions: **158a** (0.2 mmol), 0.4 M in DCE; b) Isolated yields; c) er were determined by HPLC

Despite the fact that *N*-Boc-protected allene **158a** showed better results than *N*-Boc-protected alkyne **152a**, they are somewhat inferior to the results of the *N*-Ts-protected alkyne **152b**. Therefore , we decided to try the hydroamination with the more rigid allene **158b**. An extensive study of chiral ligands was screened for a broad spectrum. Unfortunately, (*S*)-$^{i}$Pr-Phox, (*S*)-Ferrocenyl-Phox, Davephos, (*R*)-Phanephos, (*R*)-P-phos, (*R*)-*xyl*-phos failed in the hydroamination of allene **158b** (Table 10, entries 1-6). The first positive result was found with JoSPOphos-SL-J688-2 that gave **153b** in a low 25% yield with 70:30 er (Table 10, entry 7). Then, a combination of (*R*)-DTBM-Segphos (a good ligand for the *N*-Boc derivatives) with different Brønsted acids and concentrations of **158b** was evaluated (Table 10, entries 8-10). At 0.2 M **[158b]**, *rac*-BNP acid gave a low 25% yield of **153b** with 86:14 er (Table 10, entry 8) whereas PPTS gave a good 70% yield with the same 86:14 er (Table 10, entry 9). Interestingly, at 0.4 M **[158b]**, using PPTS as Brønsted acid, both yield and enantiomeric ratio increased to 80% and 90:10, respectively (Table 10, entry 10). Nonetheless, less electron-rich ligands of the Segphos family, gave lower chemical yields and er of allene **158b** (Table 10, entries 11-12). We then explore the reactivity of other chiral biaryl phosphine ligands, the Garphos family. Either the electron-deficient (*S*)-BTFM-Garphos (Table 10, entry 13) and the electronically neutral (*R*)-Ph-Garphos (Table 10, entry 14) failed in the cyclization. However, the relative electron-rich (*R*)-*xyl*-Garphos gave an excellent 90:10 er albeit the chemical yield was a low 15% (Table 10, entry 15) and (*R*)-*tol*-Garphos gave a good 70% yield, but with a slightly lower 80:20 er (Table 10, entry 16). To our delight, with the more electron-rich (*R*)-DTBM-Garphos, the allene **158b** smoothly cyclized to the 1,4-BZD **153b** in a fairly good 70% yield with 95:05 er (Table 10, entry 17). A fine tuning of the Brønsted acid used was then tested. Acetic acid (pka = 4.76) showed same enantiomeric ratio of **153b** than PPTS (pka = 5.21), however the chemical yield dropped to 50% (Table 10, entry 18). Chloroacetic acid (pka = 2.81) favored the reaction and gave better

chemical yields (90%) than PPTS, however the enantiomeric ratio slightly dropped to 91:9 (Table 10, entry 19). 4-Chloropyridinium chloride (pka = 3.84) gave the best chemical yield (95%), however the enantiomeric ratio was a bit lower 90:10 (Table 10, entry 20). Final attempts with *rac*-BNP acid gave **153b** with a low 25% yield and low er 85:15 (Table 10, entry 21) and with PPTS at rt for 1 week also with a low 15% without erosion of er (Table 10, entry 22). Interestingly, temperature seems to affect the chemical yield but not the enantiomeric ratio since the reaction at 70 °C gave a slightly lower 60% yield but without erosion of er (Table 10, entry 23).

**Table 10**. Optimization of reaction conditions for Rh-catalyzed hydroamination of allene **158b**




**158b** **153b**

| Entry[a] | Ligand | Brønsted acid | [M] | %yield[b] | er[c] |
|---|---|---|---|---|---|
| 1 | (*S*)-$^{i}$Pr-Phox | *rac*-BNP acid | 0.4 | - | - |
| 2 | (*S*)-Ferrocenyl-Phox | *rac*-BNP acid | 0.4 | - | - |
| 3 | Davephos | *rac*-BNP acid | 0.4 | - | - |
| 4 | (*R*)-Phanephos | PPTS | 0.4 | - | - |
| 5 | (*R*)-P-phos | PPTS | 0.4 | - | - |
| 6 | (*R*)-*xyl*-phos | PPTS | 0.4 | - | - |
| 7 | JoSPOphos-SL-J688-2 | *rac*-BNP acid | 0.4 | 25 | 70:30 |
| 8 | (*R*)-DTBM-Segphos | *rac*-BNP acid | 0.2 | 25 | 86:14 |
| 9 | (*R*)-DTBM-Segphos | PPTS | 0.2 | 70 | 86:14 |
| 10 | (*R*)-DTBM-Segphos | PPTS | 0.4 | 80 | 90:10 |
| 11 | (*R*)-Segphos | PPTS | 0.4 | 60 | 78:22 |
| 12 | (*S*)-DM-Segphos | PPTS | 0.4 | 65 | 75:25 |
| 13 | (*S*)-BTFM-Garphos | PPTS | 0.4 | - | - |
| 14 | (*R*)-Ph-Garphos | PPTS | 0.4 | - | - |
| 15 | (*R*)-*xyl*-Garphos | PPTS | 0.4 | 15 | 90:10 |
| 16 | (*R*)-*tol*-Garphos | PPTS | 0.4 | 70 | 80:20 |
| **17** | **(*R*)-DTBM-Garphos** | **PPTS** | **0.4** | **70** | **95:05** |
| 18 | (*R*)-DTBM-Garphos | $CH_3CO_2H$ | 0.4 | 50 | 95:05 |
| 19 | (*R*)-DTBM-Garphos | $ClCH_2CO_2H$ | 0.4 | 90 | 91:9 |
| 20 | (*R*)-DTBM-Garphos | 4-Clpyr Cl | 0.4 | 95 | 90:10 |
| 21 | (*R*)-DTBM-Garphos | *rac*-BNP acid | 0.4 | 25 | 85:15 |
| 22[d] | (*R*)-DTBM-Garphos | PPTS | 0.4 | 15 | 95:05 |
| 23[e] | (*R*)-DTBM-Garphos | PPTS | 0.4 | 60 | 95:05 |

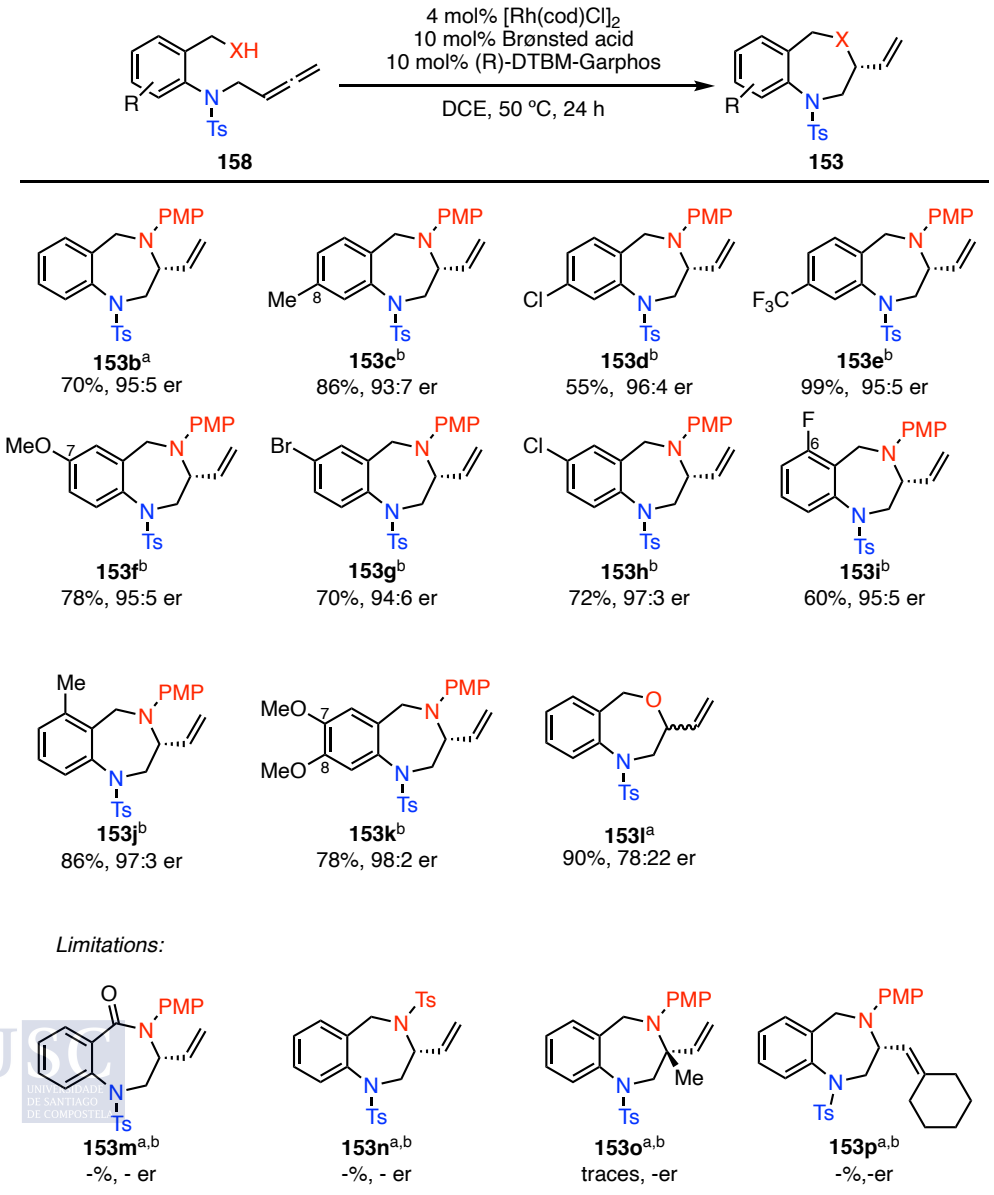
Conditions: **158b** (0.15 mmol), 0.4 M in DCE; b) Isolated yields; c) er were determined by chiral SFC; d) 40 °C instead of 50 °C, 1 week instead of 24 h; e) 70 °C instead of 50 °C. 4-Clpyr Cl = 4-chloropyridinium Chloride

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## 5. Scope and Limitations

Having established the optimized conditions, we next turned to explore the scope and limitations of the reaction (Scheme 48). All of the tested substrates bearing strong EDG (MeO-), EWG($CF_3$-), halides (Cl-, Br-, F-) or alkyl (Me-) groups in any position of the ring are

well tolerated. Thus, the 5-position of the aryl ring tolerates substitution with Me (**158c**), Cl (**158d**) and $CF_3$ (**158e**) to give the 1,4-BZDs **153c-e** in moderate to excellent yields and excellent enantioselectivities. The 4-position also tolerated substitution with MeO(**158f**), Br(**158g**) and Cl(**158h**), giving rise to the 1,4-BZDs **153f-h** in very good yields and excellent enantioselectivities. Even 6-position tolerated substitution with F (**158i**) and Me (**158j**) to give the corresponding 1,4-BZDs in a good to excellent 60%-86% yields with 95:5 er to 97:3 er, respectively. Even double substitution in 4 and 5 positions of **158** was well tolerated giving **153k** in a good 78% yield with excellent enantioselectivity. However, the nature of the nucleophile plays a capital role in the cyclization, since when the NHPMP was changed by a hydroxy group, the 1,4-BZO **153l** was obtained in an excellent 90% yield but with a low 78:22 er. There are limitations regarding the nature of the nucleophile, NHPMP amide (**158m**) or sulfonamide TsNH (**158n**) and substitution on the allene, 1,1-disubstituted allenes (**158o**) or 1,3,3-trisubstituted allenes (**158p**).




Conditions: **158** (0.15 mmol), 0.4 M. a) 10 mol% PPTS. b) 10 mol % of chloroacetic acid

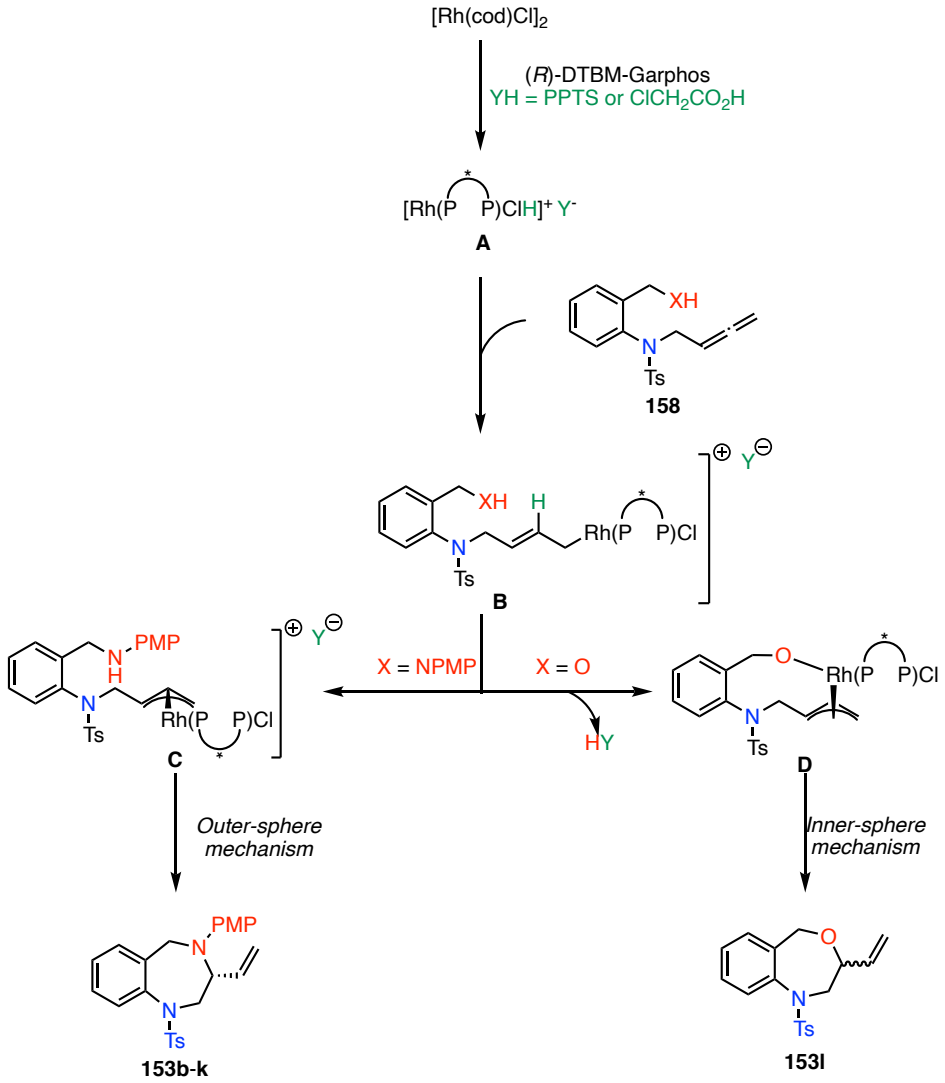
**Scheme 48.** Scope and limitations of the Rh-catalyzed hydroamination of allenes **158**

Based on the literature and our own observations during the study of the Rh-catalyzed hydrofunctionalization we propose the following mechanism (Scheme 49). The active Rh-H catalyst **A** is formed upon reaction of $[Rh(cod)Cl]_2$ with the chiral ligand (*R*)-DTBM Garphos and the corresponding Brønsted acid (YH = PPTS or $ClCH_2CO_2H$). Then, the allene **158** undergoes a regioselective 1,2-insertion into the Rh-H **A** to give the intermediate **B**. Two different paths to afford **153** might be operating, "*inner*- and *outer-sphere*". We speculate that the nature of Brønsted acid (TFA *vs* PPTS or $ClCH_2CO_2H$) and the nucleophile (XH = OH, or NHPMP) are crucial for the evolution. The 1,4-BZDs **153b**-**153k** could be obtained via cationic intermediate **C**, favored by employment of PPTS or $ClCH_2CO_2H$, that would evolve via an "*outer-sphere*" $S_N2$ mechanism (Tsuji-Trost allylic alkylation). For the case of alkynes **152** as substrates**,** a more neutral-like intermediate (with TFA) is expected, that might favor competitive pathways that would erode the enantioselectivity of the process.[175] Similarly, to explain the lower enantiomeric ratio obtained for the 1,4-BZO **153l**, the more neutral-like *inner-sphere* pathway (intermediate **D**) should be considered. In fact, it has been reported that alcohols usually follow a reductive "inner-sphere" mechanism.[176] Finally, the X-Ray structure of **153b** (Figure 9) rises the question if a π-π stacking between both protecting groups might be operating as an intermolecular force to direct the nucleophilic attack to obtain the 1,4-BZDs **153b**-**153k** in excellent er.

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[175] a) Hartwig, J. F.; Stanley, L. M. Acc. *Chem. Res.* **2010**, *43*, 1461. b) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. c) Chen, Q.-A.; Chen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 8392. d) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596. e) Yang, X.-H.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1774.

[176] Ammann, S. E.; Rice, G. T.; White, M.C. *J. Am. Chem. Soc.* **2014**, *136*, 10834.




**Scheme 49**. Proposed mechanism for the Rh-catalyzed hydrofunctionalization of allenes **158**

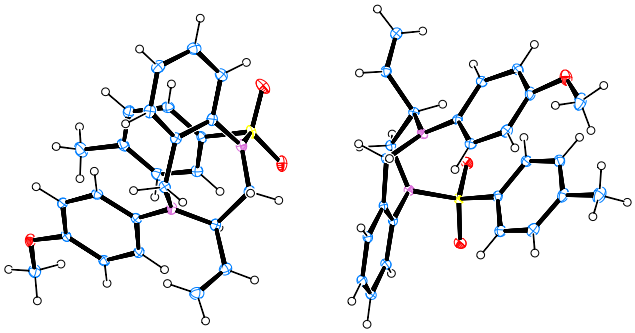


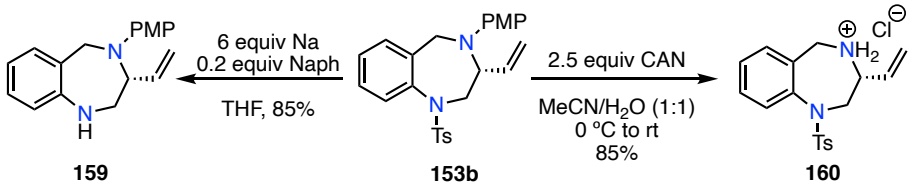
**Figure 9.** X-ray structure of **153b**. The ORTEP drawing of **153b** showing ellipsoids at the 30% contour probability level

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# 6. Substrate Derivatization

## 6.1. Orthogonal Removal of the Protecting Groups

The two different *N*-protecting groups of 1,4-BZD **153**, *N*-PMP and *N*-Ts were selectively removed under different chemical conditions (Scheme 50). The tosyl group was removed under typical one electron reduction conditions, sodium in naphthalene, to give the desired aniline **159** in an 85% yield. PMP protecting group was easily removed upon treatment with CAN to give the benzylammonium chloride **160** in an 85% yield.

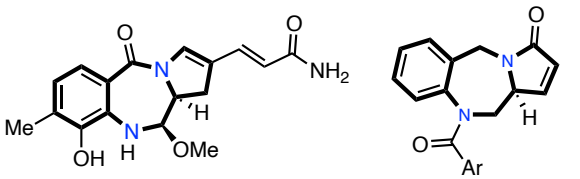



**159** **153b** **160**

**Scheme 50.** Orthogonal removal of *N*-protecting groups of **153b**

## 6.2. Straightforward Construction of the Advanced Pyrrolobenzodiazepine Metabolite of the V2-Receptor Antagonist Lixivaptan®

Pyrrolobenzodiazepines (PBZD) are one of the most biologically active 1,4-benzodiazepines. The heterobicyclic core bears by a [7,5] ring fusion with a *N*-bridgehead (Figure 10). Furthermore, the stereodefined C3 in the azepine ring, has been reported to enhance the biological activity.[177] For example anthramycin, isolated from *Streptomyces refuineus* in 1965[178] has been lately used to treat leukemia or ovarian cancer.[179] These properties are associated with the stereodefined C3 of the azepine ring, which provides a 3-dimensional shape perfectly crafted within the DNA minor groove and its stereochemistry is critical for DNA-binding.[180]




*Anthramycin* *Lixivaptan® advanced metabolite*

**Figure 10.** Selected biologically active PBZDs

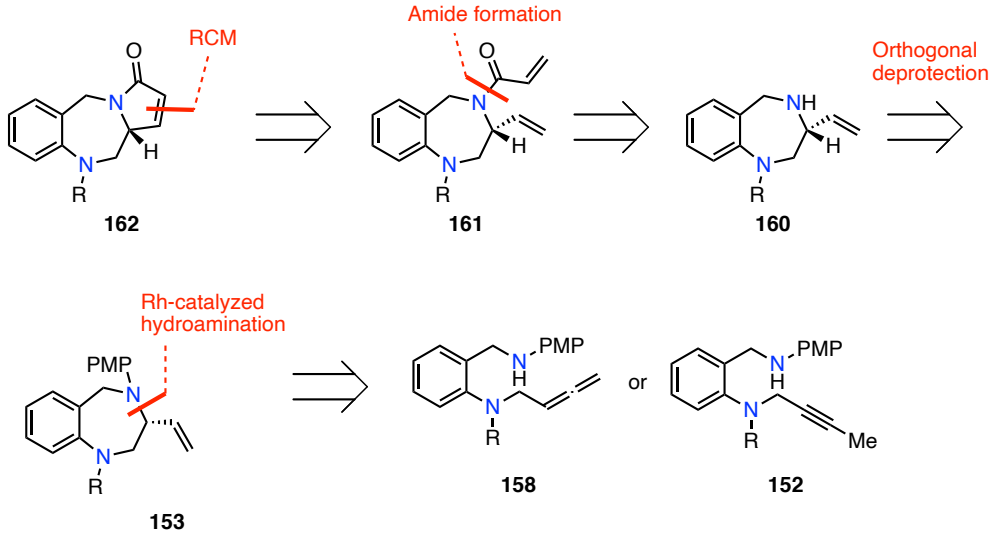
[177] a) Knabe, J.; Bender, S. *Archiv der Pharmazie* **1993**, *326*, 551. b) Barlind, J. G.; Buckett, L. K.; Crosby, S. G.; Davidsson, Ö.; Emtenäs, H.; Ertan, A.; Jurva, U.; Lemurell, M.; Gutierrez, P. M.; Nilsson, K.; O'Mahony, G.; Petersson, A. U.; Redzic, A.; Wågberg, F.; Yuan, Z.-Q. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2721. c) Sercel, Z. P.; Sun, A. W.; Stoltz, B. M. *Org. Lett.* **2019**, *21*, 9158.

[178] Leimgruber, W.; Stefanović, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791.

[179] a) Hochhauser, D.; Meyer, T.; Spanswick, V. J.; Wu, J.; Clingen, P. H.; Loadman, P.; Cobb, M.; Gumbrell, L.; Begent, R. H.; Hartley, J. A.; Jodrell, D. *Clin. Cancer Res.* **2009**, *15*, 2140. b) Janjigian, Y. Y.; Lee, W.; Kris, M. G.; Miller, V. A.; Krug, L. M.; Azzoli, C. G.; Senturk, E.; Wade Calcutt, M.; Rizvi, N. A. *Cancer Chemother. Pharmacol.* **2010**, *65*, 833.

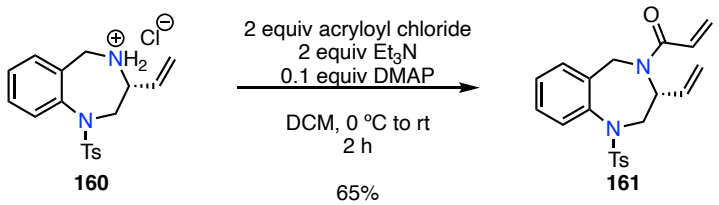
[180] Mantaj, J.; Jackson, P. J. M.; Rahman, K. M.; Thurston, D. E. *Angew. Chem. Int. Ed.* **2017**, *56*, 462.

Since our methodology allows the formation of 3-vinyl 1,4-benzodiazepines, we envisioned the following retrosynthetic analysis of an advanced metabolite of the $V_2$-receptor antagonist of Lixivaptan®, a vasopressin $V_2$-receptor antagonist to treat the congestive heart failure and liver cirrhosis (Scheme 51).[181] A last ring closing metathesis of the amide **161** would form the five-membered ring of the azabicyclic [7,5] core. Orthogonal removal of the *N*-protecting group would give rise to the desired benzylamine **160** precursors. Finally, the Rh-catalyzed asymmetric hydroamination of alkynes **152** or allenes **158** would give a straightforward access the seven-membered ring of 1,4-BZD **153**.




**Scheme 51.** Retrosynthetic analysis of the advanced metabolite **162**

The benzylammonium salt **160**, prepared from CAN treatment of **153b** (Scheme 49), was transformed into the corresponding amide **161** in a fairly good 65% yield upon treatment with acryloyl chloride, $Et_3N$ and a catalytic amount of DMAP (Scheme 52).



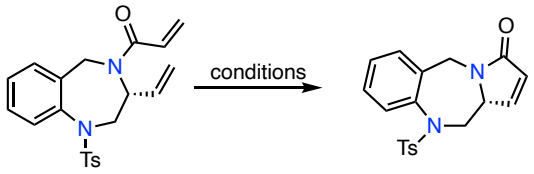

**Scheme 52.** Synthesis of amide **161**

The ring-closing metathesis of **161** was then accomplished (Table 11). While the Grubbs catalyst 2nd G was ineffective to provide the desired product **162** in toluene, the Hoveyda-Grubbs 2nd G in DCM provided moderate yield of the desired **162** at rt. To our delight, when this reaction was heated at reflux for 36 h, an 87% of the desired product **162** was isolated with a 96:4 er. This result showed that there was no erosion of the enantioselectivity during the derivatization process.

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**Table 11**. Ring-closing metathesis of amide **161**

[181] a) Hu, Y.; Phelan, V.; Ntai, I.; Farnet, C. M.; Zazopoulos, E.; Bachmann, B. O. *Chem. Biol.* **2007**, *14*, 691. b) Molinari, A. J.; Trybulski, E. J.; Bagli, J.; Croce, S.; Considine, J.; Qi, J.; Ali, K.; DeMaio, W.; Lihotz, L.; Cochran, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5796.




**161** **162**

| Entry | Conditions | **162** % yield |
|---|---|---|
| 1 | 10 mol% Grubbs 2nd G, toluene, reflux | decomposition |
| 2 | 10 mol% Hoveyda-Grubbs 2nd G, DCM, rt, 24 h | 50% |
| 3 | 10 mol% Hoveyda-Grubbs 2nd G, DCM, reflux, 36 h | 87% (96:4) |

Conditions: 0.1 mmol of **161**, 0.01 M

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# 7. Conclusions[182]

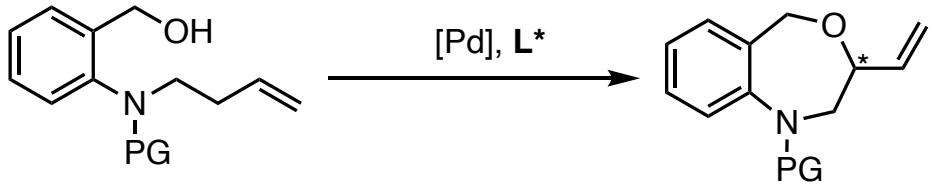
- An ecofriendly and asymmetric strategy to afford 1,4-BZDs **153** based on Rh-catalyzed hydroamination of alkynes **152** and allenes **158** has been successfully developed.
- *N*-Boc-protected alkyne **152a** and allene **158a** gave lower enantiomeric ratio of 1,4-BZD **153** than the corresponding *N*-Ts protected alkyne **152b** and allene **158b**. Thorpe-Ingold effect plays an important role in the cyclization.
- Alkyne **152b** was cyclized to the 1,4-BZD **153b** in a low 50% chemical yield with 80:20 enantiomeric ratio (Table 8, entry 7).
- Allene **158b** was cyclized to the 1,4-BZD **153b** with the best results, chemical yield 70% with 95:05 er (Table 10, entry 17). Substituted 1,4-BZDs **153c**-**153k** , bearing EDG and EWG groups in the aryl ring, were synthesized in good to excellent yields with excellent enantiomeric ratios.
- The nucleophile (nitrogenated *vs* oxygenated) plays an important role in the cyclization. Thus, 1,4-BZO **153l** was obtained in an excellent 90% yield but with moderate 78:22 er as compared to 1,4-BZD **153b** that was isolated in a fairly good 70% yield but with excellent 95:5 er. This might be explained because alcohols may follow an *"inner-sphere"* mechanism against the *"outer-sphere"* mechanism that might be operating with the NHPMP.
- *N*-Ts and *N*-PMP groups were orthogonally deprotected in fairly good yields under mild conditions.
- A straightforward derivatization of 1,4-BZD **153b** led to enantioenriched PBZD **162**, an advanced metabolite of the $V_2$-receptor antagonist of Lixivaptan®

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[182] Velasco-Rubio, Á.; Bernárdez, R.; Varela, J.A.; Saá, C. *J. Org. Chem.* **2021**, *86*, 10889.

# Chapter 4

## 1,4-Benzoxazepines *via* Pd-Catalyzed Allylic C-H Functionalization




Velasco-Rubio, Á.; Varela, J.A.; Saá, C. *Chem. Commun.* **2021**, *22*, 3591

Pd-catalyzed allylic C-H activation of simple olefins allows an easy entry to seven-membered *N,O*-heterocycles such as 1,4-benzo[*e*]oxazepines (1,4-BZOs), 1,4-benzodiazepinones (1,4-BZDs) and 1,4-oxazepanes in good to excellent yields. Straightforward derivatizations of the olefinated 1,4-BZO shows the synthetic utility of this methodology. The enantioselective Pd-catalyzed allylic C-H functionalization is also studied.

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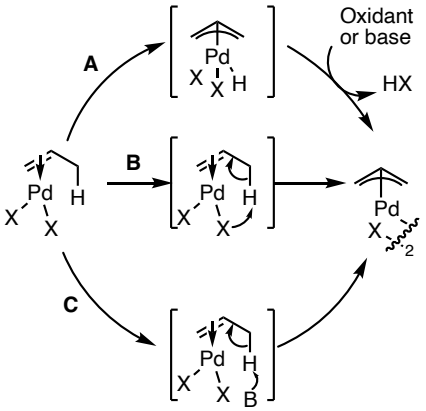
# Chapter 4

## 1,4-Benzoxazepines *via* Pd-Catalyzed Allylic C-H Functionalization

### 1. TM-Catalyzed Allylic Alkylation via C-H Bond Activation

As already pointed out in Chapter 3, one of the main drawbacks in allylic substitution is the pre-functionalization of starting materials with electrophilic groups, which would be part of the stoichiometric amounts of waste. However, allylic C-H bond activation would be a direct method to obtain π-allyl-metal complexes with high atom-economy.

Three different pathways have been proposed for the hydrogen removal step in allylic C-H bond activation (Scheme 53). Trost and coworkers suggested the insertion of palladium into the allylic C-H bond to generate the π-allylpalladium hydride intermediate, that can react later with a base or an oxidant to produce the π-allylpalladium complex (path A).[183] On the other hand, Beak and coworkers reported in the 80's a kinetic isotopic effect experiment where it was found large KIE values (3.5-5.45), what suggested a mechanism in which an internal base could remove the allyl hydrogen (path B).[184] Ketley and Braatz had already reported that the abstraction of the allylic hydrogen could be carried out by an external base (path C) .[185]



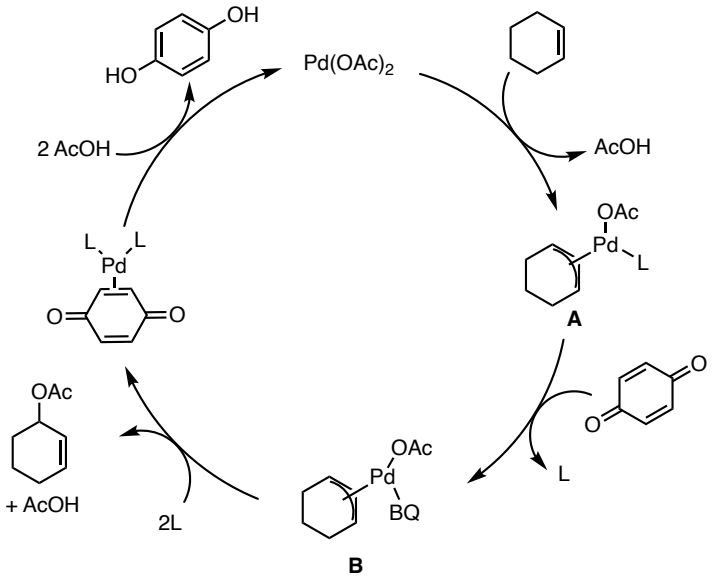

**Scheme 53.** Proposed pathways for the formation of π-allylpalladium complexes

In 1966, Haszeldine and coworkers reported the first Pd-catalyzed C-H allylic acetoxylation of cyclohexene (Scheme 54). [186] The proposed mechanism begins with the generation of the π-allylpalladium complex (intermediate A). Then BQ coordinates to the metal center (intermediate B) and promotes the nucleophilic attack by the acetate. Finally, the acetoxylated product is released with the concomitant formation of a $Pd^0$ species which

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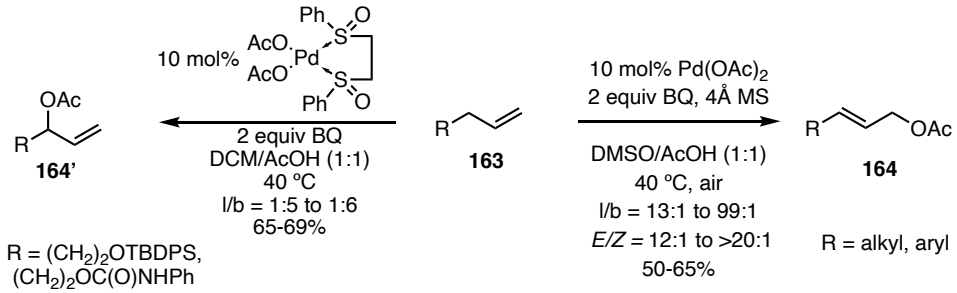
[183] Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407.
[184] a) Chrisope, D. R.; Beak, P. *J. Am. Chem. Soc.* **1986**, *108*, 334. b) Chrisope, D. R.; Beak, P.; Saunders, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 230.
[185] Ketley, A. D.; Braatz, J. *Chem. Commun.* **1968**, 169.
[186] Green, M.; Haszeldine, R. N.; Lindley, J. *J. Organomet. Chem.* **1966**, *6*, 107.

is reoxidized by BQ/AcOH to regenerate the catalyst. BQ is required as an oxidant for $Pd^0$ reoxidation and as a promoter (a π-acid) for the nucleophilic attack reaction.




**Scheme 54.** Pd-catalyzed allylic C-H bond acetoxylation of cyclohexene by Haszeldine

Despite the fact that Pd-catalyzed acetoxylation of cyclic alkenes was known since 60's, it was in 2004 when White reported the first Pd-catalyzed acetoxylation of terminal linear alkenes **163** using benzoquinone (BQ) as oxidant (Scheme 55).[187] The sulfoxide group coordination to the palladium center was a key point of the process. Furthermore, the regioselectivity of the reaction could be switched depending on the coordinated ligand to Pd. Thus, when DMSO was used as co-solvent, linear product **164** was isolated as a major product, whereas if DMSO is substituted by a disulfoxide ligand (White-catalyst), the branched product **164'** is obtained as the major one isomer. Mechanistic studies suggest that sulfoxide ligands are essential to promote the allylic C-H activation. In addition, BQ was not playing only the role of an oxidant, it was also crucial as a π-acid in effecting the reductive elimination.

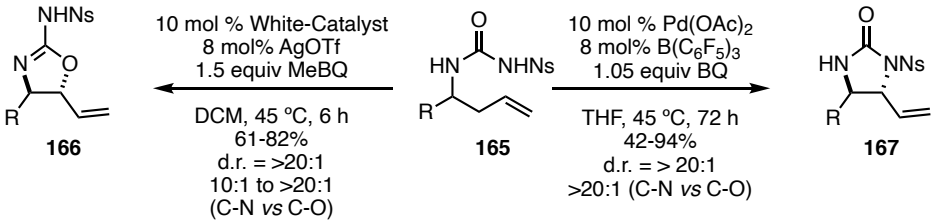



**Scheme 55.** Pd-catalyzed allylic C-H bond acetoxylation by White

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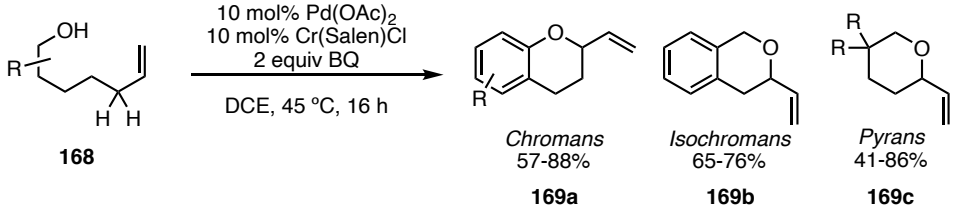
[187] Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.

Afterwards, other examples to functionalize allylic C-H bonds have been reported to make new C-C,[119,188] C-O[176,189] and C-N[190] bonds. Interestingly, in 2013, White found a catalyst-controlled C-O vs C-N allylic functionalization of ureas **165**.[191] The combination of White-catalyst with AgOTf led to the C-O bond formation and afford *anti*-aminooxazolines **166** in good yields and excellent diastereoselectivities. On the other hand, $Pd(OAc)_2$ in combination with $B(C_6F_5)_3$ as Lewis acid gave rise to the C-N bond formation and afforded *anti*-imidazolidinones **167** in good yields and excellent diastereoselectivities (Scheme 56).




**Scheme 56.** Catalyst-controlled C-O vs C-N bond functionalization of ureas **166** by White

In 2014, White reported the synthesis of chromanes **169a**, isochromanes **169b** and pyrans **169c** by a Pd-catalyzed C-H allylic activation employing Cr(salen) salts (Lewis acids)[192] as cocatalyst (Scheme 57).[176] The mechanistic investigations suggested an "*inner-sphere*" nucleophilic substitution (reductive elimination) to yield the chromane derivatives in fairly good yields.




**Scheme 57.** Pd-catalyzed allylic oxidations to chromane derivatives by White

In 2015, Gong described the Pd-catalyzed asymmetric allylic C-H oxidation for the synthesis of chromanes **171** (Scheme 58).[189d] The employment of phosphoramidites as chiral ligand (L⋆) in combination with *o*-fluorobenzoic acid (OFBA) as Brønsted acid gave rise to

[188] a) Lin, S.; Song, C.-X; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901. b) Young, A. J; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. c) Trost, B. M.; Thaisrivongs, D. A.; Donckele, E. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1523. d) Howell, J. M.; Liu, W.; Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 5750. e) Trost, B. M.; Donckele, E. J.; Thaisrivongs, D. A.; Osipov, M.; Masters, J. T. *J. Am. Chem. Soc.* **2015**, *137*, 2776. f) For the work of Gong on Pd-Catalyzed asymmetric allylic C-H functionalization see: Wang, P.-S.; Gong, L.-Z. *Acc. Chem. Res.* **2020**, *53*, 2841.

[189] a) Takenaka, K.; Akita, M.; Tanigaki, Y.; Takizawa, S.; Sasai, H. *Org. Lett.* **2011**, *13*, 3506. b) Gormisky, P. E; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584. c) Kondo, H.; Yu, F.; Yamaguchi, J.; Liu, G.; Itami, K. *Org. Lett.* **2014**, *16*, 4212. d) Wang, P.-S.; Liu, P.; Zhai, Y.-J.; Lin, H.-C.; Han, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 12732.

[190] a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590. b) Patillo, C. C.; Strambeanu, I. I.; Calleja, P.; Vermeulen, N. A.; Mizuno, T.; White, M. C. *J. Am. Chem. Soc.* **2016**, *138*, 1265. c) Vemula, S. R.; Kumar, D.; Cook, G. R. *ACS Catal.* **2016**, *6*, 5295. d) Xu, C.; Wu, Z.; Chen, J.; Xie, F.; Zhang, W. *Tetrahedron* **2017**, *73*, 1904. e) Ma, R.; White, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 3202.

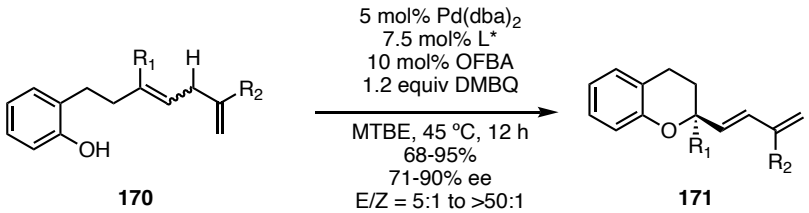
[191] Strambeanu, I. I.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 12032.

[192] Covell, D. J.; White, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 6448.

[119] Liu, W.; Ali, S. Z.; Ammann, S. E.; White, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 10658.

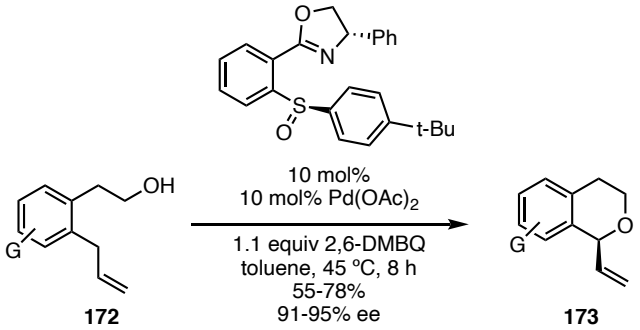
[176] Ammann, S. E.; Rice, G. T.; White, M.C. *J. Am. Chem. Soc.* **2014**, *136*, 10834.

the desired chromanes **171** in good to excellent yields and enantioselectivities. Mechanistic experiments suggested that the reaction proceeds via an initial counteranion-assisted Pd-catalyzed allylic C-H activation followed by an allylic alkoxylation, rather than a formal Wacker-type cyclization.



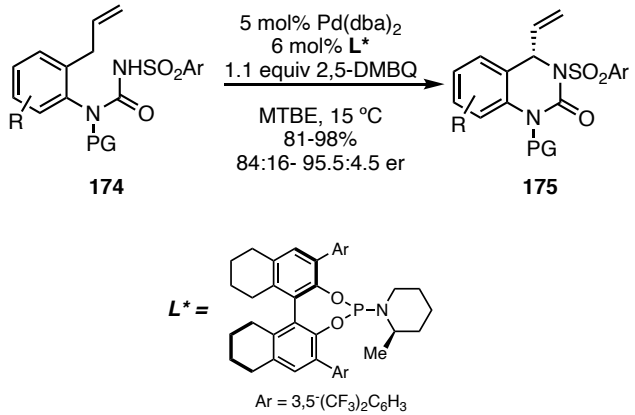

**Scheme 58**. Pd-catalyzed asymmetric allylic C-H oxidation for the synthesis of chromans by Gong

The Pd-catalyzed asymmetric allylic C-H bond functionalization had also been studied by White and coworkers.[115] In 2016, White had reported the enantioselective synthesis of isochromanes **173** via sulfoxide-oxazolidine ligand (SOX ligand family)[193] (Scheme 59).




**Scheme 59.** Pd-catalyzed enantioselective synthesis of isochromanes by White

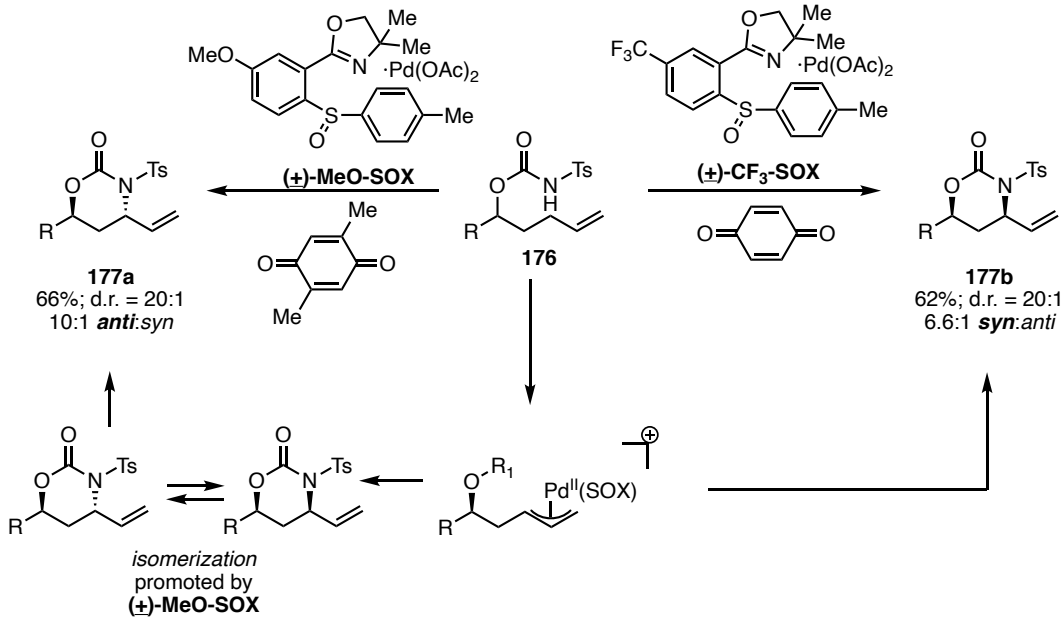
Pd-catalyzed allylic C-H activation has also been applied to the synthesis of azaheterocycles. In 2016, Gong described the access to chiral hydropyrimidines **175** through Pd-catalyzed asymmetric allylic C-H amination (Scheme 60).[194] With the employment of phosphoramidite **L*** as chiral ligand a variety of hydropyrimidines in excellent yields and enantioselectivities is accessed.




**Scheme 60.** Pd-catalyzed asymmetric synthesis of hydropyrimidines by Gong

[193] Sipos, G.; Drinkel, E. E.; Dorta, R. *Chem. Soc. Rev.* **2015**, *44*, 3834.
[194] Wang, P.-S.; Shen, M.-L.; Wang, T.-C.; Lin, H.-C.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 16032.
[115] Ammann, S. E.; Liu, W.; White, M. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 9571.

Very recently, White reported a Pd-catalyzed allylic C-H amination to 1,3 amino alcohols in a ligand-controlled *syn*/*anti* selectivity (Scheme 61).[195] It was found that (±)-MeO-SOX ligand gave *anti* 1,3 amino alcohol **177a** whereas (±)-$CF_3$-SOX produced the kinetic *syn* 1,3 amino alcohol **177b**. Excellent yields and diastereomeric ratios were obtained. The mechanistic investigations reveal that a cationic π-allyl Pd intermediate is obtained which rapidly isomerizes via π-σ- π. The C-N bond formation is the stereodetermining step. The *syn*-product is obtained in both cases, however in the case of the Pd/(±)-MeO-SOX combination an isomerization to the thermodynamic *anti*-product takes place. This isomerization is not promoted by the electron-deficient (±)-$CF_3$-SOX ligand.



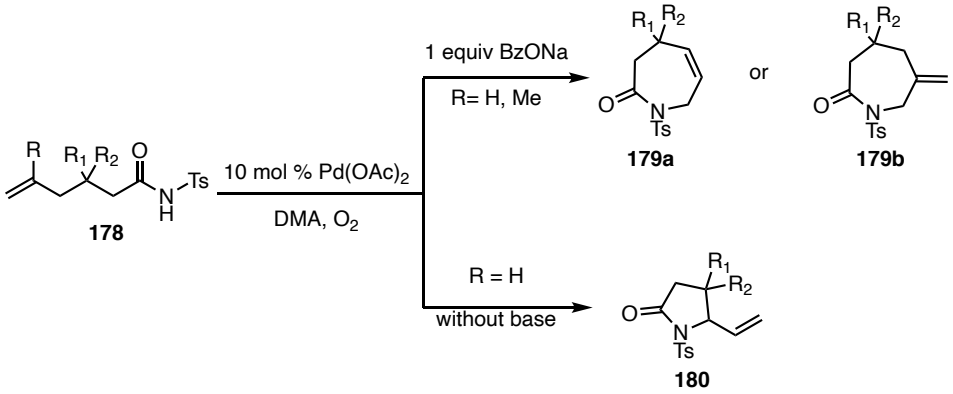

**Scheme 61.** Ligand-controlled *syn*/*anti* selectivity in the Pd-catalyzed C-H amination by White

In 2009, Liu reported the Pd-catalyzed synthesis of seven- and five- membered azaheterocycles **179** and **180**, respectively (Scheme 62).[196] The regioselectivity is modulated by the addition of a Brønsted base that favors the formation of the seven-membered ring. Mechanistic investigations suggest that the reaction proceeds via rate-determining C-H allylic activation/irreversible reductive elimination to form the C-N bond.

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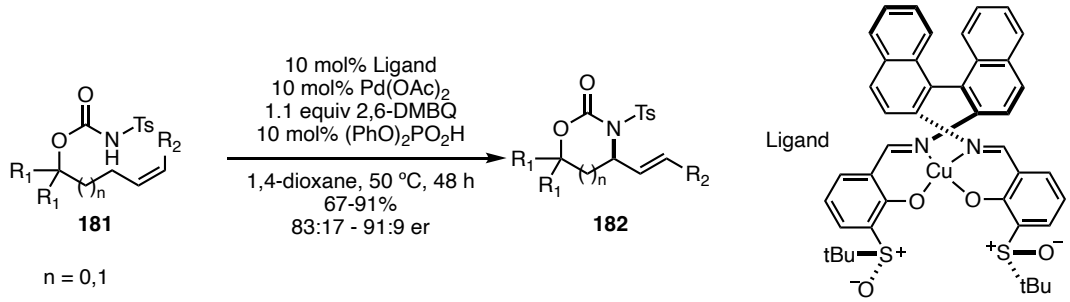
[195] Ma, R.; Young, J.; Promontorio, R.; Dannheim, F. M.; Pattillo, C. C.; White, M. C. *J. Am. Chem. Soc.* **2019**, *141*, 9468.

[196] Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707.




**Scheme 62.** Pd-catalyzed synthesis of seven- and five-membered azaheterocycles by Liu

Very recently Matsunaga reported the Pd-catalyzed asymmetric allylic C-H aminations of terminal and internal alkenes **181** (Scheme 63).[197] A new family of chiral ligands for Pd-catalyzed allylic C-H activation was introduced. The employment of metal-containing Schiff base ligands allows tuning the selectivity and reactivity of the Pd catalyst, even for the activation of internal alkenes. Good to excellent yields and enantioselectivities were achieved for the desired five- and six-membered rings **182**.



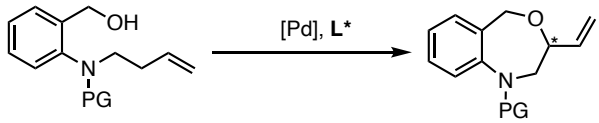

**Scheme 63.** Pd-catalyzed asymmetric allylic C-H amination by Matsunaga

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[197] Bunno, Y.; Tsukimawashi, Y.; Kojima, M.; Yoshino, T.; Matsunaga, S. *ACS Catal.* **2021**, *11*, 2663.

## 2. Objective

1,4-Benzoxazepines (1,4-BZOs) possess a remarkable biological activity that made them useful as anti-cancer, anti-Alzheimer, antiinflamatory, to treat schizophrenia or as psychotropic substances (See Chapter 1). Continuing with our main thesis goal, the sustainable synthesis of benzofused seven-membered heterocycles, we would like to explore a new synthetic approach to 1,4-benzoxazepines through Pd-catalyzed allylic C-H activation (intramolecular alkoxylation) of arylalkenols (Scheme 64). An enantioselective variant is also disclosed.



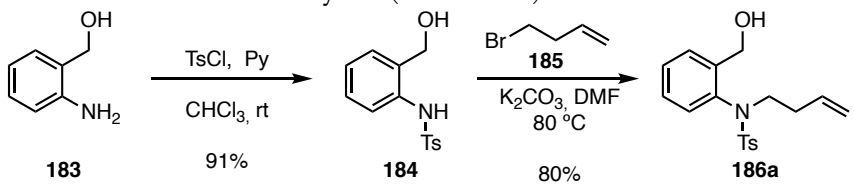

**Scheme 64.** Pd-catalyzed C-H allylic activation of arylalkenols to 1,4-benzoxazepines (1,4-BZOs)

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# 3. Results and Discussion

## 3.1. Synthesis of Starting Materials

We started the optimization of the cyclization with the alkenol **186a.** It was synthesized from commercially available (2-hydroxymethyl)aniline **183** in two steps. Firstly, protection of the commercially available aniline **183** with tosyl chloride gave the corresponding *N*-Ts derivative **184**. Secondly, *N*-alkylation with 4-bromo-1-butene (**185**) to the desired alkenol **186a** occurred in an excellent overall yield (Scheme 65).[198]



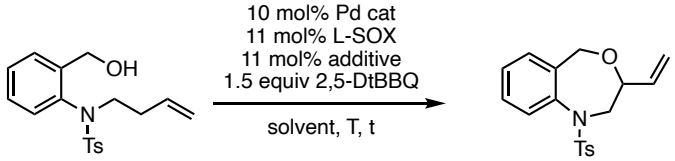

**183** **184** **186a**

**Scheme 65.** Synthesis of alkenol **186a**

## 3.2. Optimization of the Reaction Conditions

We initiated our investigation by examining the conditions for the cyclization of benzylic alkenol **186a** (Table 11).[187] . Firstly, the combination of White's catalyst and Cr salts as co-catalyst[187] gave a low 20% yield of the desired product **187a** (entry 1) or a moderate 40 % yield when using *rac*-BNP as Brønsted acid (entry 2). Application of slightly modified White's conditions,[115] 10 mol% of $Pd(OAc)_2$, 11 mol% of *rac*-BNP acid, 11 mol% of rac-L1-SOX, 1.5 equiv 2,5-DtBBQ in toluene 0.15 M at 60 °C, gave a 45% yield of **187a** after 24 h of reaction (entry 3), that could be increased to 90% when the reaction was carried out for 2 days (entry 4). The reaction seemed to be very sensitive to the Brønsted acid (Table 11, entries 5-7), PPTS, chloroacetic acid or 4-chloro-pyridinium chloride failed to react. Changes in solvent polarity by using ethereal solvents gave lower yields (Table 11, entries 8 and 9), and failed to react in MeCN, MeOH and non-polar chlorinated DCE (Table 11, entries 10-12). Finally, some control experiments were performed that showed temperature as an important factor since, when the reaction was run at 45 °C the yield dropped to 45% (Table 11, entry 13), while when the reaction was run at rt for 10 days the reaction did not start (Table 11, entry 14). In the absence of palladium catalyst or *rac*-L1-SOX ligand the reaction met with failure (Table 11, entries 15 and 16) whereas with chiral (*S*)-BNP acid afforded 1,4-BZO **187a** in an excellent 92% yield but as racemic mixture (Table 11, entry 15).

**Table 11**. Optimization of Pd-catalyzed intramolecular alkoxylation of **186a**[a]




**186a** **187a**

| Entry | Catalyst | Additive | Solvent | **187a**[b] |
|---|---|---|---|---|
| 1[c,d] | White's Catalyst | Cr(Salen) Cl | DCE | 20 |

[198] Bernárdez, R.; Suárez, J.; Fañanás-Mastral, M.; Varela, J.-A.; Saá, C. *Org. Lett.* **2016**, *18*, 642.
[187] Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.
[115] Ammann, S. E.; Liu, W.; White, M. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 9571.

| | | | | |
|---|---|---|---|---|
| 2[c] | White's Catalyst | *rac*-BNP acid | toluene | 40 |
| 3[e] | $Pd(OAc)_2$ | *rac*-BNP acid | toluene | 45 |
| 4 | $Pd(OAc)_2$ | *rac*-BNP acid | toluene | 90 |
| 5 | $Pd(OAc)_2$ | PPTS | toluene | traces |
| 6 | $Pd(OAc)_2$ | $ClCH_2CO_2H$ | toluene | - |
| 7 | $Pd(OAc)_2$ | 4-Clpyr Cl | toluene | - |
| 8 | $Pd(OAc)_2$ | *rac*-BNP acid | Dioxane | 60 |
| 9 | $Pd(OAc)_2$ | *rac*-BNP acid | THF | 45 |
| 10 | $Pd(OAc)_2$ | *rac*-BNP acid | MeCN | - |
| 11 | $Pd(OAc)_2$ | *rac*-BNP acid | MeOH | - |
| 12 | $Pd(OAc)_2$ | *rac*-BNP acid | DCE | - |
| 13[f] | $Pd(OAc)_2$ | *rac*-BNP acid | toluene | 45 |
| 14[g] | $Pd(OAc)_2$ | *rac*-BNP acid | toluene | - |
| 15 | - | *rac*-BNP acid | toluene | - |
| 16[c] | $Pd(OAc)_2$ | *rac*-BNP acid | toluene | - |
| 17 | $Pd(OAc)_2$ | (*S*)-BNP acid | toluene | 92 |

a) 0.1 mmol **186a**, (0.15 M). b) Isolated yields. c) Without rac-L1-SOX. d) BQ instead of 2,5-DtBBQ. e) 1 day. f) 45°C. g) rt, 10 days. 2,5-DtBBQ= 2,5-di-*tert*-butyl-1,4-benzoquinone, White's cat = 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate, *rac*-BNP acid = binaphthyl hydrogen phosphate, 4-Clpyr Cl = 4-Chloro-pyridinium chloride.

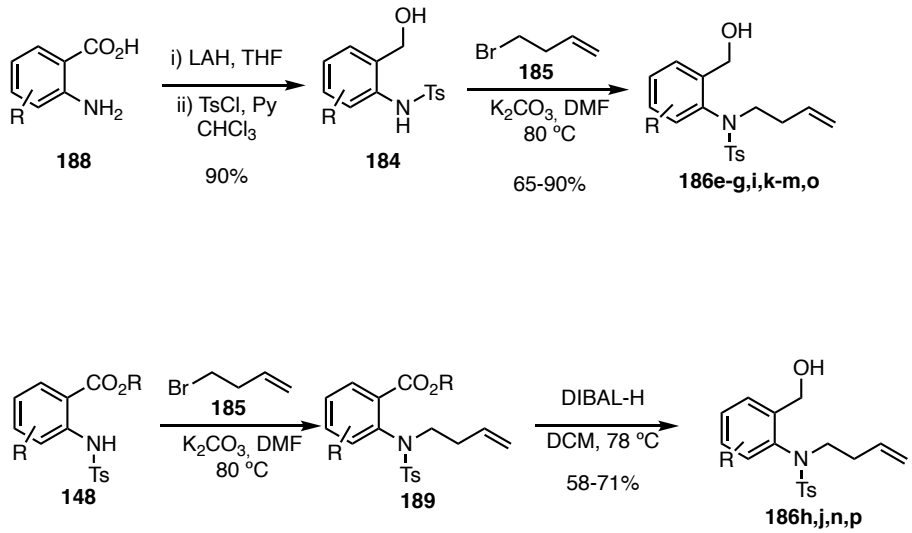
After optimization studies, the main conclusions are:

- The reaction requires the employment of BNP acid (binaphthyl hydrogen phosphate) as additive.
- The best solvent to perform the reaction is toluene although the reaction also occurs in ethereal solvents (Table 11, entries 8 and 9).
- The temperature is a quite important factor since lower temperature than 60 °C (Table 11, entry 4) gives rise to the product in low yield (Table 11, entry 13) or even no reaction is observed at rt (Table 11, entry 14).
- Both Pd catalyst and *rac*-L1-SOX ligand are mandatory for the reaction to occur (Table 11, entries 15 and 16).
- The chirality of the Brønsted acid was not transferred to the reaction product **187a** since a racemic mixture was obtained (Table 1, entry 17).

## 4. Scope and Limitations

In order to explore the scope and limitations of the reaction we have prepared a variety of arylalkenols with substitution in the aryl ring **186e-p**. Two different general procedures were followed (Scheme 66). The first synthetic strategy starts with the reduction of the corresponding 2-aminobenzoic acid **188** with LAH, followed by protection of the aniline with tosyl chloride to tosylamide **184**. Finally, a last *N*-alkylation step with **185** delivers the desired products **186**.

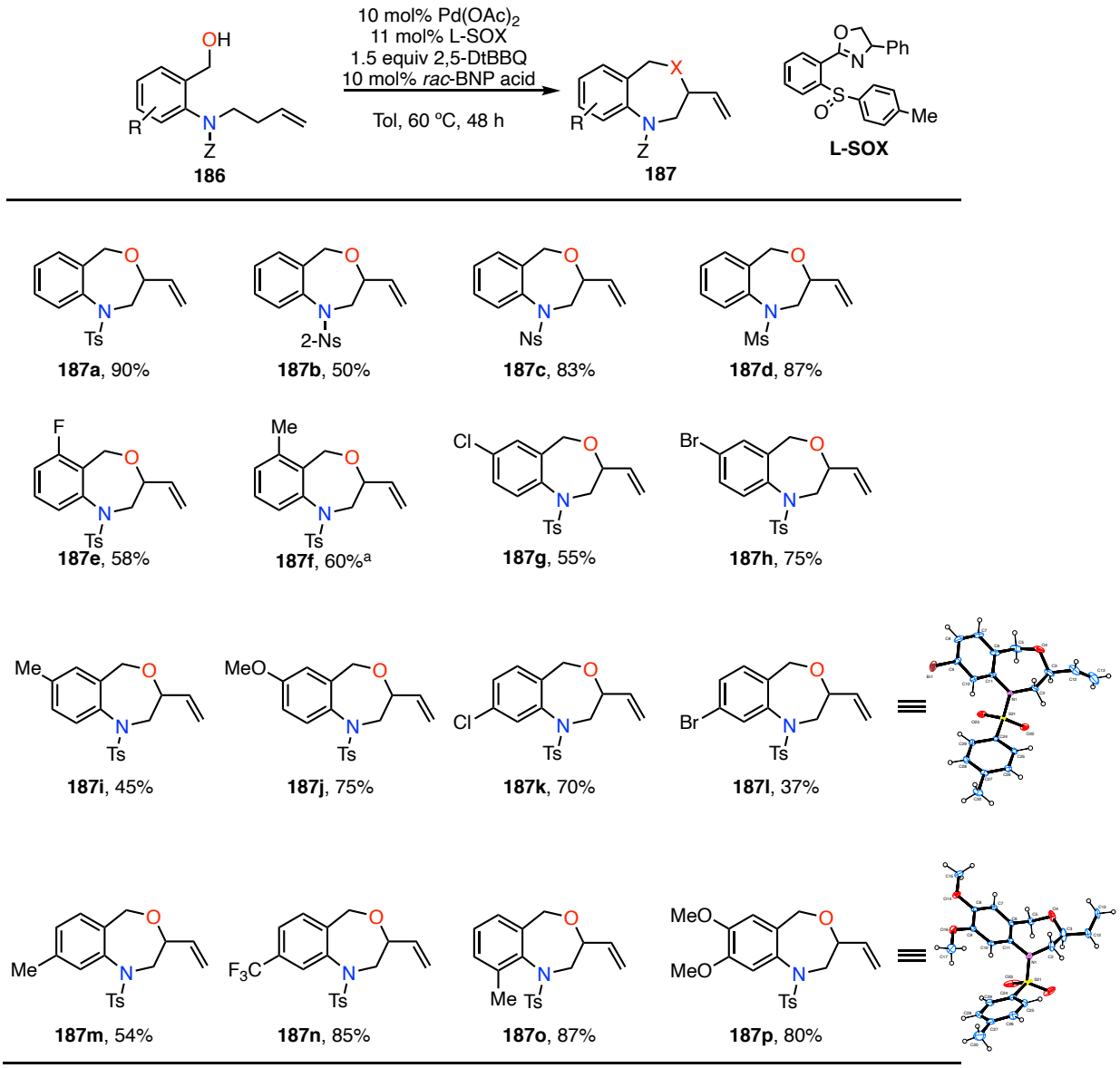
The second synthetic strategy starts with the protection of the corresponding aniline with tosyl chloride. Then, *N*-alkylation of the resulting tosyl amide **148** with **185** followed by a reduction with DIBAL-H gives rise to the desired products **186**.




**Scheme 66.** Synthesis of aryl-substituted arylalkenols **186e-p**

Having established the optimized conditions, we next turned to explore the scope of the reaction (Scheme 67). A variety of sulfonamides as *N*-protecting groups are well tolerated providing the 1,4-BZOs **187a**-**187d** in good to excellent yields. In addition, aryl substituted with EWG ($CF_3$) and EDG (OMe), halides (Cl, Br, F) and alkyl (Me) groups are well tolerated in any position (*ortho-, meta-, para-*) giving the corresponding substituted 1,4-BZOs **187e**-**187p** in moderate to excellent yields

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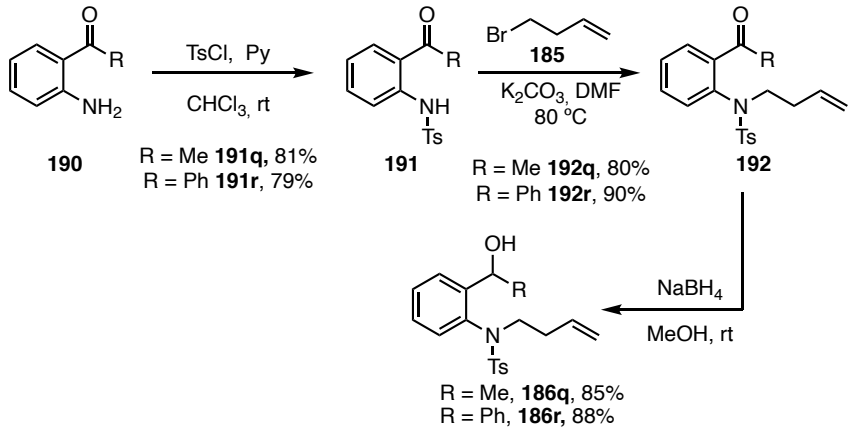



Conditions: 0.1 mmol **186**, 10 mol% $Pd(OAc)_2$, 11 mol% *rac*-BNP acid, 11 mol% L-SOX, toluene (0.15 M), 60 °C, 2 days. a) 15 mol% $Pd(OAc)_2$, 16 mol% *rac*-BNP acid, 16 mol% L-SOX

**Scheme 67.** Scope of the reaction with *N*-sulfonamides and aryl substituted substrates **186a-p**

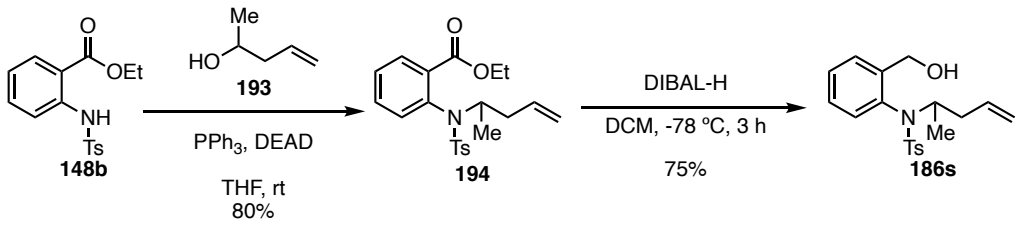
Diastereoselectivity of the reaction was then explored on substituted arylalkenols **186q-s**. The synthesis of the benzylic substituted substrates **186q,r** was carried out following the described literature (Scheme 68).[198] Protection of the starting aniline **190** with tosyl chloride followed by *N*-alkylation provided the desired *N*-tosyl ketones **192**. Then, their reduction with $NaBH_4$ gave rise to the desired benzylic substituted alkenols **186q,r**.

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**Scheme 68.** Synthesis of the benzylic substituted alkenols **186q,r**

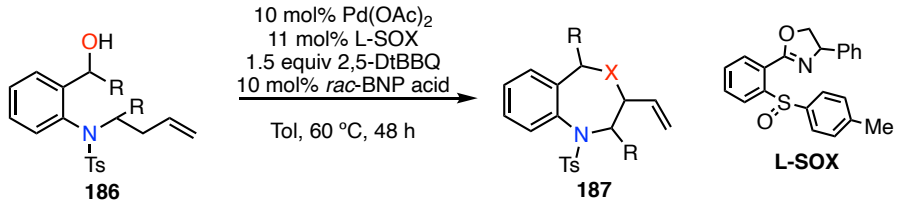
Synthesis of the homoallylic alkenol **186s** starts with a Mitsunobu reaction between tosylamide **148b** and alcohol **193** to provide the ester **194**. Then, a reduction with DIBAL-H gives rise to the desired homolallylic alkenol **186s** (Scheme 69).




**Scheme 69.** Synthesis of olefin **186s**

The secondary benzylic alcohol **186q** bearing a small Me substituent gave rise to the 1,4-BZO **187q** in a 70% yield with a low 2:1 dr. Pleasingly, on changing the nature of the substituent to a Ph group, the diastereoselectivity of the reaction increased to a 10:1 dr but with a moderate 54% yield of the 1,4-BZO **187r**. When the Me substituent is located in the alkyl chain **186s** (homoallylic position) the reaction smoothly proceeds to give **187s** with an 88% yield in a good 5:1 dr (Scheme 70).

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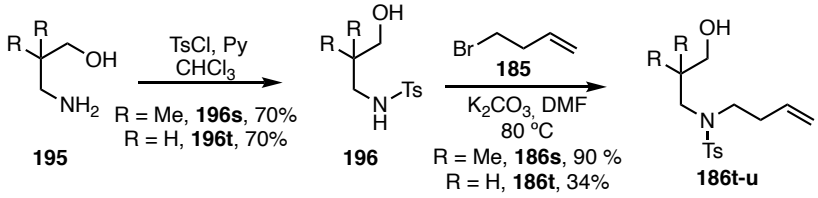



| Entry | Olefin **186** | Product **187** |
|---|---|---|
| 1 | **186q** | **187q**, 70%, d.r. = 2:1 |
| 2 | **186r** | **187r**, 52%, d.r. = 10:1 |
| 3 | **186s** | **187s**, 88% dr: 5:1 |

Conditions: 0.1 mmol **186**, 10 mol% $Pd(OAc)_2$, 11 mol% *rac*-BNP acid, 11 mol% L-SOX, toluene (0.15 M), 60 °C, 2 days

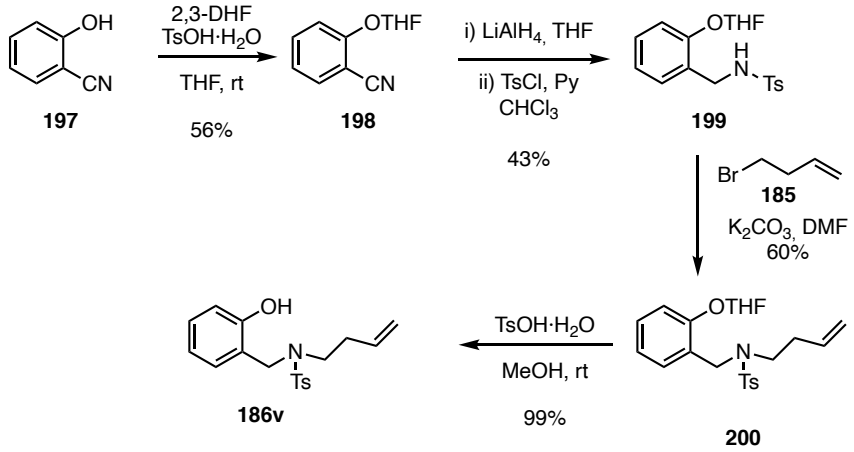
**Scheme 70.** Study of the diastereoselectivity of the cyclization

We then pursued the evaluation of the Thorpe-Ingold[94] effect and the nature of the nucleophile in the course of the cyclization with appropriate substrates. The synthesis of the non-benzofused substrates **186t,u** was carried out following the described literature, which involves a protection of the corresponding amine **195** with tosyl chloride followed by *N*-alkylation with **185** to the corresponding alkenos **186t,u** (Scheme 71).[198]



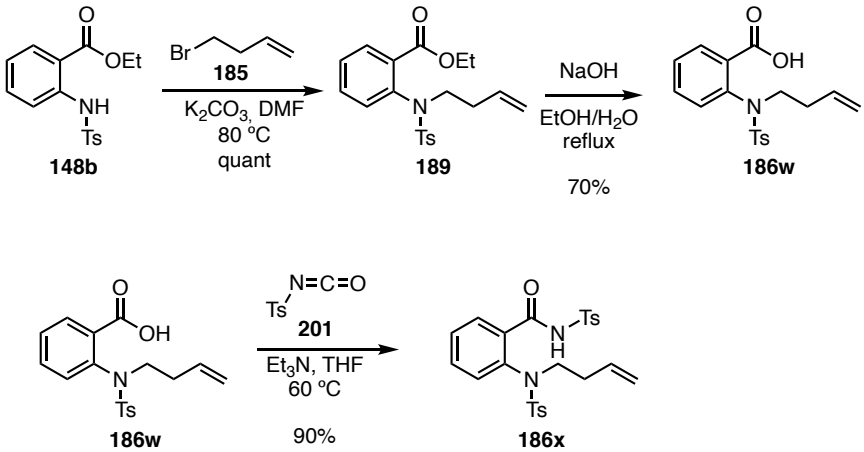

**Scheme 71.** Synthesis of olefins **186t-u**

The synthesis of phenol **186v** was carried out following the procedure described in the literature (Scheme 72).[198] Protection of the 2-hydroxybenzonitrile (**197**) with 2,3-dihydrofuran in acidic media gave rise to the ether derivative **198**. Then, the reduction of the benzonitrile, followed by protection of the resultant benzyl amine gave rise to the tosylamide **199**. Finally, *N*-alkylation step with **185** followed by deprotection of the phenol provides the desired phenol derivative **186v.**




**Scheme 72.** Synthesis of phenol **186v**

Finally, the carboxylic acid **186w** and tosylamide **186x** were synthesized according to published procedures (Scheme 73).[199] Firstly, the *N*-alkylation of **148b** with **185** afforded the ester **189**, which is then hydrolyzed to the carboxylic acid **186w**. Secondly, tosylamide **186x** was obtained upon treatment of carboxylic acid **186w** with tosylisocyanate **201**.



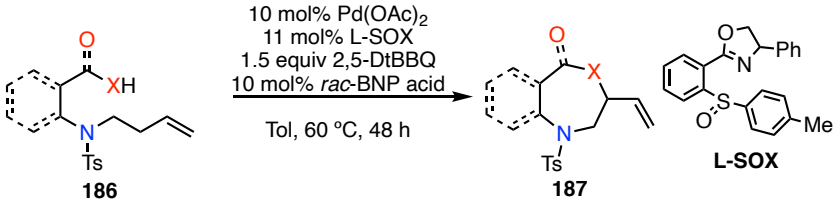

**Scheme 73.** Synthesis of carboxylic acid **186w** and tosyl amide **186x**

Firstly, we examined the Thorpe-Ingold effect in the course of the reaction (Scheme 74). The reaction resulted unaffected on changing the nature of the carbon tether ($C_{sp^3}$ *vs* $C_{sp^2}$) between functionalities. Thus, the cyclization of the neopentyl alcohol derivative **186t** under standard conditions gave the expected dimethyl substituted oxazepane **187t** in 65% yield (entry 1). Moreover, the parent unsubstituted primary alcohol **186u**, with no added beneficial Thorpe-Ingold effect, could be cyclized to the oxazepane **187u** in a very good 72% yield, although a bit more loading of the Pd catalyst was needed (entry 2). Regarding the nature of the nucleophile, phenol **186v** could also be cyclized under standard conditions to give 1,4-BZO **187v** in a reasonable 60% yield (entry 3). Satisfactorily, even the less nucleophilic benzoic acid **186w** could also be transformed into the expected 1,4-benzoxazepinone **187w** in a 75% yield (entry 4). On changing the nature of the

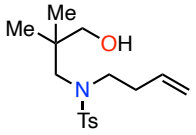
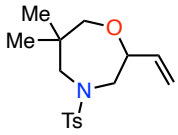
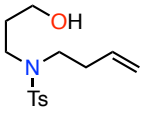
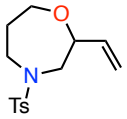
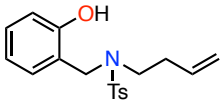
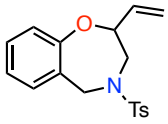
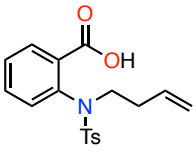
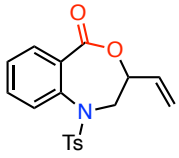
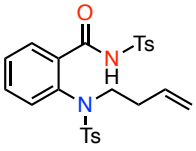
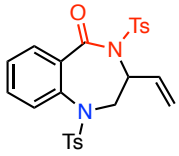
[199] Youn, S. W.; Ko, T. Y.; Kim, Y. H.; Kim, Y. A. *Org. Lett.* **2018**, *20*, 7869.

[94] a) Beesley, R. M.; Ingold, C, K.; Thorpe, J. F. *J. Chem. Soc., Trans.*, **1915**, *107*, 1080. b) Shaw, B. L. *J. Am. Chem. Soc.* **1975**, *97*, 1080.

heteronucleophile **186x**, the cyclization also smoothly occurred to give the desired 1,4-benzodiazepinone **187x** in 55% yield (entry 5).




**186** **187**

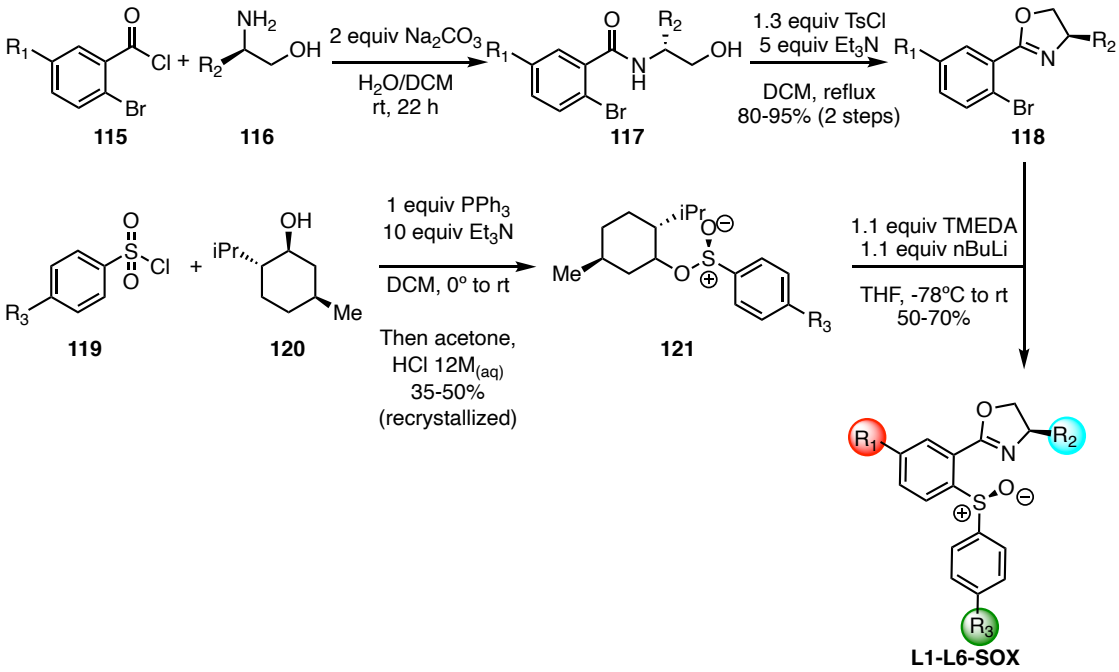
| Entry | Olefin **186** | Product **187** |
|---|---|---|
| 1 |  **186t** |  **187t**, 65% |
| 2 |  **186u** |  **187u**, 72%[a] |
| 3 |  **186v** |  **187v**, 60 % |
| 4 |  **186w** |  **187w**, 75% |
| 5 |  **186x** |  **187x**, 55% |

Conditions: 0.1 mmol **186**, 10 mol% $Pd(OAc)_2$, 11 mol% *rac*-BNP acid, 11 mol% L-SOX, toluene (0.15 M), 60 °C, 48 h. a) 15 mol% $Pd(OAc)_2$, 16 mol% *rac*-BNP acid, 16 mol% L-SOX

**Scheme 74**. Non-benzofused oxazepanes and nucleophile type

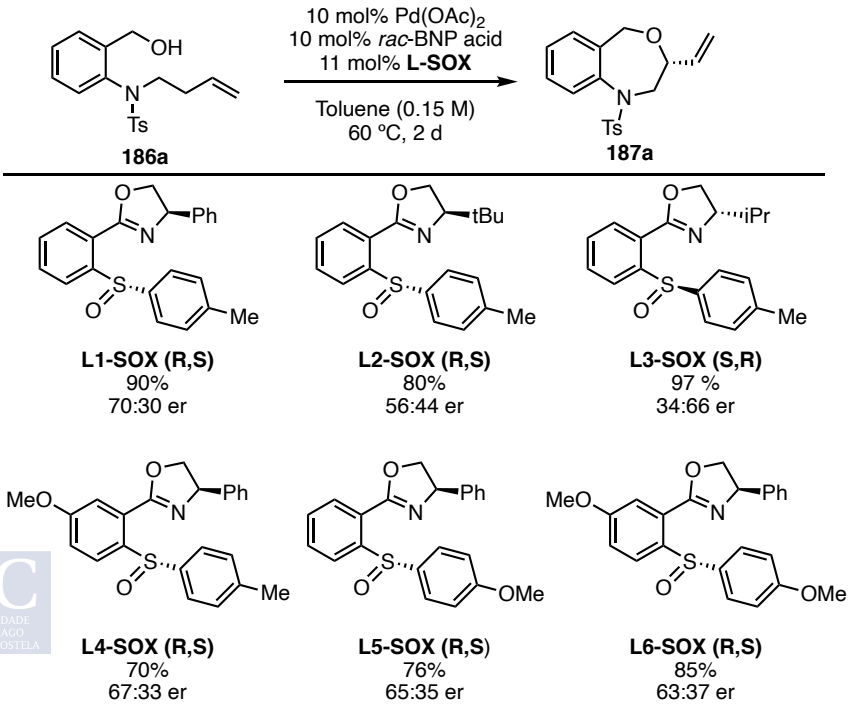
## 5. Pd-Catalyzed Asymmetric Allylic C-H Functionalization

Once checked that the chirality of the Brønsted acid was not transferred to the cyclized product **187a** since a racemic mixture was obtained (Table 11, entry 17), we decided to evaluate the Pd-catalyzed asymmetric allylic C-H functionalization of **186a** with different chiral L-SOX ligands (Scheme 76). For the preparation of chiral **L1-L6-SOX** ligands (Scheme 75), we followed the conditions reported by White and coworkers and previously described in Chapter 2, Scheme 26.




**Scheme 75**. Syntheses of L1-L6 SOX ligands

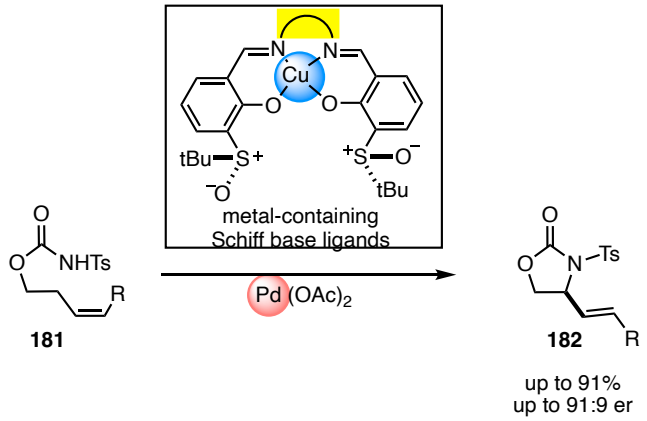
Interestingly, the cyclization of **186a** under standard conditions in the presence of **L1-SOX** ligand gave an excellent 90% yield of **187a** in a promising 70:30 er. Unfortunately, modifications of the size of the substituent in **L2-SOX (R,S)** or **L3-SOX (S,R)** did not improve the enantiomeric ratio. Changes of the electronic richness in the SOX part of the ligand by introducing OMe groups in each of the phenyl rings or in both of them (**L4-L6-SOX**) met with failure, even with lower isolated product yield.



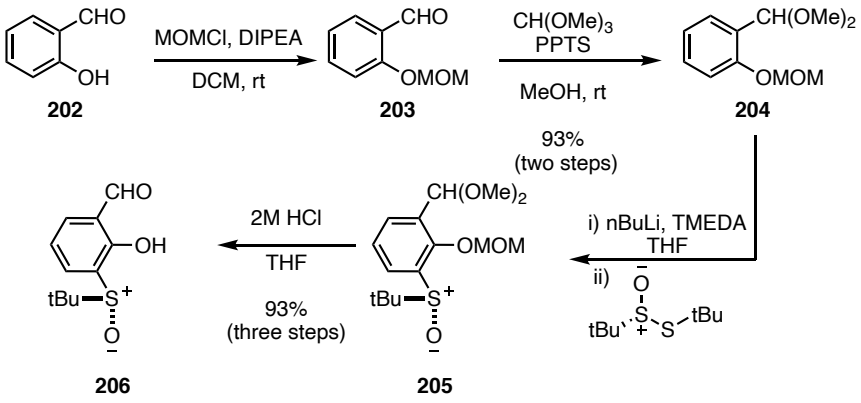

**Scheme 76.** Pd-catalyzed asymmetric allylic C-H functionalization of **186a** with **L1-L6-SOX** ligands

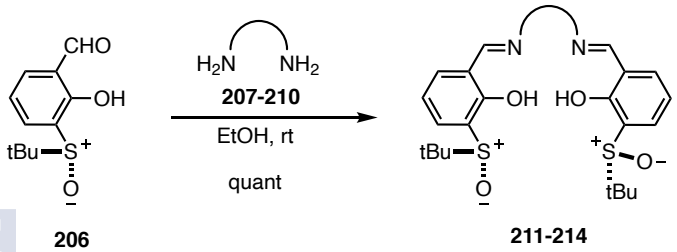
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Due to these unfruitful results with L-SOX ligands, we turned our attention to the Schiff base / sulfoxide ligands developed by Matsunaga for Pd-catalyzed asymmetric intramolecular allylic aminations of internal alkenes (Scheme 77).[197] For an initial evaluation, the four sulfoxide ligands **211-214** were synthesized following the procedures described by Matsunaga (Scheme 78). Protected phenol **204** was obtained after treatment of salicylaldehyde **202** with MOMCl and trimethoxy methane in a 93% overall yield. Then, the MOM assisted *ortho*-lithiation of **204** followed by nucleophilic attack over the chiral sulfinothioate provided aryl sulfoxide **205**, which after hydrolysis and condensation with the corresponding diamines **207-210** gave rise to the chiral sulfoxide ligands **211-214**.




**Scheme 77**. Pd-catalyzed asymmetric allylic C-H amination by Matsunaga

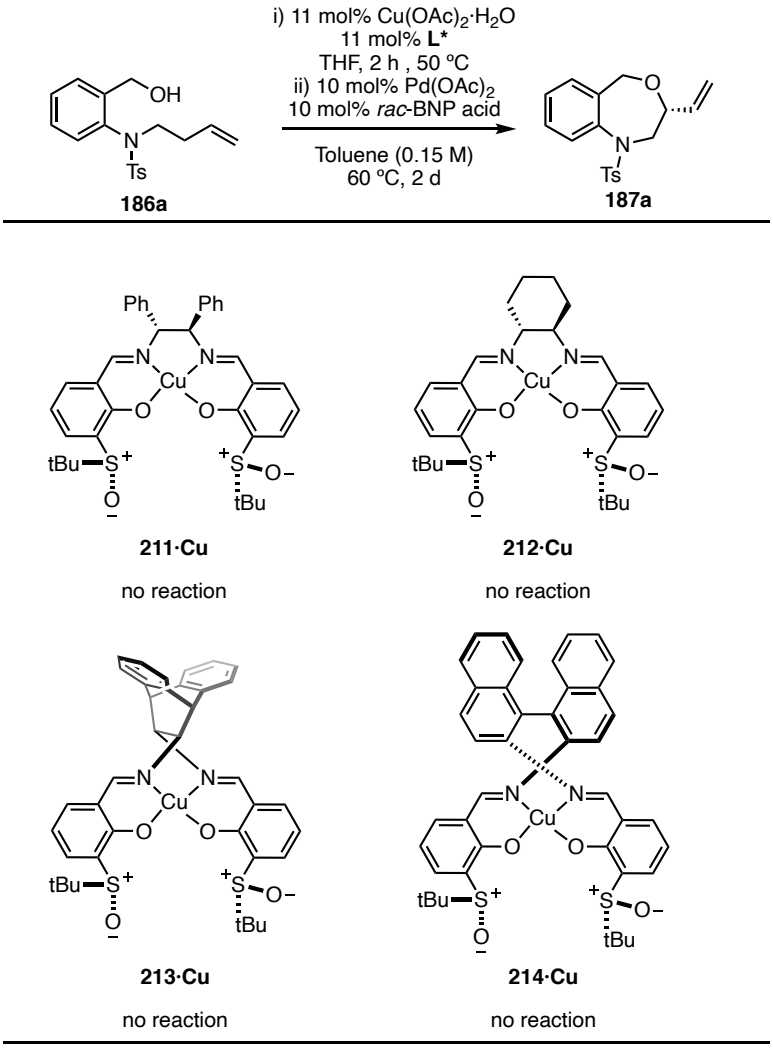



**Scheme 78.** Synthesis of chiral sulfoxide ligands **211-214**

Once prepared the sulfoxide ligands **211-214**, we next explore the cyclization of alkenol **186a**. The chiral ligands (salen) used are Cu(II) salen complexes (**211-214·Cu** complexes), that were formed "*in situ*" by reacting with $Cu(OAc)_2$ in THF at 50 °C. The reactivity of these ligands under typical conditions were explored under air and moisture, and also under

argon. Unfortunately, no reaction was observed with these **211-214·Cu** complexes used as ligands for the Pd catalyst (Scheme 79).




**Scheme 79.** Pd-catalyzed asymmetric allylic C-H functionalization of alkenol **186a** with Matsunaga type ligands

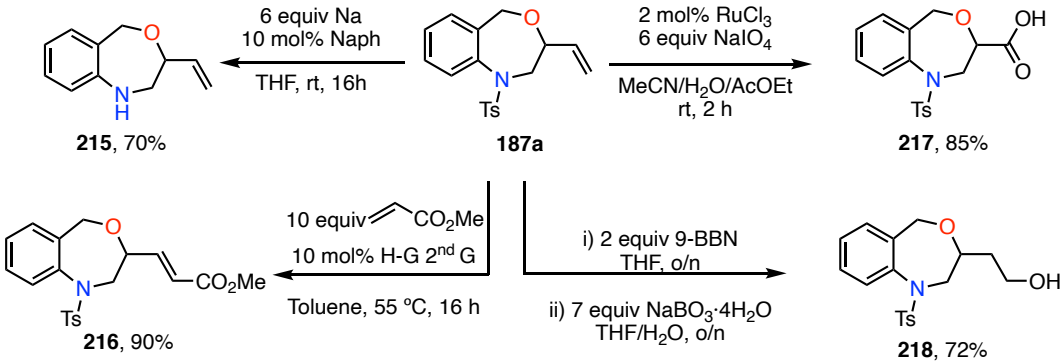
The main conclusions of this Pd-catalyzed asymmetric allylic C-H functionalization are:

- The Pd-catalyzed asymmetric C-H activation occurs when the combination of an oxazoline (a strong N-sp2 ligand) with a labile sulfoxide (L-SOX type ligands) were employed.
- The steric bulkiness of the substituent in the oxazoline part of the L-SOX ligand is crucial to obtain an enantioenriched 1,4-BZO **187a**. Good to excellent yields of **187a** are obtained with promising enantiomeric ratios when R = Ph. Unfortunately, electronic variations in the SOX part of the ligand did not positively affect the enantiomeric ratio of the reaction.
- The Matsunaga type ligands did not show reactivity in the Pd-catalyzed cyclization of **186a**. Most probably, the lack of a strong coordinating atom to Pd is the main reason for the failures.

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## 6. Derivatizations of 1,4-Benzoxazepine 187a

Derivatizations of 1,4-BZO **187a** were then analyzed (Scheme 80). The protecting tosyl group can be removed under mild conditions (Na/naphthalene) to afford the aniline **215** in 70% yield. The alkene of **187a** participates in a Hoveyda-Grubbs 2nd G-catalyzed cross-metathesis with methyl acrylate to provide the ester **216** in an excellent 90% yield. Interestingly, a Ru-catalyzed oxidative cleavage of the alkene affords the carboxylic acid **217** in an excellent 85% yield. Finally, hydroboration of the alkene followed by oxidation with $NaBO_3$ provides the primary alcohol **218** in a 72% yield in two steps.

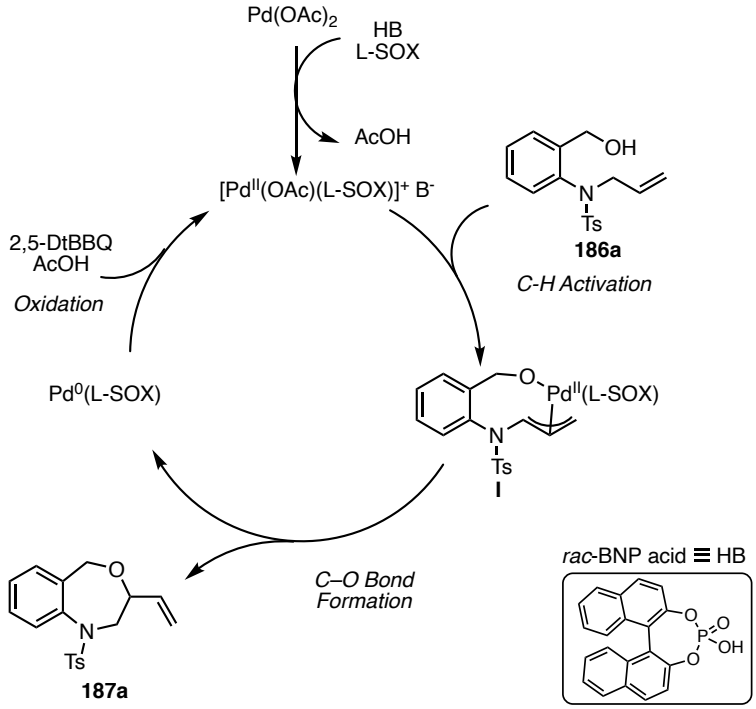



**Scheme 80.** Derivatizations of 1,4-BZO **187a**

## 7. Proposed Mechanism for the Pd-Catalyzed Allylic C-H Activation

The following catalytic cycle is proposed for the Pd-catalyzed allylic C-H activation (Scheme 81). Initially, the active cationic Pd species is preformed upon combination of $Pd(OAc)_2$ with the L-SOX ligand and the Brønsted acid. Alkenol **186a** coordinates to the Pd which subsequently undergoes an allylic C-H activation to generate the Pd-π-allyl intermediate **I**. Then, this Pd(II) complex evolves via reductive elimination to the desired 1,4-BZO **187a** with release of the Pd(0) species. The active Pd(II) catalyst is recovered after oxidation of Pd(0) with the combination of 2,5-DtBBQ and AcOH

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**Scheme 81**. Proposed Mechanism for the Pd-Catalyzed Allylic C-H Activation of **186a**

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## 8. Conclusions[200]

- An efficient and ecofriendly, atom- and step-economy strategy to afford 1,4-benzoxazepines **187** based on Pd-catalyzed allylic C-H functionalization of alkenols **186** has been developed.
- Diastereoselectivity of the reaction ranged from low to good when the benzylic position of the alkenol **186** was substituted with Me or Ph substituents. In addition, a good diastereoselectivity was also observed when the homoallylic position of **186** was substituted with a Me group.
- Interestingly, the cyclization was not dramatically affected by the Thorpe-Ingold effect of the substrates and tolerates a range of heteronucleophiles. Non-benzofused alkenols and phenol, carboxylic acid and tosyl amide groups efficiently undergo the Pd-catalyzed allylic C-H functionalization.
- Asymmetric Pd-catalyzed allylic C-H activation was analyzed using two different families of chiral ligands, L-SOX and Matsunaga ligands. While a promising enantioselective Pd-catalyzed allylic C-H activation of 1,4-BZO **187a** was observed with L1-SOX ligand, no reaction with Matsunaga ligands was observed.
- Derivatization of the alkene unit of 1,4-BZO **187a** allows an easy entry to a variety of compounds in good to excellent yields, which highlights the methodology developed.

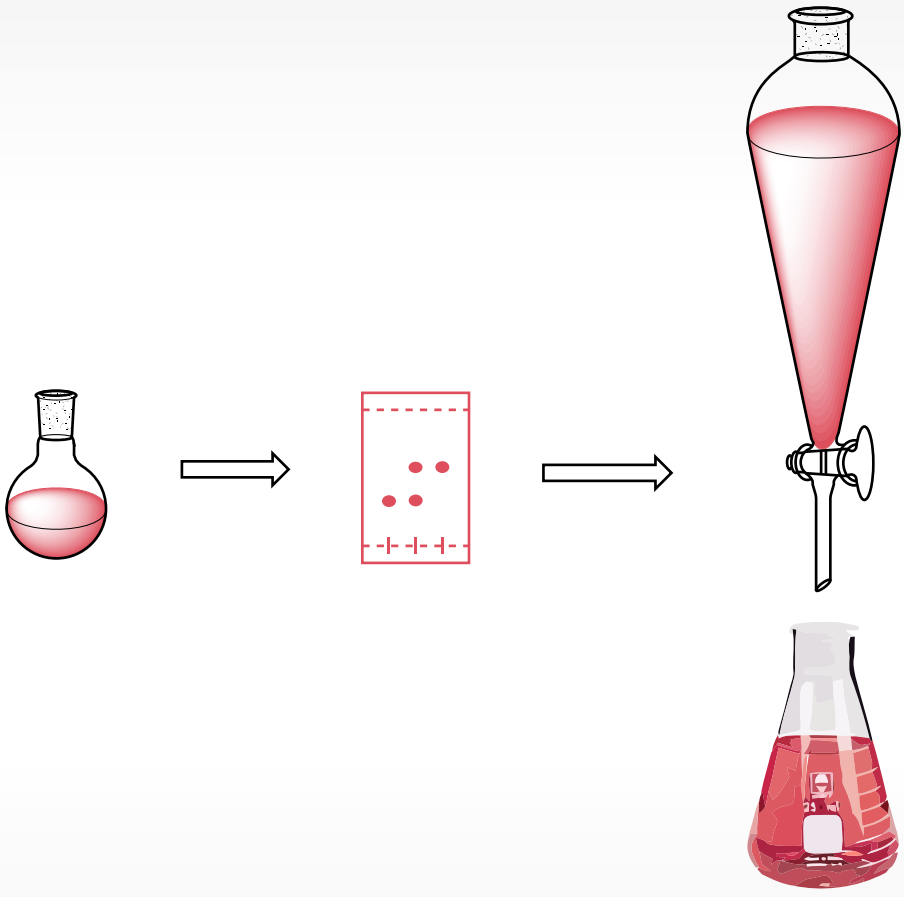
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[200] Velasco-Rubio, Á.; Varela, J.A.; Saá, C. *Chem. Commun.* **2021** *57*, 10915-10918.

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# Chapter 5

## Experimental Section



In this chapter it is recorded the general procedures for the preparation of starting materials and final products. NMR spectra, HPLC spectra, X-ray crystallographic structures and computational details are also included.

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# Chapter 5
## Experimental Section

### 1. General Experimental Procedures

All reactions were performed under an inert atmosphere of argon and with anhydrous solvents in glassware oven or flame dried at 80 ºC unless otherwise stated. All chemicals were purchased from Acros Organics Ltd., Aldrich Chemical Co. Ltd., Alfa Aesar, Strem Chemicals Inc., Fluorochem Ltd. or TCI Europe N.V. chemical companies and used without further purification, unless otherwise stated. Analytical thin layer chromatography was carried out on silica-coated aluminium plates (silica gel 60 $F_{254}$ Merck) or on aluminium sheets (aluminium oxide 60 $F_{254}$ neutral Merck) using UV light as visualizing agent (254 nm) and $KMnO_4$ (solution of 1.5 g of potassium permanganate, 10 g of potassium bicarbonate and 1.25 mL of 10% sodium hydroxide in 200 mL of water) with heat as developing agents. Flash column chromatography was performed on silica gel 60 (Merck, 230-400 mesh) with the indicated eluent. All other reagents and solvents: acetonitrile, dichloromethane, dichloroethane, tetrahydrofuran, toluene and methanol were used dry, unless otherwise indicated.

Reactions at 0 °C were performed by using an ice/water bath. Reactions between -30 and -52 °C were conducted by using an immersion cooler (Neslab Cryocool CC-100) in an acetone bath. Reactions at -78 °C were carried out with a dry ice/acetone bath.

Enantiomeric ratios (er) were determined on an Agilent HPLC 1100 Series or on a Jasco SFC 4000 series using commercially available chiral columns. Diastereomeric ratio was determined in the $^1$H NMR of the crude mixture.

$^1$H-NMR, $^{13}$C-NMR, DEPT and $^{19}$F-NMR experiments were carried out using a Varian Inova 500, Varian Inova 400 MHz or Varian Mercury 300 MHz. All NMR experiments were recorded at 298 K otherwise stated. All chemical shifts are reported in parts per million (ppm) and referenced to residual solvent peaks. Coupling constants *J* are given in Hertz (Hz). Multiplicities are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet or as a combination of them.

Mass spectrometry analysis was carried out using a Micromass Autospec, a TRACE MS or a HP-5988-A with chemical ionization and a Bruker Microtof APCI using chemical ionization spectrometers at CACTUS Facility (Universidade de Santiago de Compostela).

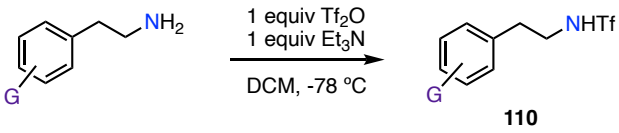
X-ray crystallographic analysis was performed at the CACTUS facility of the Universidade de Santiago de Compostela.

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# 2. Experimental Procedures for Chapter 2

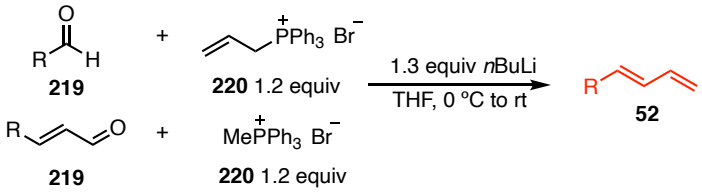
## 2.1. General Procedure to Synthesize Phenethyltriflamides (110a-110h) [97, 201]




**110**

To a solution of the corresponding phenethylamine (1 equiv) in dichloromethane (0.5M) was added triethylamine (1 equiv) at -78 °C under argon atmosphere. After stirring for 5 min at -78 °C, trifluoromethanesulfonic anhydride (1 equiv) was added dropwise and the mixture was stirred at that temperature. The solution was quenched by ice water (20 mL) when the starting material disappeared (judged by TLC). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combination of organic layers was washed with brine (50 mL), and then dried over $Na_2SO_4$. Evaporation and column chromatography on silica gel, typically using ethyl acetate/ hexanes (10:90 to 30:70), afforded corresponding trifluoromethanesulfonamide **110** as an amorphous white solid.

## 2.2. General Procedure to Synthesize 1,3-Dienes 52[202]




To a stirred suspension of the corresponding Wittig reagent **220** (1.2 equiv) in THF (0.3 M) at 0 °C was added nBuLi (1.3 equiv) dropwise. After stirring for 30 min at that temperature, a solution of the corresponding aldehyde **219** (1 equiv) in THF (1 M) was added and the reaction was allowed to warm up to rt. The reaction was quenched by ice water (50 mL) when the aldehyde disappeared (judged by TLC). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 50 mL). The combination of organic layers was washed with a saturated solution of $NH_4Cl$(aq), dried over $Na_2SO_4$ and evaporated in

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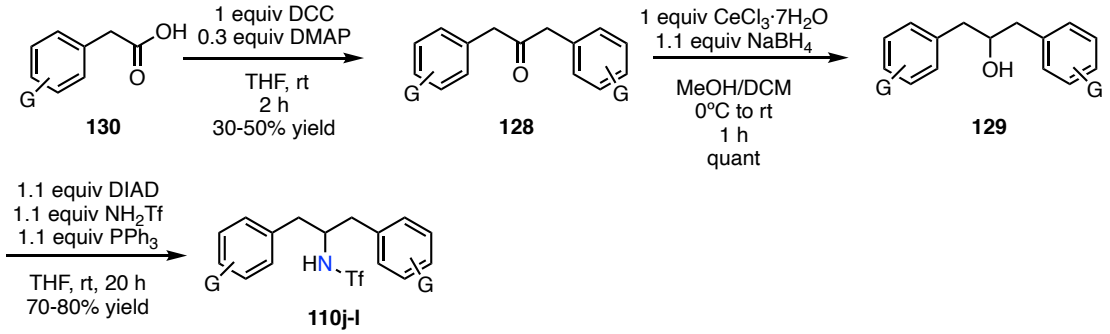
[201] a) Ma, R.; White, M.C. *J. Am. Chem. Soc.* **2018**, *140*, 3202; b) Norsikian, S.; Bereta, M.; Canillo, A.; Auvray, M.; Martin, A.; Retailleau, P.; Iorga, B.I.; Beau, J.-M. *Eur. J. Org. Chem.* **2017**, 1940.

[202] a) Madden, K. S.; David, S.; Knowles, J. P.; Whiting, A. *Chem. Commun.* **2015**, *51*, 11409; b) Brun, E.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2016**, *81*, 8206; c) Landesberg, J. M.; Slam, M. A.; Mandel, M. *J. Org. Chem.* **1981**, *46*, 5025; d) Zhang, M.; Watanabe, K.; Tsukamoto, M.; Shibuya, R.;Morimoto, H.; Ohshima, T. *Chem. Eur. J.* **2015**, *21*, 3937; e) Bernardi, L.; López-Cantarero, J.; Niess, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5772; f) Barluenga, S.; Moulin, E.; López, P.; Winssinger, N. *Chem. Eur. J.* **2005**, *11*, 4935.

[97] Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.

vacuo. A column chromatography on silica gel using hexanes as eluent afforded the corresponding 1,3-dienes **52** as oils.

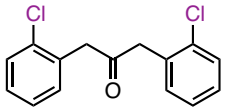
## 2.3. General Procedure to Synthesize Phenethyltriflamides 110i-110l




### 2.3.1. Synthesis of Dibenzylketones 128

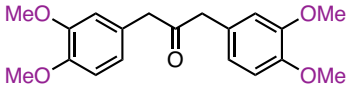
The corresponding phenylacetic acid **130** (1 equiv) was added to a stirred solution of DCC (1 equiv) and DMAP (0.3 equiv) in THF (0.28 M) under argon atmosphere at room temperature. The reaction was stirred for 1 h. Then the reaction was filtered through a Celite® plug and washed with $Et_2O$. After evaporation of volatiles under vacuum. The crude was purified by column chromatography on Silica gel using as eluent a mixture of Hexanes/AcOEt to give the ketone **128** as an amorphous white solid.

**1,3-bis(2-chlorophenyl)propan-2-one (128j)**



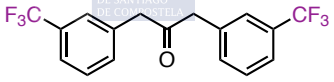
Purified by column chromatography Hexane:AcOEt (9:1) to give the product as white solid (1.4g, 35% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.33 (m, 1H), 7.27 – 7.16 (m, 3H), 3.93 (s, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 203.1, 134.5, 132.6, 131.8, 129.5, 128.7, 127.0, 47.2. **HRMS(APCI)** m/z: $[M+H]^+$ Calc'd for $C_{15}H_{12}Cl_2O$ 278.0265; found 278.0265.

**1,3-bis(3,4-dimethoxyphenyl)propan-2-one (128k)**



Purified by column chromatography Hexane:AcOEt (3:2). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.80 (d, $J$ = 8.1 Hz, 1H), 6.68 (dd, $J$ = 8.1, 2.1 Hz, 1H), 6.61 (d, $J$ = 2.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.64 (s, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 206.4, 149.1, 148.2, 126.5, 121.7, 112.6, 111.4, 55.9, 55.8, 48.5. **HRMS(APCI)** m/z: $[M+H]^+$ Calc'd for $C_{19}H_{22}O_5$ 330.1467; found 330.1470.

**1,3-bis(3-(trifluoromethyl)phenyl)propan-2-one (128l)**



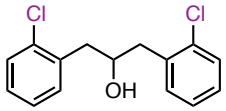
Purified by column chromatography Hexane:AcOEt (9:1). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.54 (d, $J$ = 7.8 Hz, 1H), 7.49 – 7.32 (m, 3H), 3.83 (s, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 203.5, 134.4, 132.9, 131.1 (q, $J_{CF}$= 32Hz), 129.2, 126.2 (d, $J_{CF}$= 3.8Hz), 125.7, 124.1 (d, $J_{CF}$=

3.8Hz),122.1, 48.9. **$^{19}$F NMR** (282 MHz, $CDCl_3$) -62.8. **HRMS(APCI)** m/z: $[M+H]^+$ Calc'd for $C_{17}H_{12}F_6O$ 346.0792; found 346.0789.

## 2.3.2. Reduction of Dibenzylketones 128 to Dibenzylalcohols 129

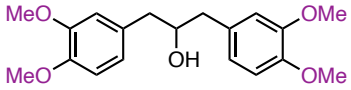
To a solution of the corresponding dibenzylketone **128** (1 equiv) and $CeCl_3{\cdot}7H_2O$ (1 equiv) in MeOH/DCM (9:1) (0.3 M) at 0 °C, $NaBH_4$ (145 mg, 3.85 mmol, 1.1 equiv) was added portion-wise. The reaction was stirred 1 h at room temperature. The reaction was washed with water (2 x 30 mL), brine (1 x 30 mL) and the organic layer was dried over $Na_2SO_4$. The desired product **129** was isolated as colorless oil or white solid and it was used in the next without further purification.

**1,3-bis(2-chlorophenyl)propan-2-ol (129j)**



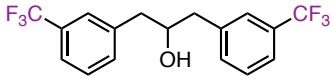

Isolated as colorless oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 4H), 7.19 (tt, $J$ = 7.3, 5.3 Hz, 4H), 4.27 (tt, $J$ = 8.1, 4.0 Hz, 1H), 3.10 (dd, $J$ = 13.7, 4.2 Hz, 2H), 2.89 (dd, $J$ = 13.7, 8.5 Hz, 2H), 1.66 (d, $J$ = 3.6 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 136.3, 134.4, 131.8, 129.6, 128.0, 126.7, 70.6, 41.2. **HRMS(APCI)** m/z: $[M\text{-}OH]^+$ Calc'd for $C_{15}H_{13}Cl_2$ 263.0394; found 263.0395.

**1,3-bis(3,4-dimethoxyphenyl)propan-2-ol (129k)**




Isolated as colorless oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.86 – 6.70 (m, 6H), 3.97 (tq, $J$ = 8.1, 4.5 Hz, 1H), 3.84 (d, $J$ = 3.1 Hz, 12H), 2.79 (dd, $J$ = 13.7, 4.5 Hz, 2H), 2.66 (dd, $J$ = 13.8, 8.1 Hz, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 148.9, 147.7, 131.0, 121.4, 112. 7, 111.4, 73.6, 55.9, 55.9, 42.9. **HRMS(APCI)** m/z: $[M\text{-}OH]^+$ Calc'd for $C_{19}H_{23}O_4$ 315.1596; found 315.1600.

**1,3-bis(3-(trifluoromethyl)phenyl)propan-2-ol (129l)**

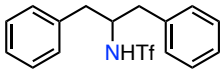



Isolated as colorless oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.51 (d, $J$ = 5.9 Hz, 4H), 7.46 – 7.39 (m, 4H), 4.10 (dd, $J$ = 8.5, 4.4 Hz, 1H), 3.03 – 2.67 (m, 4H), 1.57 (d, $J$ = 3.7 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 139.2, 132.9, 130.8 (q, $J_{CF}$ =32Hz), 128.9, 126.1, 126.1, 126.0, 123.5, 123.4, 122.4, 72.9, 43.2. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -62.9. **HRMS(APCI)** m/z: $[M\text{-}OH]^+$ Calc'd for $C_{17}H_{13}F_6$ 331.0921; found 331.0927.

## 2.3.3. Mitsunobu Reaction

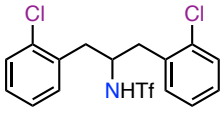
Triphenylphosphine (1.1 equiv), trifluoromethanesulfonamide (1.1 equiv) and a solution of DIAD (40 % wt in toluene) (1.3 equiv) were added to a solution of the corresponding dibenzylalcohol **129** (1 equiv) obtained in the previous step without further purification (1 equiv) in THF (0.1 M) at 0 °C were added. The reaction mixture was then stirred for 20 h at room temperature. The volatiles were removed and the triphenylphosphine oxide precipitated by addition of a 1:1 mixture of $Et_2O$/Hexanes (40 mL). The precipitate was filtered through a plug of Celite® and the volatiles were evaporated under reduced pressure to afford a crude residue which was purified by column chromatography in silica gel to give the product **110** as an amorphous white solid.

***N*-(1,3-diphenylpropan-2-yl)-1,1,1-trifluoromethanesulfonamide (110i)**



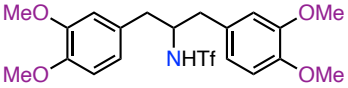

Purified by column chromatography in Hexanes:Acetone (9:1) to give the product as a white solid (70% yield). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.36 (dd, $J$ = 8.1, 6.7 Hz, 4H), 7.32 – 7.27 (m, 2H), 7.23 – 7.16 (m, 4H), 4.71 (d, $J$ = 9.1 Hz, 1H), 4.08 (dp, $J$ = 9.0, 6.4 Hz, 1H), 2.93 (dd, $J$ = 13.9, 6.5 Hz, 2H), 2.82 (dd, $J$ = 14.0, 6.4 Hz, 2H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 136.0, 129.6, 129.4, 128.9, 128.6, 127.3, 126.6, 119.27(q, $J_{CF}$= 320.9 Hz, C), 58.3, 43.4, 41.0. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -78.4. **HRMS(APCI)** m/z: $[M+H]^+$ Calc'd for $C_{16}H_{17}F_3NO_2S$ 344.0932; found 344.0934.

***N*-(1,3-bis(2-chlorophenyl)propan-2-yl)-1,1,1-trifluoromethanesulfonamide (110j)**



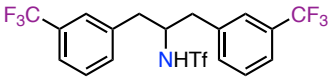

Purified by column chromatography in Hexanes/AcOEt (9:1) to give the product **1i** as an amorphous white solid (70% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 2H), 7.26 – 7.19 (m, 5H), 5.05 (d, $J$ = 9.2 Hz, 1H), 4.22 (dtd, $J$ = 14.6, 8.7, 6.0 Hz, 1H), 3.19 – 2.95 (m, 4H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 134.4, 134.3, 131.8, 129.8, 128.8, 127.1, 119.0 (q, $J_{CF}$= 322 Hz, C), 57.5, 39.6. **$^{19}$F NMR** (282 MHz, $CDCl_3$) 78.7. **HRMS(APCI)** m/z: $[M+H]^+$ Calc'd for $C_{16}H_{15}Cl_2F_3NO_2S$ 412.0153; found 412.0150.

***N*-(1,3-bis(3,4-dimethoxyphenyl)propan-2-yl)-1,1,1-trifluoromethanesulfonamide (110k)**



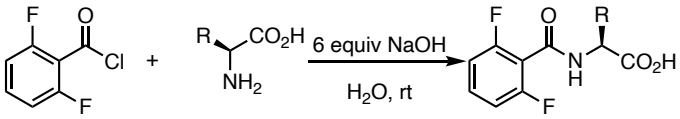

Purified by column chromatography in Hexanes/AcOEt (3:2) to give the product **1j** as an amorphous white solid (80% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.82 (d, $J$ = 8.1 Hz, 1H), 6.78 – 6.61 (m, 2H), 3.98 (dq, $J$ = 13.2, 6.4 Hz, 1H), 3.85 (s, 5H), 2.91 – 2.67 (m, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 149.1, 128.5, 121.8, 119.3 (q, $J_{CF}$= 320 Hz, C) 111.5, 58.4, 55.9, 40.6. **$^{19}$F NMR** (282 MHz, $CDCl_3$) -78.4. **HRMS(APCI)** m/z: $[M+H]^+$ Calc'd for $C_{20}H_{25}F_3NO_6S$ 463.1355; found 464.1360.

***N*-(1,3-bis(3-(trifluoromethyl)phenyl)propan-2-yl)-1,1,1-trifluoromethanesulfonamide (110l)**




Purified by column chromatography in Hexanes:Acetone (9:1) to give the product as a yellow oil (60% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.57 (d, $J$ = 7.7 Hz, 2H), 7.53 – 7.33 (m, 6H), 5.29 (d, $J$ = 6.0 Hz, 1H), 4.03 (q, $J$ = 6.3 Hz, 1H), 3.06 – 2.84 (m, 4H).**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 136.9, 132.8, 131.2 (q, $J$ = 32.3 Hz), 129.4, 126.2 (q, $J$ = 3.5 Hz), 125.8, 124.3 (q, $J$ = 3.5 Hz), 122.2, 119.0 (q, $J_{CF}$= 324 Hz, C), 58.7, 41.4. **$^{19}$F NMR** (282 MHz, $CDCl_3$) -63.3, -78.7. **HRMS(APCI)** m/z: $[M+H]^+$ Calc'd for $C_{18}H_{14}F_9NO_2S$ 480.0680 for ($C_{18}H_{15}F_9NO_2S$), found ($M^+$ + 1): 480.0682.

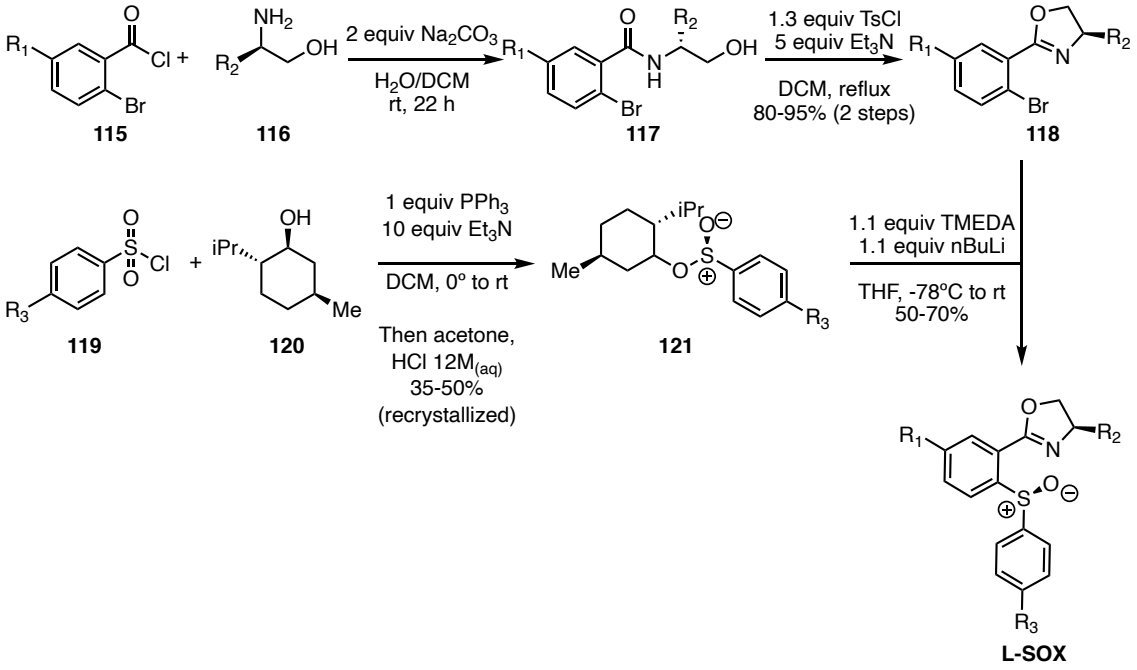
## 2.4. General Procedure to Synthesize MPAAs L1-L2[117]




The corresponding aminoacid **114** (1 equiv) was added to a stirred solution of NaOH (6 equiv) in $H_2O$ (0.7 M) in an ice-water bath. After 10 min stirring at that temperature, **113** (0.96 equiv) was added by syringe pump over 1 h. Once the reaction was finished, the

resulting crude was acidified (pH = 3) with $HCl_c$, and the resulting solution was cooled in an ice-water bath until a white precipitate appeared. Then, the precipitate was filtered and washed with abundant cold water (≈5 ºC). After evaporation of the solvent, a white solid was obtained in almost quantitative yield, and it was used in catalytic reactions without further purification. *NOTE*: $^1$H NMR signals matched previous reported.

## 2.5. Synthesis of L-Sox Ligands[119]




### 2.5.1. Synthesis of Amide 117

Following the procedure described by Stoltz and coworkers.[203] The appropriate amino alcohol **116** (10 mmol, 1.0 equiv) was dissolved in DCM (33 mL). A solution of $Na_2CO_3$ (30 mmol, 3 equiv) in water (25 mL) was added. To the vigorously stirring biphasic mixture was added the corresponding benzoyl chloride **115** (11.5 mmol, 1.15 equiv) dropwise. The reaction was stirred vigorously for 12 hours at room temperature, after which the layers were separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were treated with KOH (6 mL, 1M methanolic solution) for 15 minutes. The solution was neutralized with 2M HCl, and water (20 mL) was added. The layers were separated, and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The desired amide **117** was used in the next step without further purification. *NOTE*: $^1$H NMR signals matched with previous reported.

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### 2.5.2. Synthesis of Oxazoline 118

[203] Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004,** *126*, 15044-15045.
[117] Plata, R. E.; Hill, D. E.; Haines, B. E.; Musaev, D. G.; Chu, L.; Hickey, D. P.; Sigman, M. S.; Yu, J.-Q.; Blackmond, D. G. *J. Am. Chem. Soc.* **2017**, *139*, 9238.
[119] Liu, W.; Ali, S. Z.; Ammann, S. E.; White, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 10658.

Following the procedure described by Stoltz and coworkers.[203] To a solution of the amide **117** obtained in the previous step, in $CH_2Cl_2$ (30 mL) was added tosyl chloride (13 mmol, 1.3 equiv) and $Et_3N$ (50 mmol, 5 equiv). The reaction was refluxed at 55 °C for 22 hours. Afterwards, $H_2O$ (10 mL) was added, and the reaction was refluxed for 2 hours. The reaction was cooled, and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified via column chromatography on silica gel using as eluent acetone/Hexane (0 to 10%) to afford the desired oxazoline **118**. *NOTE*: $^1$H NMR signals matched with previous reported.

### 2.5.3. Synthesis of Andersen Sulfinates 121

Following the procedure described by Trost and coworkers. [204] A round-bottom flask equipped with magnetic stir bar was charged with the corresponding menthol **120** (1.0 equiv.) and tosyl chloride **119** (1.0 equiv.). DCM (0.2 M) and $Et_3N$ (10.0 equiv.) were added, and the resulting solution was cooled to 0 ℃. Triphenylphosphine (1.0 equiv.) was slowly added portionwise at 0 ℃. The reaction mixture was allowed to warm to room temperature over 4 h. After this time, the reaction mixture was concentrated in vacuo, and the resulting crude was purified by silica gel chromatography. The resulting white solid was then recrystallized from hot acetone with a drop of 12 M HCl, affording a 40% of the desired Andersen Sulfinate **121** as colorless needles. *NOTE*: $^1$H NMR signals and [α] matched with previous reported.

### 2.5.4. Synthesis of L-SOX Ligands

Following the procedure described by White and coworkers.[115] To an oven-dried round-bottom flask equipped with a magnetic stir bar, the corresponding oxazoline (5.0 mmol, 1.0 equiv), THF (25 ml, 0.2 M), and TMEDA (5.5 mmol, 1.1 equiv) were added. The reaction flask was cooled to -78 °C and n-butyllithium (1.6 M in hexane, 5.5 mmol, 1.1 equiv) was added dropwise. The reaction was stirred 20 minutes at -78 °C. Subsequently, the corresponding Andersen sulfinate (6.0 mmol, 1.2 equiv) was added as a solution in THF (12 ml, 0.5 M) dropwise. The reaction was stirred 1 hour at -78 °C, then 1 hour at 0 °C, then 1 hour at room temperature. The reaction was quenched with water. The mixture was diluted with diethyl ether, and the layers were separated. The aqueous layer was extracted with diethyl ether (20 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel in a mixture of acetone/hexanes (0 to 15%) to afford the **L-SOX** as a white solid or yellowish gum (recrystallized in toluene). *NOTE*: $^1$H NMR signals and [α] matched with previous reported.

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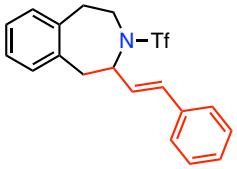
[204] Trost, B. M.; Rao, M.; Dieskau, A. P., *J. Am. Chem. Soc.* **2013,** *135*, 18697

[115] Ammann, S. E.; Liu, W.; White, M. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 9571.

## 2.6. General Procedure for Pd-Catalyzed Heteroannulation of Phenethyltriflamides 110a-110h with 1,3-Dienes 52

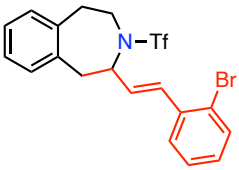
A 5 mL sealed tube equipped with a magnetic stir bar was charged with **110** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol, 0.5 equiv), **52** (0.4 mmol, 2 equiv), $Et_3N$ (3 µl ,0.02 mmol, 0.1 equiv), DMF (0.1 mL) and MeCN (0.4 mL). The solution was saturated in oxygen with stirring for 10 min and the reaction was heated at 105 °C in an oil bath for 24 h. The reaction mixture was quenched with a saturated solution of $NH_4Cl_{(aq)}$ and extracted with AcOEt (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated *in vacuo*. The product was purified by silica gel column chromatography using Hexanes/AcOEt as eluent to afford **111**.

**(*E*)-2-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111aa)**



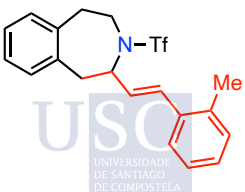

Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent, isolated as a pale-yellow oil in 95% yield (75 mg, 0.195 mmol). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.28 (d, $J$ = 6.5 Hz, 2H), 7.22 (d, $J$ = 4.7 Hz, 5H), 7.18 – 7.11 (m, 2H), 6.61 (d, $J$ = 16.0 Hz, 1H), 5.91 (dd, $J$ = 16.0, 6.7 Hz, 1H), 5.06 (s, 1H), 4.11 (d, $J$ = 11.0 Hz, 1H), 3.43 (dd, $J$ = 15.0, 2.9 Hz, 1H), 3.40 – 3.33 (m, 1H), 3.23 – 3.14 (m, 1H), 3.09 (dd, $J$ = 15.0, 6.3 Hz, 1H), 2.96 (dd, $J$ = 19.6, 6.3 Hz, 1H). **$^{13}$C NMR** (75 MHz $CDCl_3$) δ 139.3, 136.2, 135.9, 134.4, 133.3, 130.9, 129.6, 128.9, 128.8, 128.6, 128.3, 127.5, 127.2, 126.16, 124.7, 119.8 (q, $J_{CF}$ = 322.5 Hz, C), 58.2, 43.8, 32.3. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.8. **HRMS (APCI)** m/z: $[M+H]^+$ Calc'd for $C_{19}H_{19}F_3NO_2S$ 382.1089; found 382.1090.

**(*E*)-2-(2-bromostyryl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ab)**




Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent, isolated as a pale-yellow oil in 87% yield (80 mg, 0.174 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, $J$ = 8.0 Hz, 1H), 7.31 – 7.03 (m, 7H), 6.94 (dd, $J$ = 15.9, 1.5 Hz, 1H), 5.85 (dd, $J$ = 15.9, 6.2 Hz, 1H), 5.11 (q, $J$ = 5.3, 4.3 Hz, 1H), 4.22 – 4.08 (m, 1H), 3.53 – 3.33 (m, 2H), 3.26 – 3.09 (m, 2H), 2.96 (ddd, $J$ = 15.5, 5.8, 2.0 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 139.3, 136.1, 136.0, 133.2, 132.9, 130.9, 129.6, 129.4, 127.4, 127.2, 127.1, 123.8, 119.8 (q, $J_{CF}$ = 322.5 Hz, C), 57.798 43.9, 31.1. **$^{19}$F NMR** (282 MHz, $CDCl_3$*d*) δ -76.8. **HRMS(APCI)** m/z: $[M+H]^+$ Calc'd for $C_{19}H_{18}BrF_3NO_2S$ 462.0173; found 462.0168.

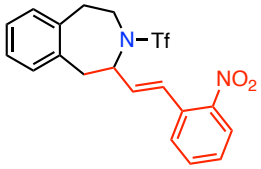
**(*E*)-2-(2-methylstyryl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ac)**




Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent, isolated as a pale-yellow oil in 76% yield (60 mg, 0.152 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.06 (m, 7H), 6.84 (d, $J$ = 15.8 Hz, 1H), 5.79 (dd, $J$ = 15.8, 6.6 Hz, 1H), 5.11 (tdt, $J$ = 6.4, 2.9, 1.4 Hz, 1H), 4.22 – 4.03 (m, 1H), 3.54 – 3.32 (m, 2H), 3.28 – 3.08 (m, 2H), 2.96 (ddd, $J$ = 15.5, 5.9, 1.8 Hz, 1H), 2.25 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 139.4, 136.3, 135.8, 135.3, 133.0, 132.6, 130.9, 130.5, 130.3, 130.2, 130.0, 129.6, 128.7, 128.1, 127.6, 127.4, 127.2, 127.0, 126.1, 125.8, 125.8, 125.1, 119.9 (q, $J_{CF}$ =322.6 Hz, C), 58.2, 43.9, 19.6. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.9. **HRMS(APCI** m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}F_3NO_2S$ 396.1245; found 396.1236.

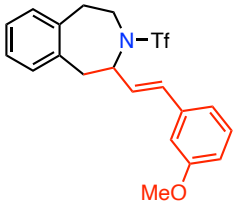
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**(*E*)-2-(2-nitrostyryl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ad)**



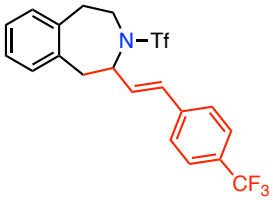

Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent, isolated as a pale-yellow oil in 75% yield (71 mg, 0.14 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.52 (td, *J* = 7.6, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.24 – 7.12 (m, 4H), 7.07 (dd, *J* = 15.9, 1.6 Hz, 1H), 5.85 (dd, *J* = 15.9, 5.9 Hz, 1H), 5.12 (tdt, *J* = 6.4, 3.1, 1.4 Hz, 1H), 4.25 – 4.10 (m, 1H), 3.52 – 3.37 (m, 2H), 3.25 – 3.11 (m, 2H), 3.03 – 2.89 (m, 1H) **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 147.5, 139.3, 135.8, 133.3, 132.1, 130.8, 129.9, 129.6, 129.0, 128.7, 127.5, 127.2, 124.7, 119.8 (q, $J_{CF}$ =322.4 Hz, C), 57.7, 45.4, 43.9, 36.5. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.6. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{19}H_{18}F_3N_2O_4S$ 427.0939; found 527.0937.

**(*E*)-2-(3-methoxystyryl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ae)**



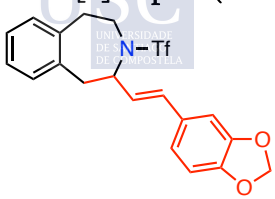

Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent, isolated as a pale-yellow oil in 60% yield (50 mg, 0.12 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.10 (m, 5H), 6.93 – 6.72 (m, 3H), 6.58 (d, *J* = 15.9 Hz, 1H), 5.91 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.06 (ddd, *J* = 6.6, 4.1, 2.3 Hz, 1H), 4.12 (d, *J* = 14.9 Hz, 1H), 3.78 (s, 3H), 3.50 – 3.31 (m, 2H), 3.26 – 3.04 (m, 2H), 2.95 (ddd, *J* = 15.4, 6.0, 2.2 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 159.7, 139.2, 137.4, 136.1, 134.2, 130.8, 129.6, 127.2, 119.8 (q, $J_{CF}$ = 322.89 Hz, C), 119.1, 113.5, 112.2, 58.0, 55.2, 43.8. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -77.3. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}F_3NO_3S$ 412.1194; found 412.1188.

**(*E*)-2-(4-(trifluoromethyl)styryl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111af)**




Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent to afford **3af** as a pale-yellow oil in 98% yield (88 mg, 0.196 mmol). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.24 – 7.16 (m, 2H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.06 (dd, *J* = 16.0, 6.6 Hz, 1H), 5.13 (qd, *J* = 6.2, 4.7, 2.2 Hz, 1H), 4.19 (dd, *J* = 14.9, 5.7 Hz, 1H), 3.56 – 3.33 (m, 2H), 3.31 – 3.09 (m, 2H), 3.00 (ddd, *J* = 15.5, 5.9, 2.0 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 139.4, 139.3, 135.9, 132.9, 130.8, 130.3, 129.8, 129.7, 129.5, 127.6, 127.3, 126.8, 126.3, 125.8, 125.7, 125.6, 125.5, 125.5, 122.2, 119.8 (q, $J_{CF}$= 321.89 Hz, C),118.6, 113.4, 58.0, 43.9. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -63.1, -76.2. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{20}H_{17}F_6NO_2S$ 450.0962; found 450.0952.

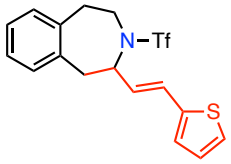
**(*E*)-2-(2-(benzo[*d*][1,3]dioxol-5-yl)vinyl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ah)**




Purified by silica gel column chromatography using Hexanes/AcOEt (95:5) as eluent, isolated as a pale-yellow oil in 80% yield (68 mg, 0.16 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 7.14 (dt, *J* = 6.7, 2.4 Hz, 2H), 6.76 – 6.64 (m, 3H), 6.52 (d, *J* = 15.9 Hz, 1H), 5.92 (t, *J* = 1.1 Hz, 2H), 5.73 (dd, *J* = 15.9, 6.9 Hz, 1H), 5.02 (td, *J* = 6.8, 6.1, 3.2 Hz, 1H), 4.18 – 4.01 (m, 1H), 3.42 (dd, *J* = 15.0, 3.1 Hz, 1H),

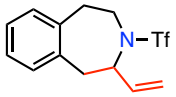
3.39 – 3.29 (m, 1H), 3.17 (ddd, *J* = 13.9, 10.6, 2.8 Hz, 1H), 3.06 (dd, *J* = 15.0, 6.3 Hz, 1H), 2.99 – 2.89 (m, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 148.0, 147.7, 139.3, 136.1, 134.0, 130.8, 130.3, 129.5, 127.4, 127.2, 121.6, 119.8 (q, $J_{CF}$ = 322.78 Hz, C), 108.3, 105.6, 101.1, 58.1, 43.8. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -77.1. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{20}H_{19}F_3NO_4S$ 426.0987; found 426.0982.

**(*E*)-2-(2-(thiophen-2-yl)vinyl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ai)**



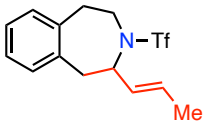

Purified by silica gel column chromatography using Hexanes/AcOEt (98:2) as eluent, isolated as a colorless oil in 50% yield (40 mg, 0.1 mmol). **$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 2H), 7.14 (d, *J* = 4.2 Hz, 3H), 6.97 – 6.88 (m, 2H), 6.71 (d, *J* = 15.7 Hz, 1H), 5.74 (dd, *J* = 15.8, 6.7 Hz, 1H), 5.01 (s, 1H), 4.10 (d, *J* = 13.5 Hz, 1H), 3.46 – 3.30 (m, 2H), 3.22 – 3.11 (m, 1H), 3.07 (dd, *J* = 15.0, 6.4 Hz, 1H), 2.95 (dd, *J* = 15.1, 4.4 Hz, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.8, 139.2, 136.0, 130.8, 129.6, 127.5, 127.4, 127.2, 126.8, 125.1, 119.9 (q, $J_{CF}$ = 322.5 Hz, C), 58.0, 43.8, 30.1. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.9. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}F_3NO_2S_2$ 388.0653; found 388.0647.

**3-((trifluoromethyl)sulfonyl)-2-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111aj)**




Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent, isolated as a colorless oil in 60% yield (37 mg, 0.12 mmol). **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 1H), 7.12 (ddd, *J* = 6.3, 3.2, 1.3 Hz, 2H), 5.59 (ddd, *J* = 16.7, 10.5, 5.8 Hz, 1H), 5.33 – 5.18 (m, 2H), 4.89 (dddt, *J* = 6.2, 4.9, 3.4, 1.6 Hz, 1H), 4.16 – 4.02 (m, 1H), 3.32 (ddd, *J* = 24.8, 15.0, 2.7 Hz, 2H), 3.14 (ddd, *J* = 15.4, 10.5, 3.0 Hz, 1H), 3.02 (dd, *J* = 15.0, 6.4 Hz, 1H), 2.92 (ddd, *J* = 15.5, 5.9, 2.2 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 139.2, 136.1, 132.9, 130.8, 129.5, 128.7, 127.3, 127.0, 119.8 (q, $J_{CF}$ = 322.54 Hz, C), 119.2, 58.2, 43.6, 29.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.8. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{13}H_{15}F_3NO_2S$ 306.0776; found 306.0770.

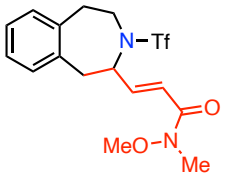
**(*E*)-2-(prop-1-en-1-yl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ak)**




Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent, isolated as a colorless oil of a mixture E/Z (9:1) in 60% yield (39 mg, 0.12 mmol). **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.16 (m, 2H), 7.16 – 7.06 (m, 2H), 5.75 (dd, *J* = 15.1, 6.8 Hz, 1H), 5.23 (dd, *J* = 16.8, 6.8 Hz, 1H), 4.83 (s, 1H), 4.04 (d, *J* = 14.3 Hz, 1H), 3.37 – 3.22 (m, 2H), 3.19 – 3.05 (m, 1H), 2.94 (m, 3H), 1.62 (d, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 139.3, 136.5, 136.4, 131.1, 130.8, 129.4, 128.8, 127.2, 127.2, 127.0, 126.9, 119.8 (q, $J_{CF}$ = 322.40 Hz, C), 119.5, 58.0, 43.5, 35.4, 17.8. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.1. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{14}H_{17}F_3NO_2S$ 320.0932; found 320.0926.

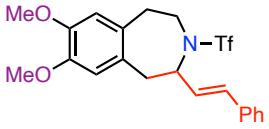
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**(*E*)-*N*-methoxy-*N*-methyl-3-(3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-2-yl)acrylamide (111al)**



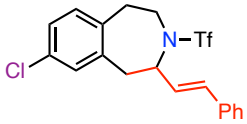

Purified by silica gel column chromatography using Hexanes/AcOEt (80:20) as eluent, isolated as an orange oil in 60% yield (47 mg, 0.12 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.22 – 7.07 (m, 4H), 6.69 (dd, *J* = 15.6, 5.5 Hz, 1H), 6.54 (d, *J* = 15.6 Hz, 1H), 5.05 (s, 1H), 4.10 (d, *J* = 12.8 Hz, 1H), 3.62 (s, 3H), 3.45 – 3.29 (m, 2H), 3.20 (s, 3H), 3.18 – 3.07 (m, 2H), 2.95 (dd, *J* = 14.6, 4.8 Hz, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 165.2, 140.3, 139.0, 135.4, 132.1, 130.8, 129.6, 127.7, 127.4, 122.4, 119.7 (q, $J_{CF}$ = 322.40 Hz, C) 61.9, 57.4, 44.1, 42.4, 38.5, 34.1, 32.3. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.6. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{16}H_{20}F_3N_2O_4S$ 393.1096; found 393.1088.

**(*E*)-7,8-dimethoxy-2-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ba)**



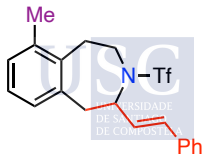

Purified by silica gel column chromatography using Hexanes/AcOEt (90:10) as eluent, isolated as a yellow oil in 75% yield (66.2 mg, 0.150 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.29 (dddd, *J* = 19.3, 9.6, 5.8, 1.6 Hz, 5H), 6.79 – 6.56 (m, 3H), 5.97 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.05 (d, *J* = 7.2 Hz, 1H), 4.10 (d, *J* = 11.0 Hz, 1H), 3.90 (d, *J* = 11.7 Hz, 6H), 3.53 – 3.31 (m, 2H), 3.16 (t, *J* = 13.2 Hz, 1H), 3.02 (dd, *J* = 15.1, 6.3 Hz, 1H), 2.95 – 2.80 (m, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 147.5, 136.0, 134.5, 131.6, 128.3, 128.2, 126.6, 123.7, 119.9 (q, $J_{CF}$ = 322.6 Hz, C), 114.4, 113.3, 58.3, 56.0, 44.0, 29.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -77.3. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}F_3NO_4S$ 442.1300; found 442.0857.

**(*E*)-8-chloro-2-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ca)**




Purified by silica gel column chromatography using Hexanes/AcOEt (90:10) as eluent, isolated as an orange oil in 80% yield (66.5 mg, 0.160 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 6H), 7.22 – 7.15 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 5.92 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.06 (q, *J* = 5.6 Hz, 1H), 4.17 – 4.01 (m, 1H), 3.37 (ddd, *J* = 18.1, 13.4, 2.7 Hz, 2H), 3.13 (ddd, *J* = 14.2, 10.5, 3.0 Hz, 1H), 3.06 (dd, *J* = 15.1, 6.4 Hz, 1H), 2.99 – 2.89 (m, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$δ 138.1, 137.8, 135.7, 134.9, 132.8, 131.0, 130.6, 128.7, 128.5, 127. 4, 126.7, 122.8, 119.9 (q, $J_{CF}$= 322.6 Hz, C), 58.0, 48.7, 43.5, 33.5. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.8. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{19}H_{18}ClF_3NO_2S$ 416.0699; found 416.0691.

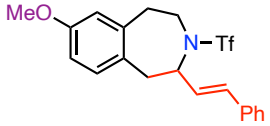
**(*E*)-6-methyl-2-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111da)**




Purified by silica gel column chromatography using Hexanes/AcOEt (99:1) as eluent, isolated as an orange oil in 85% yield (67 mg, 0.170 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 5H), 7.16 – 7.09 (m, 2H), 7.02 (dd, *J* = 6.1, 2.7 Hz, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.01 (dd, *J* = 15.9, 6.6 Hz, 1H), 5.02 (s, 1H), 4.12 (d, *J* = 13.5 Hz, 1H), 3.37 (ddd, *J* = 18.5, 12.2, 5.0 Hz, 2H), 3.18 (ddd, *J* = 15.7, 6.3, 3.1 Hz, 1H), 3.11 (dd, *J* = 14.8, 7.4 Hz, 1H), 3.03 (ddd, *J* = 15.2, 9.0, 3.5 Hz, 1H), 2.35 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 137.3, 136.4, 136.0, 136.0, 133.8, 129.7, 128.7, 128.3, 126.8, 126.7, 119.8 (q, $J_{CF}$ = 322.6 Hz, C), 58.5, 43.2,

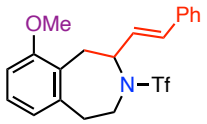
20.5. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -77.3. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}F_3NO_2S$ 396.1245; found 396.1242.

**(*E*)-7-methoxy-2-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ea)**



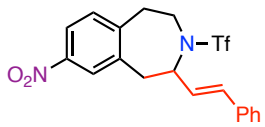

The mixture of isomers was separated on Preparative Chromatography TLC Silica Gel 60 $F_{254}$ plates using Hexanes/AcOEt (95:5) as eluent. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 16.1 Hz, 1H), 5.93 (dd, *J* = 16.1, 5.5 Hz, 1H), 5.04 (s, 1H), 4.08 (d, *J* = 14.6 Hz, 1H), 3.83 (s, 3H), 3.68 (dd, *J* = 15.1, 7.0 Hz, 1H), 3.42 – 3.30 (m, 1H), 3.19 – 3.03 (m, 2H), 2.98 – 2.88 (m, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 157.4, 141.0, 136.2, 133.5, 128.5, 128.0, 126.5, 124.5, 119.8 (q, $J_{CF}$ = 322.6 Hz, C), 109.4, 57.9, 55.8, 43.6, 29.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$δ -77.3. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}F_3NO_3S$ 412.1194; found 412.1188.

**(*E*)-9-methoxy-2-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ea')**



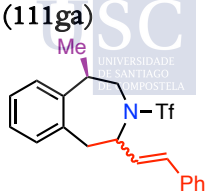

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.26 (qd, *J* = 7.8, 7.3, 5.4 Hz, 6H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.78 – 6.67 (m, 2H), 6.60 (d, *J* = 15.9 Hz, 1H), 5.92 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.01 (d, *J* = 7.0 Hz, 1H), 4.16 – 4.03 (m, 1H), 3.80 (s, 3H), 3.42 – 3.29 (m, 2H), 3.15 (ddd, *J* = 13.9, 10.8, 2.7 Hz, 1H), 3.03 (dd, *J* = 15.1, 6.2 Hz, 1H), 2.90 (td, *J* = 15.1, 14.7, 6.7 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 158.7, 140.6, 135.9, 134.30 131.9, 128.6, 128.2, 128.0, 126.6, 119.8 (q, $J_{CF}$ = 322.6 Hz, C), 115.6, 111.6, 58.3, 55.2, 43.8, 29.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.9. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}F_3NO_3S$ 412.1194; found 412.1188.

**(*E*)-8-nitro-2-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111fa)**




Purified by silica gel column chromatography using Hexanes/AcOEt (85:15) as eluent, isolated as a pale-yellow oil in 30% yield (26 mg, 0.06 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.14 – 8.06 (m, 2H), 7.44 – 7.16 (m, 6H), 6.63 (dd, *J* = 16.2, 1.4 Hz, 1H), 5.90 (dd, *J* = 15.9, 6.4 Hz, 1H), 5.10 (d, *J* = 4.2 Hz, 1H), 4.16 (td, *J* = 18.7, 6.4 Hz, 1H), 3.55 – 3.37 (m, 2H), 3.25 (dt, *J* = 15.0, 5.6 Hz, 2H), 3.16 – 3.07 (m, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 147.1, 146.6, 138.1, 135.4, 135.2, 130.8, 128.7, 128.7, 126.7, 125.4, 122.7, 119.7 (q, $J_{CF}$ = 322.2 Hz, C), 57.9, 42.7, 29.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -76.3. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{19}H_{18}F_3N_2O_4S$ 427.0939; found: 427.0937.

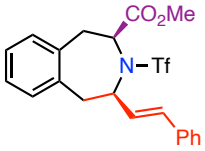
**(*R*)-1-methyl-4-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ga)**

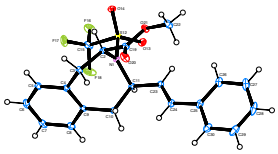



Purified by silica gel column chromatography using Hexanes/Acetone (95:5) as eluent, isolated as a pale-yellow oil in 80% yield (60 mg, 0.16 mmol, as 3:1 mixture of diastereoisomers). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.12 (m, 15H), 6.67 (t, *J* = 16.8 Hz, 2H), 6.09 (ddd, *J* = 22.8, 15.9, 6.7 Hz, 2H), 5.02 (q, *J* = 6.3 Hz, 1H), 3.87 – 3.69 (m, 2H), 3.53 (d, *J* = 15.3 Hz, 1H), 3.31 – 3.06 (m, 4H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.39 (d, *J* = 7.1 Hz, 1H). **$^{13}$C NMR** (126

MHz, $CDCl_3$) δ 135.4, 134.7, 130.7, 128.6, 128.3, 128.2, 127.8, 127.6, 127.1, 126.9, 126.60, 124.1, 121.2, 118.6, 58.0, 49.3, 48.9, 19.2, 16.5. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ 76.6. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}F_3NO_3S$ 395.1167; found 396.1242.

**Methyl (2S,4R)-4-((E)-styryl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-2-carboxylate (111ha)**

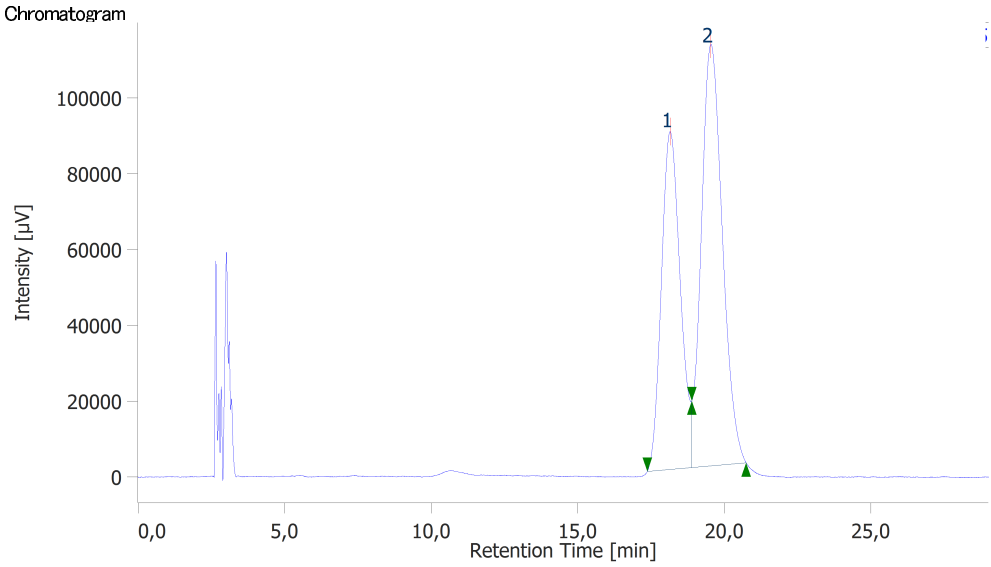


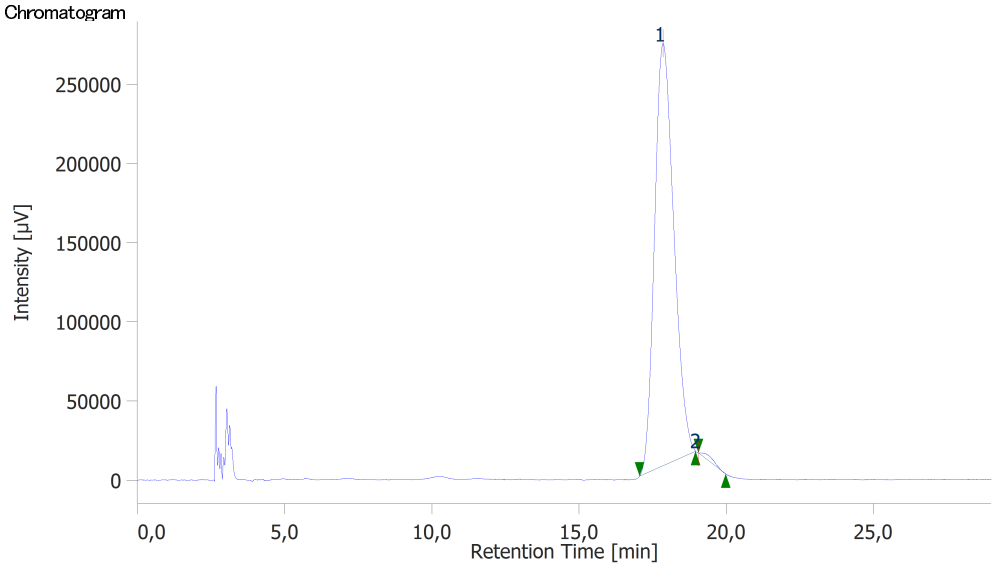
Purified by silica gel column chromatography using Hexanes/Acetone (95:5) as eluent, isolated as a pale-yellow oil in 50% yield (44 mg, 0.1 mmol). $[\alpha]_D^{25}$ 22.85 (c 1, $CHCl_3$) **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 8H), 7.16 (d, $J$ = 5.5 Hz, 1H), 6.66 (d, $J$ = 15.9 Hz, 1H), 6.14 (dd, $J$ = 15.8, 7.5 Hz, 1H), 5.05 – 4.97 (m, 1H), 4.90 (t, $J$ = 7.1 Hz, 1H), 3.58 – 3.50 (m, 4H), 3.29 – 3.14 (m, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.0, 136.3, 136.2, 135.6, 129.9, 129.6, 128.6, 128.2, 127.8, 127.6, 126.6, 119.5 (q, $J_{CF}$= 322.00 Hz,C) 59.6, 57.2, 52.6, 38.5. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ 77.0. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{21}H_{21}F_3NO_4S$ 440.1143; found 440.1135.

*Diastereoselectivity and enantioselectivity were determined by chiral SFC analysis on Phenomenex Amylose-1 at 40 ºC ($CO_2$ : MeOH= 95:05, 1mL/min)*

*Racemic sample.*




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**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 17,847 | 12112754 | 266500 | 99,266 | 99,981 | N/A | 3474 | N/A | 1,223 | |
| 2 | Unknown | 5 | 19,050 | 89541 | 51 | 0,734 | 0,019 | N/A | N/A | N/A | N/A | |

## 2.7. General Procedure A for the Pd-Catalyzed Enantioselective Heteroannulation of Phenethylflamides 110i-110l with 1,3-Diene 52

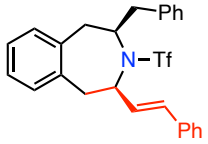
A 5 mL sealed tube equipped with a magnetic stir bar was charged with **110** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), *L*-pGlu-OH (12 mg, 0.08 mmol, 0.4 equiv), *rac*-Binol (6 mg, 0.02 mmol, 0.1 equiv), $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.1 mmol, 0.5 equiv), **52a** (52 mg, 0.4 mmol, 2 equiv), $Et_3N$ (11 µl, 0.08 mmol, 0.4 equiv) and MeCN (0.4 mL). The solution was saturated in oxygen with stirring for 10 min and the reaction was heated at 105 °C in an oil bath for 24 h. The reaction mixture was quenched with a saturated solution of $NH_4Cl_{(aq)}$ and extracted with AcOEt (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated *in vacuo*. The product **111** was purified by silica gel column chromatography using Hexanes/Acetone as eluent.

## 2.8. General procedure B for the Pd-Catalyzed Enantioselective Heteroannulation of Phenethyltriflamides 110i-110l with 1,3-Diene 52a

A 5 mL sealed tube equipped with a magnetic stir bar was charged with **110** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), *L*-pGlu-OH (12 mg, 0.08 mmol, 0.4 equiv), *rac*-Binol (6 mg, 0.02 mmol, 0.1 equiv), $Cu(OAc)_2 \cdot H_2O$ (8 mg, 0.1 mmol, 0.2 equiv), **52a** (52 mg, 0.4 mmol, 2 equiv), $Et_3N$ (11 µl, 0.08 mmol, 0.4 equiv) and MeCN (0.4 mL). The solution was saturated in oxygen with stirring for 10 min and the reaction was heated at 105 °C in an oil bath for 24 h. The reaction mixture was quenched with a saturated solution of $NH_4Cl_{(aq)}$ and extracted with AcOEt (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated *in vacuo*. The product **111** was purified by silica gel column chromatography using Hexanes/Acetone as eluent.

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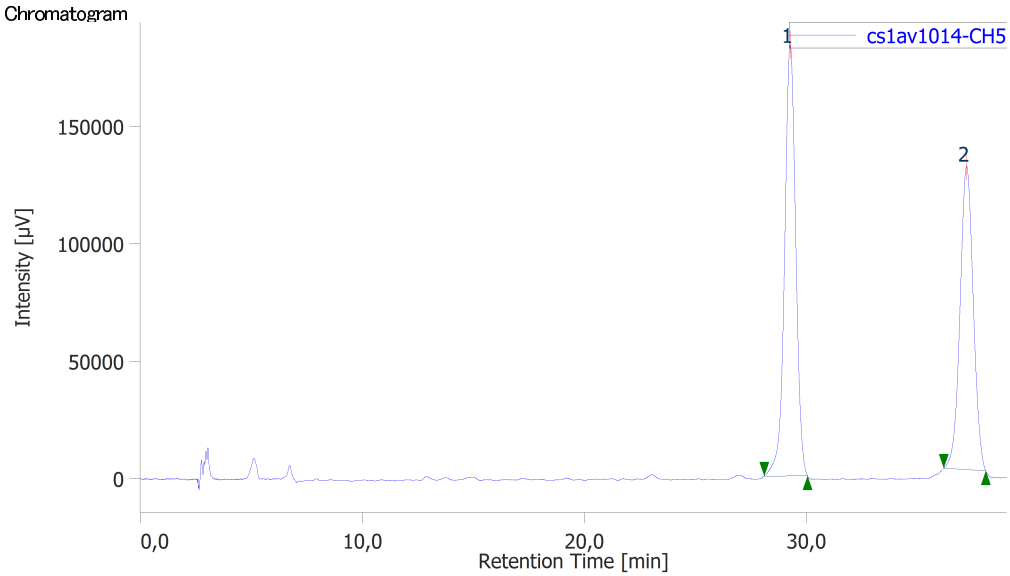
**(*E*)-2-benzyl-4-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ia)**




Purified by silica gel column chromatography using Hexanes/Acetone (95:5) as eluent, isolated as a pale-yellow oil in (method **A**: 45% yield, 20:80 er,43 mg, 0.091 mmol, $[\alpha]_D^{25}$ -21.45 (c 1, $CHCl_3$)) (method **B**: 25% yield, 5:95 er, 35 mg, 0.05 mmol, $[\alpha]_D^{25}$ -24.55 (c 1, $CHCl_3$)). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.11 (m, 15H), 7.09 – 6.99 (m, 1H), 6.79 (d, *J* = 15.9 Hz, 1H), 6.15 (s, 1H), 5.11 (s, 1H), 4.59 (s, 1H), 3.48 – 3.29 (m, 1H), 3.25 – 2.92 (m, 3H), 2.82 (dt, *J* = 14.8, 7.5 Hz, 2H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 137.9, 136.7, 136.7, 136.3, 134.0, 130.2, 129.2, 128.7, 128.2, 127.5, 127.4, 126.9, 126.6, 60.0, 58.3, 43.1, 39.4, 37.4. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -77.3. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{26}H_{25}F_3NO_2S$ 472.5462; found 473.5460.

*Diastereoselectivity and enantioselectivity were determined by chiral SFC analysis on Phenomenex Cellulose-1 at 40°C ($CO_2$: MeOH= 90:10, 1mL/min).*

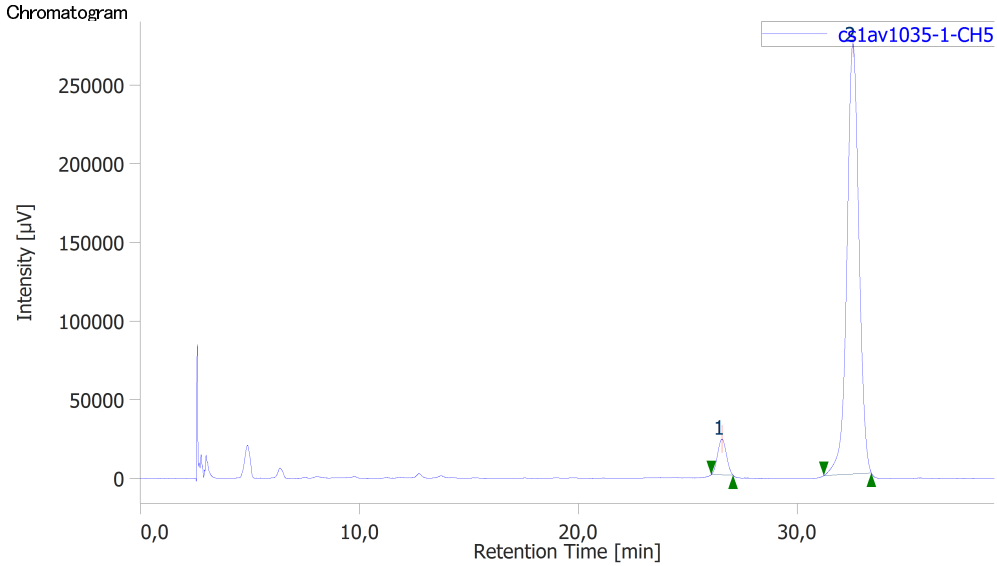
*Racemic sample.*




Signals in the range around 2-4 min are due to the front arriving to the detector.

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*Asymmetric sample (er: 5:95)*

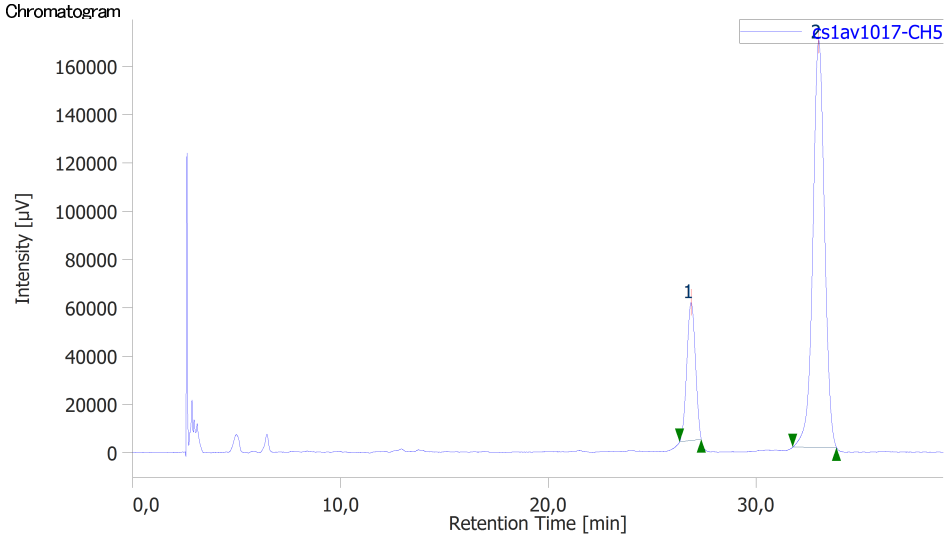



**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 26,557 | 635619 | 22754 | 5,746 | 7,681 | N/A | 19441 | 6,889 | 1,012 | |
| 2 | Unknown | 5 | 32,533 | 10426645 | 273477 | 94,254 | 92,319 | N/A | 17712 | N/A | 0,973 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

*Asymmetric sample (er 20:80)*



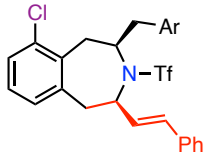

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 26,863 | 1637694 | 57150 | 19,965 | 25,326 | N/A | 19108 | 6,909 | 0,979 | |
| 2 | Unknown | 5 | 33,000 | 6564992 | 168506 | 80,035 | 74,674 | N/A | 17294 | N/A | 0,963 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

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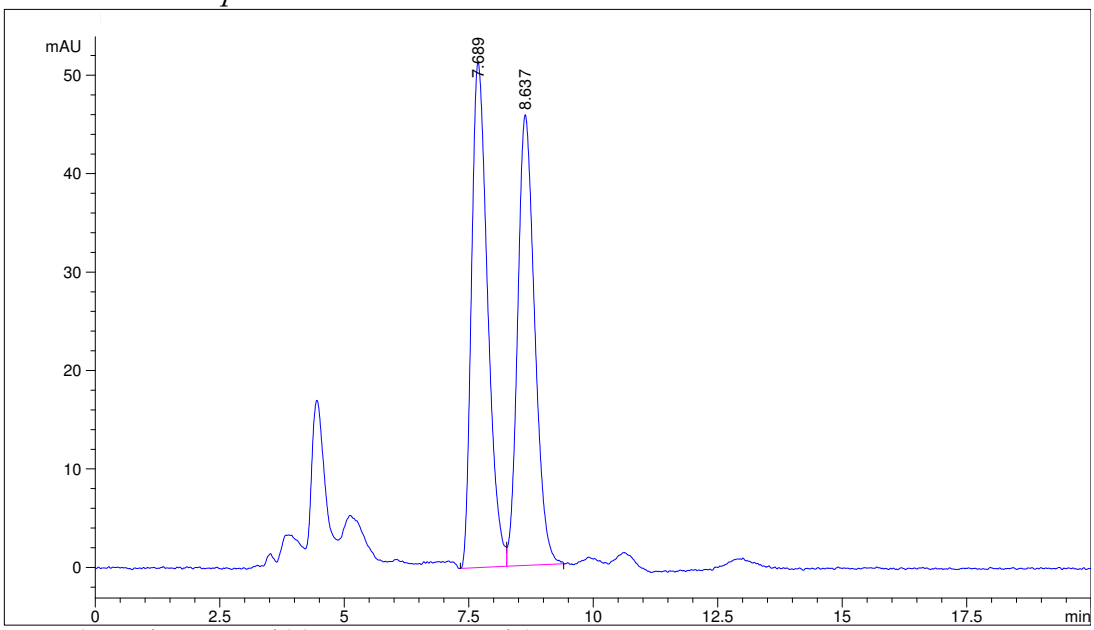
**(*E*)-6-chloro-4-(2-chlorobenzyl)-2-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (111ja)**




Purified by silica gel column chromatography using Hexanes/Acetone (95:5) as eluent, isolated as a pale-yellow oil in (method **A**: 50% yield, 62:38, 43 mg, 0.1 mmol, $[\alpha]_D^{25}$ -1.65 (c 1, $CHCl_3$)) (method **B**: 25% yield, 81:19, 35 mg, 0.08 mmol, $[\alpha]_D^{25}$ -13.03 (c 1, $CHCl_3$)). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.40 – 7.34 (m, 3H), 7.32 (ddd, *J* = 6.6, 4.9, 2.8 Hz, 2H), 7.21 – 7.13 (m, 4H), 6.87 (d, *J* = 15.9 Hz, 1H), 6.48 (s, 1H), 5.02 (s, 1H), 4.63 (s, 1H), 3.49 (s, 1H), 3.44 – 3.24 (m, 3H), 3.24 – 3.00 (m, 2H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 138.6, 136.0, 135.0, 134.6, 134.4, 130.9, 129.7, 128.8, 128.6, 128.4, 128.4, 128.3, 127.1, 126.7, 126.5, 58.4, 32.4, 31.5, 22.6. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -76.6. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{26}H_{23}Cl_2F_3NO_2S$ 540.0779; found 540.0780.

*Diastereoselectivity and enantioselectivity were determined by chiral HPLC analysis on Chiralpak IA3 at rt (hexanes: iPrOH 98:2, 1 mL/min)*

*Racemic sample*

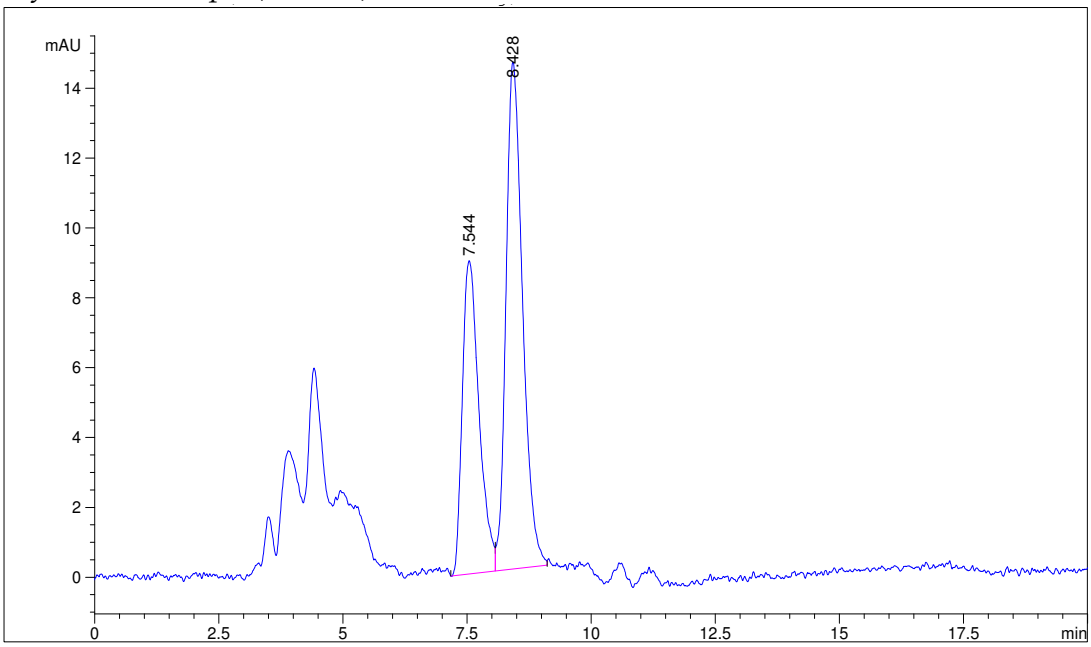



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 7.689 | PV | 0.3491 | 1157.90039 | 51.35395 | 51.5044 |
| 2 | 8.637 | VB | 0.3597 | 1090.25977 | 45.79893 | 48.4956 |
| Totals : | | | | 2248.16016 | 97.15289 | |

Signals in the range around 2-5 min are due to the front arriving to the detector.

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*Asymmetric sample (er 38:62)*



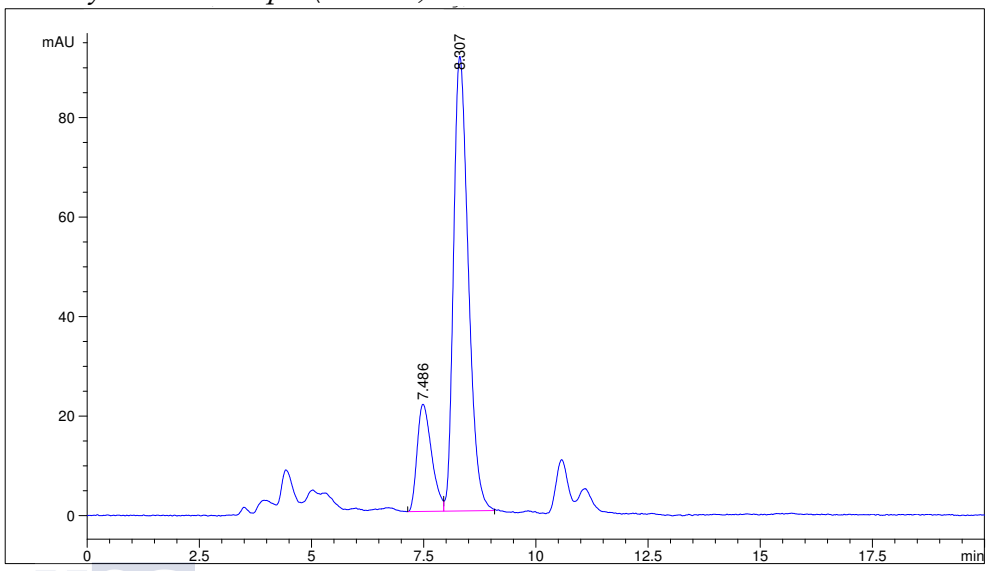

```
Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.544 PV    0.3103  209.45255    8.97379  38.3300
   2   8.428 VB    0.3408  336.99252   14.51955  61.6700

Totals :                   546.44507   23.49335
```

Signals in the range around 2-5 min are due to the front arriving to the detector.

*Asymmetric sample (er 19:81)*



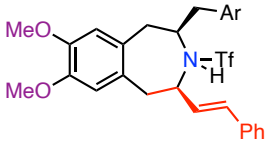

```
Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.486 PV    0.3375  482.53458   21.52496  18.7539
   2   8.307 VB    0.3510 2090.44849   91.35308  81.2461

Totals :                  2572.98306  112.87804
```

Signals in the range around 2-5 min are due to the front arriving to the detector.

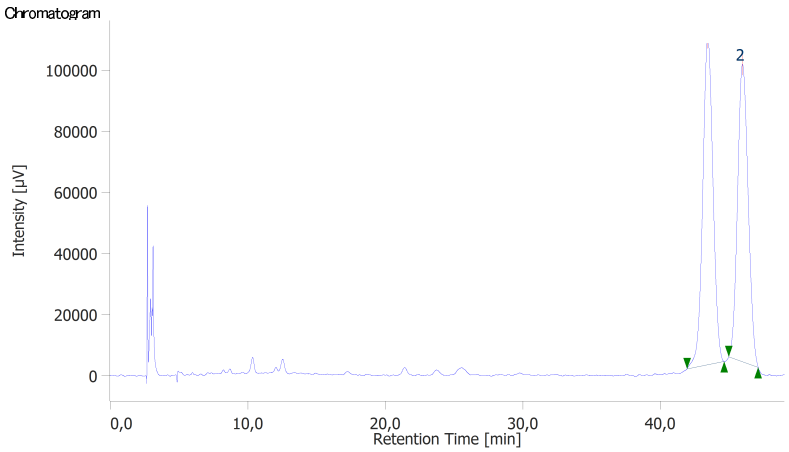
**(*E*)-2-(3,4-dimethoxybenzyl)-7,8-dimethoxy-4-styryl-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111ka)**




Purified by silica gel column chromatography using Hexanes/AcOEt (8:2) as eluent, isolated as a yellow oil (method **A**: 40% yield, 73:27 er, 38 mg, 0.091 mmol, $[\alpha]_D^{25}$ -2.03 (c 1, $CHCl_3$)) (method **B**: 25% yield, 85:15 er, 35 mg, 0.05 mmol, $[\alpha]_D^{25}$ -7.5 (c 1, $CHCl_3$)). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 6H), 6.84 – 6.77 (m, 2H), 6.77 – 6.71 (m, 3H), 6.60 (s, 1H), 6.22 – 6.14 (m, 1H), 5.10 (s, 1H), 4.56 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.37 (d, *J* = 14.9 Hz, 1H), 3.12 – 3.03 (m, 2H), 2.95 (d, *J* = 13.5 Hz, 1H), 2.82 – 2.68 (m, 2H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 149.4, 148.4, 148.3, 148.1, 136.2, 134.0, 130.7, 129.0, 128.7, 128.2, 128.0, 126.6, 121.4, 114.4, 113.0, 111.7, 60.0, 58.4, 56.3, 56.3, 56.1, 56.0, 42.5, 39.1, 37.1. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -77.3. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{30}H_{33}F_3NO_6S$ 592.1981; found 592.1976.

*Diastereoselectivity and enantioselectivity were determined by chiral SFC analysis on Phenomenex Cellulose-1 at 40°C ($CO_2$: MeOH= 90:10, 1mL/min).*

*Racemic sample*



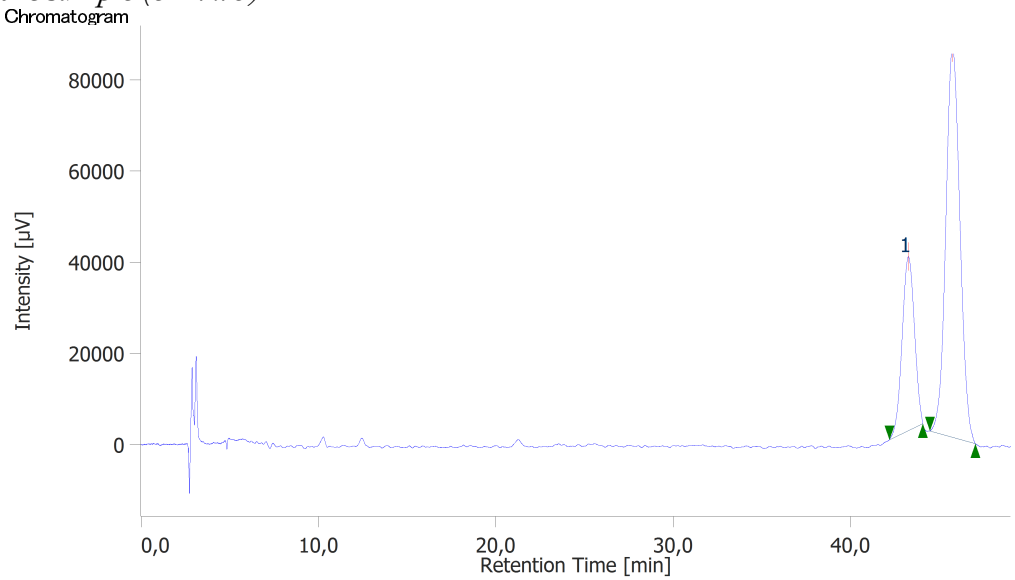

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [μV*sec] | Height [μV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 43,413 | 5537809 | 107008 | 51,577 | 52,365 | N/A | 16593 | 1,819 | 1,008 | |
| 2 | Unknown | 5 | 45,933 | 5199139 | 97341 | 48,423 | 47,635 | N/A | 16519 | N/A | 1,089 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

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*Asymmetric sample (er 27:73)*

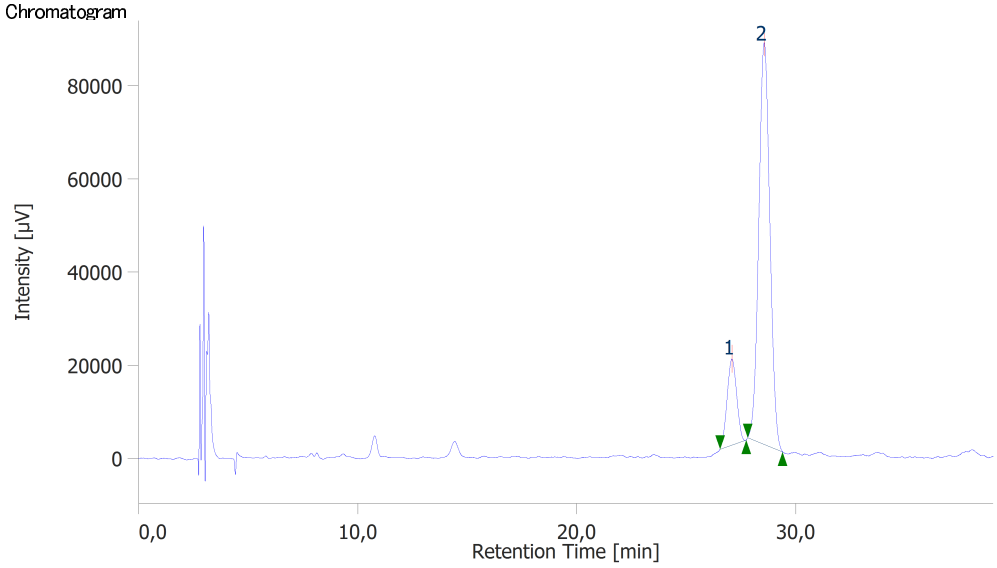



**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV*sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 43,227 | 1829193 | 38154 | 27,860 | 30,880 | N/A | 18050 | 1,815 | 0,966 | |
| 2 | Unknown | 5 | 45,713 | 4736569 | 85402 | 72,140 | 69,120 | N/A | 15663 | N/A | 1,050 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

*Asymmetric sample (er 15:85)*



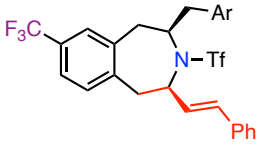

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV*sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 27,070 | 557871 | 18472 | 15,574 | 17,633 | N/A | 17462 | 1,689 | 0,996 | |
| 2 | Unknown | 5 | 28,540 | 3024108 | 86282 | 84,426 | 82,367 | N/A | 15196 | N/A | 1,039 | |

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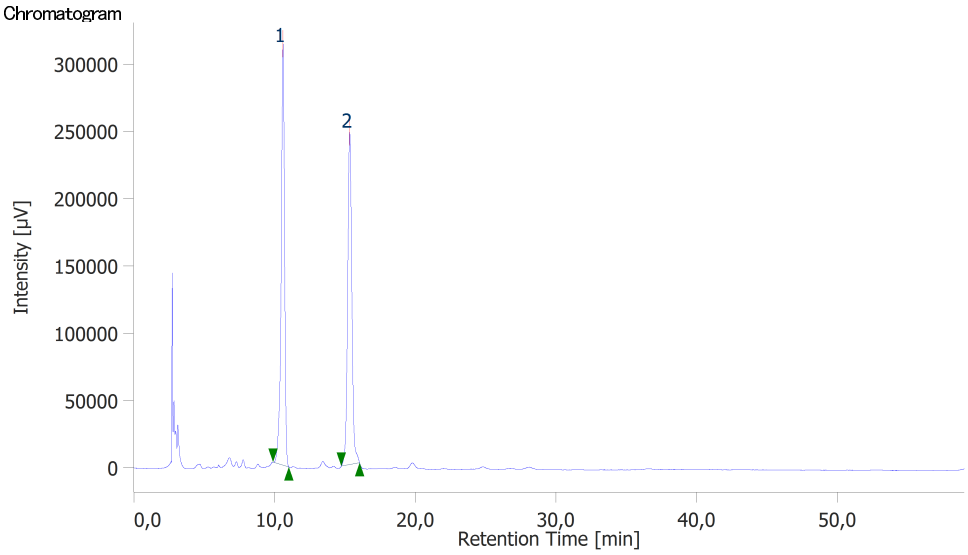
Signals in the range around 2-4 min are due to the front arriving to the detector.

**(*E*)-styryl)-7-(trifluoromethyl)-4-(3-(trifluoromethyl)benzyl)-3-((trifluoromethyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111la)**




Purified by silica gel column chromatography using Hexanes/Acetone (95:5) as eluent, isolated as a pale-yellow oil in (method **A**: 30% yield, 70:30 er, 30 mg, 0.061 mmol, $[\alpha]_D^{25}$ -1.75 (c 1, $CHCl_3$)) (method **B**: 25% yield, 85:15 er, 25 mg, 0.05 mmol, $[\alpha]_D^{25}$ -15.06 (c 1, $CHCl_3$)). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.51 (m, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 4H), 7.35 – 7.27 (m, 6H), 6.85 (d, *J* = 15.9 Hz, 1H), 6.25 – 6.06 (m, 1H), 5.16 (d, *J* = 14.3 Hz, 1H), 4.73 – 4.58 (m, 1H), 3.51 – 3.42 (m, 1H), 3.28 (dd, *J* = 14.8, 7.3 Hz, 1H), 3.23 – 3.06 (m, 2H), 2.96 – 2.79 (m, 2H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.8, 138.2, 137.3, 135.8, 132.4, 129.4, 128.8, 128.6, 128.4, 126.6, 125.8 (q, *J* = 3.8 Hz), 125.0, 124.6 (q, *J* = 4.0 Hz), 124.2 (q, *J* = 3.8 Hz), 122.8, 119.6 (q, *J* = 273.4 Hz), 59.3, 57.9, 39.3, 37.3, 29.6. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -63.3, -63.4, -77.3. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{28}H_{23}F_9NO_2S$ 608.1306; found 608.1310.

*Diastereoselectivity and enantioselectivity were determined by chiral SFC analysis on Phenomenex Cellulose-1 at 40°C ($CO_2$ : MeOH= 90:10, 1mL/min)*



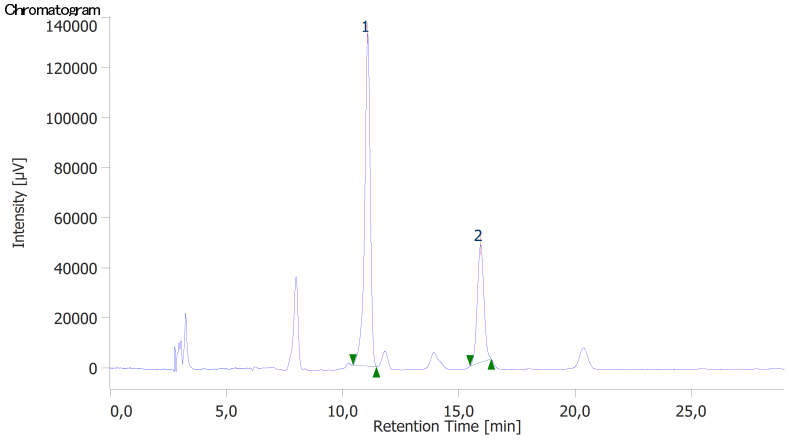

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 10,600 | 5225179 | 312836 | 50,577 | 55,884 | N/A | 10777 | 10,181 | 0,836 | |
| 2 | Unknown | 5 | 15,337 | 5105953 | 246961 | 49,423 | 44,116 | N/A | 13677 | N/A | 1,042 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

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*Asymmetric sample (er 70:30)*

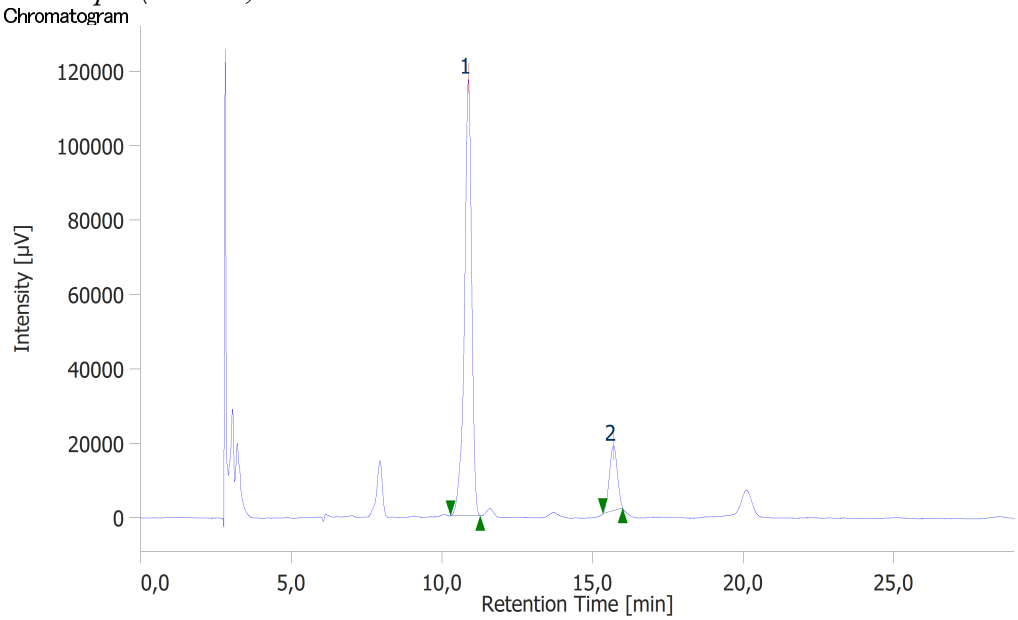



**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 11,077 | 2241293 | 132902 | 70,733 | 73,848 | N/A | 11554 | 10,458 | 0,819 | |
| 2 | Unknown | 5 | 15,930 | 927387 | 47064 | 29,267 | 26,152 | N/A | 15103 | N/A | 1,015 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

*Asymmetric sample (er 85:15)*




**Peak Information**

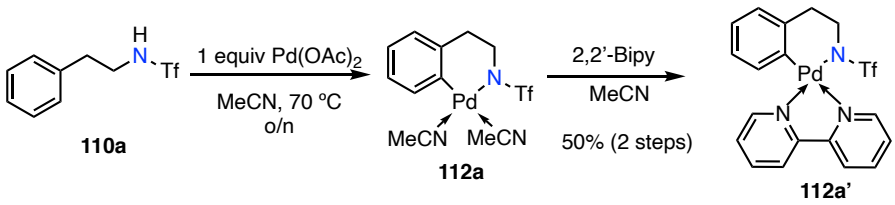
| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 10,877 | 1954731 | 117370 | 85,984 | 87,100 | N/A | 11142 | 10,589 | 0,844 | |
| 2 | Unknown | 5 | 15,690 | 318632 | 17383 | 14,016 | 12,900 | N/A | 15793 | N/A | 0,963 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

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## 2.9. Mechanistic Studies

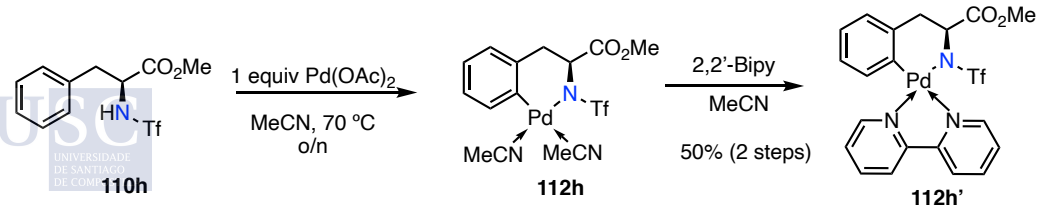
### 2.9.1. Formation of Palladacycle 112a'




A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (50 mg, 0.223 mmol, 1 equiv). Then 40 mL of $CH_3CN$ were added to form a suspension. **110a** (56 mg, 0.223 mmol, 1 equiv) was added to the suspension and heated at 70 °C in an oil bath overnight. The reaction was filtrated through a Celite® plug. The solvent was evaporated *in vacuo* and the residue was dissolved in a minimum amount of DCM. Then hexanes were added, and a grey precipitate was observed. After filtration, the residue was washed with hexanes to give the palladacycle (**112a**) as grey solid (49 mg, 50% yield). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.09 (d, $J$ = 7.6 Hz, 1H), 7.00 (d, $J$ = 7.0 Hz, 1H), 6.89 (dd, $J$ = 15.6, 7.5 Hz, 2H), 3.19 (s, 2H), 2.92 (s, 2H), 2.27 (s, 3H), 2.22 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.5, 139. 2, 133.7, 126.2, 125.1, 124.8, 120.7 (q, $J_{CF}$= 323.58 Hz), 77.3, 76.8, 44.1, 41.0, 3.5. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -74.72.

**112a** (50 mg, 0.11 mmol) was dissolved in 15 mL of $CH_3CN$ and a solution of bipyridine (17 mg, 0.11 mmol) in 1 mL of $CH_3CN$ was added dropwise. After stirring for 4 h at room temperature, the solvent was removed *in vacuo*. The crude was dissolved in DCM and hexanes were added until a grey precipitate appears **112a'** (56 mg, 100% yield). Crystallization of **112a'** as off-white crystals occurred after dissolving the sample in hot DCM until reaching rt (8h). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.20 (d, $J$ = 5.3 Hz, 1H), 8.80 – 8.73 (m, 1H), 8.12 (d, $J$ = 8.1 Hz, 1H), 8.09 – 7.98 (m, 3H), 7.65 – 7.59 (m, 1H), 7.43 (dd, $J$ = 7.3, 5.7 Hz, 1H), 7.39 – 7.28 (m, 1H), 7.10 – 7.04 (m, 2H), 6.98 – 6.93 (m, 1H), 3.64 (s, 1H), 3.43 (s, 1H), 3.04 (s, 1H), 2.86 (s, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.6, 152.8, 152.6, 151.5, 150.8, 142.0, 139.0, 138.9, 133.9, 129.1, 128.8, 127.3, 126.3, 125.7, 124.6, 124.4, 122.0, 120.9, 45.8, 41.1, 29.7, 29.4, 26.7, 22.7. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -74.2. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{19}H_{17}F_3N_3O_2PdS$ 514.0028; found 514.0030.

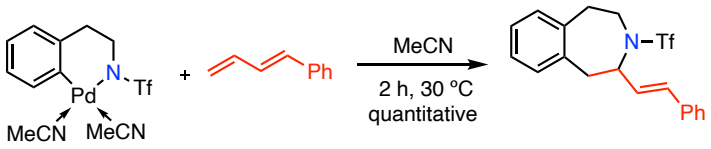
### 2.9.2. Formation of Palladacycle 112h'




A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (0.020 g, 0.089 mmol, 1 equiv). Then 15 mL of $CH_3CN$ were added to form a suspension. **110h** (28 mg, 0.089 mmol, 1 equiv) was added to the suspension and heated at

70 °C in an oil bath overnight. The solvent was evaporated *in vacuo* and the residue was dissolved in a minimum amount of DCM. The reaction was filtrate through a Celite® plug. Then a solution of bipyridine (14 mg, 0.089 mmol, 1equiv) in 1 mL of $CH_3CN$ was added dropwise to the above solution and stirred for 4 h at room temperature. Then the solvent was eliminated *in vacuo*. The crude was dissolved in DCM and hexanes were added until a grey precipitate appears **112h'** (26 mg, 50% yield). This precipitate was recrystallized in DCM/hexanes to obtain **112h'** as off-white crystals. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.46 (d, $J$ = 5.0 Hz, 1H), 8.70 (d, $J$ = 5.4 Hz, 1H), 8.21 (d, $J$ = 8.0 Hz, 1H), 8.10 – 8.01 (m, 2H), 7.94 (td, $J$ = 7.8, 1.4 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.41 (t, $J$ = 6.5 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.13 – 7.05 (m, 2H), 7.01 (dd, $J$ = 7.0, 1.6 Hz, 1H), 3.94 (dd, $J$ = 12.2, 3.8 Hz, 1H), 3.81 (s, 3H), 3.65 (t, $J$ = 12.6 Hz, 1H), 3.23 (dd, $J$ = 13.1, 4.4 Hz, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.9, 152.6, 152.3, 151.9, 151.5, 140.1, 139.2, 139.0, 134.1, 126.4, 126.2, 125.3, 124.5, 122.4, 121.1, 120,6 (q, $J_{CF}$ =324.24 Hz) 58.2, 52.2, 44.5. **$^{19}$F NMR** (282 MHz $CDCl_3$) δ -75.0. **HRMS(APCI)** m/z: $[M+H]^+$ Calcd for $C_{21}H_{19}F_3N_3O_4PdS$ 572.0083; found 572.0088.

## 2.9.3. Stoichiometric Reaction




**112a** **52a** **111aa**

A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with palladacycle (**112a**) (50 mg, 0.111 mmol, 1 equiv), **52a** (0.133 mmol,1.2 equiv) and 0.25 mL MeCN. The reaction was heated at 30 °C in a water bath for 2 h. The solution was quenched with a saturated solution of $NH_4Cl_{(aq)}$ (10 mL) and extracted with AcOEt (2 x 10 mL). The combine organic phases were dried over $Na_2SO_4$ and concentrated *in vacuo.* The residue was purified by column chromatography in silica gel using Hexanes:AcOEt (99:1) as eluent to afford the product **111aa** as a pale yellow oil in 95% yield (30 mg, 0.105 mmol).

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## 2.10. X-Ray Crystallographic Data

### 2.10.1. Crystallographic Data for Compound 111ha

An X-ray crystal of compound **111ha** (CCDC 1985306) was grown by vapor diffusion using DCM and hexanes as mixture of solvents.

**Figure 11.** X-Ray coordinate of compound **111ha** (CCDC 1985306). ORTEP drawing of **111ha** showing ellipsoids at the 30% contour probability level

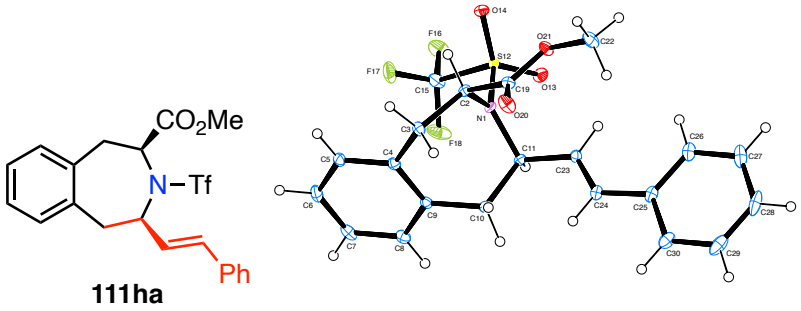



**Table 12.** Crystal data and structure refinement for **111ha** (CCDC 1985306)

| | | |
|---|---|---|
| Deposition Number CCDC | CCDC 1985306 | |
| Chemical formula | $C_{21}H_{20}F_3NO_4S$ | |
| Formula weight | 439.44 g/mol | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal size | 0.144 x 0.201 x 0.252 mm | |
| Crystal habit | colorless block | |
| Crystal system | orthorhombic | |
| Space group | P 21 21 21 | |
| Unit cell dimensions | a = 9.2593(2) Å | α = 90° |
| | b = 10.5732(2) Å | β = 90° |
| | c = 20.4005(4) Å | γ = 90° |
| Volume | 1997.22(7) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.461 g/cm$^3$ | |
| Absorption coefficient | 1.954 mm$^{-1}$ | |
| F(000) | 912 | |

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## 2.10.2. Crystallographic Data of Compound 4a'

An X-ray crystal of **112a'** (CCDC 1985307) was grown after solving the sample in hot DCM until reaching rt (8 h).

**Figure 12**. X-Ray coordinate of compound **112a'** (CCDC 1985307). ORTEP drawing of **112a'** showing ellipsoids at the 30% contour probability level

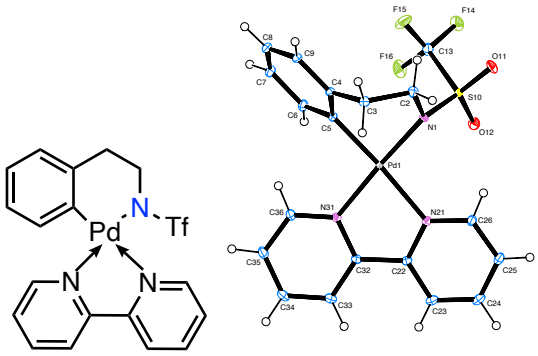



**Table 13.** Crystal data and structure refinement for **112a'** (CCDC 1985307)

| | | |
|---|---|---|
| Deposition Number CCDC | CCDC 1985307 | |
| Chemical formula | $C_{19}H_{16}F_3N_3O_2PdS$ | |
| Formula weight | 513.81 g/mol | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal size | 0.074 x 0.176 x 0.187 mm | |
| Crystal habit | clear colorless block | |
| Crystal system | monoclinic | |
| Space group | P 1 21/c 1 | |
| Unit cell dimensions | a = 8.6760(5) Å | α = 90° |
| | b = 20.7478(11) Å | β = 106.5081(19)° |
| | c = 10.7533(5) Å | γ = 90° |
| Volume | 1855.89(17) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.839 $g/cm^3$ | |
| Absorption coefficient | 1.164 $mm^{-1}$ | |
| F(000) | 1024 | |

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## 2.10.3. Crystallographic Data of Compound 112h'

An X-ray crystal of compound **112h'** (CCDC 1985308) was grown by vapor diffusion using DCM and hexanes as a mixture of solvents.

**Figure 13.** X-Ray coordinate of compound **112h'** (CCDC 1985308). ORTEP drawing of **112h'** showing ellipsoids at the 30% contour probability level

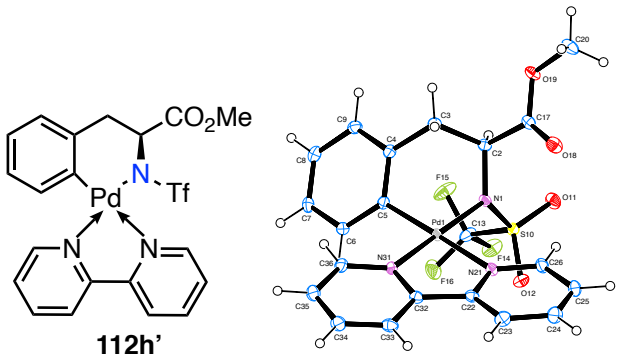



**Table 14.** Crystal data and structure refinement for **112h'** (CCDC 1985308)

| | | |
|---|---|---|
| Deposition Number CCDC | CCDC 1985308 | |
| Chemical formula | $C_{21}H_{18}F_3N_3O_4PdS$ | |
| Formula weight | 571.84 g/mol | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal size | 0.017 x 0.074 x 0.204 mm | |
| Crystal habit | clear colourless plate | |
| Crystal system | monoclinic | |
| Space group | P 1 21 1 | |
| Unit cell dimensions | a = 15.5343(8) Å | α = 90° |
| | b = 18.2025(9) Å | β = 113.353(2)° |
| | c = 16.6229(8) Å | γ = 90° |
| Volume | 4315.3(4) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.760 $g/cm^3$ | |
| Absorption coefficient | 1.017 $mm^{-1}$ | |
| F(000) | 2288 | |

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## 2.11. DFT Calculations

### 2.11.1. Computational Details

All electronic structure calculations were performed using the Gaussian 16 software package[205] at the CESGA facilities. The geometries of all minima and transition states involved were optimized at the B3LYP[206] level with the addition of Grimme´s D3 dispersion corrections[207] (B3LYP-D3) within the self-consistent reaction field (SCRF) using the SMD model (acetonitrile)[208] with a small basis set (BS1) featuring the double-ζ LANL2DZ[209] basis set and the LANLD2Z pseudopotential[210] to describe the electrons of the palladium atom and the 6-31G(d,p) basis set[211] for all other atoms. Frequency calculations were performed at the same level to evaluate the zero-point vibrational energy and thermal corrections at 298 K and to confirm the nature of the stationary points, yielding one imaginary frequency for the transition states and none for the minima. Each transition state was further confirmed by following the steepest descent to both sides and identifying the minima present in the reaction energy profile. Single-point energies were calculated using B3LYP with the addition of Grimme´s D3 dispersion corrections (B3LYP-D3) within the self-consistent reaction field (SCRF) using the SMD model (acetonitrile) and a larger basis set (BS2) featuring the cc-pVTZ-pp basis set and pseudopotential[212] for the palladium atom and 6-311++G(d,p)[213] for all other atoms. The resulting energies were used to correct the gas-phase energies obtained from B3LYP calculations. The reaction profiles were built up in terms of $\Delta G_{sol}$.

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[205] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; J. A. Montgomery, J.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16, Revision B.01*, Gaussian, Inc., Wallingford CT, 2016.

[206] a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789. b) Parr, R. G.; Wang, Y. Density Functional Theory of Atoms and Molecules. Oxford University Press: New York, 1989. c) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200-206. d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.

[207] Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.

[208] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *Journal of Physical Chemistry B* **2009**, *113*, 6378-6396.

[209] Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310.

[210] Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270-283.

[211] a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. d) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654. e) Gordon, M. S.; Binkley, J. S.; Pople, J. A.; Pietro, W. J.; Hehre, W. J. *J. Am. Chem. Soc.* **1982**, *104*, 2797.

[212] Peterson, K. A.; Figgen, D.; Dolg, M.; Stoll, H. *J. Chem. Phys.* **2007**, *126*, 124101.

[213] (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650. (b) McLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980**, *72*, 5639. (c) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294. (d) Spitznagel, G. W.; Clark, T.; Schleyer, P.; Hehre, W. J. *J. Comput. Chem.* **1987**, *8*, 1109.

### 2.11.2. DFT Calculations for the Diastereoselective [5+2] Heteroannulation of Phenethyltriflamide 110h with the 1,3-Diene 52a

We initiated the DFT calculations studying the 1,2-migratory insertion of the *trans*-1-phenyl-1,3-butadiene (**52a**) either in its *s*-cis or *s*-trans conformation into the six-membered palladacycle **112h**. In the case of the *s*-trans conformation four possible perpendicular $\eta^2$-coordination modes of the less substituted olefin of the *S-trans*-1,3-diene could be considered depending on the position of the substituent respect to the palladacycle plane (left/right and up/down) giving rise to four structures. Each one was split into two conformers for the 6-membered palladacycle (Figure 14, up). Thus, for clarity throughout all the Supporting Information, compound **I** in the main text (abbreviated) will be fully named $\mathbf{I_{l\text{-}d}Pd_{up}}$, where **l** and **d** indicate the position of the 1,3-diene substituent respect to the plane of the palladacycle (Figure 14, left, down), while $\mathbf{Pd_{up}}$ indicates the boat-like conformation of the palladacycle (the Pd atom up, Figure 14). Following this rule, compound **I'** in main text (abbreviated) will be fully named $\mathbf{I_{l\text{-}u}Pd_{up}}$ in the Supporting Information and the other isomers will be, respectively: $\mathbf{I_{r\text{-}d}Pd_{up}}$, $\mathbf{I_{r\text{-}u}Pd_{up}}$, $\mathbf{I_{l\text{-}d}Pd_{down}}$, $\mathbf{I_{l\text{-}u}Pd_{down}}$, $\mathbf{I_{r\text{-}d}Pd_{down}}$ and $\mathbf{I_{r\text{-}u}Pd_{down}}$ (l = left, r = right, d = down, u = up, Figure 14).

On the other hand, for the s-cis conformation of the *trans*-1-phenyl-1,3-butadiene (**52a**), two isomers, $\mathbf{V_uPd_{up}}$ and $\mathbf{V_nPd_{down}}$, of $\eta^4$-1,3-butadiene coordinated to Pd were found (Figure 14, down). In the $\mathbf{V_uPd_{up}}$ complex, the *s-cis* conformation of the 1,3-diene is $\eta^4$-coordinated to the Pd with a **u**-like shape in the $\mathbf{Pd_{up}}$ boat-like conformation of the palladacycle. In the $\mathbf{V_nPd_{down}}$ complex, the *s-cis*-1,3-butadiene is coordinated to the Pd with a **n**-like shape (Figure 14).

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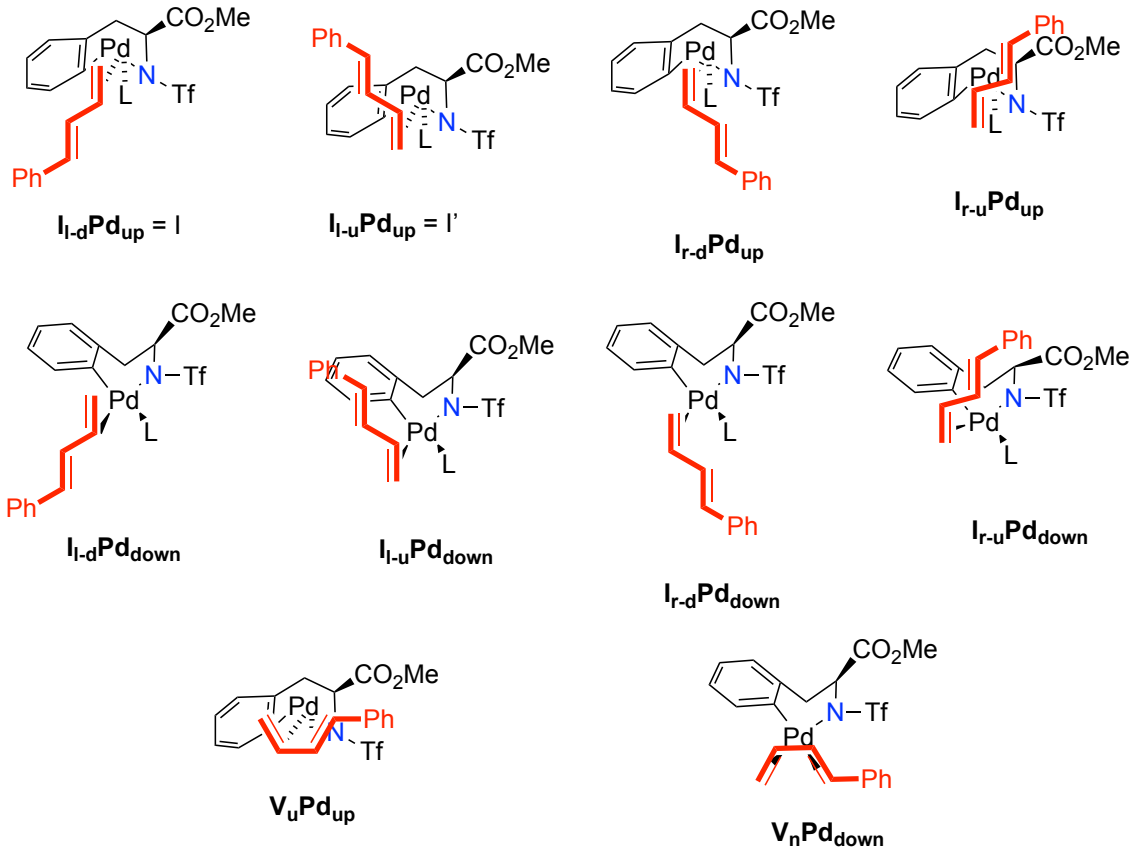



**Figure 14**. Eight possible isomers depending on perpendicular η²-coordination modes of the less substituted olefin of the *s*-trans conformer of the 1,3-diene to the palladacycle plane (substituent left/right and up/down), and boat-like conformation of the palladacycle ($\mathbf{Pd_{up}}$ and $\mathbf{Pd_{down}}$) and two isomers $\mathbf{V_uPd_{up}}$ and $\mathbf{V_nPd_{down}}$ for the η⁴-coordination modes of the *s-cis* conformation of the 1,3-diene to the palladacycle (**u**-like and **n**-shape coordination), and boat-like conformation of the palladacycle ($\mathbf{Pd_{up}}$ and $\mathbf{Pd_{down}}$)

Direct transition states of the 1,2-migratory insertion were only found for $\mathbf{I_{l\text{-}d}Pd_{up}}$, $\mathbf{I_{l\text{-}u}Pd_{up}}$, their boat-like conformers $\mathbf{I_{l\text{-}d}Pd_{down}}$ and $\mathbf{I_{l\text{-}u}Pd_{down}}$ and for the two isomers, $\mathbf{V_uPd_{up}}$ and $\mathbf{V_nPd_{down}}$. Thus, while 1,2-migratory insertion of $\mathbf{I_{l\text{-}d}Pd_{up}}$ and $\mathbf{I_{l\text{-}d}Pd_{down}}$ conformers gave rise to the eight-membered *trans*-palladacycle, 1,2-migratory insertion of $\mathbf{I_{l\text{-}u}Pd_{up}}$ and $\mathbf{I_{l\text{-}u}Pd_{down}}$ gave rise to the eight-membered *cis*-palladacycle. On the other hand, 1,2-migratory insertion of $\mathbf{V_nPd_{down}}$ and $\mathbf{V_uPd_{up}}$ gave rise directly to the *trans*-π-allyl-palladacycle and *cis*-π-allyl-palladacycle, respectively (Figure 15).

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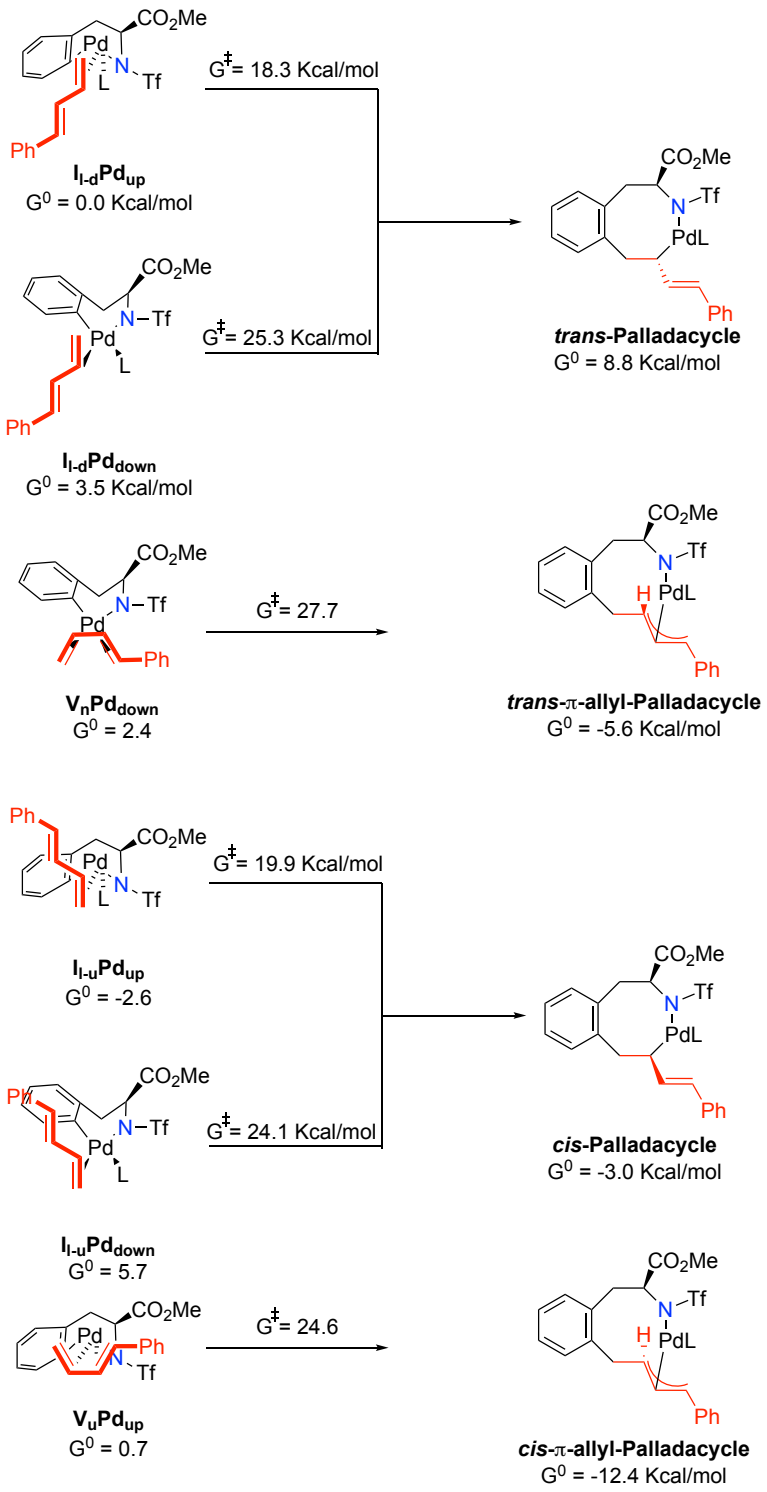



**Figure 15**: Calculated Gibb's energies for the migratory insertion of isomers $\mathbf{I_{l\text{-}d}Pd_{up}}$ and $\mathbf{I_{l\text{-}d}Pd_{down}}$ to ***trans*-Palladacycle**, $\mathbf{I_{l\text{-}u}Pd_{up}}$ and $\mathbf{I_{l\text{-}u}Pd_{down}}$ to ***cis*-Palladacycle**, $\mathbf{V_nPd_{down}}$ to ***trans*-π-allyl-Palladacycle** and $\mathbf{V_uPd_{up}}$ to ***cis*-π-allyl-Palladacycle**. Energies are relative to $\mathbf{I_{l\text{-}d}Pd_{up}}$ complex, combined with those of the relevant substrates

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Due to the energy values obtained for the transition states for the 1,2-migratory insertion from the η⁴-coordination mode of the diene ($\mathbf{V_uPd_{up}}$ $G^{\ddagger}$= 27.7 Kcal/mol and $\mathbf{V_nPd_{down}}$ $G^{\ddagger}$ = 24.6 Kcal/mol) compared with the η²-coordination dienes, this transformation was ruled as direct pathways to obtain the π-allyl-palladacycle intermediates.

*Trans*-palladacycle obtained by 1,2-migratory insertion of $\mathbf{II_{l\text{-}d}Pd_{up}}$ and $\mathbf{II_{l\text{-}d}Pd_{down}}$ could then evolve to the more stable π-allyl-palladacycle intermediate $\mathbf{III_{l\text{-}d}Pd_{down}}$ ($\Delta G^{o}$ = -18.2 Kcal mol$^{-1}$). Direct reductive elimination from $\mathbf{III_{l\text{-}d}Pd_{down}}$ would afford ***trans*-111ha** ($\Delta G^{\ddagger}$ = 28.2 Kcal mol$^{-1}$experimentally not observed). Nevertheless, a more favored pathway involving initial transformation of π-allyl-palladacycle intermediate $\mathbf{III_{l\text{-}d}Pd_{down}}$ to the less stable zwitterionic π-allyl palladium complex $\mathbf{IV_{l\text{-}d}Pd_{down}}$ ($\Delta G^{o}$ = 9.2 Kcal mol$^{-1}$) followed by a $S_N2$ type reaction would afford the experimentally observed ***cis*-111ha** product ($\Delta G^{\ddagger}$ = 8.7 Kcal mol$^{-1}$, Figure 16).

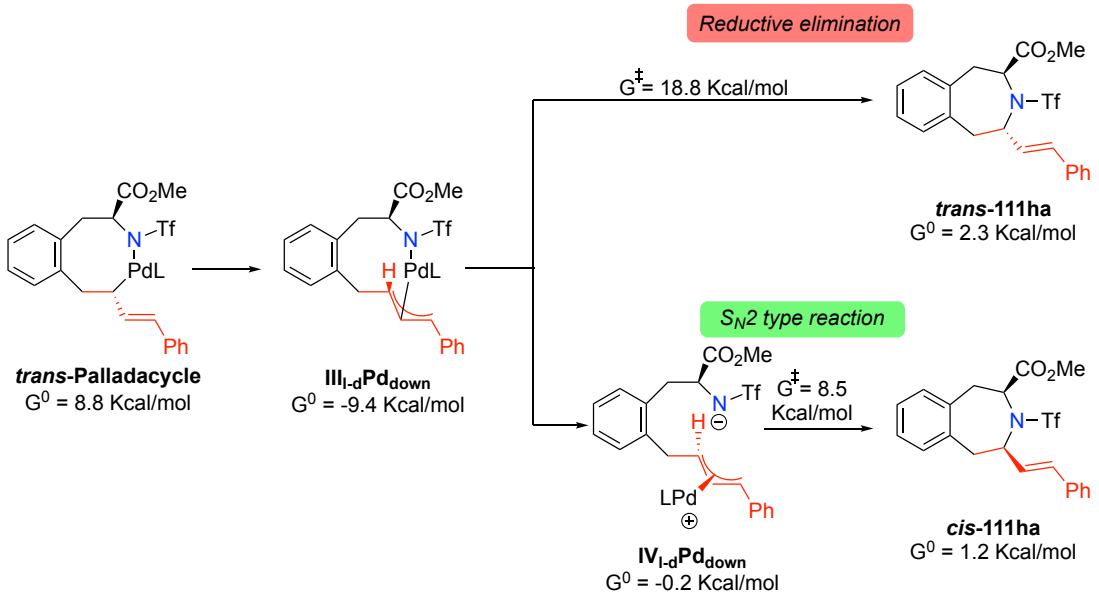



**Figure 16**. Transformation of *trans*-palladacycle into ***trans*-111ha** or ***cis*-111ha** either by reductive elimination or $S_N2$ type reaction from π-allyl-palladacycle intermediate $\mathbf{III_{l\text{-}d}Pd_{down}}$. Energies are relative to $\mathbf{I_{l\text{-}d}Pd_{up}}$ complex, combined with those of the relevant substrates

Analogous to the *trans*-palladacycle, *cis*-palladacycle obtained by 1,2-migratory insertion of $\mathbf{II_{l\text{-}u}Pd_{up}}$ and $\mathbf{II_{l\text{-}u}Pd_{down}}$ could evolved to the ***cis*-111ha** by direct reductive elimination of the more stable π-allylpalladium complexes $\mathbf{III_{l\text{-}u}Pd_{down}}$ ($\Delta G^{\ddagger}$ = 33.1 Kcal mol$^{-1}$) or to the ***trans*-111ha** from the zwitterionic π-allyl palladium complexes $\mathbf{IV_{l\text{-}u}Pd_{down}}$ ($\Delta G^{\ddagger}$ = 14.7 Kcal mol$^{-1}$, Figure 17).

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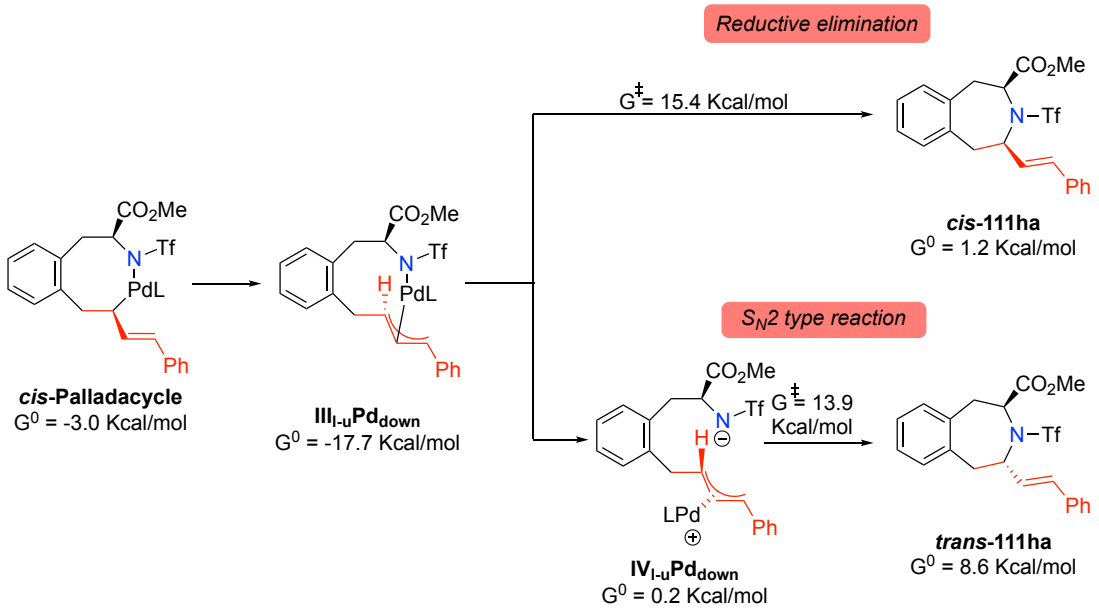



**Figure 17**. Potential energy curves for the reductive elimination of $\mathbf{III_{l\text{-}u}Pd_{down}}$ to ***cis*-111ha** and for $S_N2$-type reaction of $\mathbf{IV_{l\text{-}u}Pd_{down}}$ to ***trans*-111ha**. Energies are relative to $\mathbf{I_{l\text{-}d}Pd_{up}}$ complex, combined with those of the relevant substrates

According with the previously results, the most favorable pathway of the [5+2] heteroannulation of the phenethyltriflamide **110h** with the 1,3-diene **52a** is shown in Figure 18.

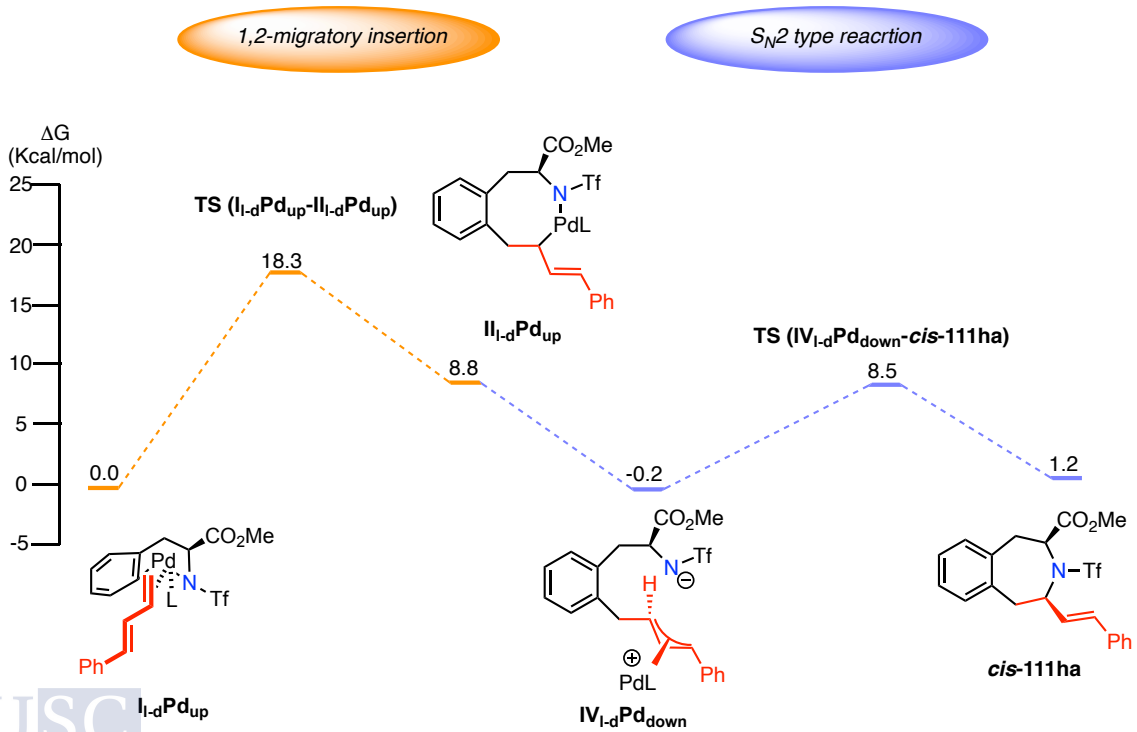
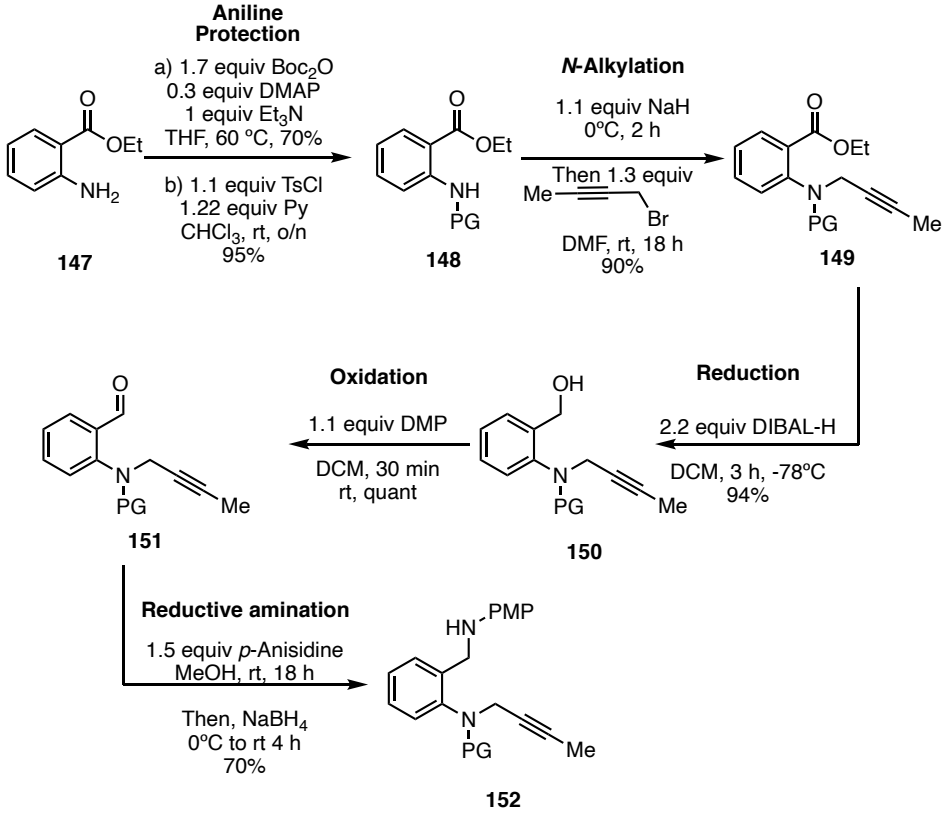



**Figure 18**. Energy profile of the diastereoselective [5+2] heteroannulation of the phenethyltrifamide **110h** with the 1,3-diene **52a**. Energies are relative to $\mathbf{I_{l\text{-}d}Pd_{up}}$ complex, combined with those of the relevant substrates

# 3. Experimental Procedures for Chapter 3

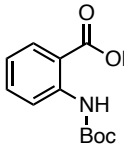
## 3.1. Preparation of Alkynes 152




***PG-amine protection***: $Boc_2O$ (9.3 g, 42 mmol, 1.7 equiv), DMAP (0.92 g, 7.5 mmol, 0.3 equiv) and $Et_3N$ (3.5 mL, 25 mmol, 1 equiv) were added at rt to a solution of ethyl 2-aminobenzoate (4.13 g, 25 mmol, 1 equiv) in 250 mL of dry THF (0.1 M) and the reaction mixture was then stirred at 60 °C in an oil bath for 24 h. Then the reaction was quenched at rt with $H_2O$ and both layers were separated. The aqueous layer was extracted with $Et_2O$ (3 x 50 mL) and the combination of organic layers was washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo. The compound **148a** was purified by silica gel column chromatography with hexane / EtOAc (39:1) as the eluent.

The Ts-derivative **148b** was synthesized according to the literature.[198]

**Ethyl 2-((tert-butoxycarbonyl)amino) benzoate (148a)**

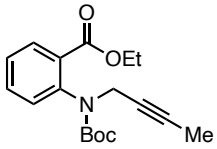


Isolated in 70% yield (5.57 g, 21 mmol); amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.47 – 8.41 (m, 1H), 8.01 (dd, $J$ = 8.1, 1.7 Hz, 1H), 7.55 – 7.46 (m, 1H), 6.99 (ddd, $J$ = 8.3, 7.3, 1.2 Hz, 1H), 4.37 (q, $J$ = 7.2 Hz, 2H), 1.53 (d, $J$ = 0.9 Hz, 8H), 1.44 – 1.37 (m, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 168.0, 152.8, 142.3, 134.3, 130.8, 120.9, 118.6, 114.5, 80.3, 61.1, 28.3, 14.2. **MS** (CI), m / z (%): 266 ($M^+$+1, 100).

***N-Alkylation***: A round-bottomed flask equipped with a stirring magnetic bar was flamed-dried under vacuum and backfilled with argon. Then, it was charged with NaH (1.2 equiv) and put under vacuum and backfilled with argon for three times. Then DMF (0.33 M) was added, and the mixture was cooled to 0 °C. A solution of *N*-protected aniline **149** (1 equiv) in DMF (2 mL) was then added slowly and the mixture was stirred at 0 °C for 2 h.

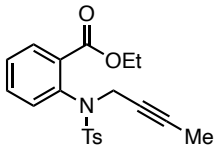
Afterwards, propargyl bromide derivative (1.3 equiv) was added and the reaction was allowed to warm slowly to rt and stirred for 16 h. The reaction was quenched with a saturated solution of $NH_4Cl_{(aq)}$ and extracted with EtOAc. The aqueous layer was extracted with EtOAc and the combination of organic layers was washed with a saturated solution of $NH_4Cl_{(aq)}$ (3 x 100 mL). The combination of organic layers was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography with hexanes/EtOAc (8:2) as the eluent to give the desired products **149.**

**Ethyl 2-(but-2-yn-1-yl(tert-butoxycarbonyl)amino) benzoate (149a)**




Isolated in 93% yield (2.95 g, 9.3 mmol); colorless oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.7 Hz, 1H), 7.58 – 7.22 (m, 3H), 4.69 (d, *J* = 17.5 Hz, 1H), 4.41 – 4.20 (m, 2H), 3.96 (d, *J* = 17.4 Hz, 1H), 1.75 (s, 3H), 1.51 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.28 (s, 6H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 163.2, 133.0, 132.4, 131.6, 131.0, 130.3, 129.8, 128.8, 127.1, 80.3, 74.9, 61.1, 39.5, 28.0, 14.1, 3.6. **MS** (CI), m/z (%): 318 ($M^+$+1, 100).

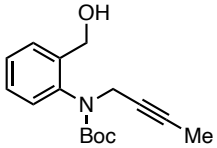
**Ethyl 2-((N-(but-2-yn-1-yl)-4-methylphenyl)sulfonamido)benzoate (149b)**




Isolated in 90% yield (3.34 g, 9 mmol); amorphous off-white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 1H), 7.64 – 7.56 (m, 2H), 7.45 – 7.36 (m, 2H), 7.26 – 7.19 (m, 2H), 7.17 – 7.10 (m, 1H), 4.54 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.69 (t, *J* = 2.4 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 166.1, 143.1, 137.9, 137.4, 133.0, 131.8, 131.5, 131.1, 129.1, 128.7, 127.8, 81.5, 74.0, 61.4, 42.0, 21.5, 14.1, 3.4. **MS** (CI), m/z (%): 372 ($M^+$+1, 100).

***Ester Reduction***: DIBAL-H (1M in DCM, 2.2 equiv) was added dropwise to a stirred solution of the ester **S2** (1 equiv) in DCM (0.3 M) at -78°C. The reaction was then stirred at that temperature for 3 h. Afterwards, MeOH (5 mL) was added followed by a saturated solution of the Rochelle Salt at -78°C. The reaction was then warmed up to rt and stirred for 1h. The mixture was extracted with DCM (3 x 30 mL) and the combination of organic layers was washed with a saturated solution of $NaCl_{(aq)}$, dried over $Na_2SO_4$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography with hexanes/EtOAc (9:1 to 7:3) as the eluent to afford the desired product **150**.

**tert-Butyl but-2-yn-1-yl(2-(hydroxymethyl)phenyl)carbamate (150a)**




Isolated in 99% yield (2.53 g, 9.2 mmol); amorphous white solid. It was used in the next step without further purification.

**N-(But-2-yn-1-yl)-N-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (150b)**



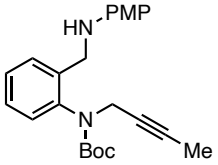

Isolated in 91% yield (2.8 g, 8.5 mmol); amorphous off-white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 3H), 7.37 (td, *J* = 7.5, 1.3 Hz, 1H), 7.33 – 7.23 (m, 2H), 7.15 (td, *J* = 7.7, 1.7 Hz, 1H), 6.65 (dd, *J* = 8.0, 1.3 Hz, 1H), 4.93 (s, 1H), 4.60 (s, 1H), 4.33 (s, 2H), 3.00 – 2.89 (m, 1H), 2.45 (s, 3H), 1.65 (d, *J* = 2.4 Hz, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$): 144.0, 142.2, 137.3,

135.2, 131.0, 129.4, 129.3, 128.3, 128.3, 128.2, 82.0, 72.8, 61.3, 42.6, 21.6, 3.4. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}N_2O_3S$ $[M-H_2O]^+$: 312.1053, found: 312.1059.

***Alcohol Oxidation***: DMP (1.1 equiv) was added to a stirred solution of the alcohol **150** (1 equiv) in DCM (0.25 M) at rt. The mixture was stirred for 30 min. The reaction was quenched with a 1 M solution of $NaOH_{(aq)}$ and extracted with DCM (2 x 30 mL). The combination of organic layers was washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo. The residue was used in the next step without further purification.

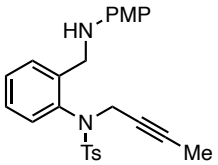
***Reductive Amination***: *p*-Anisidine (1.5 equiv) was added to a stirred solution of the aldehyde previously synthesized in MeOH (0.25 M) or (mixture 1:1 MeOH/DCM) under argon atmosphere. The reaction was stirred at room temperature for 18 h. Then the reaction was cooled to 0 ºC and $NaBH_4$ (1.1 equiv) was added portion-wise. The reaction was then allowed to warm up to rt and stirred for 2 h. The reaction was quenched with water and extracted with DCM. The combination of organic layers was washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography with hexanes/EtOAc (9:1 to 8:2) as the eluent to give the desired products **152**.

**tert-Butyl but-2-yn-1-yl(2-(((4-methoxyphenyl)amino)methyl)phenyl)carbamate (152a)**




Isolated in 80% yield (826 mg, 2.17 mmol) amorphous off-white solid. **$^1$H NMR** (300 MHz, DMSO-$d_6$, 80 °C) δ 7.46 – 7.35 (m, 1H), 7.31 – 7.18 (m, 3H), 6.74 – 6.63 (m, 2H), 6.58 – 6.47 (m, 2H), 5.46 (bs, 1H), 4.30 (bs, 2H), 4.21 (bs, 3H), 3.64 (s, 3H), 1.75 (t, $J$ = 2.4 Hz, 3H), 1.39 (s, 9H). **$^{13}$C NMR** (75 MHz, DMSO-$d_6$, 80 °C), δ (ppm): 153.0, 150.7, 142.7, 139.5, 137.6, 127.5, 127.1, 126.9, 126.8, 114.5, 113.0, 79.5, 79.4, 75.0, 55.2), 43.3, 27.6, 2.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{28}N_2O_3$ $[M+H]^+$: 381.2173, found: 381.2171.

**N-(But-2-yn-1-yl)-N-(2-(((4-methoxyphenyl)amino)methyl)phenyl)-4-methylbenzenesulfonamide (152b)**



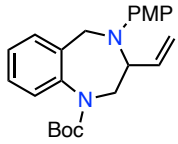

Isolated in 70% yield (2 g, 4.8 mmol); amorphous off-white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.64 (d, $J$ = 7.9 Hz, 2H), 7.52 (d, $J$ = 7.7 Hz, 1H), 7.29 (d, $J$ = 8.1 Hz, 3H), 7.13 (t, $J$ = 7.7 Hz, 1H), 6.76 (t, $J$ = 7.1 Hz, 3H), 6.62 (d, $J$ = 8.4 Hz, 2H), 4.52 (s, 2H), 4.33 (s, 2H), 4.08 – 4.01 (m, 1H), 3.74 (s, 3H), 2.45 (s, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.8, 142.6, 141.1, 137.7, 135.8, 129.4, 129.3, 129.1, 128.4, 127.4, 114.9, 114.3, 81.8, 73.0, 55.8, 45.4, 42.3, 21.6, 3.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{27}N_2O_3S$ $[M+H]^+$: 435.1737, found: 435.1730.

## 3.2. General Procedure for the Cyclization of Alkynes 152

A 5 mL sealed tube equipped with stirring magnetic bar was flamed-dried under vacuum, cooled to rt and backfilled with argon. Then it was charged with $[Rh(cod)Cl]_2$ (4 mg, 8 μmol, 0.04 equiv), *rac*-BNP acid (5.6 mg, 16 μmol, 0.08 equiv) and the ligand (, 16 μmol, 0.08 equiv). Afterwards, it was put in vacuum and backfilled with argon for 3 times. Then 0.5 mL of DCE was added and the mixture was stirred for 10 min at rt. Finally, the alkyne **152** (0.2 mmol, 1 equiv) was added under flow of argon and the mixture was stirred

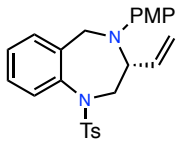
at 70 ºC in an oil bath for 24 h. After cooling at rt, the solvent was evacuated in vacuo and the residue was purified by silica gel column chromatography with EtOAc/Hexanes (1:9) as the eluent to give the desired seven-membered heterocycle **153**.

**tert-Butyl 4-(4-methoxyphenyl)-3-vinyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-1-carboxylate (153a)**




Isolated as an amorphous off-white solid. **$^1$H NMR** (300 MHz, DMSO-$d_6$, 80 °C), δ 7.43 – 7.30 (m, 1H), 7.29 – 7.09 (m, 3H), 6.70 (d, $J$ = 9.1 Hz, 2H), 6.62 (d, $J$ = 9.1 Hz, 2H), 6.03 (ddd, $J$ = 17.2, 10.5, 4.7 Hz, 1H), 5.42 – 5.19 (m, 2H), 4.81 – 4.60 (m, 1H), 4.68 (d, $J$ = 17.3 Hz, 1H), 4.39 (d, $J$ = 17.3 Hz, 1H), 4.07 (dd, $J$ = 14.6, 5.2 Hz, 1H), 3.62 (s, 3H), 3.48 (dd, $J$ = 14.6, 9.9 Hz, 1H), 1.22 (s, 9H). **$^{13}$C NMR** (75 MHz, DMSO-$d_6$, 80 °C), δ (ppm): 152.5, 151.2, 143.8, 140.7, 135.3, 132.8, 127.8, 126.9, 125.7, 124.9, 115.4, 114.3, 113.9, 79.3, 59.4, 55.2, 51.3, 48.1, 27.3. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{23}H_{28}N_2O_3Na$ $[M+Na]^+$: 403.1992, found: 403.1990.

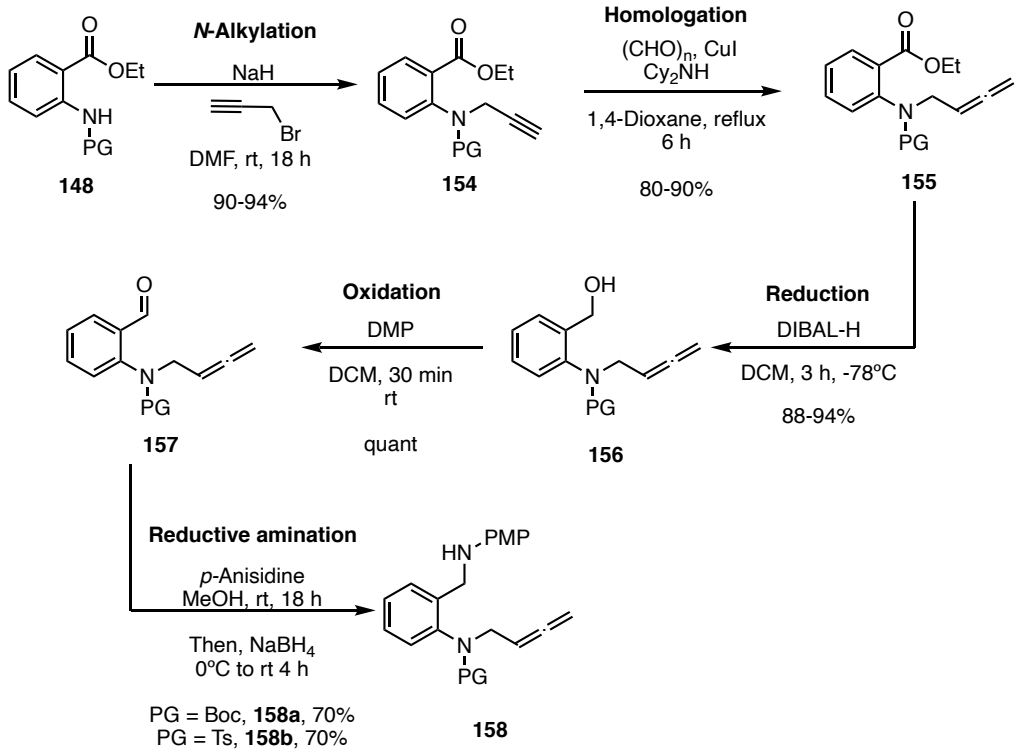
**(R)-4-(4-Methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine (153b)**




Isolated as an amorphous off-white solid. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, $J$ = 8.1 Hz, 1H), 7.22 – 7.03 (m, 5H), 6.64 (d, $J$ = 7.9 Hz, 2H), 6.51 (d, $J$ = 8.7 Hz, 2H), 6.25 (d, $J$ = 8.6 Hz, 2H), 5.75 (ddd, $J$ = 17.3, 10.6, 3.9 Hz, 1H), 5.16 (dd, $J$ = 28.1, 13.9 Hz, 2H), 4.57 – 4.36 (m, 3H), 4.04 (d, $J$ = 17.2 Hz, 1H), 3.65 (s, 3H), 3.47 (q, $J$ = 13.4, 12.7 Hz, 1H), 2.08 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 152.0, 143.9, 142.9, 139.5, 136.1, 133.9, 129.0, 128.4, 127.6, 126.7, 126.4, 126.3, 117.1, 114.3, 60.2, 55.6, 54.2, 21.4. **HRMS** (MM: ESI-APCI+) $m/z$ calc'd for $C_{25}H_{27}N_2O_3S$ $[M+H]^+$: 435.1737, found: 435.1738.

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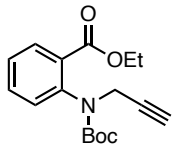
## 3.3. Preparation of Allenes 158a-c, 158e-g, 158k-l




Tosyl derivatives were synthesized according to literature procedures.[214]

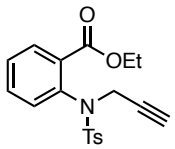
See general procedure of *N-Alkylation* of alkynes:

**Ethyl 2-((*tert*-butoxycarbonyl) (prop-2-yn-1-yl) amino) benzoate (154a)**



Isolated in 94% yield (2.85 g, 9.4 mmol), colorless oil. **$^1$H NMR** (300 MHz, $CDCl_3$), δ 7.96 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.65 – 7.33 (m, 3H), 4.82 (dd, *J* = 17.7, 2.5 Hz, 1H), 4.34 (dtd, *J* = 9.7, 7.1, 3.4 Hz, 2H), 4.03 (dd, *J* = 17.7, 2.5 Hz, 1H), 2.33 – 2.15 (m, 1H), 1.60 (s, 2H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.31 (s, 8H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 166.0, 154.0, 153.7, 141.6, 141.1, 132.6, 132.5, 131.0, 129.8, 129.5, 129.1, 127.3, 81.0, 80.4, 80.0, 79.8, 72.2, 71.8, 61.1, 60.9, 40.2, 39.1, 28.2, 28.0, 14.1. **MS** (CI), m/z (%): 304 ($M^+$+1, 100).

**Ethyl 2-((4-methyl-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido) benzoate (154b)**

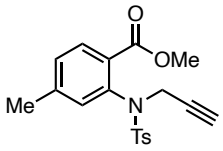


Isolated in 90% yield (3.2 g, 9 mmol); amorphous yellow solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.94 – 7.83 (m, 1H), 7.66 – 7.54 (m, 2H), 7.51 – 7.35 (m, 2H), 7.30 – 7.13 (m, 3H), 5.02 – 4.35 (m, 2H), 4.28 (s, 2H), 2.42 (s, 3H), 2.21 (t, *J* = 2.5 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 166.0, 143.4, 137.4, 137.1, 132.9, 132.1, 131.9, 131.3, 129.3, 129.0, 127.7, 73.6, 61.5, 41.3, 21.6, 14.1. **MS** (CI), m/z (%): 358 ($M^+$+1, 100).

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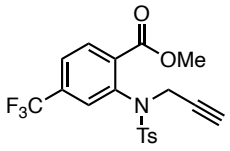
[214] a) Zhao, C.-Y.; Li, K.; Pang, Y.; Li, J.-Q.; Liang, C.; Su, G.-F.; Mo, D.-L. *Adv. Synth. Catal.* **2018**, *360*, 1919. b) Yang, F.; Ding, D.; Wang, C. *Org. Lett.* **2020**, *22*, 9203. c) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017. d) Nishiguchi, A.; Ikemoto, T.; Ito, T.; Miura, S.; Tomimatsu, K. *Heterocycles* **2007**, *71*, 1183. e) Iioka, R.; Yorozu, K.; Sakai, Y.; Kawai, R.; Hatae, N.; Takashima, K.; Tanabe, G.; Wasada, H.; Yoshimatsu, M. *Eur. J. Org. Chem.* **2021**, 1553. f) Jia, M.-Q.; You, S.-L. *ACS Catalysis* **2013**, *3*, 622. g) Guo, Z.; Jia, H.; Liu, H.; Wang, Q.; Huang, J.; Guo, H. *Org. Lett.* **2018**, *20*, 2939.

**Methyl 4-methyl-2-((4-methyl-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)benzoate (154c)**



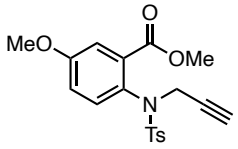
Isolated in 90% yield (3.21 g, 9 mmol); amorphous off-white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.9 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.20 (dd, *J* = 8.1, 4.0 Hz, 3H), 7.01 (d, *J* = 1.7 Hz, 1H), 4.64 (s, 1H), 3.69 (s, 3H), 2.38 (s, 3H), 2.28 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 166.1, 143.3, 143.2, 137.5, 137.2, 133.0, 131.3, 129.7, 129.3, 129.0, 128.9, 127.9, 127.6, 78.9, 73.4, 52.1, 41.3, 21.5, 21.3. **MS** (CI), m/z (%): 358 ($M^+$+1, 100).

**Methyl 2-((4-methyl-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)-4-(trifluoromethyl)benzoate (154e)**



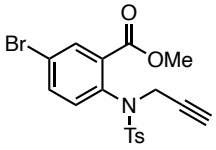
Isolated in 84% yield (1.8 g, 4.5 mmol); amorphous yellow solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.0 (d, *J* = 8.1 Hz, 1H), 7.7 (d, *J* = 8.1 Hz, 1H), 7.6 (d, *J* = 8.0 Hz, 2H), 7.4 (s, 1H), 7.3 – 7.1 (m, 2H), 4.6 (s, 2H), 3.9 (s, 3H), 2.4 (s, 3H), 2.2 (d, *J* = 2.5 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 165.5, 144.2, 138.3, 136.5 (d, *J* = 8.1 Hz), 133.9 (q, *J* = 33.6 Hz), 131.8, 129.6, 129.1 (d, *J* = 3.8 Hz), 127.9, 125.8 (d, *J* = 3.9 Hz), 124.8, 121.2, 74.5, 52.9, 41.3, 21.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -63.2. **MS** (CI), m/z (%): 412 ($M^+$+1, 100).

**Methyl 5-methoxy-2-((4-methyl-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)benzoate (154f)**



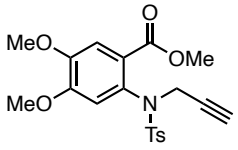
Isolated in 83% yield (0.62 g, 1.7 mmol); yellow oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.6 (d, *J* = 7.9 Hz, 2H), 7.3 (d, *J* = 3.0 Hz, 1H), 7.2 (d, *J* = 7.9 Hz, 2H), 7.1 (d, *J* = 8.7 Hz, 1H), 6.9 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.9 (s, 1H), 4.3 (s, 1H), 3.8 (d, *J* = 13.9 Hz, 6H), 2.4 (s, 3H), 2.2 (s, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 166.3, 159.6, 143.2, 137.3, 133.54, 133.4, 129.9, 129.4, 127.8, 117.8, 116.0, 79.1, 73.6, 55.8, 52.5, 41.5, 21.6. **MS** (CI), m/z (%): 423 ($M^+$+1, 100).

**Methyl 5-bromo-2-((4-methyl-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)benzoate (154g)**



Isolated in 70% yield (2.95 g, 7 mmol); amorphous off-white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 2.5 Hz, 1H), 7.48 (dd, *J* = 8.3, 6.3 Hz, 3H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 1H), 4.49 (s, 1H), 3.71 (s, 3H), 2.33 (s, 3H), 2.16 (t, *J* = 2.3 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 164.9, 143.8, 136.8, 136.6, 135.3, 134.2, 134.1, 133.6, 129.5, 127.7, 123.1, 78.5, 74.1, 52.7, 41.2, 21.6.**MS** (CI), m/z (%): 374 ($M^+$+1, 100).

**Methyl 4,5-dimethoxy-2-((4-methyl-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)benzoate (154k)**



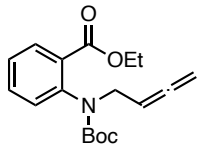
Isolated in 99% yield (0.8 g, 1.98 mmol); white foam. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.9 Hz, 2H), 7.36 (s, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.67 (s, 1H), 4.88 (s, 1H), 4.27 (s, 1H), 3.90 (s, 3H), 3.70 (d, *J* = 2.9 Hz, 6H), 2.40 (s, 3H), 2.23 (t, *J* = 2.5 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 165.7, 151.5, 148.8, 143.5, 137.4, 131.5, 129.3, 127.9, 123.9, 115.4, 113.2, 79.3, 73.5, 56.2, 56.0, 52.2, 41.4, 21.6. **MS** (CI), m/z (%): 404 ($M^+$+1, 100).

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***Homologation of alkynes to allenes:*** CuI (0.5 equiv), $(CHO)_n$ (2.5 equiv) and $Cy_2NH$ (1.8 equiv) was added to a stirred solution of the alkyne **154** (1 equiv) in dioxane (0.2 M). The reaction was then heated to reflux in an oil bath for 6 h. Then, the reaction was cooled to rt and the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$ (50 mL), washed with 10% $NH_4OH$ (2 x 50 mL) and $H_2O$ (2 x 50 mL). The combination of organic layers was

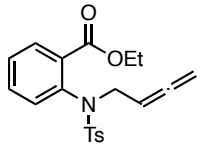
dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexanes/EtOAc (8:2) as the eluent to give the allenes **155**.

**Ethyl 2-(buta-2,3-dien-1-yl(*tert*-butoxycarbonyl) amino) benzoate (155a)**



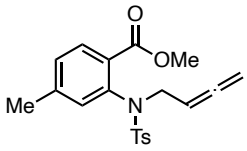
Isolated in 82% yield (2.44 g, 7.7 mmol); yellow oil. **$^1$H NMR** (300 MHz, $CDCl_3$), δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.17 (m, 2H), 5.30 (p, *J* = 6.6 Hz, 1H), 4.78 – 4.60 (m, 2H), 4.58 – 4.41 (m, 1H), 4.38 – 4.21 (m, 2H), 3.94 – 3.79 (m, 1H), 1.50 (s, 3H), 1.36. **$^{13}$C NMR** (75 MHz, $CDCl_3$) 209.1, 166.3, 153.9, 141.9, 132.3, 131.0, 129.2, 126.7, 87.4, 80.0, 75.8, 61.1, 49.1, 28.0, 14.2. **MS** (CI), m/z (%): 318 ($M^+$+1, 100).

**Ethyl 2-((*N*-(buta-2,3-dien-1-yl)-4-methylphenyl) sulfonamido) benzoate (155b)**



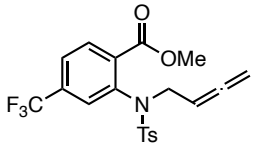
Isolated in 90% yield (3 g, 8.1 mmol); amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 1H), 7.52 – 7.44 (m, 2H), 7.36 (hept, *J* = 5.3 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.97 – 6.88 (m, 1H), 5.21 (p, *J* = 7.0 Hz, 1H), 4.55 (dt, *J* = 6.6, 2.3 Hz, 2H), 4.38 – 4.15 (m, 5H), 2.36 (s, 4H), 1.34 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 209.6, 166.18, 143.3, 137.7, 136.9, 133.1, 131.8, 131.3, 130.9, 129.4, 128.4, 127.5, 86.6, 75.9, 61.3, 50.9, 21.5, 14.1. **MS** (CI), m/z (%): 372 ($M^+$+1, 100).

**Methyl 2-((*N*-(buta-2,3-dien-1-yl)-4-methylphenyl)sulfonamido)-4-methylbenzoate (155c)**



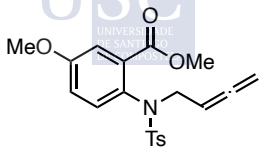
Isolated in 85% yield (2.84 g, 7.65 mmol); amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.20 (dd, *J* = 14.1, 7.9 Hz, 3H), 6.86 (s, 1H), 5.37 – 5.08 (m, 1H), 4.58 (dt, *J* = 5.8, 2.4 Hz, 2H), 4.27 (s, 2H), 3.68 (d, *J* = 1.1 Hz, 3H), 2.39 (s, 3H), 2.30 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 209.6, 166.3, 143.2, 142.9, 137.9, 137.2, 132.5, 131.4, 129.4, 129.1, 129.1, 127.5, 86.8, 75.9, 51.9, 51.0, 21.5, 21.3. **MS** (CI), m/z (%): 372 ($M^+$+1, 100).

**Methyl 2-((*N*-(buta-2,3-dien-1-yl)-4-methylphenyl)sulfonamido)-4-(trifluoromethyl)benzoate (155e)**



Isolated in 70% yield (1.3 g, 3 mmol); brown oil **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.0 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.6 (ddd, *J* = 8.2, 1.8, 0.8 Hz, 1H), 7.5 – 7.5 (m, 2H), 7.3 – 7.2 (m, 2H), 7.1 (d, *J* = 1.8 Hz, 1H), 5.2 (ddd, *J* = 7.4, 6.6, 0.9 Hz, 1H), 4.6 (dt, *J* = 6.6, 2.3 Hz, 2H), 4.3 (dt, *J* = 7.4, 2.3 Hz, 3H), 3.9 (s, 4H), 2.4 (s, 4H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 210.2, 165.7, 144.0, 138.7, 133.7 (q, *J* = 33.2 Hz), 131.8, 129.8, 128.0 (q, *J* = 3.6 Hz), 127.6, 125.1 (q, *J* = 3.7 Hz), 123.1 (q, *J* = 272.8 Hz), 86.1, 76.2, 52.8, 50.9, 21.6. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -63.0. **MS** (CI), m/z (%): 426 ($M^+$+1, 100).

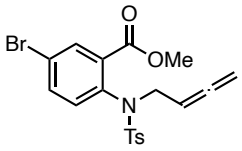
**Methyl 2-((*N*-(buta-2,3-dien-1-yl)-4-methylphenyl)sulfonamido)-5-methoxybenzoate(155f)**



Isolated in 70 % yield (0.45 g, 1.16 mmol); brown oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 2.6 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.94 – 6.90 (m, 2H), 5.22 (q, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.5 Hz, 2H), 4.34 (s, 1H), 4.21 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 2.41 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 209.8, 166.4, 159.1, 143.2, 137.3,

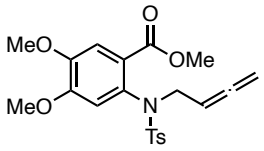
133.5, 132.8, 130.3, 129.5, 127.6, 117.9, 115.9, 86.8, 75.9, 55. 8, 52.4, 51.7, 21.6. **MS** (CI), m/z (%): 388 ($M^+$+1, 100).

**Methyl 5-bromo-2-((*N*-(buta-2,3-dien-1-yl)-4-methylphenyl)sulfonamido)benzoate (155g)**



Isolated in 80% yield (2.44 g, 5.6 mmol); amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 11.0, 8.3 Hz, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 1H), 5.19 (p, *J* = 7.0 Hz, 1H), 4.58 (dd, *J* = 6.6, 2.4 Hz, 2H), 4.25 (dd, *J* = 7.4, 2.4 Hz, 2H), 3.75 (s, 3H), 2.38 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 209.8, 165.1, 143.6, 136.9, 136.6, 135.0, 134.3, 134.2, 132.79, 129.6, 127.5, 122.3, 86.4, 76.1, 52.5, 50.9, 21.5. **MS** (CI), m/z (%): 437 ($M^+$1, 100).

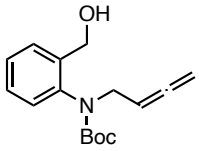
**Methyl 2-((*N*-(buta-2,3-dien-1-yl)-4-methylphenyl)sulfonamido)-4,5-dimethoxybenzoate (155k)**



Isolated in 56% yield (0.46 g, 1.1 mmol); brown foam. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.37 (s, 1H), 7.31 – 7.18 (m, 3H), 6.52 (s, 1H), 5.26 (t, *J* = 6.9 Hz, 1H), 4.61 (s, 2H), 4.40 (s, 1H), 4.15 (s, 1H), 3.92 (s, 4H), 3.75 (s, 4H), 3.66 (s, 3H), 2.40 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 209.8, 165.9, 151.5, 148.5, 143.2, 137.5, 132.0, 129.4, 127.7, 124.0, 115.0, 113.4, 87.0, 76.0, 56.2, 56.2, 52.1, 51.4, 21.6. **MS** (CI), m/z (%): 418 ($M^+$+1, 100).

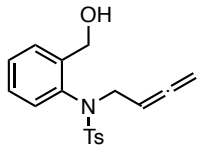
See general procedure of *Ester Reduction* of alkynes:

***tert*-Butyl buta-2,3-dien-1-yl(2-(hydroxymethyl) phenyl) carbamate (156a)**



Isolated in 88% yield; colorless oil. **$^1$H NMR** (300 MHz, DMSO-$d_6$, 80 °C), δ 7.52 (d, *J* = 7.1 Hz, 1H), 7.34 – 7.17 (m, 2H), 7.12 (dd, *J* = 7.4, 1.7 Hz, 1H), 5.26 (p, *J* = 6.6 Hz, 1H), 4.90 – 4.69 (m, 3H), 4.45 (d, *J* = 5.3 Hz, 2H), 4.06 (bs, 2H), 1.35 (s, 9H). **$^{13}$C NMR** (75 MHz, DMSO-$d_6$, 80 °C), δ (ppm): 208.2, 153.2, 139.4, 139.0, 127.5, 127.1, 126.6, 126.5, 86.6, 78.9, 75.7 58.7, 48.3, 27.5. **MS** (CI), m/z (%): 276 ($M^+$-[OH], 100).

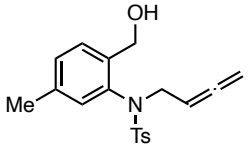
***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(hydroxymethyl) phenyl)-4-methylbenzenesulfonamide (158l)**



Isolated in 94% yield (2.5 g, 7.6 mmol); amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.63 – 7.50 (m, 3H), 7.39 – 7.24 (m, 3H), 7.14 (td, *J* = 7.7, 1.7 Hz, 1H), 6.46 (dd, *J* = 8.0, 1.3 Hz, 1H), 5.10 – 4.93 (m, 2H), 4.66 – 4.38 (m, 4H), 3.84 (dd, *J* = 13.8, 8.3 Hz, 1H), 3.09 – 2.97 (m, 1H), 2.45 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 209.9, 144.0, 142.4, 136.9, 134.8, 131.0, 129.6, 129.1, 128.3, 128.1, 127.7, 85.3, 76.1, 61.2, 51.4, 21.6. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}N_2O_3S$ [M-$H_2O$]$^+$: 312.1053, found: 312.1059.

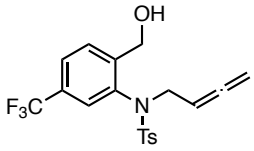
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**_N_-(Buta-2,3-dien-1-yl)-_N_-(2-(hydroxymethyl)-5-methylphenyl)-4-methylbenzenesulfonamide (156c)**



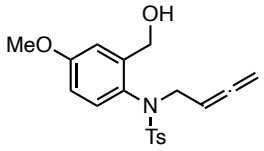
Isolated in 90% yield (2.37 g, 6.9 mmol); amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.56 (d, $J$ = 8.0 Hz, 2H), 7.47 (d, $J$ = 7.8 Hz, 1H), 7.31 (d, $J$ = 7.9 Hz, 2H), 7.16 (d, $J$ = 7.8 Hz, 1H), 6.24 (s, 1H), 5.09 – 4.97 (m, 1H), 4.93 (d, $J$ = 11.9 Hz, 1H), 4.61 (d, $J$ = 7.1 Hz, 1H), 4.57 – 4.37 (m, 3H), 3.88 – 3.73 (m, 1H), 2.46 (s, 3H), 2.16 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 209.9, 144.1, 139.2, 138.3, 136.9, 134.8, 130.9, 129.9, 129.5, 128.3, 128.2, 85.5, 76.2, 61.1, 51.4, 21.7, 20.9. **MS** (CI), m/z (%): 326 $M^+$-[OH], 100).

**_N_-(buta-2,3-dien-1-yl)-_N_-(2-(hydroxymethyl)-5-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide (156e)**



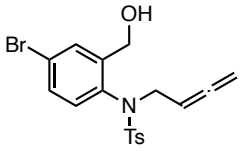
Isolated in 64% yield (0.7 g, 1.86 mmol); amorphous yellow solid. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.8 (d, $J$ = 8.0 Hz, 1H), 7.6 (d, $J$ = 8.1 Hz, 1H), 7.5 (dd, $J$ = 8.2, 1.7 Hz, 2H), 7.3 (d, $J$ = 7.8 Hz, 2H), 6.6 (s, 1H), 5.1 – 5.0 (m, 2H), 4.7 – 4.6 (m, 2H), 4.5 (q, $J$ = 10.1 Hz, 2H), 3.8 (dd, $J$ = 13.6, 8.5 Hz, 1H), 2.5 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 210.5, 146.8, 144.8, 137.5, 134.0, 130.4 (q, $J$ = 33.0 Hz), 129.9, 128.2, 125.8 (q, $J$ = 3.7 Hz), 125.0 (q, $J$ = 3.7 Hz), 123.4 (1, $J$ = 272.3 Hz), 85.0, 76.4, 61.0, 51.4, 21.7. **MS** (CI), m/z (%): 380 $M^+$-[OH], 100).

**_N_-(buta-2,3-dien-1-yl)-_N_-(2-(hydroxymethyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (156f)**



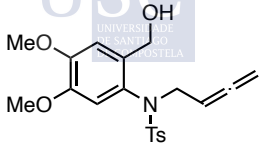
Isolated in 54% yield (0.23 g, 0.663 mmol), brown oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.3 – 7.3 (m, 2H), 7.1 (d, $J$ = 3.0 Hz, 1H), 6.6 (dd, $J$ = 8.8, 3.0 Hz, 1H), 6.4 (d, $J$ = 8.8 Hz, 1H), 5.1 – 5.0 (m, 1H), 4.9 (d, $J$ = 12.2 Hz, 1H), 4.6 (dddd, $J$ = 11.2, 6.6, 2.9, 1.6 Hz, 1H), 4.6 – 4.4 (m, 3H), 3.8 (s, 4H), 3.0 (s, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 210.0, 159.8, 144.0, 143.9, 135.1, 129.7, 129.4, 128.9, 128.2, 115.0, 114.6, 85.5, 76.2, 61.6, 55.6, 51.7, 21.7. **MS** (CI), m/z (%): 342 ($M^+$-[OH], 100).

**_N_-(4-Bromo-2-(hydroxymethyl)phenyl)-_N_-(buta-2,3-dien-1-yl)-4-methylbenzenesulfonamide (156g)**



Isolated in 90% yield (2 g, 5 mmol); amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, $J$ = 2.5 Hz, 1H), 7.56 (d, $J$ = 8.1 Hz, 2H), 7.39 – 7.17 (m, 3H), 6.33 (d, $J$ = 8.5 Hz, 1H), 5.09 – 4.91 (m, 2H), 4.70 – 4.35 (m, 4H), 3.88 – 3.75 (m, 1H), 2.48 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.0, 144.7, 144.4, 135.8, 134.4, 133.6, 131.2, 129.8, 129.2, 128.0, 123.0, 85.2, 76.41, 60.8, 51.3, 21.7. **MS** (CI), m/z (%): 391 ($M^+$-[OH], 100).

**_N_-(buta-2,3-dien-1-yl)-_N_-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (156k)**

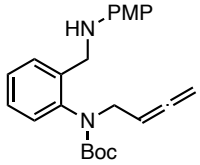


Isolated in 57% yield (0.24 g, 0.61 mmol), amorphous white solid. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.3 (d, $J$ = 7.9 Hz, 2H), 7.0 (s, 1H), 5.8 (s, 1H), 5.0 (dt, $J$ = 7.9, 6.6 Hz, 1H), 4.9 (d, $J$ = 11.9 Hz, 1H), 4.7 – 4.6 (m, 1H), 4.5 (ddt, $J$ = 9.4, 6.5, 2.3 Hz, 1H), 4.5 (ddt, $J$ = 13.5, 5.9, 2.8 Hz, 1H), 4.4 (d, $J$ = 12.0 Hz, 1H), 3.9 (s, 3H), 3.8 (ddt, $J$ = 13.7, 8.2, 1.7 Hz, 1H), 3.5 (s, 3H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 210.1, 149.4, 148.4, 144.2,

135.4, 135.1, 129.7, 128.9, 128.4, 112.9, 110.5, 85.6, 76.3, 61.2, 56.1, 55.8, 51.6, 21.7. **MS** (CI), m/z (%): 382 ($M^+$-[OH], 100).

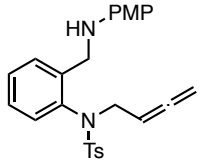
See general procedure of *Oxidation and Reductive Amination* of alkynes:

***tert*-Butyl buta-2,3-dien-1-yl(2-(((4-methoxyphenyl) amino) methyl) phenyl) carbamate (158a)**



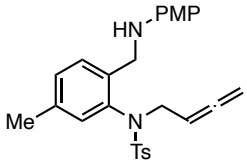

Isolated in 70% yield (1.8 g, 4.8 mmol); yellow oil.
**$^1$H NMR** (300 MHz, DMSO-$d_6$, 80 °C), δ (ppm): 7.45 – 7.36 (m, 1H), 7.30 – 7.14 (m, 3H), 6.68 (d, $J$ = 8.9 Hz, 2H), 6.50 (d, $J$ = 8.8 Hz, 2H), 5.46 (bs, 1H), 5.33 (p, $J$ = 6.6 Hz, 1H), 4.87 – 4.76 (m, 2H), 4.25 (bs, 1H), 4.15 (s, 2H), 3.97 (bs, 1H), 364 (s, 3H), 1.40 (s, 9H). **$^{13}$C NMR** (75 MHz, DMSO-$d_6$, 80 °C) δ 208.2, 153.2, 150.8, 142.6, 140.0, 137.3, 127.8, 127.3, 126.7, 114.5, 113.0, 86.7, 79.2, 75.9, 55.2, 48.4, 43.4, 27.6. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{28}N_2O_3$ $[M+H]^+$: 381.2173, found: 381.2176.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(((4-methoxyphenyl) amino) methyl) phenyl)-4-methylbenzenesulfonamide (158b)**



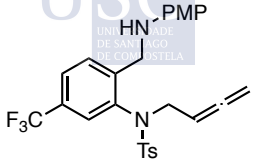

Isolated in 70% yield (1.5 g, 3.5 mmol); amorphous white solid.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 2H), 7.53 (dd, $J$ = 7.7, 1.6 Hz, 1H), 7.28 (dd, $J$ = 10.4, 7.2 Hz, 3H), 7.12 (td, $J$ = 7.7, 1.6 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.64 – 6.56 (m, 3H), 5.12 (p, $J$ = 6.9 Hz, 1H), 4.70 – 4.32 (m, 5H), 3.90 (dd, $J$ = 13.7, 8.4 Hz, 1H), 3.74 (s, 3H), 2.45 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 210.0, 152.1, 143.8, 142.6, 141.3, 137.3, 135.5, 129.7, 129.6, 129.3, 128.8, 128.2, 127.9, 127.4, 114.9, 114.3, 85.6, 76.0, 55.8, 51.4, 45.3, 21.6. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{27}N_2O_3S$ $[M+H]^+$: 435.1737, found: 435.1738.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(((4-methoxyphenyl)amino)methyl)-5-methylphenyl)-4-methylbenzenesulfonamide (158c)**




Isolated in 80% yield (716 mg, 1.6 mmol), amorphous white solid.
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.60 (d, $J$ = 7.9 Hz, 2H), 7.39 (d, $J$ = 7.8 Hz, 1H), 7.29 (d, $J$ = 8.0 Hz, 2H), 7.09 (d, $J$ = 7.8 Hz, 1H), 6.81 – 6.72 (m, 2H), 6.67 – 6.57 (m, 2H), 6.41 (s, 1H), 5.11 (p, $J$ = 6.9 Hz, 1H), 4.69 – 4.48 (m, 2H), 4.37 (dd, $J$ = 16.7, 6.7 Hz, 3H), 3.88 (dd, $J$ = 13.6, 8.5 Hz, 1H), 3.74 (d, $J$ = 1.1 Hz, 3H), 2.45 (s, 3H), 2.18 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.0, 152.2, 143.9, 142.6, 137.9, 137.4, 137.3, 135.6, 129.7, 129.5, 129.4, 128.9, 128.3, 114.9, 114.5, 85.8, 76.1, 55.9, 51.4, 45.2, 21.7, 20.9. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{29}N_2O_3S$ $[M+H]^+$: 449.1893, found: 449.1896.

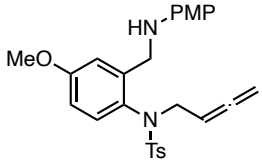
***N*-(buta-2,3-dien-1-yl)-*N*-(2-(((4-methoxyphenyl)amino)methyl)-5-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide (158e)**




Isolated in 73% yield, (0.7 g, 1.4 mmol), brown oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.7 (d, $J$ = 8.1 Hz, 1H), 7.6 – 7.5 (m, 3H), 7.3 (d, $J$ = 7.9 Hz, 2H), 6.8 (d, $J$ = 8.5 Hz, 2H), 6.7 (s, 1H), 6.6 (d, $J$ = 8.8 Hz, 2H), 5.2 – 5.1 (m, 1H), 4.7 (d, $J$ = 16.3 Hz, 1H), 4.6 (t, $J$ = 8.8 Hz, 1H), 4.6 – 4.4 (m, 3H), 3.9 – 3.8 (m, 1H), 3.7 (s, 3H), 2.5 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 210.5, 152.4, 146.3, 144.6, 142.1, 138.0, 134.5, 129.9, 129.6,

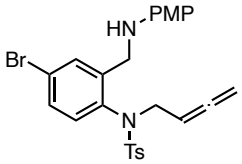
129.6 (q, $J$ = 32.9 Hz), 125.5 (q, $J$ = 3.7 Hz), 125.2 (q, $J$ = 3.7 Hz), 123.6 (q, $J$ = 272.2 Hz), 114.4, 85.2, 76.3, 55.9, 51.4, 45.4, 21.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -62.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{26}F_3N_2O_3S$ $[M+H]^+$: 503.1649, found: 503.1639.

***N*-(buta-2,3-dien-1-yl)-*N*-(4-methoxy-2-(((4-methoxyphenyl)amino)methyl)phenyl)-4-methylbenzenesulfonamide(158f)**



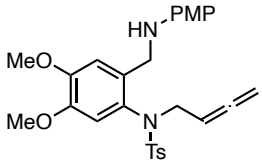

Isolated in 50 % yield, (0.26 g, 0.56 mmol), brown oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.7 – 7.5 (m, 2H), 7.3 (dt, $J$ = 10.8, 5.3 Hz, 2H), 7.1 (d, $J$ = 3.1 Hz, 1H), 6.8 – 6.7 (m, 2H), 6.7 – 6.6 (m, 3H), 6.6 – 6.5 (m, 1H), 5.2 – 5.0 (m, 1H), 4.7 – 4.5 (m, 3H), 4.5 – 4.3 (m, 2H), 4.0 – 3.8 (m, 1H), 3.7 (d, $J$ = 2.7 Hz, 6H), 2.5 – 2.4 (m, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$ δ 210.0, 159.6, 152.2, 143.8, 142.8, 142.6, 135.6, 129.7, 129.6, 129.3, 128.1, 114.9, 114.5, 114.0, 113.0, 85.8, 77.4, 76.0, 55.8, 55.4, 51.5, 45.6, 21.6. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{29}N_2O_4S$ $[M+H]^+$: 465.1843, found: 465.1840.

***N*-(4-Bromo-2-(((4-methoxyphenyl)amino)methyl)phenyl)-*N*-(buta-2,3-dien-1-yl)-4-methylbenzenesulfonamide (158g)**




Isolated in 65% yield (1.28 g, 2.5 mmol), amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.70 (d, $J$ = 2.4 Hz, 1H), 7.58 (d, $J$ = 8.3 Hz, 2H), 7.31 (d, $J$ = 8.0 Hz, 2H), 7.27 – 7.18 (m, 1H), 6.82 – 6.72 (m, 2H), 6.65 – 6.56 (m, 2H), 6.43 (d, $J$ = 8.4 Hz, 1H), 5.10 (p, $J$ = 6.9 Hz, 1H), 4.70 – 4.49 (m, 3H), 4.41 (d, $J$ = 15.6 Hz, 2H), 3.88 – 3.77 (m, 1H), 3.75 (s, 3H), 2.45 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.2, 152.4, 144.2, 144.0, 132.3, 130.6, 129.8, 129.6, 128.2, 115.0, 114.5, 85.9, 76.4, 55.9, 51.4, 45.4, 21.7. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{25}BrN_2O_3S$ $[M+H]^+$: 513.0842, found: 513.0851.

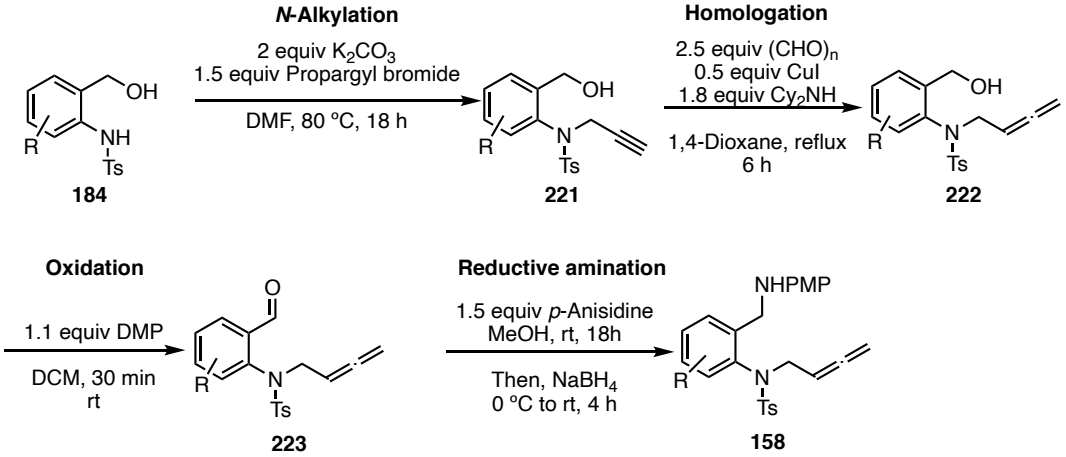
***N*-(buta-2,3-dien-1-yl)-*N*-(4,5-dimethoxy-2-(((4-methoxyphenyl)amino)methyl)phenyl)-4-methylbenzenesulfonamide (158k)**




Isolated in 64% yield (0.18 g, 0.36 mmol), amorphous white solid. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 (dt, $J$ = 8.2, 2.0 Hz, 2H), 7.3 – 7.2 (m, 2H), 7.1 – 7.0 (m, 1H), 6.8 (dt, $J$ = 8.8, 2.0 Hz, 3H), 6.6 (dq, $J$ = 6.7, 2.1 Hz, 3H), 6.1 – 5.9 (m, 1H), 5.2 – 5.0 (m, 1H), 4.7 – 4.5 (m, 2H), 4.5 – 4.3 (m, 3H), 3.9 (dd, $J$ = 13.7, 8.6 Hz, 1H), 3.8 (t, $J$ = 1.9 Hz, 3H), 3.8 – 3.7 (m, 5H), 3.6 – 3.5 (m, 3H), 2.4 (d, $J$ = 2.6 Hz, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 210.0, 152.3, 149.2, 147.7, 143.9, 142.7, 135.7, 133.8, 129.5, 129.1, 128.3, 114.9, 114.8, 111.7, 111.2, 85.8, 76.1, 55.9, 55.8, 55.7, 51.5, 45.4, 21.6. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{27}H_{31}N_2O_5S$ $[M+H]^+$: 495.1948, found: 495.1951.

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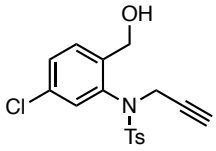
## 3.4. Preparation of Allenes 158d,158h-j




Tosylamides **184** were synthesized according to literature.[214]

***N-Alkylation.*** A round-bottomed flask equipped with a stirring magnetic bar was flamed-dried under vacuum and backfilled with argon. Then, it was charged with $K_2CO_3$ (2 equiv) and the corresponding tosylamide **184** put under vacuum and backfilled with argon for three times. Then DMF (0.25 M) was added and the mixture was stirred for 30 min at rt. Afterwards, propargyl bromide derivative (1.5 equiv) was added and the reaction was warmed to 80 °C in an oil bath for 16 h. The reaction was quenched with a saturated solution of $NH_4Cl_{(aq)}$ and extracted with EtOAc. The aqueous layer was extracted with EtOAc and the combination of organic layers was washed with a saturated solution of $NH_4Cl_{(aq)}$ (3 x 100 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography with hexanes/EtOAc (7:3) as the eluent to give the propargylated products **221.**

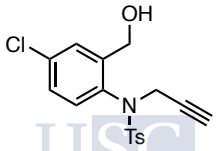
***N*-(5-chloro-2-(hydroxymethyl)phenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (221d)**



Isolated in 60% yield (1 g, 3 mmol), yellow oil.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.67 – 7.53 (m, 3H), 7.31 (s, 2H), 7.11 (dd, $J$ = 8.5, 2.5 Hz, 1H), 6.58 (d, $J$ = 8.5 Hz, 1H), 4.89 (s, 1H), 4.60 (s, 1H), 4.36 (d, $J$ = 2.5 Hz, 2H), 2.86 (d, $J$ = 7.7 Hz, 1H), 2.45 (s, 3H), 2.17 (t, $J$ = 2.5 Hz, 1H). **$^{13}$C NMR** (75 MHz, CDCl3) δ 144.6, 144.4, 135.6, 135.3, 134.8, 130.8, 129.8, 129.6, 128.5, 128.4, 128.3, 77.2, 74.5, 60.9, 41.9, 21.7. **MS** (CI), m/z (%): 332 ($M^+$-[OH], 100).

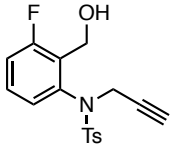
***N*-(4-chloro-2-(hydroxymethyl)phenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (221h)**



Isolated in 60% yield (1 g, 2.8 mmol), brown oil.

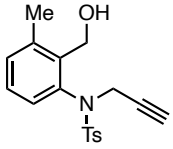
**$^1$H NMR** (300 MHz, cdcl$_3$) δ 7.66 – 7.50 (m, 3H), 7.34 (t, $J$ = 8.8 Hz, 3H), 6.61 (t, $J$ = 1.7 Hz, 1H), 4.96 – 4.48 (m, 2H), 4.40 – 4.29 (m, 2H), 2.91 (s, 1H), 2.46 (s, 3H), 2.24 – 2.14 (m, 1H). **$^{13}$C NMR** (75 MHz, DMSO-d6) δ 144.8, 141.1, 137.9, 134.5, 133.4, 131.9, 130.0, 129.9, 129.8, 129.6, 128.5, 128.3, 77.0, 74.6, 60.7, 41.9, 21.7. **MS** (CI), m/z (%): 332 ($M^+$-[OH], 100).

**N-(3-fluoro-2-(hydroxymethyl)phenyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (226i)**



Isolated in 53% yield (600 mg, 1.8 mmol), yellow oil.
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.24 (m, 3H), 7.22 – 7.09 (m, 2H), 6.53 – 6.44 (m, 1H), 4.82 (s, 2H), 4.40 (d, *J* = 2.5 Hz, 2H), 3.07 (t, *J* = 6.9 Hz, 1H), 2.46 (s, 3H), 2.18 (t, *J* = 2.5 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 162.3 (d, *J* = 248.7 Hz), 144.6, 138.9, 134.7, 129.7, 129.3(d, *J* = 9.8 Hz), 128.5, 124.2, 124.1, 117.2, 116.9, 77.1, 74.5, 54.8, 54.8, 42.3, 21.8. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -113.1. **MS** (CI), m/z (%): 316 ($M^+$-[OH], 100).

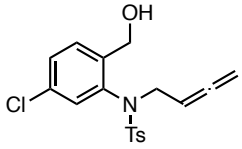
**N-(2-(hydroxymethyl)-3-methylphenyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (221j)**



Isolated in 53% yield (600 mg, 1.82 mmol), colorless oil.
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.35 – 7.18 (m, 4H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 7.9 Hz, 1H), 4.98 (d, *J* = 11.6 Hz, 1H), 4.59 (t, *J* = 11.3 Hz, 1H), 4.38 (t, *J* = 1.9 Hz, 2H), 2.99 (dd, *J* = 10.8, 3.1 Hz, 1H), 2.52 (s, 3H), 2.43 (d, *J* = 3.6 Hz, 3H), 2.15 (q, *J* = 2.1 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 144.3, 140.7, 140.5, 137.5, 135.0, 131.6, 129.6, 128.5, 128.2, 125.6, 74.2, 57.9, 42.3, 21.7, 19.6. **MS** (CI), m/z (%): 312 ($M^+$-[OH], 100).

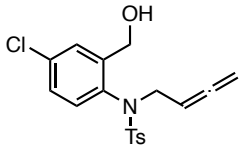
See General Procedure for *Homologation* of Alkynes to Allenes

**N-(buta-2,3-dien-1-yl)-N-(5-chloro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (222d)**



Isolated in 54% yield (450 mg, 1.24 mmol), yellow oil.
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.3, 1.8 Hz, 3H), 7.34 (d, *J* = 8.0 Hz, 3H), 6.43 (t, *J* = 1.6 Hz, 1H), 5.10 – 4.88 (m, 2H), 4.72 – 4.33 (m, 4H), 3.79 (d, *J* = 10.8 Hz, 1H), 2.87 (t, *J* = 6.5 Hz, 1H), 2.47 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.3, 144.6, 141.3, 138.2, 134.4, 133.4, 132.1, 129.9, 129.5, 128.2, 128.0, 85.2, 76.5, 60.8, 51.4, 21.7. **MS** (CI), m/z (%): 346 ($M^+$-[OH], 100).

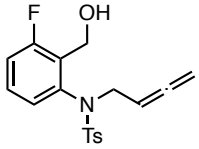
**N-(buta-2,3-dien-1-yl)-N-(4-chloro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (222h)**



Isolated in 72% yield (750 mg, 2 mmol), brown oil.
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.6 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.10 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.40 (d, *J* = 8.5 Hz, 1H), 5.09 – 4.82 (m, 2H), 4.70 – 4.36 (m, 4H), 3.87 – 3.75 (m, 1H), 2.86 (s, 1H), 2.46 (s, 3H). **$^{13}$C NMR**{ (75 MHz, $CDCl_3$) δ 210.2, 144.6, 144.4, 135.5, 135.0, 134.7, 130.9, 129.9, 129.1, 128.4, 128.2, 85.3, 76.4, 61.0, 51.5, 21.7.**MS** (CI), m/z (%): 346 ($M^+$-[OH], 100).

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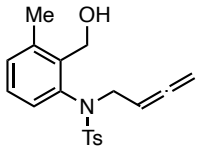
**N-(buta-2,3-dien-1-yl)-N-(3-fluoro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (222i)**



Isolated in 50% yield (310 mg, 0.9 mmol), yellow oil.
**$^1$H NMR** (300 MHz, $CDCl_3$ δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.13 (qd, *J* = 8.3, 6.3 Hz, 2H), 6.30 (dd, *J* = 7.0, 2.2 Hz, 1H), 5.04 (q, *J* = 7.0 Hz, 1H), 4.94 – 4.39 (m, 5H), 3.82 (t, *J* = 10.9 Hz, 1H), 3.25 – 3.13 (m,

1H), 2.46 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.0, 162.3 (d, *J* = 248.7 Hz), 144.3, 134.4, 129.7, 129.0 (d, *J* = 9.9 Hz), 128.1, 123.5 (d, *J* = 3.4 Hz), 116.5, 116.2, 85.2, 76.3, 54.8, 54.8, 51.5, 21.6. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -113.5. **MS** (CI), m/z (%): 330 ($M^+$-[OH], 100).

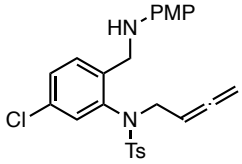
***N*-(buta-2,3-dien-1-yl)-*N*-(2-(hydroxymethyl)-3-methylphenyl)-4-methylbenzenesulfonamide (222j)**




Isolated in 70 % yield (435 mg, 1.27 mmol), yellow oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 2H), 7.37 – 7.26 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 1H), 5.15 – 4.98 (m, 2H), 4.72 – 4.36 (m, 4H), 3.89 – 3.75 (m, 1H), 3.09 (dd, *J* = 11.0, 2.8 Hz, 1H), 2.54 (s, 3H), 2.45 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.0, 144.1, 140.6, 137.6, 134.9, 131.1, 129.7, 128.3, 128.0, 125.1, 85.6, 76.2, 58.0, 51.6, 21.7, 19.6. **MS** (CI), m/z (%): 326 ($M^+$-[OH], 100).

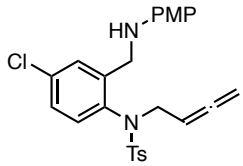
See General Procedure for *Oxidation* and *Reductive Amination*

***N*-(buta-2,3-dien-1-yl)-*N*-(5-chloro-2-(((4-methoxyphenyl)amino)methyl)phenyl)-4-methylbenzenesulfonamide (158d)**



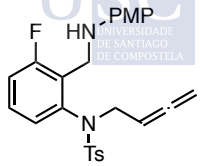

Isolated in 57% yield (330 mg, 0.71 mmol), brown oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.9 Hz, 2H), 7.38 (s, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.15 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.75 – 6.62 (m, 2H), 6.54 – 6.40 (m, 3H), 5.01 (p, *J* = 7.0 Hz, 1H), 4.62 – 4.18 (m, 5H), 3.80 – 3.70 (m, 1H), 3.63 (s, 3H), 2.36 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.2, 152.4, 144.2, 143.8, 142.3, 135.9, 135.3, 134.9, 129.8, 129.4, 129.3, 128.2, 127.5, 115.0, 11447.5, 85.5, 76.3, 55.9, 51.4, 45.4, 21.7.**HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}ClN_2O_3S$ $[M+H]^+$: 469.1347, found: 469.1351.

***N*-(buta-2,3-dien-1-yl)-*N*-(4-chloro-2-(((4-methoxyphenyl)amino)methyl)phenyl)-4-methylbenzenesulfonamide (158h)**




Isolated in 56 % yield (530 mg, 1.13 mmol), amorphous brown solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.62 – 7.50 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.09 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.51 (d, *J* = 8.5 Hz, 1H), 5.11 (p, *J* = 7.0 Hz, 1H), 4.72 – 4.48 (m, 3H), 4.41 (d, *J* = 15.5 Hz, 2H), 3.83 (dd, *J* = 13.9, 8.3 Hz, 1H), 3.74 (s, 3H), 2.45 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.2, 152.4, 144.2, 143.8, 142.3, 135.9, 135.3, 134.9, 129.8, 129.4, 129.3, 128.2, 127.5, 115.0, 11447.5, 85.5, 76.3, 55.9, 51.4, 45.4, 21.7. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}ClN_2O_3S$ $[M+H]^+$: 469.1347, found: 469.1348.

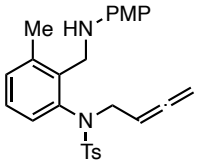
***N*-(buta-2,3-dien-1-yl)-*N*-(3-fluoro-2-(((4-methoxyphenyl)amino)methyl)phenyl)-4-methylbenzenesulfonamide (158i)**




Isolated in 52 % yield (210 mg, 0.47 mmol), amorphous white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.21 – 7.04 (m, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.77 – 6.67 (m, 2H), 6.47 (d, *J* = 7.7 Hz, 1H), 5.03 (p, *J* = 6.9 Hz, 1H), 4.67 – 4.45 (m, 3H), 4.41 – 4.21 (m, 2H), 3.97 – 3.84 (m, 1H), 3.76 (s, 3H), 2.45 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 210.0, 162.3 (d, *J* = 248.7 Hz), 152.6, 144.2, 142.8, 139.8 (d, *J* = 6.3 Hz), 135.2, 129.7,

128.9, 128.6 (d, $J$ = 9.9 Hz), 128.4, 128.2, 124.5 (d, $J$ = 3.4 Hz), 116.2 (d, $J$ = 22.8 Hz), 115.2, 114.9, 85.5, 76.2, 55.9, 51.7, 39.8, 21.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -113.1 (t, $J$ = 7.8 Hz). **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}FN_2O_3S$ $[M+H]^+$: 453.1643, found: 453.1645.

**_N_-(buta-2,3-dien-1-yl)-_N_-(2-(((4-methoxyphenyl)amino)methyl)-3-methylphenyl)-4-methylbenzenesulfonamide (158j)**



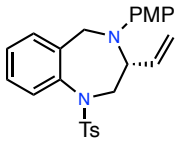

Isolated in 58% yield (330 mg, 0.74 mmol), brown oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.60 (d, $J$ = 8.1 Hz, 2H), 7.27 (d, $J$ = 8.0 Hz, 2H), 7.20 (d, $J$ = 7.6 Hz, 1H), 7.08 (t, $J$ = 7.7 Hz, 1H), 6.88 – 6.78 (m, 2H), 6.75 – 6.67 (m, 2H), 6.48 (d, $J$ = 7.8 Hz, 1H), 5.05 (dq, $J$ = 8.0, 6.6 Hz, 1H), 4.68 – 4.46 (m, 2H), 4.46 – 4.20 (m, 3H), 3.90 (ddt, $J$ = 13.8, 8.2, 1.8 Hz, 1H), 3.77 (s, 3H), 2.47 (s, 3H), 2.44 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 209.8, 152.3, 143.8, 143.4, 140.2, 138.8, 138.2, 135.6, 131.0, 129.6, 128.2, 127.6, 125.9, 114.9, 114.6, 85.6, 76.0, 55.9, 51.6, 42.6, 21.6, 19.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{29}N_2O_3S$ $[M+H]^+$: 449.1893, found: 449.1896.

## 3.5. General Procedure for the Asymmetric Cyclization of Allenes 158

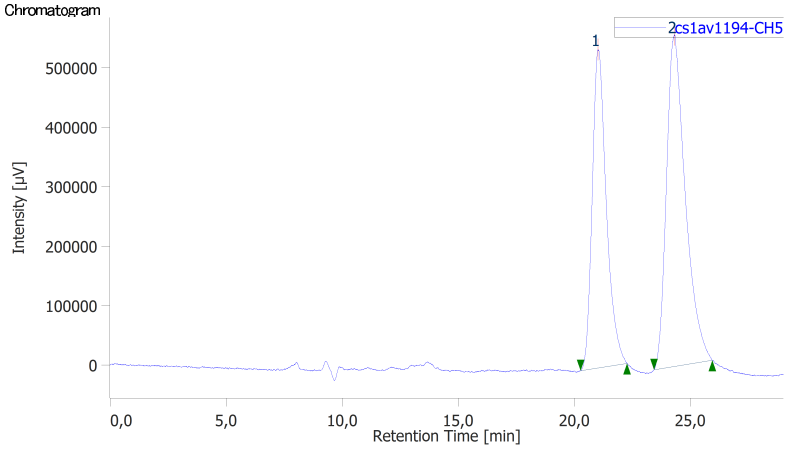
A 5 mL sealed tube equipped with stirring magnetic bar was flamed-dried under vacuum, cooled to rt and backfilled with argon. Then it was charged with $[Rh(cod)Cl]_2$ (3 mg, 6 μmol, 0.04 equiv), PPTS (4 mg, 15 μmol, 0.1 equiv) or $ClCH_2CO_2H$ (1.4 mg, 15μmol, 0.1 equiv) and (*R*)-DTBM-Garphos (19 mg, 15 μmol, 0.1 equiv). Afterwards, it was put in vacuum and backfilled with argon for three times. Then 0.4 mL of DCE was added and the mixture was stirred for 10 min at rt. Finally, the allene **158** (0.15 mmol, 1 equiv) was added under flow of argon and the mixture was stirred at 50 °C in an oil bath for 24 h. After cooling at rt and stripping off the solvent, the resulting residue was purified by silica gel column chromatography with hexanes/EtOAc (9:1) as the eluent to give the desired seven-membered heterocycle **153**.

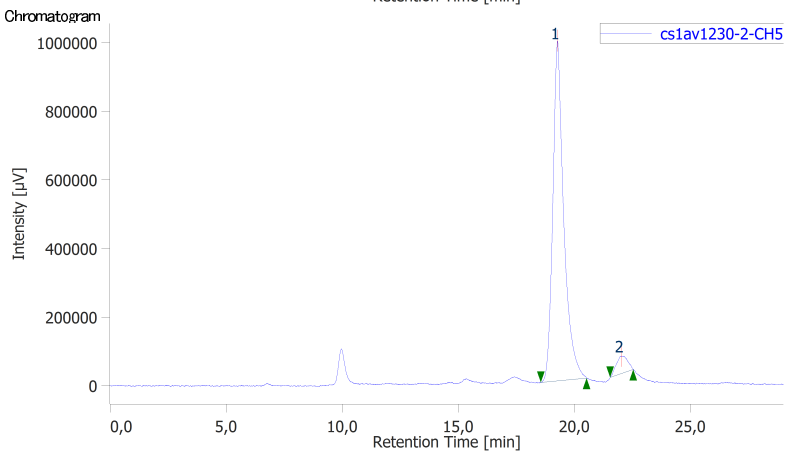
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**(*R*)-4-(4-Methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153b)**




PPTS as Brønsted acid, 70% yield, amorphous off-white solid, 90% ee, $[\alpha]_D^{25}$ -22.4 (c 0.5, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.03 (m, 5H), 6.64 (d, *J* = 7.9 Hz, 2H), 6.51 (d, *J* = 8.7 Hz, 2H), 6.25 (d, *J* = 8.6 Hz, 2H), 5.75 (ddd, *J* = 17.3, 10.6, 3.9 Hz, 1H), 5.16 (dd, *J* = 28.1, 13.9 Hz, 2H), 4.57 – 4.36 (m, 3H), 4.04 (d, *J* = 17.2 Hz, 1H), 3.65 (s, 3H), 3.47 (q, *J* = 13.4, 12.7 Hz, 1H), 2.08 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 152.1, 144.0, 143.0, 139.5, 136.2, 133.6, 129.9, 129.1, 128.5, 127.7, 126.8, 126.5, 126.4, 117.2, 114.8, 114.4, 60.3, 55.7, 54.3, 51.3, 21.4. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{27}N_2O_3S$ $[M+H]^+$: 435.1737, found: 435.1738. **SFC conditions**: 30% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 70:30, 1mL/min)*, λ=210 nm, $t_R$ (min): major = 19.26, minor = 22.02).



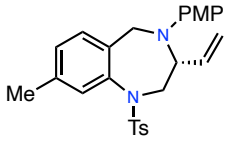

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV*sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 19,267 | 32337694 | 991169 | 94,914 | 95,117 | N/A | 9650 | 3,096 | 1,383 | |
| 2 | Unknown | 5 | 22,023 | 1732934 | 50881 | 5,086 | 4,883 | N/A | 7743 | N/A | 1,011 | |

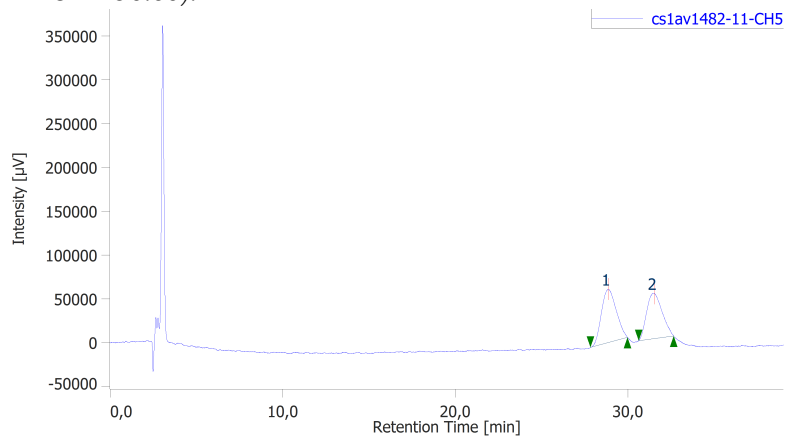
Signals in the range around 5-11 min are due to the front arriving to the detector.

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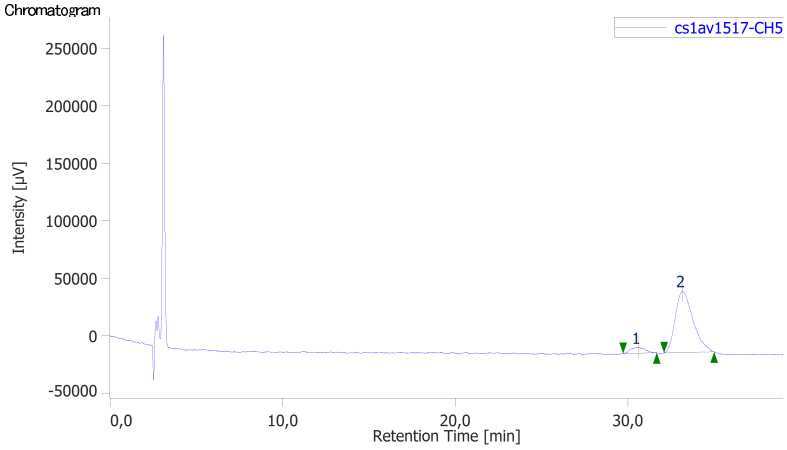
**(*R*)-4-(4-Methoxyphenyl)-8-methyl-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153c)**




$ClCH_2CO_2H$ as Brønsted acid, 86% yield, amorphous off-white solid, 86% ee, $[\alpha]_D^{25}$ -70.17(c 1, $CHCl_3$). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.08 – 6.91 (m, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 6.65 – 6.52 (m, 2H), 6.36 – 6.25 (m, 2H), 5.82 (ddd, *J* = 16.9, 10.9, 3.5 Hz, 1H), 5.31 – 5.14 (m, 2H), 4.61 – 4.37 (m, 3H), 4.07 (d, *J* = 17.1 Hz, 1H), 3.73 (d, *J* = 2.1 Hz, 3H), 3.61 – 3.43 (m, 1H), 2.34 (s, 3H), 2.16 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$ δ 152.05, 144.0, 143.0, 139.4, 137.6, 136.2, 133.7, 130.6, 129.1, 128.3, 127.2, 126.9, 126.8, 117.1, 114.9, 114.4, 60.3, 55.7, 54.3, 51.1, 21.5, 21.3. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{29}N_2O_3S$ $[M+H]^+$: 449.1893, found: 449.1896. **SFC conditions**: 30% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 70:30, 1mL/min)*, λ=210 nm, $t_R$ (min): major = 33.15, minor = 30.60).




Chromatogram



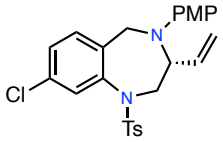

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 30,600 | 300312 | 5056 | 7,318 | 8,626 | N/A | 5657 | 1,475 | 1,100 | |
| 2 | Unknown | 5 | 33,157 | 3803265 | 53554 | 92,682 | 91,374 | N/A | 5150 | N/A | 1,365 | |

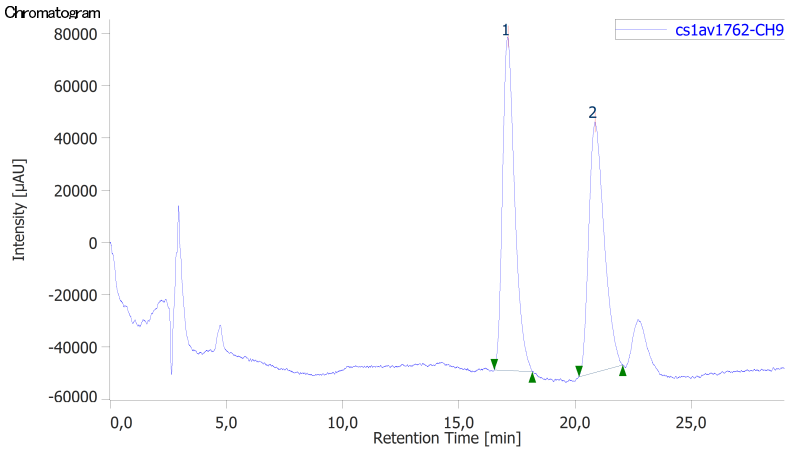
Signals in the range around 2-4 min are due to the front arriving to the detector.

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**(*R*)-8-chloro-4-(4-methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153d)**



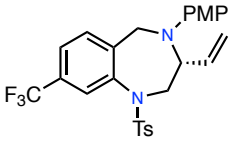

$ClCH_2CO_2H$ as Brønsted acid, 55% yield, amorphous off-white solid, 92% ee, $[\alpha]_D^{25}$ -17.20 (c 1, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.8 (d, *J* = 2.2 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.07 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.58 – 6.48 (m, 2H), 6.23 (d, *J* = 8.5 Hz, 2H), 5.75 (ddd, *J* = 17.2, 10.5, 3.8 Hz, 1H), 5.27 – 5.11 (m, 2H), 4.57 – 4.38 (m, 3H), 4.03 (d, *J* = 17.4 Hz, 1H), 3.66 (s, 4H), 3.52 – 3.38 (m, 1H), 2.10 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 152.3, 143.9, 143.5, 140.7, 135.4, 133.1, 130.1, 129.5, 129.3, 127.0, 126.4, 126.1, 117.4, 114.9, 114.5, 60.5, 55.8, 54.1, 50.9, 21.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}ClN_2O_3S$ $[M+H]^+$: 469.1347 , found: 469.1348. **SFC conditions**: 30% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 70:30, 1mL/min)*, λ=210 nm, $t_R$ (min): major =19.78, minor =16.24).



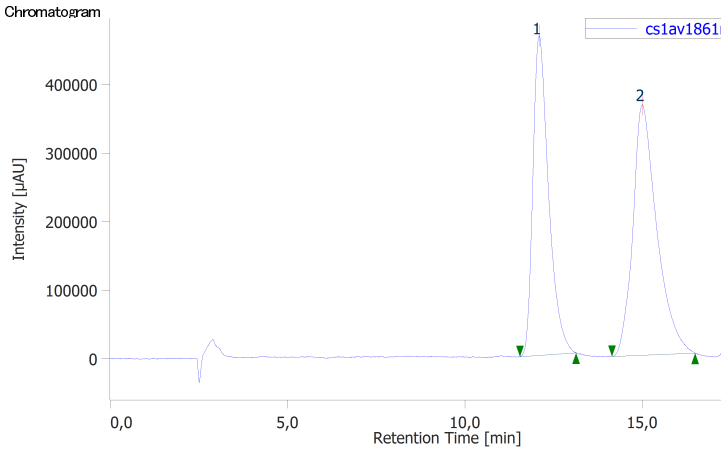

Signals in the range around 2-4 min are due to the front arriving to the detector.

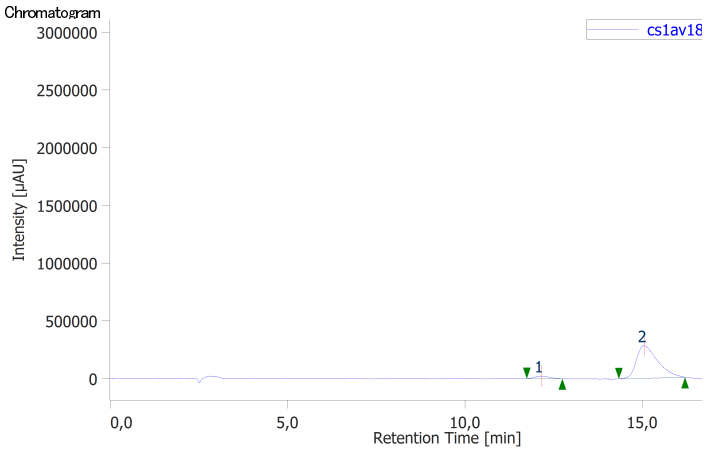
USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

**(*R*)-4-(4-methoxyphenyl)-1-tosyl-8-(trifluoromethyl)-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153e)**




ClCH$_2$CO$_2$H as Brønsted acid, 99% yield, amorphous off-yellow solid, 90% ee, $[\alpha]_D^{25}$ -37.40 (c 1, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.1 (s, 1H), 7.4 (d, *J* = 7.9 Hz, 1H), 7.3 (d, *J* = 8.0 Hz, 1H), 7.2 (d, *J* = 7.9 Hz, 2H), 6.7 (d, *J* = 8.0 Hz, 2H), 6.6 (d, *J* = 8.5 Hz, 2H), 6.3 (d, *J* = 8.4 Hz, 2H), 5.8 (ddd, *J* = 17.2, 10.3, 3.5 Hz, 1H), 5.3 – 5.2 (m, 2H), 4.6 (d, *J* = 17.5 Hz, 1H), 4.6 – 4.5 (m, 2H), 4.2 (d, *J* = 17.5 Hz, 1H), 3.7 (d, *J* = 1.3 Hz, 3H), 3.5 (s, 1H), 2.2 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 152.4, 143.8, 143.6, 140.2, 137.3, 135.6, 133.3, 129.3, 127.2, 123.8 (q, *J* = 272.5 Hz), 123.0 – 122.9 (m), 117.4, 115.0, 114.9, 114.6, 60.5, 55.8, 54.0, 51.1, 21.5.**$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -62.4. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{27}F_3N_2O_3S$ $[M+H]^+$: 504.1689, found: 504.1683. **SFC conditions**: 20% MeOH, *Phenomenex Amylose-1 at 40°C (CO$_2$ : MeOH= 80:20, 1mL/min)*, λ=210 nm, $t_R$ (min): major =15.05, minor =12.15).



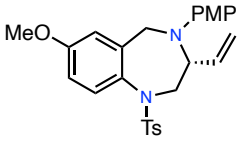

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 9 | 12,147 | 604593 | 22313 | 4,925 | 7,347 | N/A | 4284 | 3,216 | 1,190 | |
| 2 | Unknown | 9 | 15,053 | 11671016 | 281376 | 95,075 | 92,653 | N/A | 3164 | N/A | 1,508 | |

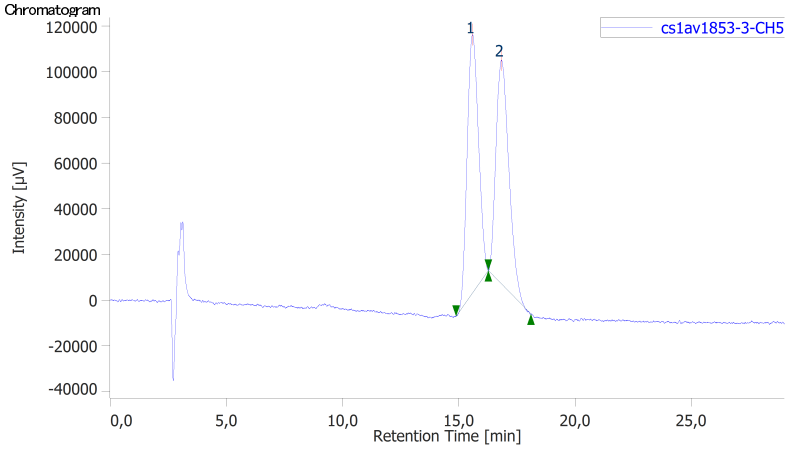
Signals in the range around 2-4 min are due to the front arriving to the detector.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

**(*R*)-7-methoxy-4-(4-methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153f)**




$ClCH_2CO_2H$ as Brønsted acid, 86% yield, amorphous off-yellow solid, 90% ee, $[\alpha]_D^{25}$ -66.28 (c 1, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.8 (d, *J* = 8.9 Hz, 1H), 7.2 (d, *J* = 7.9 Hz, 2H), 6.8 – 6.7 (m, 3H), 6.7 (d, *J* = 3.0 Hz, 1H), 6.6 – 6.5 (m, 2H), 6.3 (d, *J* = 8.5 Hz, 2H), 5.8 (ddd, *J* = 17.3, 10.6, 4.0 Hz, 1H), 5.3 – 5.1 (m, 2H), 4.6 – 4.4 (m, 4H), 4.0 (d, *J* = 17.1 Hz, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 3.5 (s, 1H), 2.2 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 157.9, 152.3, 144.0, 142.9, 136.4, 135.8, 133.8, 132.4, 129.1, 128.2, 126.7, 117.2, 115.4, 114.3, 113.9, 112.2, 60.3, 55.7, 55.6, 54.5, 51.8, 21.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{29}N_2O_4S$ $[M+H]^+$: 465.1843 , found: 465.1858. **SFC conditions**: 20% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 80:20, 1mL/min)*, λ=210 nm, $t_R$ (min): major =15.71, minor =16.97).



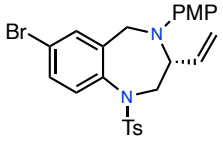

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV*sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 15,713 | 556418 | 18342 | 4,226 | 5,904 | N/A | 5386 | 1,185 | 0,892 | |
| 2 | Unknown | 5 | 16,877 | 12609985 | 292344 | 95,774 | 94,096 | N/A | 3683 | N/A | 1,426 | |

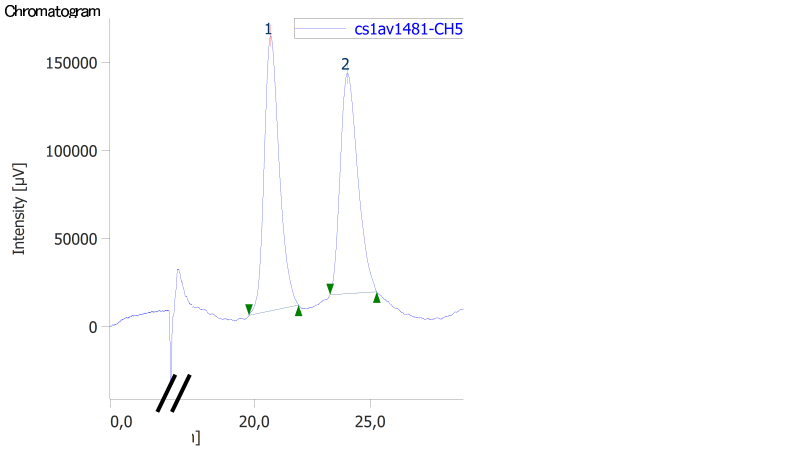
Signals in the range around 2-4 min are due to the front arriving to the detector.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

**(*R*)-7-Bromo-4-(4-methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153g)**




$ClCH_2CO_2H$ as Brønsted acid, 70% yield, amorphous off-white solid, 88% ee, $[\alpha]_D^{25}$ -11.69 (c 1, $CHCl_3$)). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 1H), 7.34 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.29 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.67 – 6.55 (m, 2H), 6.34 – 6.24 (m, 2H), 5.81 (ddd, *J* = 17.2, 10.5, 3.7 Hz, 1H), 5.35 – 5.18 (m, 2H), 4.69 – 4.40 (m, 3H), 4.05 (d, *J* = 17.5 Hz, 1H), 3.74 (s, 3H), 3.47 (dd, *J* = 14.7, 10.7 Hz, 1H), 2.16 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 152.3, 143.7, 143.4, 138.8, 135.8, 133.2 131.2, 130.6, 130.0, 129.3, 128.0, 126.9, 119.6, 117.43, 114.8, 114.5, 60.2, 55.7, 54.2, 50.9, 21.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}BrN_2O_3S$ $[M+H]^+$: 513.0842, found: 513.0851. **SFC conditions**: 30% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 70:30, 1mL/min)*, λ=210 nm, $t_R$ (min): major = 24.37, minor = 21.15).



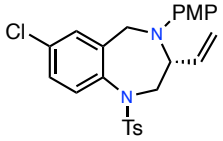

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV*sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 21,150 | 918860 | 20164 | 6,200 | 7,783 | N/A | 4968 | 2,416 | 1,286 | |
| 2 | Unknown | 5 | 24,387 | 13900989 | 238916 | 93,800 | 92,217 | N/A | 4310 | N/A | 1,532 | |

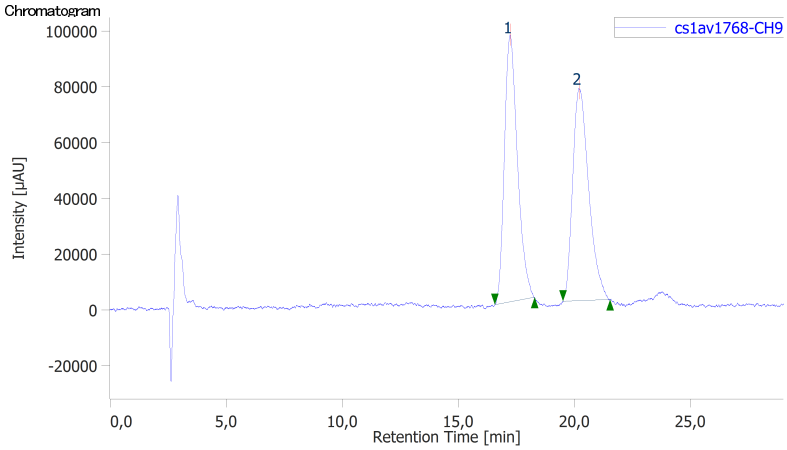
Signals in the range around 2-4 min are due to the front arriving to the detector.

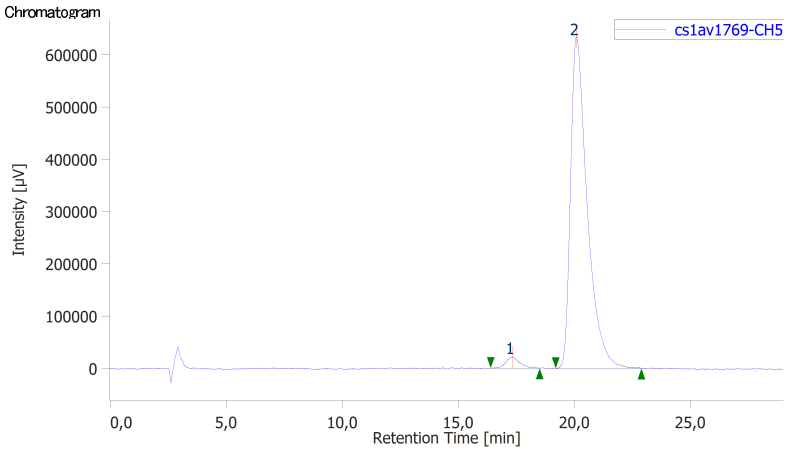
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**(*R*)-7-chloro-4-(4-methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153h)**




$ClCH_2CO_2H$ as Brønsted acid, 72 % yield, amorphous off-white solid, 94% ee, $[\alpha]_D^{25}$ -17.20 (c 1, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 1H), 7.18 – 7.09 (m, 2H), 7.06 (s, 1H), 6.65 (d, *J* = 7.9 Hz, 2H), 6.58 – 6.51 (m, 2H), 6.23 (d, *J* = 8.5 Hz, 2H), 5.74 (ddd, *J* = 17.3, 10.5, 4.0 Hz, 1H), 5.25 – 5.07 (m, 2H), 4.55 – 4.36 (m, 3H), 3.98 (d, *J* = 17.4 Hz, 1H), 3.66 (s, 3H), 3.40 (d, *J* = 15.6 Hz, 1H), 2.09 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$ δ 152.4, 143.8, 143.3, 138.3, 135.9, 135.6, 133.3, 131.7, 129.3, 128.3, 127.7, 127.6, 126.9, 117.4, 114.9, 114.5, 60.3, 55.7, 54.3, 51.1, 21.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}ClN_2O_3S$ $[M+H]^+$: 469.1347, found: 469.1348. **SFC conditions**: 30% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 70:30, 1mL/min)*, λ=210 nm, $t_R$ (min): major =20.09, minor =17.33).



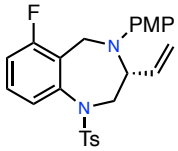

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV*sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 17,330 | 876466 | 20679 | 2,700 | 3,158 | N/A | 4235 | 2,405 | 1,205 | |
| 2 | Unknown | 5 | 20,093 | 31588334 | 634079 | 97,300 | 96,842 | N/A | 4206 | N/A | 1,678 | |

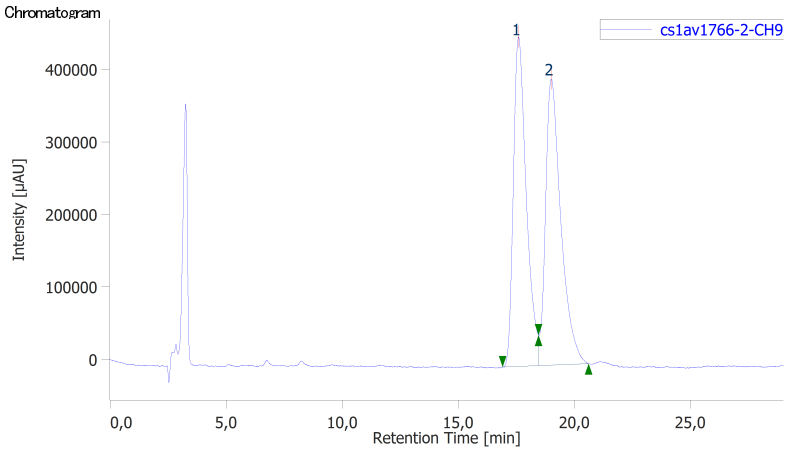
Signals in the range around 2-4 min are due to the front arriving to the detector.

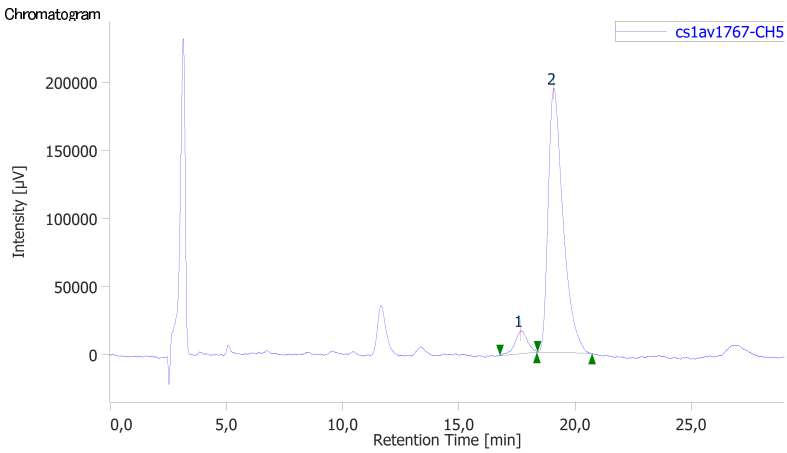
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**(*R*)-6-fluoro-4-(4-methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153i)**




$ClCH_2CO_2H$ as Brønsted acid, 60% yield, amorphous off-white foam, 90% ee, $[\alpha]_D^{25}$ -6.50 (c 1, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.59 (d, $J$ = 8.3 Hz, 1H), 7.23 – 7.05 (m, 3H), 6.84 (t, $J$ = 8.8 Hz, 1H), 6.66 (d, $J$ = 7.8 Hz, 2H), 6.60 – 6.49 (m, 2H), 6.26 (d, $J$ = 8.4 Hz, 2H), 5.77 (ddd, $J$ = 17.3, 10.5, 3.7 Hz, 1H), 5.27 – 5.12 (m, 2H), 4.56 (d, $J$ = 17.8 Hz, 1H), 4.46 (dd, $J$ = 10.7, 5.4 Hz, 2H), 4.29 (d, $J$ = 17.8 Hz, 1H), 3.66 (s, 3H), 3.55 – 3.41 (m, 1H), 2.09 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 159.9 (d, $J$ = 244.3 Hz), 152.1, 143.7, 143.2, 141.4 (d, $J$ = 5.0 Hz), 135.8, 133.2, 129.1, 127.8 (d, $J$ = 10.0 Hz), 126.8, 121.5, 121.4, 117.3, 114.6, 114.4, 112.8 (d, $J$ = 23.0 Hz), 60.1, 55.6, 54.10 42.7, 21.4. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -116.32 (t, $J$ = 8.3 Hz). **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}FN_2O_3S$ $[M+H]^+$: 453.1643, found: 453.1643. **SFC conditions**: 20% MeOH, *Phenomenex Amylose-1 at 40°C ($CO_2$ : MeOH= 80:20, 1mL/min)*, λ=210 nm, $t_R$ (min): major =19.08, minor = 17.66).



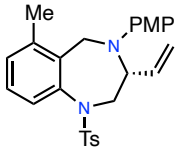

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 17,663 | 447665 | 14915 | 5,130 | 7,231 | N/A | 7215 | 1,456 | 1,101 | |
| 2 | Unknown | 5 | 19,080 | 8279094 | 191356 | 94,870 | 92,769 | N/A | 4646 | N/A | 1,546 | |

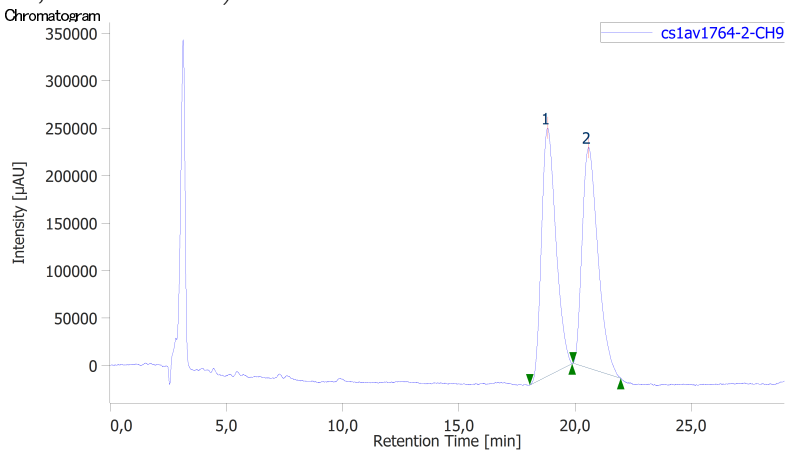
Signals in the range around 2-4 min are due to the front arriving to the detector.

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**(*R*)-4-(4-methoxyphenyl)-6-methyl-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153j)**




$ClCH_2CO_2H$ as Brønsted acid, 86% yield, brown oil, 94% ee, $[\alpha]_D^{25}$ -20.65 (c 1, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.18 (s, 2H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 2H), 6.58 – 6.50 (m, 2H), 6.25 (d, *J* = 8.6 Hz, 2H), 5.71 (ddd, *J* = 17.2, 10.6, 4.5 Hz, 1H), 5.21 – 5.11 (m, 2H), 4.49 – 4.36 (m, 2H), 4.25 (q, *J* = 17.3 Hz, 2H), 3.66 (s, 3H), 3.36 (dd, *J* = 14.7, 10.8 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 152.6, 144.7, 142.9, 140.0, 136.5, 136.1, 134.1, 131.7, 129.2, 128.7, 126.9, 124.6, 119.4, 117.4, 116.3, 114.4, 60.4, 55.7, 54.6, 48.5, 21.5, 20.3. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{29}N_2O_3S$ $[M+H]^+$: 449.1893, found: 449.1896. **SFC conditions**: 20% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 80:20, 1mL/min)*, λ=210 nm, $t_R$ (min): major =20.98, minor =19.36).



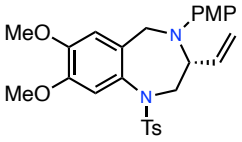

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 19,367 | 896769 | 23679 | 2,670 | 3,388 | N/A | 5687 | 1,439 | 0,987 | |
| 2 | Unknown | 5 | 20,980 | 32685719 | 675169 | 97,330 | 96,612 | N/A | 4722 | N/A | 1,565 | |

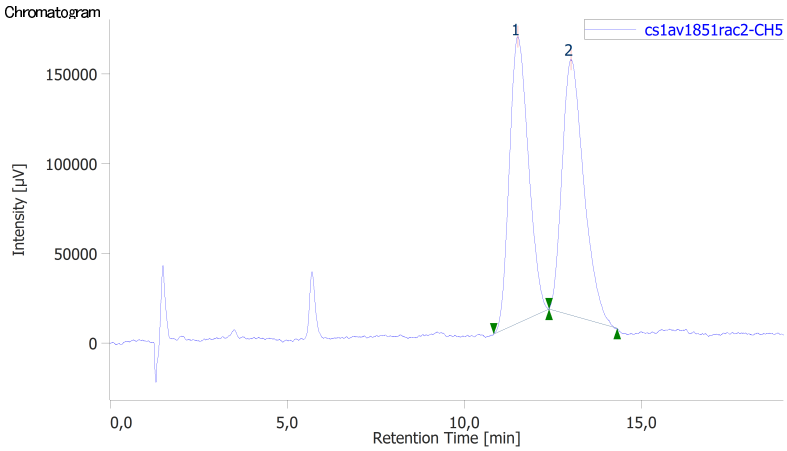
Signals in the range around 2-4 min are due to the front arriving to the detector.

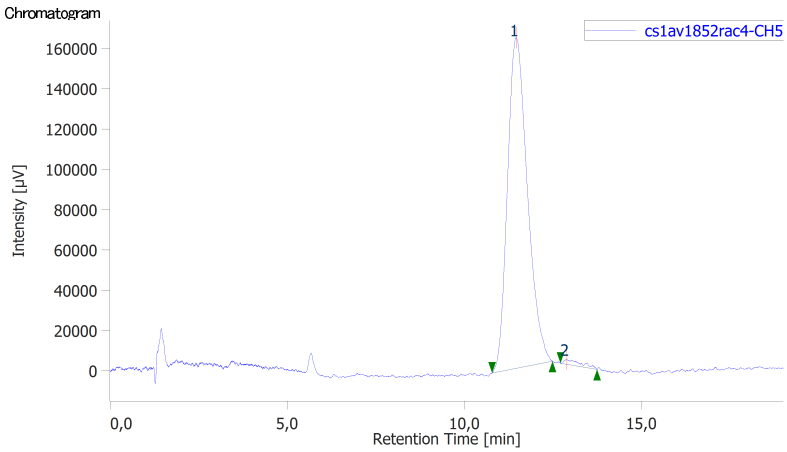
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**(*R*)-7,8-dimethoxy-4-(4-methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153k)**




$ClCH_2CO_2H$ as Brønsted acid, 78% yield, amorphous off-white foam, 96% ee, $[\alpha]_D^{25}$ -76.38 (c 1, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.5 – 7.4 (m, 1H), 7.2 (d, *J* = 7.9 Hz, 2H), 6.7 (d, *J* = 7.9 Hz, 2H), 6.6 – 6.5 (m, 3H), 6.3 (d, *J* = 8.4 Hz, 2H), 5.8 (ddd, *J* = 17.1, 10.5, 4.1 Hz, 1H), 5.3 – 5.1 (m, 2H), 4.5 (d, *J* = 17.0 Hz, 2H), 4.4 (dd, *J* = 10.6, 4.8 Hz, 1H), 4.0 (d, *J* = 17.1 Hz, 1H), 3.9 (d, *J* = 2.6 Hz, 6H), 3.7 (s, 3H), 3.5 (d, *J* = 14.6 Hz, 1H), 2.2 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 152.3, 147.7, 147.2, 144.0, 143.0, 136.2, 133.8, 132.3, 129.2, 126.8, 126.0, 122.2, 117.2, 115.3, 114.3, 110.7, 60.5, 56.2, 56.1, 55.7, 54.6, 51.4, 21.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{27}H_{31}N_2O_5S$ $[M+H]^+$: 495.1948, found: 495.1958. **SFC conditions**: 20% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 80:20, 2mL/min)*, λ=210 nm, $t_R$ (min): major =11.50, minor =12.90).



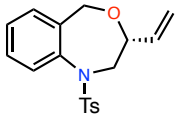

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV*sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 11,470 | 6414490 | 163916 | 98,592 | 98,569 | N/A | 1994 | 1,136 | 1,242 | |
| 2 | Unknown | 5 | 12,883 | 91607 | 2380 | 1,408 | 1,431 | N/A | 1232 | N/A | 3,552 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

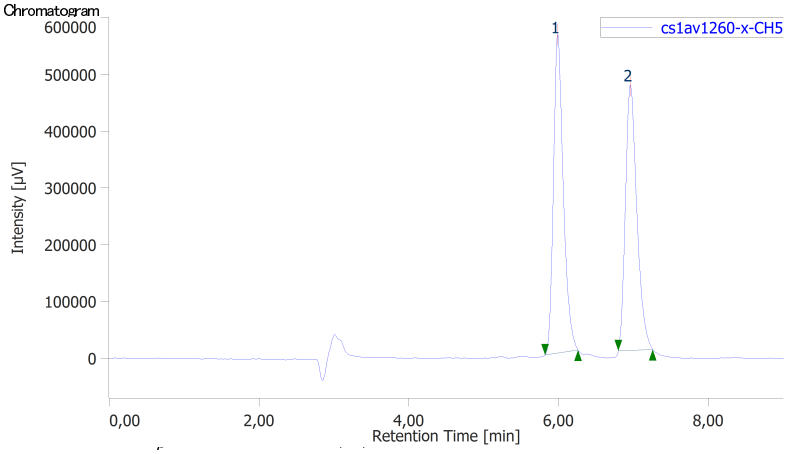
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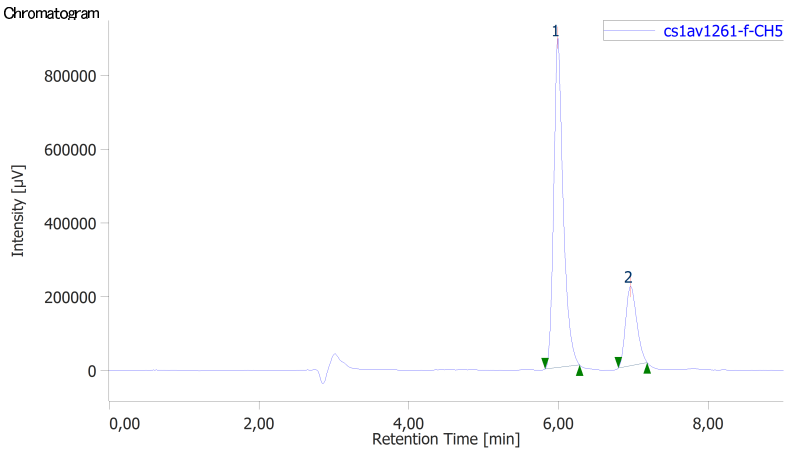
**1-Tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (153l)**




Following General Procedure with PPTS as Brønsted acid, 90% yield, colorless oil (amorphous off-white solid at 4 °C), 56% ee, $[\alpha]_D^{25}$ -7.54 (c 1, $CHCl_3$). **$^1$H NMR** (300 MHz, $CDCl_3$), δ (ppm): 7.65 – 7.58 (m, 2H), 7.40 – 7.34 (m, 1H), 7.32 – 7.18 (m, 5H), 5.74 (ddd, *J* = 17.4, 10.7, 5.3 Hz, 1H), 5.37 (t, *J* = 1.5 Hz, 1H), 5.31 (t, *J* = 1.5 Hz, 1H), 5.22 (t, *J* = 1.4 Hz, 1H), 5.19 (t, *J* = 1.5 Hz, 1H), 4.49 (d, *J* = 13.4 Hz, 1H), 4.38 (dd, *J* = 15.1, 1.9 Hz, 1H), 4.27 – 4.13 (m, 1H), 4.17 (d, *J* = 13.4 Hz, 1H), 2.98 (dd, J = 15.1, 10.3 Hz, 1H), 2.43 (s, 3H).**$^{13}$C NMR** (75 MHz, $CDCl_3$), δ (ppm): 143.7, 139.7, 138.5, 138.2, 135.1, 129.8, 129.6, 128.9, 128.8, 128.0, 127.1, 117.2, 80.7, 72.2, 55.6, 21.6. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{19}NO_3S$ $[M+H]^+$: 330.1158, found: 330.1158.

**SFC conditions**: 30% MeOH, Phenomenex Amylose 1 at 40° C, ($CO_2$ : MeOH = 70:30, 1mL/min), λ=210 nm, $t_R$ (min): major = 5.98, minor = 6.96).




**Peak Information**

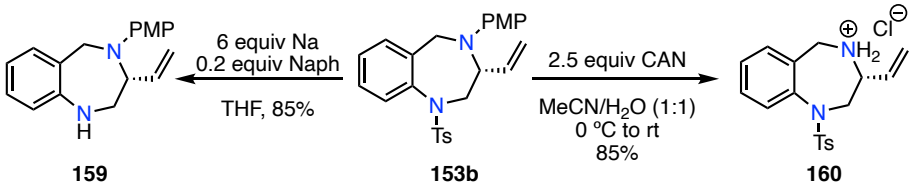
| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 5,987 | 7826242 | 893059 | 77,966 | 80,616 | N/A | 12201 | 3,958 | 1,345 | |
| 2 | Unknown | 5 | 6,960 | 2211838 | 214730 | 22,034 | 19,384 | N/A | 10152 | N/A | 1,182 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

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## 3.6. Derivatization of (*R*)-4-(4-methoxyphenyl)-1-tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (153e)

### 3.6.1. Orthogonal Removal of Protecting Groups




**159** **153b** **160**

#### 3.6.1.1. (*R*)-4-(4-Methoxyphenyl)-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (159)

To a solution of naphthalene (4 mg, 0.02 mmol, 0.2 equiv) in anhydrous THF (1 mL) in an oven-dried Schlenk flask under a stream of argon, hexane-rinsed sheets of sodium metal were added (21.2 mg, 0.885 mmol, 6 equiv). The mixture was then sonicated at rt until green color persisted when a solution of **153b** (62 mg, 0.143 mmol) in THF (4 mL) was then added, resulting in a rapid loss of the green color. The turbid yellow reaction mixture was removed from sonicator and stirred at rt for 15 h. Afterwards, the reaction was cooled to 0 °C and 10 mL of MeOH was slowly added to quench the Na followed by addition of a saturated solution of $NaHCO_3$ (only after consumption). The reaction was diluted with $Et_2O$ and washed with $NaHCO_3$ and $H_2O$. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography with hexanes/EtOAc (8:2) as the eluent to give the desired product **159**, 85% yield (34 mg), colorless oil, $[\alpha]_D^{25}$ -50.1 (c 1, $CHCl_3$)). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.88 – 6.55 (m, 5H), 6.50 (d, *J* = 7.9 Hz, 1H), 5.90 (ddd, *J* = 17.0, 10.3, 3.9 Hz, 1H), 5.29 (dd, *J* = 25.6, 13.9 Hz, 2H), 5.01 (d, *J* = 17.1 Hz, 1H), 4.50 – 4.37 (m, 1H), 4.19 (d, *J* = 17.1 Hz, 1H), 3.70 (s, 3H), 3.67 – 3.58 (m, 1H), 3.40 (dd, *J* = 14.3, 5.4 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 151.3, 147.8, 145.0, 135.4, 129.4, 127.4, 124.8, 119.0, 116.6, 115.5, 114.7, 113.1, 64.8, 55.8, 50.2, 48.5. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{21}ClN_2O_2S$ $[M\text{-}Cl+H]^+$: 281.1648, found 281.1647.

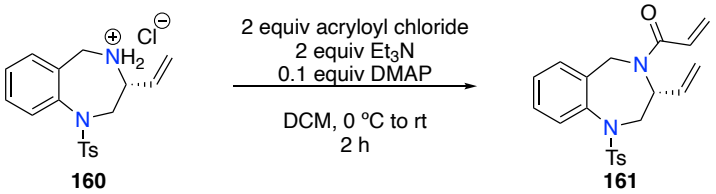
#### 3.6.1.2. (*R*)-1-Tosyl-3-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-4-ium chloride (160)

A solution of PMP-protected amine **153b** (110 mg, 0.25 mmol) in 8.0 mL of MeCN was cooled in an ice-bath and treated with a solution of CAN (275 mg, 0.5 mmol, 2.5 equiv) in water (8 mL) dropwise. The reaction allowed to warm to 25 °C and stirred for 3 h. The crude reaction was diluted with water, washed with $Et_2O$, and the organic layer discarded. The aqueous layer was basified to pH 10 with a saturated $Na_2CO_3$ solution and extracted with $Et_2O$. The combined organic layers were dried with $MgSO_4$ and treated with a 1 M HCl solution in $Et_2O$ and concentrated to afford the hydrochloride salt **160** as an amorphous white solid (77 mg, 85% yield, $[\alpha]_D^{25}$ 122.7 (c 0.70, MeOH)). **$^1$H NMR** (300 MHz, Methanol-$d_4$) δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.56 (dd, *J* = 5.8, 3.2 Hz, 1H), 7.45 (dd, *J* = 8.5, 4.5 Hz, 4H), 7.31 – 7.17 (m, 1H), 5.86 (ddd, *J* = 17.4, 10.5, 7.0 Hz, 1H), 5.73 – 5.54 (m, 2H), 4.51 (dd, *J* = 15.7, 2.6 Hz, 1H), 4.31 (d, *J* = 14.1 Hz, 1H), 4.25 – 4.15 (m, 1H), 4.09 (d, *J* = 14.0 Hz, 1H),

3.44 – 3.29 (m, 1H), 2.48 (s, 3H).**$^{13}$C NMR** (75 MHz, Methanol-$d_4$) δ 148.8, 144.374 141.2, 135.5, 135.3, 134.6, 133.9, 133.7, 132.8, 132.2, 131.1, 126.3, 66.2, 52.8, 24.1. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{21}ClN_2O_2S$ [M-Cl+H]$^+$: 329.1324, found 329.1320.

## 3.6.2. Construction of 7,5-Ring Fusion

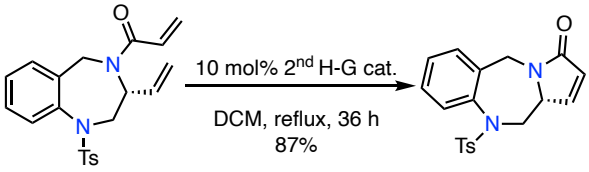
### 3.6.2.1. (*R*)-1-(1-Tosyl-3-vinyl-1,2,3,5-tetrahydro-4*H*-benzo[*e*] [1,4] diazepin-4-yl) prop-2-en-1-one (162)




**160** **161**

To a suspension of **160** (45 mg, 0.123 mmol) and DMAP (1.5 mg, 0.012 mmol, 0.1 equiv) in DCM (0.1 M) cooled in an ice-bath $Et_3N$ (60 µl, 0.5 mmol, 4 equiv) was added. After stirring for 5 min acryloyl chloride (20 µl, 0.247 mmol, 2 equiv) was added dropwise. The reaction was allowed to warm to rt and stirred for 2 h. The crude reaction was diluted with $H_2O$ and extracted with DCM. The organic layer was washed with an aqueous solution of 5% HCl, brine, dried over $Na_2SO_4$ and concentrated in vacuo. The resulting product was purified by silica gel column chromatography with hexanes/EtOAc (7:3) as the eluent to give the desired product **161** as an amorphous off-white solid ( 30 mg, 65% yield), $[\alpha]_D^{25}$ -8.90 (c 0.7, $CHCl_3$)). **$^1$H NMR** (300 MHz, DMSO-$d_6$, 80°C) δ 7.62 (d, $J$ = 7.9 Hz, 2H), 7.40 – 7.09 (m, 6H), 6.54 (dd, $J$ = 16.7, 10.5 Hz, 1H), 5.99 (ddd, $J$ = 16.4, 13.8, 3.5 Hz, 2H), 5.63 (dd, $J$ = 10.4, 2.3 Hz, 1H), 5.24 (dd, $J$ = 22.5, 14.0 Hz, 2H), 4.60 (d, $J$ = 132.9 Hz, 3H), 4.11 – 4.00 (m, 2H), 2.35 (s, 3H). **$^{13}$C NMR** (75 MHz, DMSO-$d_6$, 80°C) δ 170.9, 148.8, 144.8, 139.3, 137.6, 135.0, 134.6, 133.5, 132.7, 132.6, 132.0, 131.2, 129.6, 122.1, 26.1. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{21}ClN_2O_2S$ [M-Cl+H]$^+$: 383.1424, found 383.1422.

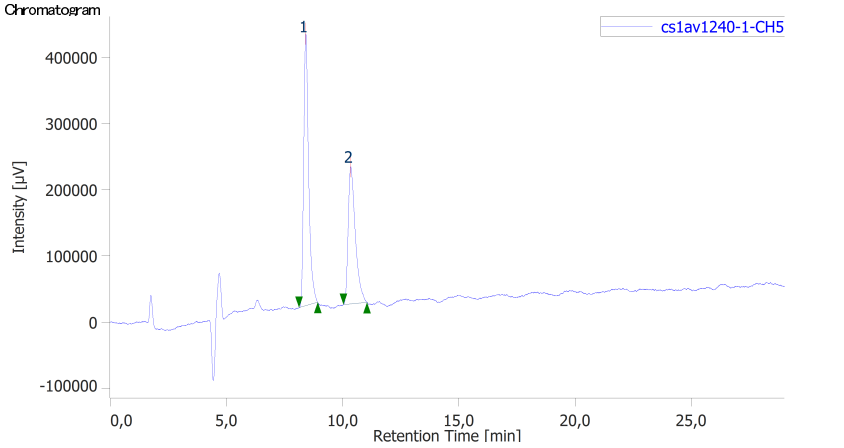
### 3.6.2.2. (R)-10-Tosyl-5,10,11,11a-tetrahydro-3H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (163)

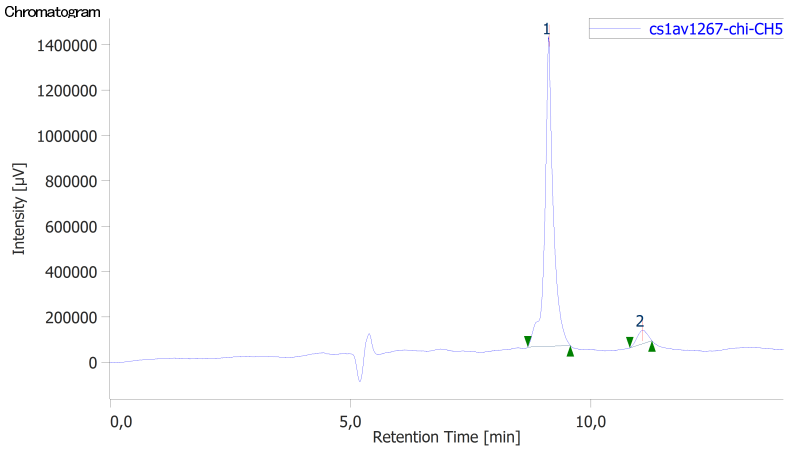



**161** **162**

A flame-dried schlenk was charged with the Hoveyda-Grubbs 2$^{nd}$ generation catalyst (2.5 mg, 0.004 mmol, 0.1 equiv) and it was put under vacuum and backfilled with argon. Afterwards, a solution of **161** (15 mg, 0.04 mmol, 1 equiv) in dry DCM (1.5 mL) was added and the reaction was refluxed in an oil bath for 36 h. Then, the reaction crude was purified by silica gel column chromatography with a gradient of hexanes/EtOAc (60:40) to 100% EtOAc as the eluent to give the desired product **162** as white foam(12 mg, 87% yield), 88% ee, $[\alpha]_D^{25}$ -8.10 (c 0.5, $CHCl_3$)). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 2H), 7.39 (dd, $J$ = 7.3, 1.8 Hz, 1H), 7.32 – 7.21 (m, 4H), 7.16 (dd, $J$ = 7.6, 1.6 Hz, 1H), 6.93 (dd, $J$ = 6.0, 1.7

Hz, 1H), 6.19 (dd, $J$ = 6.0, 1.7 Hz, 1H), 4.84 (d, $J$ = 14.9 Hz, 1H), 4.72 (dd, $J$ = 14.5, 3.4 Hz, 1H), 4.67 – 4.55 (m, 1H), 3.83 (d, $J$ = 14.9 Hz, 1H), 2.73 (dd, $J$ = 14.5, 11.3 Hz, 1H), 2.44 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 168.0, 143.1, 141.6, 138.6, 137.1, 136.0, 129.0, 128.9, 128.4, 127.9, 127.8, 126.1, 52.6, 42.8, 20.6. **HRMS** (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{21}ClN_2O_2S$ $[M\text{-}Cl+H]^+$: 355.1111, found 355.1111. **SFC conditions**: 40% MeOH, *Phenomenex Amylose-1 at 40ºC ($CO_2$ : MeOH= 60:40, 1mL/min)*, λ=210 nm, $t_R$ (min): major = 9.12, minor = 11.06).




**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 9,123 | 16461841 | 1369051 | 94,940 | 95,795 | N/A | 21000 | 5,863 | 0,943 | |
| 2 | Unknown | 5 | 11,063 | 877306 | 60094 | 5,060 | 4,205 | N/A | 11551 | N/A | 0,902 | |

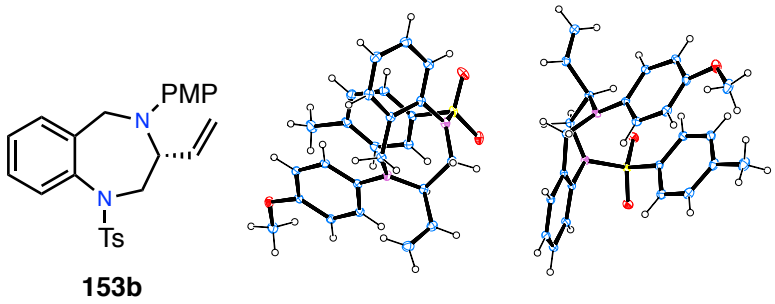
Signals in the range around 3-6 min are due to the front arriving to the detector.

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## 3.7. X-ray Crystallographic Data of 153b

An X-ray crystal of compound **153b** (CCDC 1983304) was grown by vapor diffusion using DCM and hexanes as a mixture of solvents.

**Figure 19**. X-Ray coordinate of compound **153b** (CCDC 1983304). The ORTEP drawing of **153b** showing ellipsoids at the 30% contour probability level




**153b**

**Table 15**. Sample and crystal data refinement for **153b** (CCDC 1983304)

| | | |
|---|---|---|
| CCDC code | CCDC 1983304 | |
| Chemical formula | $C_{25}H_{26}N_2O_3S$ | |
| Formula weight | 434.54 g/mol | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal size | 0.094 x 0.149 x 0.248 mm | |
| Crystal habit | colorless prism | |
| Crystal system | monoclinic | |
| Space group | P 1 21 1 | |
| Unit cell dimensions | a = 12.9168(3) Å | α = 90° |
| | b = 8.5270(2) Å | β = 104.2520(10)° |
| | c = 20.0414(5) Å | γ = 90° |
| Volume | 2139.45(9) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.349 g/cm$^3$ | |
| Absorption coefficient | 1.588 mm$^{-1}$ | |
| F(000) | 920 | |

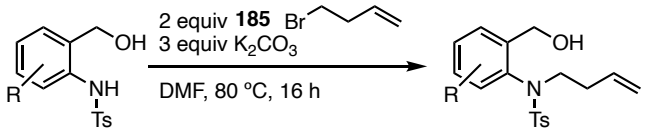
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# 4. Experimental Procedures for Chapter 4

**186a**, **186c**, **186d**, **186p** and **186q** were synthesized according to the literature procedure.[198] **L-SOX** were synthesized according to the literature procedure reported by White and coworkers (See Chapter 5, 2.5). Sulfonamides **184** and **191** were synthesized according to literature procedures.[214]

## 4.1. Synthesis of Alkenes 186

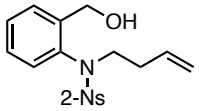
### 4.1.1. General Procedure A for the Synthesis of Alkenes 187




**184** **186**

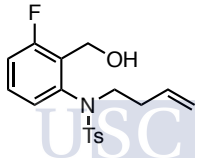
A round-bottomed flask equipped with a stirring magnetic bar was flamed-dried under vacuum and backfilled with argon. Then, it was charged with the corresponding tosylamide **184** and $K_2CO_3$ (3 equiv), and it was put under vacuum and backfilled with argon for three times. Afterwards, DMF (0.25M) was added and the mixture was stirred for 30 min at rt. Finally, 4-bromo 1-butene **185** was added and the reaction was heated to 80 °C for 16 h. The reaction was quenched with a saturated solution of $NH_4Cl_{(aq)}$ and extracted with EtOAc. The organic phase was washed with a saturated solution of $NH_4Cl_{(aq)}$ (3 x 50 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue was purified in silica gel column chromatography with Hexanes/EtOAc (8:2) as eluent to give the desired product **186**.

***N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)phenyl)-2-nitrobenzenesulfonamide (186b)**



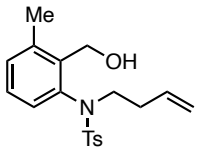

Isolated in 87% yield (0.9 g, 2.6 mmol) as pale-yellow solid at 4 °C. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.8 – 7.6 (m, 4H), 7.5 – 7.5 (m, 1H), 7.4 (dt, *J* = 12.6, 4.5 Hz, 2H), 7.2 (t, *J* = 7.7 Hz, 1H), 6.8 (d, *J* = 7.9 Hz, 1H), 5.8 – 5.6 (m, 1H), 5.1 – 5.0 (m, 2H), 4.8 (d, *J* = 12.5 Hz, 1H), 4.5 (d, *J* = 12.5 Hz, 1H), 4.1 (dt, *J* = 14.8, 7.9 Hz, 1H), 3.6 (ddd, *J* = 14.0, 7.7, 5.1 Hz, 1H), 2.6 (s, 1H), 2.2 (qq, *J* = 14.1, 7.7 Hz, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 148.4, 142.4, 135.7, 134.2, 134.1, 132.2, 131.3, 131.3, 131.2, 129.8, 129.1, 128.8, 123.9, 117.6, 60.8, 52.6, 32.9. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{17}H_{19}N_2O_5S$ $[M\text{-}OH_2]^+$: 345.0904, found 345.0904.

***N*-(but-3-en-1-yl)-*N*-(3-fluoro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (186e)**



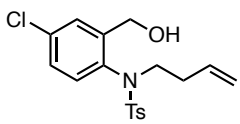

Isolated in 77% yield (0.76 g, 2.31 mmol) as brown solid at 4 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.5 (d, *J* = 8.2 Hz, 1H), 7.3 – 7.3 (m, 1H), 7.2 – 7.0 (m, 1H), 5.1 – 4.8 (m, 1H), 4.7 (d, *J* = 11.8 Hz, 1H), 4.0 (dt, *J* = 12.9, 8.0 Hz, 1H), 3.1 (ddd, *J* = 13.0, 8.2, 5.1 Hz, 1H), 2.5 (s, 2H), 2.3 – 1.9 (m, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 162.7 (d, *J* = 250.5 Hz), 144.4, 139.4 (d, *J* = 6.6 Hz), 134.3, 130.7 (d, *J* = 16.6 Hz), 129.8, 129.2 (d, *J* = 9.8 Hz), 128.3, 122.8 (d, *J* = 3.5 Hz), 117.6, 116.3 (d, *J* = 22.5 Hz), 55.0 (d, *J* = 3.9 Hz), 51.5, 32.5, 21.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -113.0 (t, *J* = 7.6 Hz). **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{21}FNO_3S$ $[M\text{-}OH_2]^+$: 332.1115, found 332.1118.

***N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)-3-methylphenyl)-4-methylbenzenesulfonamide (186f)**



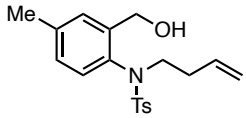

Isolated in 70% yield (0.69 g, 2. 1 mmol) as white solid at 4 °C. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.3 (s, 2H), 7.2 (d, *J* = 7.5 Hz, 1H), 7.0 (d, *J* = 7.8 Hz, 1H), 6.3 (d, *J* = 7.9 Hz, 1H), 5.7 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.1 (d, *J* = 11.9 Hz, 1H), 5.0 – 4.9 (m, 2H), 4.5 (d, *J* = 11.9 Hz, 1H), 4.0 (ddd, *J* = 12.8, 9.0, 7.2 Hz, 1H), 3.1 (ddd, *J* = 13.3, 8.7, 5.0 Hz, 1H), 2.5 (s, 3H), 2.4 (s, 3H), 2.3 – 2.1 (m, 1H), 2.1 – 2.0 (m, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 144.0, 140.7, 137.7, 134.5, 134.3, 131.0, 129.6, 128.3, 128.2, 127.3, 124.3, 117.4, 58.0, 51.5, 32.5, 21.7, 19.6 **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{24}NO_3S$ $[M\text{-}OH_2]^+$: 328.1366, found 328.1369.

***N*-(but-3-en-1-yl)-*N*-(4-chloro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (186g)**



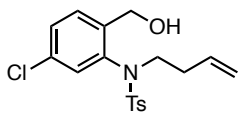

Isolated in 83% yield (0.68 g, 1.95 mmol) as yellow oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.6 (t, *J* = 2.2 Hz, 1H), 7.5 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.3 (d, *J* = 8.2 Hz, 2H), 7.1 (dt, *J* = 8.6, 2.2 Hz, 1H), 6.3 (d, *J* = 8.5 Hz, 1H), 5.6 (ddt, *J* = 17.0, 12.5, 6.7 Hz, 1H), 5.1 – 4.9 (m, 3H), 4.5 (d, *J* = 12.7 Hz, 1H), 3.9 (dt, *J* = 15.1, 7.9 Hz, 1H), 3.1 (ddd, *J* = 13.1, 8.2, 5.2 Hz, 2H), 2.4 (s, 3H), 2.1 (tq, *J* = 15.0, 7.0 Hz, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 144.7, 144.3, 135.6, 134.8, 134.3, 134.1, 130.8, 129.8, 128.5, 128.2, 128.2, 117.5, 60.8, 51.3, 32.4, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{21}ClNO_3S$ $[M\text{-}OH_2]^+$: 348.0820, found 348.0820.

***N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)-4-methylphenyl)-4-methylbenzenesulfonamide (186i)**



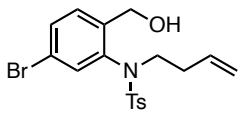

Isolated in 83% yield (0.82 g, 2.5 mmol) as whjite-off solid at 4 °C. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.5 (d, *J* = 8.1 Hz, 2H), 7.4 (d, *J* = 2.2 Hz, 1H), 7.3 (s, 2H), 6.9 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.3 (d, *J* = 8.1 Hz, 1H), 5.7 (ddt, *J* = 17.1, 10.7, 6.6 Hz, 1H), 5.0 – 4.9 (m, 3H), 4.4 (d, *J* = 12.0 Hz, 1H), 3.9 (ddd, *J* = 12.8, 8.9, 7.3 Hz, 1H), 3.1 (ddd, *J* = 13.0, 8.5, 5.1 Hz, 2H), 2.4 (s, 3H), 2.3 (s, 3H), 2.3 – 2.0 (m, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.9, 142.2, 139.1, 134.6, 134.5, 134.4, 131.9, 129.6, 129.2, 128.2, 126.7, 117.2, 61.2, 51.4, 32.4, 21.6, 21.2. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{24}NO_3S$ $[M\text{-}OH_2]^+$: 328.1366, found 328.1367.

***N*-(but-3-en-1-yl)-*N*-(5-chloro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (186k)**



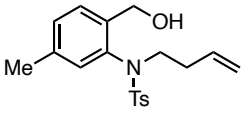

Isolated in 75% yield (0.78 g, 2.25 mmol) as brown solid at 4 °C. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 (d, *J* = 8.3 Hz, 1H), 7.5 – 7.5 (m, 2H), 7.3 (td, *J* = 5.7, 2.7 Hz, 3H), 6.4 (d, *J* = 2.1 Hz, 1H), 5.7 – 5.6 (m, 1H), 5.1 – 4.9 (m, 3H), 4.5 (d, *J* = 12.4 Hz, 1H), 3.9 (dt, *J* = 12.8, 8.0 Hz, 1H), 3.1 (ddd, *J* = 13.2, 8.4, 5.1 Hz, 1H), 3.0 (s, 1H), 2.5 (s, 3H), 2.2 – 2.0 (m, 2H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 144.5, 141.5, 138.3, 134.3, 133.8, 133.5, 132.3, 129.8, 129.4, 128.3, 127.1, 117.6, 60.7, 51.3, 32.4, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{21}ClNO_3S$ $[M\text{-}OH_2]^+$: 348.0820, found 348.0810.

***N*-(5-bromo-2-(hydroxymethyl)phenyl)-*N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (186l)**



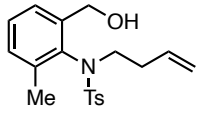
Isolated in 80% yield (0.76 g, 2.31 mmol) as brown oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.5 – 7.5 (m, 3H), 7.3 (d, *J* = 8.0 Hz, 2H), 6.5 (d, *J* = 1.7 Hz, 1H), 5.7 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.1 – 4.9 (m, 3H), 4.5 (d, *J* = 12.5 Hz, 1H), 3.9 (dt, *J* = 12.9, 8.0 Hz, 1H), 3.1 (ddd, *J* = 13.1, 8.3, 5.0 Hz, 1H), 2.5 (s, 3H), 2.3 – 2.0 (m, 2H). **$^{13}$C NMR**[1] (126 MHz, $CDCl_3$) δ 144.6, 142.0, 138.5, 134.3, 133.7, 132.6, 132.3, 130.1, 129.8, 128.3, 121.2, 117.6, 60.7, 51.3, 32.5, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{21}BrNO_3S$ $[M\text{-}OH_2]^+$: 392.0314, found 392.0315.

***N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)-5-methylphenyl)-4-methylbenzenesulfonamide (186m)**



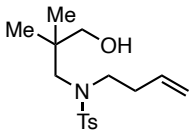
Isolated in 90% yield (0.88 g, 2.7 mmol) as brown solid at 4 °C. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.5 (d, *J* = 8.1 Hz, 2H), 7.5 (d, *J* = 7.8 Hz, 1H), 7.3 (d, *J* = 8.0 Hz, 2H), 7.2 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.2 (d, *J* = 1.7 Hz, 1H), 5.7 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.1 – 4.9 (m, 3H), 4.5 – 4.4 (m, 1H), 3.9 (ddd, *J* = 12.8, 9.0, 7.2 Hz, 1H), 3.2 – 3.0 (m, 2H), 2.5 (s, 3H), 2.2 (m, 4H), 2.1 (dq, *J* = 13.0, 6.3 Hz, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 144.0, 139.6, 138.5, 137.1, 134.5, 134.4, 131.2, 129.9, 129.5, 128.3, 127.5, 117.3, 61.0, 51.4, 32.5, 21.7, 21.0. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{24}NO_3S$ $[M\text{-}OH_2]^+$: 328.1366, found 328.1367.

***N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)-6-methylphenyl)-4-methylbenzenesulfonamide (1)**



Isolated in 60% yield in two steps (0.62 g, 1.8 mmol) as yellow oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.6 (m, 2H), 7.5 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.3 – 7.3 (m, 3H), 7.1 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.6 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.1 – 4.9 (m, 2H), 4.8 (dd, *J* = 12.2, 2.4 Hz, 1H), 4.4 (dd, *J* = 12.1, 9.2 Hz, 1H), 3.8 (ddd, *J* = 13.7, 10.6, 5.7 Hz, 1H), 3.3 (ddd, *J* = 13.7, 10.5, 5.3 Hz, 1H), 2.9 (dd, *J* = 9.9, 4.0 Hz, 1H), 2.4 (s, 3H), 2.4 – 2.3 (m, 1H), 2.3 – 2.2 (m, 1H), 1.7 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 143.8, 142.9, 137.6, 137.3, 135.4, 134.4, 131.3, 129.9, 129.0, 129.0, 127.5, 117.4, 61.9, 51.1, 33.6, 21.7, 18.3. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{24}NO_3S$ $[M\text{-}OH_2]^+$: 328.1366, found 328.1378.

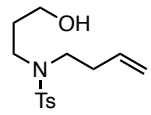
***N*-(but-3-en-1-yl)-*N*-(3-hydroxy-2,2-dimethylpropyl)-4-methylbenzenesulfonamide (186t)**



Isolated in 90% yield (0.79 g, 2.7 mmol) as colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.7 – 7.6 (m, 2H), 7.3 (d, *J* = 8.0 Hz, 2H), 5.7 – 5.5 (m, 1H), 5.1 – 4.9 (m, 1H), 3.4 (s, 2H), 3.2 – 3.0 (m, 2H), 3.0 (s, 2H), 2.4 (s, 3H), 2.3 (dddd, *J* = 8.4, 6.9, 4.9, 2.1 Hz, 2H), 0.9 (s, 6H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 143.8, 136.0, 134.6, 129.9, 127.6, 117.1, 67.9, 55.5, 51.1, 38.0, 32.8, 23.3, 21.6. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{26}NO_3S$ $[M\text{-}OH_2]^+$: 294.1522, found 294.1522.

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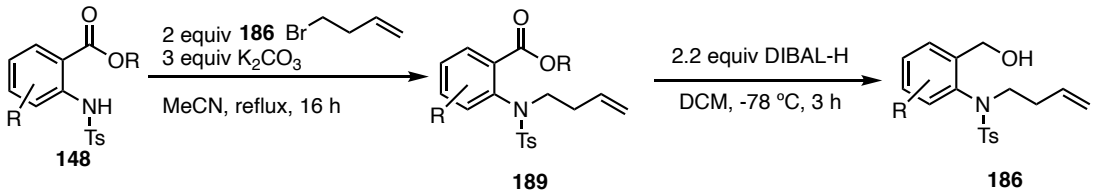
***N*-(but-3-en-1-yl)-*N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (186u)**



Isolated in 70% yield (0.57 g, 2.1 mmol) as colorless oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.7 (d, *J* = 7.9 Hz, 1H), 7.4 – 7.3 (m, 1H), 5.7 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 0H), 5.1 – 5.0 (m, 1H), 3.8 (q, *J* = 5.9 Hz, 1H), 3.3

– 3.1 (m, 2H), 2.4 (s, 2H), 2.4 – 2.2 (m, 1H), 1.8 (p, *J* = 5.9 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.3, 136.4, 134.5, 129.7, 127.0, 117.1, 58.9, 48.2, 45.2, 33.2, 31.3, 21.4. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{14}H_{22}NO_3S$ $[M\text{-}OH_2]^+$: 266.1192, found 266.1199.

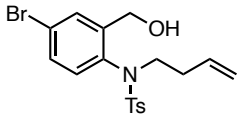
### 4.1.2. General Procedure B for the Synthesis of Alkenes 186




A round-bottomed flask equipped with a stirring magnetic bar was flamed-dried under vacuum and backfilled with argon. Then, it was charged with the corresponding tosylamide **148** and $K_2CO_3$ (3 equiv), and it was put under vacuum and backfilled with argon for three times. Afterwards, MeCN (0.1M) was added followed by 4-bromo-1-butene **185** and the reaction was heated to reflux for 16 h. The reaction was quenched with a saturated solution of $NH_4Cl_{(aq)}$ and extracted with EtOAc. The organic phase was washed with a saturated solution of $NH_4Cl_{(aq)}$ (3 x 50 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue **192** was used in the next step without further purification.

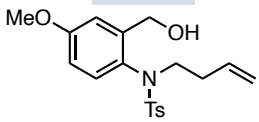
DIBAL-H (1M in DCM, 2.2 equiv) was added dropwise to a stirred solution of the ester **189** (1 equiv) in DCM (0.3 M) at -78°C. The reaction was then stirred at that temperature for 3 h. Afterwards, MeOH (5 mL) was added followed by a saturated solution of the Rochelle Salt at -78°C. The reaction was then warmed up to rt and stirred for 1h. The mixture was extracted with DCM (3 x 30 mL) and the combination of organic layers was washed with a saturated solution of NaCl(aq), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography with hexanes/EtOAc (8:2) as the eluent to afford the desired product **186**.

***N*-(4-bromo-2-(hydroxymethyl)phenyl)-*N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (186h)**



Isolated in 71% yield in two steps (0.83 g, 2.13 mmol) as brown oil.
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.8 (d, *J* = 2.4 Hz, 1H), 7.5 (d, *J* = 8.0 Hz, 2H), 7.3 (t, *J* = 8.4 Hz, 3H), 6.3 (d, *J* = 8.5 Hz, 1H), 5.6 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.0 (ddd, *J* = 16.3, 8.1, 4.5 Hz, 3H), 4.5 (d, *J* = 12.8 Hz, 1H), 3.9 (dt, *J* = 13.0, 8.0 Hz, 1H), 3.1 (ddd, *J* = 13.1, 8.1, 5.2 Hz, 2H), 2.4 (s, 3H), 2.1 (qt, *J* = 15.0, 7.2 Hz, 2H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 144.9, 144.3, 136.0, 134.3, 133.9, 133.8, 131.4, 129.7, 128.4, 128.1, 122.9, 117.4, 60.6, 51.1, 32.3, 21.6. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{21}BrNO_3S$ $[M\text{-}OH_2]^+$: 392.0314, found 392.0329.

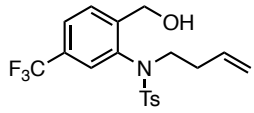
***N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (186j)**



Isolated in 70% yield in two steps (0.72 g, 2.1 mmol) as white-off solid at 4 °C.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.4 (d, *J* = 7.9 Hz, 2H), 7.2 (s, 2H), 7.0 (d, *J* = 3.0 Hz, 1H), 6.6 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.3 (d, *J* = 8.7 Hz, 1H), 5.6 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.0 – 4.8 (m, 3H), 4.4 (d, *J* = 12.2 Hz, 1H), 3.9 (dt, *J*

= 12.6, 7.9 Hz, 1H), 3.7 (s, 4H), 3.0 (ddd, *J* = 13.3, 8.6, 5.0 Hz, 2H), 2.4 (s, 4H), 2.1 (dq, *J* = 15.1, 7.6 Hz, 1H), 2.0 – 1.9 (m, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 159.6, 144.0, 144.0, 134.6, 134.4, 129.6, 129.5, 128.2, 128.0, 117.3, 115.0, 114.7, 61.4, 55.5, 51.4, 32.4, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{24}NO_4S$ $[M\text{-}OH_2]^+$: 344.1315, found 344.1312.

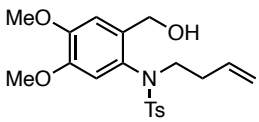
**_N_-(but-3-en-1-yl)-_N_-(2-(hydroxymethyl)-5-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide (186n)**



Isolated in 67% yield in two steps (0.8 g, 2.0 mmol) as pale-yelow solid at 4 °C.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.8 (d, *J* = 8.0 Hz, 1H), 7.6 (d, *J* = 8.0 Hz, 1H), 7.5 (d, *J* = 7.9 Hz, 2H), 7.3 (d, *J* = 7.9 Hz, 2H), 6.6 (s, 1H), 5.7 (ddt, *J* = 17.1, 10.5, 6.6 Hz, 1H), 5.1 – 4.9 (m, 4H), 4.6 (d, *J* = 12.9 Hz, 1H), 4.0 (dt, *J* = 13.1, 8.0 Hz, 1H), 3.1 (ddd, *J* = 13.2, 8.0, 5.1 Hz, 1H), 2.5 (s, 4H), 2.3 – 2.0 (m, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 146.9, 144.7, 137.8, 134.3, 133.5, 131.5, 130.6 (q, *J* = 33.1 Hz), 129.8, 128.2, 125.7(d, *J* = 3.7 Hz) 124.1 (q, *J* = 3.7 Hz), 123.4 (q, *J* = 272.4 Hz), 117.7, 60.8, 51.4, 32.5, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{21}F_3NO_3S$ $[M\text{-}OH_2]^+$: 382.1366, found 382.1386.

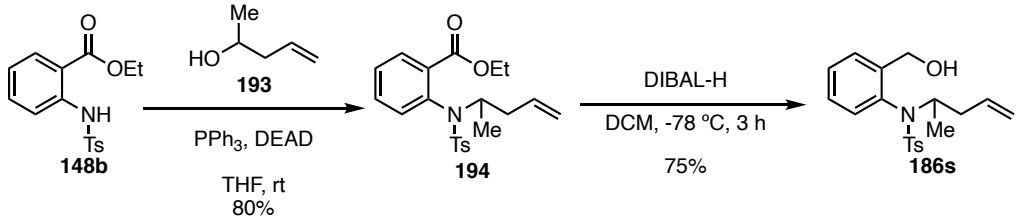
**_N_-(but-3-en-1-yl)-_N_-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (186p)**



Isolated in 58% yield in two steps (0.65 g, 1.74 mmol) as white-off solid at 4 °C.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.3 (d, *J* = 8.0 Hz, 2H), 7.1 (s, 1H), 5.8 (s, 1H), 5.7 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.1 – 4.9 (m, 3H), 4.4 (d, *J* = 12.0 Hz, 1H), 4.0 (ddd, *J* = 12.8, 8.8, 7.2 Hz, 1H), 3.9 (s, 3H), 3.5 (s, 3H), 3.1 (ddd, *J* = 13.2, 8.6, 5.0 Hz, 1H), 2.4 (s, 3H), 2.3 – 2.2 (m, 1H), 2.2 – 2.0 (m, 1H).**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 149.4, 148.5, 144.1, 135.6, 134.6, 134.6, 129.6, 129.0, 128.4, 117.4, 112.9, 109.6, 61.0, 56.1, 55.7, 51.4, 32.5, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{20}H_{26}NO_5S$ $[M\text{-}OH_2]^+$: 374.1421, found 374.1431.

## 4.1.3. Synthesis of *N*-(2-(hydroxymethyl)phenyl)-4-methyl-*N*-(pent-4-en-2-yl)benzenesulfonamide (186s)

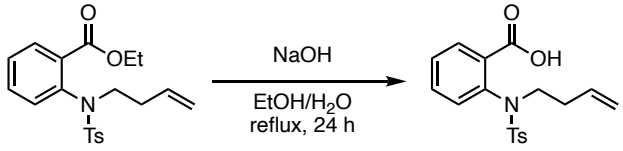



To a solution of **148b** (1 equiv), $PPh_3$ (3 equiv) and the homoallylic alcohol **193** in THF (0.15 M) at 0°C, DEAD was added (40% in toluene, 3 equiv). The reaction was stirred at rt for 4 h. Then the solvent was removed, and the residue was purified by silica gel column chromatography with Hexanes/EtOAc (9:1) to give the desired product **194** in an 80% yield.

DIBAL-H (1M in DCM, 2.2 equiv) was added dropwise to a stirred solution of the ester **194** (1 equiv) in DCM (0.3 M) at -78°C. The reaction was then stirred at that temperature for 3 h. Afterwards, MeOH (5 mL) was added followed by a saturated solution of the Rochelle Salt at -78°C. The reaction was then warmed up to rt and stirred for 1h. The mixture was

extracted with DCM (3 x 30 mL) and the combination of organic layers was washed with a saturated solution of NaCl(aq), dried over $Na_2SO4$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography with hexanes/EtOAc (8:2) as the eluent to afford the desired product **186s** in 75% yield (0.84 g, 2.56 mmol) as white-off solid and as a mixture of isomers. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.6 (dt, *J* = 7.7, 2.0 Hz, 1H), 7.6 – 7.5 (m, 2H), 7.4 – 7.3 (m, 1H), 7.2 (ddd, *J* = 8.6, 1.6, 0.8 Hz, 2H), 7.2 – 7.1 (m, 1H), 6.7 – 6.5 (m, 1H), 5.8 – 5.4 (m, 1H), 5.0 – 4.8 (m, 3H), 4.6 – 4.3 (m, 2H), 3.3 (dd, *J* = 9.5, 3.4 Hz, 1H), 2.4 (s, 3H), 0.9 (dd, *J* = 16.1, 6.8 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.9, 143.9, 143.5, 137.5, 137.2, 134.5, 134.4, 133.2, 131.0, 130.9, 130.9, 130.7, 129.4, 129.3, 129.3, 127.7, 127.5, 127.5, 127.4, 117.7, 117.6, 61.1, 61.0, 56.2, 55.8, 40.1, 40.1, 21.4, 18.7, 18.1. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{24}NO_3S$ $[M\text{-}OH_2]^+$: 328.1366, found 328.1378.

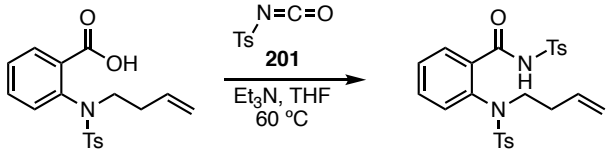
## 4.1.4. Synthesis of 2-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)benzoic acid (187w)




**189** **186w**

To a solution of **189** (1.4 g, 3.8 mmol) in EtOH (20 mL), an aqueous solution of NaOH (8.5 g, 212 mmol) in water (50 mL) was added. The mixture was heated to reflux for 24 h. Then the reaction was cooled to 0 °C, and $HCl_c$ was added to reach pH = 3. The solution was extracted with AcOEt (3 x 70 mL) and the combination of organic phases was washed with water (80 mL), brine (80 mL), dried over $Na_2SO_4$ and the solvent was removed in vacuo. The carboxylic acid **186w** was recrystallized in a mixture of Hexanes/AcOEt (1:1) to provide the product in 68% yield (885 mg, 2.56 mmol) as white-off solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.1 – 7.9 (m, 1H), 7.6 – 7.4 (m, 4H), 7.3 – 7.2 (m, 2H), 7.1 – 6.9 (m, 1H), 5.7 (ddt, *J* = 17.1, 10.5, 6.7 Hz, 1H), 5.1 – 4.9 (m, 2H), 3.8 (s, 1H), 3.6 (s, 1H), 2.4 (s, 5H). **$^{13}$C NMR** (75 MHz, $CD_3OD$) δ 169.4, 145.1, 139.3, 137.4, 136.3, 135.1, 133.1, 132.2, 131.3, 130.6, 129.4, 128.7, 117.1, 52.4, 34.3, 21.5. **HRMS** (MM: ESI-APCI-) m/z calc'd for $C_{18}H_{18}NO_4S$ [M -H]: 344.0962, found 344.0950.

## 4.1.5. Synthesis of 2-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)-*N*-tosylbenzamide (186x)



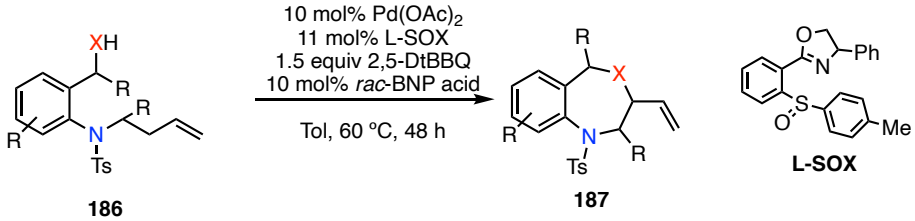

**186w** **186x**

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To a solution of **186w** (1.6 mmol, 1 equiv) in THF (8 mL, 0.2 M) were sequentially added TsNCO **201** (365µL, 2.4 mmol, 1.5 equiv) and $Et_3N$ (332 µL, 2.4 mmol, 1.5 equiv) at room temperature. After being stirred at 60 °C for 5 hours, the reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with 1.0 N HCl. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column

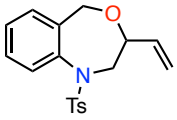
chromatography with Hexanes/AcOEt (7:3) to give the desired product **186x** as yellow solid in 90% yield (0.7 g, 1.4 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 10.5 (s, 1H), 8.2 – 8.1 (m, 2H), 7.8 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.5 – 7.5 (m, 2H), 7.4 – 7.3 (m, 3H), 7.3 – 7.3 (m, 3H), 6.4 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.4 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 4.9 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.8 (dq, *J* = 17.1, 1.6 Hz, 1H), 3.8 (ddd, *J* = 12.3, 9.9, 6.6 Hz, 1H), 3.0 (ddd, *J* = 12.7, 9.8, 5.0 Hz, 1H), 2.5 (s, 3H), 2.4 (s, 3H), 1.8 (td, *J* = 13.9, 5.4 Hz, 1H), 1.7 – 1.6 (m, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 164.7, 145.1, 144.9, 136.3, 136.0, 135.8, 133.5, 133.0, 132.2, 131.3, 130.0, 129.5, 129.4, 129.3, 128.6, 127.0, 118.0, 51.6, 32.0, 21.8, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{25}H_{27}N_2O_5S_2$ [M-H]: 499.1361, found 499.1365.

## 4.2. Synthesis and Characterization of Compounds 187



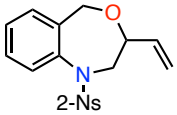

A 4 mL flamed-dried vial equipped with a stirring magnetic bar was charged with Pd-catalyst (2.2 mg, 0.01 mmol, 0.01 equiv), *rac*-BNP acid (3.8 mg, 0.011 mmol, 0.11 equiv),2,5-di-tert-butyl-1,4-benzoquinone(2,5-DtBBQ) (33 mg, 0.15 mmol, 1.5 equiv), **186** (0.1 mmol, 1 equiv) and toluene (0.67 mL, 0.15 M). The mixture was heated under air and moisture for 24 h at 60 °C. After cooling and stripping off the solvent, the residue was purified in a silica gel column chromatography with a gradient (9.5:0.5 to 8:2) of Hexanes/AcOEt to give the desired product **187**.

**1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187a = 153l)**



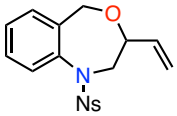

It was isolated as a white-off foam in 91% yield (30 mg, 0.091 mmol). The NMR signals matched with the previously reported **153l**.

**1-((2-nitrophenyl)sulfonyl)-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepane (187b)**




It was isolated as yellow foam in a 50% yield (18 mg, 0.05 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.8 (d, *J* = 1.3 Hz, 1H), 7.8 (d, *J* = 1.3 Hz, 1H), 7.8 – 7.7 (m, 4H), 7.6 (td, *J* = 7.6, 1.7 Hz, 3H), 5.8 (ddd, *J* = 17.5, 10.9, 5.3 Hz, 2H), 5.4 (dt, *J* = 17.6, 1.4 Hz, 2H), 5.2 (dt, *J* = 10.9, 1.4 Hz, 2H), 4.8 (d, *J* = 13.4 Hz, 3H), 4.7 (d, *J* = 13.4 Hz, 3H), 4.5 – 4.3 (m, 6H), 3.1 (dd, *J* = 15.3, 10.5 Hz, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 148.0, 139.5, 139.3, 135.0, 134.3, 134.1, 131.9, 131.6, 130.2, 129.0, 128.9, 128.4, 124.6, 117.6, 82.6, 72.6, 56.2. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{17}H_{17}N_2O_5S$ $[M+H]^+$: 361.0858, found 361.0857.

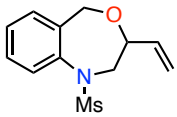
**1-((4-nitrophenyl)sulfonyl)-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepane (187c)**




It was isolated as yellow foam in an 83% yield (30 mg, mmol). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.4 (dq, *J* = 9.3, 1.9 Hz, 1H), 8.1 – 7.8 (m, 1H), 7.4 – 7.2 (m, 2H), 5.8 (dddd, *J* = 17.3, 10.7, 5.2, 1.1 Hz, 1H), 5.5 – 5.2 (m, 1H), 4.6 (dd, *J* = 13.6, 1.2 Hz, 1H), 4.4 (dt, *J* = 15.0, 1.5 Hz, 1H), 4.3 – 4.0 (m, 1H), 3.1 (dd, *J* = 15.1, 10.4 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 150.1, 146.9, 138.2, 134.6, 130.0, 129.2,

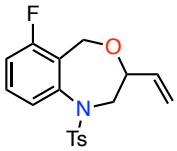
128.7, 128.4, 128.4, 124.5, 117.8, 81.1, 72.1, 55.9. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{17}H_{17}N_2O_5S$ $[M+H]^+$: 361.0858, found 361.0841.

**1-(methylsulfonyl)-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187d)**



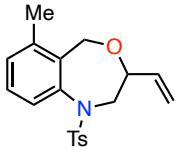

It was isolated as a colorless oil in 87% yield (22 mg, 0.087 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.4 (d, *J* = 8.2 Hz, 1H), 7.3 – 7.1 (m, 3H), 5.7 (ddd, *J* = 17.3, 10.8, 5.3 Hz, 1H), 5.3 (dt, *J* = 17.5, 1.5 Hz, 1H), 5.2 (dt, *J* = 10.7, 1.4 Hz, 1H), 4.8 – 4.7 (m, 2H), 4.4 – 4.3 (m, 1H), 4.1 (dd, *J* = 15.0, 2.1 Hz, 1H), 3.1 (s, 3H), 2.9 (dd, *J* = 15.0, 10.5 Hz, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 139.9, 138.0, 134.9, 129.9, 129.1, 128.0, 127.4, 117.5, 81.6, 72.1, 55.0, 41.5. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{16}NO_3S$ $[M+H]^+$: 254.0851, found 254.0849.

**6-fluoro-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187e)**



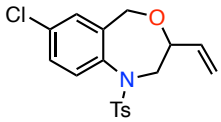

It was isolated as brown oil in 58% yield (20 mg, 0.057 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 (d, *J* = 8.1 Hz, 2H), 7.3 (s, 2H), 7.2 (td, *J* = 8.2, 6.0 Hz, 1H), 7.2 (d, *J* = 7.9 Hz, 1H), 7.0 (t, *J* = 8.6 Hz, 1H), 5.7 (ddd, *J* = 17.5, 10.8, 5.3 Hz, 1H), 5.4 – 5.3 (m, 1H), 5.2 (dd, *J* = 10.9, 1.5 Hz, 1H), 5.0 (d, *J* = 13.7 Hz, 1H), 4.4 (dd, *J* = 15.1, 2.0 Hz, 1H), 4.3 – 4.2 (m, 1H), 3.9 (dd, *J* = 13.7, 2.5 Hz, 1H), 3.0 (dd, *J* = 15.1, 10.3 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$ δ 160.1 (d, *J* = 248.5 Hz), 144.1, 141.8 (d, *J* = 4.6 Hz), 138.4, 135.0, 130.1, 129.3 (d, *J* = 9.9 Hz), 127.3, 126.1 (d, *J* = 15.2 Hz), 124.5 (d, *J* = 3.5 Hz), 117.6, 115.3 (d, *J* = 23.1 Hz), 80.9, 63.2, 55.6, 21.7. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -116.8 (t, *J* = 7.7 Hz).**$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -116.8 (t, *J* = 7.7 Hz). **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{19}FNO_3S$ $[M+H]^+$: 348.1070, found 348.1064.

**6-methyl-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187f)**



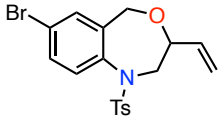

It was isolated as colorless oil in 60% yield (21 mg, 0.06 mmol). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.7 – 7.6 (m, 2H), 7.3 (d, *J* = 8.0 Hz, 2H), 7.2 – 7.0 (m, 3H), 5.7 (ddd, *J* = 17.3, 10.7, 5.4 Hz, 1H), 5.4 (dt, *J* = 17.4, 1.4 Hz, 1H), 5.2 (dt, *J* = 10.8, 1.4 Hz, 1H), 4.9 (d, *J* = 13.6 Hz, 1H), 4.4 – 4.2 (m, 4H), 3.0 (dd, *J* = 15.2, 10.7 Hz, 1H), 2.4 (s, 4H), 2.4 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.7, 140.7, 138.9, 137.2, 137.1, 135.4, 130.4, 129.9, 128.2, 127.3, 126.2, 117.6, 81.0, 67.0, 55.7, 21.7, 19.8. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{22}NO_3S$ $[M+H]^+$: 344.1320, found 344.1311.

**7-chloro-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187g)**



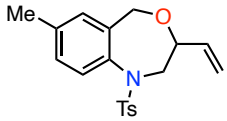

It was isolated as a white foam in 55% yield (20 mg, 0.055 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.3 – 7.2 (m, 4H), 7.1 (d, *J* = 2.4 Hz, 1H), 5.7 (ddd, *J* = 17.4, 10.8, 5.3 Hz, 1H), 5.3 (dt, *J* = 17.4, 1.5 Hz, 1H), 5.2 (dt, *J* = 10.8, 1.4 Hz, 1H), 4.4 – 4.3 (m, 3H), 4.1 (ddq, *J* = 10.4, 5.2, 1.7 Hz, 1H), 4.0 (d, *J* = 13.5 Hz, 1H), 2.9 (dd, *J* = 15.1, 10.3 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 144.1, 140.1, 138.4, 138.3, 135.0, 133.6, 130.5, 130.1, 129.8, 129.0, 127.3, 117.6, 80.8, 71.8, 55.6, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{19}ClNO_3S$ $[M+H]^+$: 364.0774, found 364.0772.

**7-bromo-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187h)**



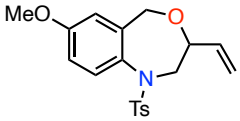
It was isolated as a brown foam in 75% yield (31 mg, 0.075 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.3 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.3 (d, *J* = 2.4 Hz, 1H), 7.2 – 7.2 (m, 3H), 5.6 (ddd, *J* = 17.4, 10.8, 5.3 Hz, 1H), 5.3 (dt, *J* = 17.4, 1.4 Hz, 1H), 5.1 (dt, *J* = 10.8, 1.4 Hz, 1H), 4.4 – 4.2 (m, 2H), 4.1 (ddq, *J* = 10.3, 5.1, 1.6 Hz, 1H), 4.0 (d, *J* = 13.5 Hz, 1H), 2.9 (dd, *J* = 15.1, 10.3 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 144.2, 140.3, 138.9, 138.3, 135.0, 132.7, 132.0, 130.7, 130.1, 127.3, 121.7, 117.6, 80.8, 71.7, 55.6, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{19}BrNO_3S$ $[M+H]^+$: 408.0269, found 408.0272.

**7-methyl-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187i)**



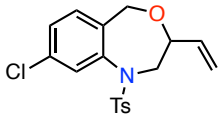
It was isolated as a colorless oil in 45% yield (16 mg, 0.045 mmol). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.7 – 7.5 (m, 2H), 7.4 – 7.2 (m, 3H), 7.2 – 7.0 (m, 2H), 5.8 (ddd, *J* = 16.9, 10.7, 5.2 Hz, 1H), 5.4 – 5.3 (m, 1H), 5.3 – 5.2 (m, 1H), 4.5 – 4.3 (m, 2H), 4.2 (t, *J* = 11.4 Hz, 2H), 3.0 (dd, *J* = 15.0, 10.3 Hz, 1H), 2.4 (s, 3H), 2.3 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.7, 138.8, 138.2, 138.1, 137.2, 135.4, 130.5, 129.9, 129.6, 128.8, 127.3, 117.3, 80.9, 72.4, 55.8, 21.7, 21.1. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{22}NO_3S$ $[M+H]^+$: 344.1320, found 344.1322.

**7-methoxy-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187j)**



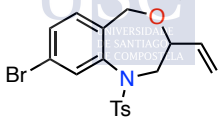
It was isolated as an amorphous white-off solid in 75% yield (27 mg, 0.075 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.5 (d, *J* = 7.8 Hz, 2H), 7.3 – 7.1 (m, 3H), 6.8 – 6.6 (m, 2H), 5.7 (ddd, *J* = 16.6, 10.8, 5.3 Hz, 1H), 5.3 (dd, *J* = 17.6, 2.0 Hz, 1H), 5.1 (d, *J* = 10.8 Hz, 1H), 4.3 (dd, *J* = 14.3, 7.4 Hz, 2H), 4.1 (dd, *J* = 10.6, 5.3 Hz, 1H), 4.0 (d, *J* = 13.4 Hz, 1H), 3.7 (d, *J* = 1.6 Hz, 3H), 2.9 (dd, *J* = 15.0, 10.4 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 157.9, 142.6, 138.8, 137.5, 134.1, 131.1, 129.3, 128.8, 126.1, 116.1, 114.0, 112.5, 79.9, 71.3, 54.6, 54.5, 20.5. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{22}NO_4S$ $[M+H]^+$: 360.1270, found 360.1273.

**8-chloro-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187k)**



It was isolated as a white foam in 70% yield (25 mg, 0.070 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.3 (s, 1H), 7.2 (d, *J* = 8.0 Hz, 2H), 7.2 – 7.1 (m, 1H), 7.1 (d, *J* = 8.1 Hz, 1H), 5.7 (ddd, *J* = 17.4, 10.8, 5.3 Hz, 1H), 5.3 – 5.2 (m, 1H), 5.1 (dt, *J* = 10.7, 1.4 Hz, 1H), 4.4 (d, *J* = 13.5 Hz, 1H), 4.3 (dd, *J* = 15.1, 1.9 Hz, 1H), 4.1 (ddq, *J* = 10.2, 5.1, 1.6 Hz, 1H), 4.1 – 4.0 (m, 1H), 2.9 (dd, *J* = 15.1, 10.3 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 144.2, 141.0, 138.3, 136.8, 135.0, 134.2, 130.7, 130.1, 129.2, 128.2, 127.3, 117.6, 80.8, 71.6, 55.6, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{19}ClNO_3S$ $[M+H]^+$: 364.0774, found 364.0771.

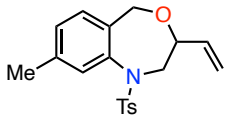
**8-bromo-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187l)**



It was isolated as a brown oil in 37% yield (15 mg, 0.037 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.5 (d, *J* = 1.9 Hz, 1H), 7.3 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.2 (d, *J* = 8.0 Hz, 2H), 7.0 (d, *J* = 8.1 Hz, 1H), 5.7 (ddd, *J* = 17.4, 10.8, 5.3 Hz, 1H), 5.3 (dt, *J* = 17.4, 1.5 Hz, 1H), 5.2 (dt, *J* = 10.8, 1.4 Hz, 1H), 4.4 (d, *J* = 13.5 Hz, 1H), 4.3 (dd, *J* = 15.2, 1.9 Hz, 1H), 4.1 (ddq, *J* = 10.2, 5.1, 1.7 Hz, 1H), 4.0 (d, *J* = 13.5 Hz, 1H), 2.9 (dd, *J* = 15.2, 10.3 Hz, 1H), 2.4 (s, 3H).

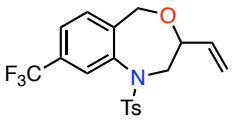
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 144.2, 141.1, 138.2, 137.3, 135.0, 132.1, 131.1, 130.9, 130.1, 127.3, 121.9, 117.6, 80.8, 71.7, 55.6, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{19}BrNO_3S$ $[M+H]^+$: 408.0269, found 408.0310.

**8-methyl-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187m)**



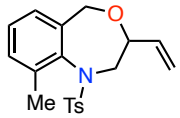

It was isolated as a colorless oil in 54% yield (19 mg, 0.054mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.2 – 7.2 (m, 2H), 7.2 – 7.1 (m, 1H), 7.0 – 6.9 (m, 2H), 5.7 (ddd, *J* = 17.4, 10.8, 5.4 Hz, 1H), 5.3 – 5.2 (m, 1H), 5.1 (dt, *J* = 10.8, 1.4 Hz, 1H), 4.4 (d, *J* = 13.3 Hz, 1H), 4.3 (dd, *J* = 15.1, 1.9 Hz, 1H), 4.1 – 4.0 (m, 1H), 4.0 (d, *J* = 13.4 Hz, 1H), 2.9 (dd, *J* = 15.1, 10.3 Hz, 1H), 2.4 (s, 3H), 2.3 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 143.8, 139.6, 139.1, 138.7, 135.4, 135.3, 129.9, 129.7, 129.6, 128.7, 127.3, 117.3, 80.6, 72.0, 55.8, 21.7, 21.2. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{22}NO_3S$ $[M+H]^+$: 344.1320, found 344.1315.

**1-tosyl-8-(trifluoromethyl)-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187n)**



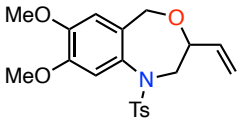

It was isolated as a yellow oil in 85% yield (34 mg, 0.085mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 (d, *J* = 8.0 Hz, 2H), 7.6 (s, 1H), 7.5 (d, *J* = 7.9 Hz, 1H), 7.4 (d, *J* = 7.9 Hz, 1H), 7.3 (d, *J* = 7.9 Hz, 2H), 5.7 (ddd, *J* = 16.8, 10.8, 5.3 Hz, 1H), 5.4 (d, *J* = 17.4 Hz, 1H), 5.2 (d, *J* = 10.8 Hz, 1H), 4.6 (d, *J* = 13.5 Hz, 1H), 4.4 (dd, *J* = 15.1, 1.9 Hz, 1H), 4.3 (d, *J* = 13.5 Hz, 1H), 4.2 (dd, *J* = 10.4, 5.4 Hz, 1H), 3.0 (dd, *J* = 15.2, 10.3 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 144.4, 142.2, 140.5, 138.1, 134.9, 131.3 (q, *J* = 33.0 Hz), 130.3, 130.1, 127.4, 126.1 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 3.7 Hz), 123.5 (d, *J* = 272.5 Hz), 117.7, 81.1, 71.8, 55.4, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{19}F_3NO_3S$ $[M+H]^+$: 398.1038, found 398.1062.

**9-methyl-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187o)**



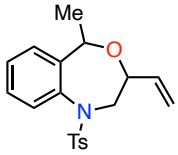

It was isolated in 87% yield (30 mg, 0.087 mmol) as a pale-yellow oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.7 – 7.6 (m, 2H), 7.3 (d, *J* = 8.1 Hz, 2H), 7.2 – 7.1 (m, 2H), 7.0 (dd, *J* = 7.2, 1.9 Hz, 1H), 5.7 (ddd, *J* = 17.4, 10.7, 5.4 Hz, 1H), 5.3 – 5.1 (m, 2H), 4.4 – 4.2 (m, 2H), 4.2 – 4.1 (m, 2H), 3.0 (dd, *J* = 15.3, 10.8 Hz, 1H), 2.4 (s, 3H), 2.4 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 144.1, 140.3, 139.7, 138.8, 138.5, 135.4, 131.6, 130.0, 128.4, 127.8, 127.4, 117.2, 79.7, 72.5, 54.9, 21.7, 19.4. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{22}NO_3S$ $[M+H]^+$: 344.1320, found 344.1316.

**7,8-dimethoxy-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187p)**



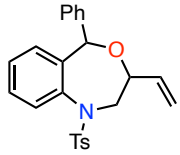

It was isolated as an amorphous white-off solid in 80% yield (31 mg, 0.08 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.7 – 7.5 (m, 2H), 7.3 (d, *J* = 8.1 Hz, 2H), 6.9 (s, 1H), 6.7 (s, 1H), 5.7 (ddd, *J* = 17.3, 10.8, 5.3 Hz, 1H), 5.3 (dt, *J* = 17.4, 1.5 Hz, 1H), 5.2 (dt, *J* = 10.8, 1.4 Hz, 1H), 4.5 – 4.3 (m, 2H), 4.1 (ddq, *J* = 10.4, 5.1, 1.6 Hz, 1H), 4.0 (d, *J* = 13.4 Hz, 1H), 3.9 (s, 3H), 3.8 (s, 3H), 3.0 (dd, *J* = 15.1, 10.4 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 148.6, 148.3, 143.8, 138.6, 135.3, 132.3, 130.9, 129.9, 127.4, 117.3, 112.9, 112.0, 80.8, 72.1, 56.2, 55.8, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{20}H_{24}NO_5S$ $[M+H]^+$: 390.1375, found 390.1374.

**5-methyl-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187q)**



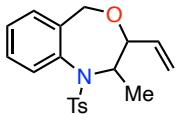

It was isolated as a colorless oil in 70% yield (24 mg, 0.07 mmol) of mixture of isomers (dr = 2:1). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.7 (t, *J* = 8.8 Hz, 3H), 7.4 (s, 2H), 7.3 – 7.1 (m, 9H), 5.8 (ddd, *J* = 16.7, 10.7, 5.7 Hz, 1H), 5.7 (ddd, *J* = 16.8, 10.9, 5.5 Hz, 1H), 5.3 (dq, *J* = 17.2, 1.7 Hz, 2H), 5.2 (t, *J* = 11.5 Hz, 2H), 4.5 (q, *J* = 6.7 Hz, 1H), 4.4 (dd, *J* = 10.6, 5.5 Hz, 2H), 4.3 (d, *J* = 14.8 Hz, 1H), 3.9 (d, *J* = 13.8 Hz, 1H), 3.5 (s, 1H), 2.9 (dd, *J* = 14.8, 10.5 Hz, 1H), 2.4 (s, 4H), 2.4 (s, 2H), 1.6 – 1.5 (m, 7H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 143.8, 143.8, 141.9, 139.9, 138.8, 135.6, 135.5, 129.9, 129.9, 128.7, 128.5, 128.5, 128.2, 127.8, 127.3, 127.2, 126.0, 117.6, 117.3, 80.8, 73.7, 73.1, 54.9, 21.7, 21.7, 19.1, 18.5. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{22}NO_3S$ $[M+H]^+$: 344.1320, found 344.1318.

**5-phenyl-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepane (187r)**



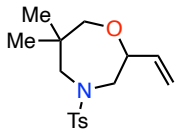

It was isolated as a colorless oil in 52% yield (21 mg, 0.052 mmol) of mixture of isomers (dr = 10:1).
**$^1$H NMR** of the major isomer (500 MHz, $CDCl_3$) δ 7.6 (d, *J* = 7.8 Hz, 2H), 7.4 (d, *J* = 7.9 Hz, 1H), 7.3 – 7.2 (m, 6H), 7.2 – 7.2 (m, 2H), 7.1 – 7.0 (m, 3H), 6.4 (d, *J* = 7.8 Hz, 1H), 5.7 (ddd, *J* = 16.3, 10.8, 4.8 Hz, 1H), 5.3 (dd, *J* = 17.5, 1.6 Hz, 1H), 5.2 – 5.1 (m, 2H), 4.4 (dt, *J* = 15.1, 1.6 Hz, 1H), 4.4 (dt, *J* = 10.8, 3.3 Hz, 1H), 3.0 (dd, *J* = 14.9, 10.6 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** of the major isomer (126 MHz, $CDCl_3$) δ 143.9, 142.6, 139.8, 139.6, 138.7, 135.1, 130.0, 129.8, 129.5, 128.7, 128.6, 128.4, 128.3, 128.0, 127.7, 127.5, 127.3, 127.0, 117.1, 80.3, 80.1, 55.0, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{24}H_{24}NO_3S$ $[M+H]^+$: 406.1477, found 406.1480.

**2-methyl-1-tosyl-3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (187s)**



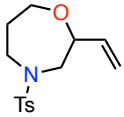

It was isolated as an amorphous white solid in 88% yield (30 mg, 0.088 mmol) of mixture of isomers (dr = 5:1).
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.6 (d, *J* = 8.0 Hz, 2H), 7.5 (d, *J* = 8.0 Hz, 1H), 7.4 – 7.2 (m, 8H), 5.7 (ddd, *J* = 16.9, 10.8, 4.8 Hz, 1H), 5.3 – 5.2 (m, 2H), 4.6 – 4.3 (m, 3H), 4.3 (dd, *J* = 4.9, 2.4 Hz, 1H), 4.1 (d, *J* = 13.4 Hz, 1H), 2.4 (d, *J* = 10.3 Hz, 4H), 1.1 (d, *J* = 6.7 Hz, 1H), 0.8 (d, *J* = 7.0 Hz, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.7, 139.1, 138.4, 136.4, 136.1, 135.9, 130.9, 129.9, 129.4, 129.3, 128.8, 128.3, 128.1, 127.8, 127.2, 118.3, 116.3, 84.7, 73.4, 71.1, 57.2, 21.7, 17.4. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{19}H_{22}NO_3S$ $[M+H]^+$: 344.1320, found 344.1328.

**6,6-dimethyl-4-tosyl-2-vinyl-1,4-oxazepane (187t)**




It was isolated as a colorless oil in 65% yield (20 mg, 0.065 mmol).
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.7 – 7.6 (m, 2H), 7.3 – 7.3 (m, 2H), 5.7 (ddd, *J* = 17.3, 10.7, 5.5 Hz, 1H), 5.3 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.2 (dt, *J* = 10.7, 1.4 Hz, 1H), 4.1 (dddt, *J* = 9.2, 5.2, 3.6, 1.4 Hz, 1H), 3.7 (ddd, *J* = 13.3, 3.7, 1.6 Hz, 1H), 3.6 (d, *J* = 12.4 Hz, 1H), 3.5 – 3.4 (m, 1H), 3.4 (dd, *J* = 13.7, 1.6 Hz, 1H), 2.6 – 2.5 (m, 2H), 2.4 (s, 3H), 1.0 (s, 3H), 1.0 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 143.5, 135.8, 135.6, 129.9, 127.3, 117.1, 82.6, 79.5, 60.4, 57.1, 37.9, 25.5, 23.8, 21.6. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{24}NO_3S$ $[M+H]^+$: 310.1477, found 310.1478.

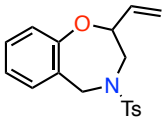
**4-tosyl-2-vinyl-1,4-oxazepane (187u)**



It was isolated as a colorless oil in 72% yield (26 mg, 0.072 mmol).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.7 – 7.6 (m, 2H), 7.3 – 7.3 (m, 2H), 5.8 (ddd, *J* = 17.3, 10.7, 5.4 Hz, 1H), 5.3 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.2 (dt, *J* = 10.7, 1.5 Hz, 1H), 4.2 – 3.9 (m, 2H), 3.8 (ddd, *J* = 13.9, 2.7, 1.4 Hz, 1H), 3.8 – 3.7 (m, 2H), 3.0 (ddd, *J* = 13.8, 8.4, 5.4 Hz, 1H), 2.7 (dd, *J* = 13.9, 9.8 Hz, 1H), 2.4 (s, 3H), 2.1 – 1.9 (m, 2H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 143.5, 136.4, 135.6, 129.9, 127.1, 116.9, 81.7, 68.0, 55.7, 47.2, 30.7, 21.6. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{17}H_{17}N_2O_5S$ $[M+H]^+$: 361.0858, found 361.0857.

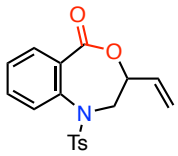
**4-tosyl-2-vinyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (187v)**



It was isolated as a colorless oil in 60% yield (20 mg, 0.06 mmol).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 (d, *J* = 8.0 Hz, 2H), 7.3 – 7.2 (m, 4H), 7.1 (t, *J* = 7.4 Hz, 1H), 7.0 (d, *J* = 7.9 Hz, 1H), 5.9 (dddd, *J* = 17.0, 10.7, 5.2, 0.8 Hz, 1H), 5.4 (dq, *J* = 17.2, 1.3 Hz, 1H), 5.4 – 5.2 (m, 1H), 4.7 (dd, *J* = 14.8, 1.6 Hz, 1H), 4.2 (dd, *J* = 14.8, 8.5 Hz, 2H), 3.9 (dt, *J* = 14.0, 2.0 Hz, 1H), 3.1 (dd, *J* = 14.0, 9.7 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 158.3, 143.6, 136.3, 134.8, 130.7, 129.8, 129.8, 129.5, 127.3, 124.3, 121.7, 117.6, 81.4, 55.5, 51.4, 21.6. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{20}N_2O_3S$ $[M+H]^+$: 330.1164, found 330.1160.

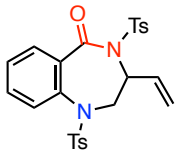
**1-tosyl-3-vinyl-2,3-dihydrobenzo[*e*][1,4]oxazepin-5(1*H*)-one (187w)**



It was isolated as a white-off solid in 75% yield (26 mg, 0.075 mmol).

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.6 (dd, *J* = 15.8, 5.9 Hz, 3H), 7.4 (d, *J* = 8.0 Hz, 3H), 7.2 (d, *J* = 8.0 Hz, 2H), 5.8 (ddd, *J* = 16.9, 10.6, 5.9 Hz, 1H), 5.4 – 5.3 (m, 2H), 4.5 (t, *J* = 8.7 Hz, 1H), 4.3 (dd, *J* = 13.5, 11.9 Hz, 1H), 3.7 (dd, *J* = 13.5, 3.2 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.2, 144.5, 135.1, 134.7, 133.8, 132.2, 131.4, 130.9, 130.5, 130.0, 129.4, 127.4, 119.9, 76.7, 54.7, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{18}NO_4S$ $[M+H]^+$: 344.0957, found 344.0954.

**1,4-ditosyl-3-vinyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (187x)**



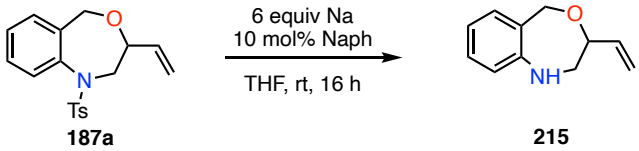
It was isolated as an amorphous yellow solid in 55% yield (27 mg, 0.055 mmol).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.9 – 7.9 (m, 2H), 7.4 – 7.4 (m, 4H), 7.3 – 7.2 (m, 3H), 7.1 (d, *J* = 8.2 Hz, 2H), 5.4 (s, 1H), 5.2 – 5.1 (m, 1H), 4.8 – 4.6 (m, 3H), 4.0 – 3.9 (m, 1H), 2.4 (s, 3H), 2.3 (s, 3H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 166.9, 145.2, 144.3, 136.0, 135.8, 135.6, 133.3, 131.1, 130.4, 130.0, 129.5, 129.3, 128.9, 127.6, 117.5, 55.7, 55.1, 21.8, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{25}H_{25}N_2O_5S_2$ $[M+H]^+$: 497.1205, found 497.1208.

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## 4.3. Derivatization of 1,4-Benzoxazepine 187a

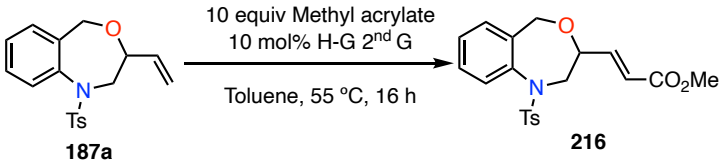
### 4.3.1. 3-vinyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepane (215)




**187a** **215**

To a solution of naphthalene (7.8 mg, 0.061 mmol, 0.2 equiv) in anhydrous THF (4 mL) in an oven-dried Schlenk flask under a stream of argon, hexane-rinsed sheets of sodium metal were added (44 mg, 1.885 mmol, 6 equiv). The mixture was then sonicated at rt until green color persisted when a solution of **187a** (100 mg, 0.304 mmol, 1 equiv) in THF (4 mL) was then added, resulting in a rapid loss of the green color. The turbid yellow reaction mixture was removed from sonicator and stirred at rt for 15 h. Afterwards, the reaction was cooled to 0 °C and 10 mL of MeOH was slowly added to quench the Na followed by addition of a saturated solution of $NaHCO_3$ (only after consumption). The reaction was diluted with $Et_2O$ and washed with $NaHCO_3$ and $H_2O$. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography with hexanes/EtOAc (8:2) as the eluent to give the desired product **215** as a colorless oil 70% yield (37 mg, 0.213 mmol). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.2 (dd, $J$ = 9.8, 7.4 Hz, 2H), 6.9 – 6.7 (m, 2H), 5.9 (ddd, $J$ = 16.9, 10.7, 5.5 Hz, 1H), 5.4 (dt, $J$ = 17.3, 1.6 Hz, 1H), 5.3 – 5.1 (m, 1H), 4.8 (d, $J$ = 13.5 Hz, 1H), 4.6 (d, $J$ = 13.4 Hz, 1H), 4.3 – 4.0 (m, 1H), 3.3 (dd, $J$ = 13.4, 2.0 Hz, 1H), 2.9 (dd, $J$ = 13.3, 9.3 Hz, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 149.6, 136.7, 130.3, 129.6, 128.7, 120.9, 118.6, 116.5, 82.7, 73.1, 54.2. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{11}H_{14}NO$ $[M+H]^+$: 176.1075, found 176.1082.

### 4.3.2. Methyl (*E*)-3-(1-tosyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepin-3-yl)acrylate (216)

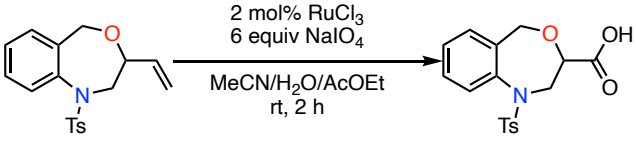



**187a** **216**

A flame-dried Schlenk charged with the 2$^{nd}$ generation Hoveyda-Grubbs catalyst (6.3 mg, 0.01 mmol, 0.1 equiv) was put under vacuum and backfilled with argon for three times. Afterwards, a solution of **187a** (33 mg, 0.1 mmol, 1 equiv) and methyl acrylate (90 ml, 1 mmol, 10 equiv) in 1mL of dry toluene was added the reaction was heated for 16 h. The solvent was removed under vacuum and the resulting residue was purified by silica gel column chromatography with a mixture of Hexanes/AcOEt (7:3) as eluent, to give the desired product **216** as a colorless oil in 90% yield (35 mg, 0.09 mmol). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H), 7.3 – 7.1 (m, 6H), 6.7 (dd, $J$ = 15.8, 4.2 Hz, 1H), 6.0 (dd, $J$ = 15.8, 1.8 Hz, 1H), 4.5 (d, $J$ = 13.4 Hz, 1H), 4.4 – 4.3 (m, 2H), 4.2 (d, $J$ = 13.4 Hz, 1H), 3.7 (s, 3H),

2.9 (dd, $J$ = 15.2, 10.3 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 166.6, 144.1, 143.7, 139.7, 138.4, 138.1, 130.0, 129.8, 129.2, 128.9, 128.3, 127.3, 122.3, 79.3, 72.5, 55.0, 51.9, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{20}H_{22}NO_5S$ [M +H]$^+$: 388.1219, found 388.1215.

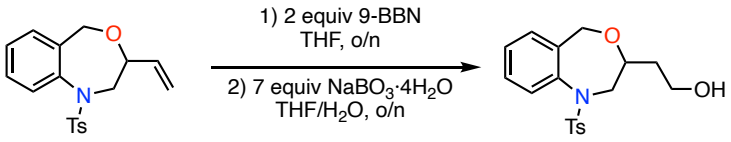
### 4.3.3. 1-tosyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine-3-carboxylic acid (217)




**187a** **217**

To a solution of **187a** (33mg, 0.1 mmol, 1 equiv) in MeCN (0.7 mL), $H_2O$ (0.35 mL) and AcOEt (0.7 mL) was added $NaIO_4$ (130 mg, 0.6 mmol, 6 equiv) and $RuCl_3$(0.5 mg, 0.002 mmol, 0.02 equiv). The reaction was stirred for 2 h. Then, the reaction was washed with brine and extracted with EtOAc. The combination of organic phases was dried over $Na_2SO_4$ and the solvent was removed in vacuo. The residue was then filtrated through a plug of celite®, Fluorisil and $SiO_2$ to give the desired product **217** as an amorphous white-off solid in 87% yield (30 mg, 0.087 mmol). (NOTE: The product was isolated with a small amount of AcOEt, which was not able to be eliminated. The product yield has been recalculated). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.7 (d, $J$ = 8.2 Hz, 2H), 7.4 – 7.2 (m, 6H), 6.3 (s, 1H), 4.7 (dd, $J$ = 15.2, 2.1 Hz, 1H), 4.7 (d, $J$ = 13.5 Hz, 1H), 4.4 (dd, $J$ = 10.3, 2.1 Hz, 1H), 4.3 (d, $J$ = 13.4 Hz, 1H), 3.2 (dd, $J$ = 15.2, 10.3 Hz, 1H), 2.4 (s, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 171.1, 144.3, 139.7, 138.1, 137.1, 130.2, 130.0, 129.6, 129.0, 128.4, 127.3, 78.7, 72.6, 52.9, 21.7. **HRMS** (MM: ESI-APCI-) m/z calc'd for $C_{17}H_{16}NO_5S$ [M -H]: 346.0755, found 346.0746.

### 4.3.4. 2-(1-tosyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepin-3-yl)ethan-1-ol (218)

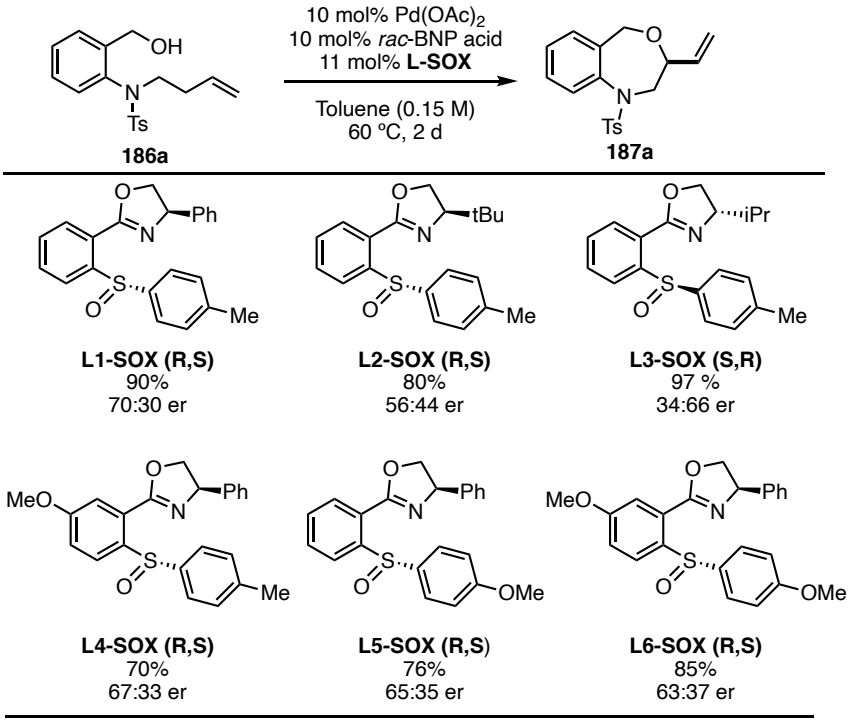



**187a** **218**

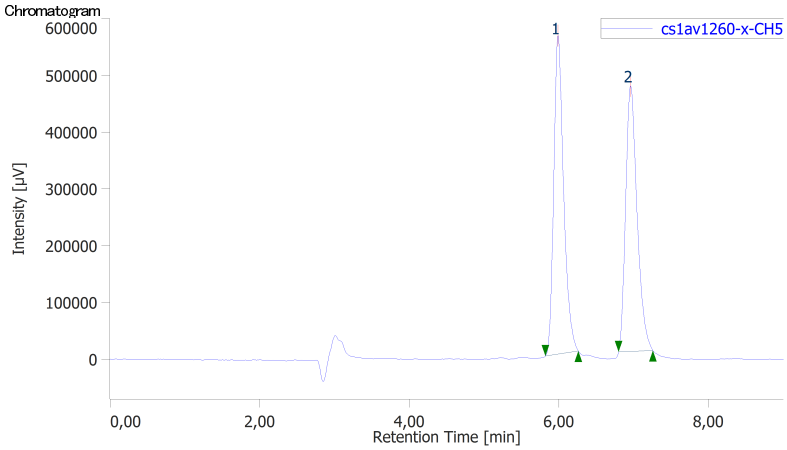
To a stirred solution of **187a** (33 mg, 0.1 mmol, 1 equiv) in 0.1 mL of THF was added 9-BBN (0.4 mL (0.5 M in THF), 0.2 mmol, 2 equiv) and the resulting mixture was stirred overnight at 60 °C. The solution was diluted with THF (0.2 mL) and cooled to 0 °C. Then 0.1 mL of water was added dropwise followed by $NaBO_3{\cdot}4H_2O$ (108 mg, 0.7 mmol, 7 equiv) and the reaction was warmed to rt and stirred overnight. Then the reaction was extracted with AcOEt, washed with brine, and dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting product was purified by silica gel column chromatography with Hexanes/EtOAC (1:1) as eluent to give the desired product **218** as a colorless oil in 72% yield (24 mg, 0.072 mmol). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.6 (d, $J$ = 7.9 Hz, 2H), 7.4 – 7.1 (m, 6H), 4.5 (d, $J$ = 13.4 Hz, 1H), 4.3 (d, $J$ = 15.0 Hz, 1H), 4.2 – 4.1 (m, 1H), 4.0 – 3.6 (m, 3H), 3.0 (dd, $J$ = 15.1, 10.2 Hz, 1H), 2.4 (s, 3H), 2.2 (s, 1H). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 143.9, 140.0,

138.6, 138.2, 129.9, 129.7, 129.1, 128.9, 128.1, 127.3, 80.4, 72.6, 60.6, 55.9, 35.5, 21.7. **HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{22}NO_4S$ $[M\text{-}OH_2]^+$: 330.1164, found 330.1161.

## 4.4. Pd-Catalyzed Asymmetric Allylic C-H Functionalization




**L1$_{rac}$-SOX** sample: SFC conditions: 30% MeOH, Phenomenex Amylose 1 at 40 °C , (CO2/MeOH = 70:30 1mL/min, l= 210 nm, $t_R$ (min): 5.98, 6.93.



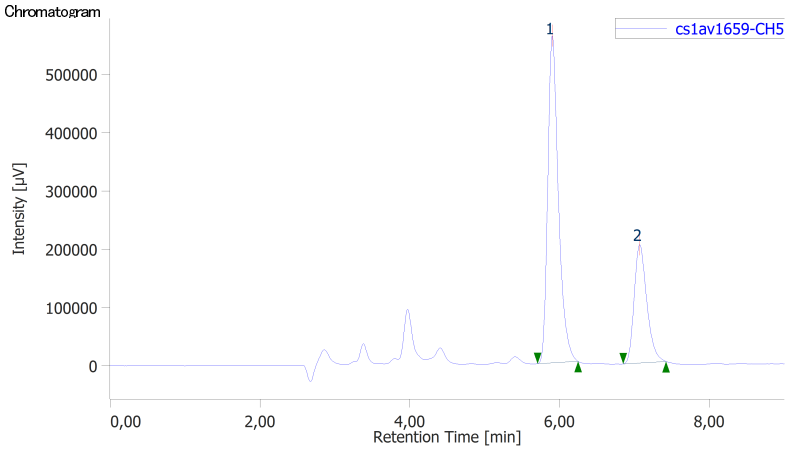

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV*sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 5,983 | 5130100 | 560793 | 50,857 | 54,539 | N/A | 10570 | 3,834 | 1,340 | |
| 2 | Unknown | 5 | 6,953 | 4957209 | 467447 | 49,143 | 45,461 | N/A | 10262 | N/A | 1,341 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

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**L1-SOX** (R,S) sample: SFC conditions:30% MeOH, Phenomenex Amylose 1 at 40ºC, (CO2/MeOH = 70:30 1mL/min, l= 210 nm, $t_R$ (min): major = 5.90, minor = 7.06.

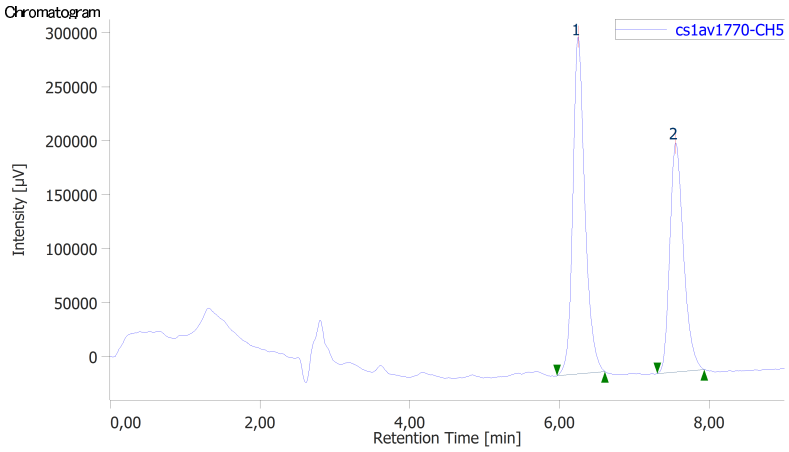



**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 5,900 | 5550281 | 561170 | 70,034 | 73,436 | N/A | 8944 | 4,243 | 1,378 | |
| 2 | Unknown | 5 | 7,067 | 2374814 | 202992 | 29,966 | 26,564 | N/A | 8766 | N/A | 1,292 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

**L2-SOX** (R,S) sample :SFC conditions: 30% MeOH, Phenomenex Amylose 1 at 40ºC, (CO2/MeOH = 70:30 1mL/min, l= 210 nm, $t_R$ (min): major = 6.27, minor = 7.54.



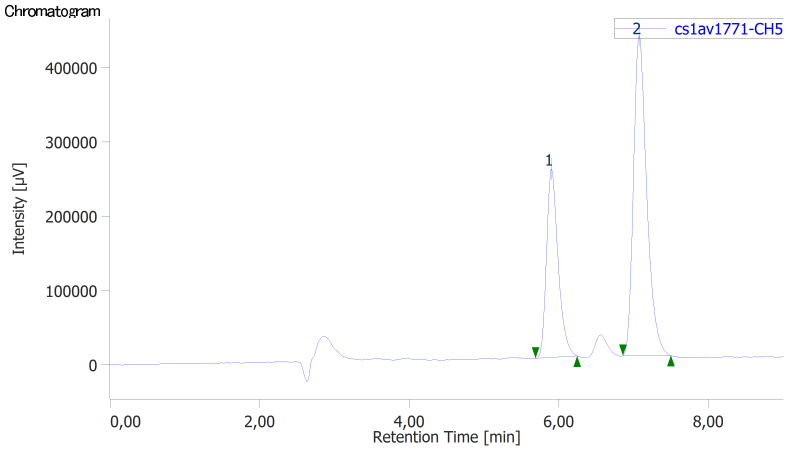

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 6,247 | 3498137 | 312209 | 56,383 | 59,533 | N/A | 8020 | 4,290 | 1,222 | |
| 2 | Unknown | 5 | 7,547 | 2706096 | 212224 | 43,617 | 40,467 | N/A | 8439 | N/A | 1,314 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

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**L3-SOX** (S,R) sample: SFC conditions: 30% MeOH, Phenomenex Amylose 1 at 40°C , (CO2/MeOH = 70:30 1mL/min, l= 210 nm, tR (min): minor = 5.89, minor = 7.07.

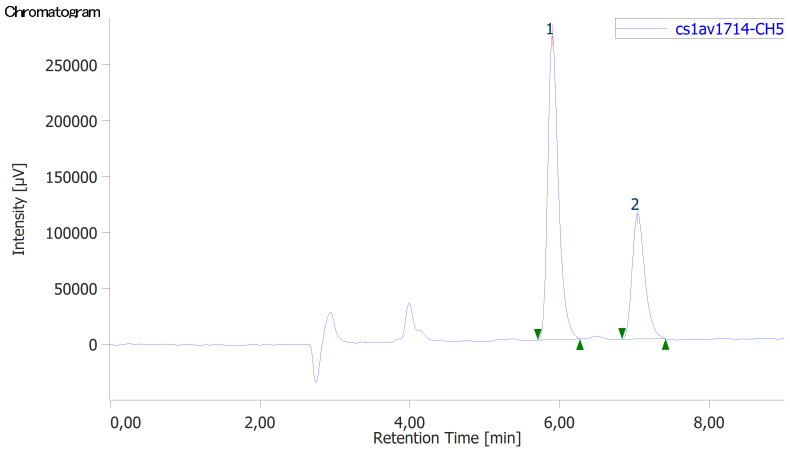



**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 5,897 | 2721710 | 253185 | 33,918 | 37,047 | N/A | 7382 | 3,990 | 1,364 | |
| 2 | Unknown | 5 | 7,070 | 5302598 | 430237 | 66,082 | 62,953 | N/A | 8051 | N/A | 1,344 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

**L4-SOX** (R,S) sample: SFC conditions: 30% MeOH, Phenomenex Amylose 1 at 40°C , (CO2/MeOH = 70:30 1mL/min, l= 210 nm, tR (min): minor = 5.9, minor = 7.03.



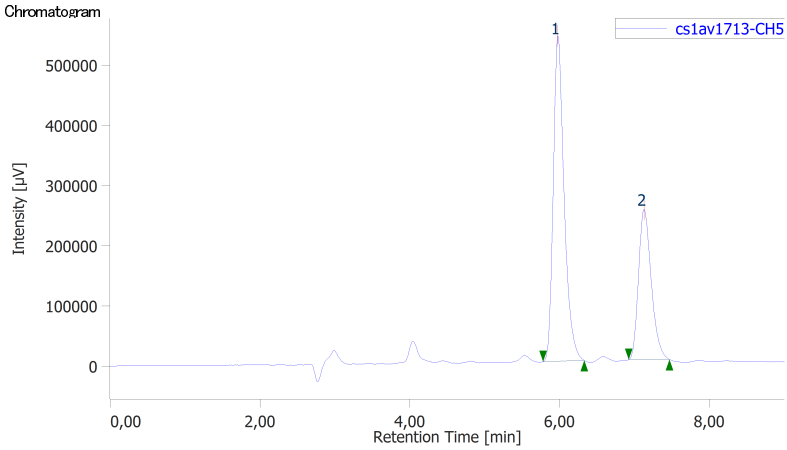

**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 5,900 | 2714051 | 271946 | 67,234 | 70,752 | N/A | 8747 | 4,108 | 1,375 | |
| 2 | Unknown | 5 | 7,037 | 1322690 | 112421 | 32,766 | 29,248 | N/A | 8657 | N/A | 1,335 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

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**L5-SOX** (R,S) sample: SFC conditions: 30% MeOH, Phenomenex Amylose 1 at 40°C , ($CO_2$/MeOH = 70:30 1mL/min, l= 210 nm, tR (min): minor = 5.97, minor = 7.12.

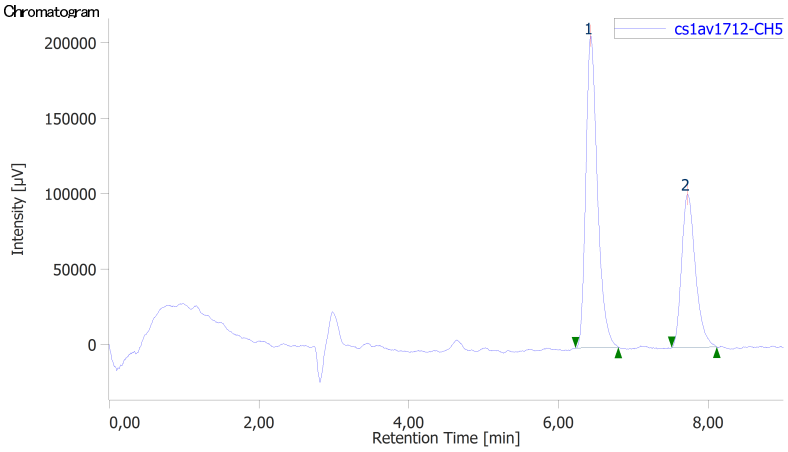



**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 5,973 | 5438317 | 540315 | 64,921 | 68,426 | N/A | 8814 | 4,110 | 1,367 | |
| 2 | Unknown | 5 | 7,123 | 2938532 | 249323 | 35,079 | 31,574 | N/A | 8640 | N/A | 1,302 | |

Signals in the range around 2-4 min are due to the front arriving to the detector.

**L6-SOX** (R,S) sample: SFC conditions: 30% MeOH, Phenomenex Amylose 1 at 40°C , ($CO_2$/MeOH = 70:30 1mL/min, l= 210 nm, tR (min): minor = 6.42, minor = 7.72.




**Peak Information**

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 5 | 6,427 | 2223064 | 206640 | 63,136 | 67,084 | N/A | 8785 | 4,299 | 1,354 | |
| 2 | Unknown | 5 | 7,720 | 1298002 | 101392 | 36,864 | 32,916 | N/A | 8805 | N/A | 1,321 | |

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## 4.5. X-Ray Crystallographic Data

### 4.5.1. X-Ray Crystallographic Data for Compound 187l

Single crystals of compound **187l** (CCDC 2108910) suitable for X-Ray diffraction analysis were grown from solution in DCM in a Hexanes atmosphere (vapor diffusion technique).

**Figure 20**. ORTEP drawing of **187l** showing ellipsoids at the 30% contour probability level

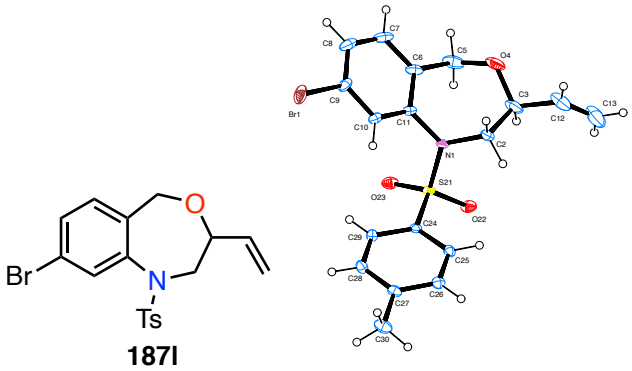



**Table 16.** Sample and crystal data for 187l (CCDC 2108910)

| | | |
|---|---|---|
| CCDC code | CCDC 2108910 | |
| Chemical formula | $C_{18}H_{18}BrNO_3S$ | |
| Formula weight | 408.30 g/mol | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal size | 0.081 x 0.125 x 0.256 mm | |
| Crystal habit | clear colourless block | |
| Crystal system | monoclinic | |
| Space group | P 1 21/n 1 | |
| Unit cell dimensions | a = 11.3536(8) Å | α = 90° |
| | b = 9.6592(7) Å | β = 107.174(3)° |
| | c = 16.8001(12) Å | γ = 90° |
| Volume | 1760.3(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.541 $g/cm^3$ | |
| Absorption coefficient | 2.469 $mm^{-1}$ | |
| F(000) | 832 | |

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### 4.5.2. X-Ray Crystallographic Data for Compound 187p

Single crystals of compound **187p** (CCDC 2108911) suitable for X-Ray diffraction analysis were grown from solution in DCM in a Hexanes atmosphere (vapor diffusion technique).

**Figure 21**. ORTEP drawing of **187p** showing ellipsoids at the 30% contour probability level

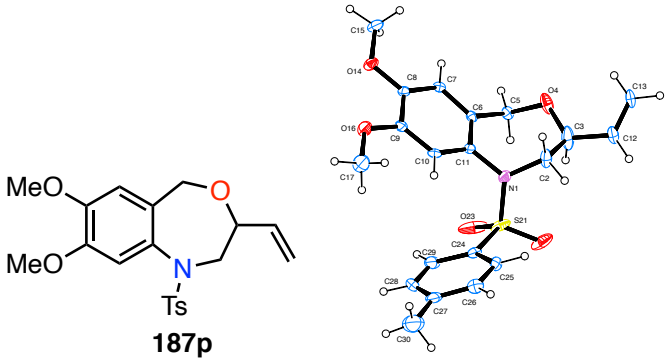



**Table 17.** Sample and crystal data for 187p (CCDC 2108911)

| | | |
|---|---|---|
| CCDC code | CCDC 2108911 | |
| Chemical formula | $C_{20}H_{23}NO_5S$ | |
| Formula weight | 389.45 g/mol | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal size | 0.066 x 0.070 x 0.318 mm | |
| Crystal habit | clear colourless prism | |
| Crystal system | monoclinic | |
| Space group | P 1 21/c 1 | |
| Unit cell dimensions | a = 9.3804(8) Å | α = 90° |
| | b = 23.7391(19) Å | β = 114.324(3)° |
| | c = 9.4372(7) Å | γ = 90° |
| Volume | 1914.9(3) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.351 $g/cm^3$ | |
| Absorption coefficient | 0.200 $mm^{-1}$ | |
| F(000) | 824 | |

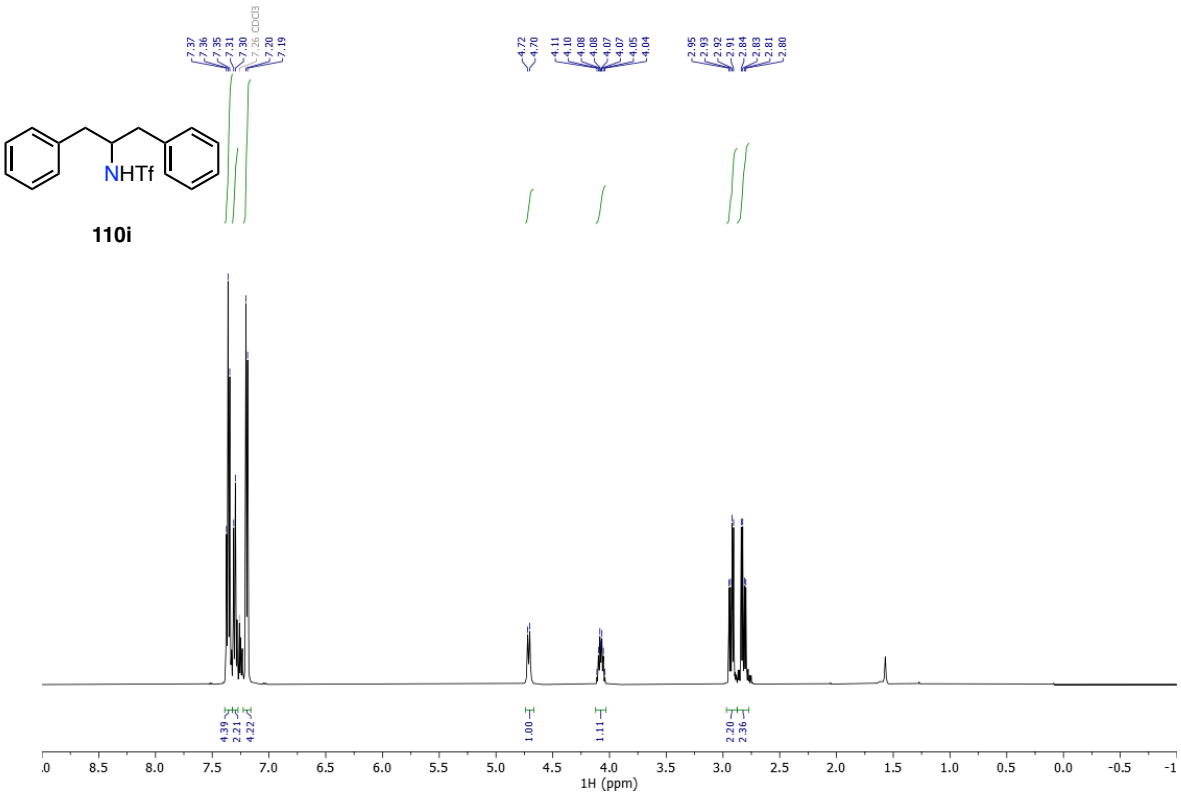
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# NMR SPECTRA

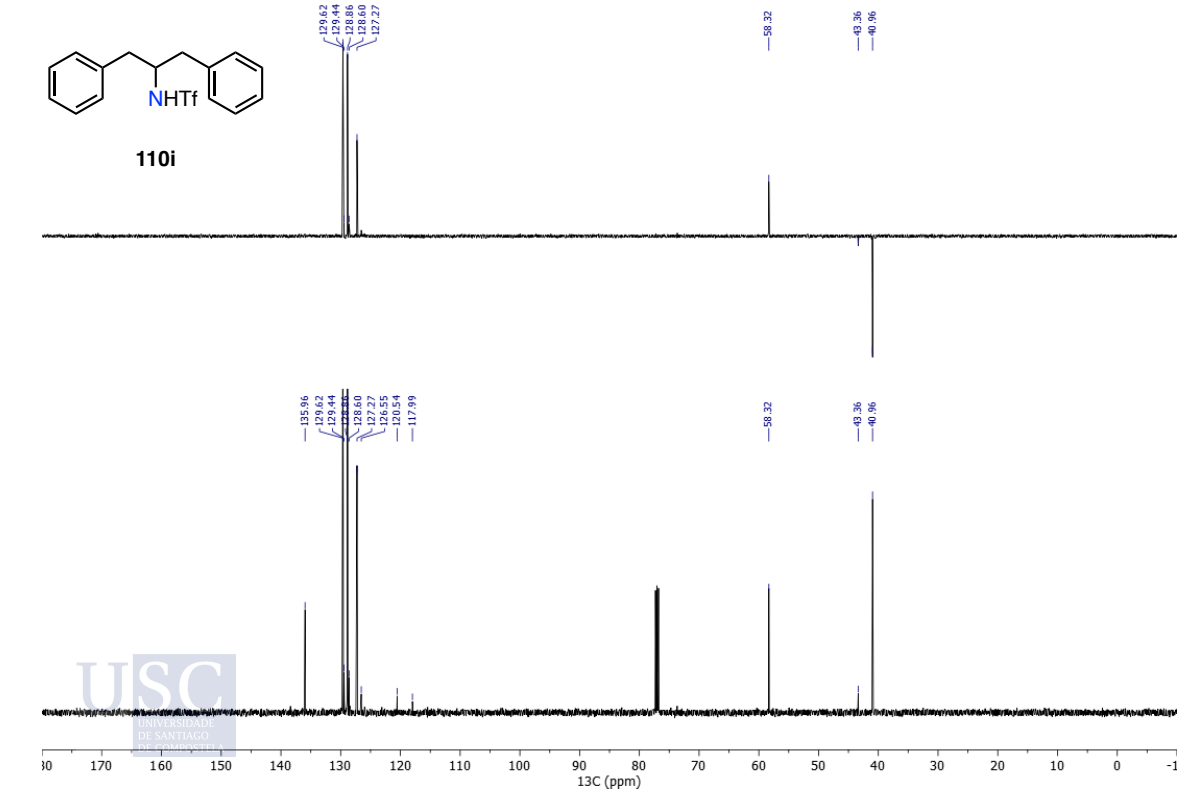
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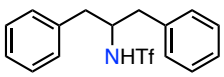
$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)



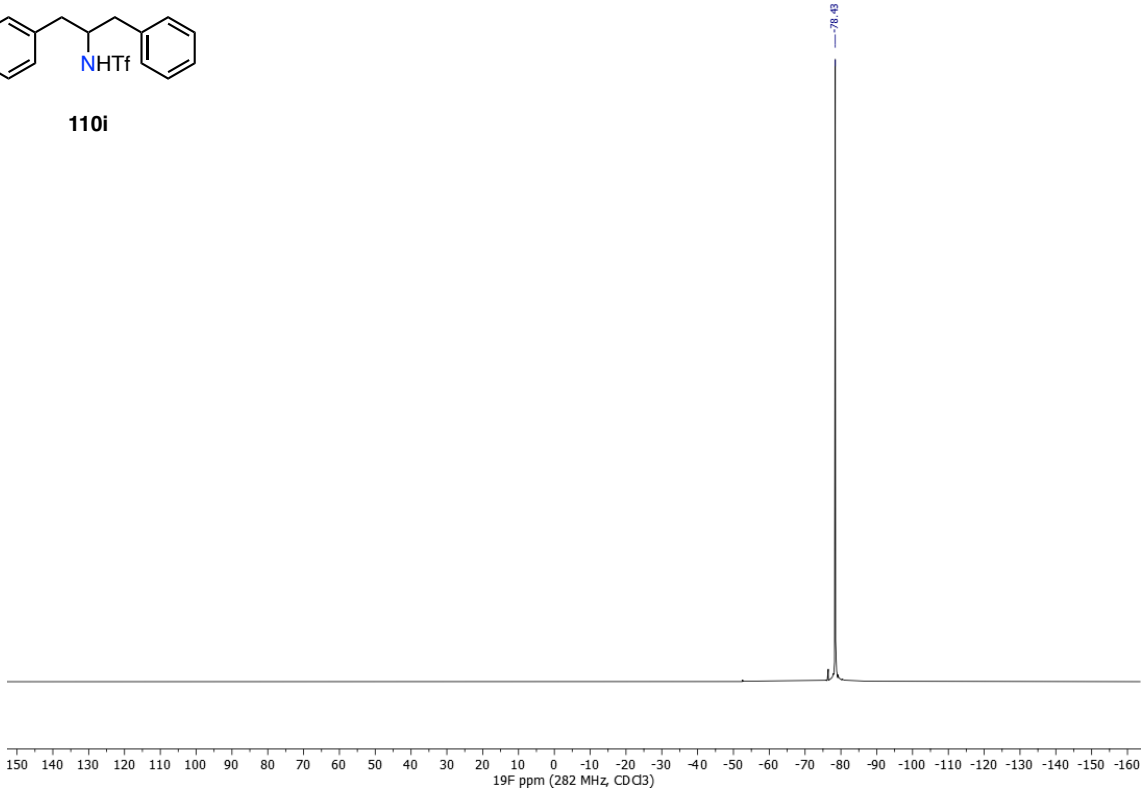

$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)



$^{19}$F-NMR (471 MHz). Solvent ($CDCl_3$)

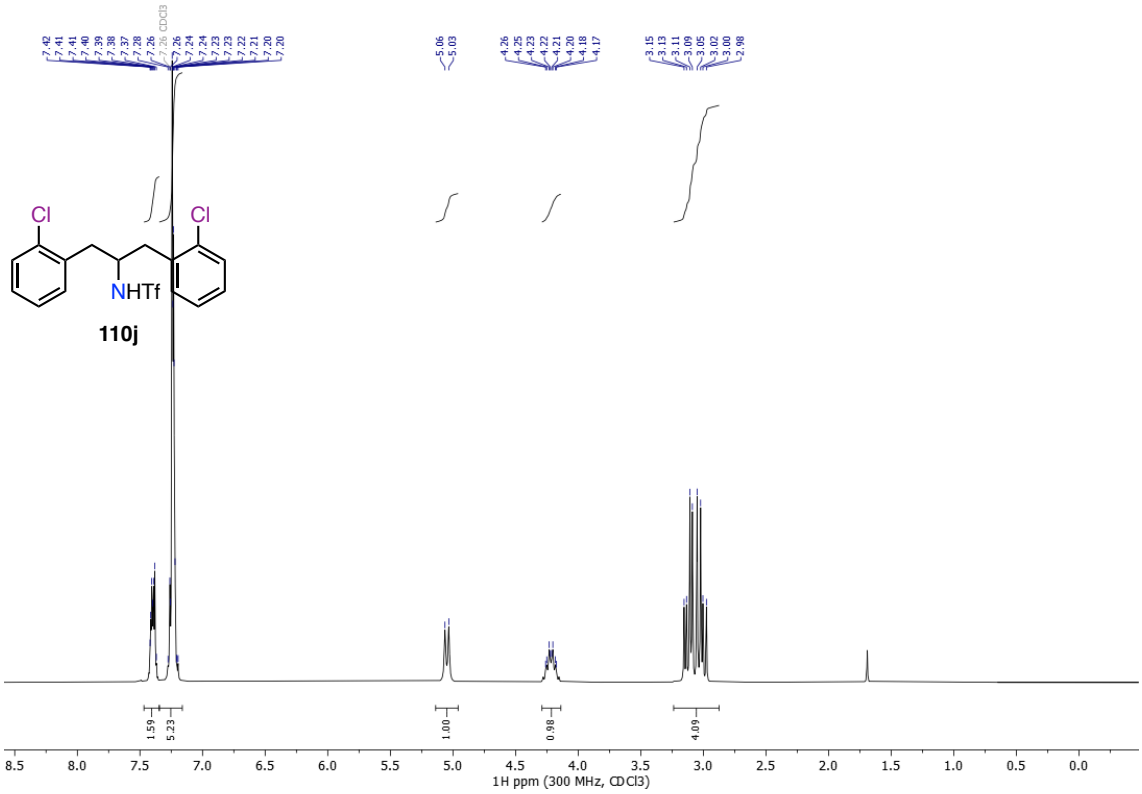



**110i**

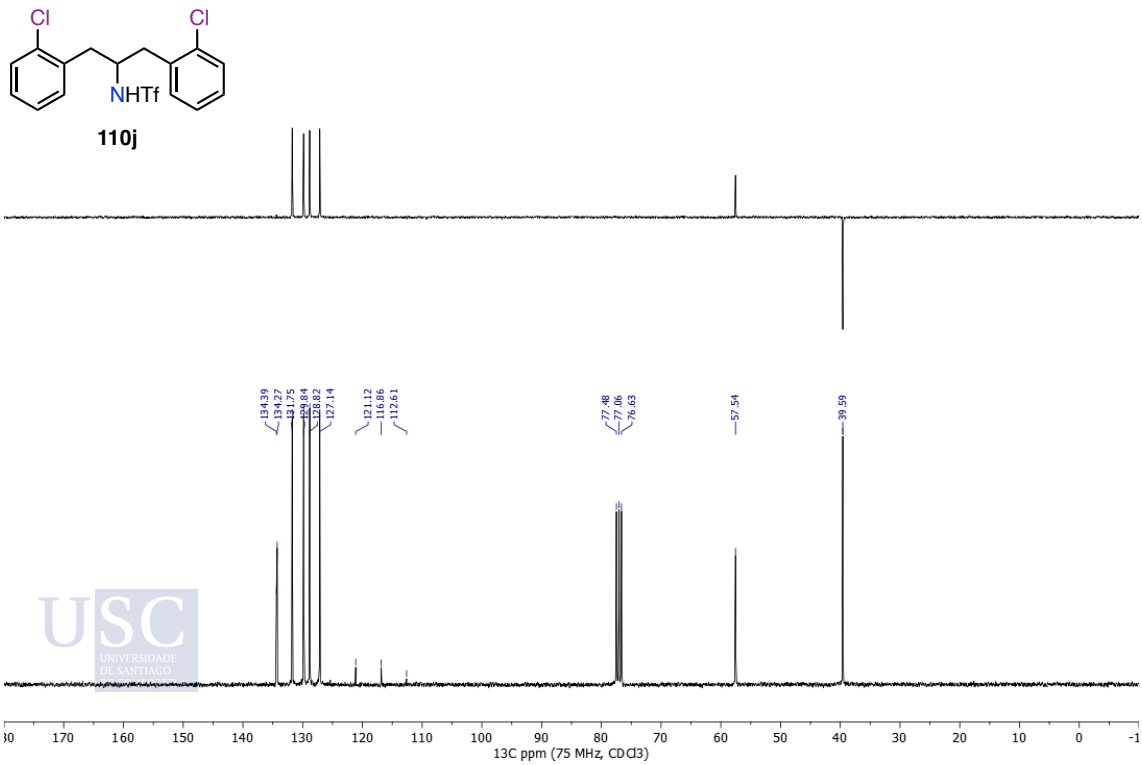



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$^{1}$H-NMR (300 MHz). Solvent ($CDCl_3$)



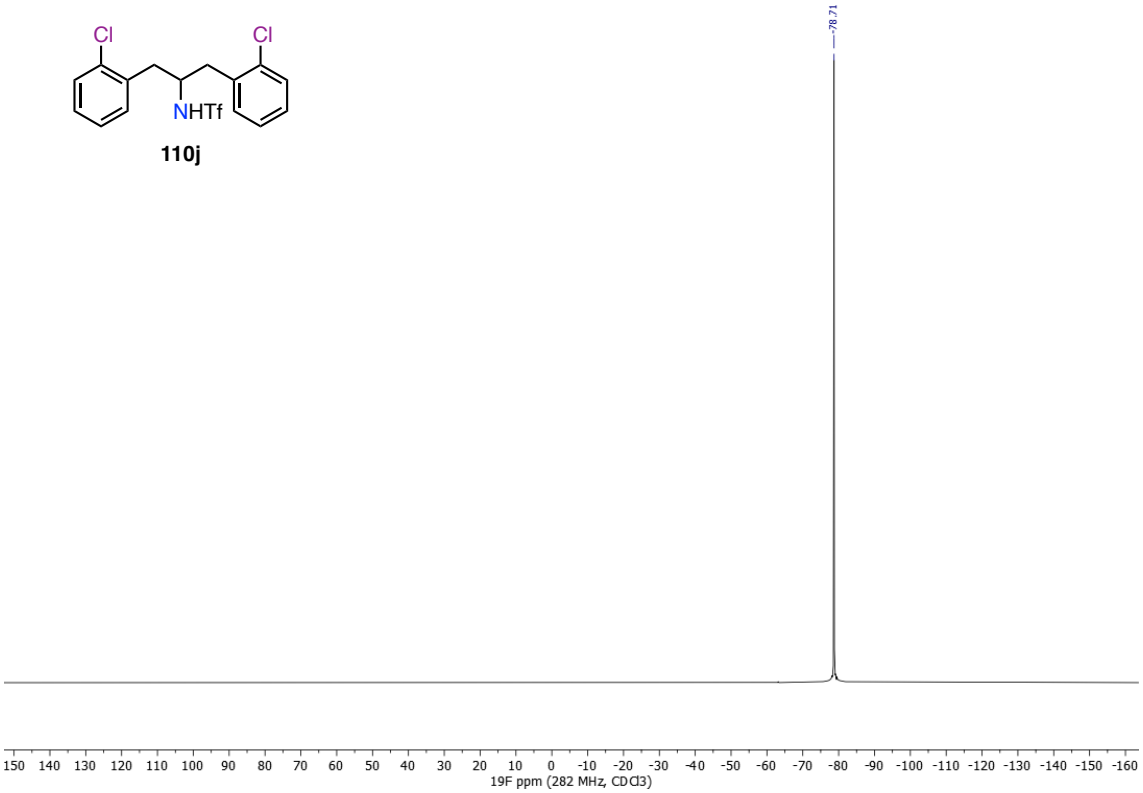

$^{13}$C-NMR(75 MHz). Solvent ($CDCl_3$)



$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

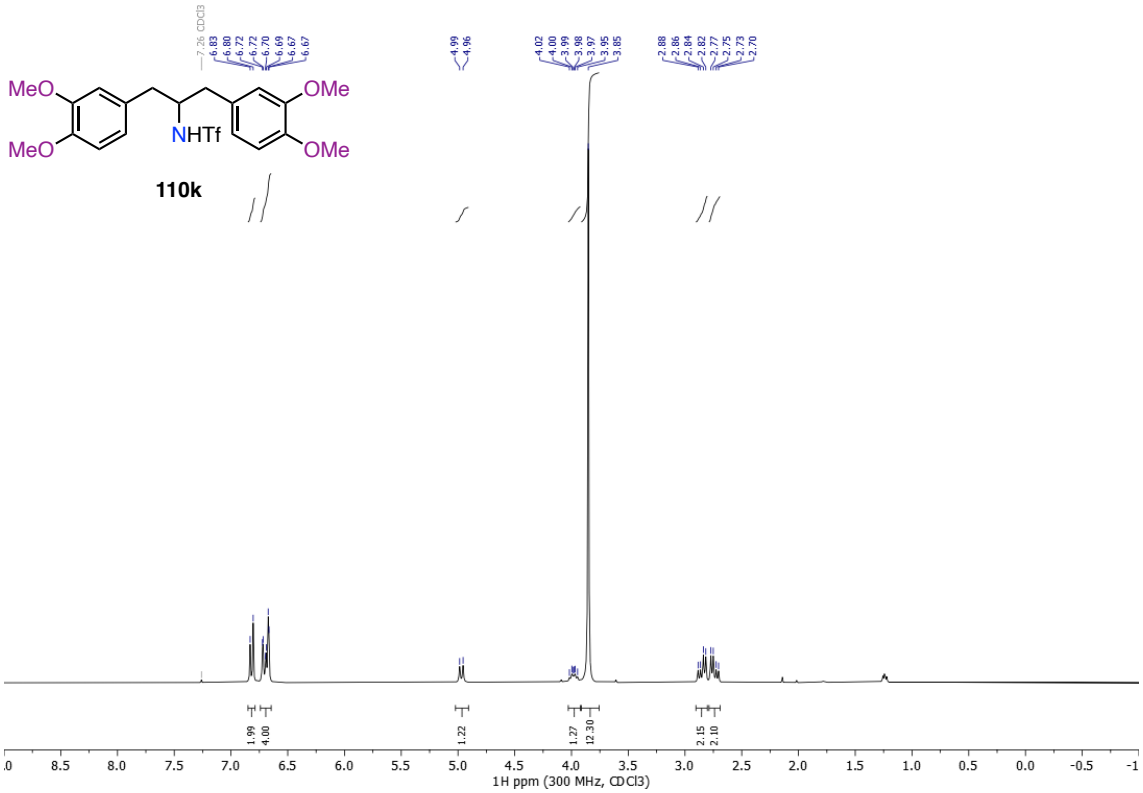



**110j**

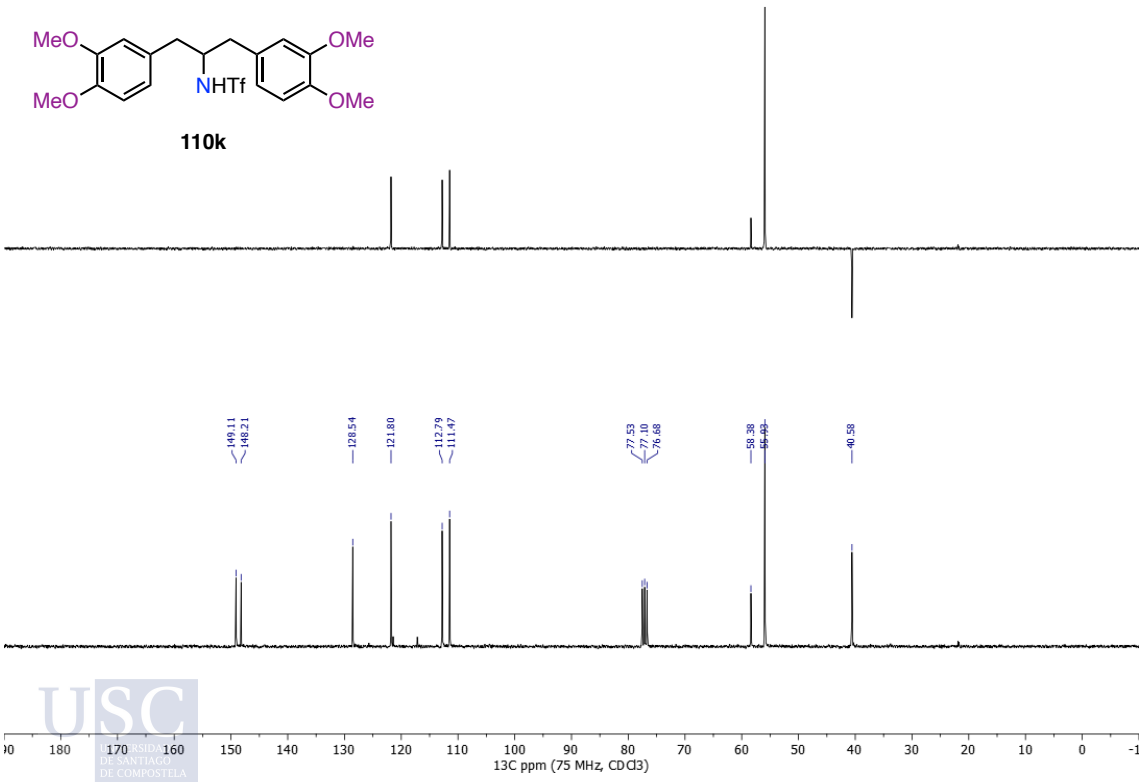



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$^{1}$H-NMR (300 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (75 MHz). Solvent ($CDCl_3$)

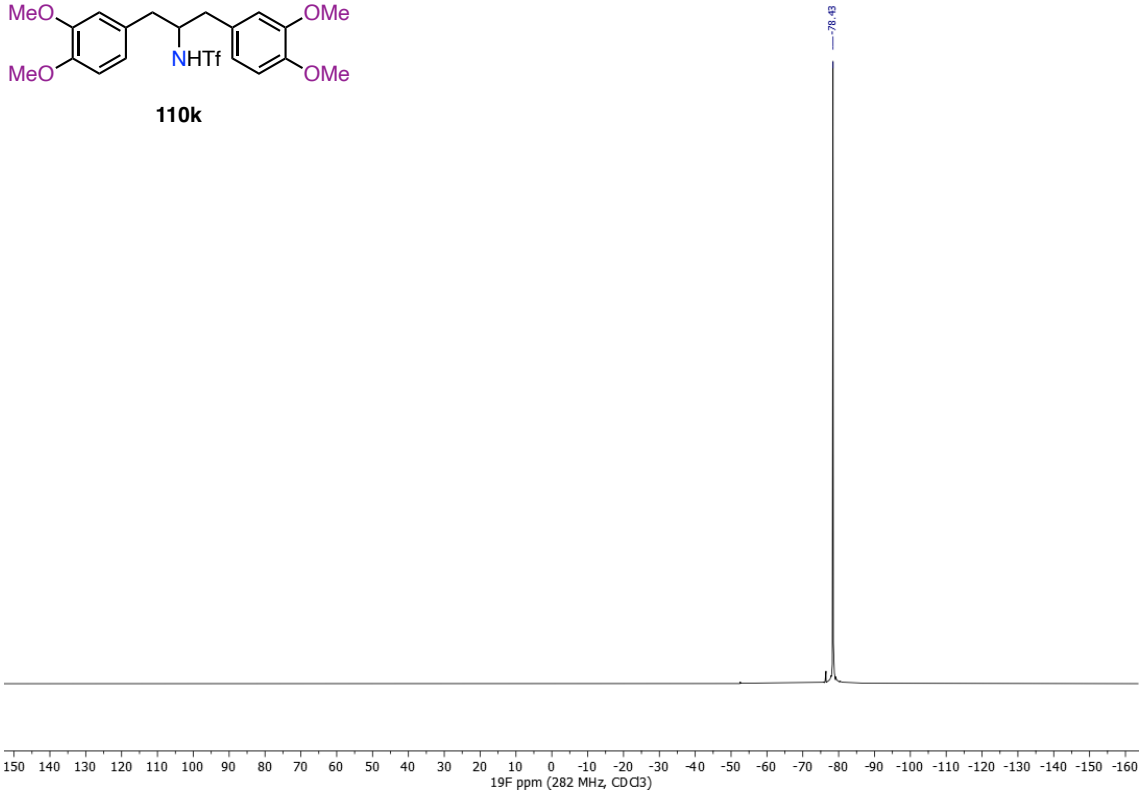



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$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

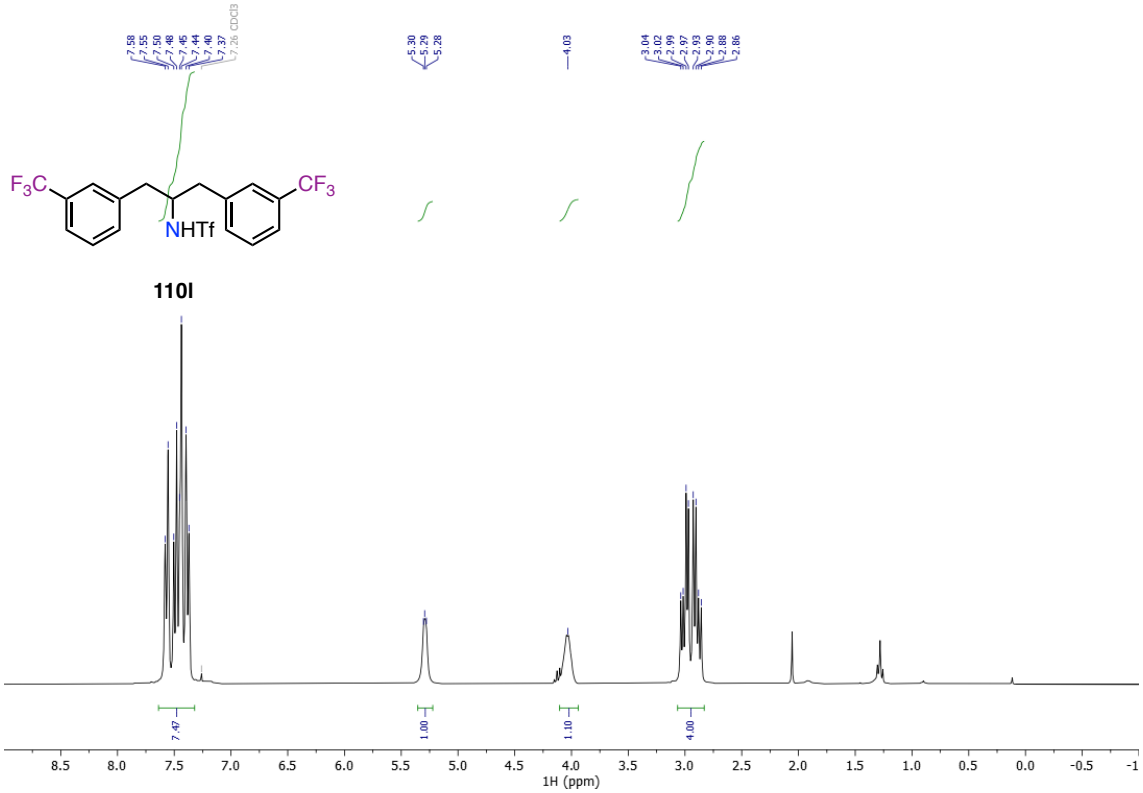



**110k**

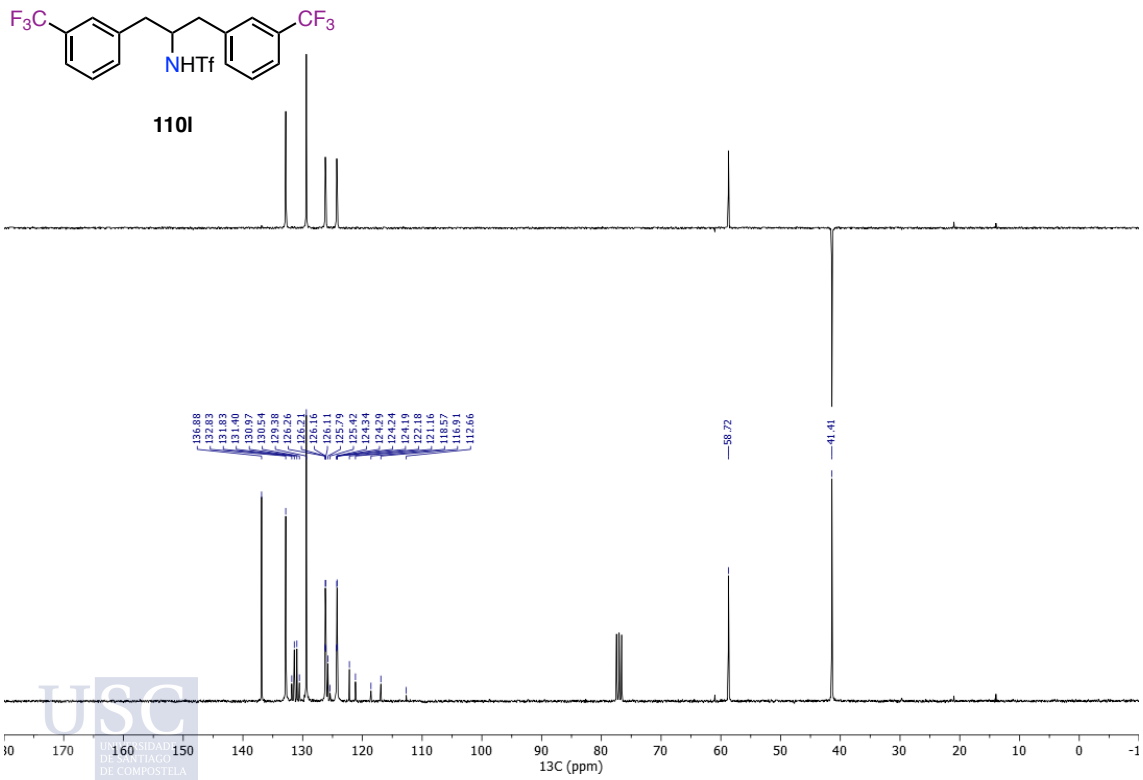



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$^{1}$H-NMR (300 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (75 MHz). Solvent ($CDCl_3$)

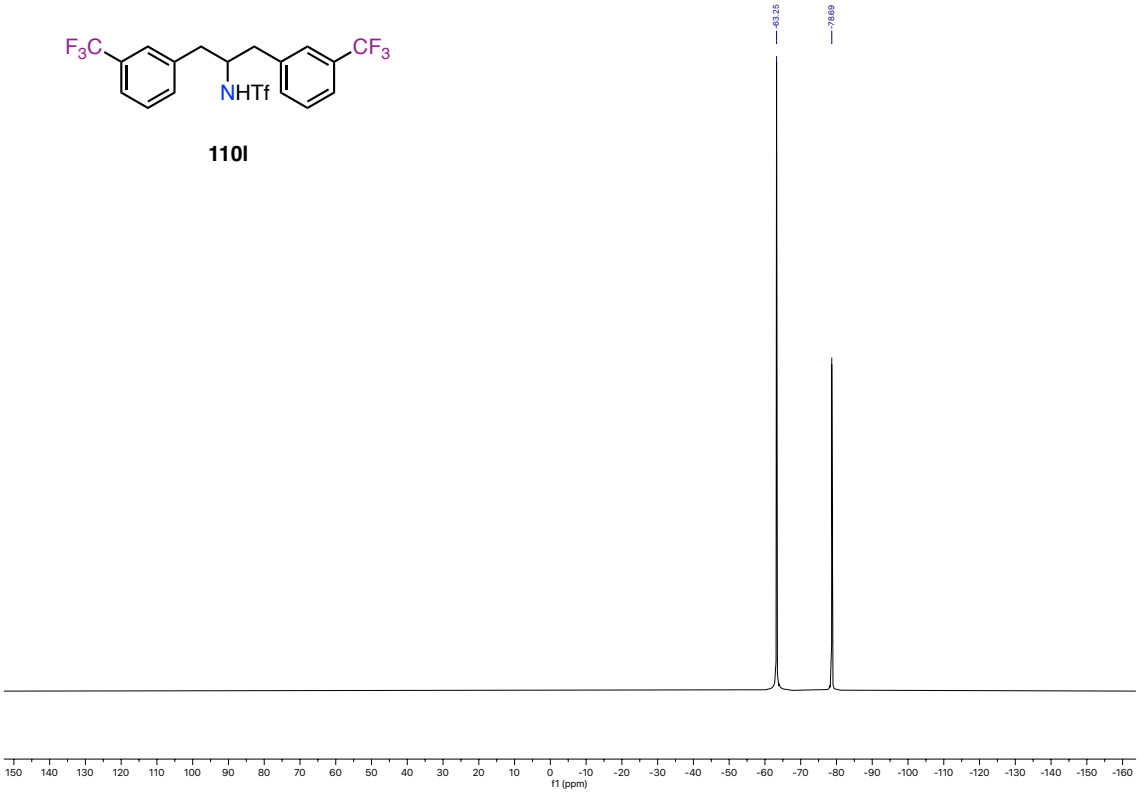



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$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

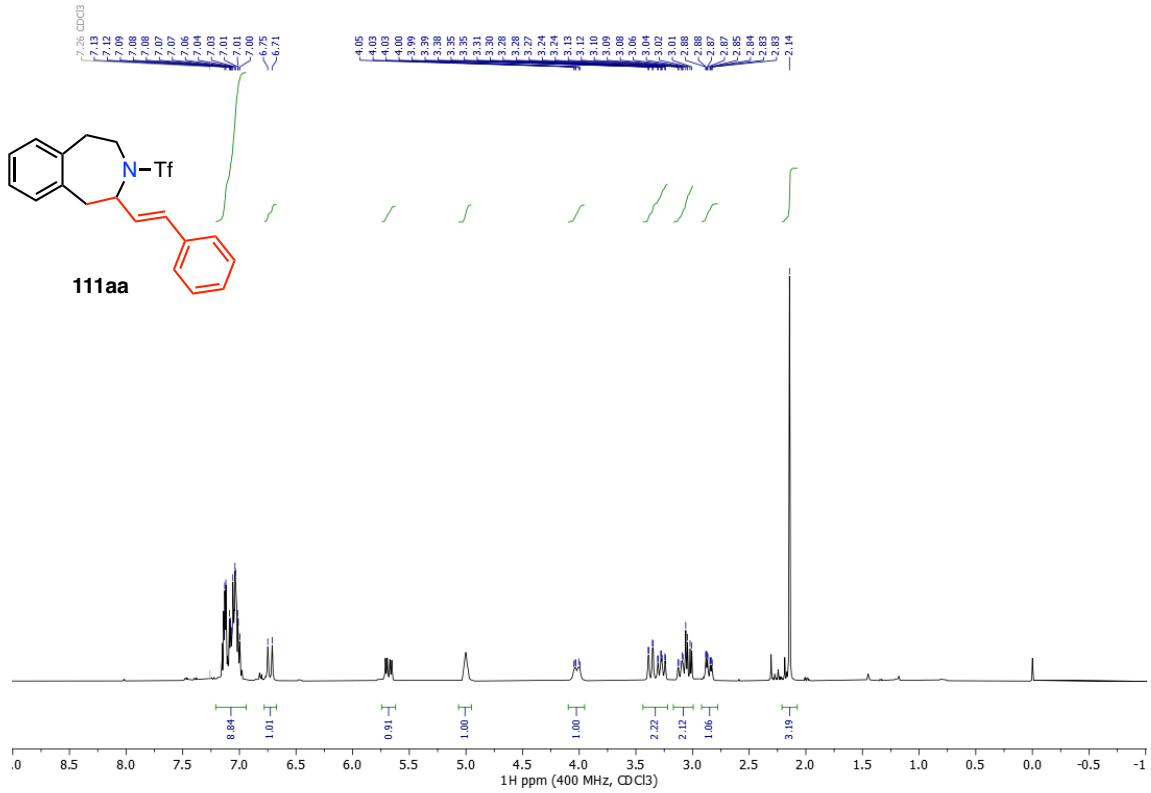



**110l**

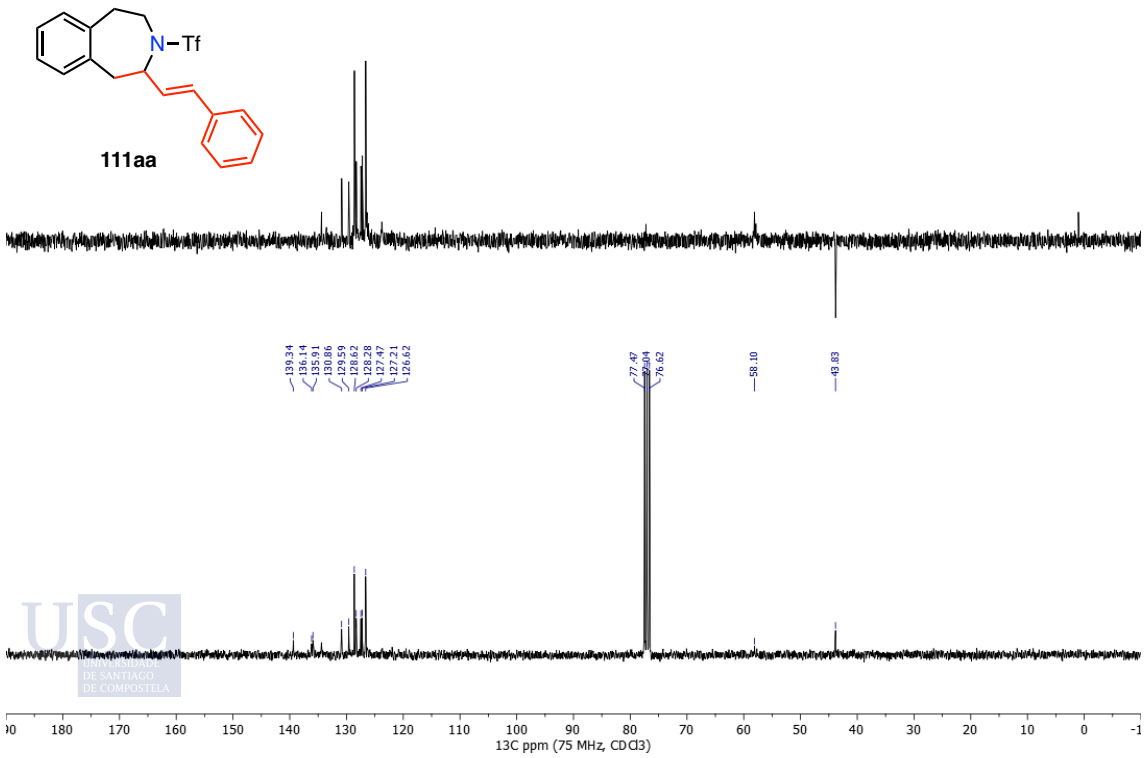



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$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)



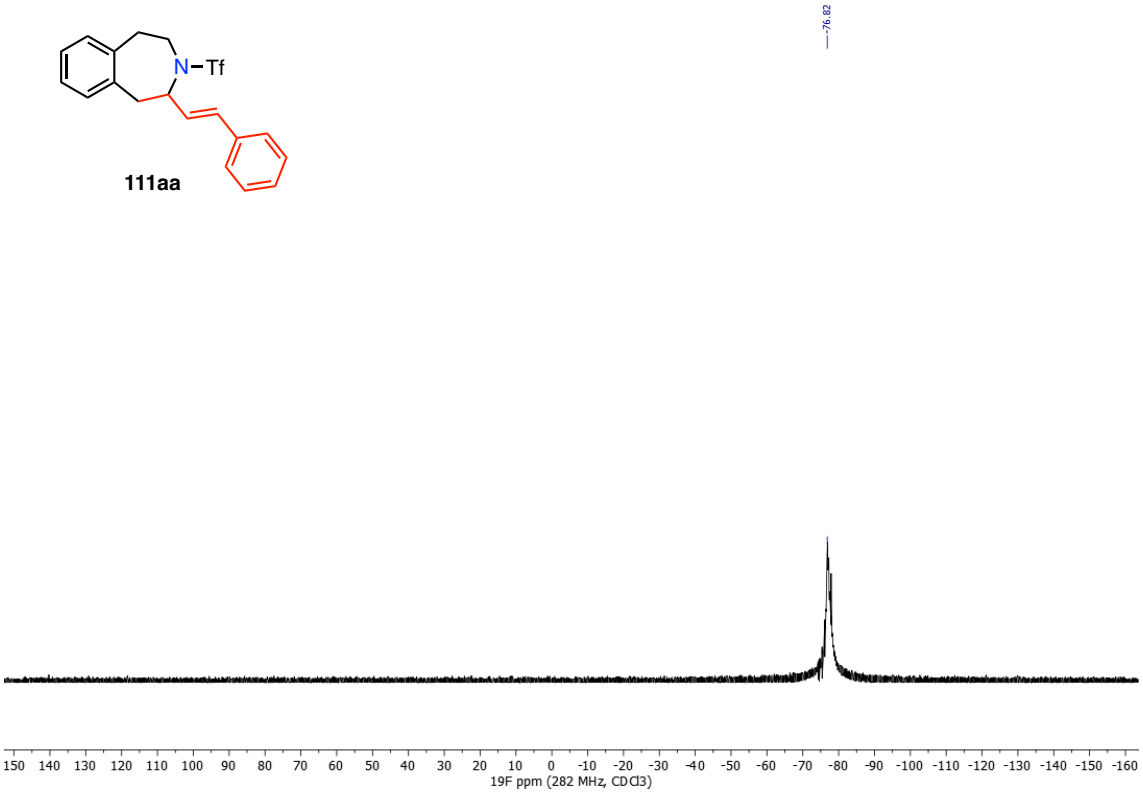

$^{13}$C-NMR (101 MHz). SOLVENT ($CDCl_3$)



$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

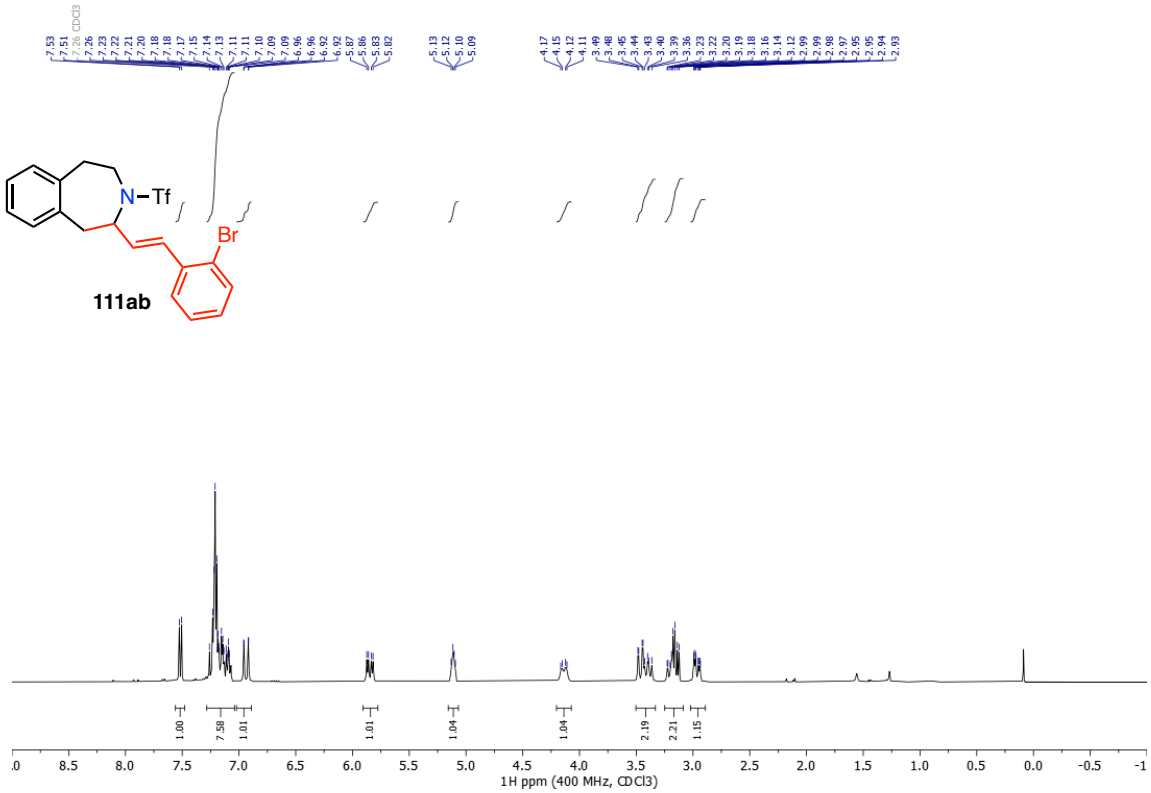



**111aa**

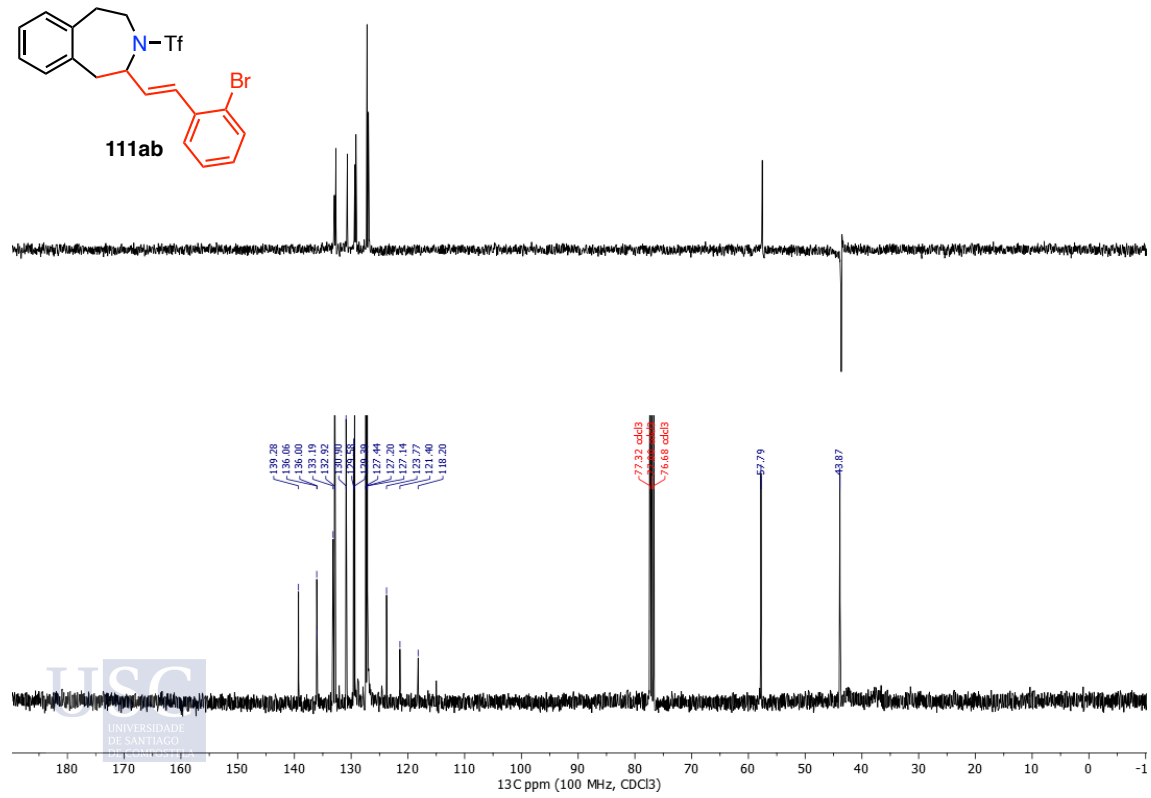



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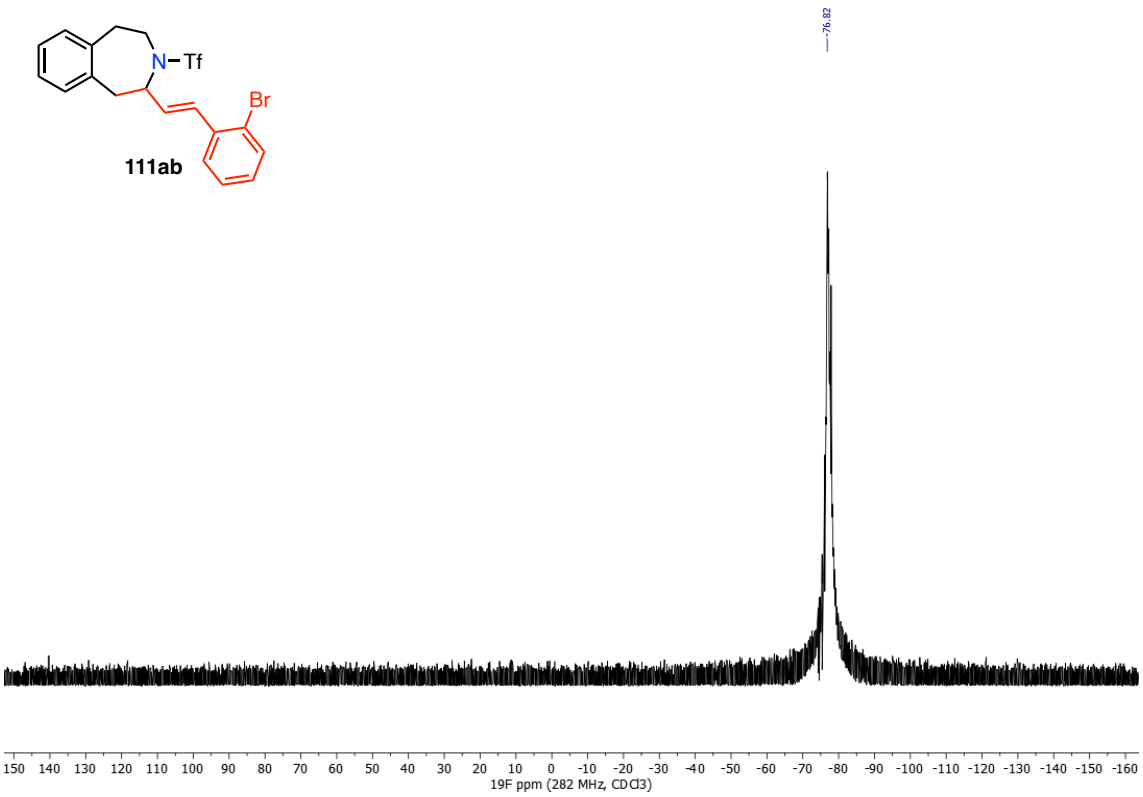
$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)

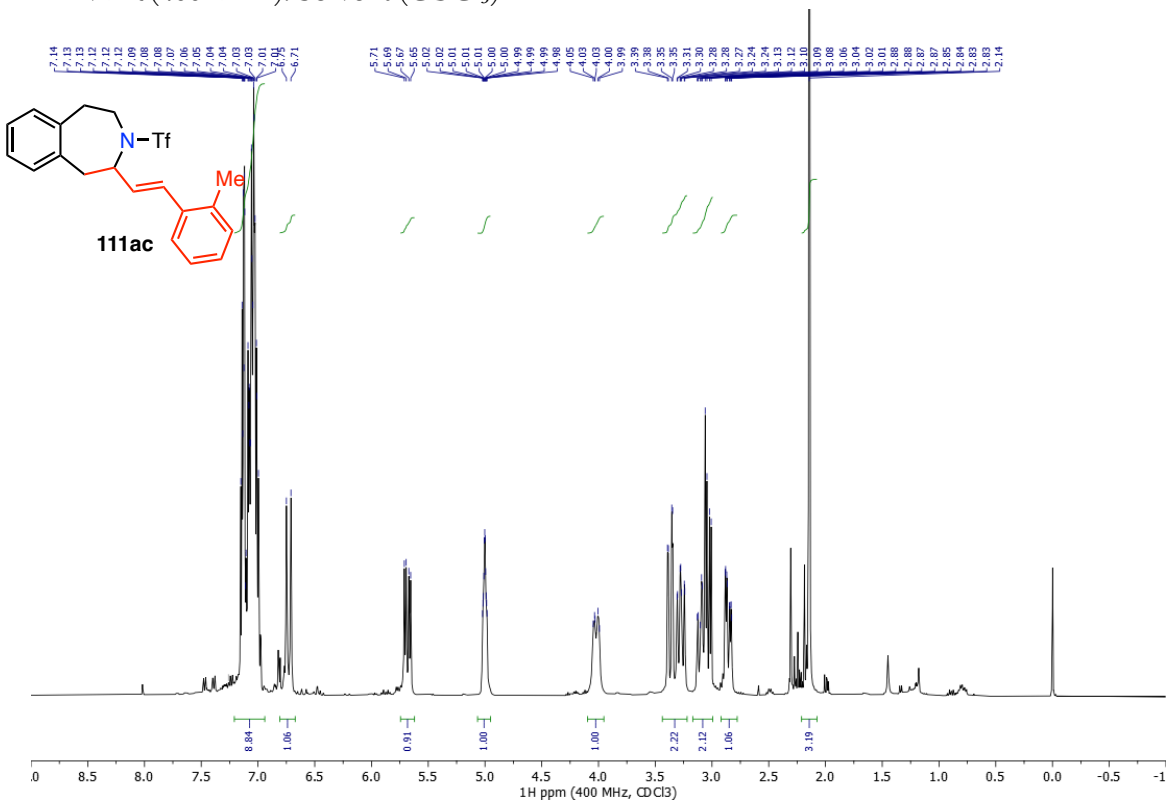


$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

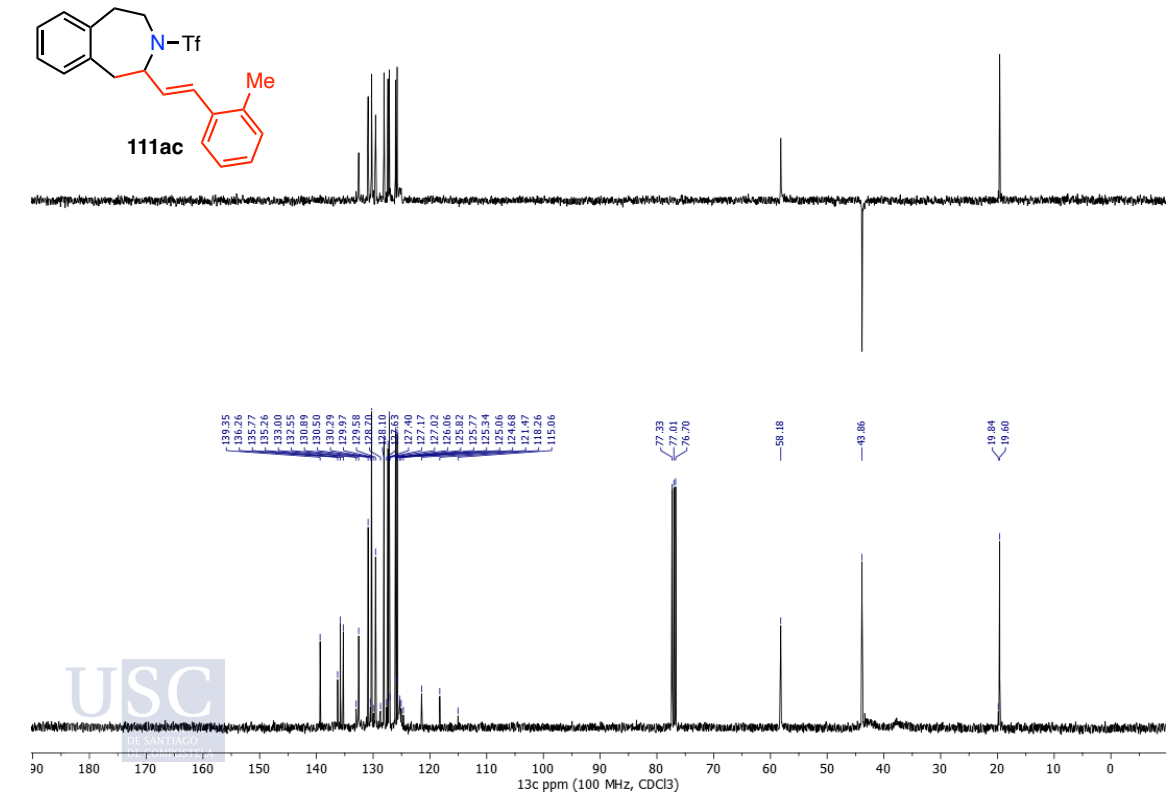



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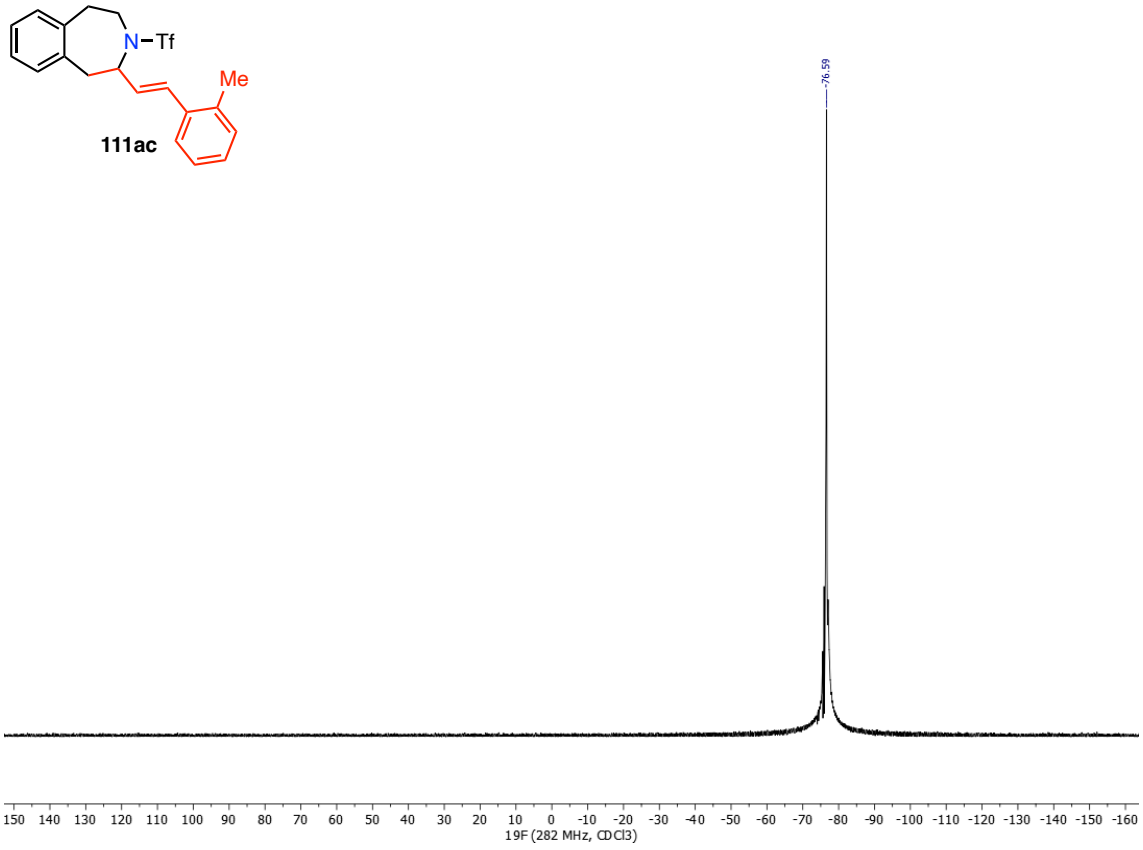
$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)

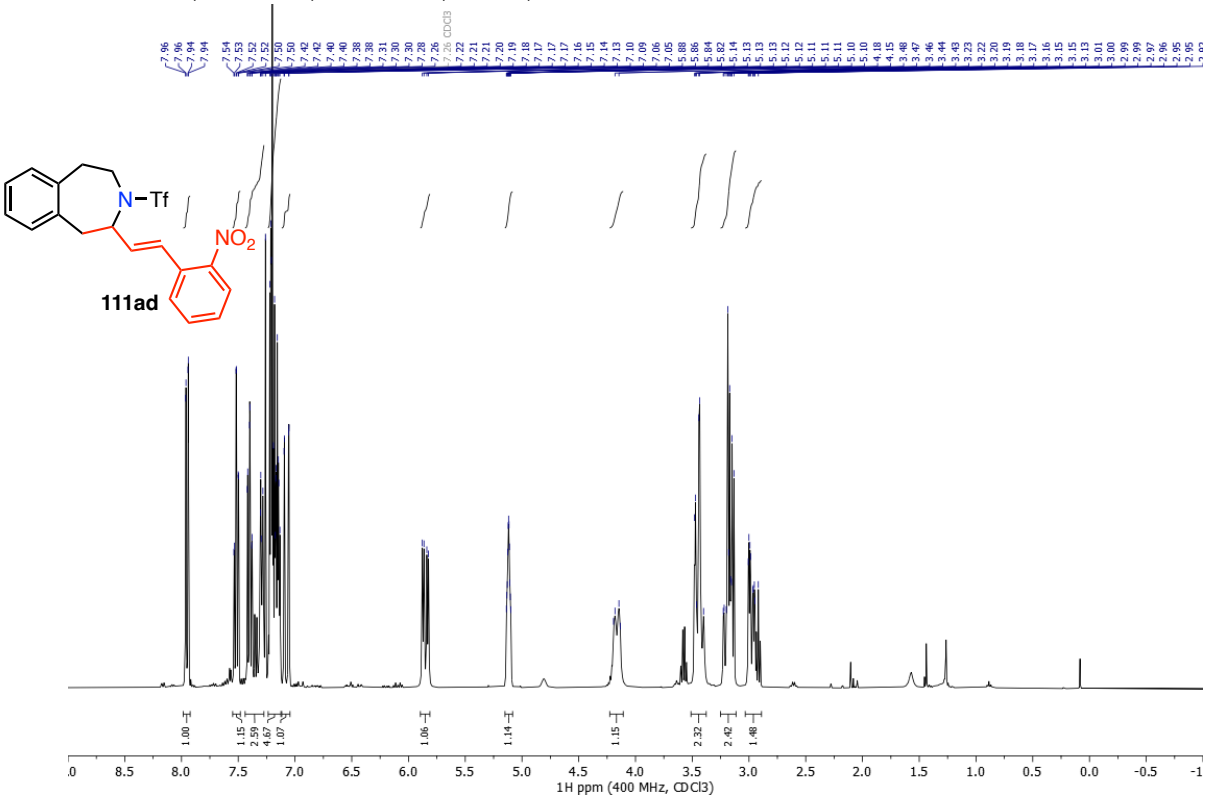


$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

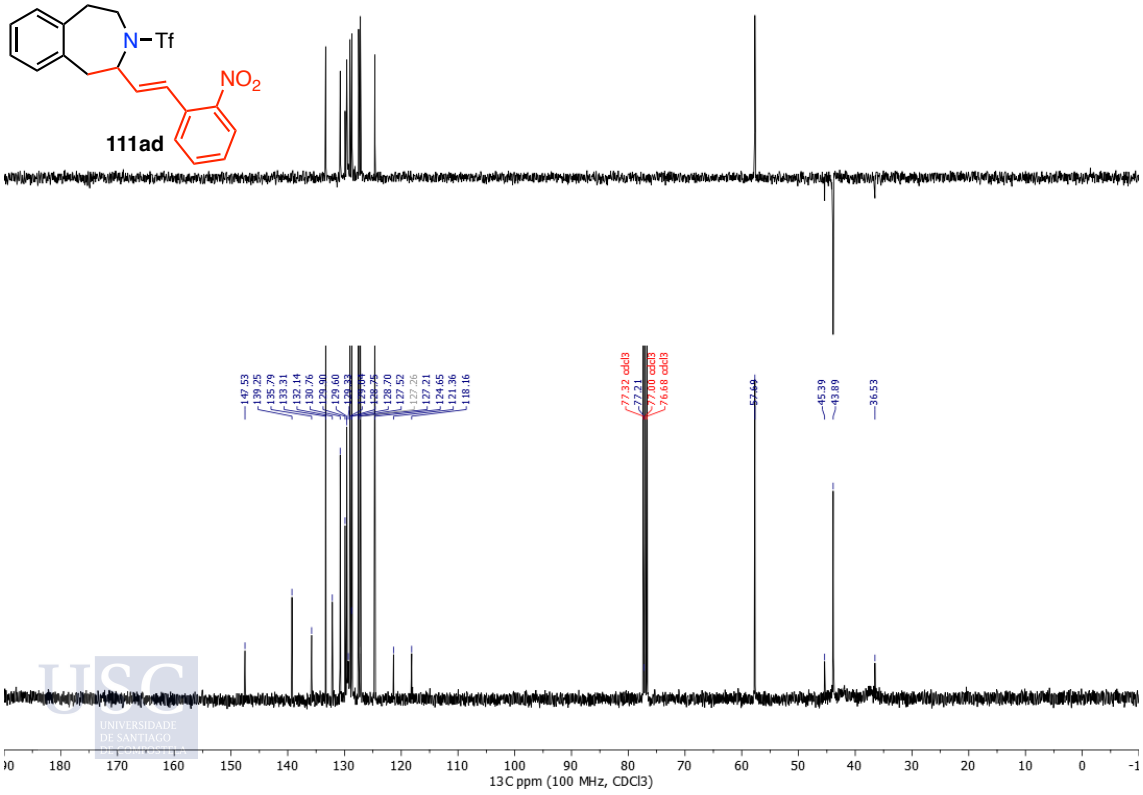



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$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)

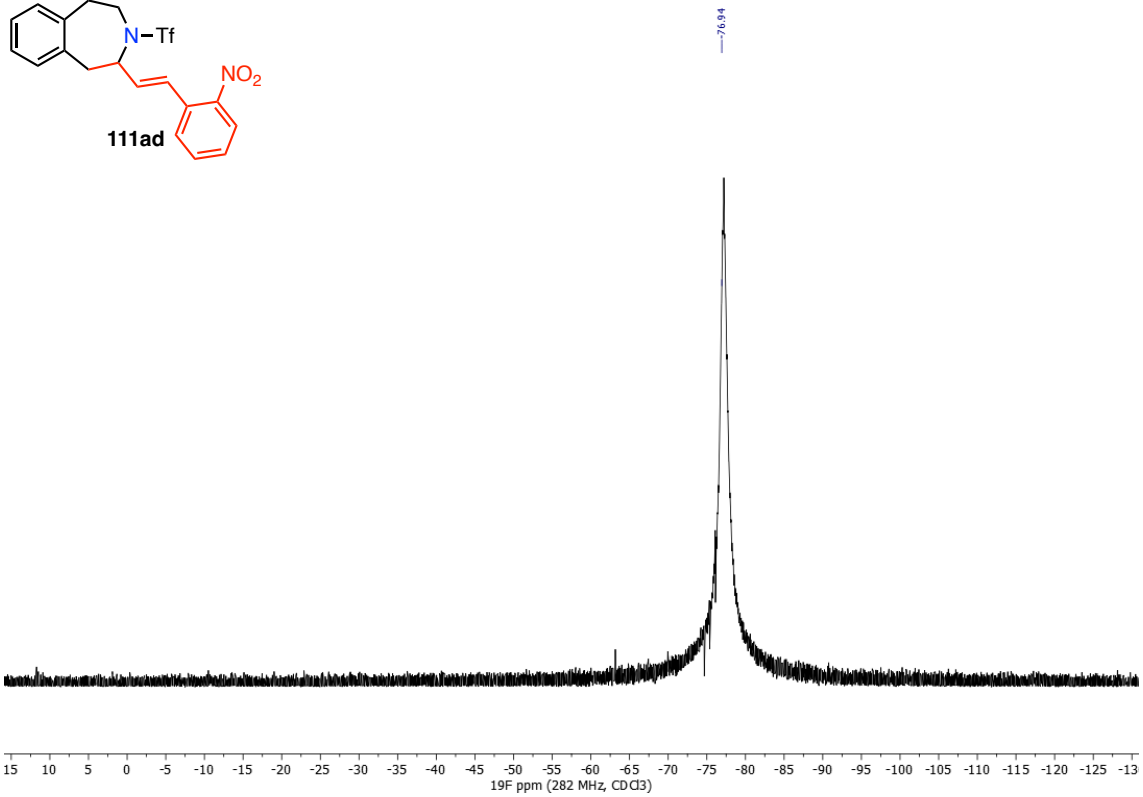



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$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

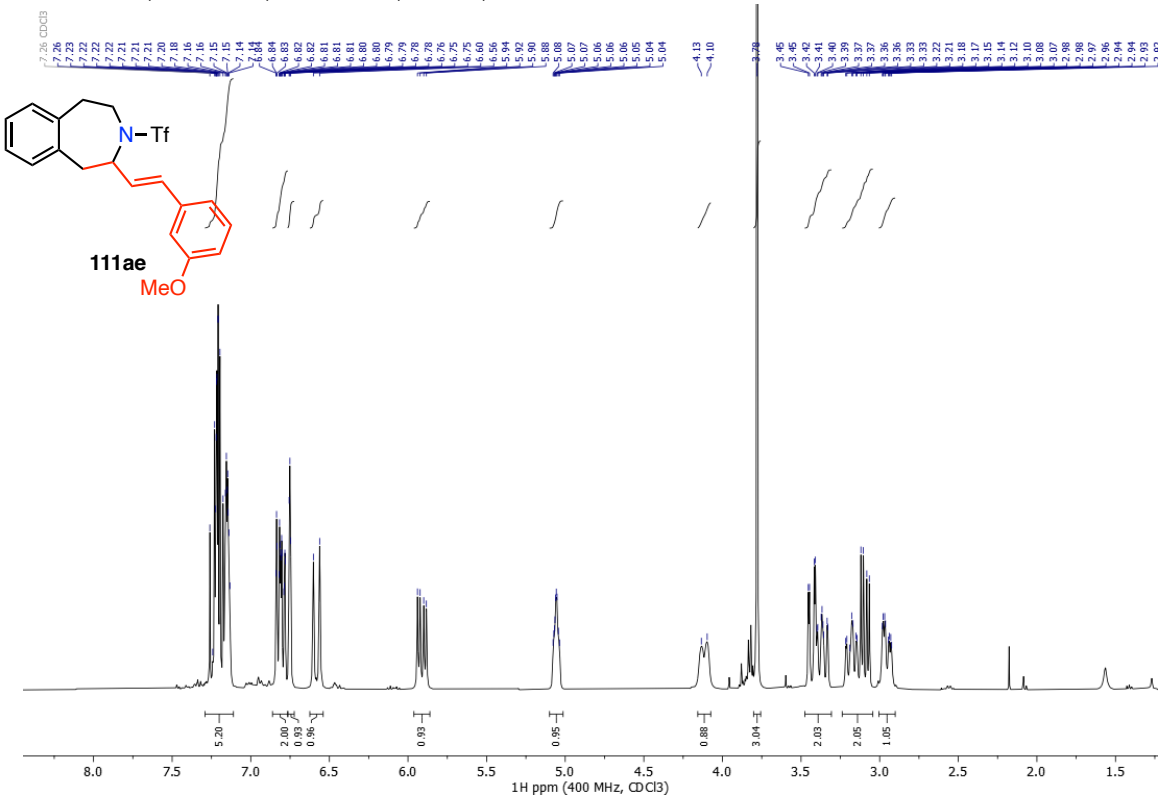



**111ad**

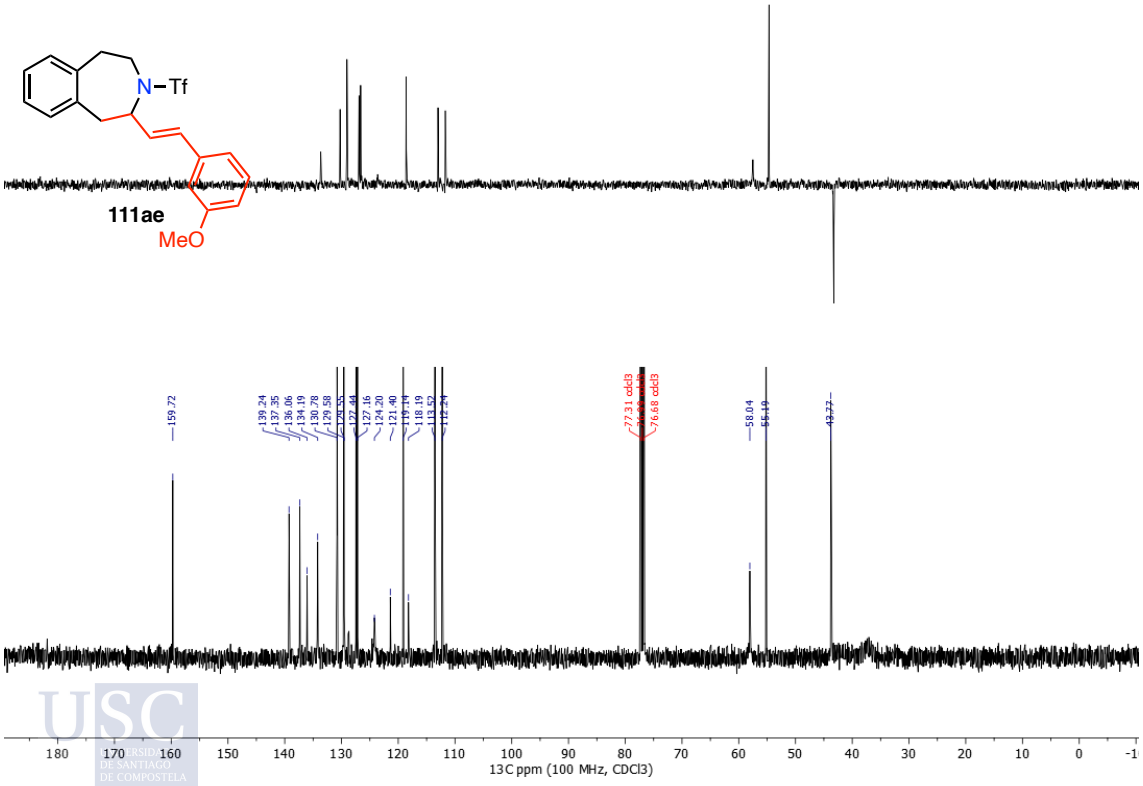



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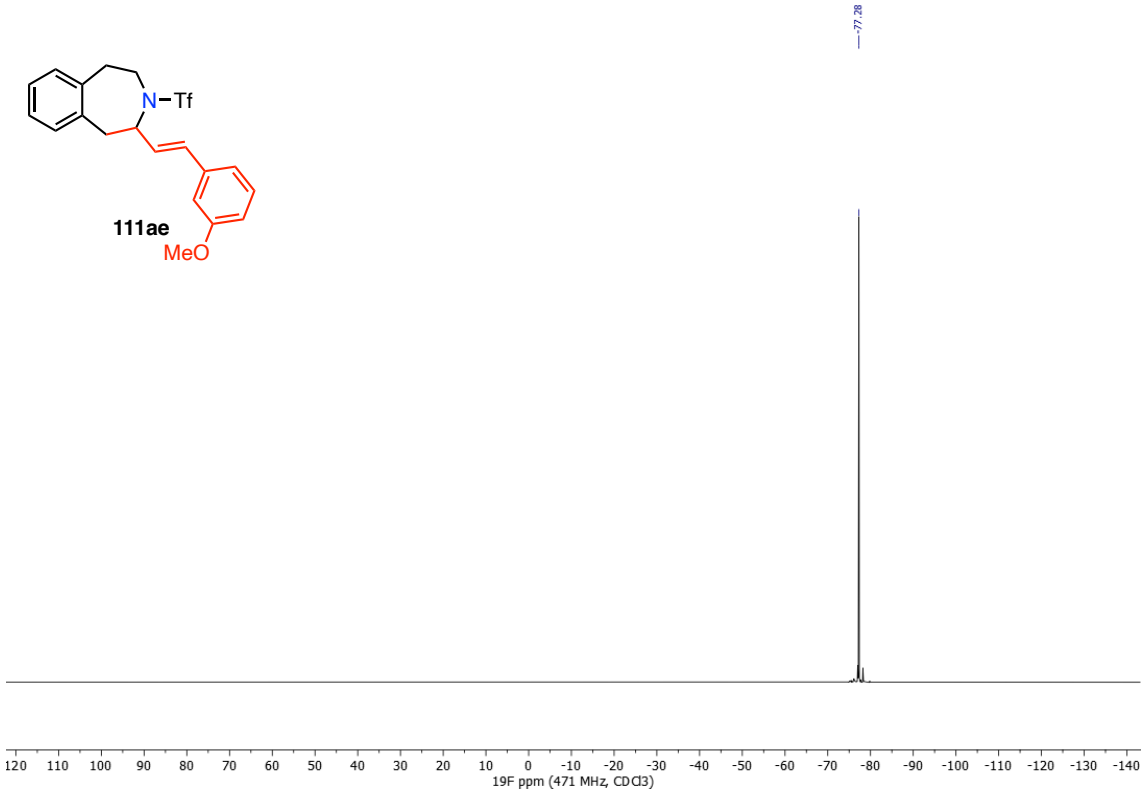
$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)

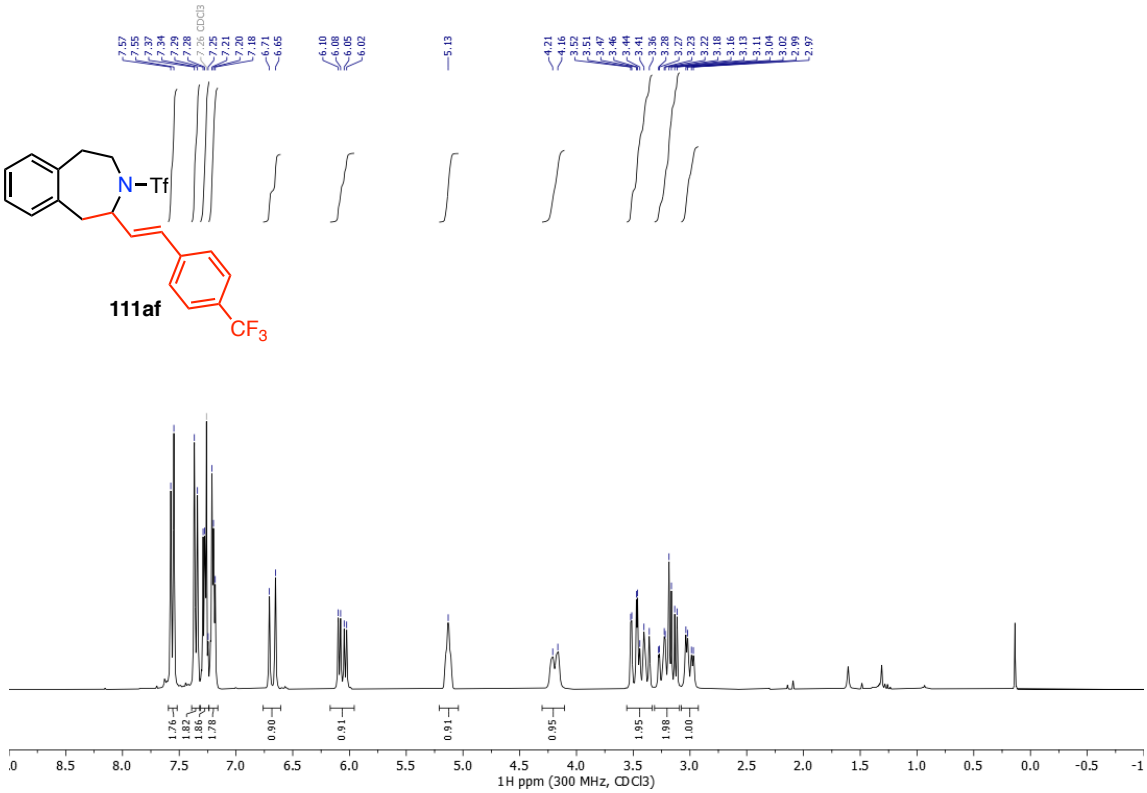


$^{19}$F-NMR (471 MHz). Solvent ($CDCl_3$)

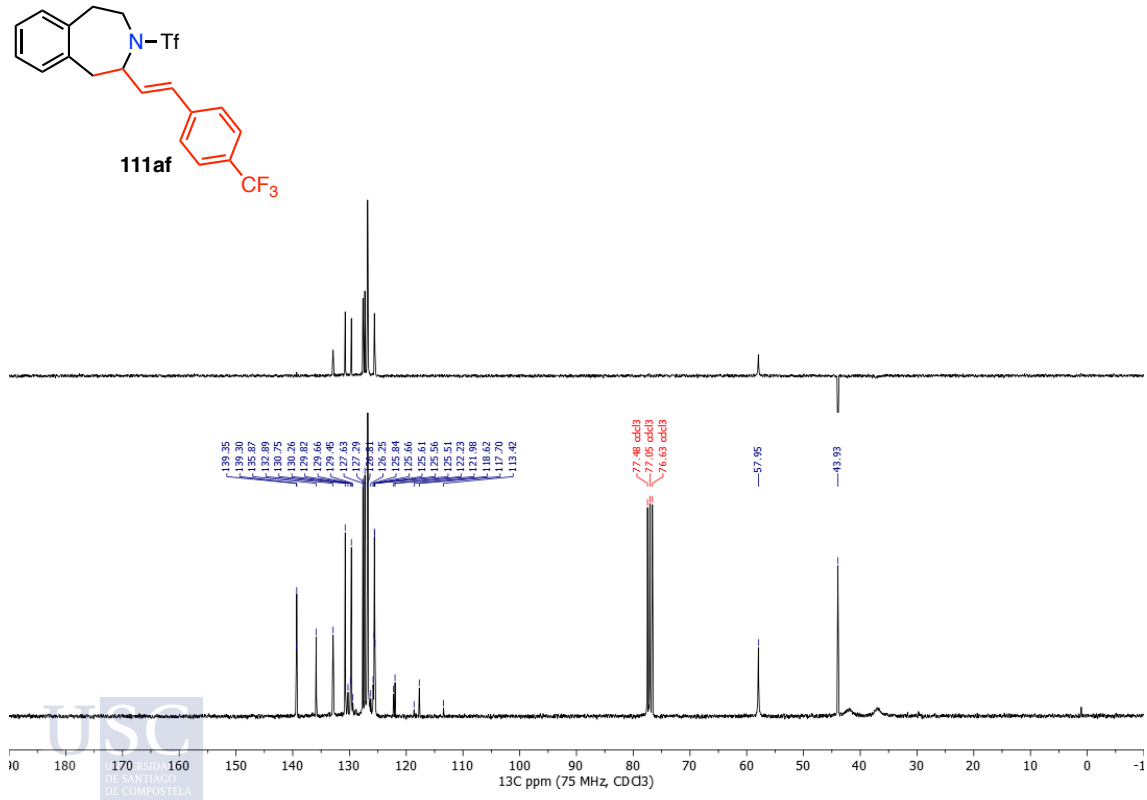



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$^{1}$H-NMR (300 MHz). Solvent ($CDCl_3$)

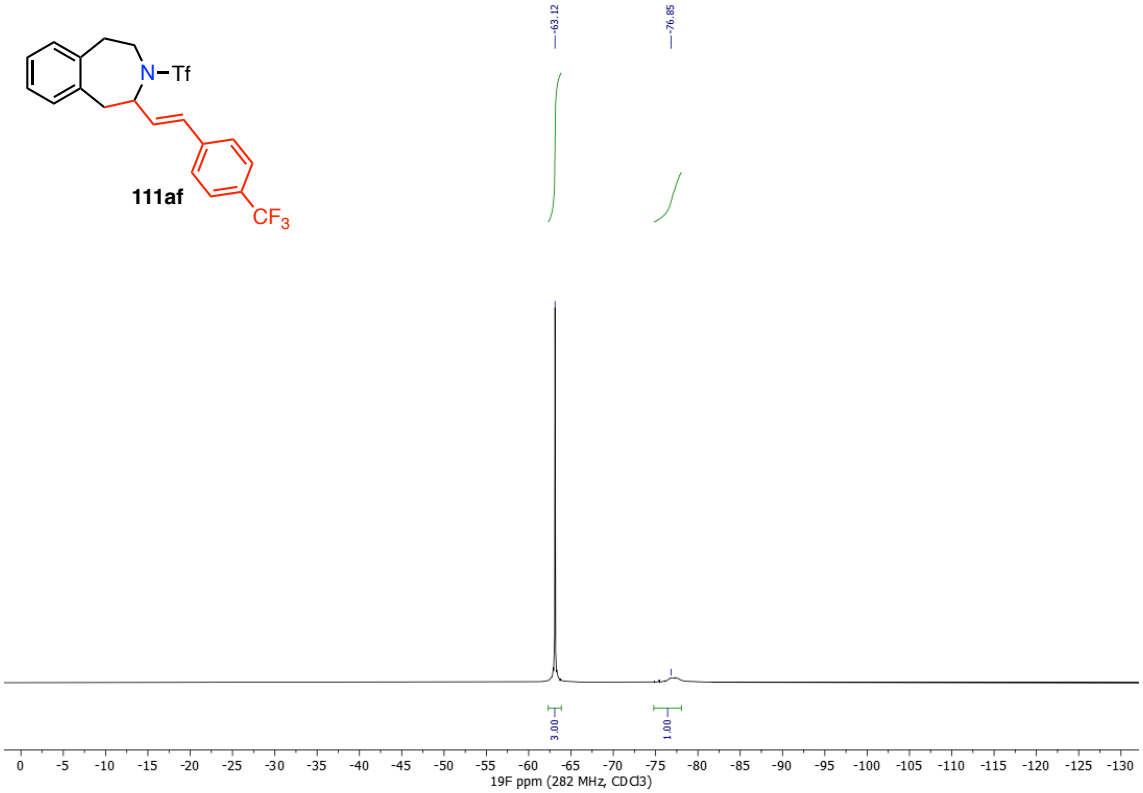



$^{13}$C-NMR (75 MHz). Solvent ($CDCl_3$)



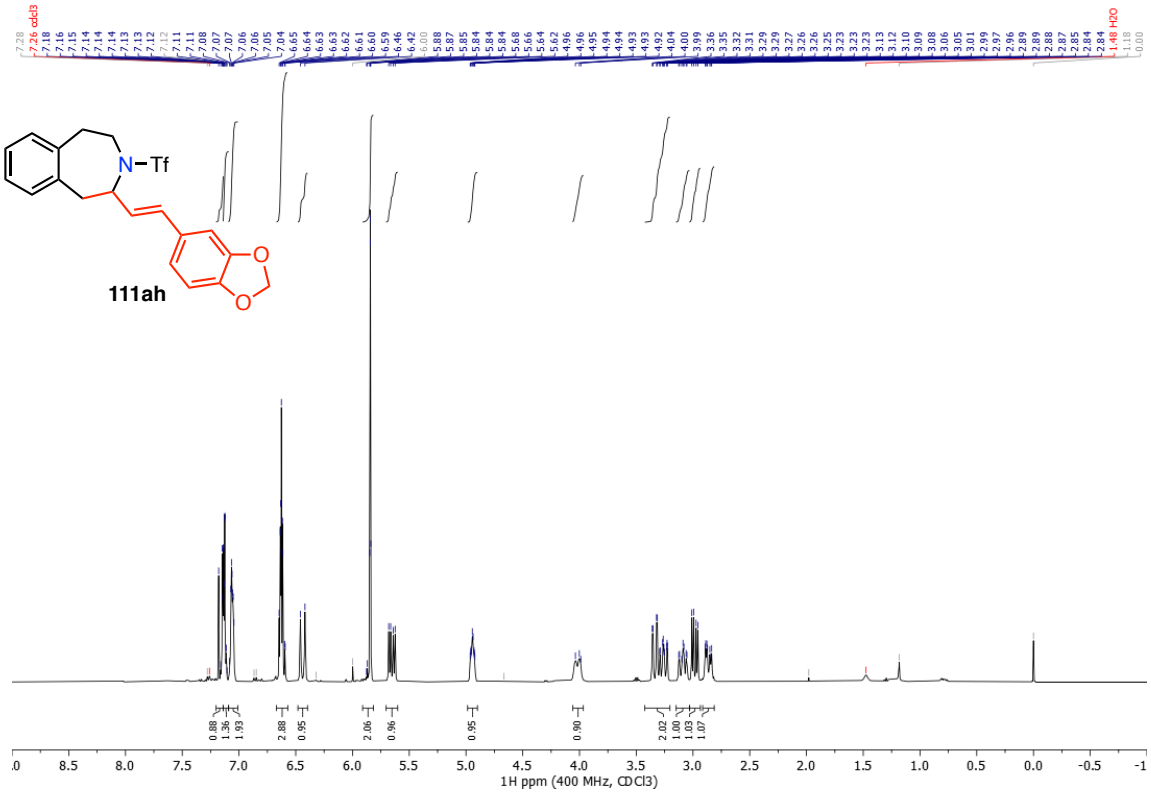

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$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

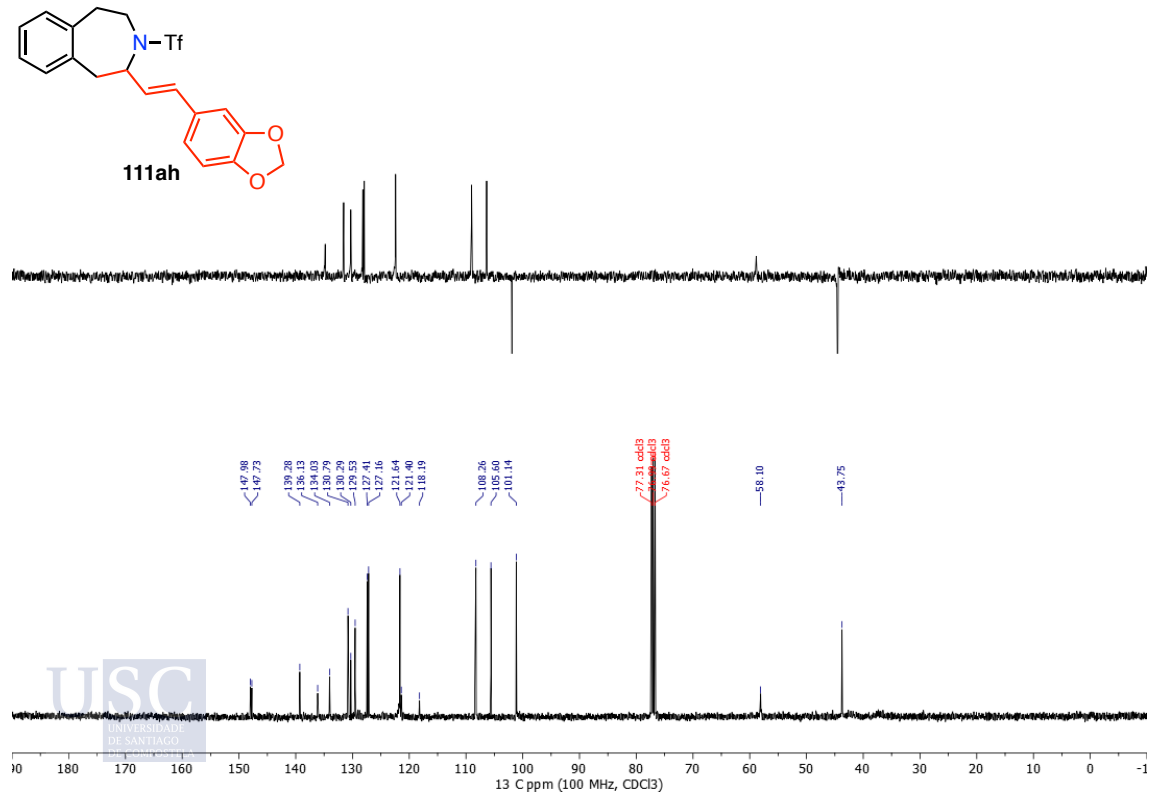



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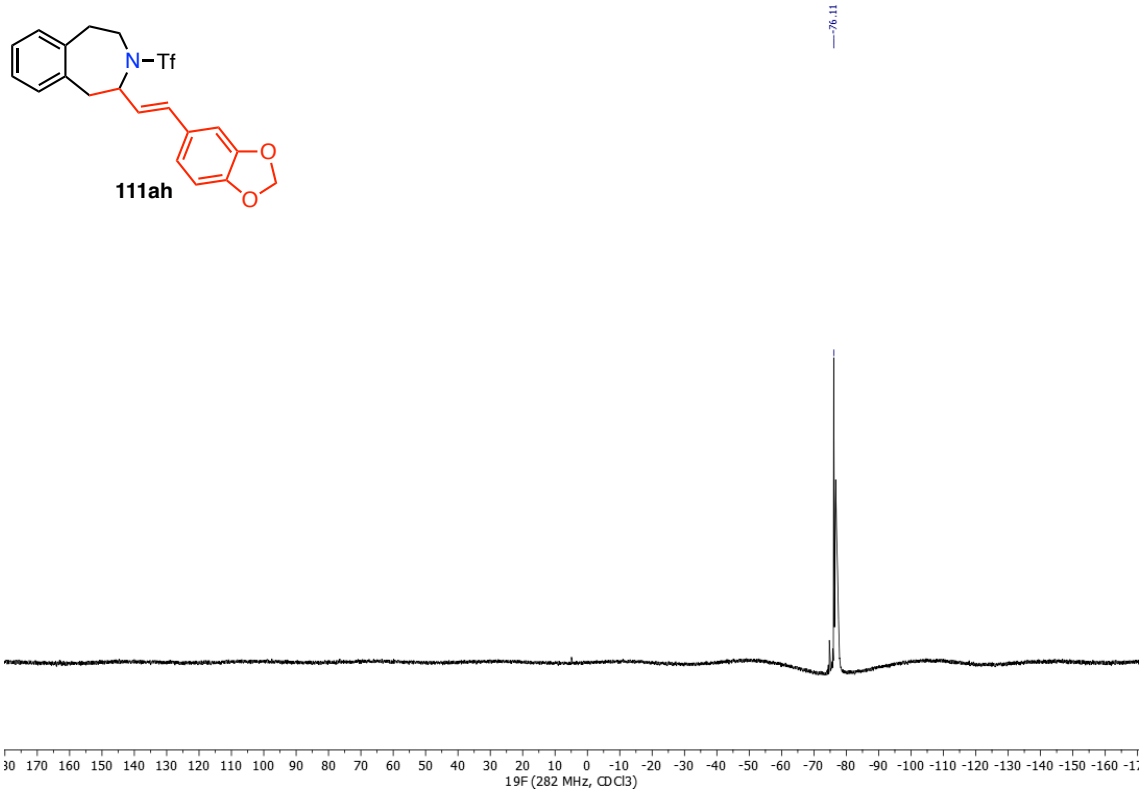
$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)

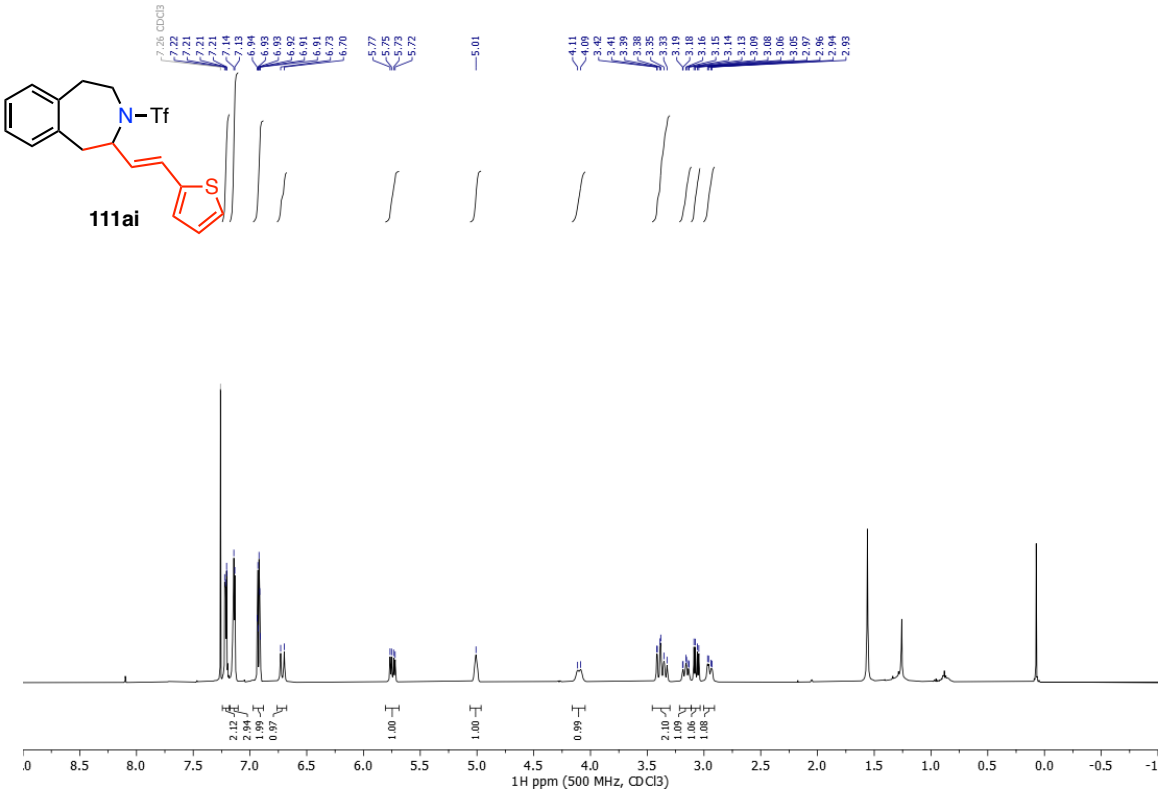


$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

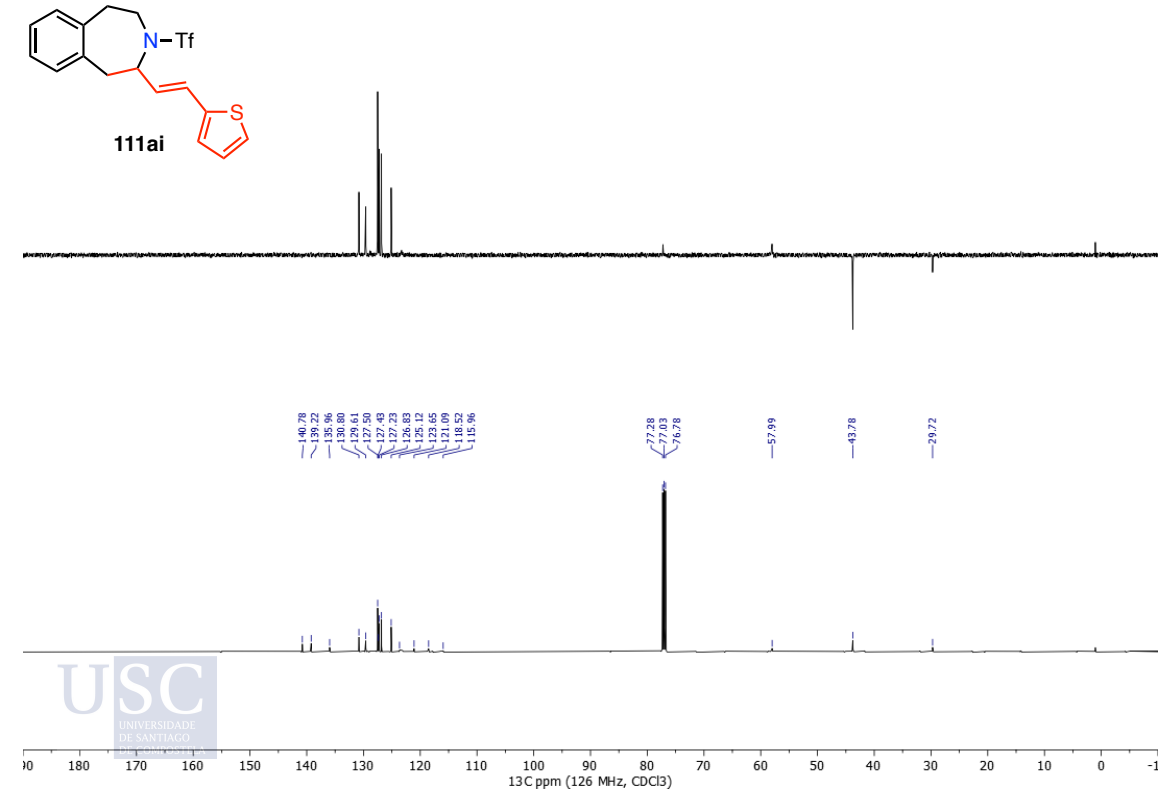



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)



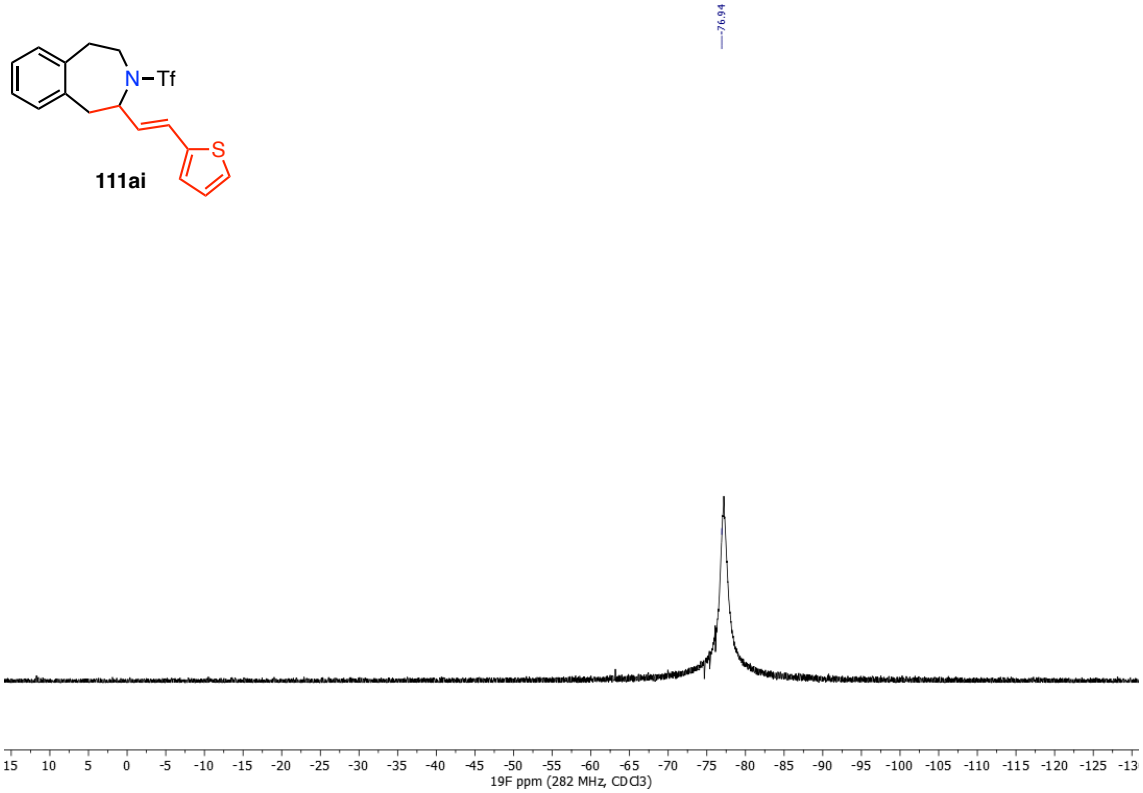

$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)



$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

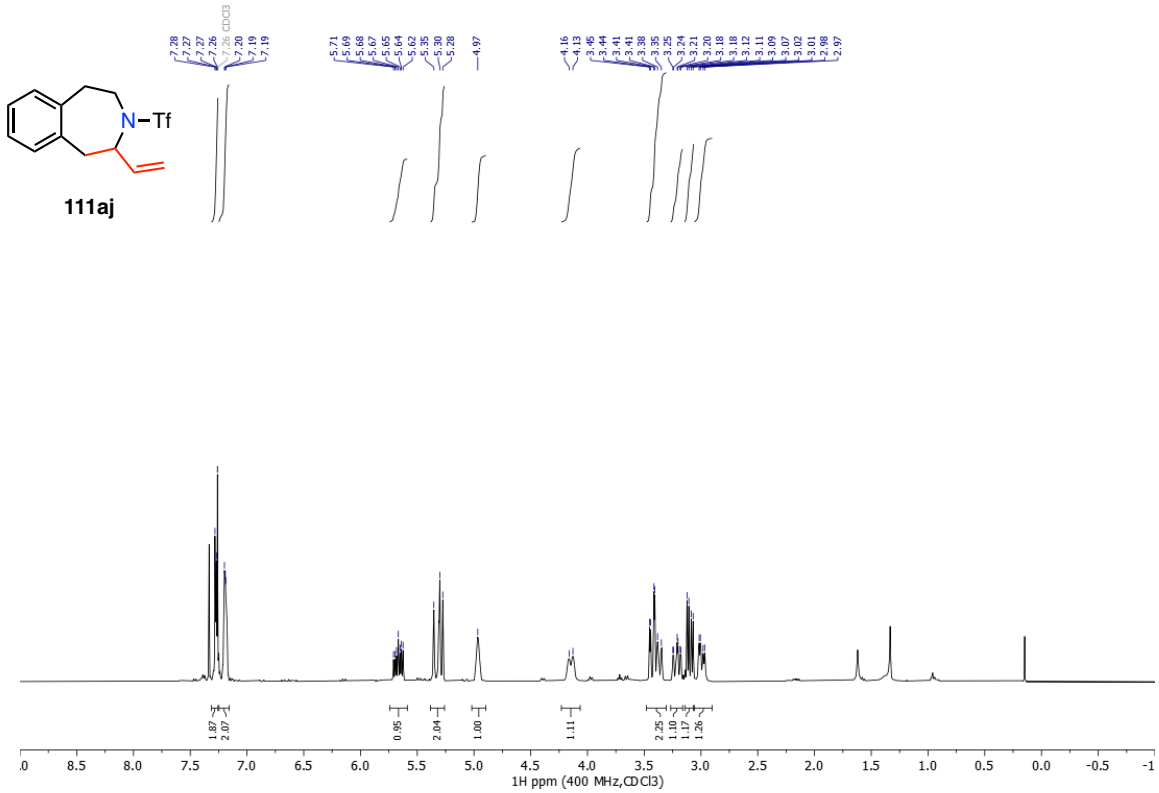



**111ai**

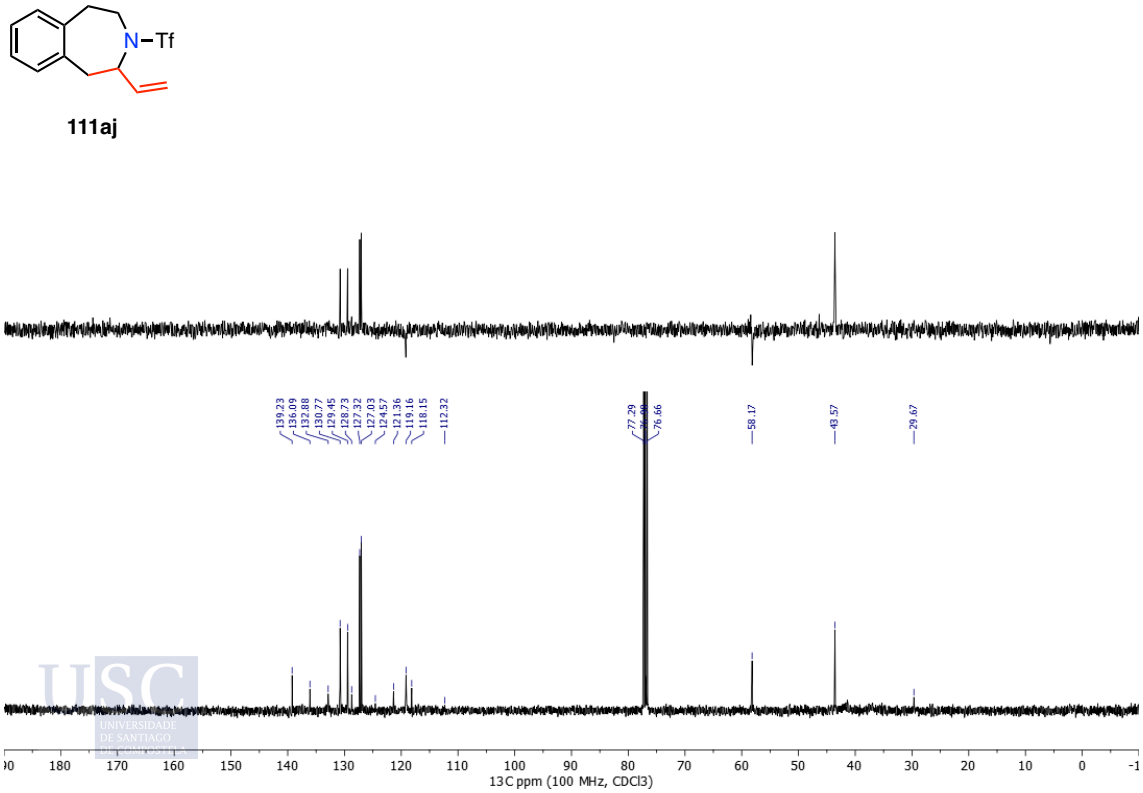



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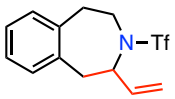
$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)



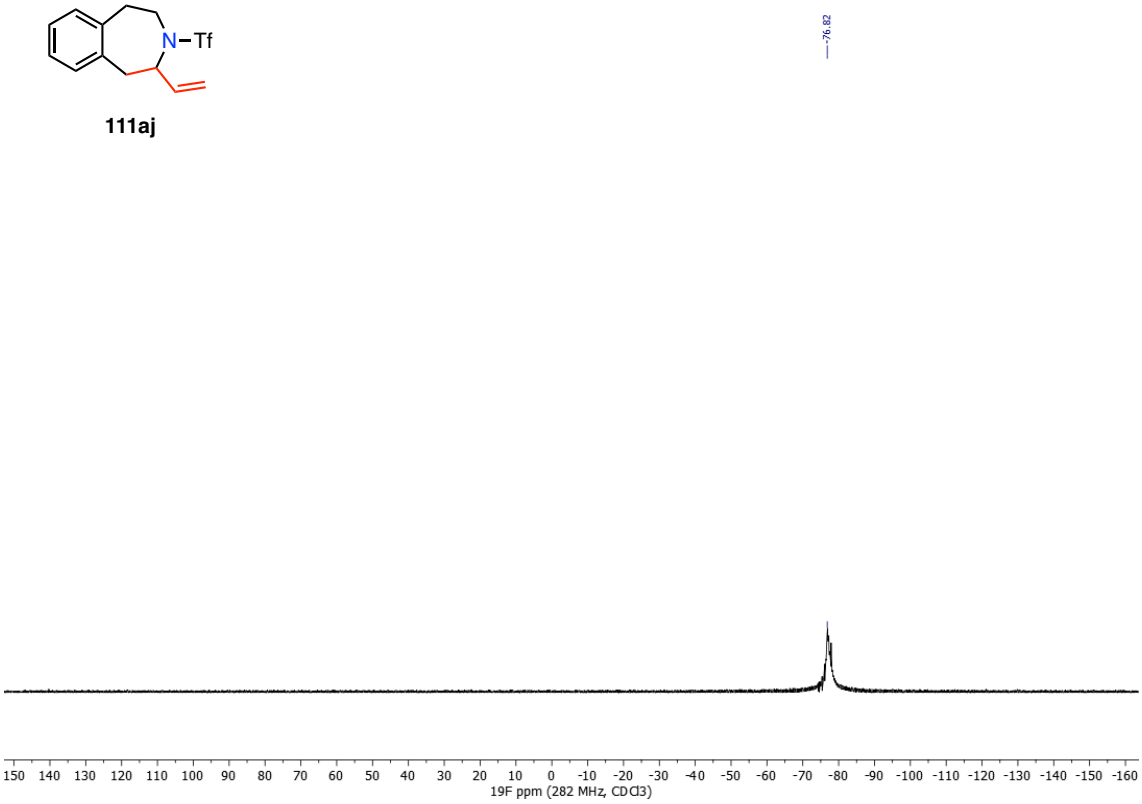

$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)



$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

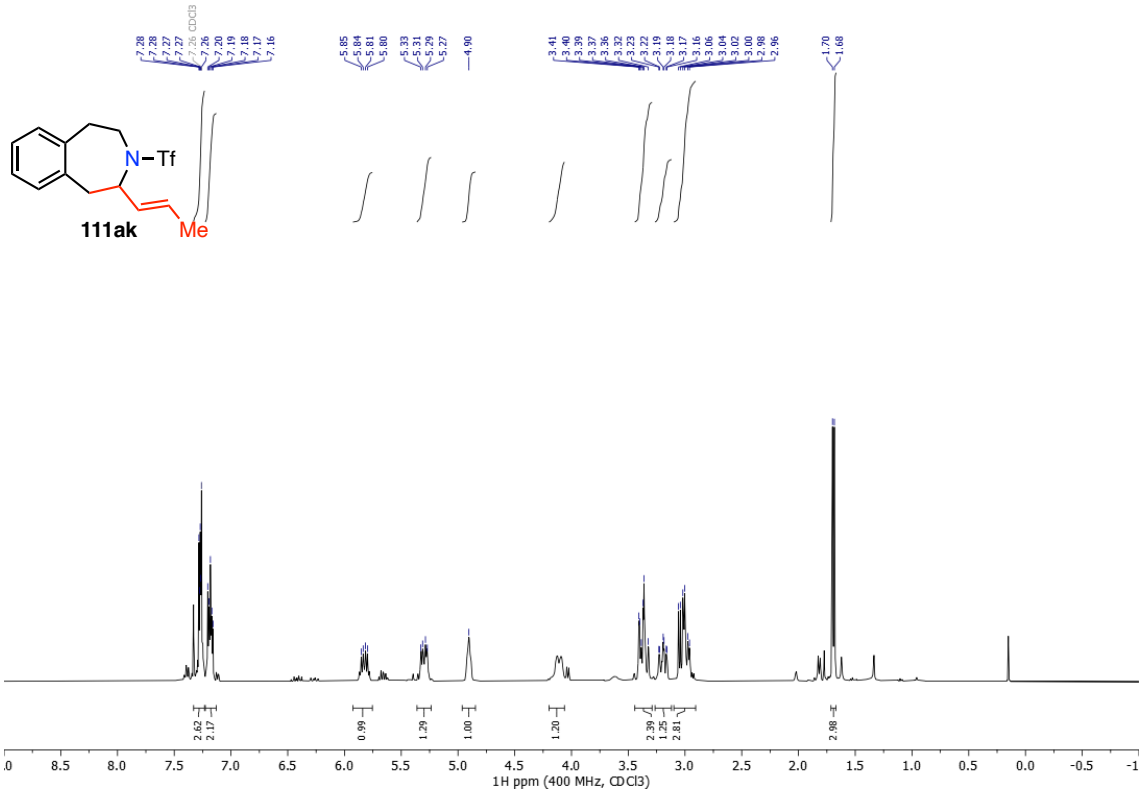



**111aj**

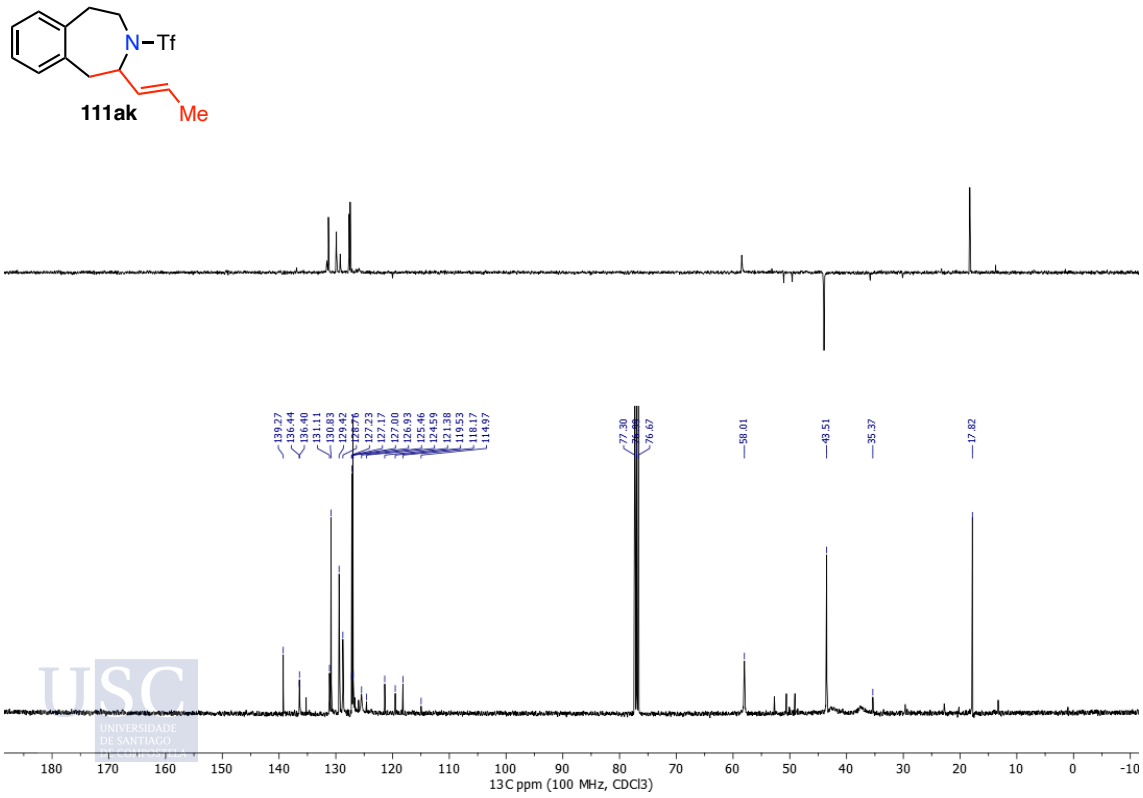



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$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)



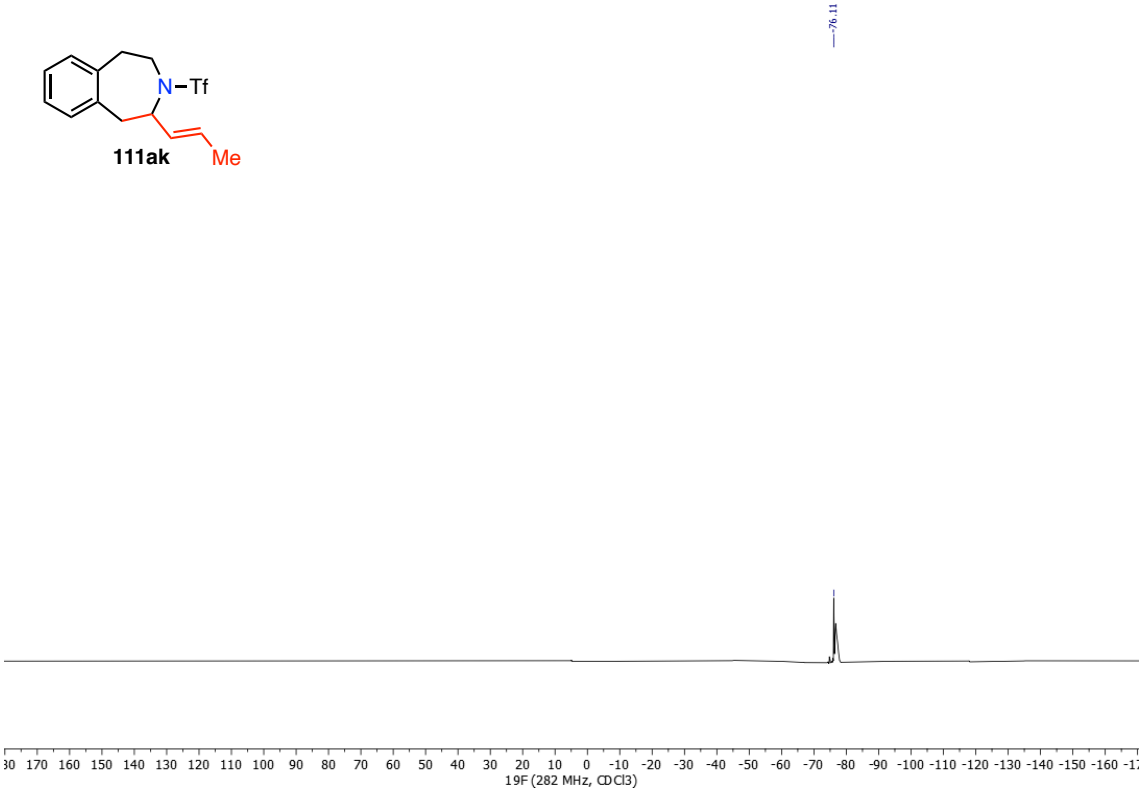

$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)



$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

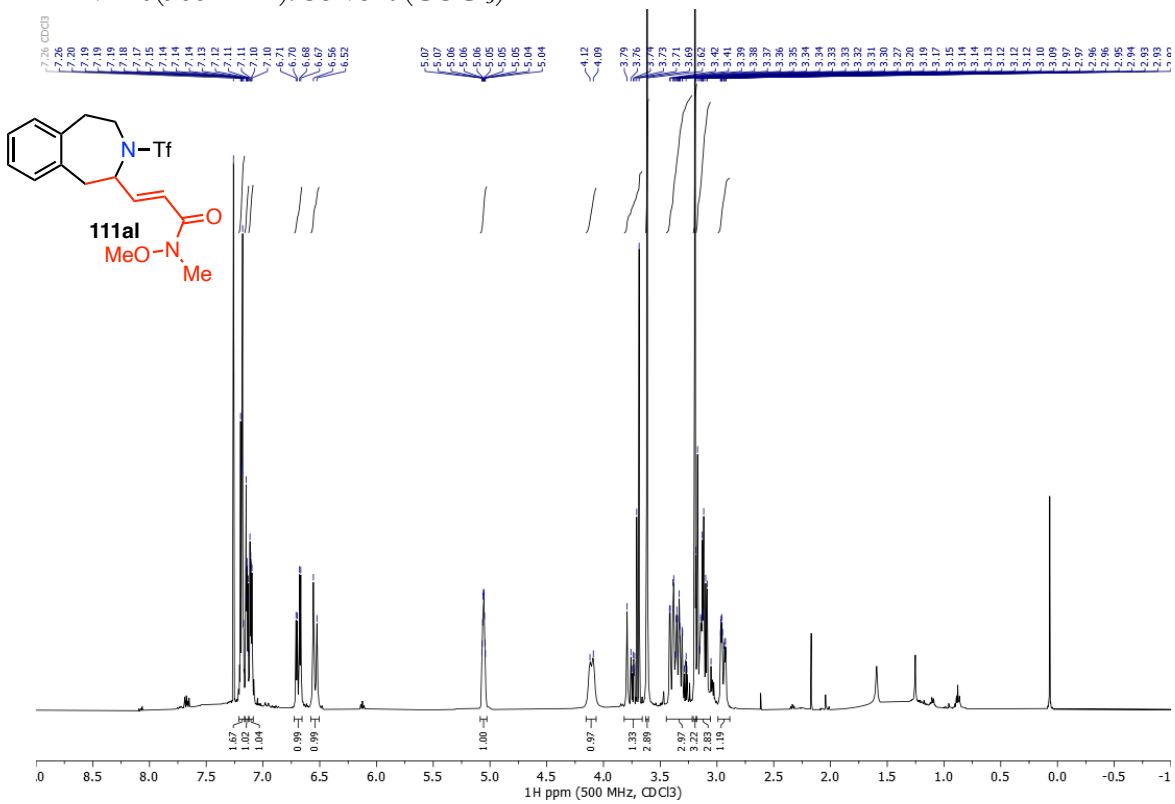



**111ak**

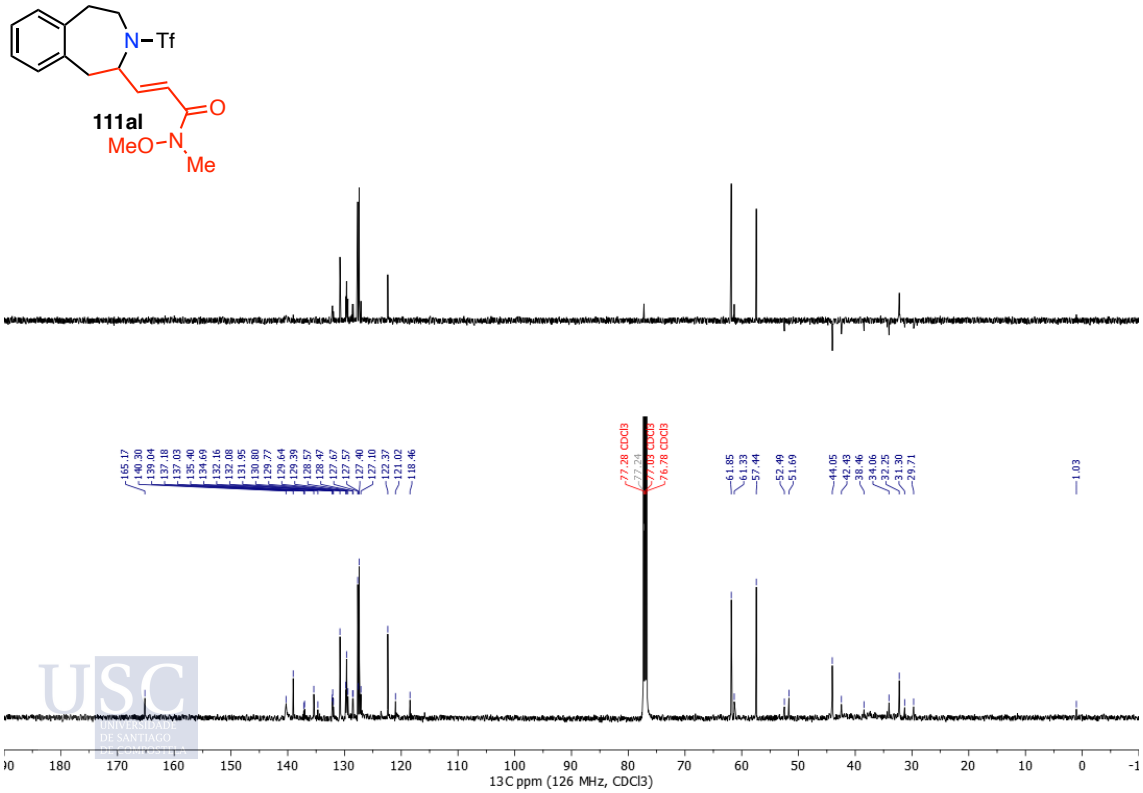



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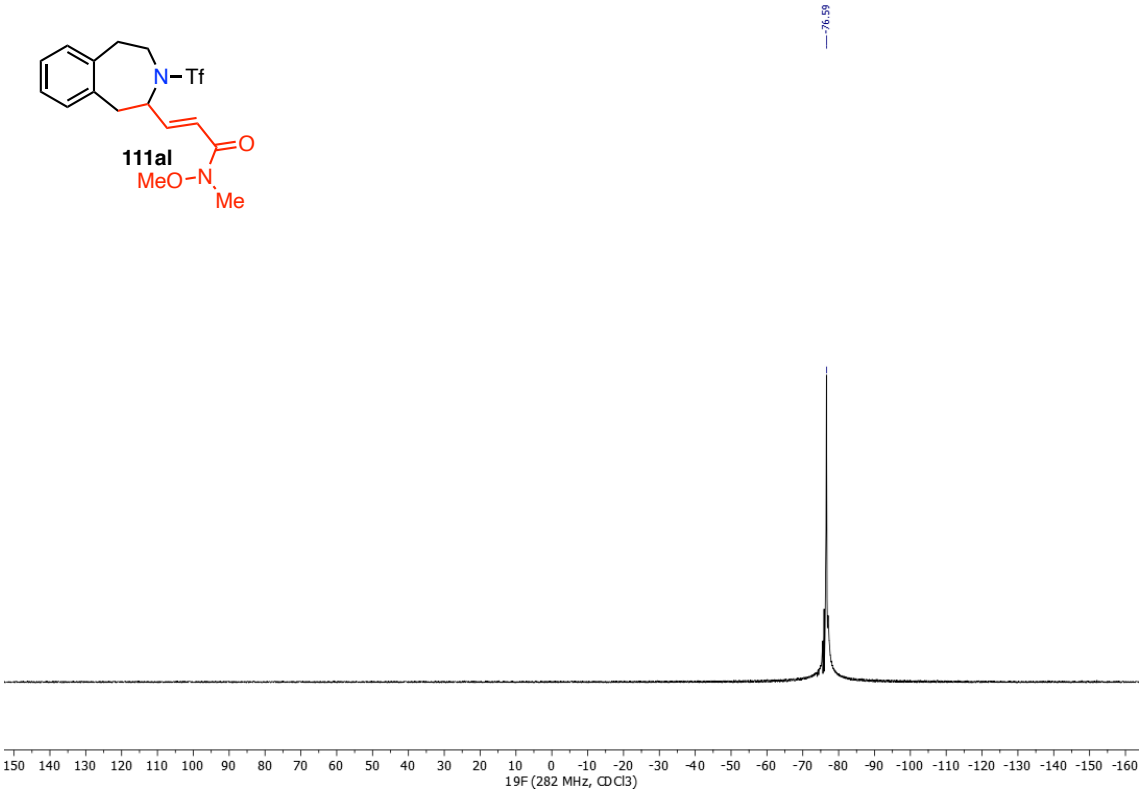
$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)

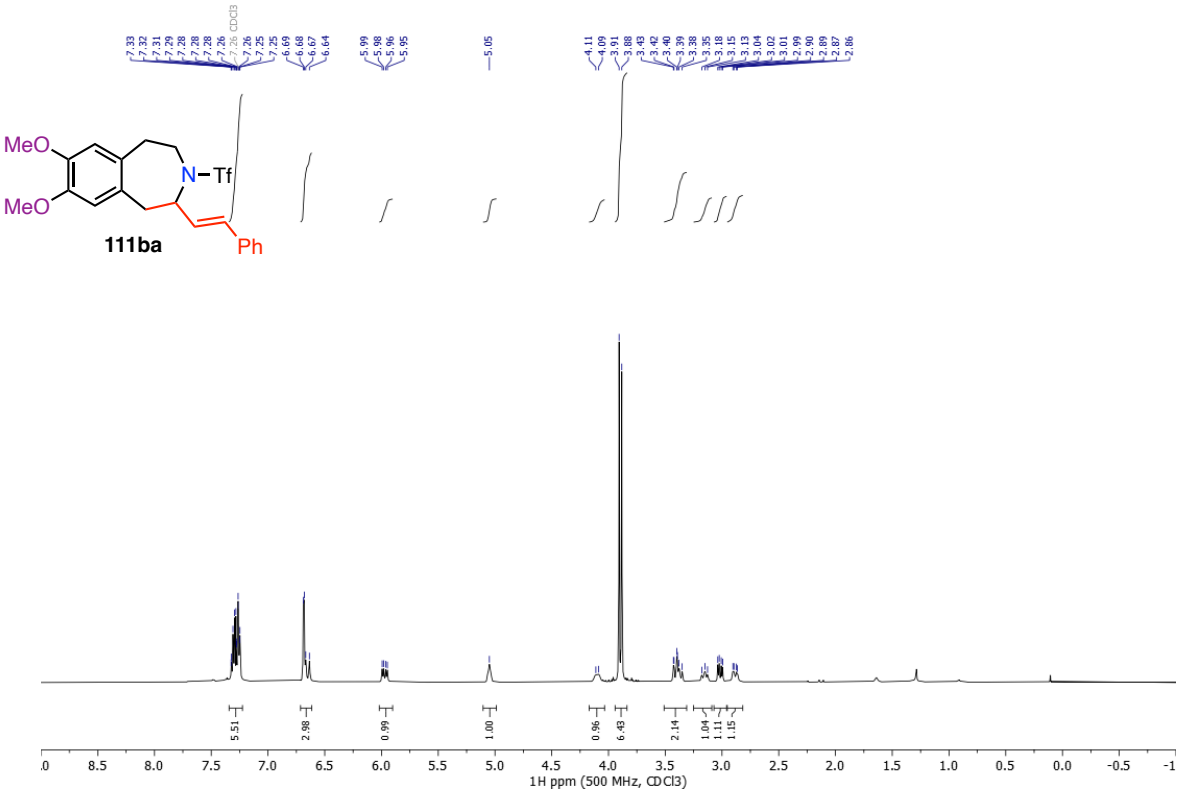


$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

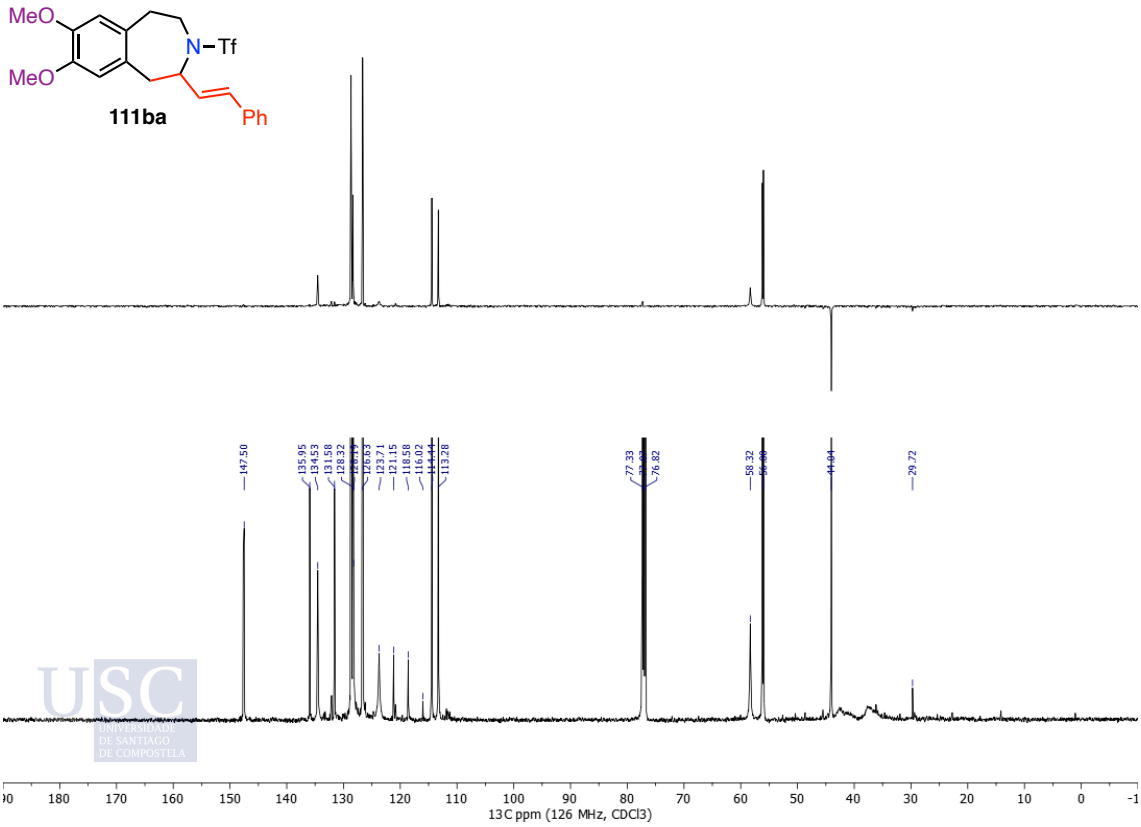



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)

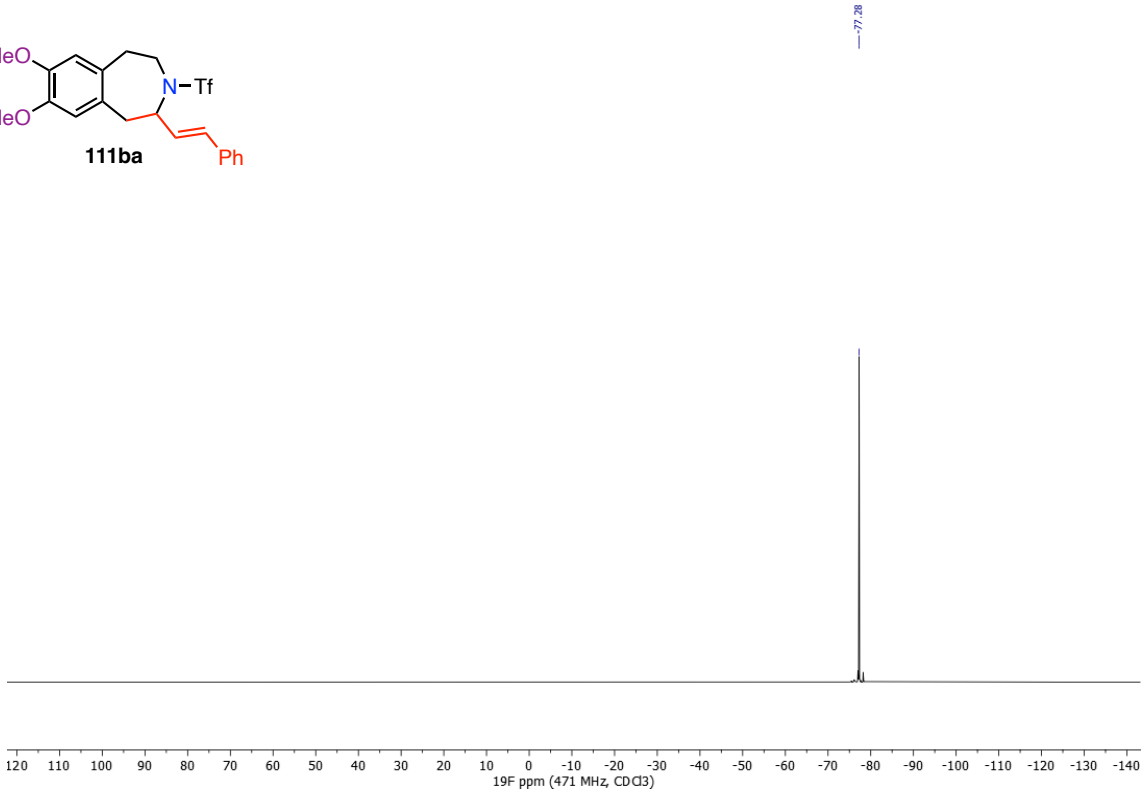



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$^{19}$F-NMR (471 MHz). Solvent ($CDCl_3$)

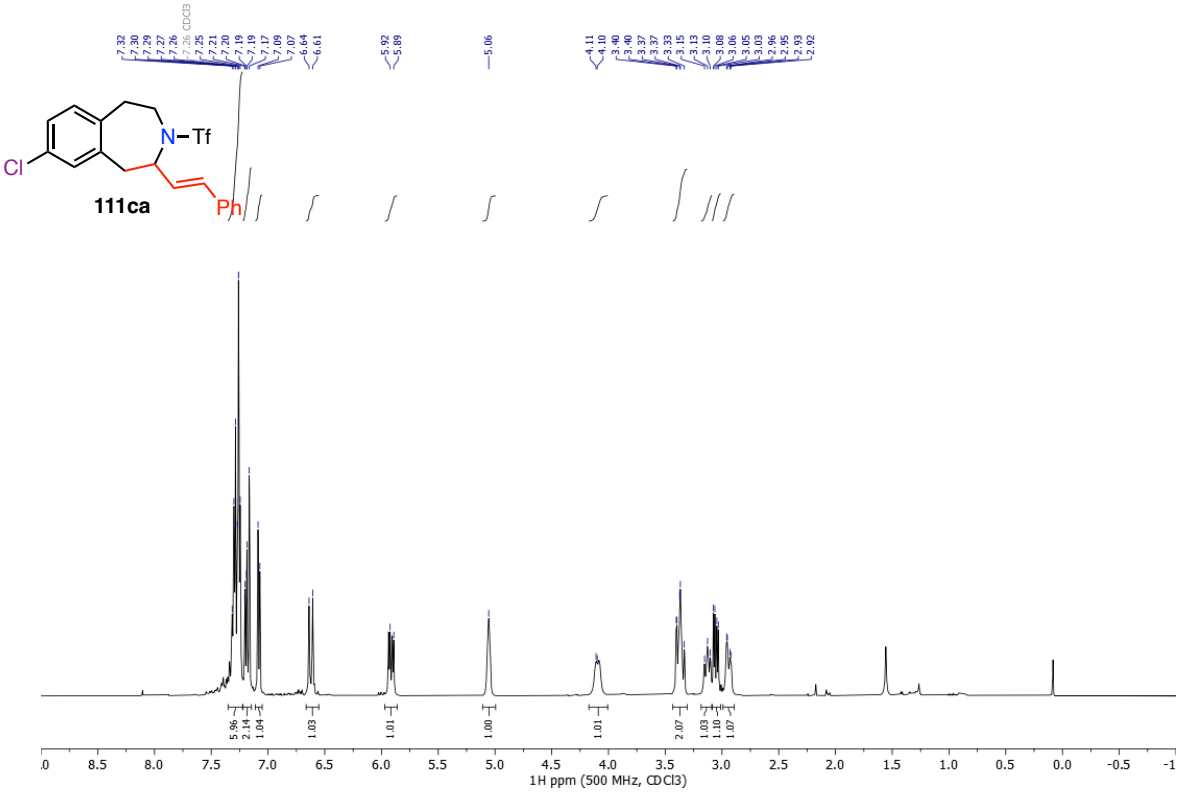



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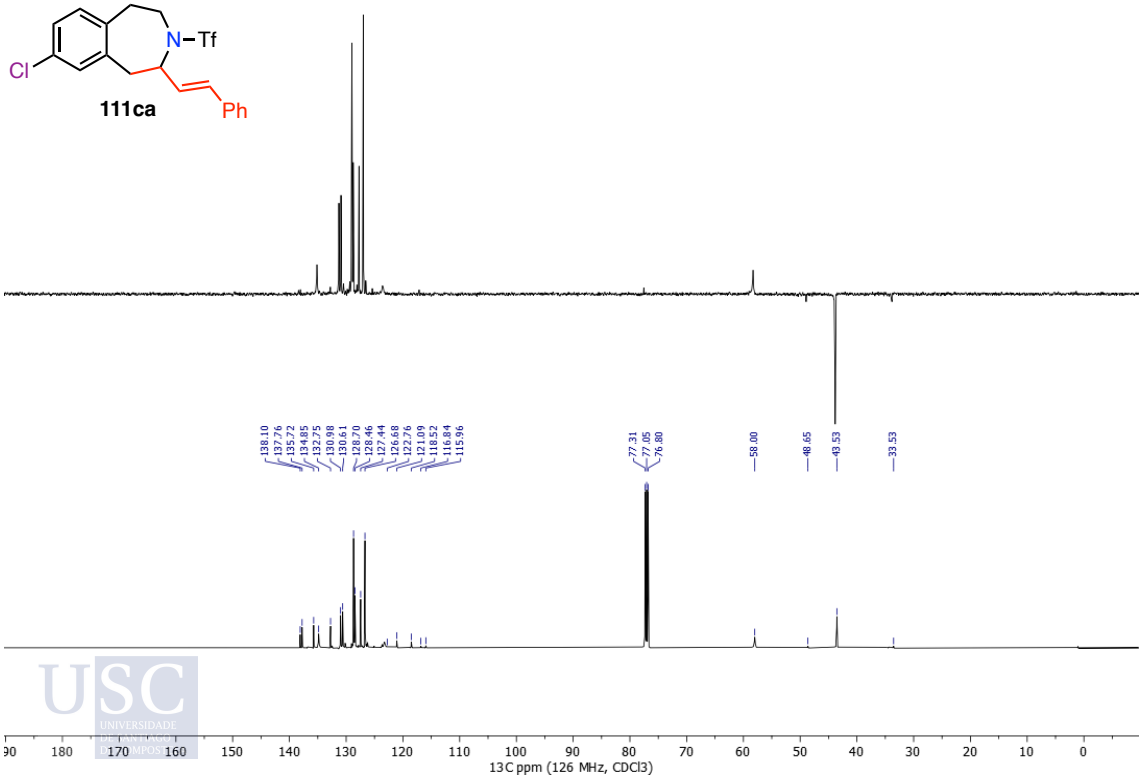



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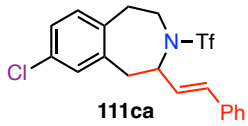
$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)



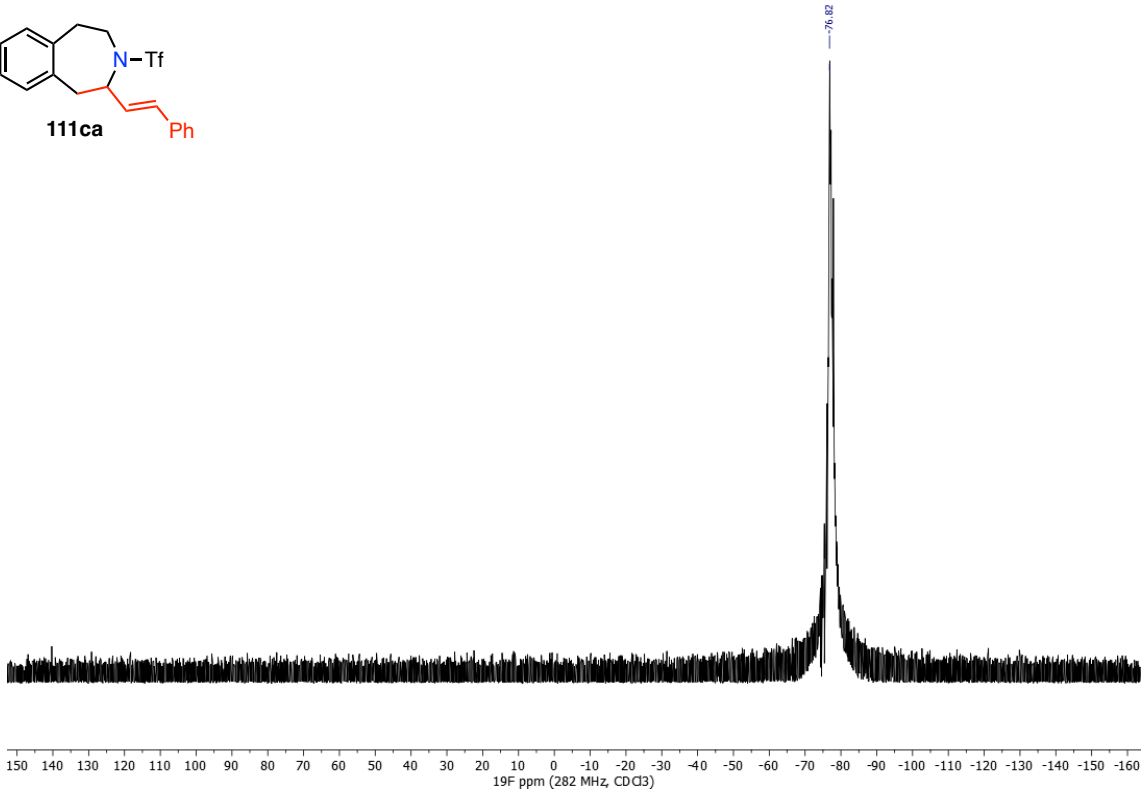

$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)



$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

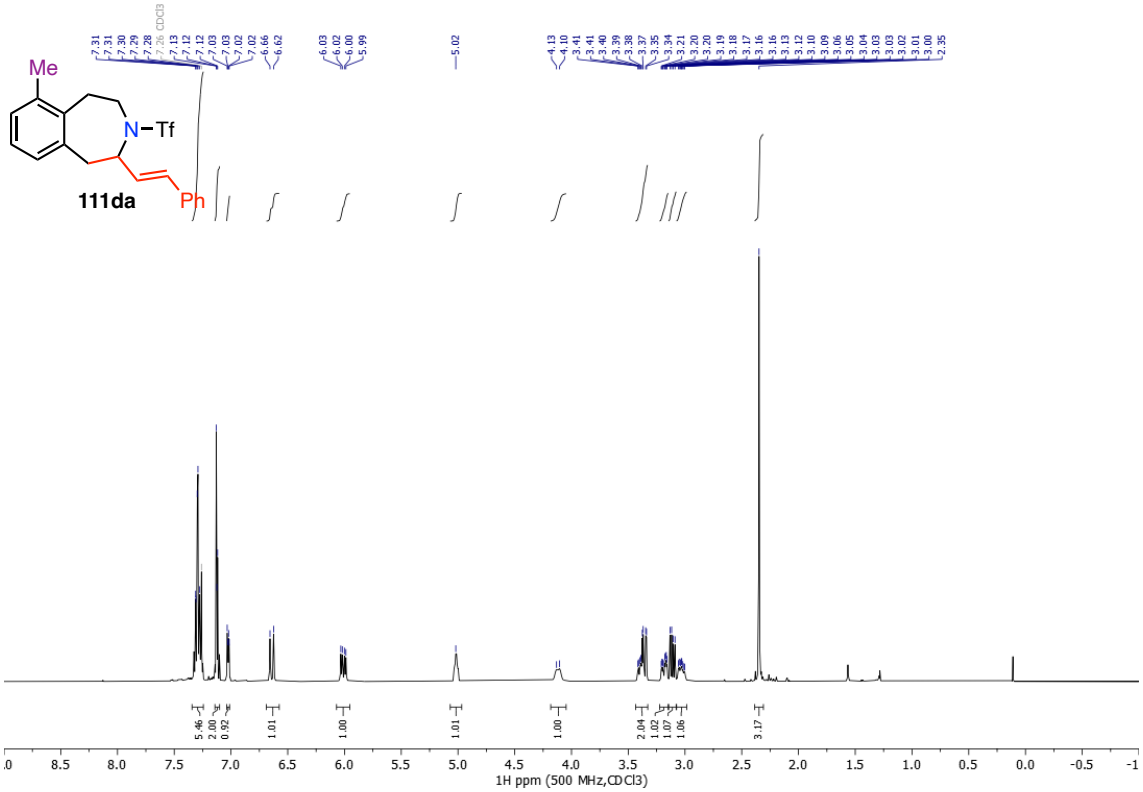



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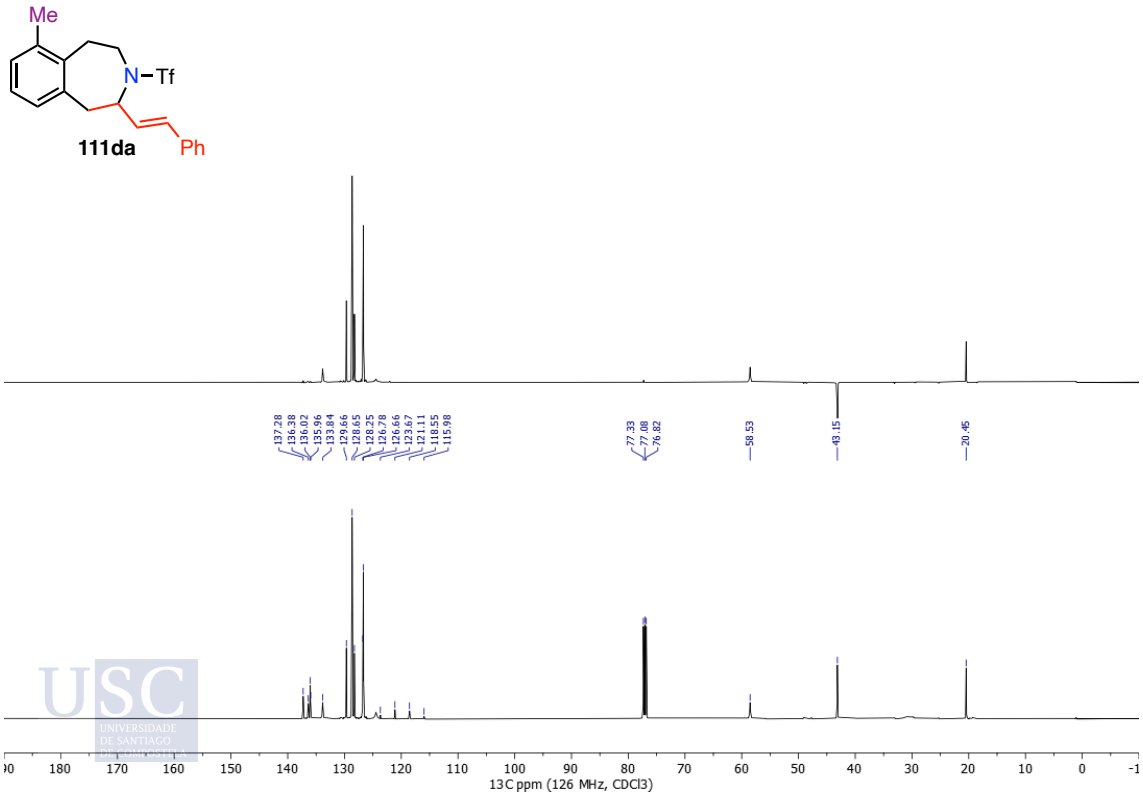



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)

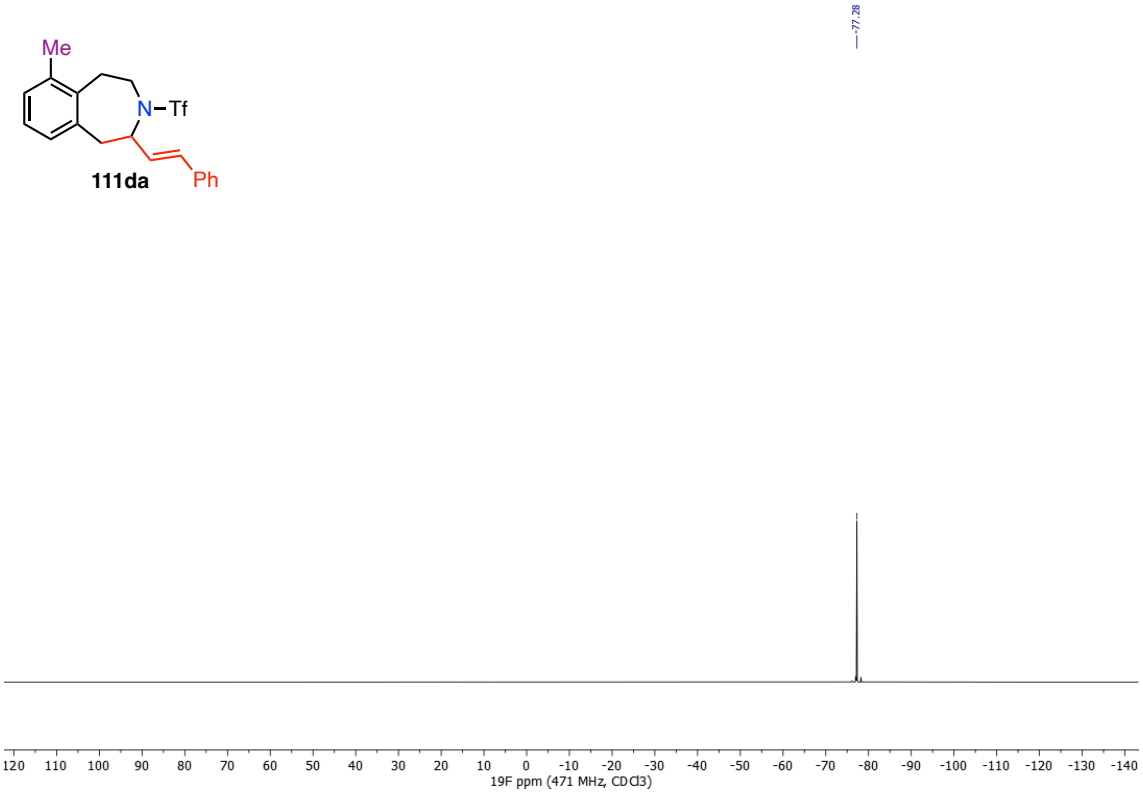



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$^{19}$F-NMR (471 MHz). Solvent ($CDCl_3$)

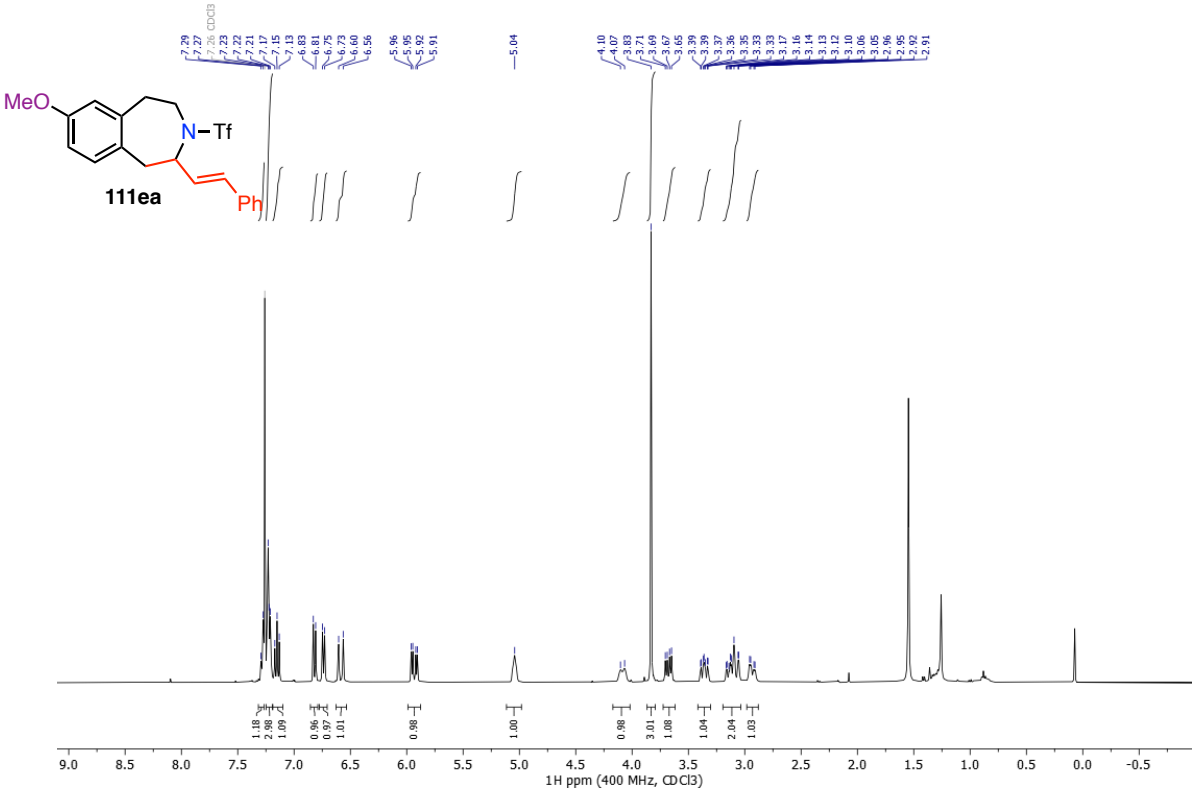



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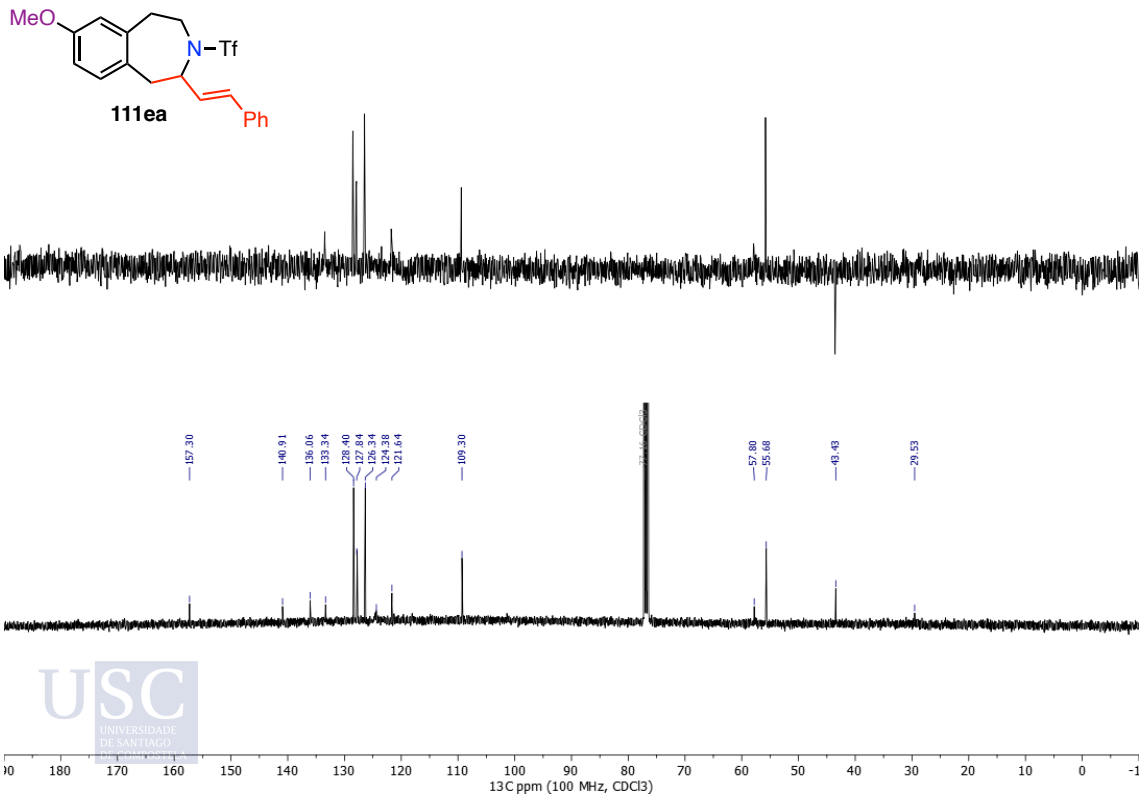



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$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)



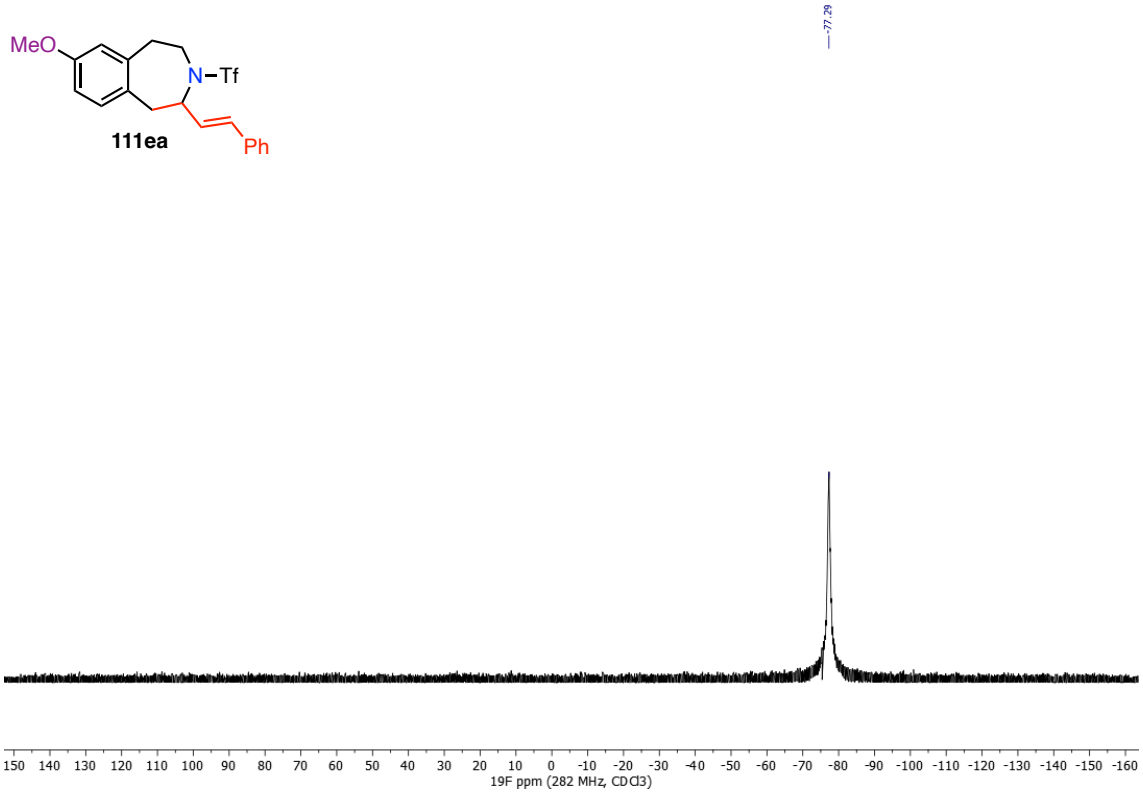

$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)



$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

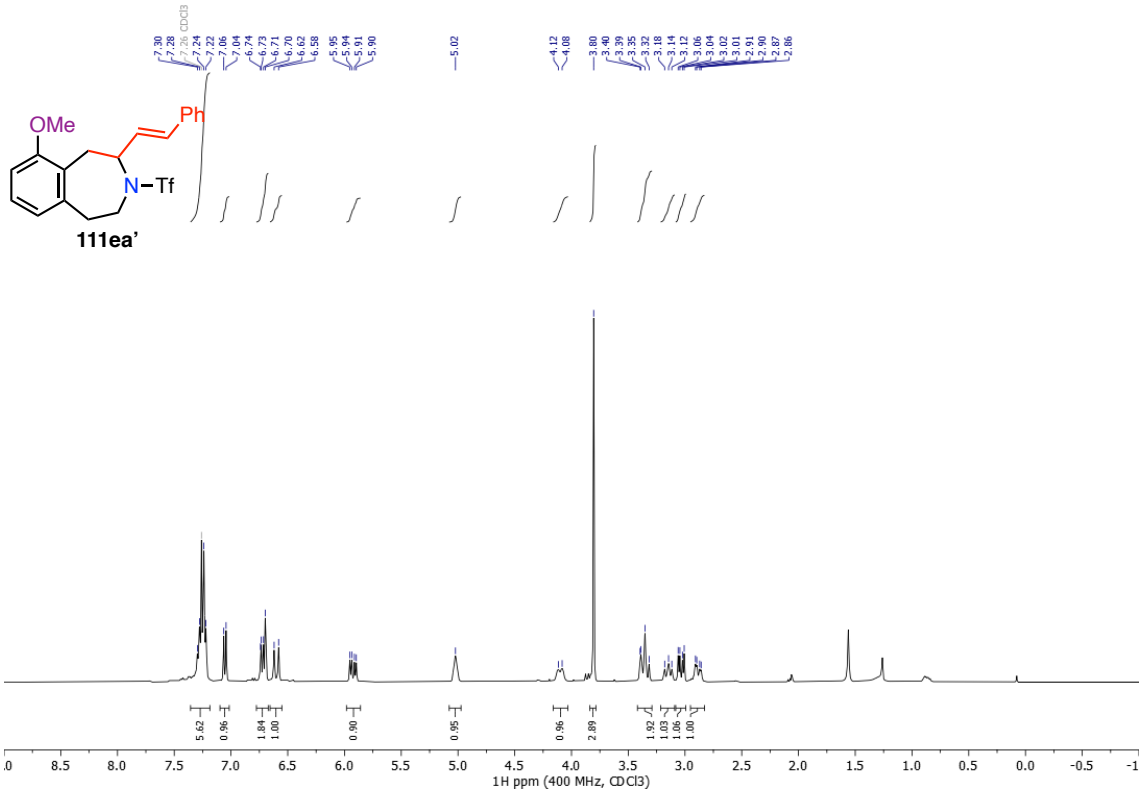



**111ea**

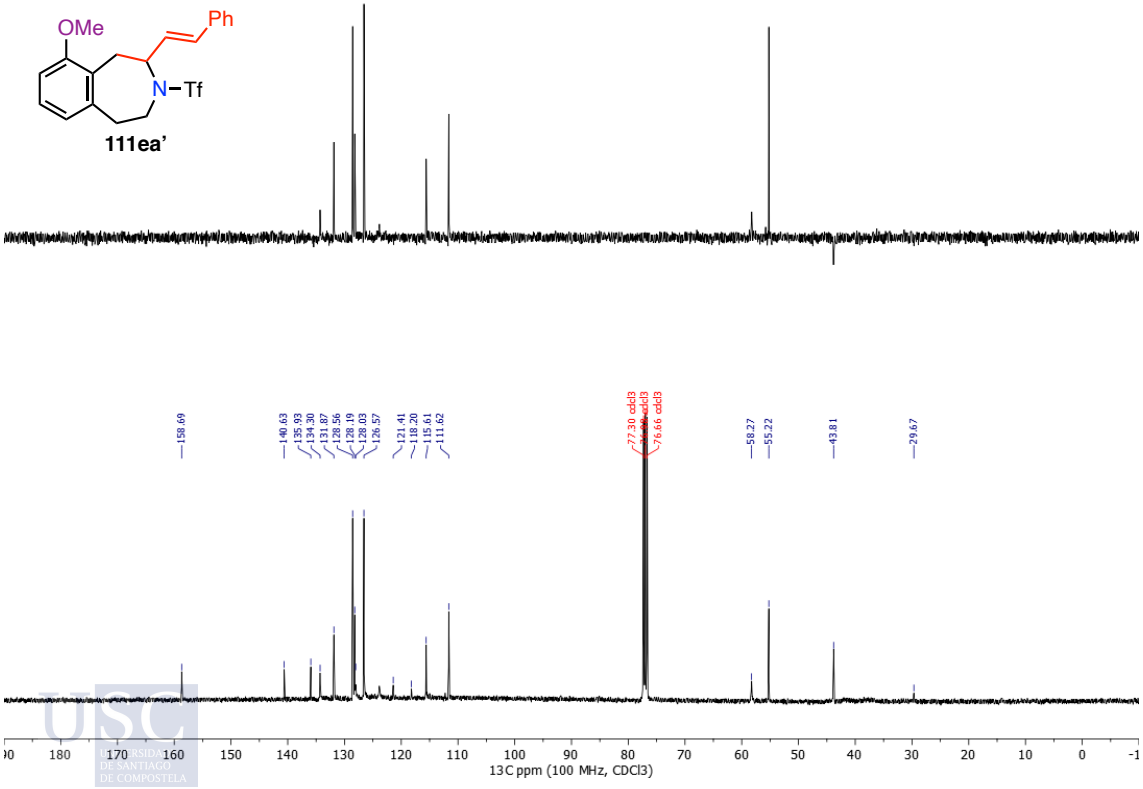



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$^{1}$H-NMR (400 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (101 MHz). Solvent ($CDCl_3$)

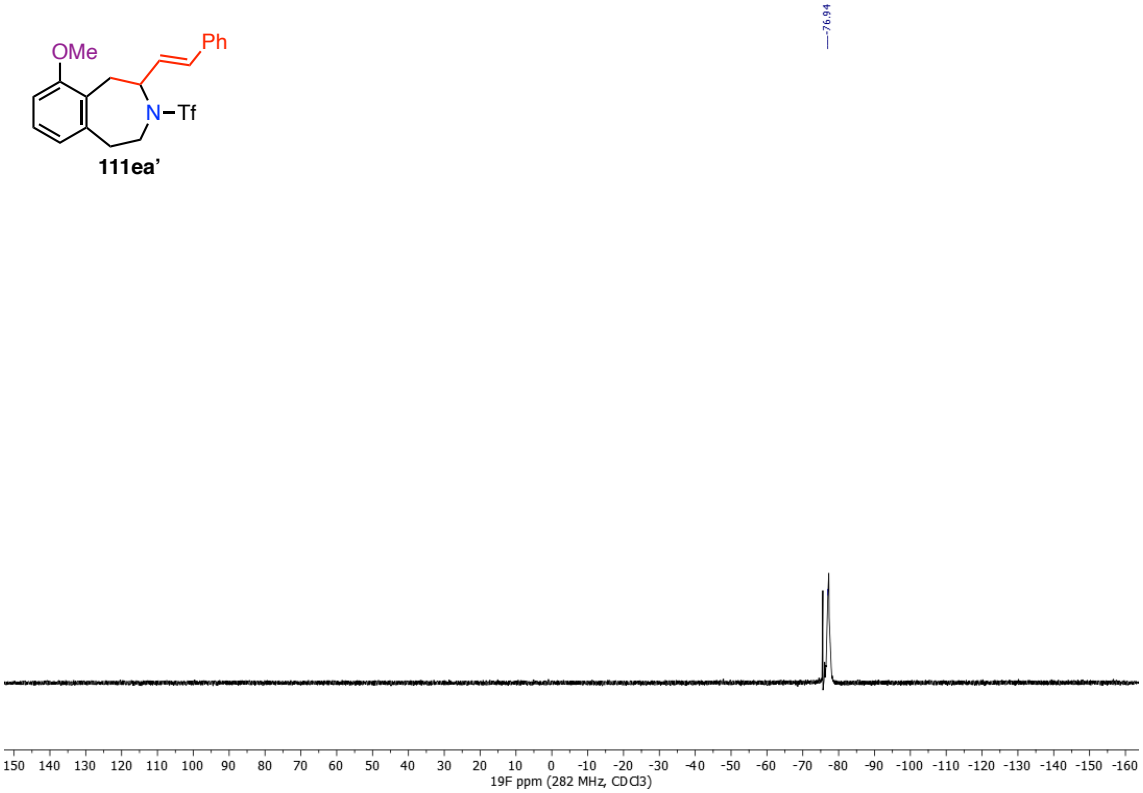



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$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

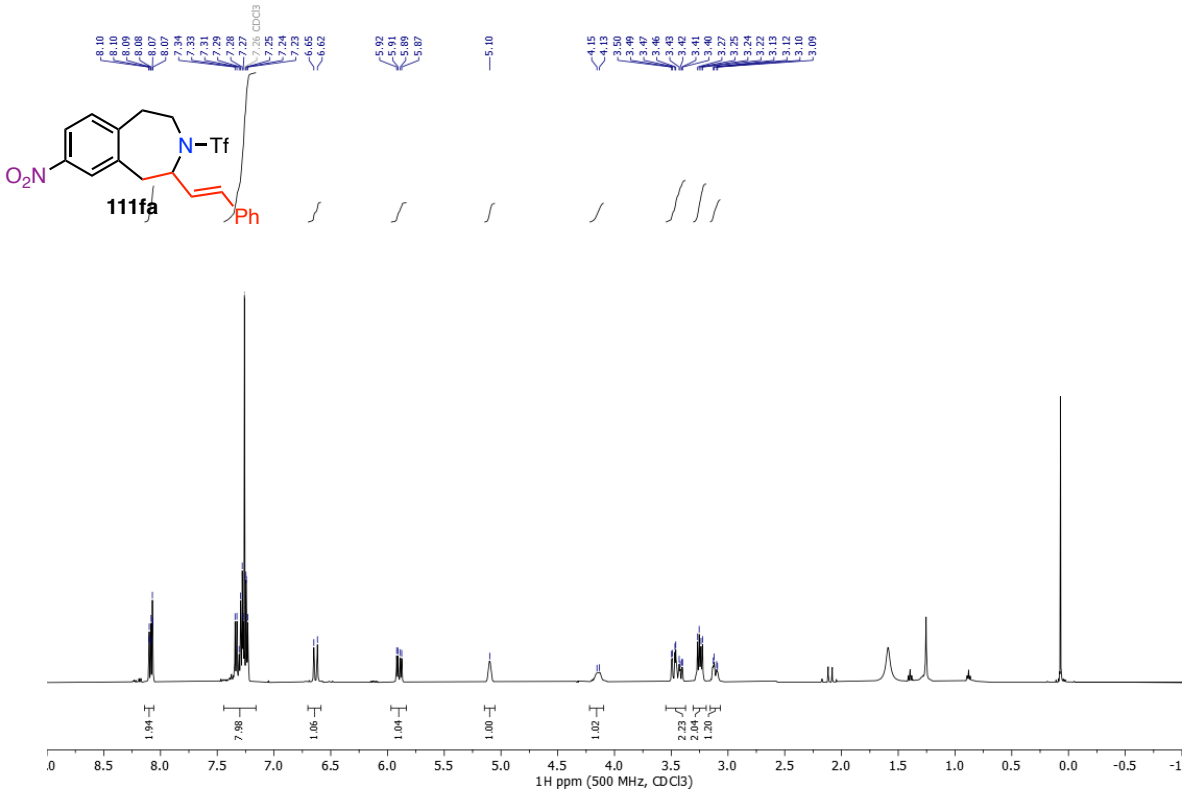



**111ea'**

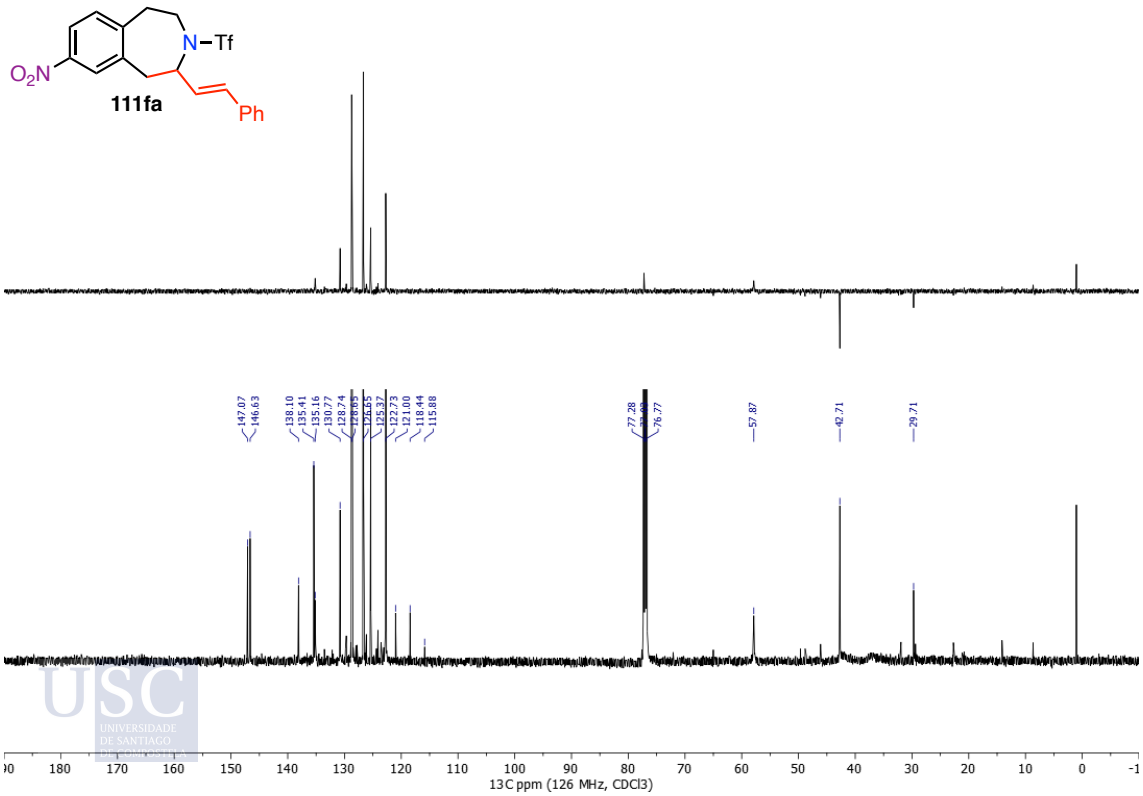



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)



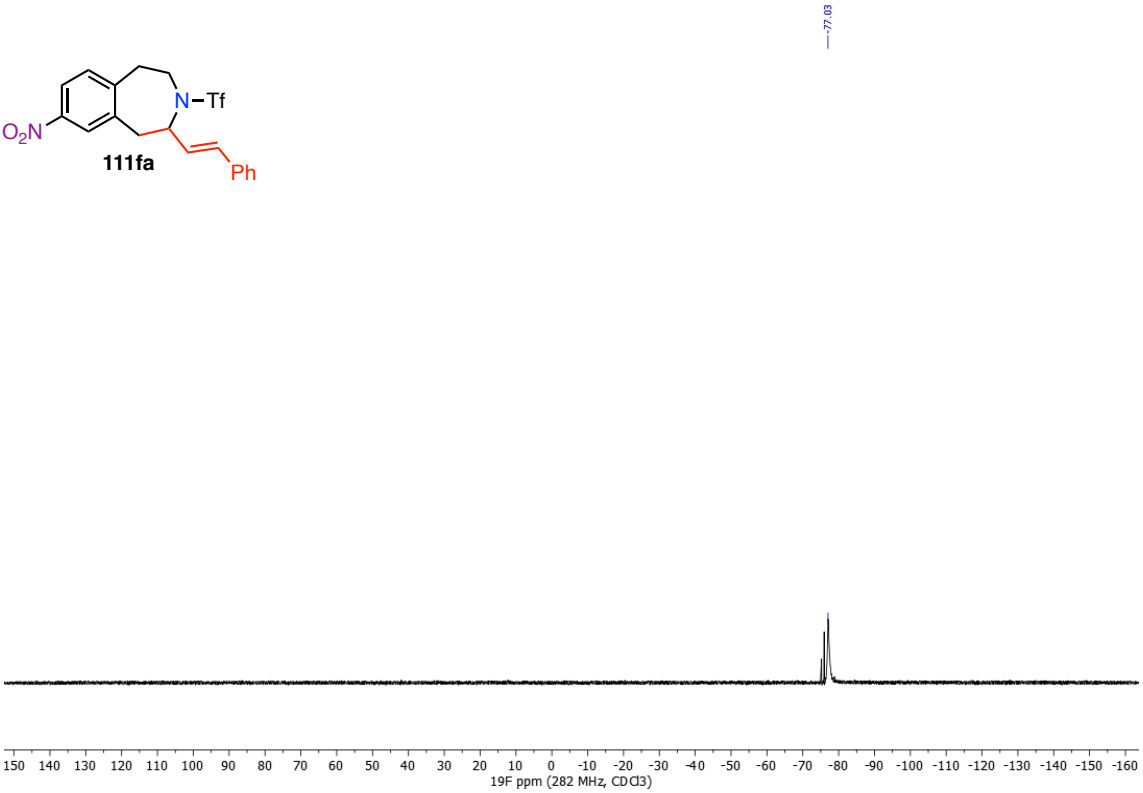

$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)



$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

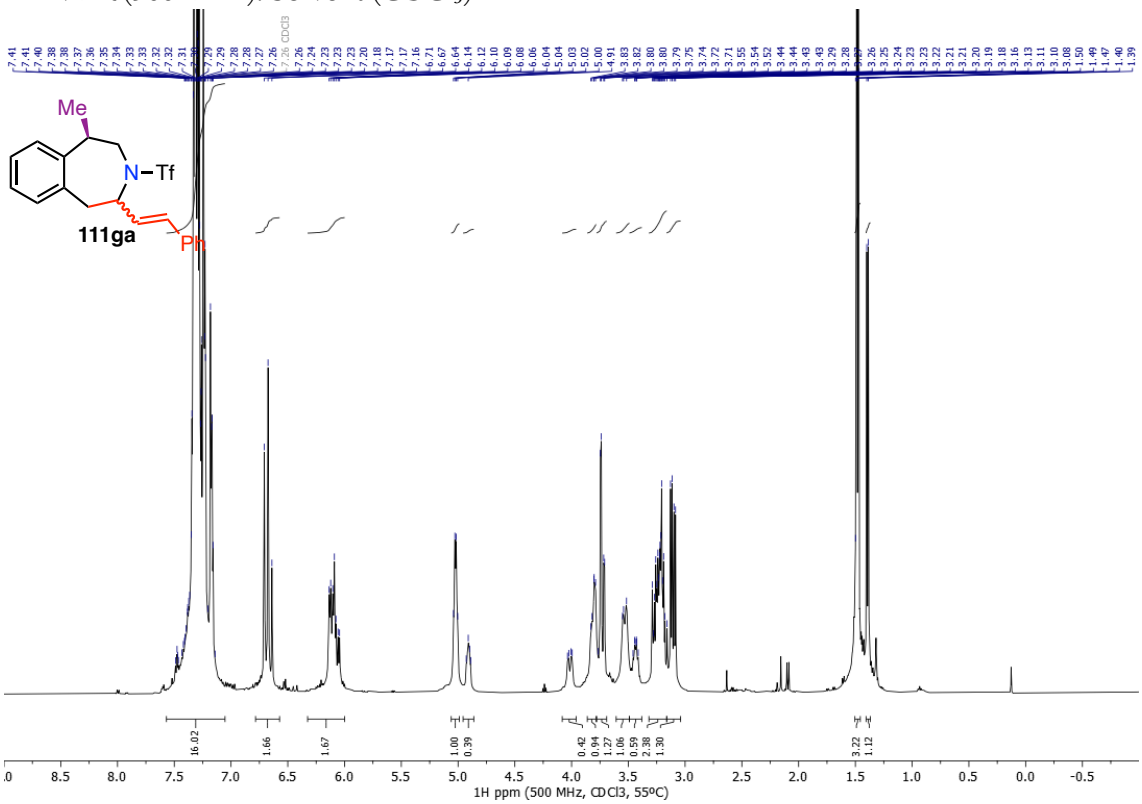



**111fa**

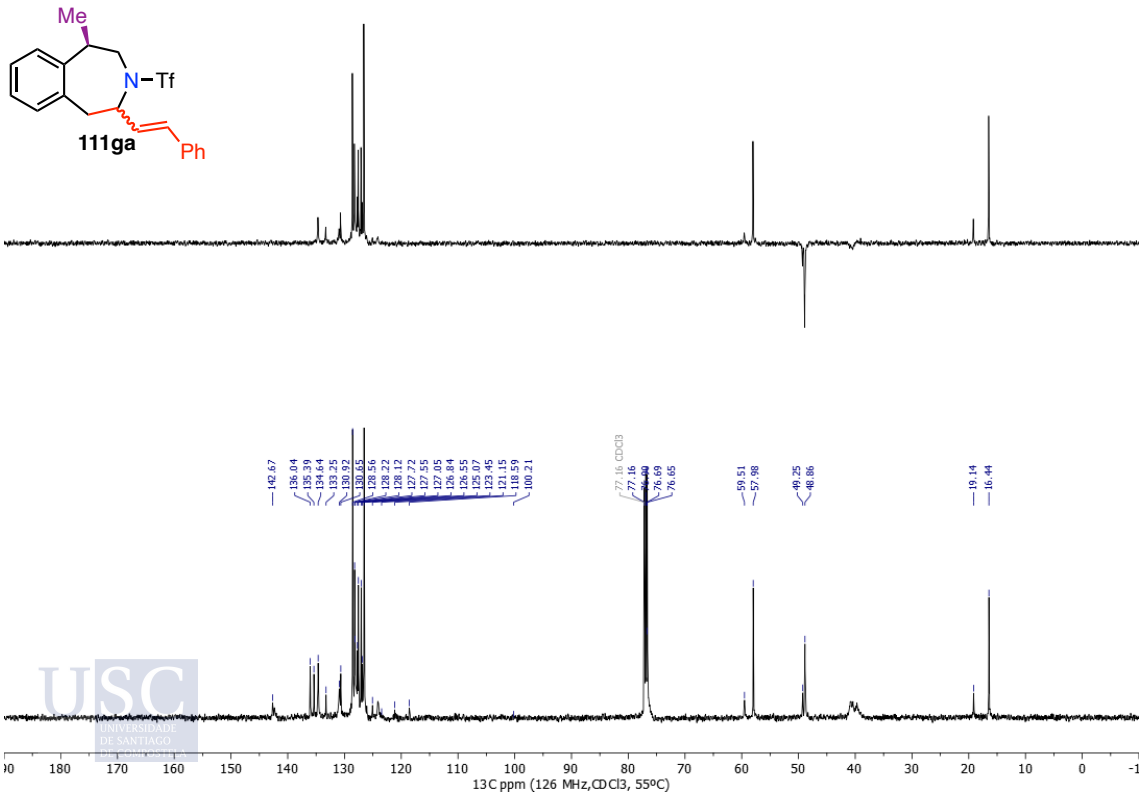



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)

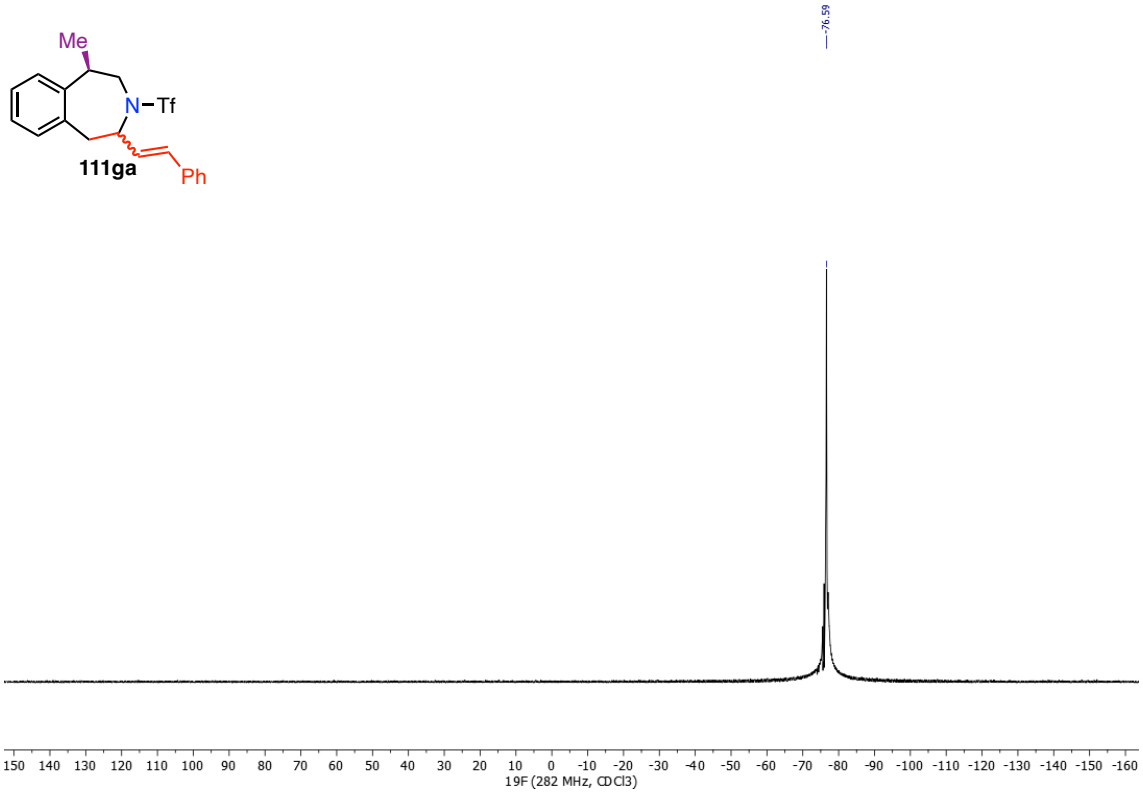



$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)



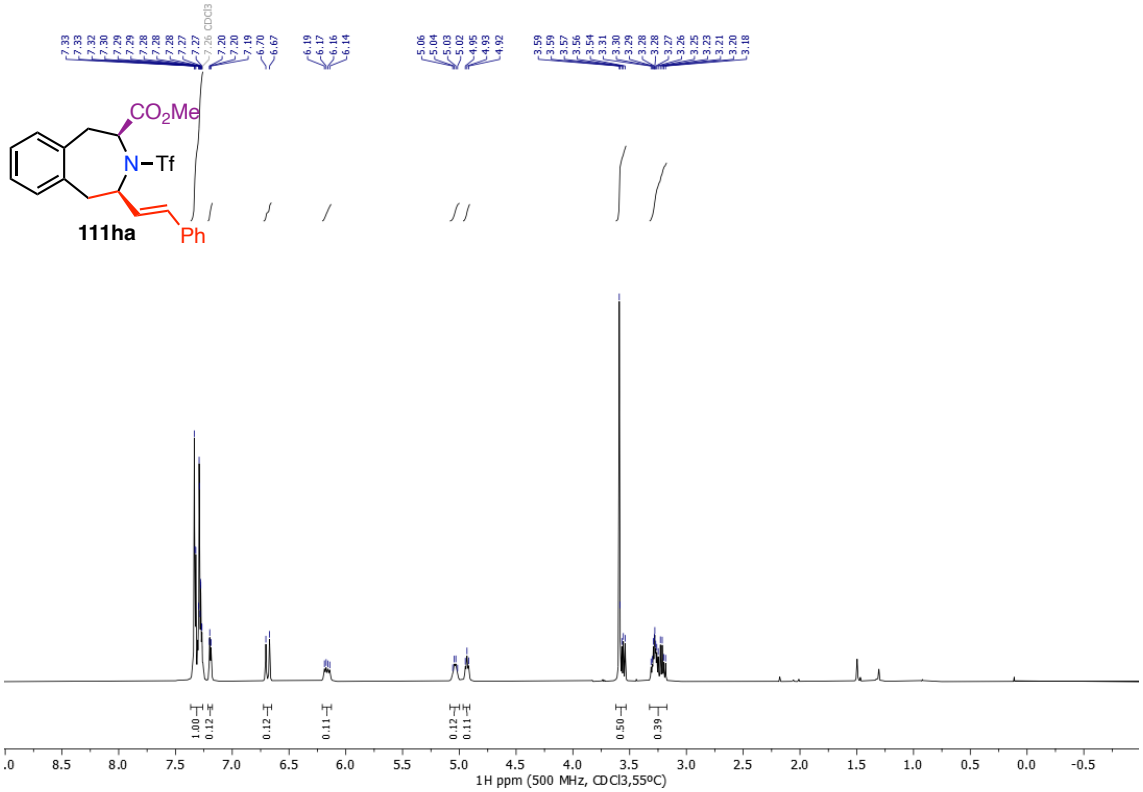

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$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

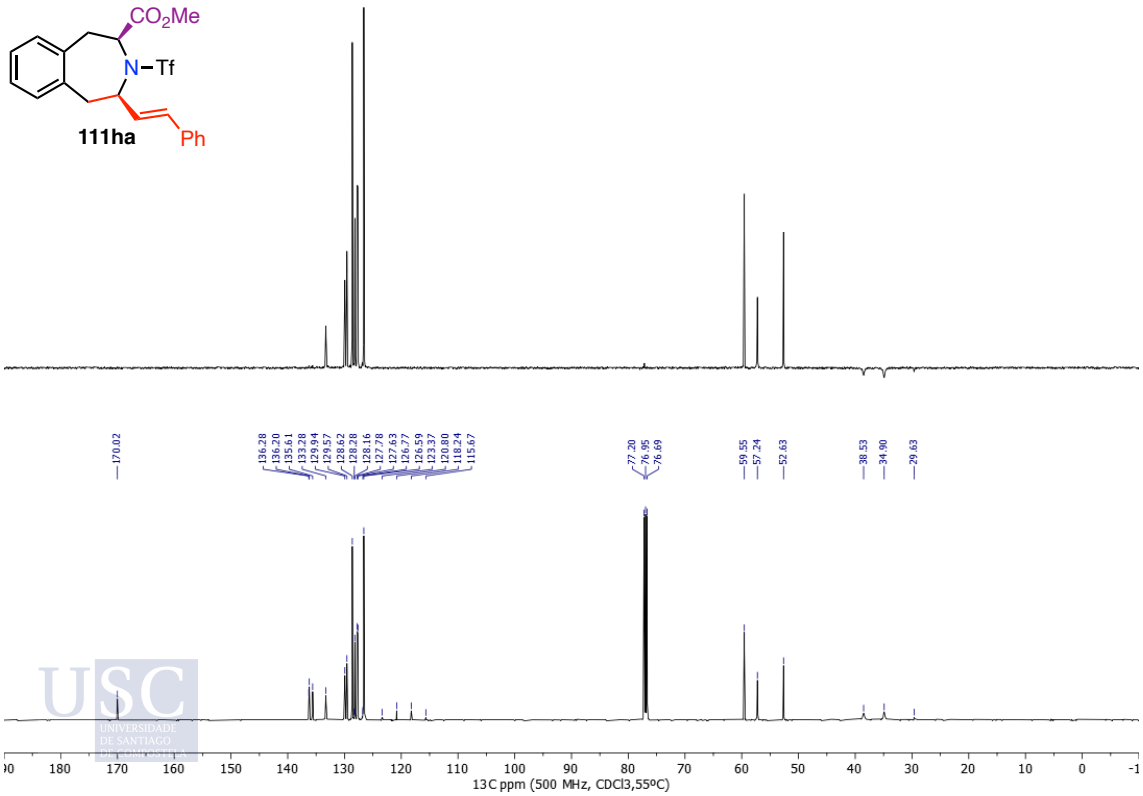



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)

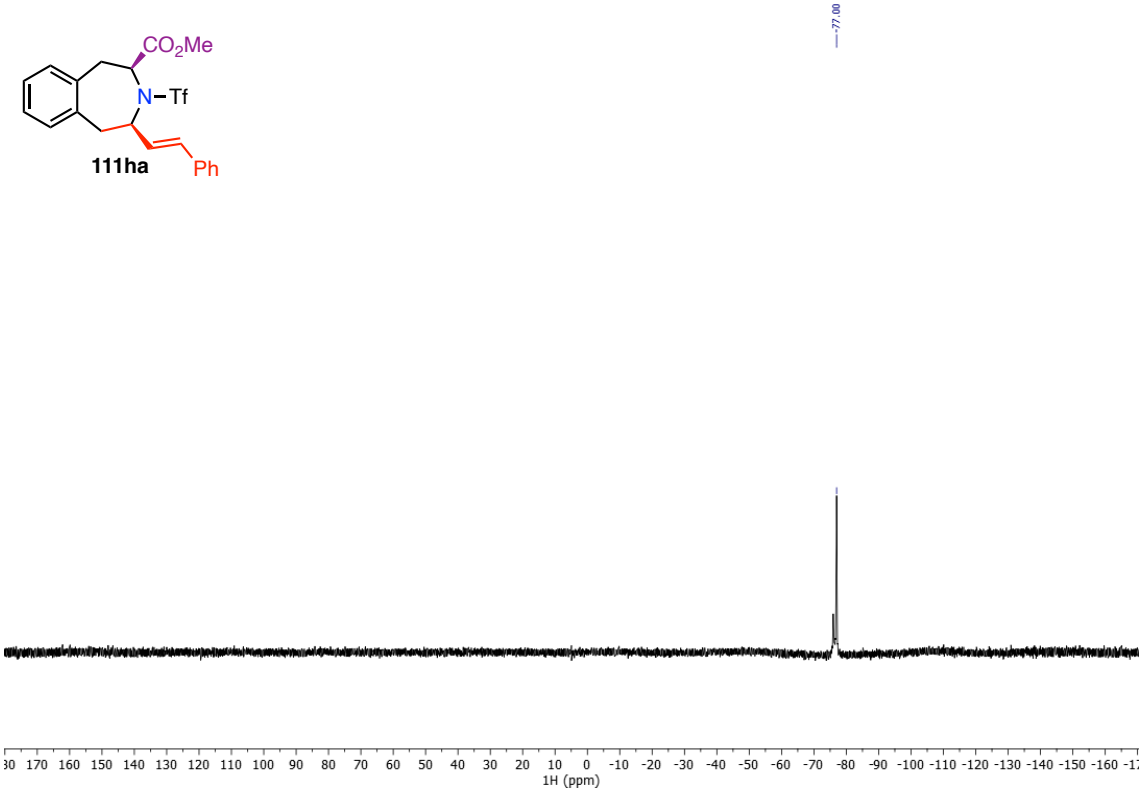



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$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

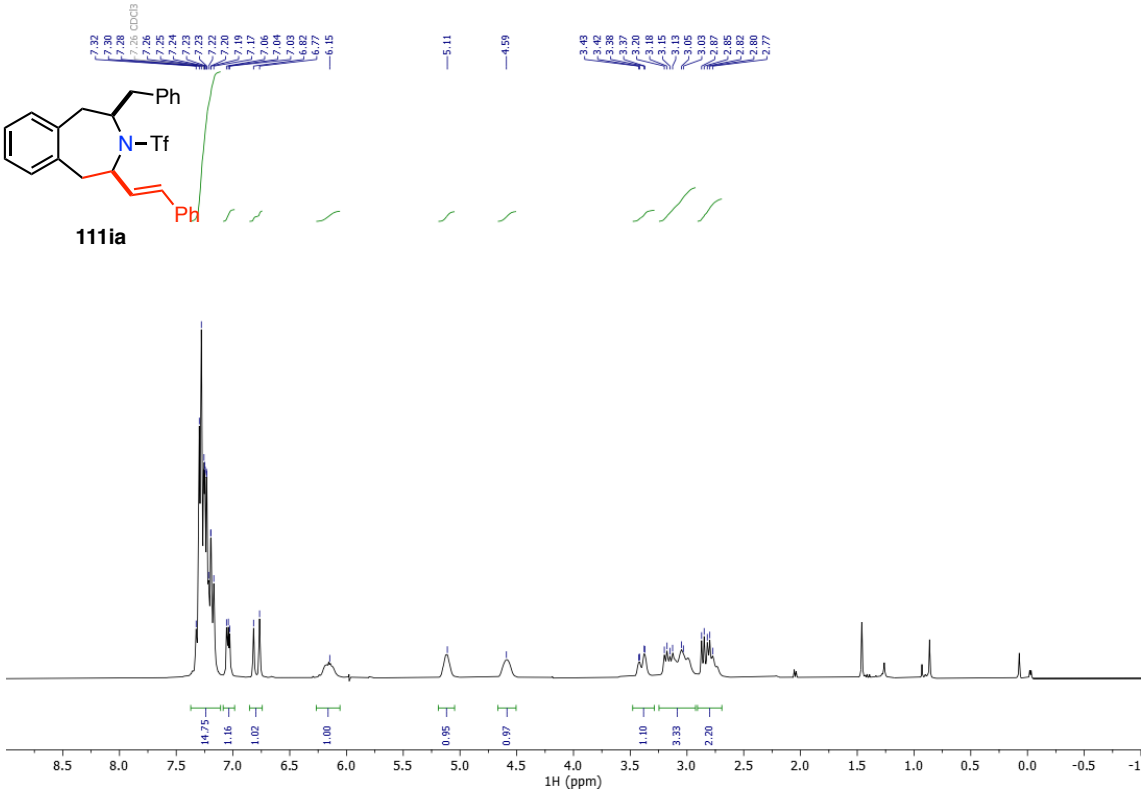



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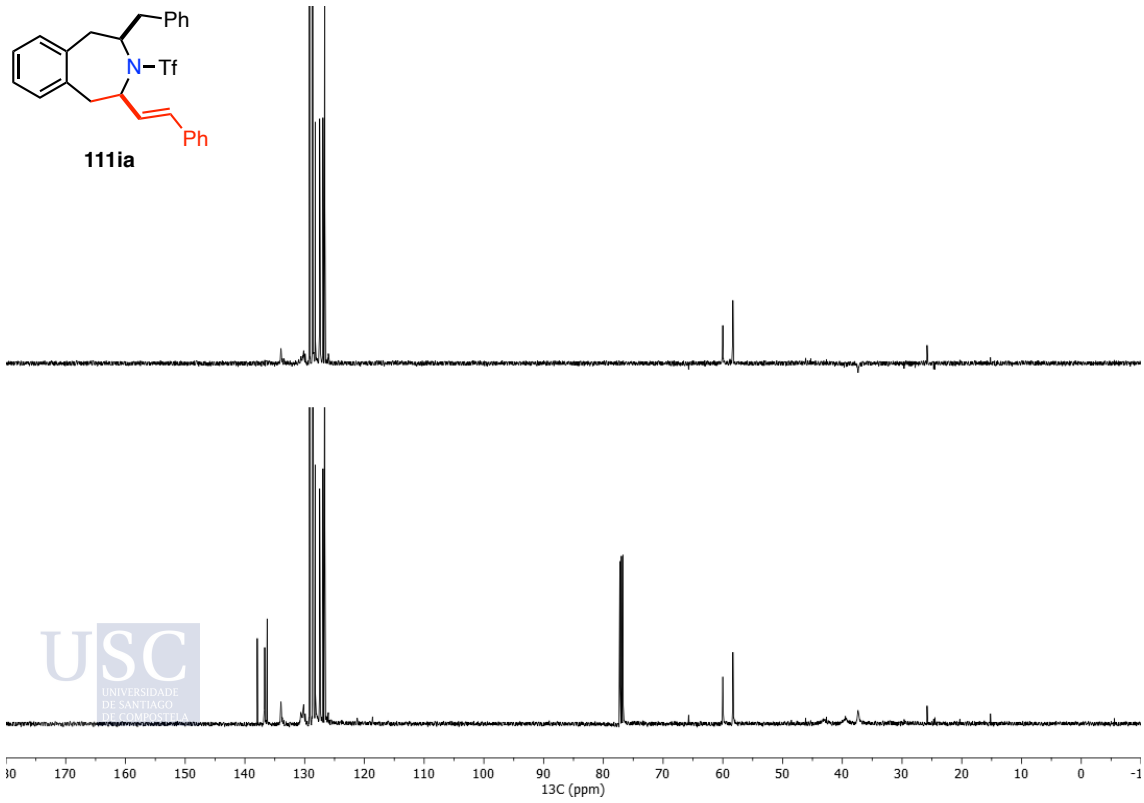



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)

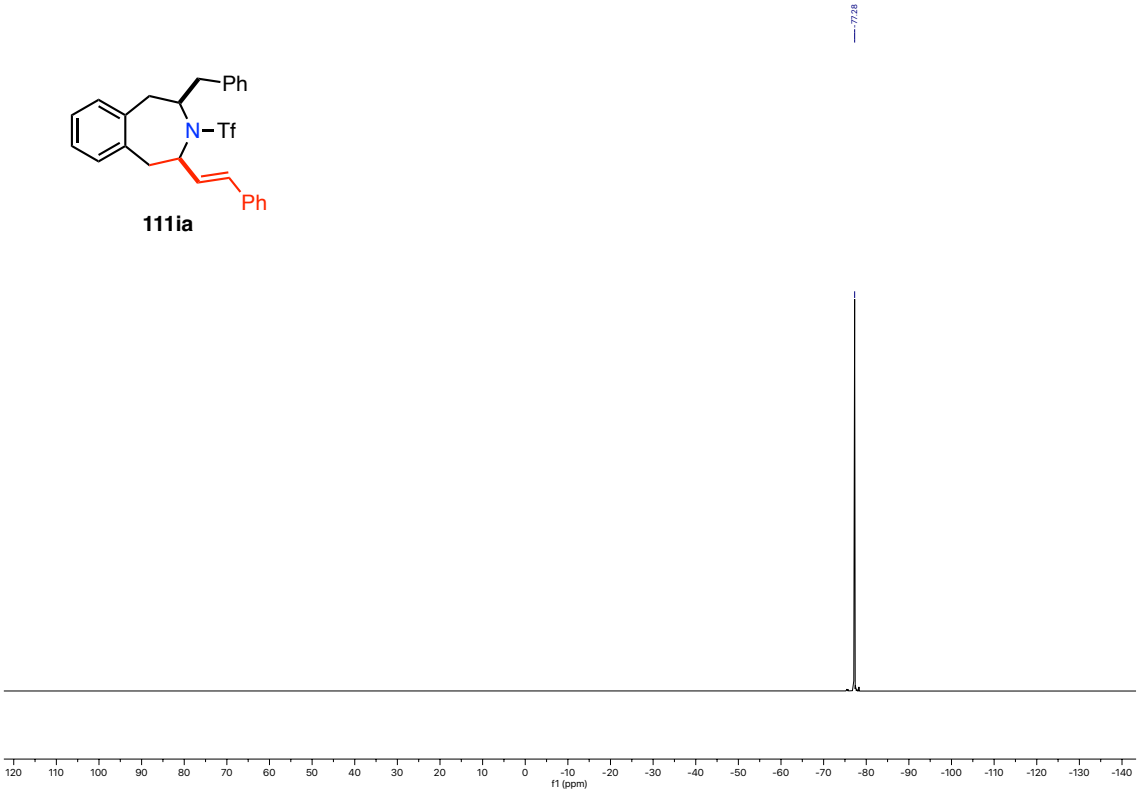



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$^{19}$F-NMR (471 MHz). Solvent ($CDCl_3$)

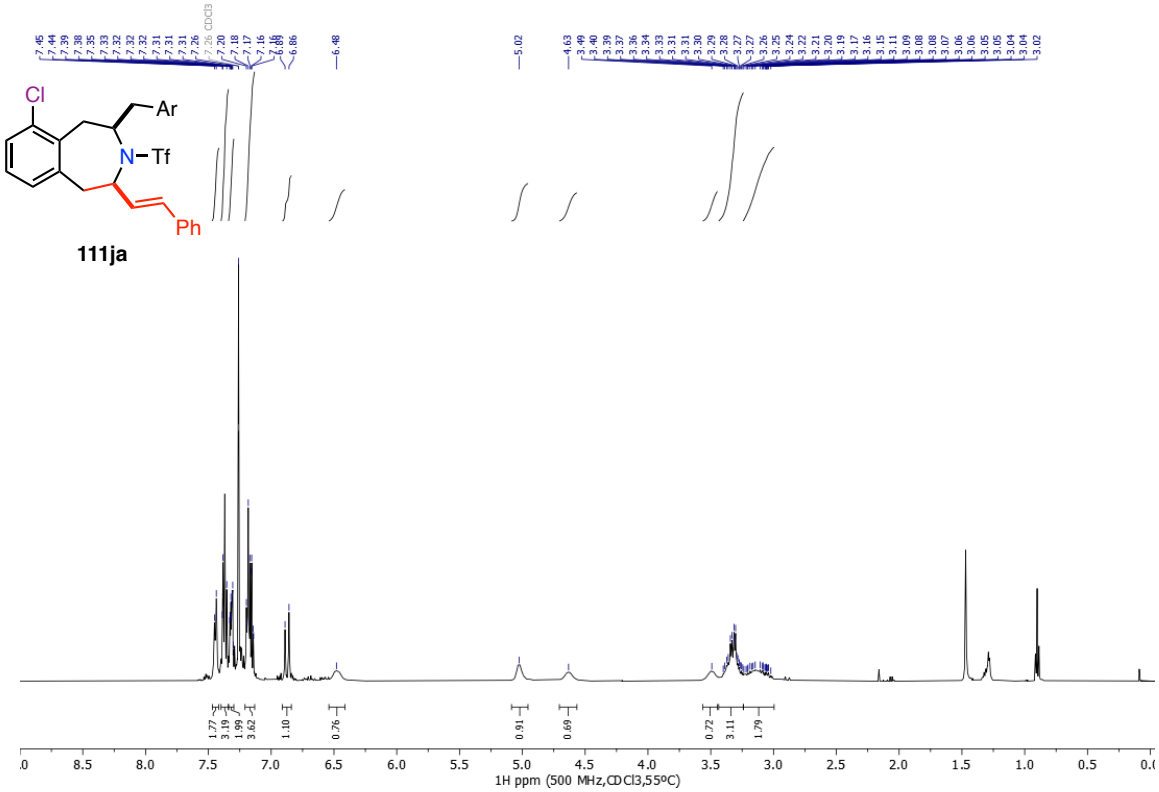



**111ia**

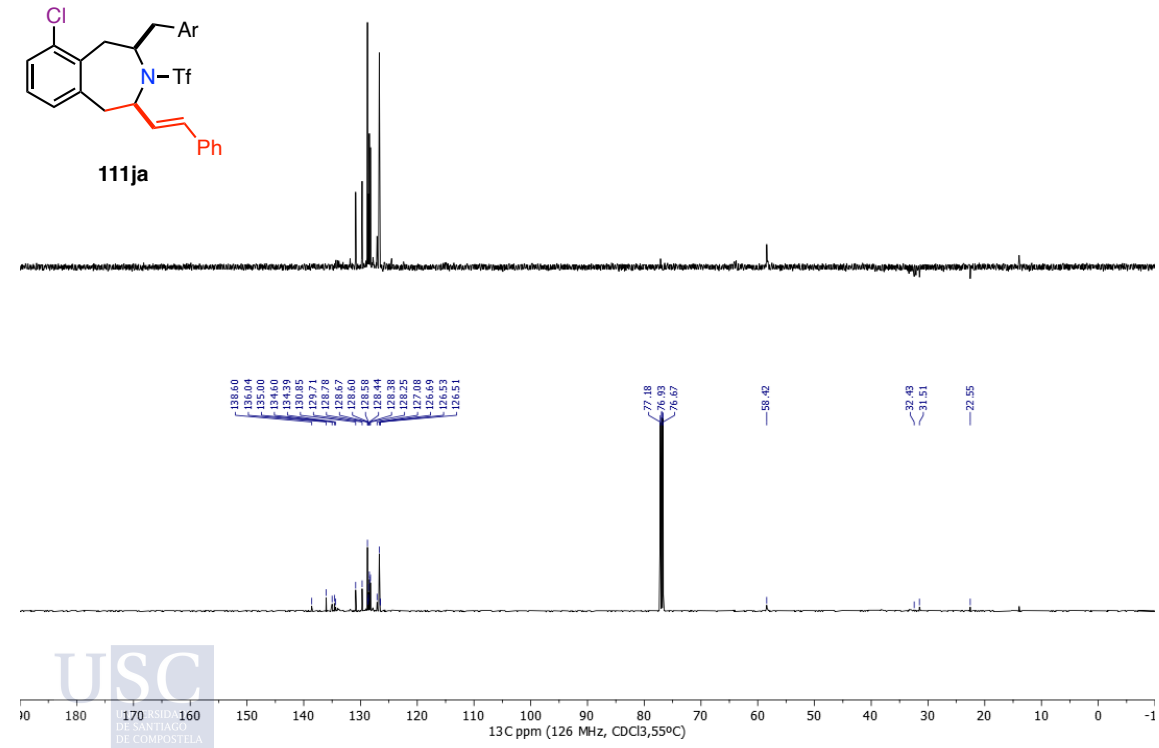



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)



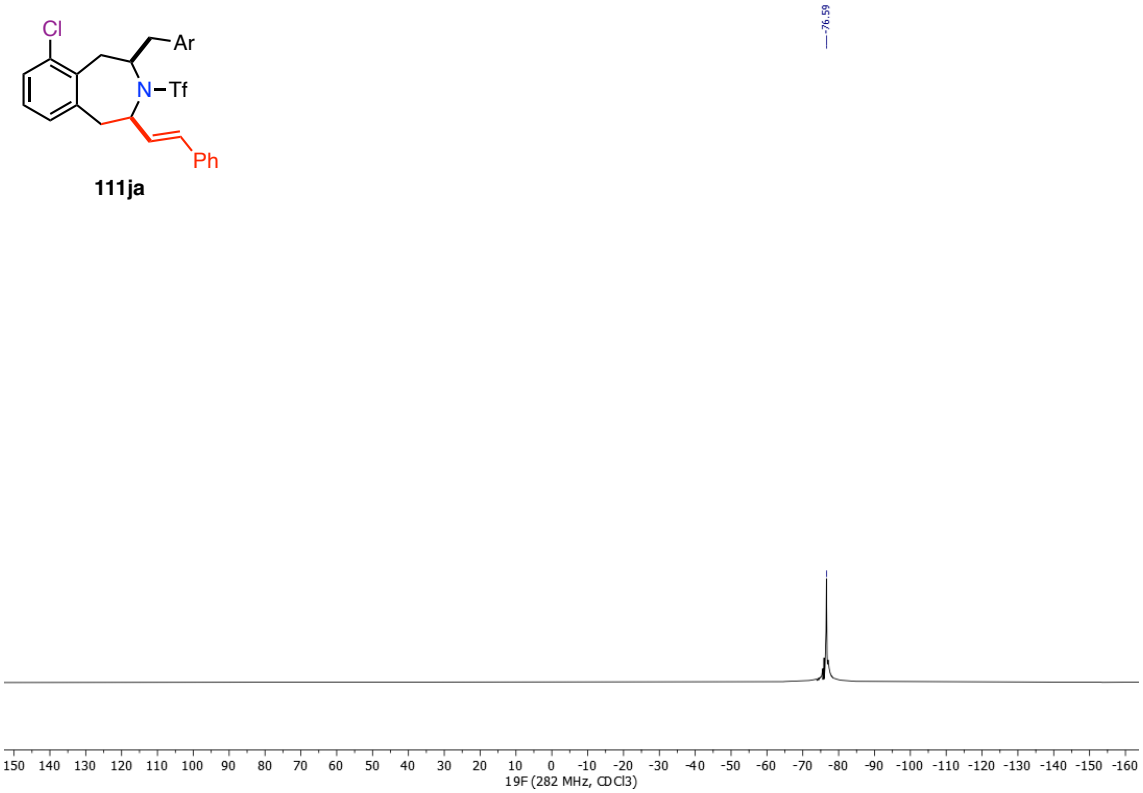

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$^{19}$F-NMR (282 MHz). Solvent ($CDCl_3$)

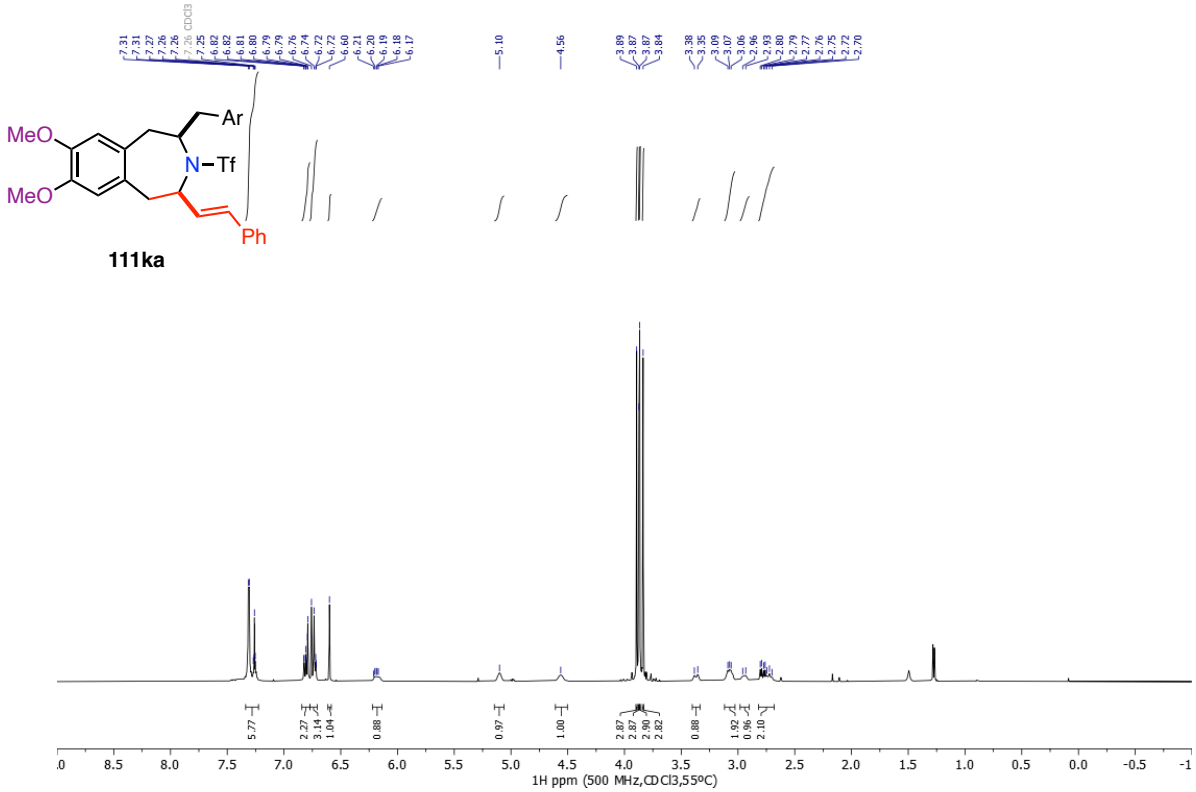



**111ja**

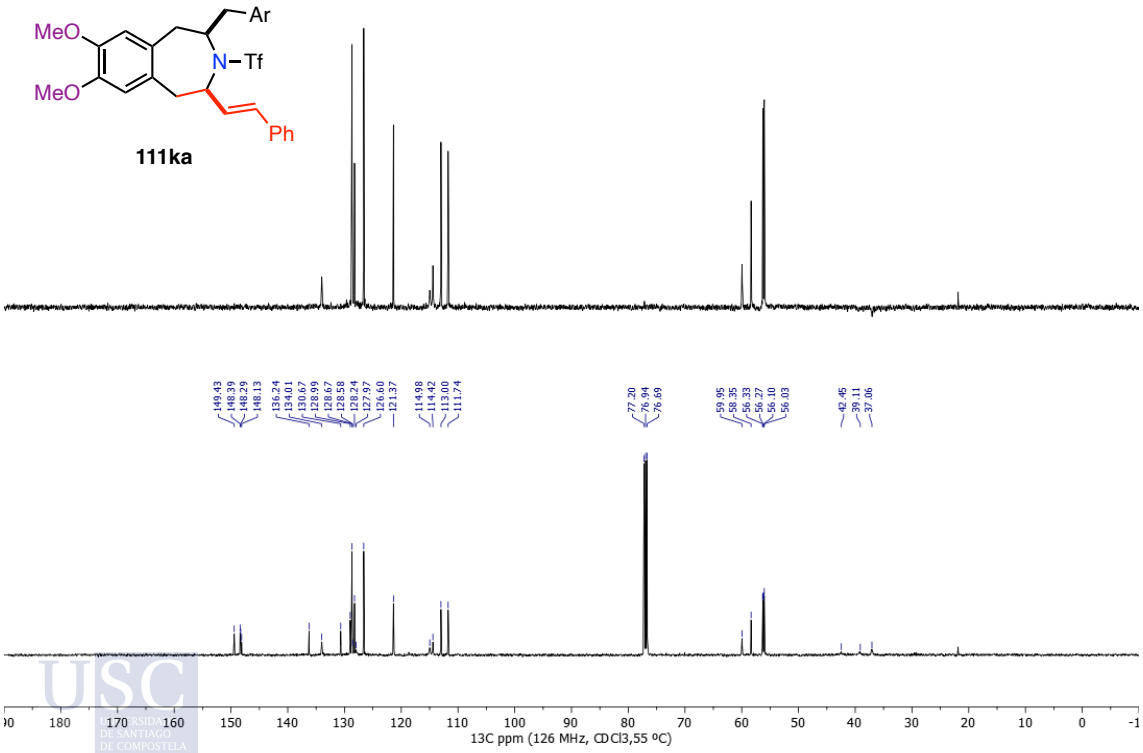



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)

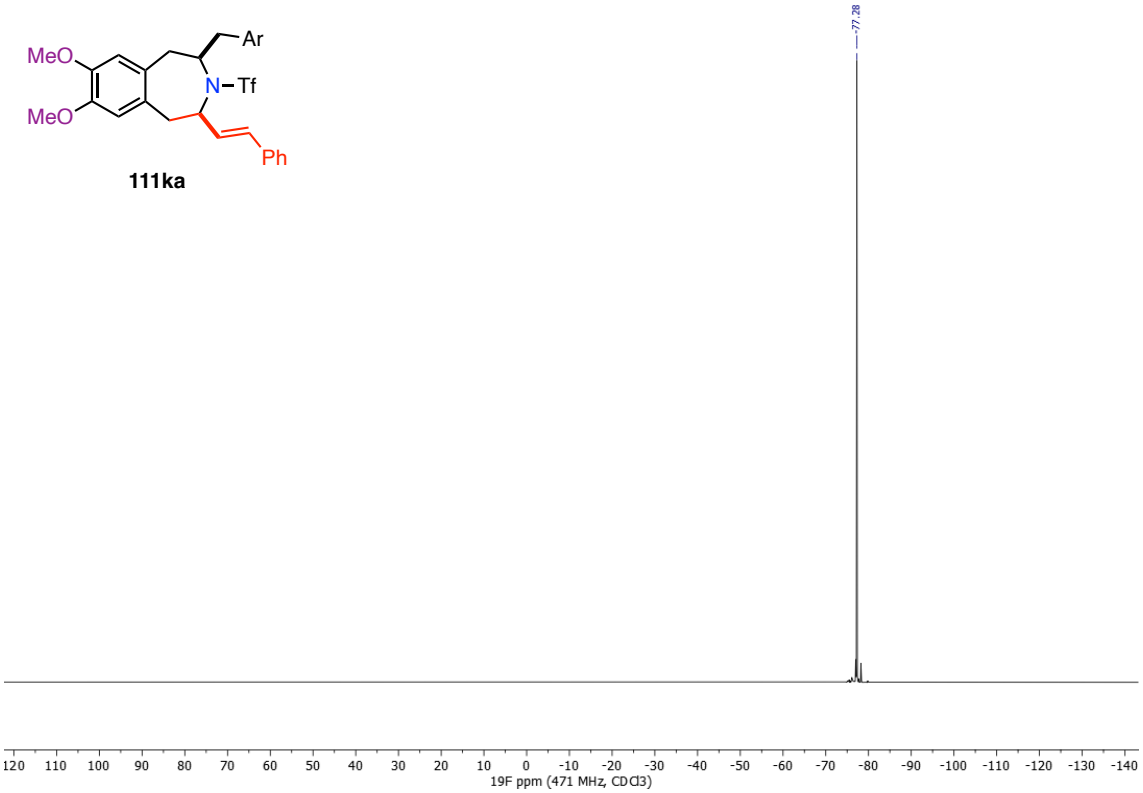



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$^{19}$F-NMR (471 MHz). Solvent ($CDCl_3$)

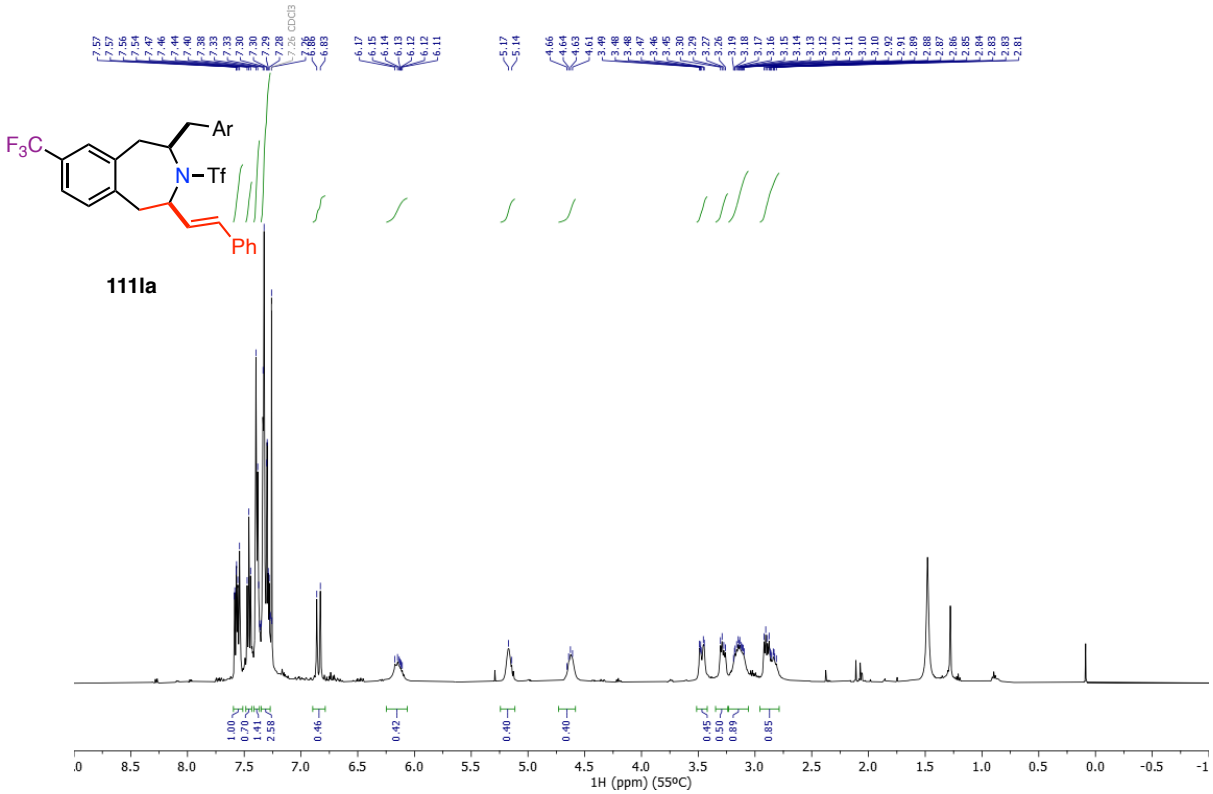



**111ka**

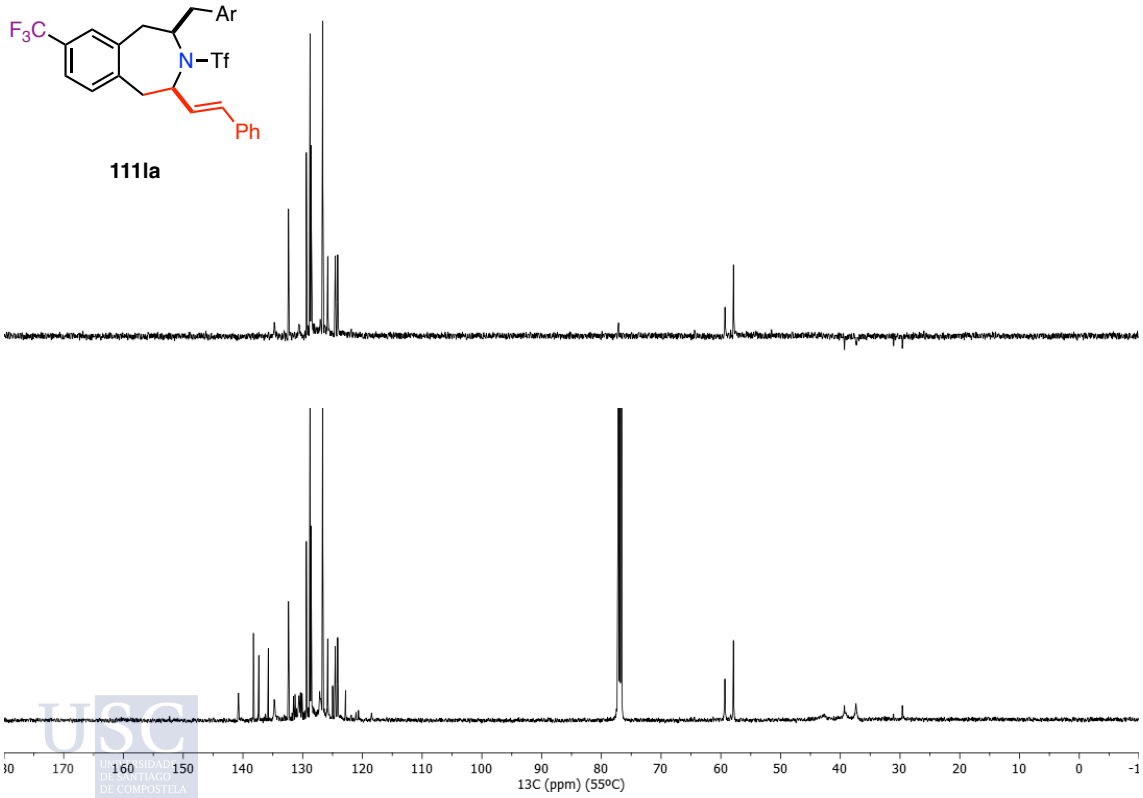



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)

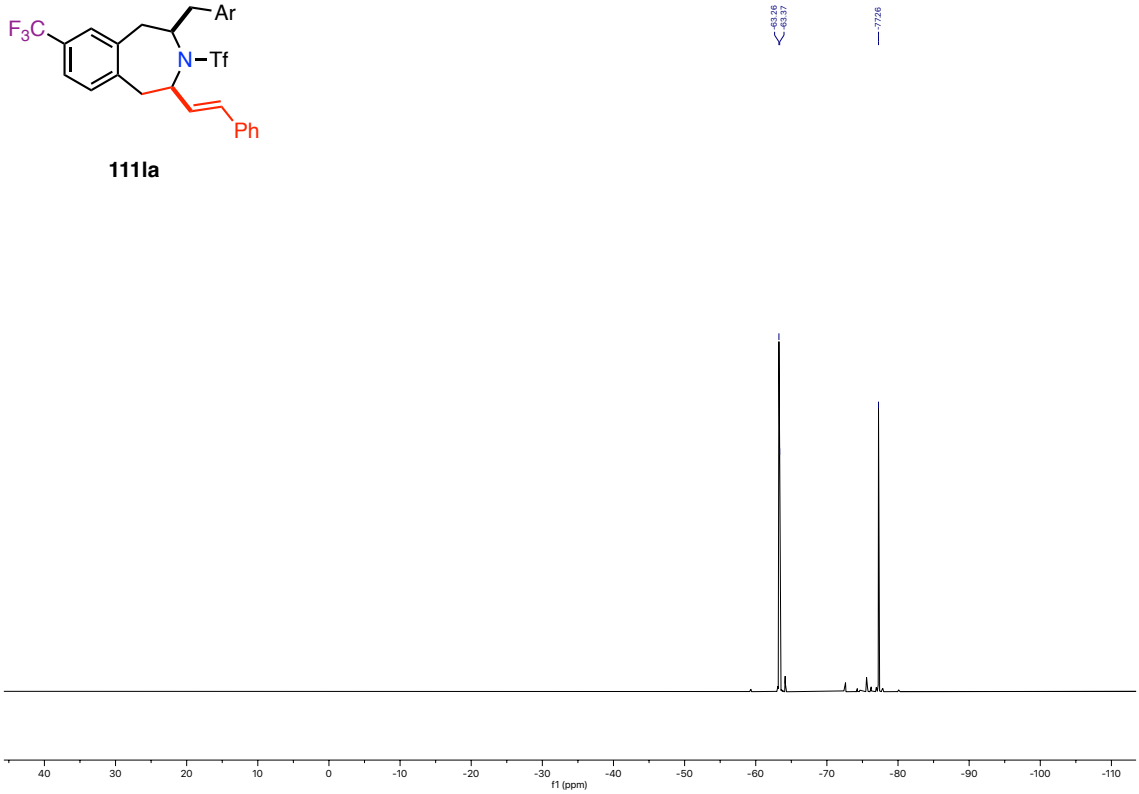



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$^{19}$F-NMR (2471 MHz). Solvent ($CDCl_3$)

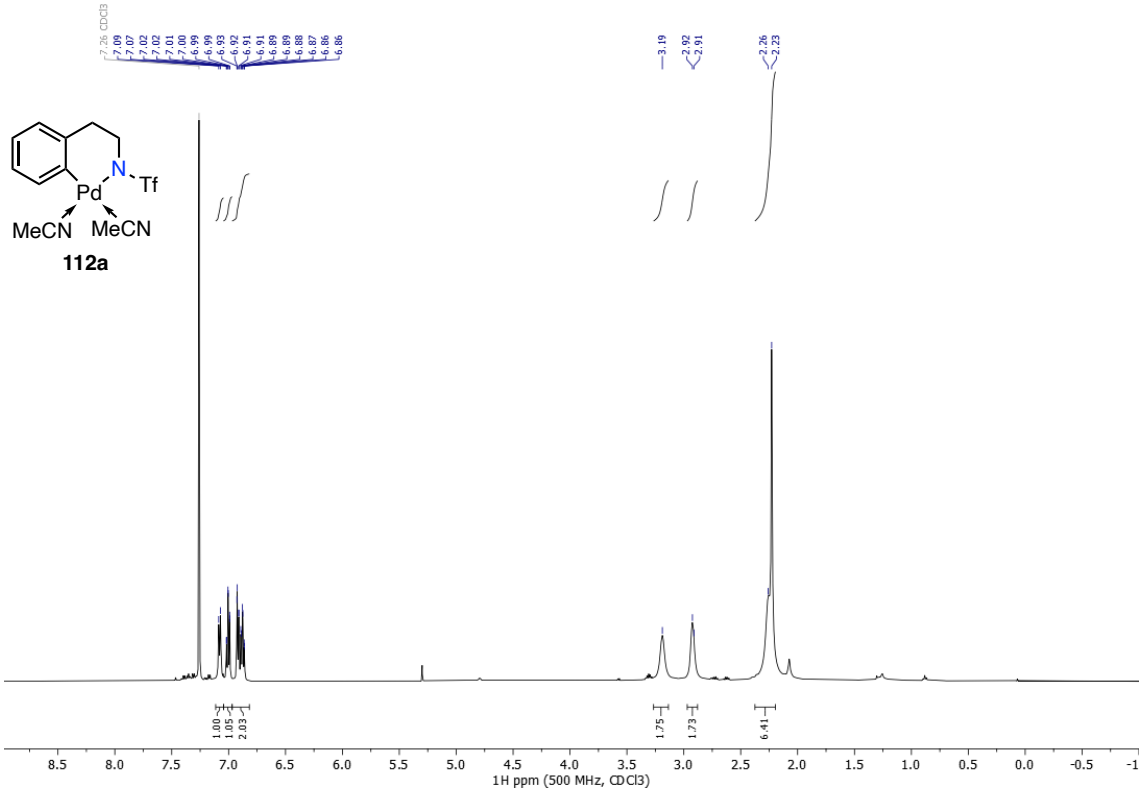



**111la**

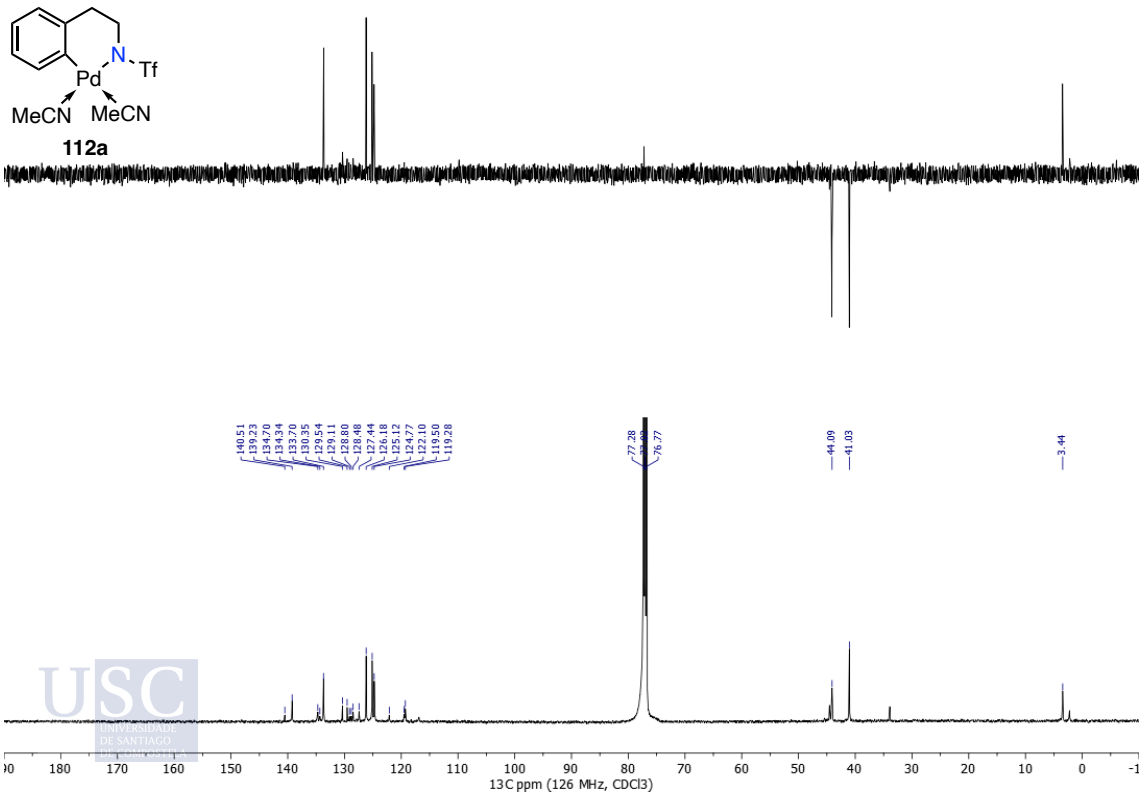



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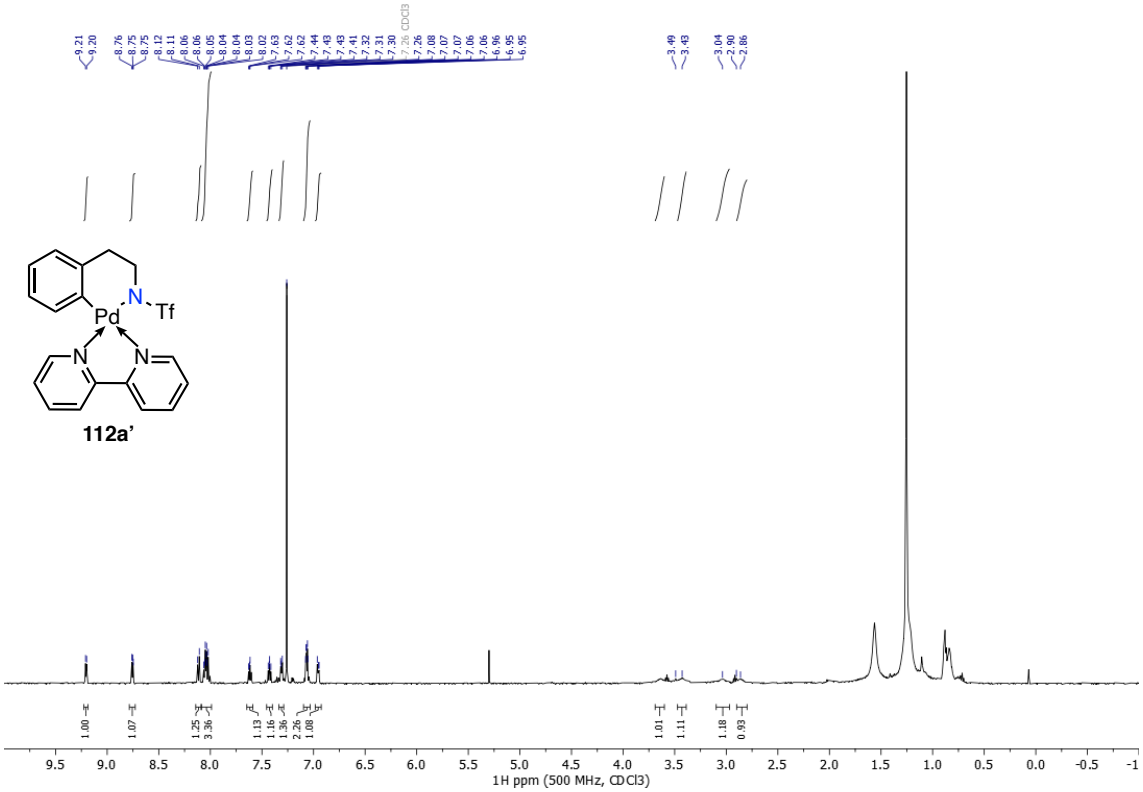
$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)



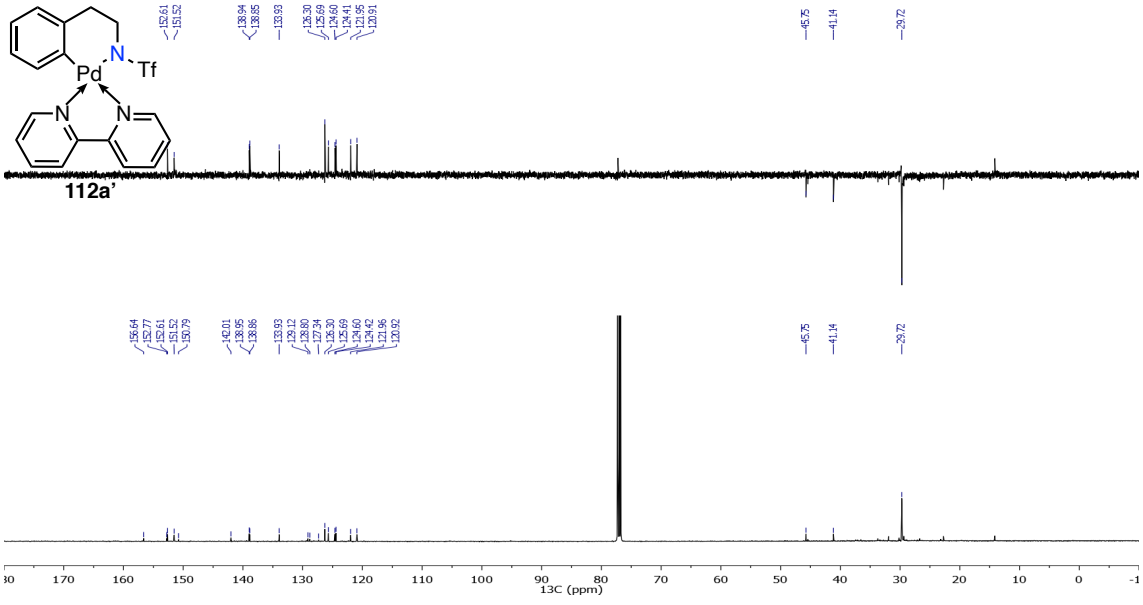

$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)



$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)




$^{13}$C-NMR (126 MHz). Solvent ($CDCl_3$)

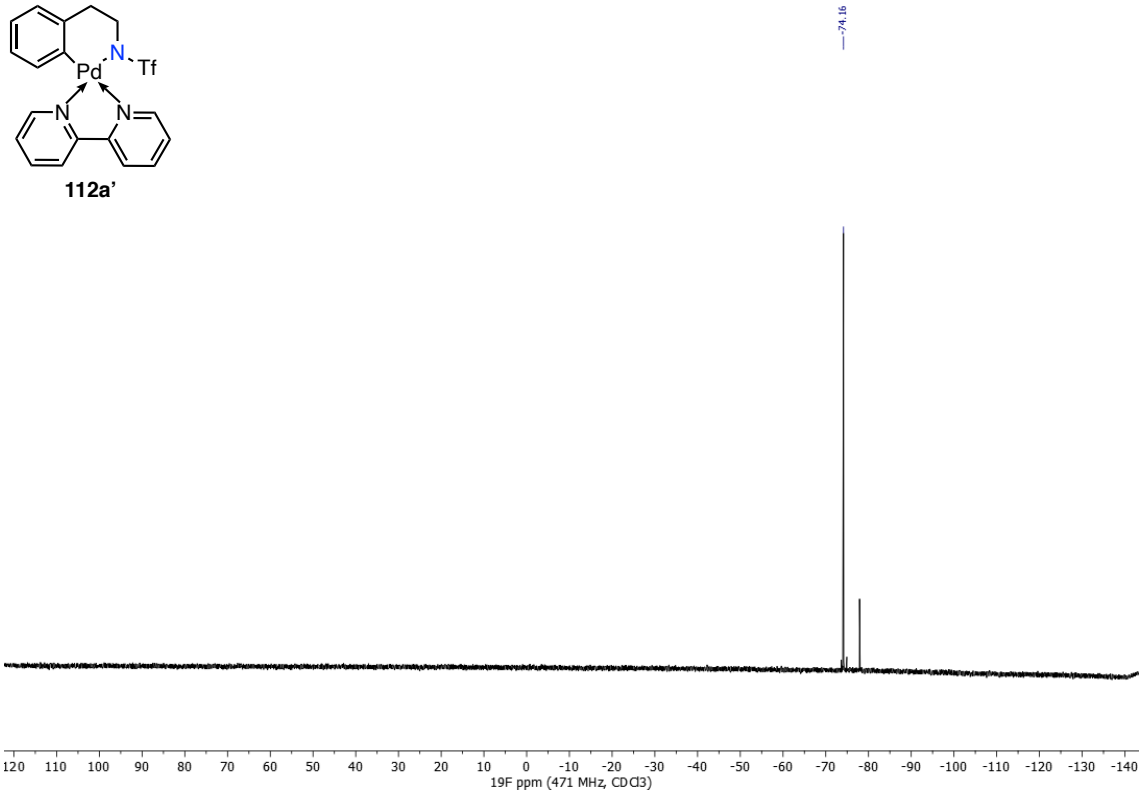



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$^{19}$F-NMR (471 MHz). Solvent ($CDCl_3$)

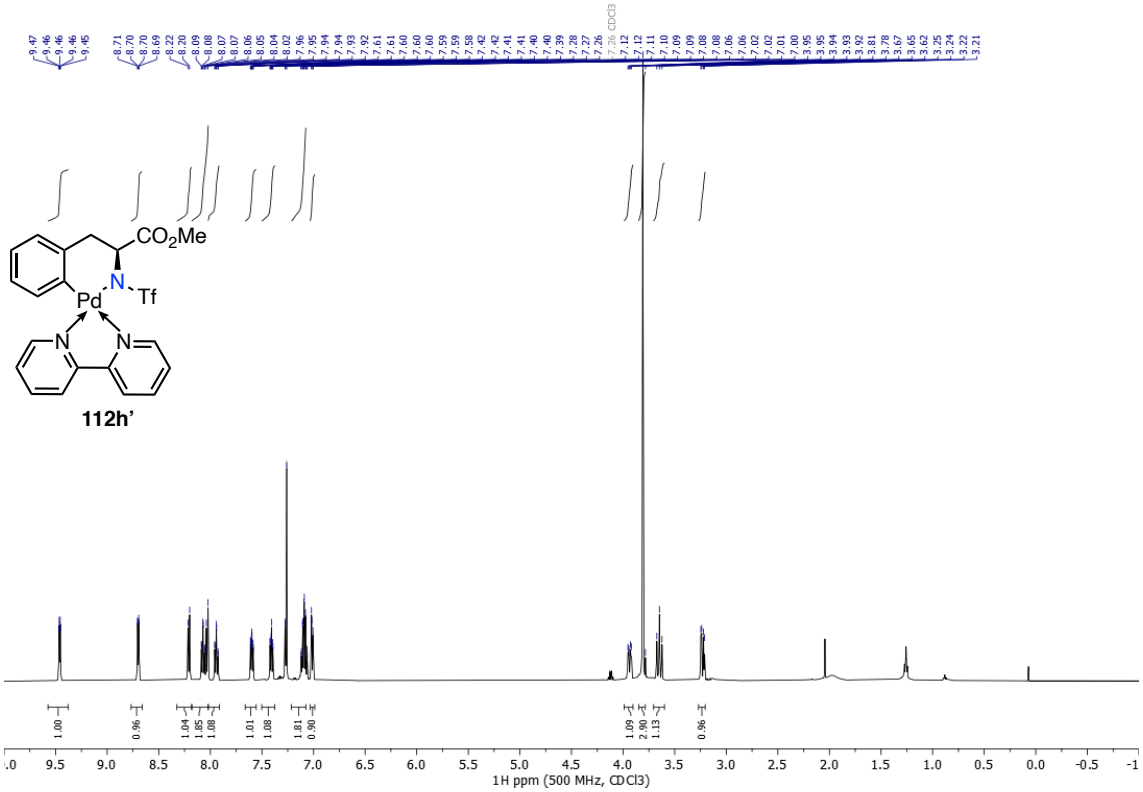



**112a'**

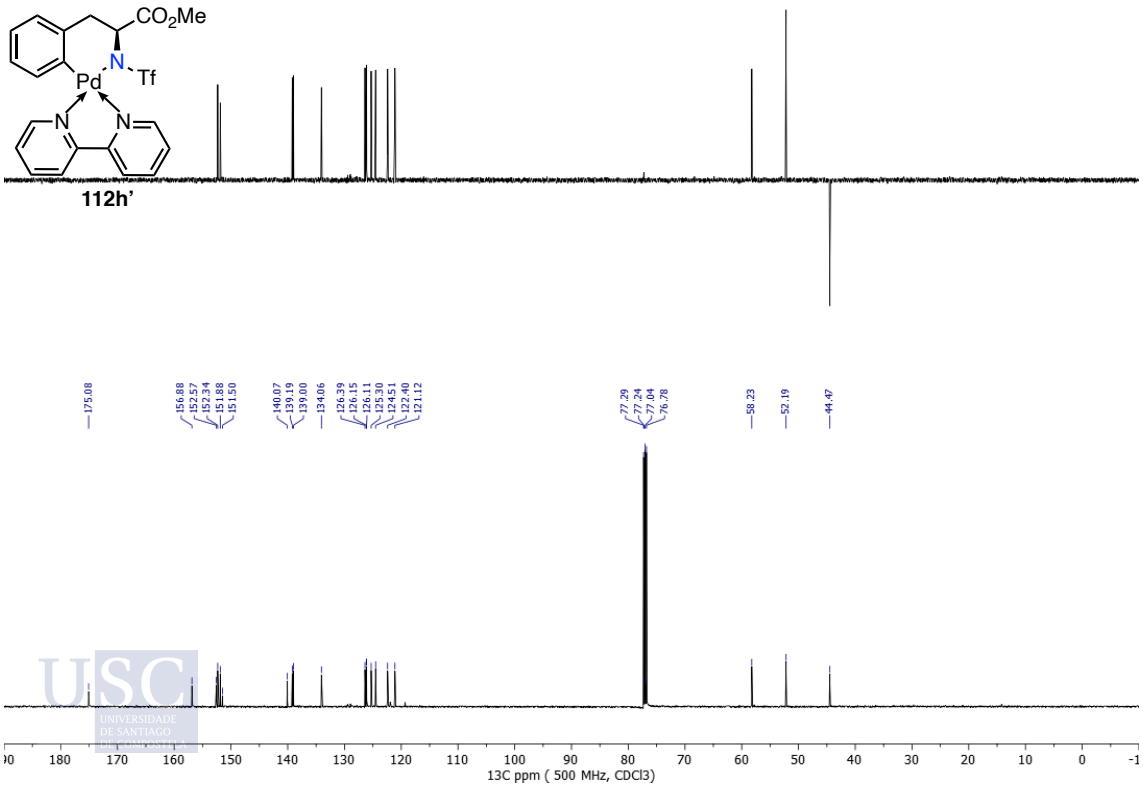



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$^{1}$H-NMR (500 MHz). Solvent ($CDCl_3$)



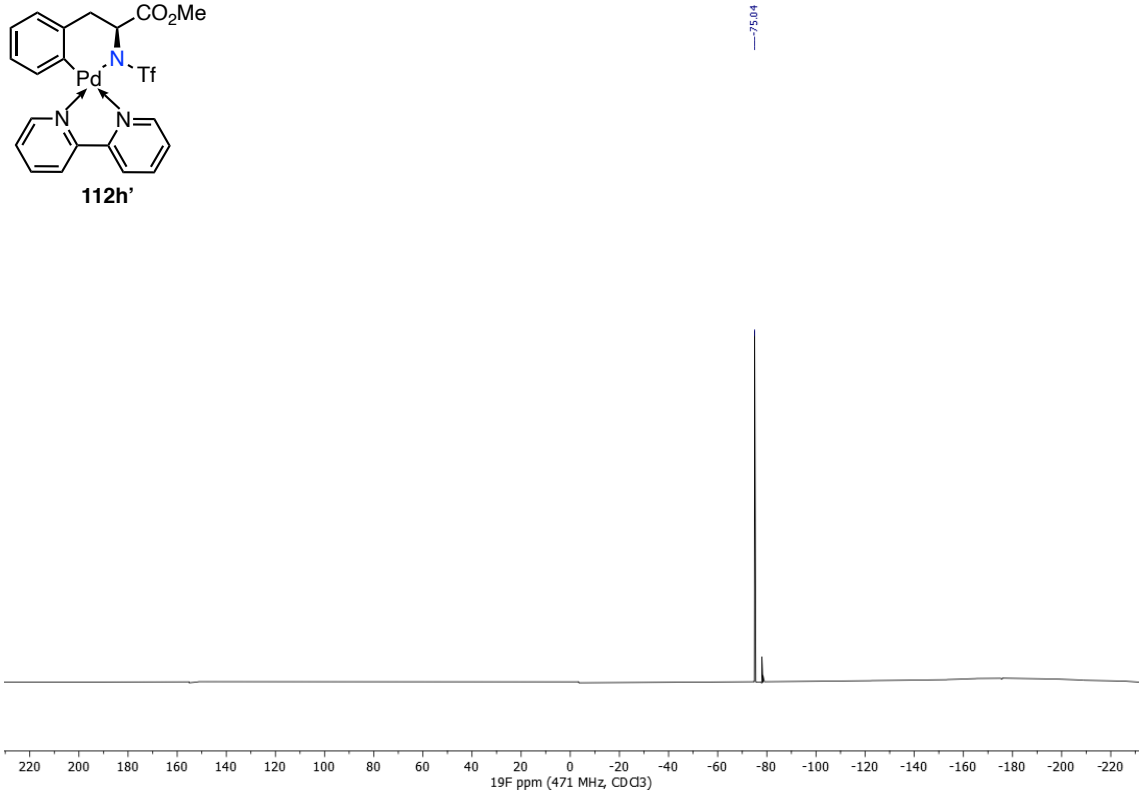

$^{13}$C-NMR (126 MHz). Solven ($CDCl_3$)



$^{19}$F-NMR (471 MHz). Solvent ($CDCl_3$)



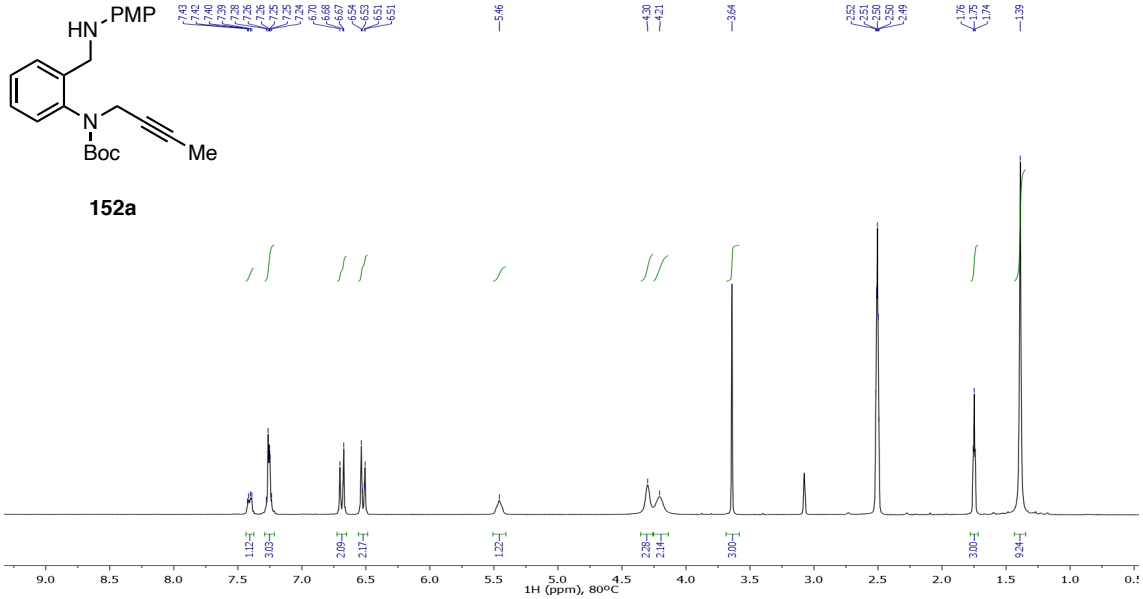

**112h'**



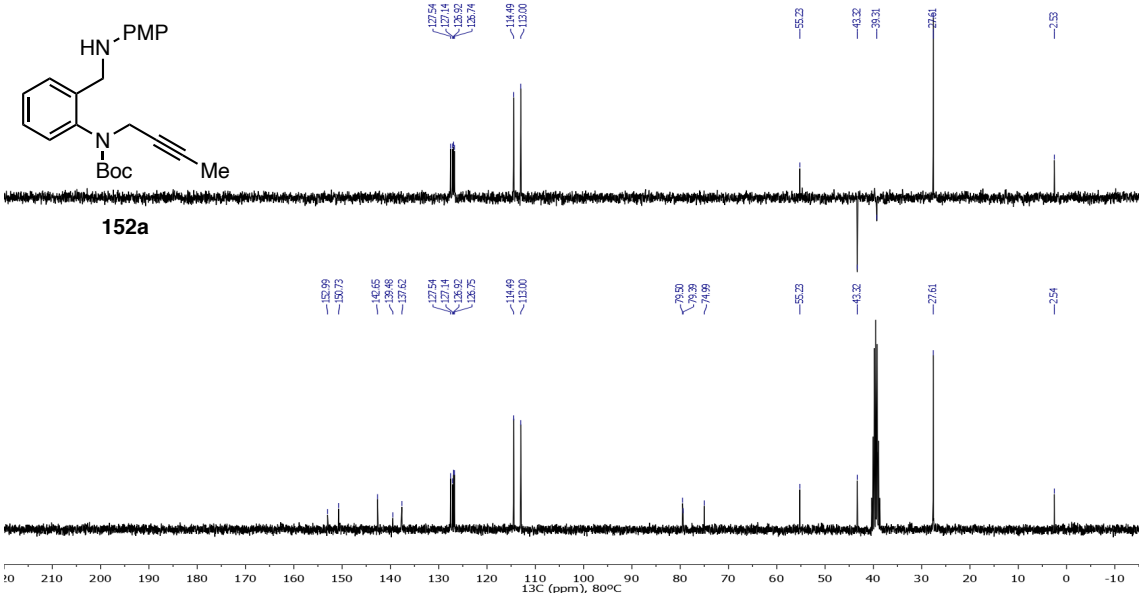

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DE COMPOSTELA

$^{1}$H-NMR (300 MHz). Solvent DMSO-$d_6$. 80º C

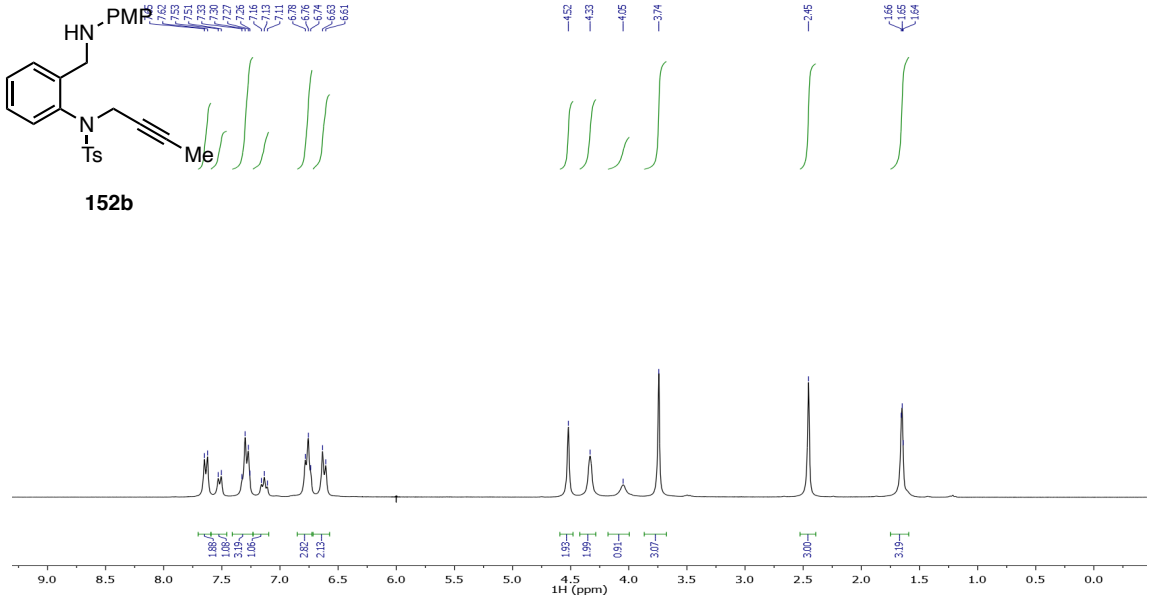



$^{13}$C-NMR(75MHz). Solvent DMSO-$d_6$80 ºC



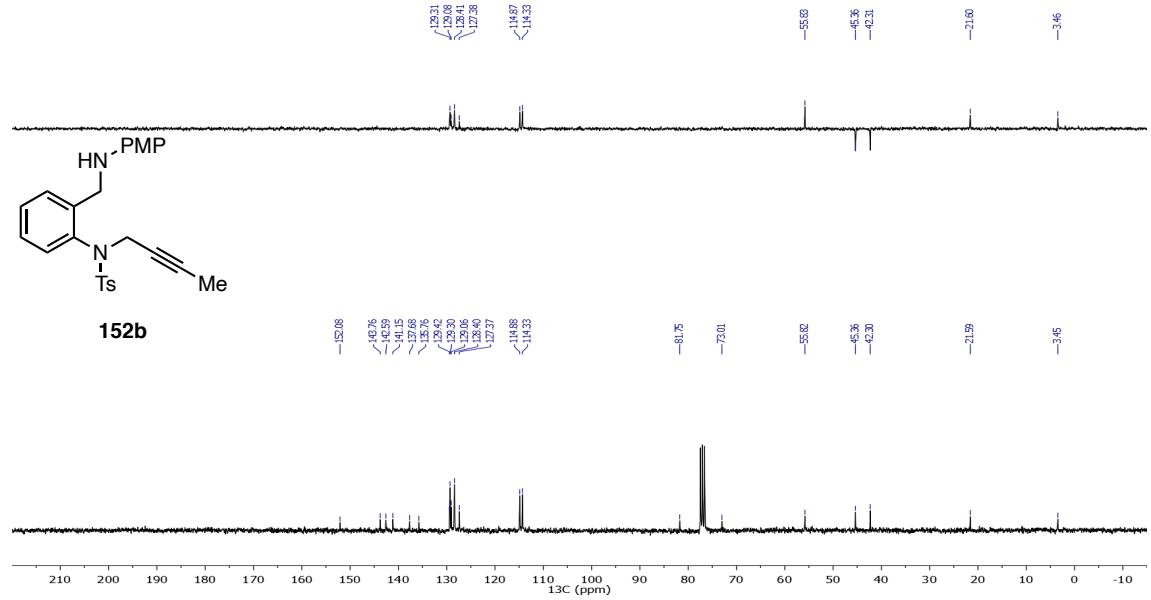

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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$




**152b**

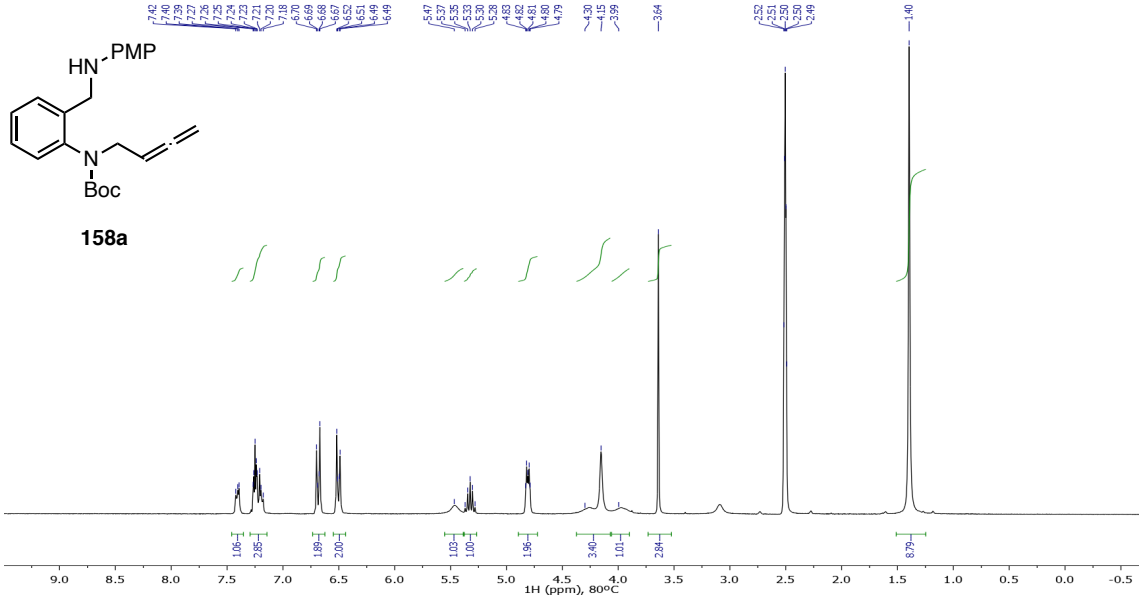
$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$



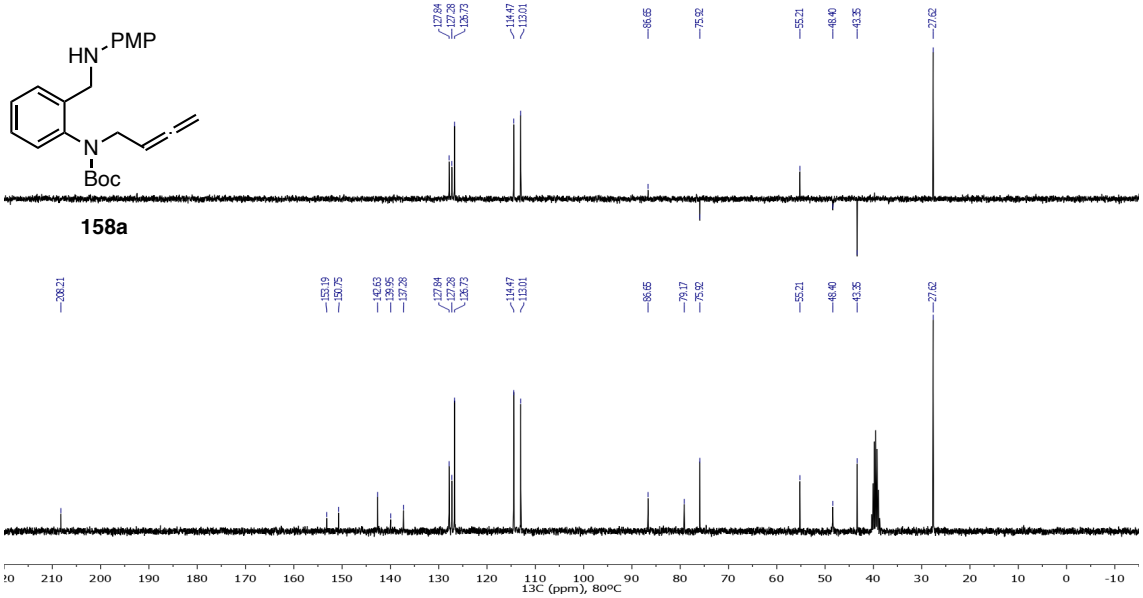

**152b**

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$^{1}$H-NMR (300 MHz). Solvent DMSO-$d_6$

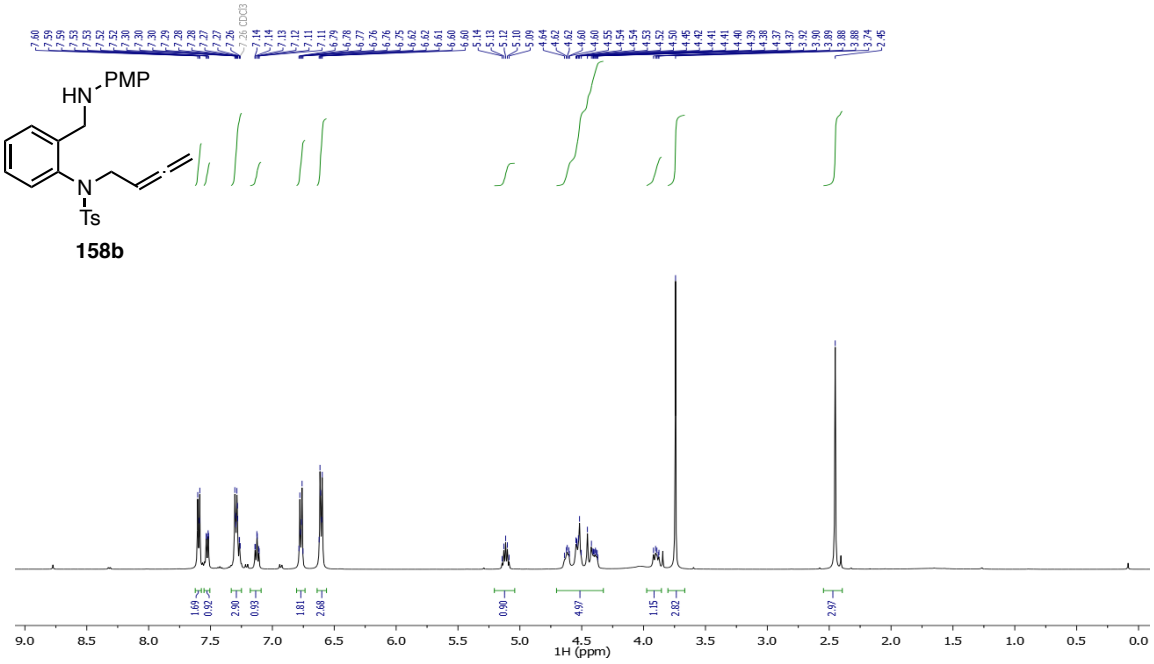



$^{13}$C-NMR (75 MHz). Solvent DMSO-$d_6$

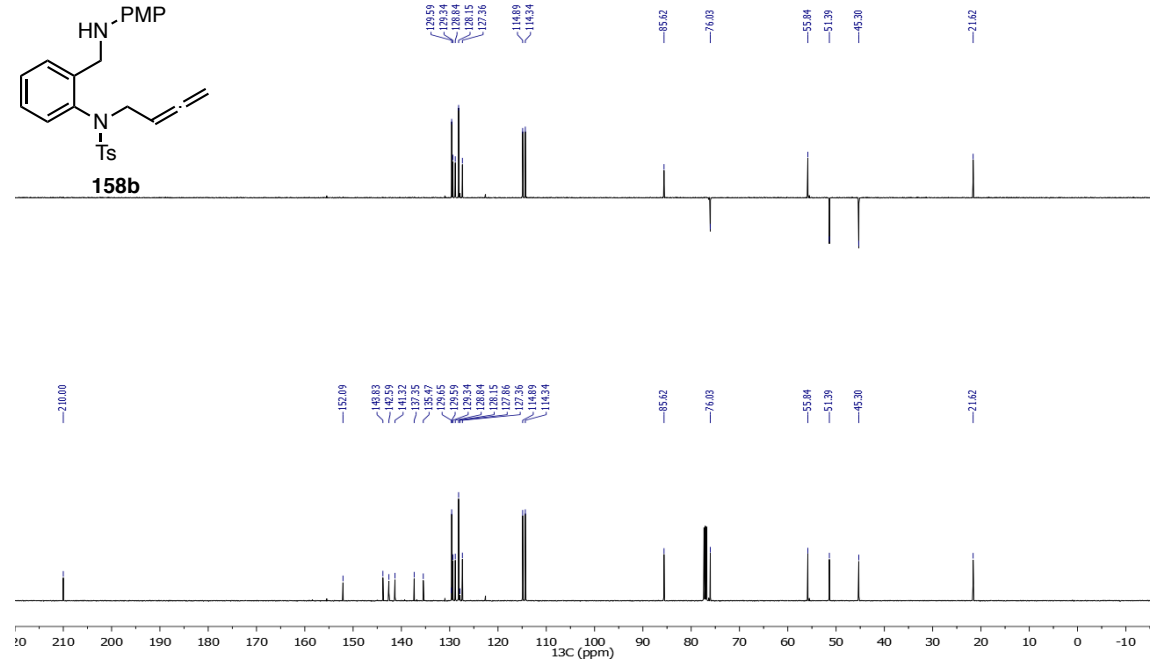



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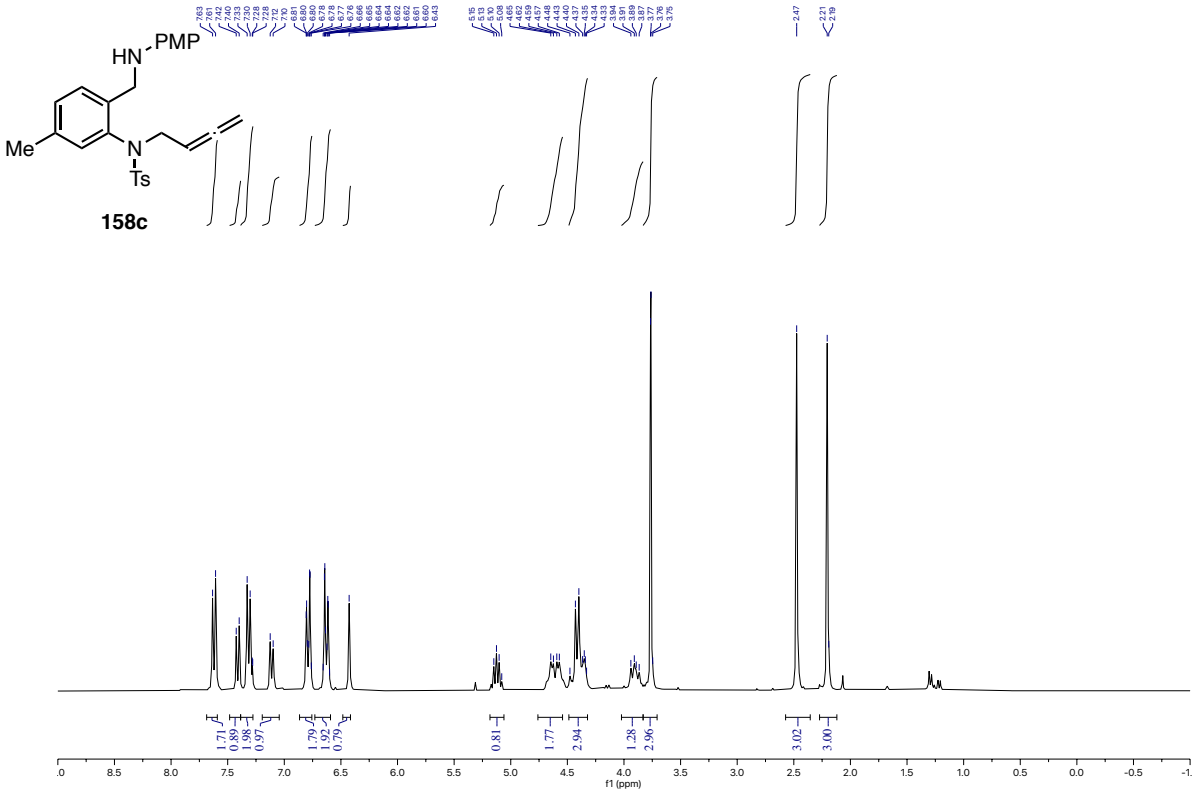
$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$



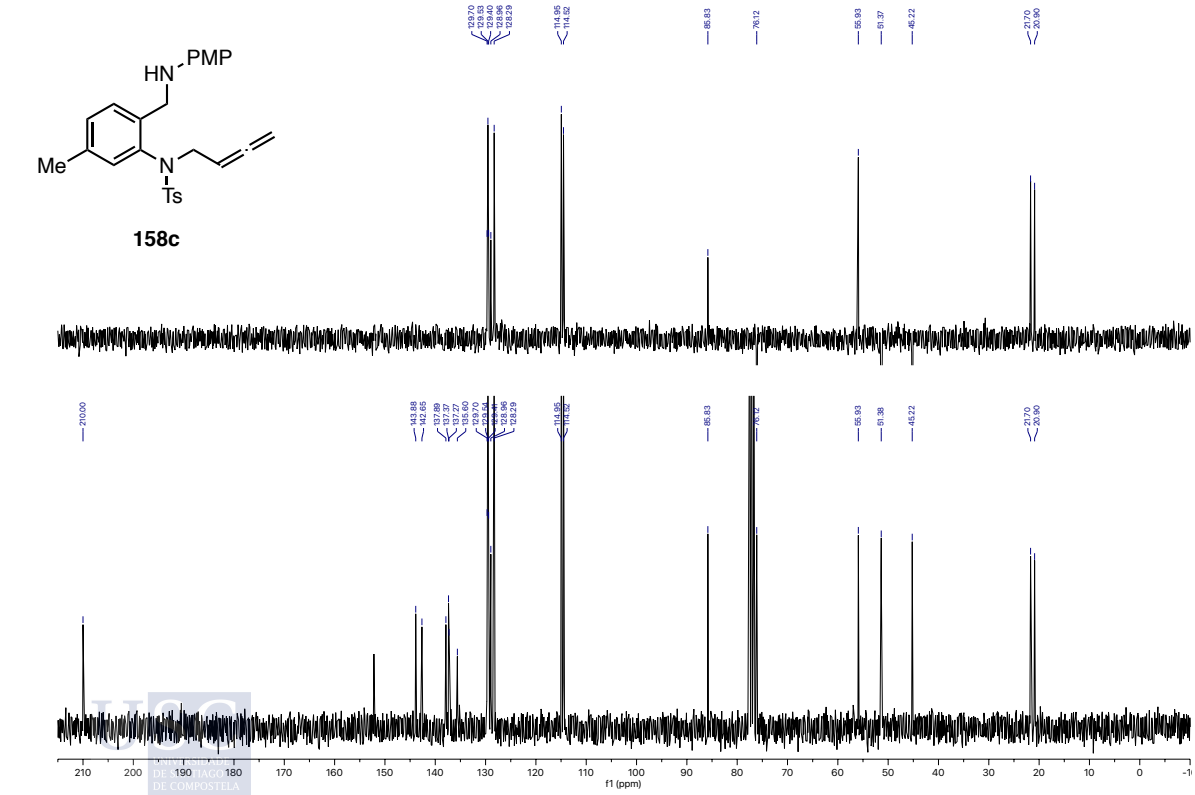

$^{13}$C-NMR(126 MHz). Solvent $CDCl_3$



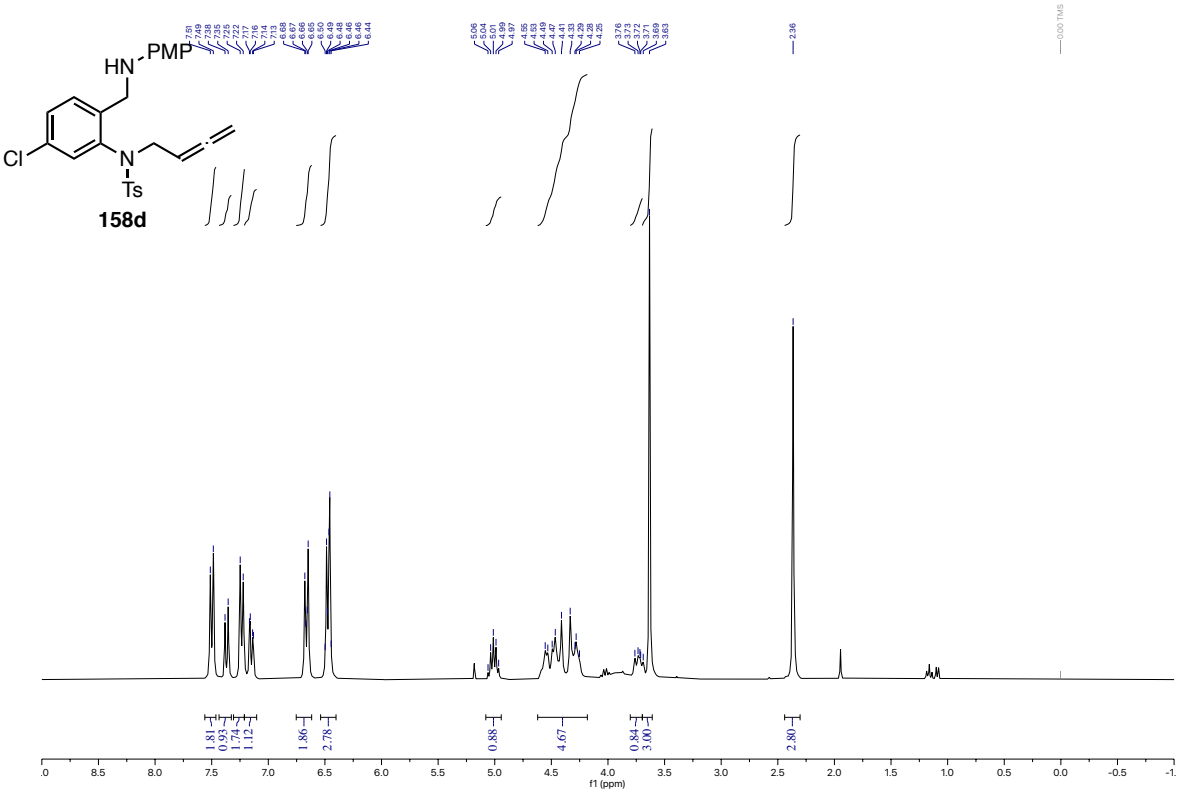
$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$



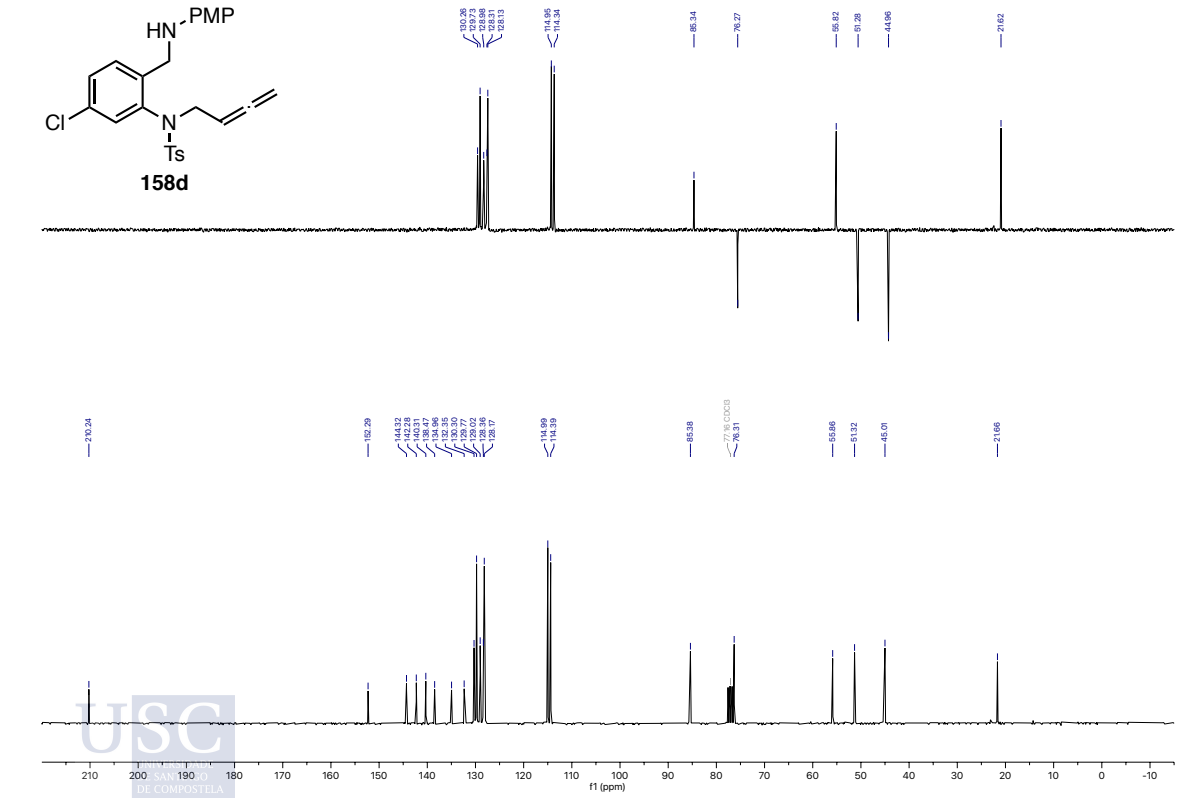

$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$



$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

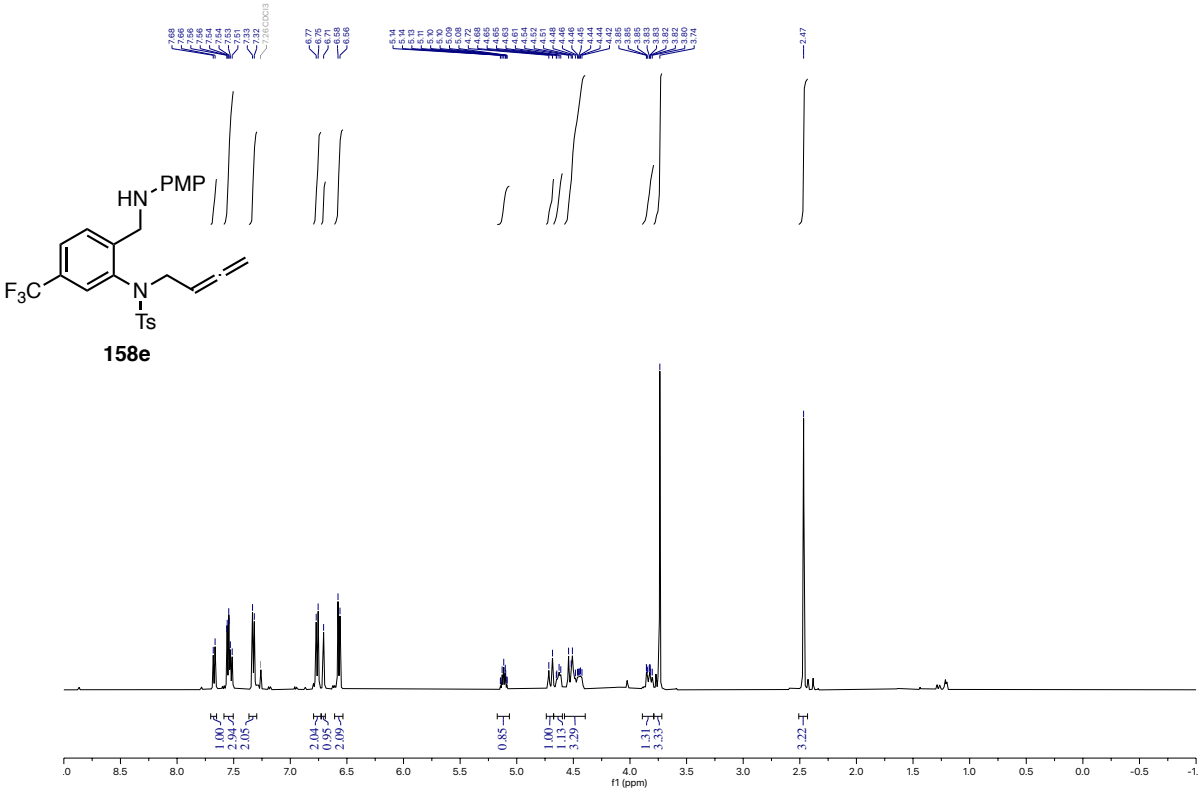



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

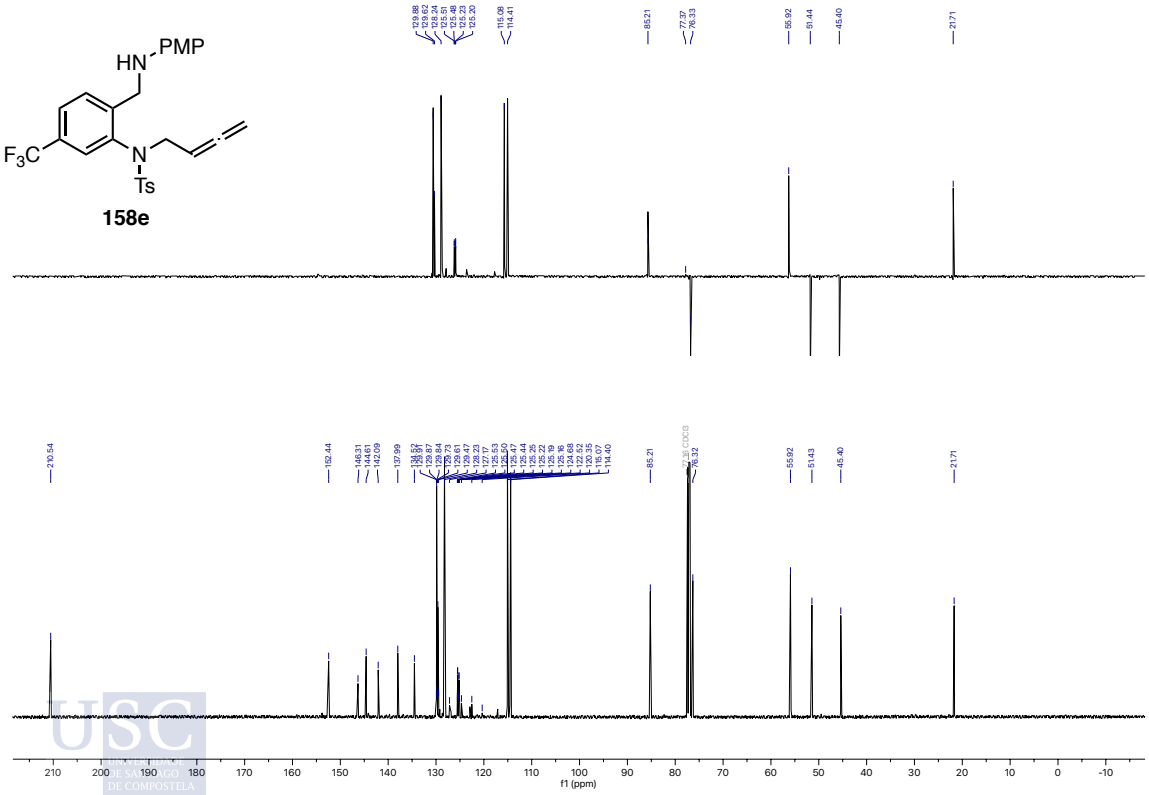



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$



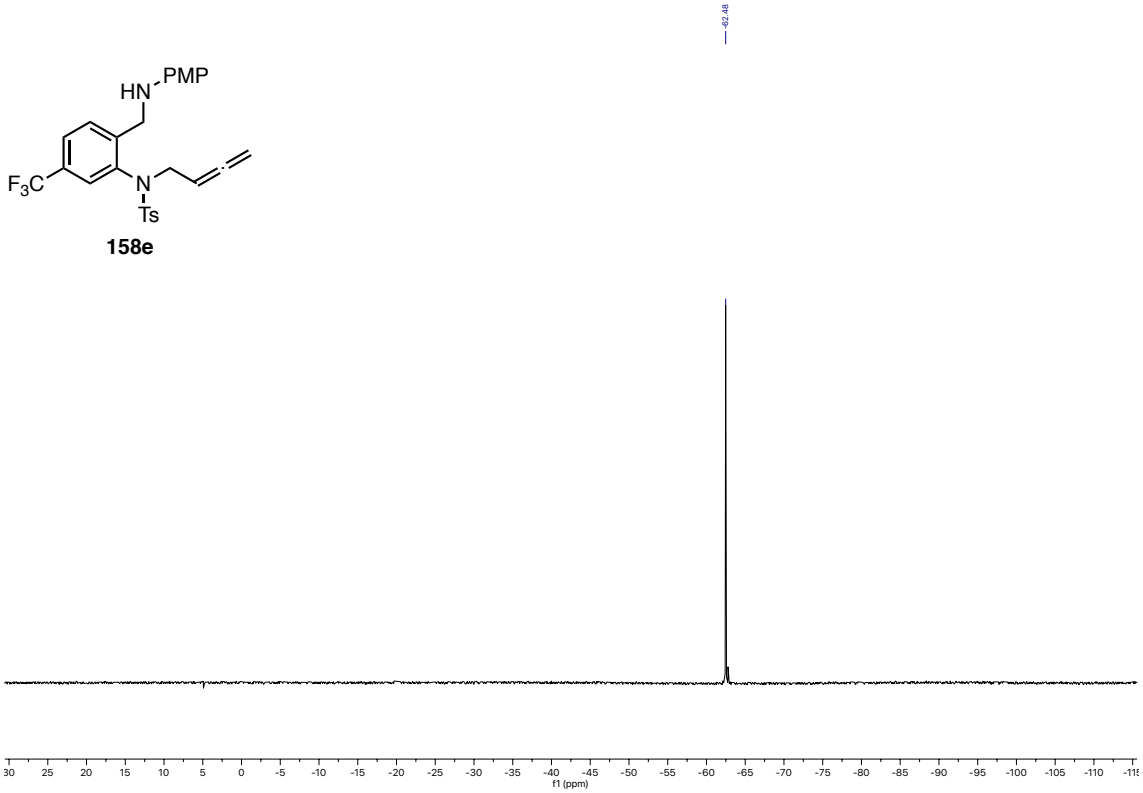

$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$



$^{19}$F-NMR (282 MHz). Solvent $CDCl_3$

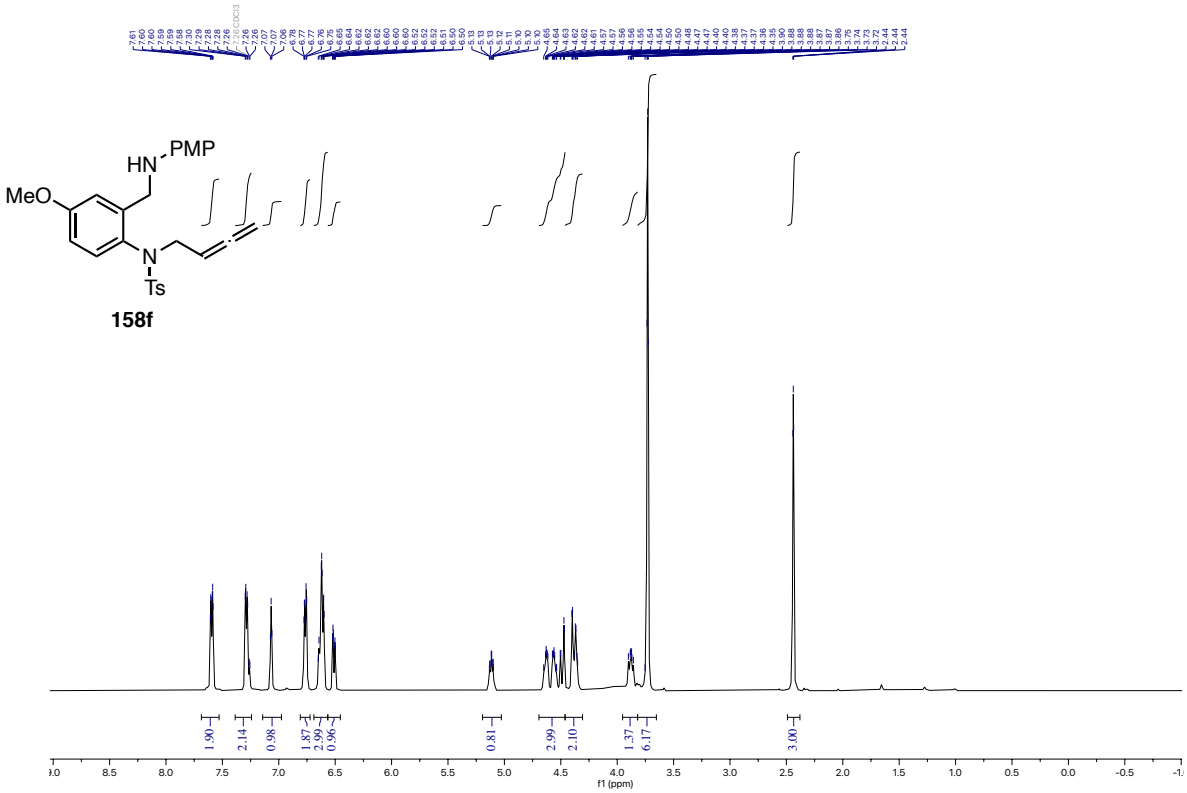



**158e**

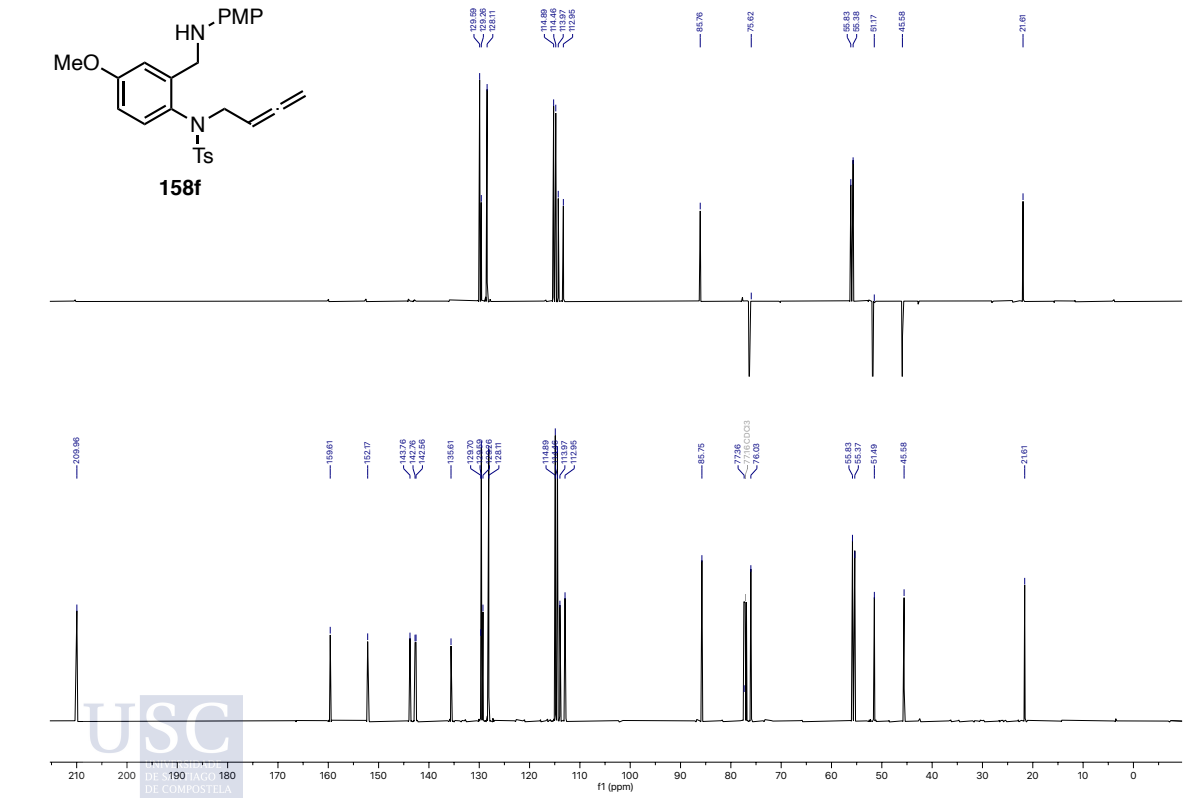



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

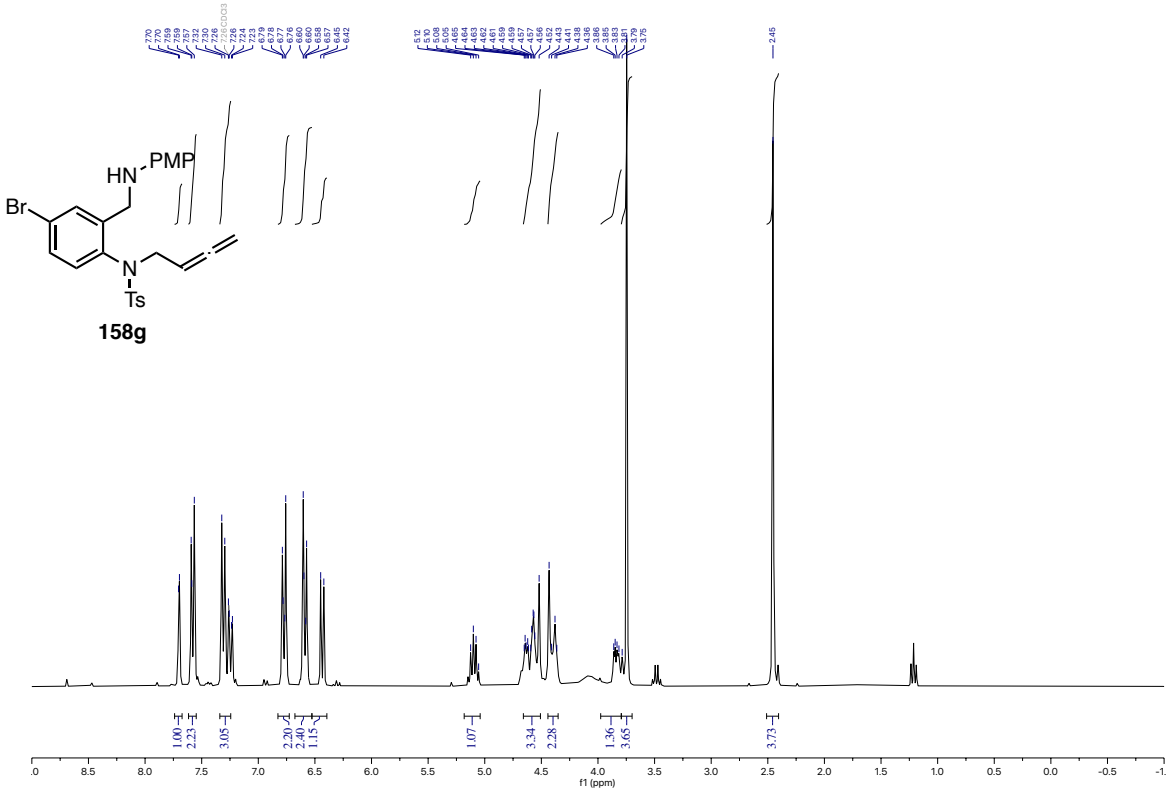



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

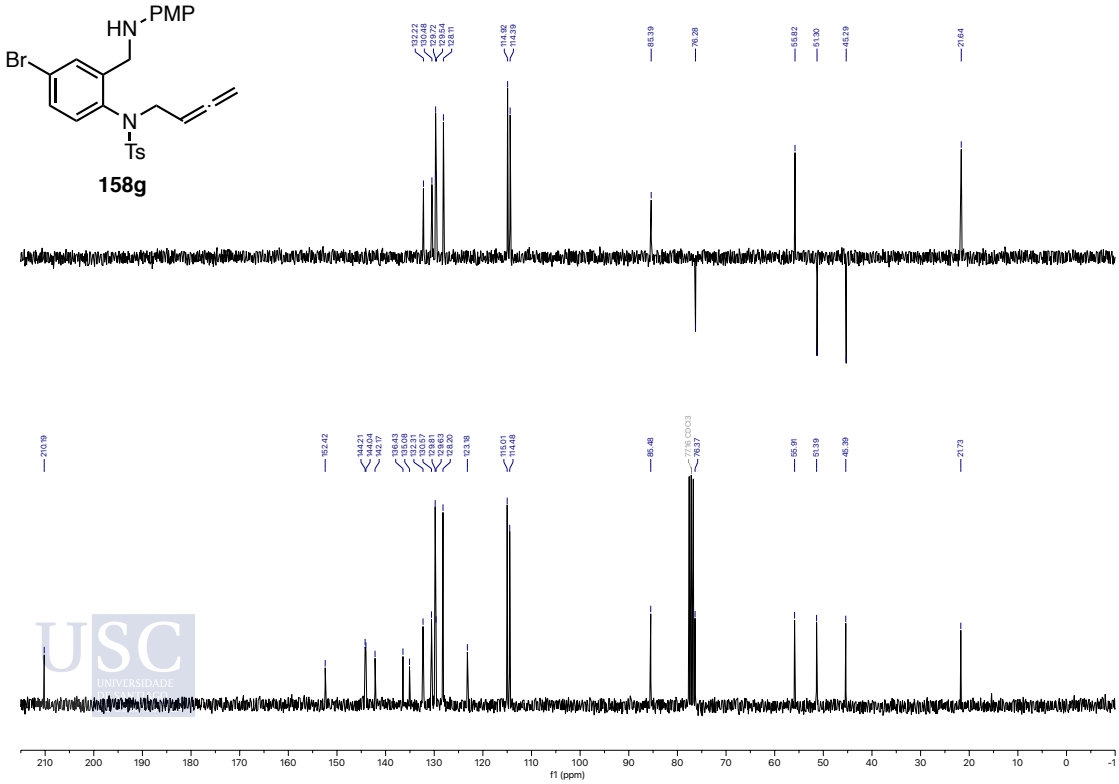



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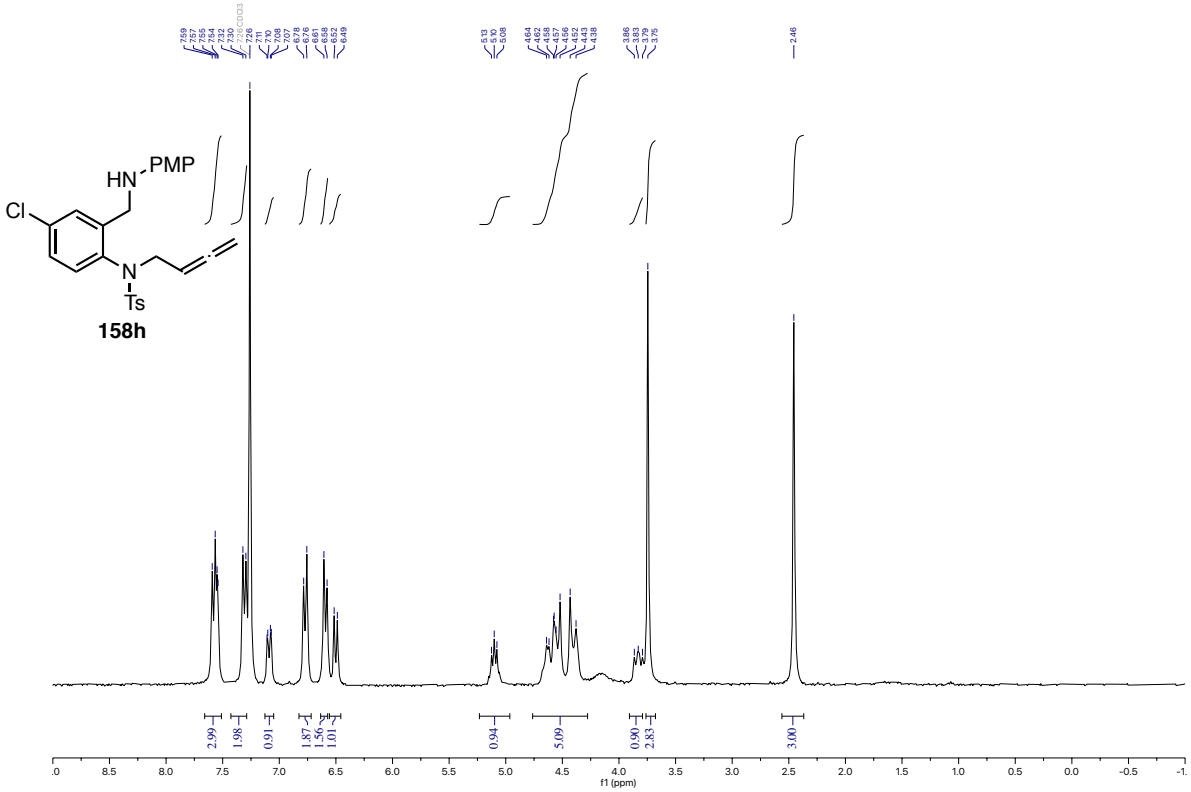
$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$



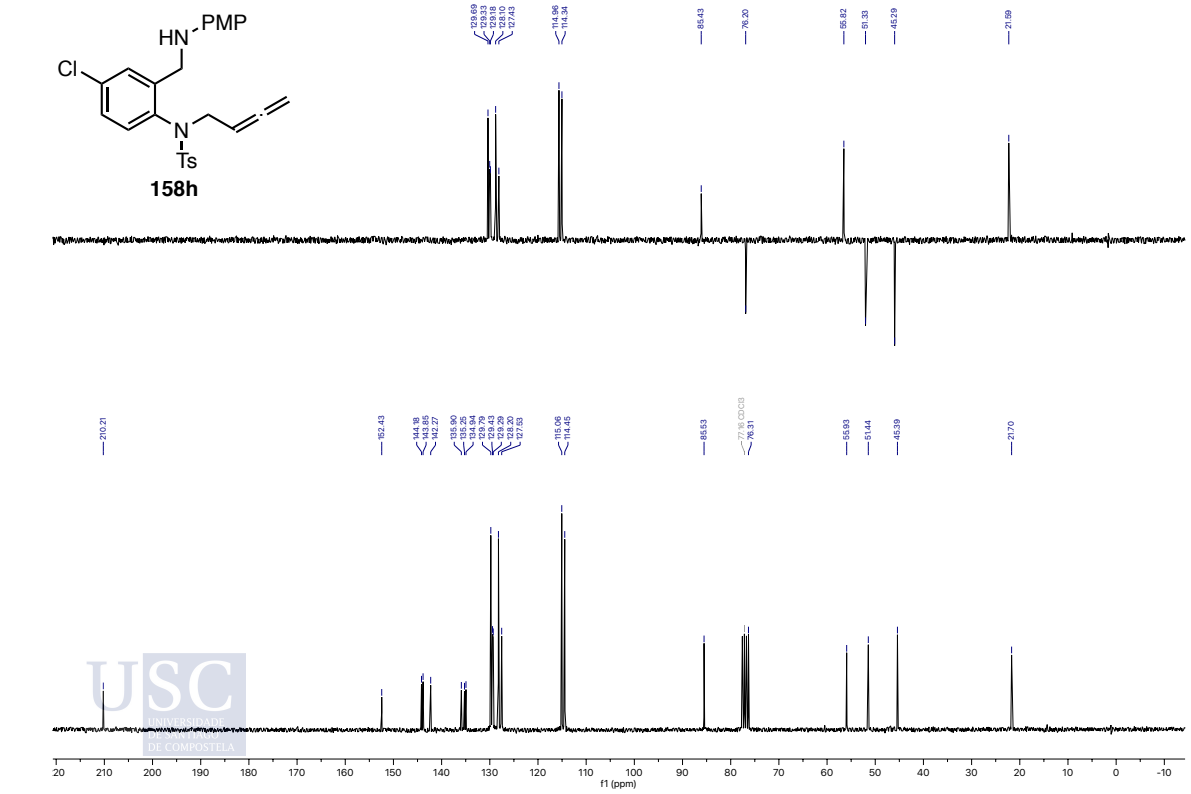

$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$



$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

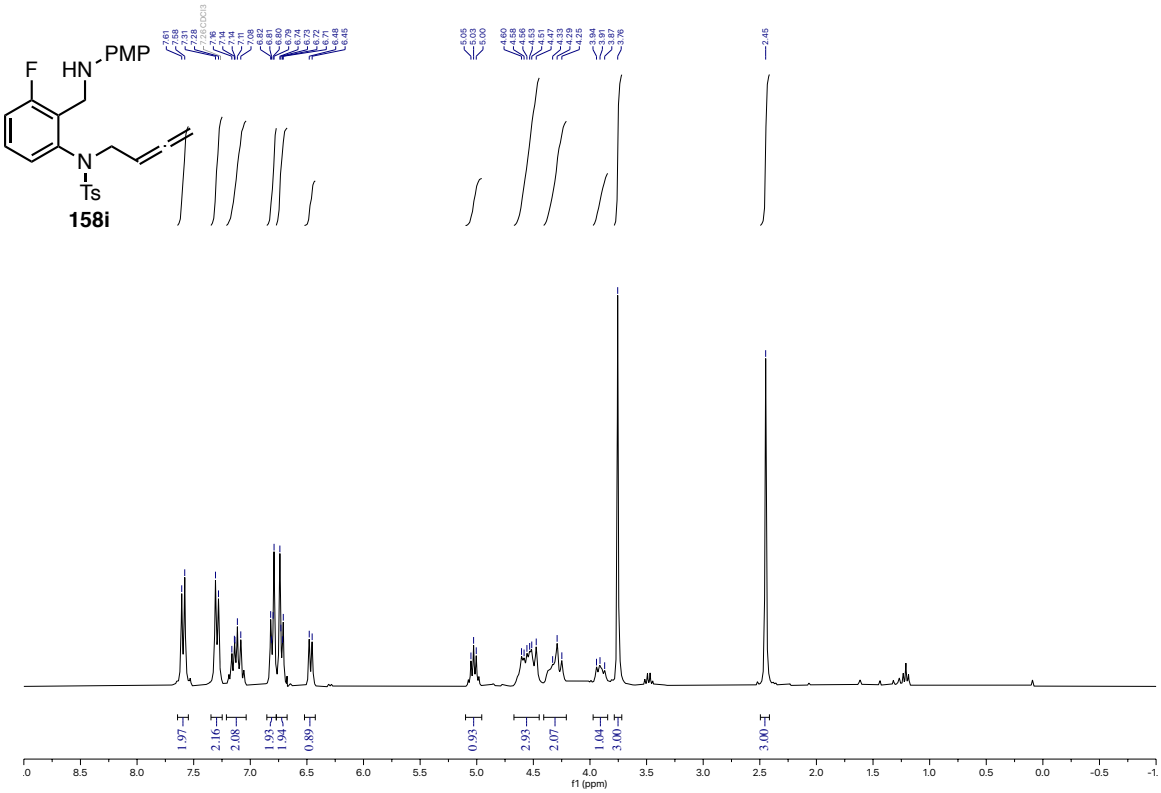



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

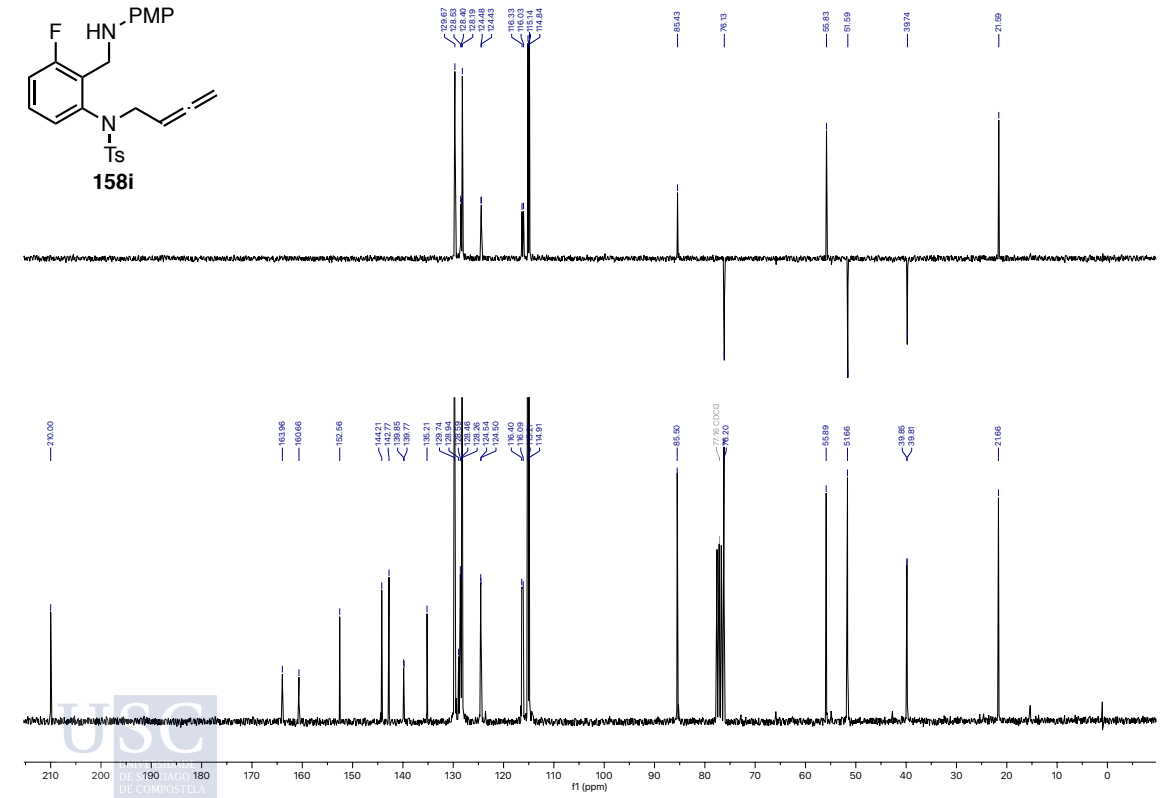



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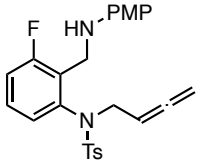
$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$



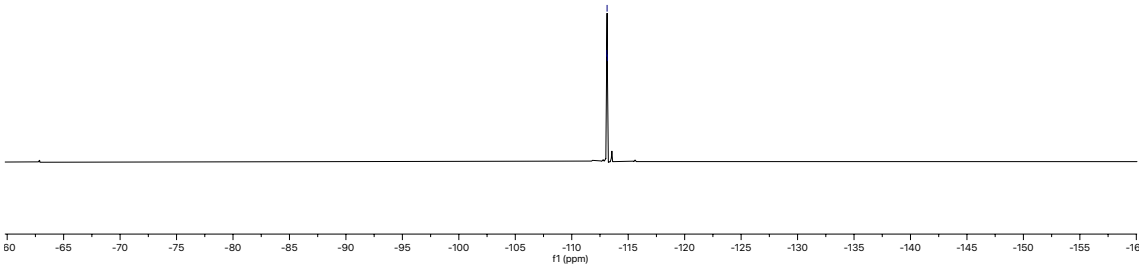

$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$



$^{19}$F-NMR (282 MHz). Solvent $CDCl_3$

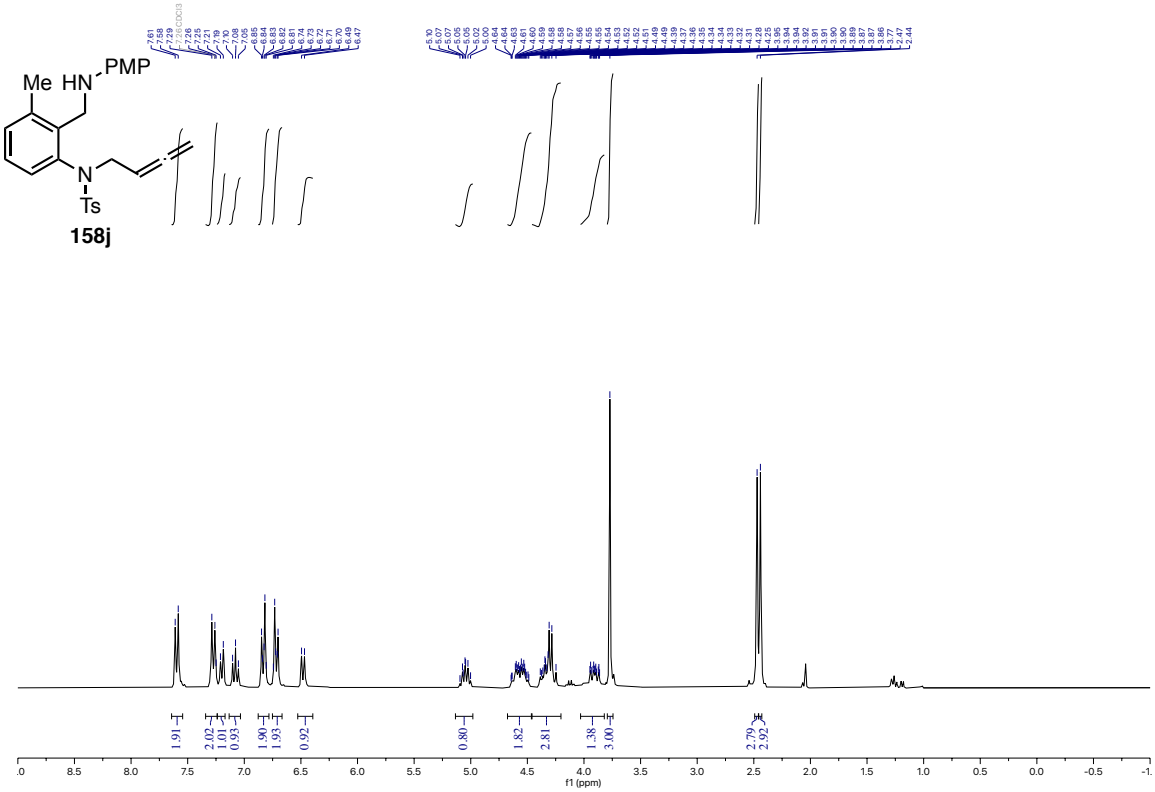



**158i**

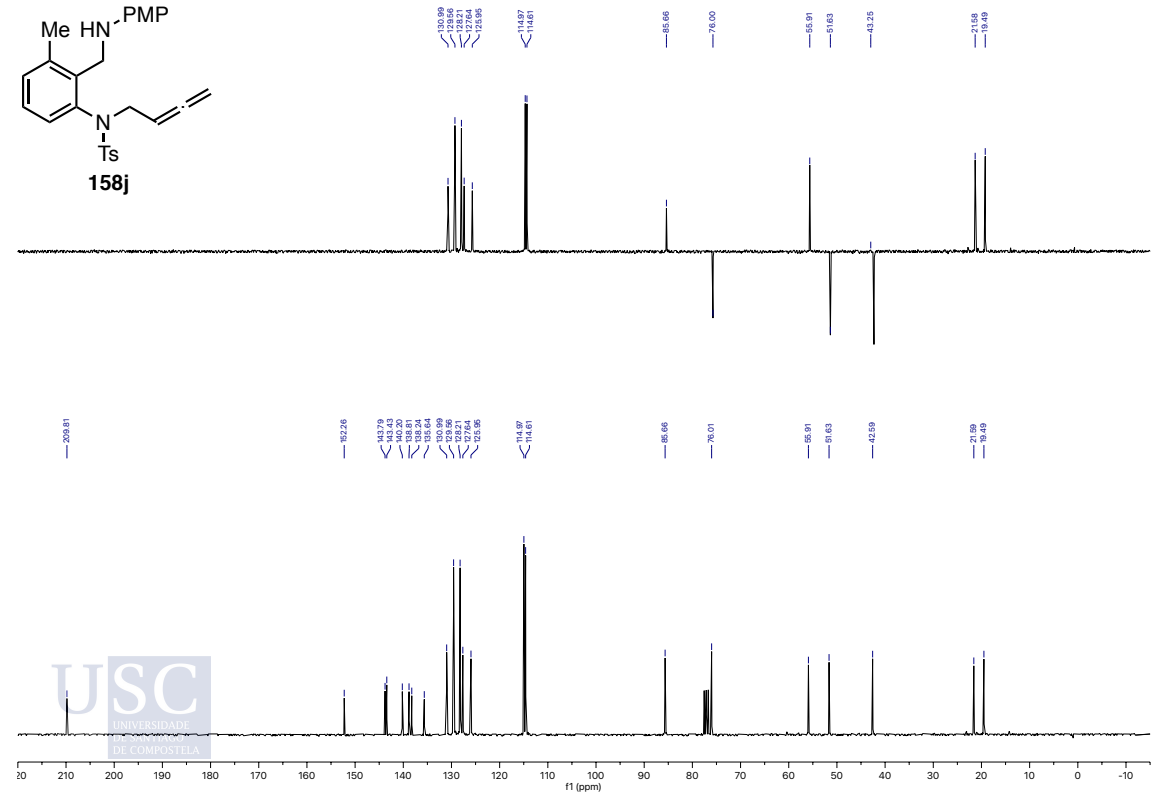



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

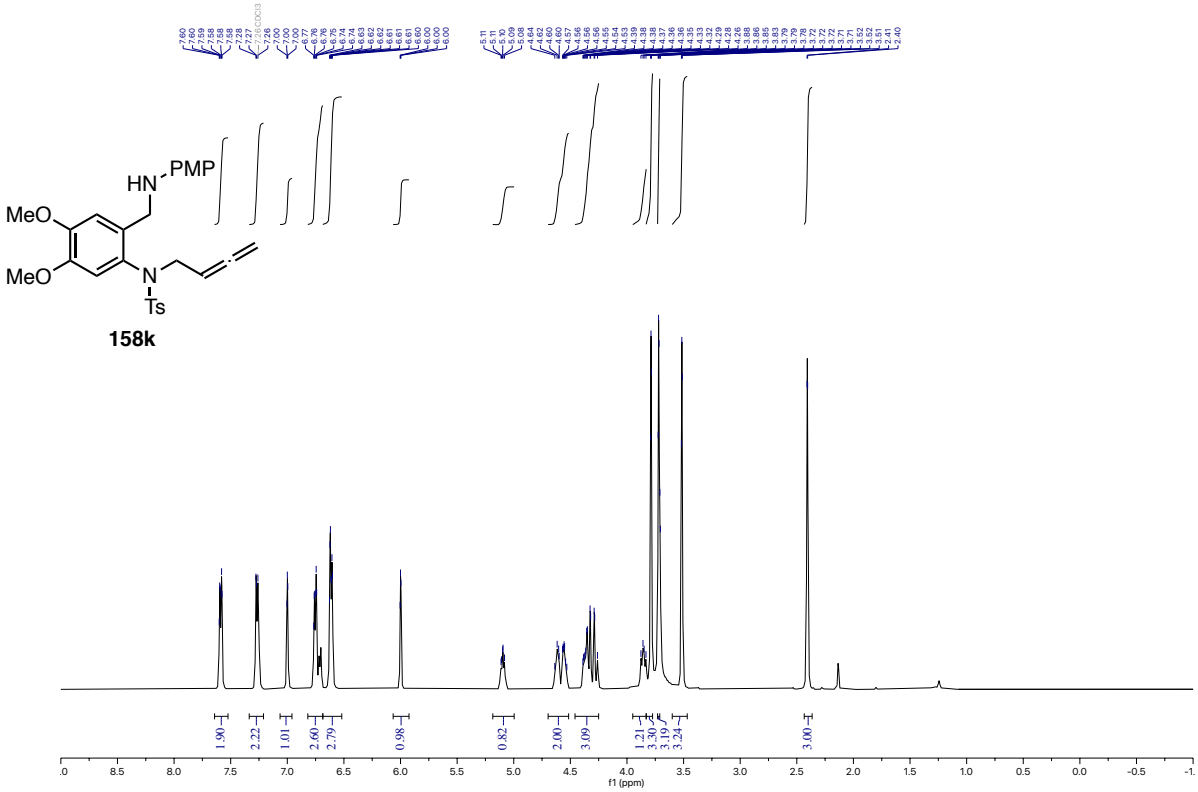



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

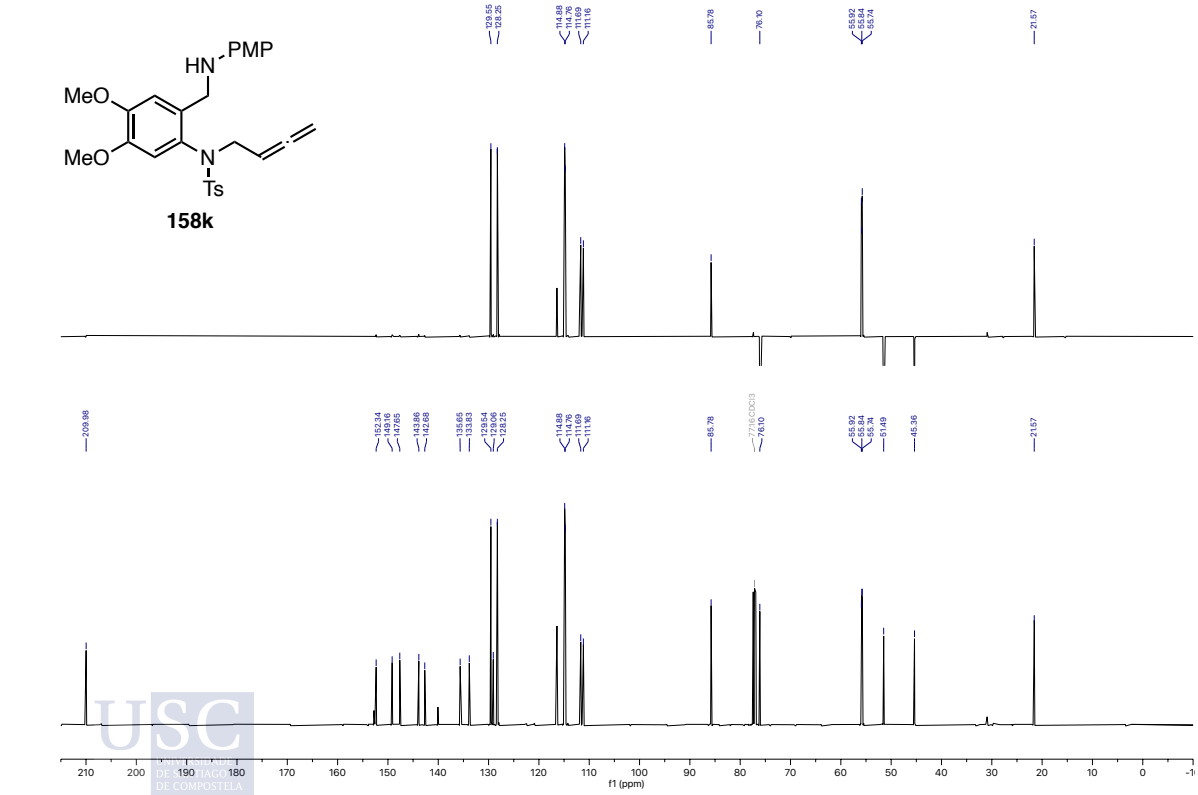



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

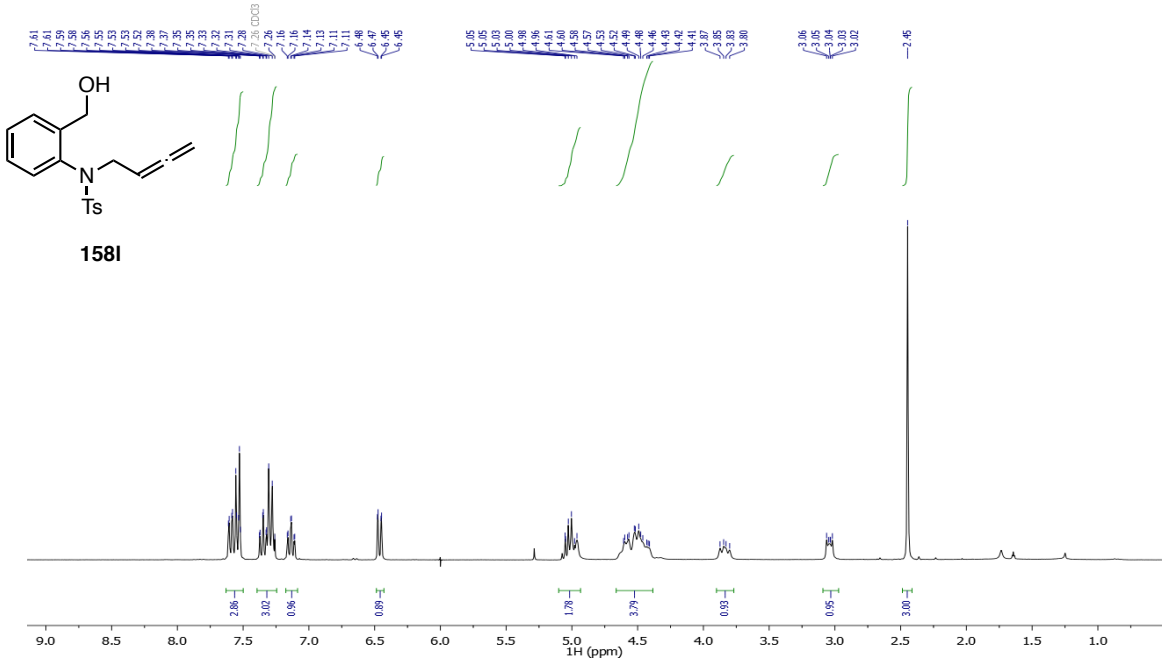



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

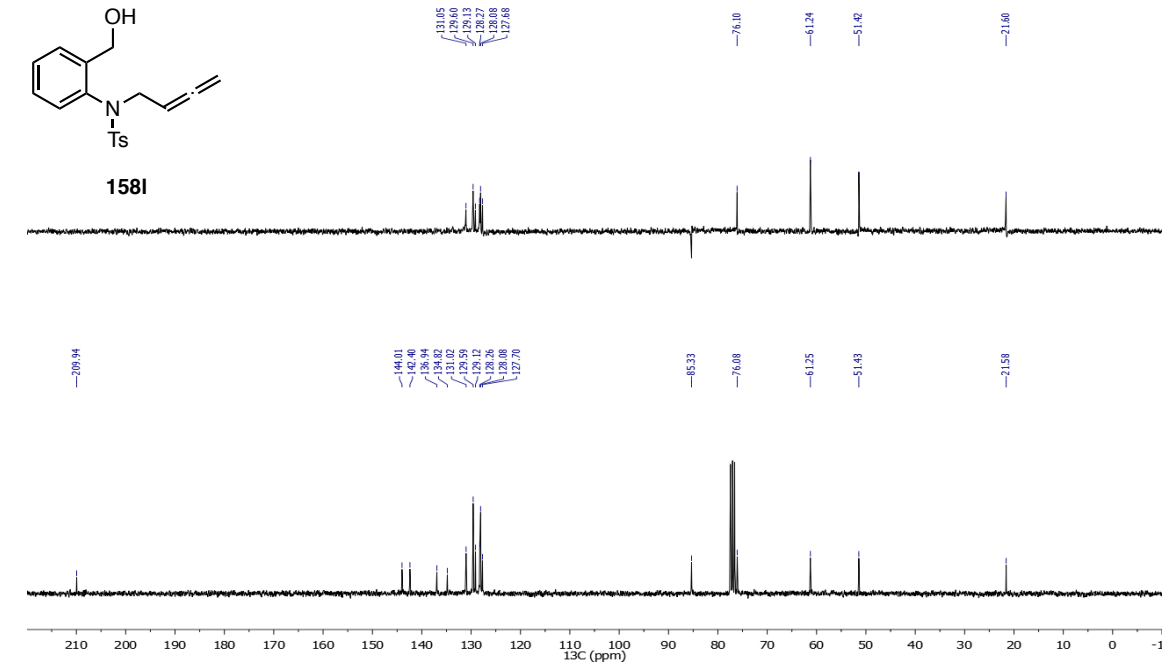



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

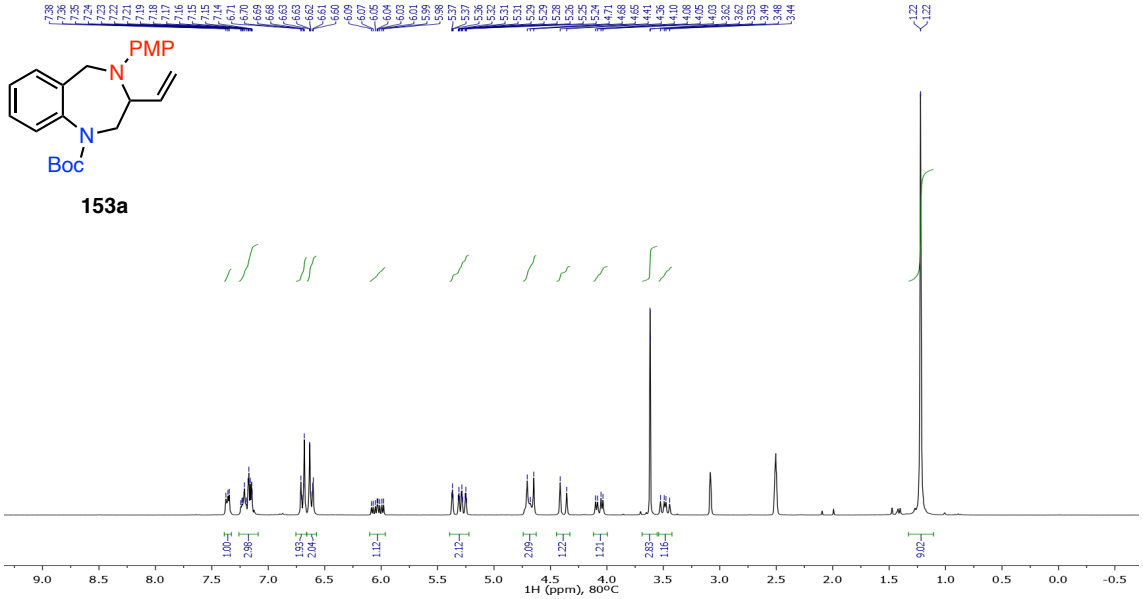



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

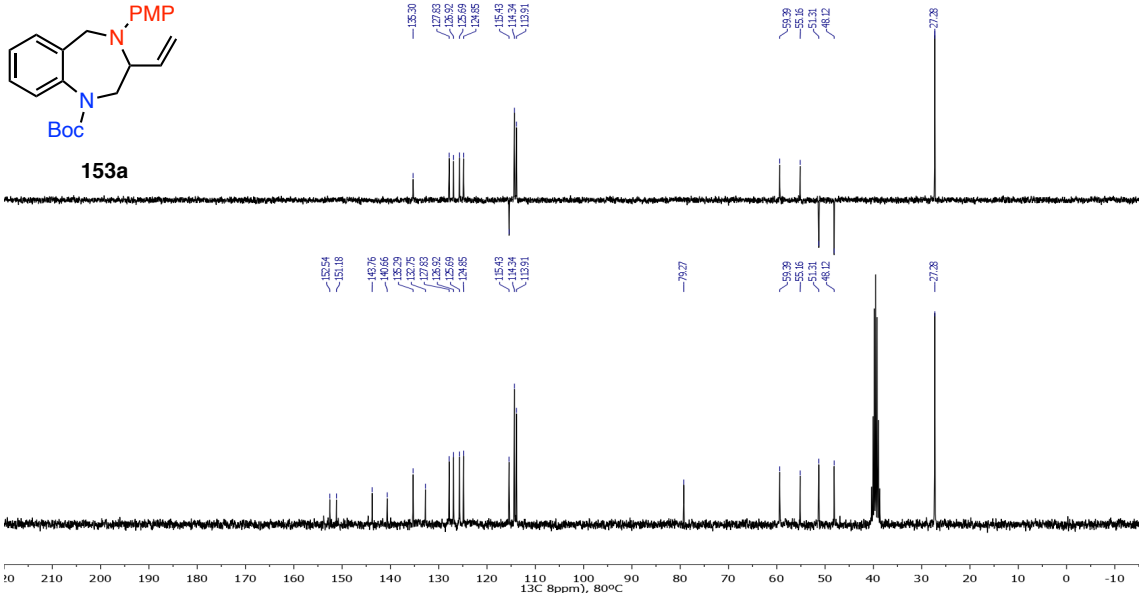



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

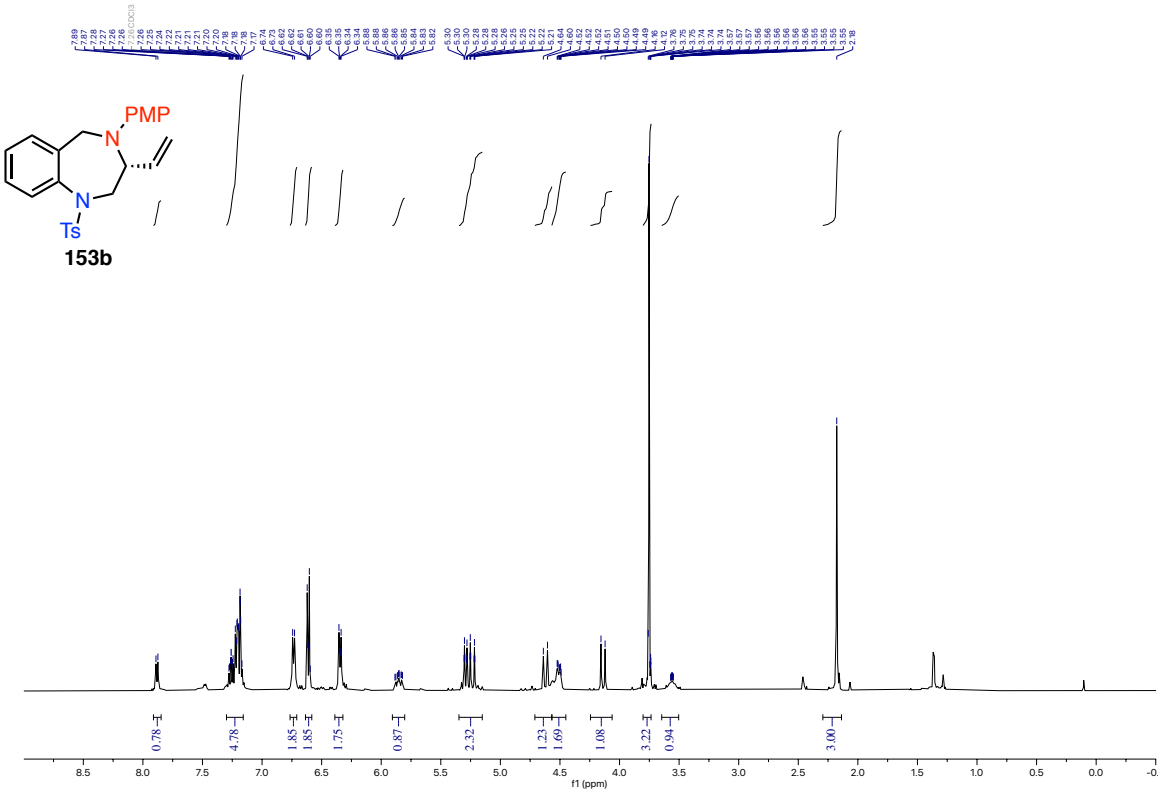



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

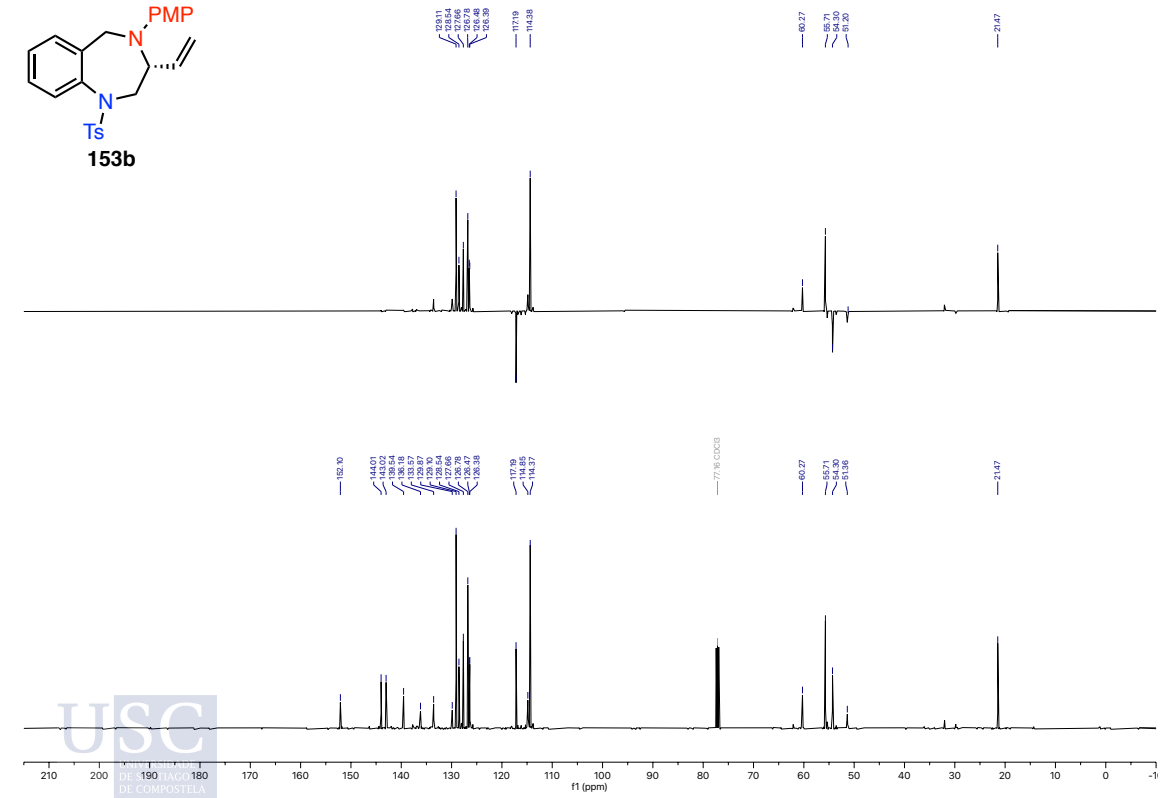



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

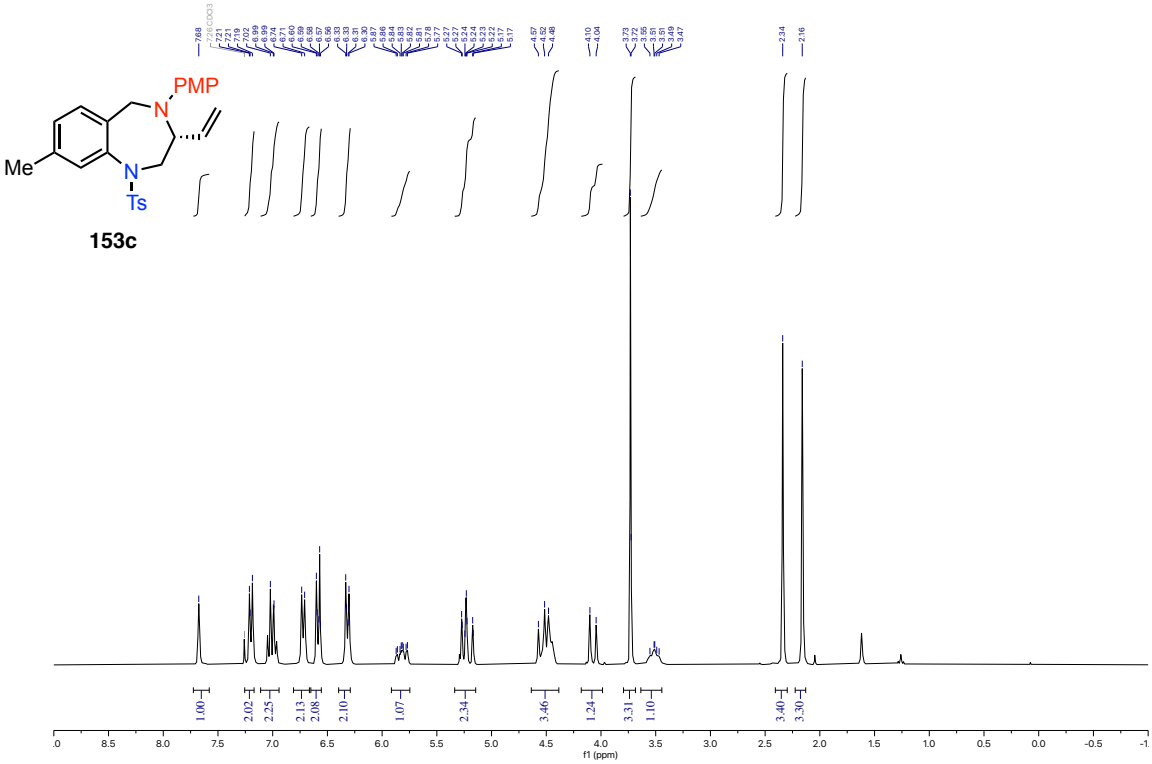



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

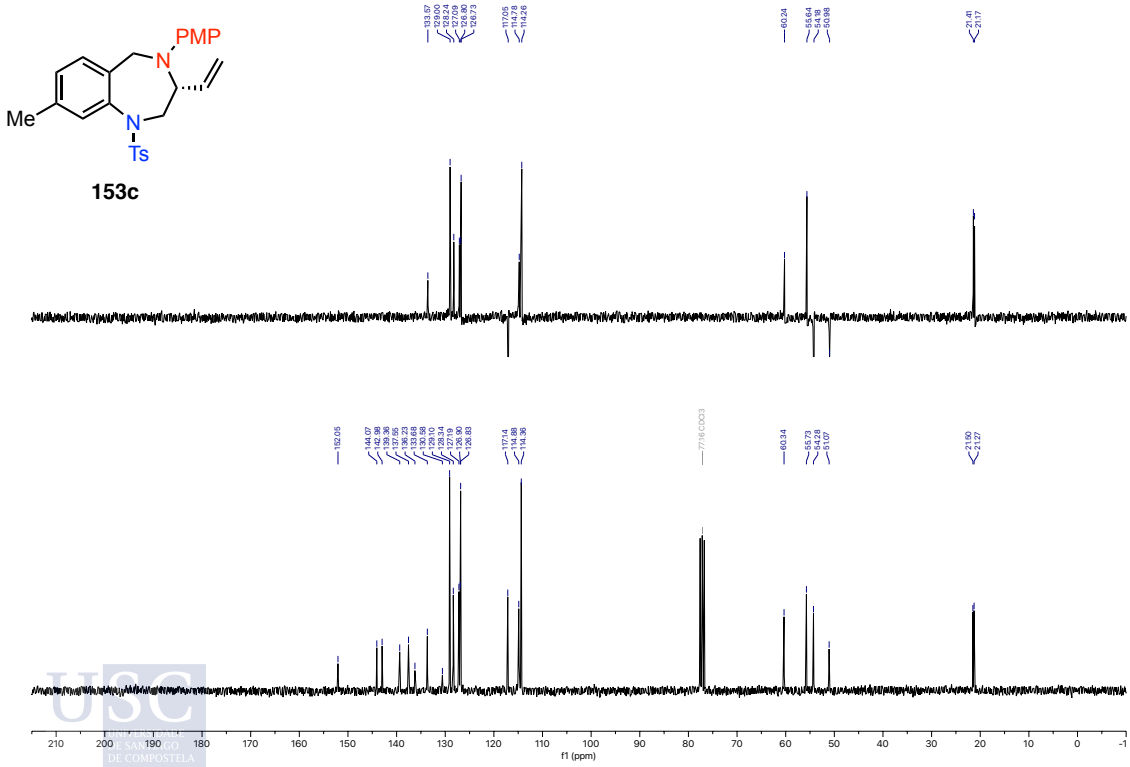



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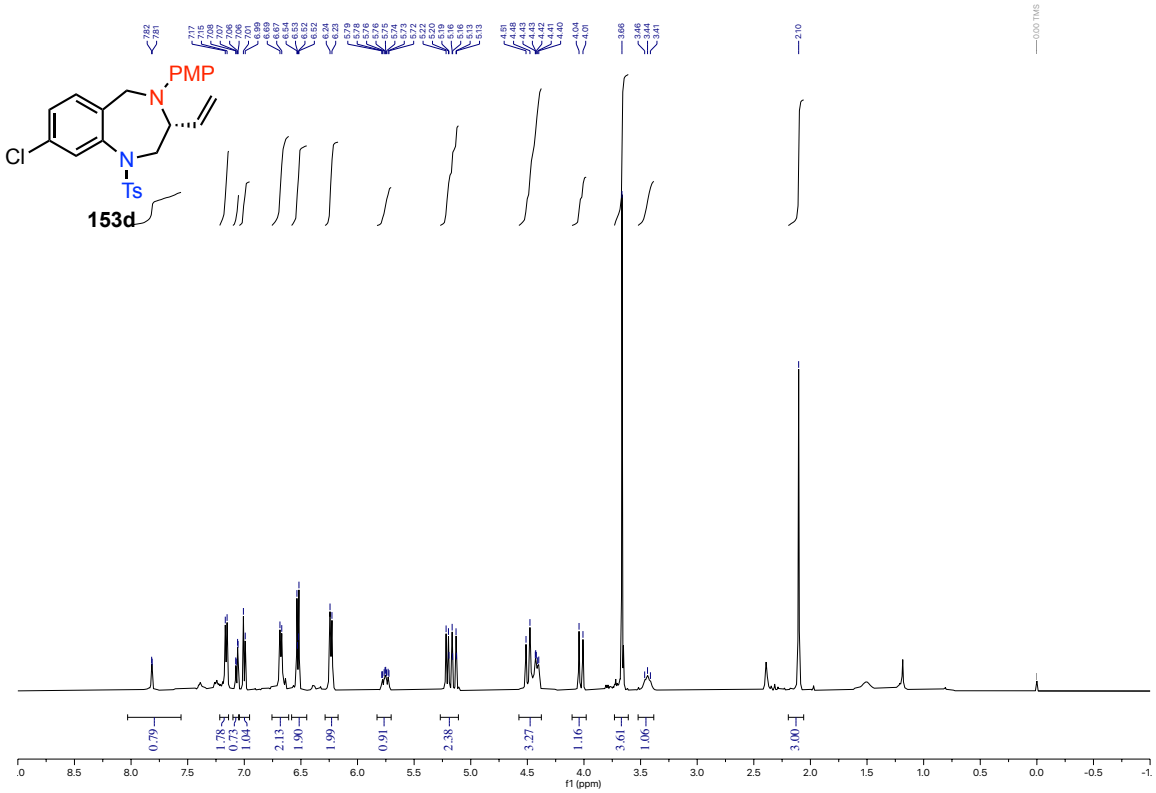
$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$



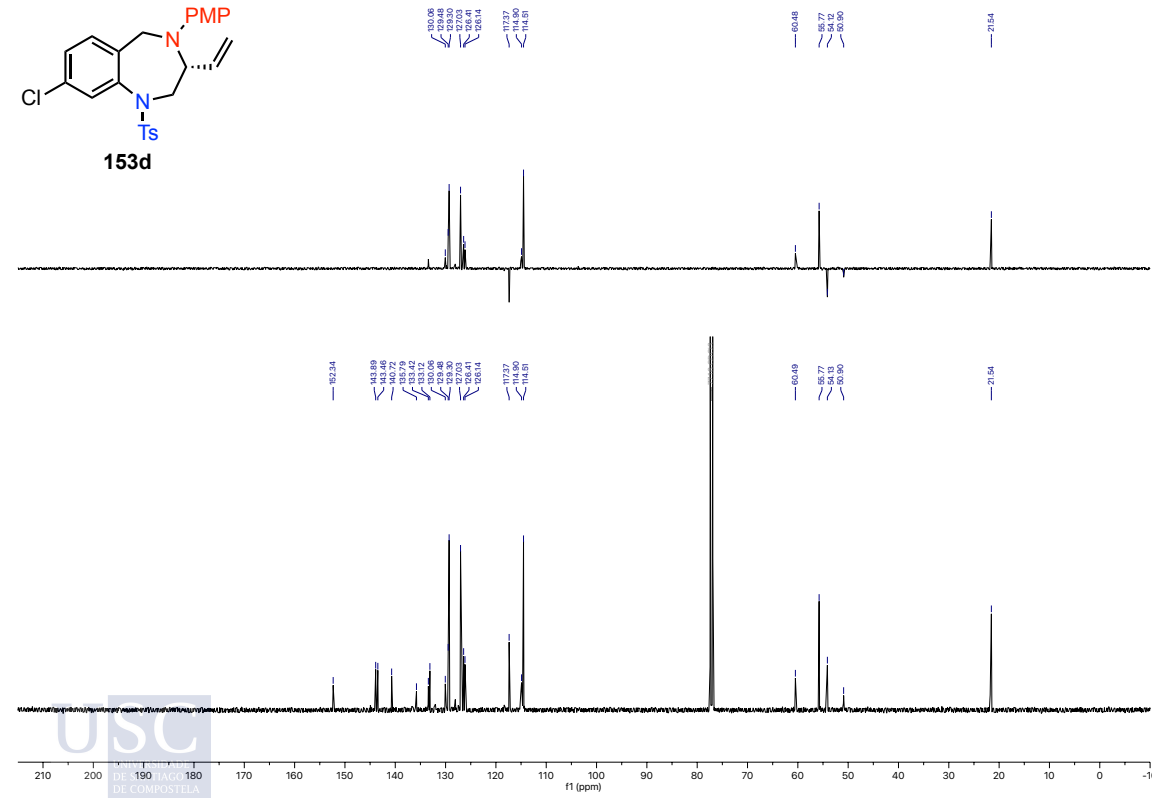

$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$



$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

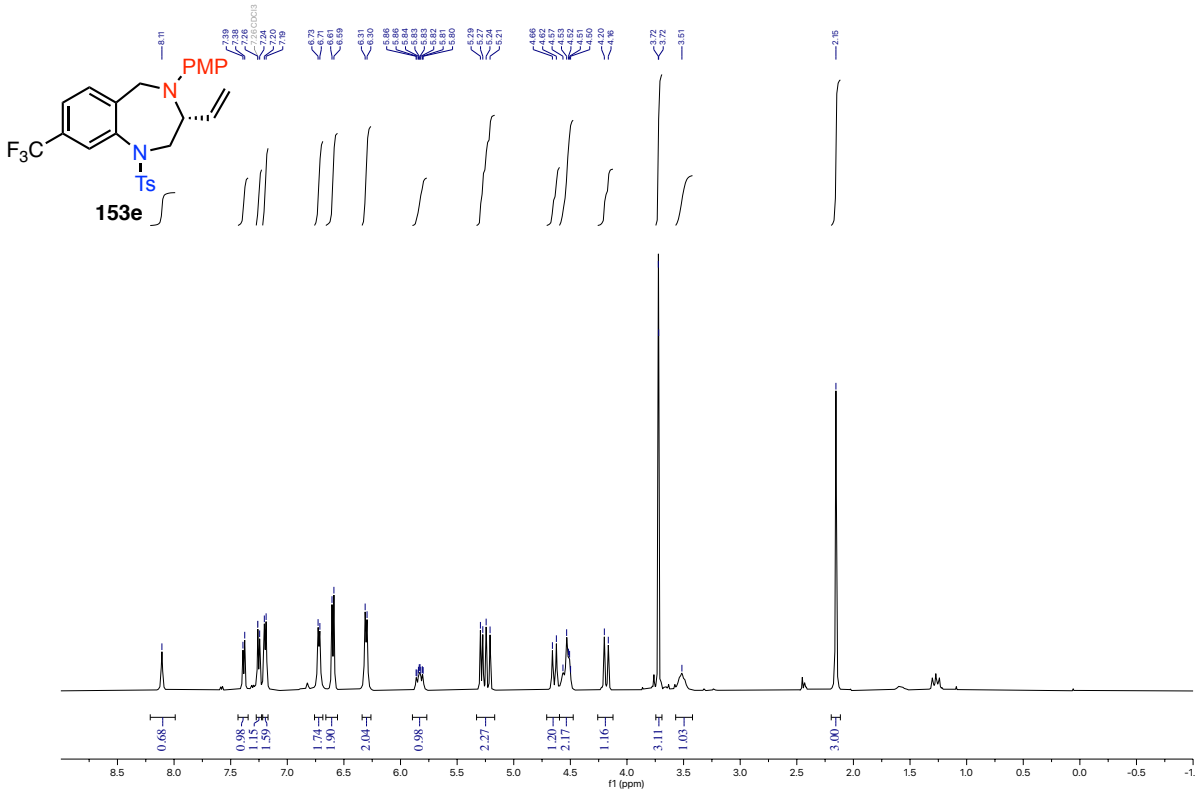



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

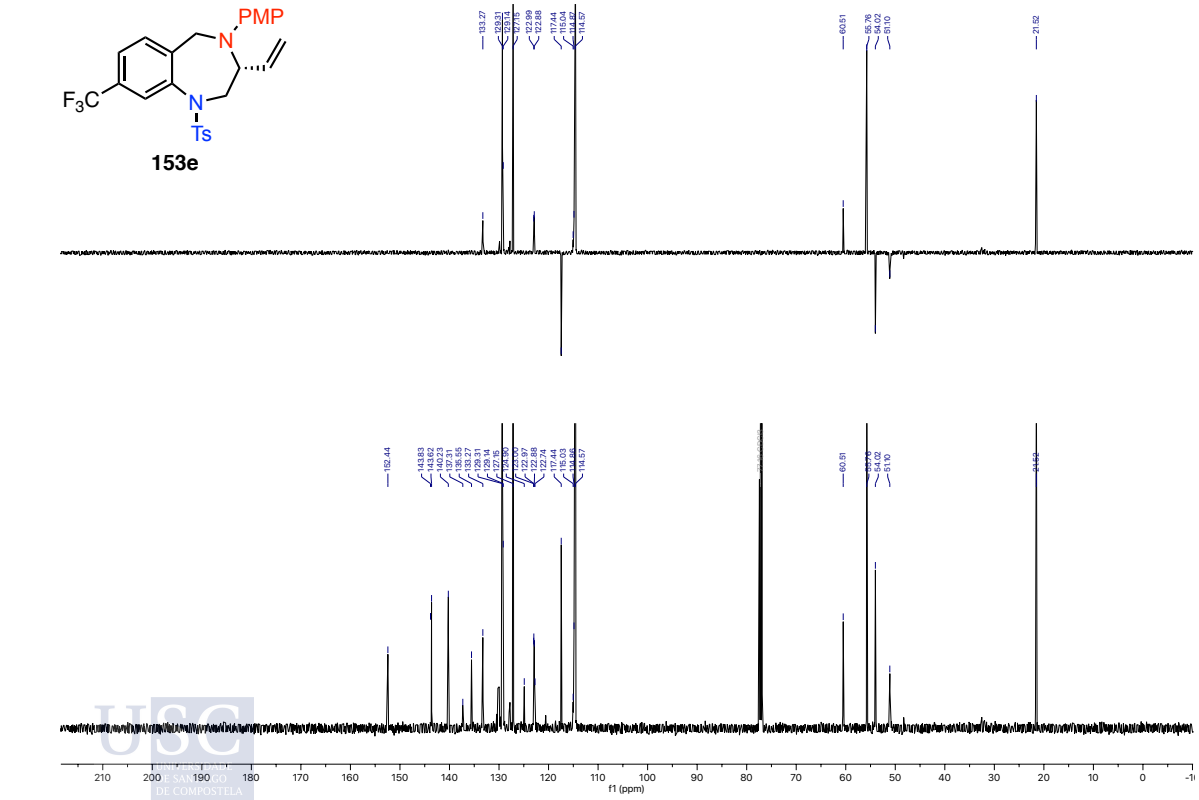



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

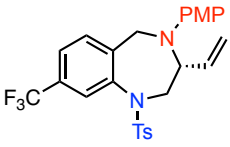



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

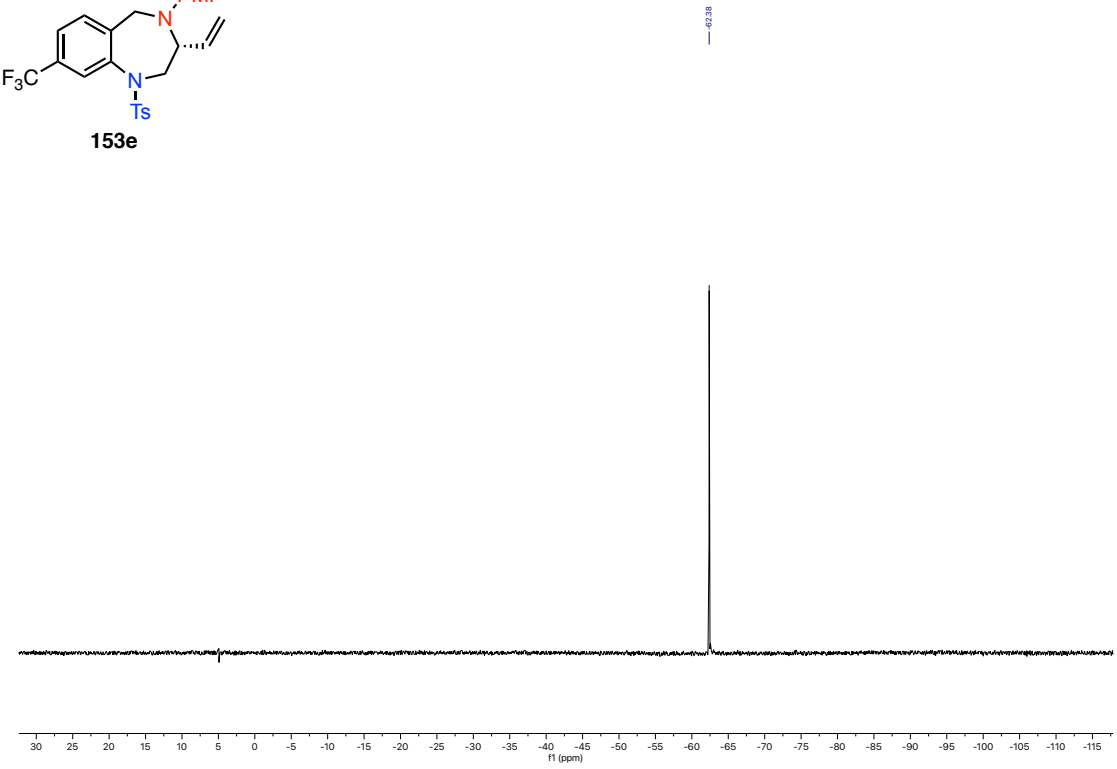



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$^{19}$F-NMR(282 MHz). Solvent $CDCl_3$

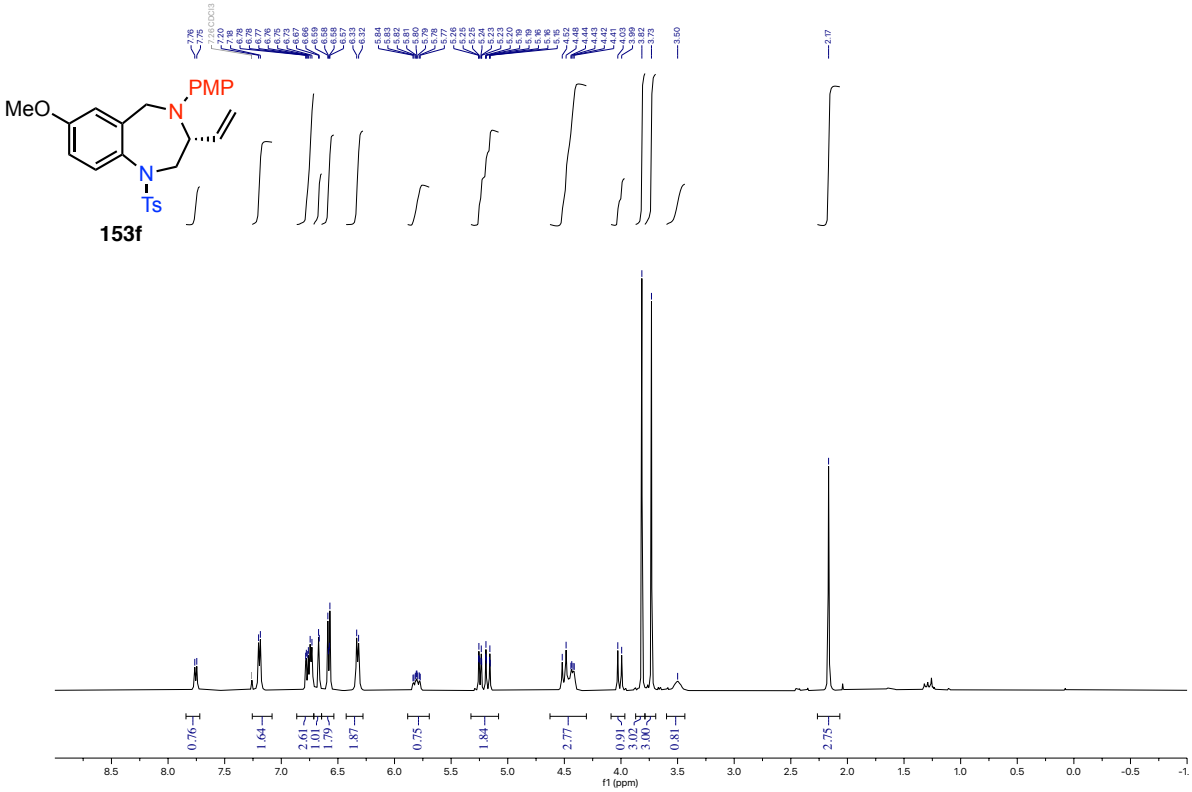



**153e**

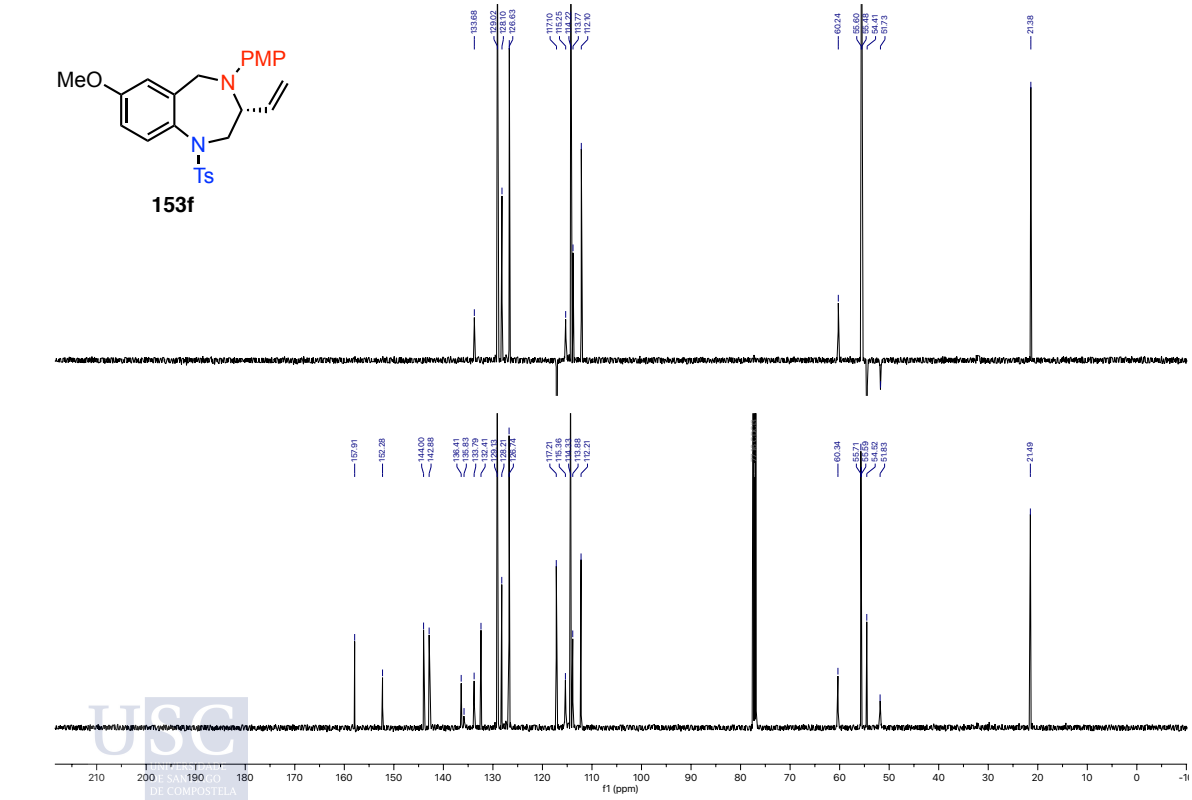



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

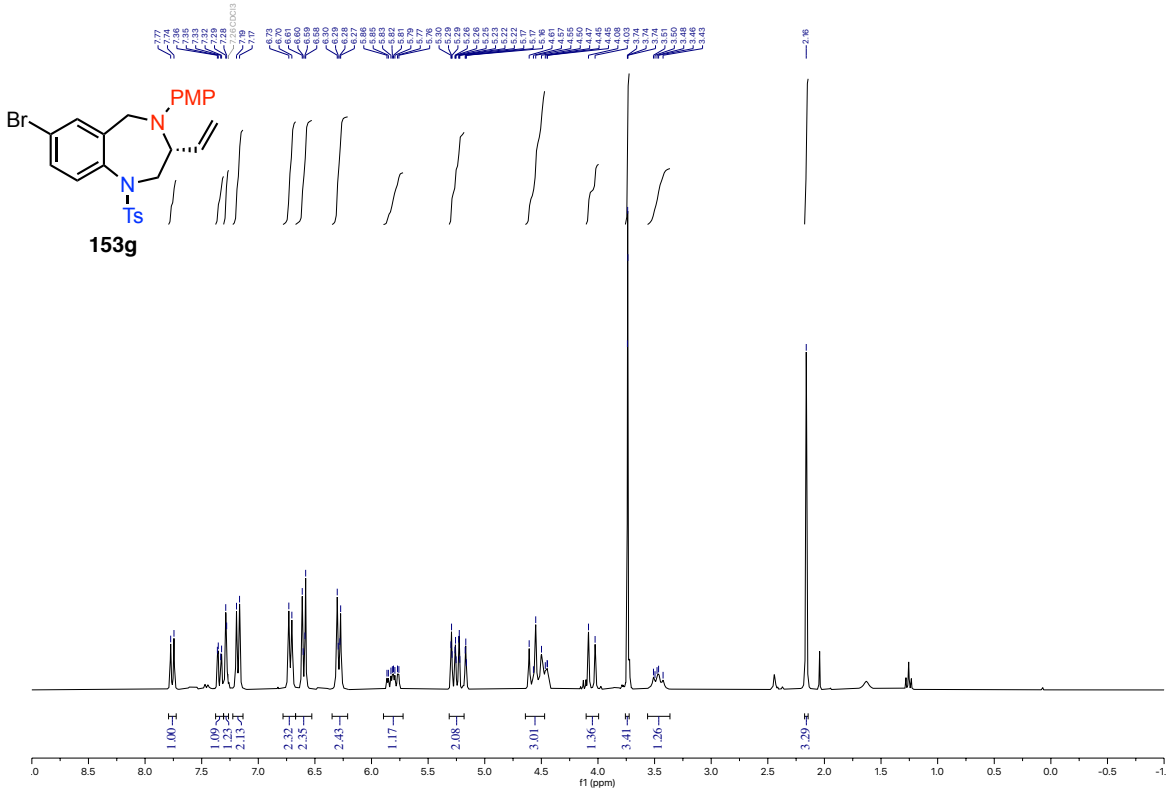



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

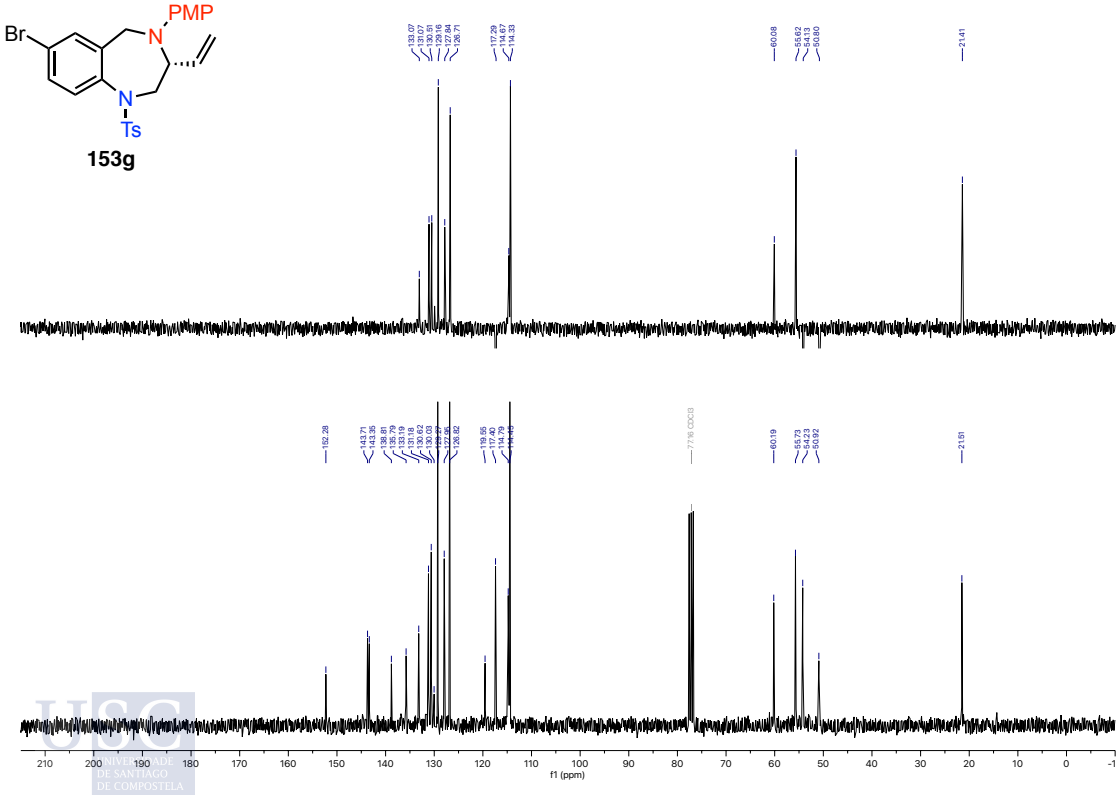



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$^{1}$H-NMR (00 MHz). Solvent $CDCl_3$

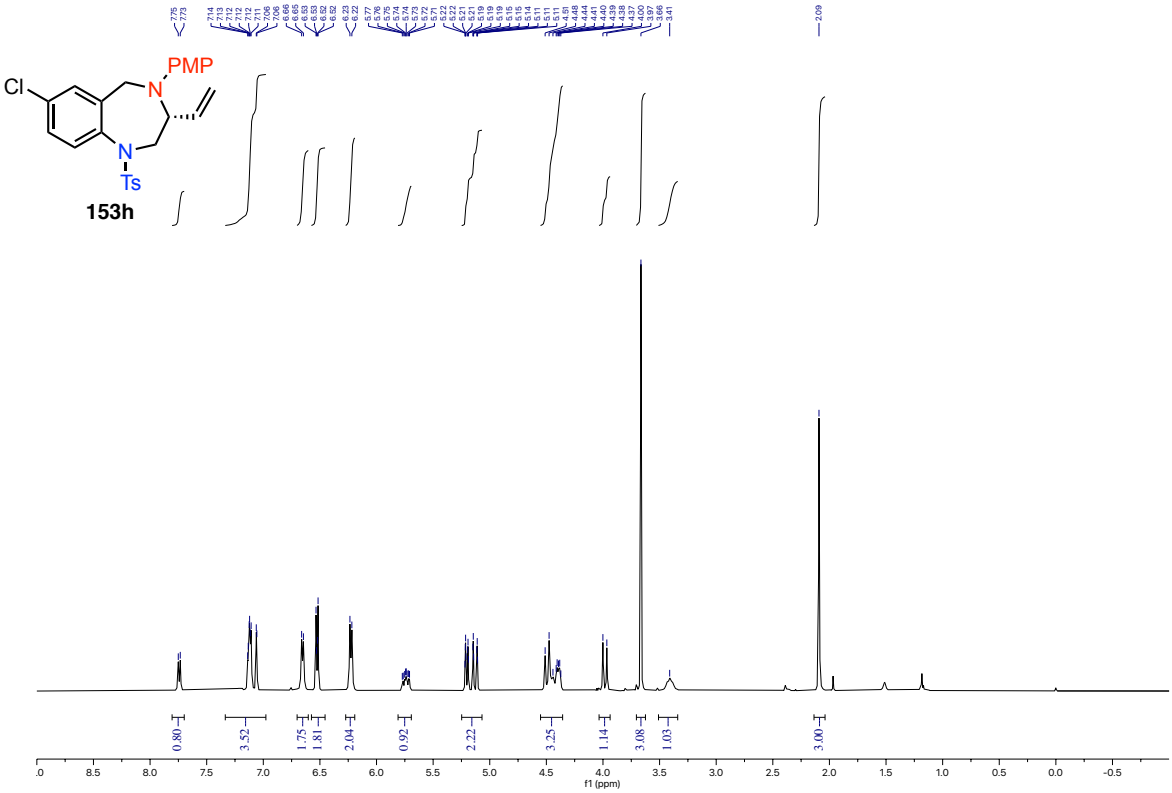



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

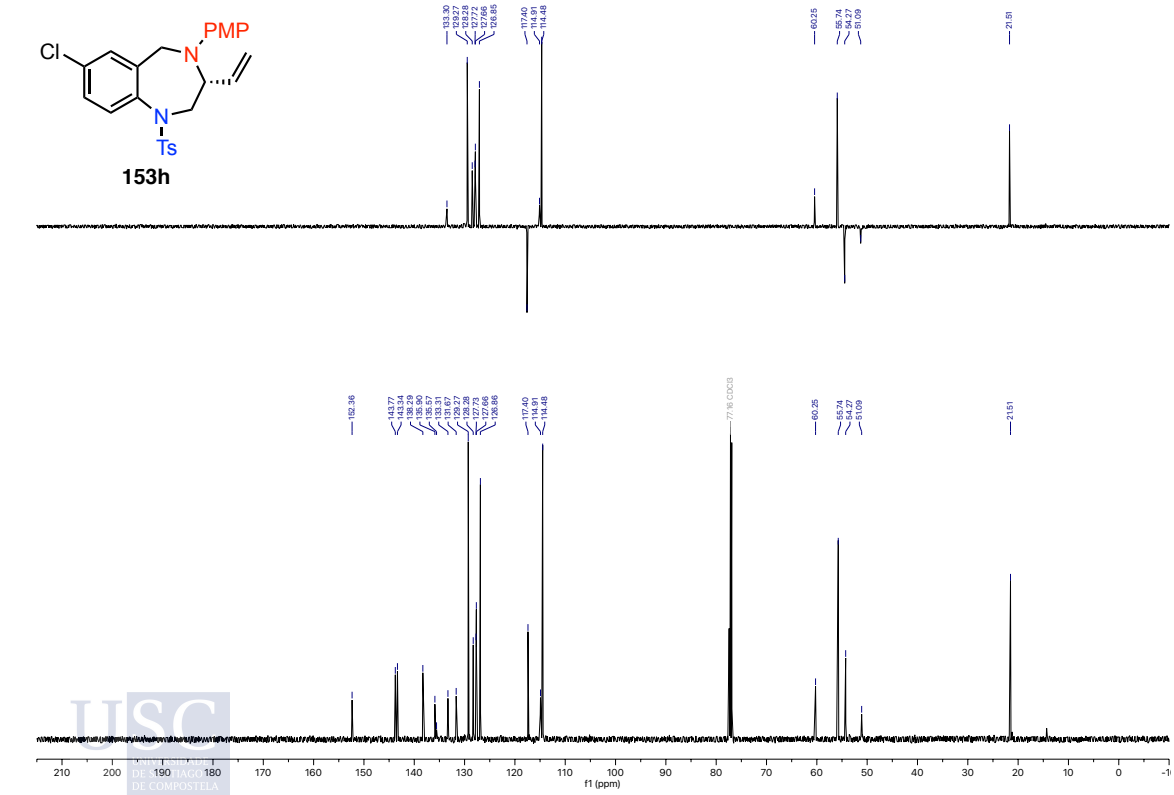



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

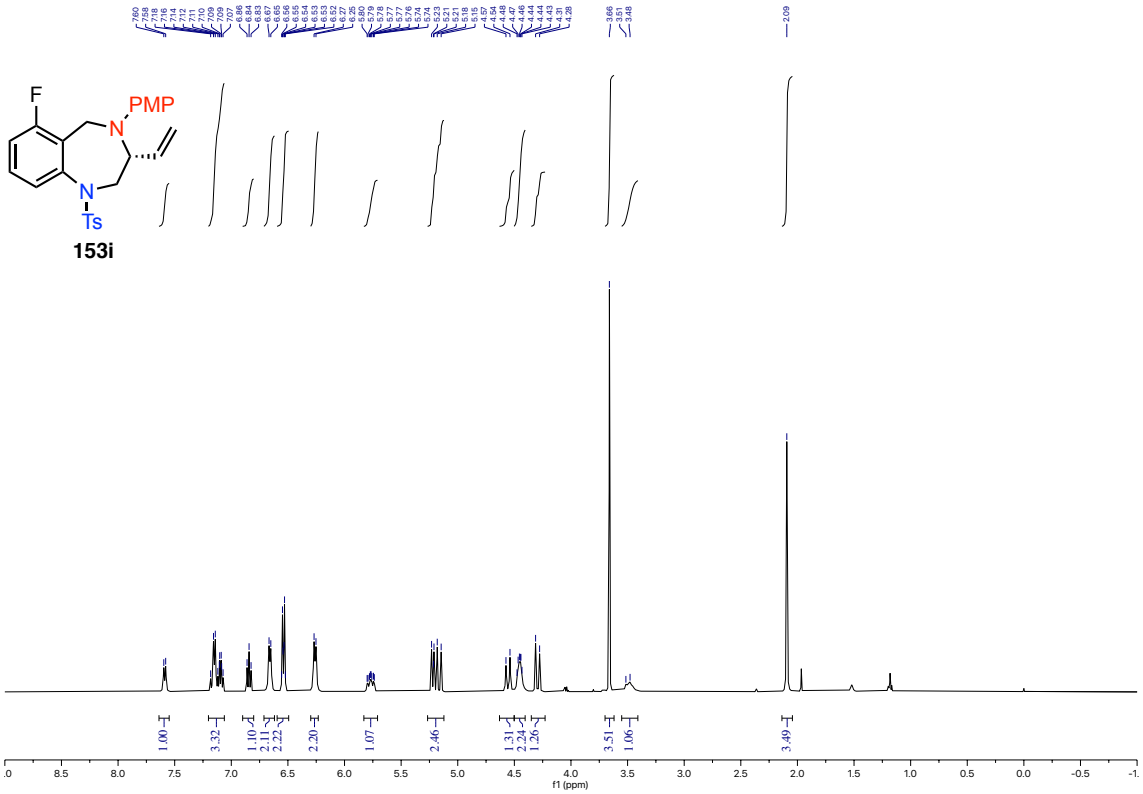



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

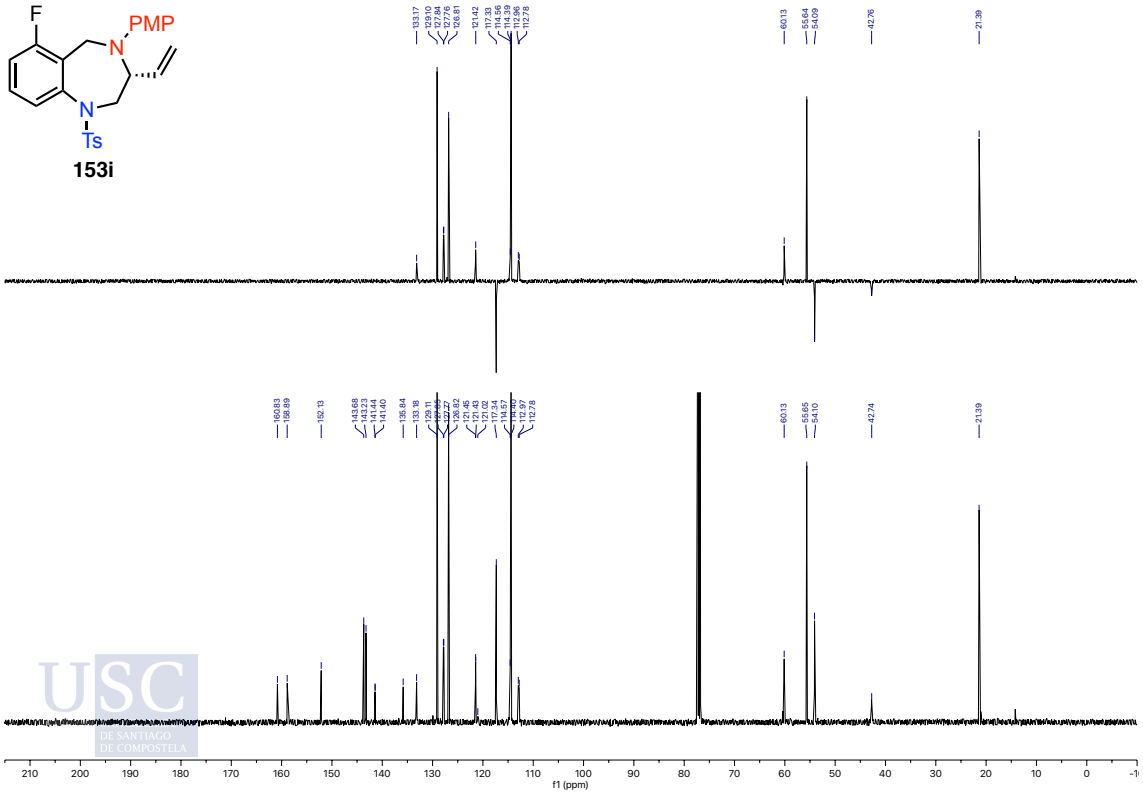



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$




$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

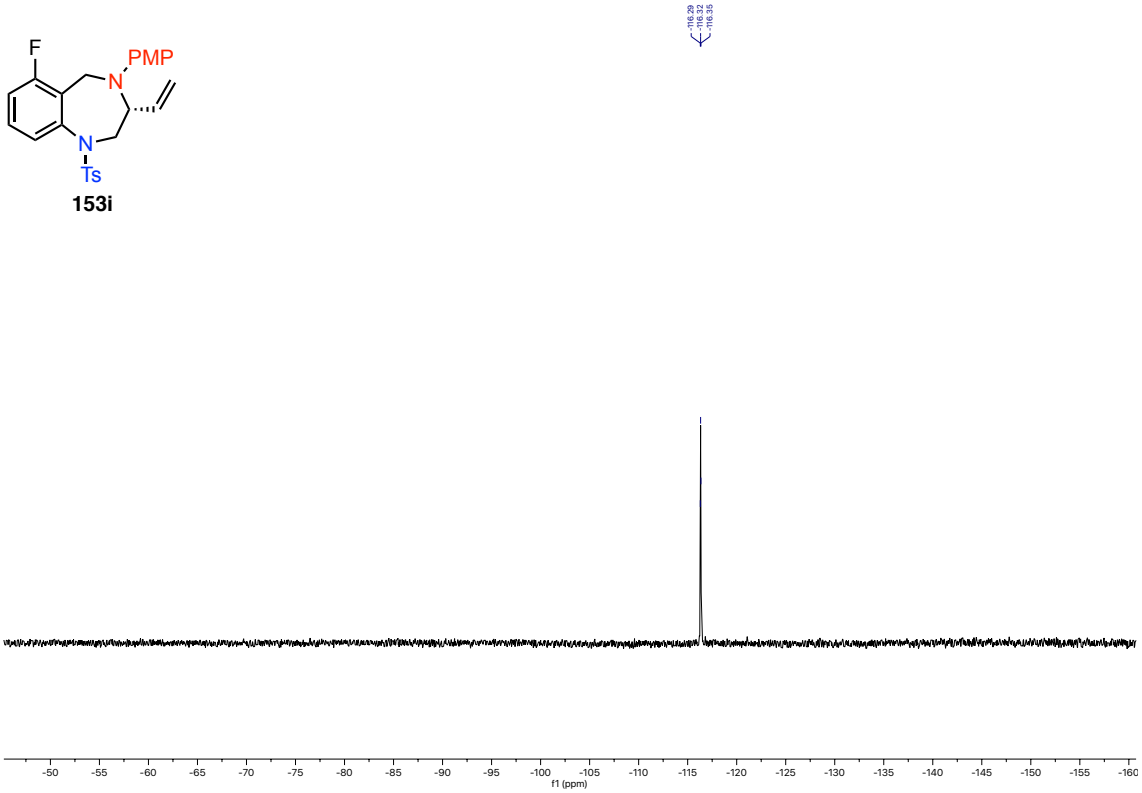



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$^{19}$F-NMR (282 MHz). Solvent $CDCl_3$

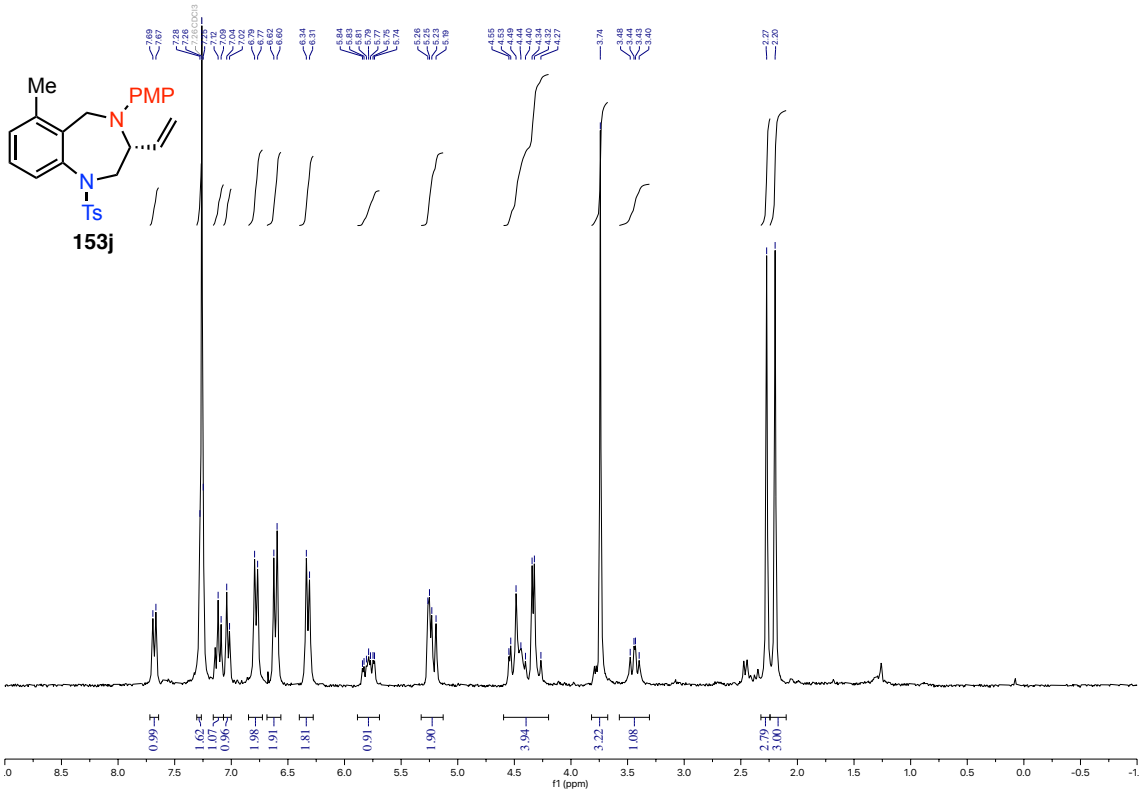



**153i**

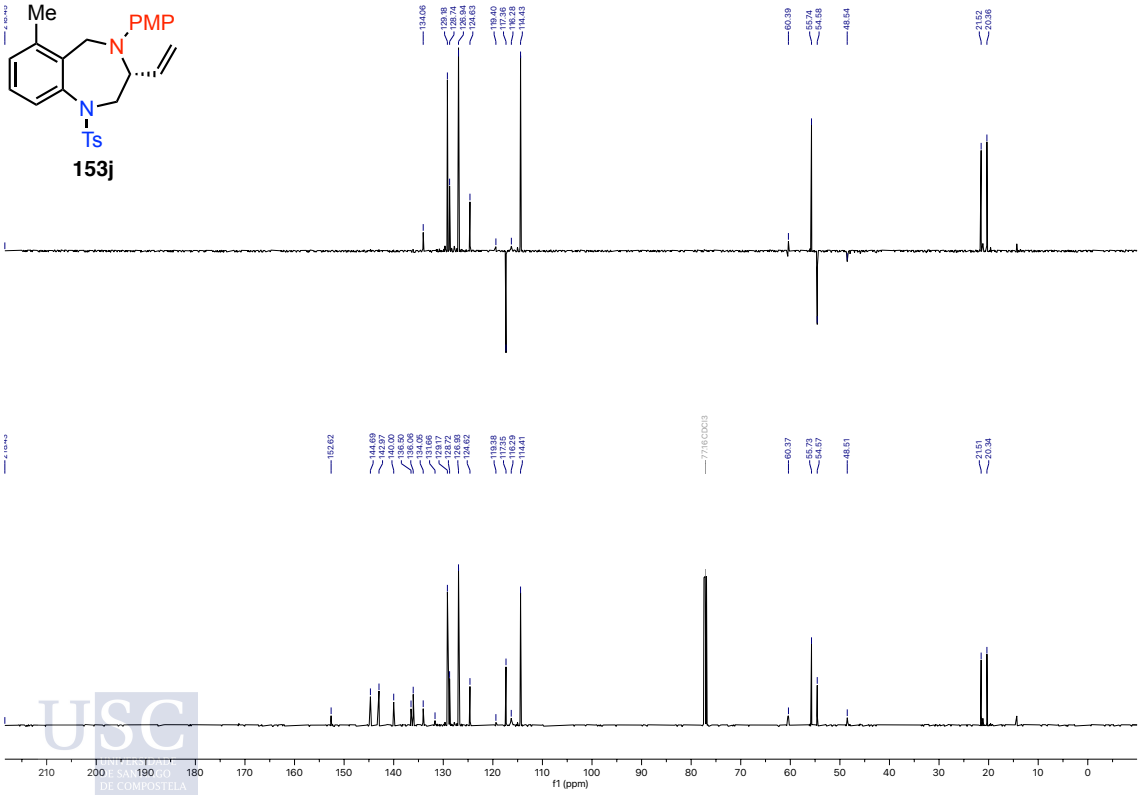



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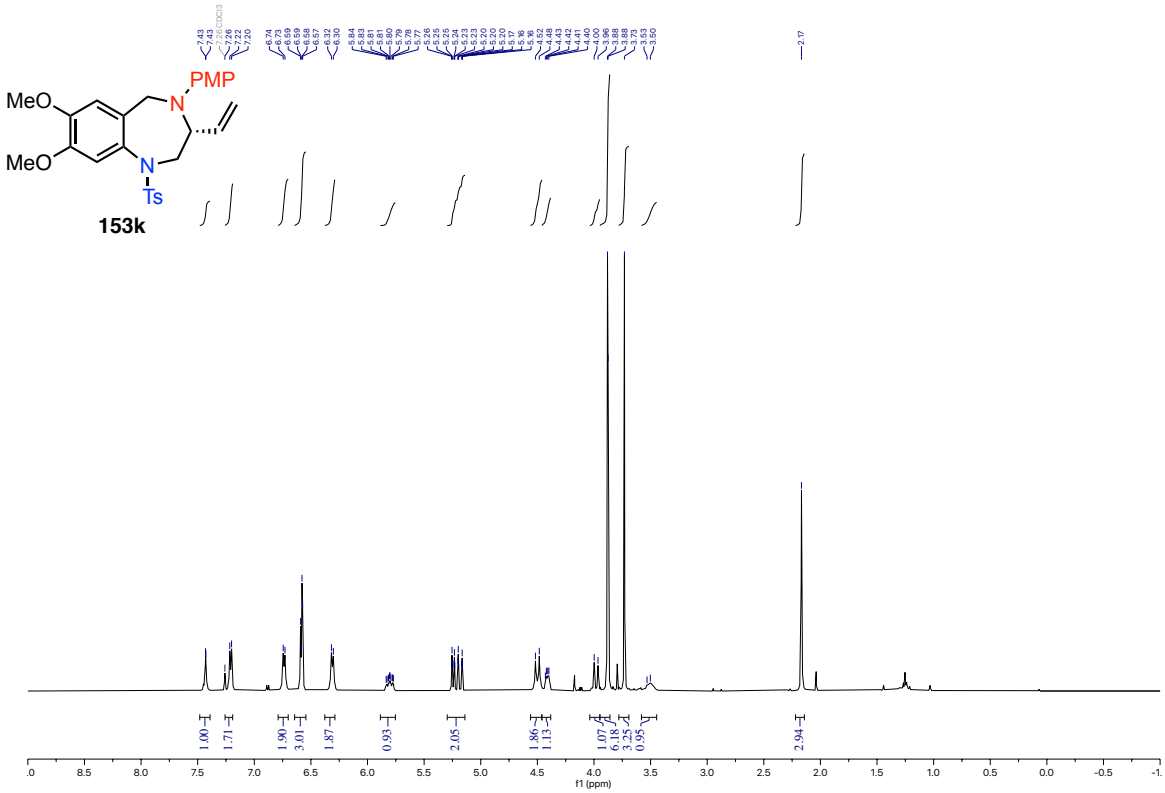
$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$



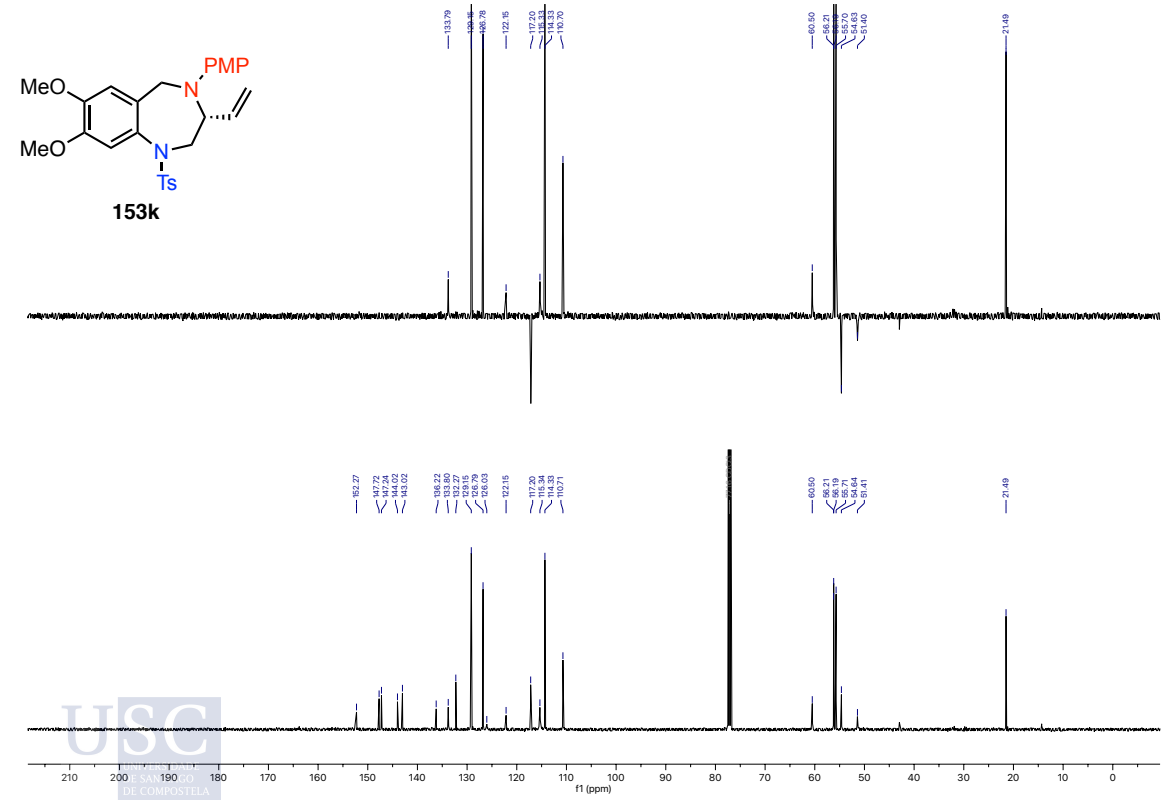

$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$



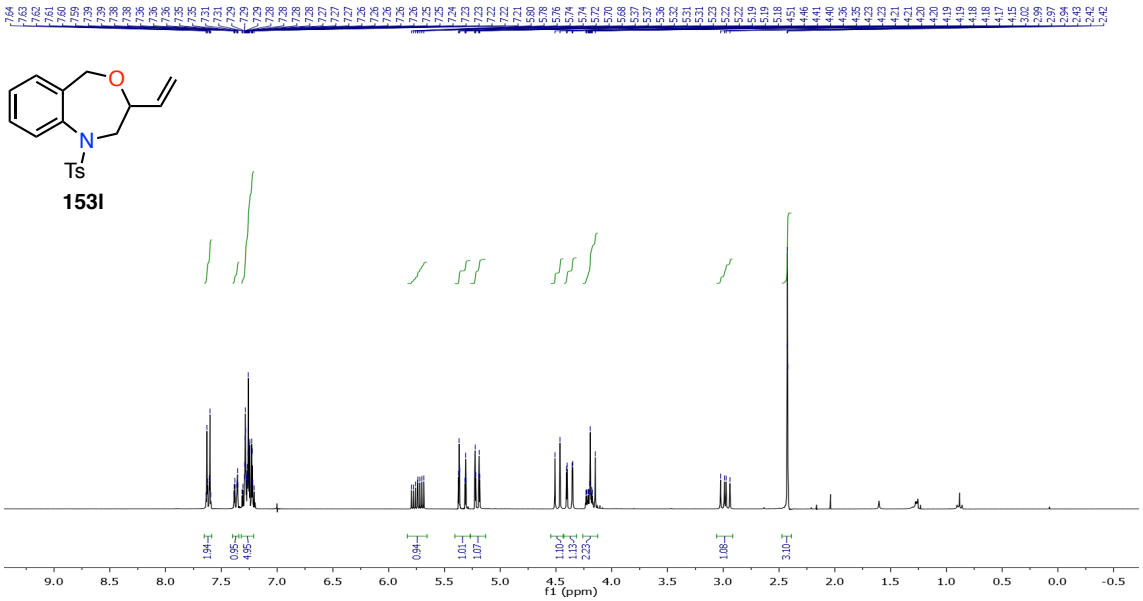
$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$



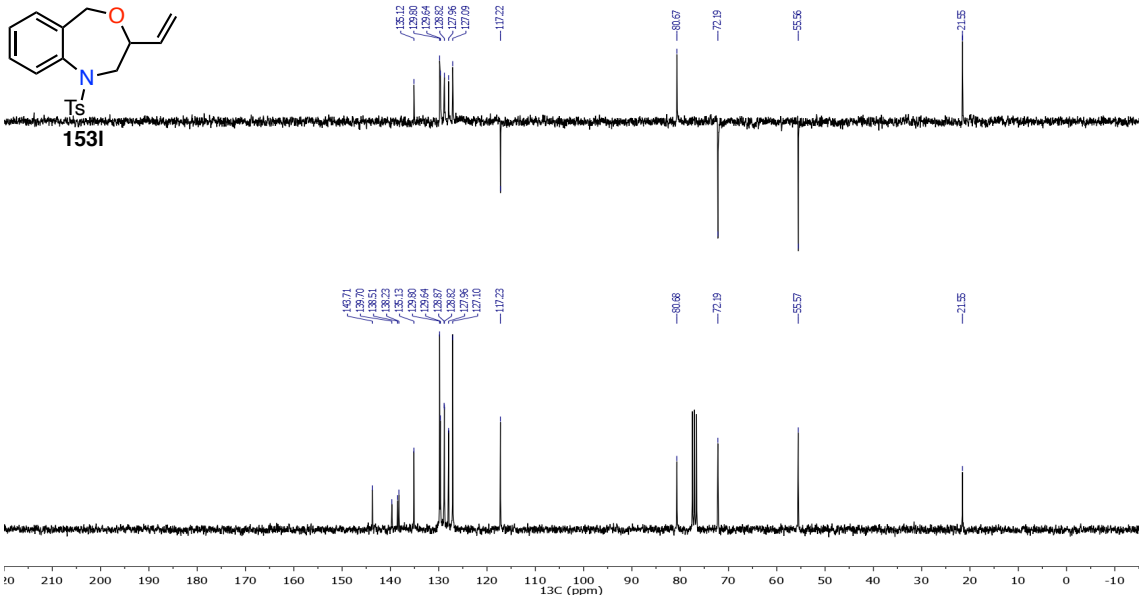

$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$



$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

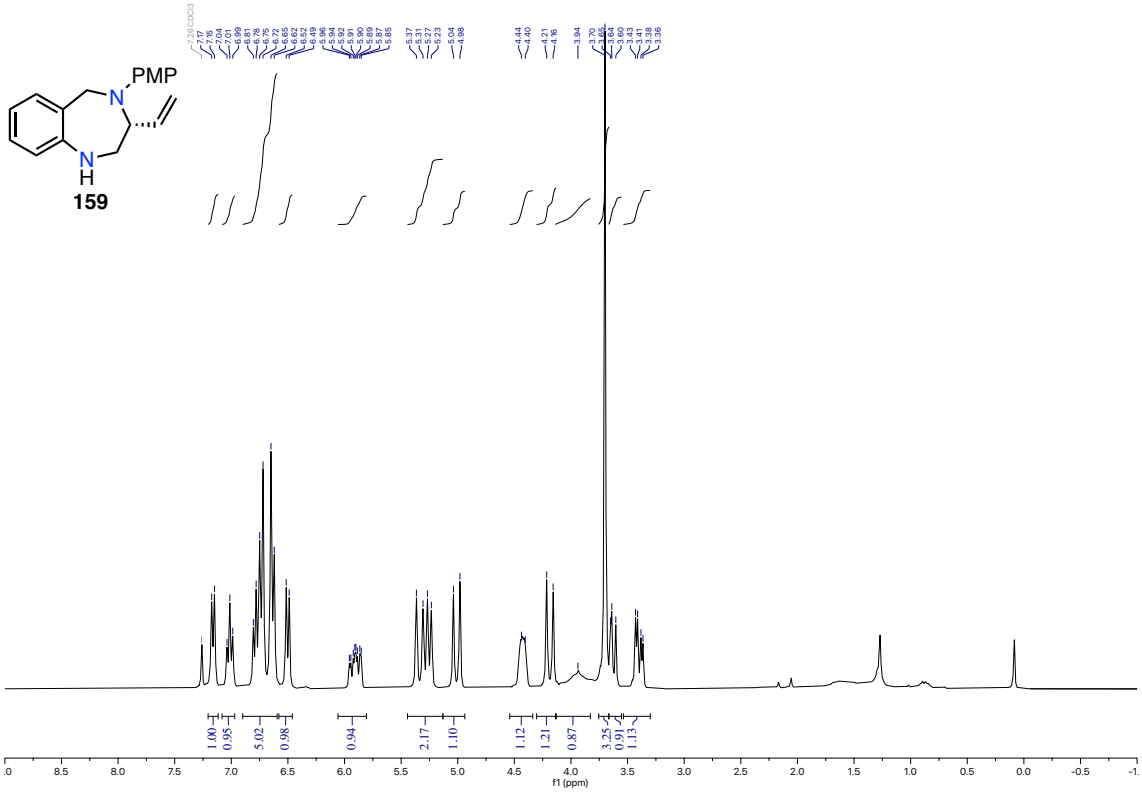



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

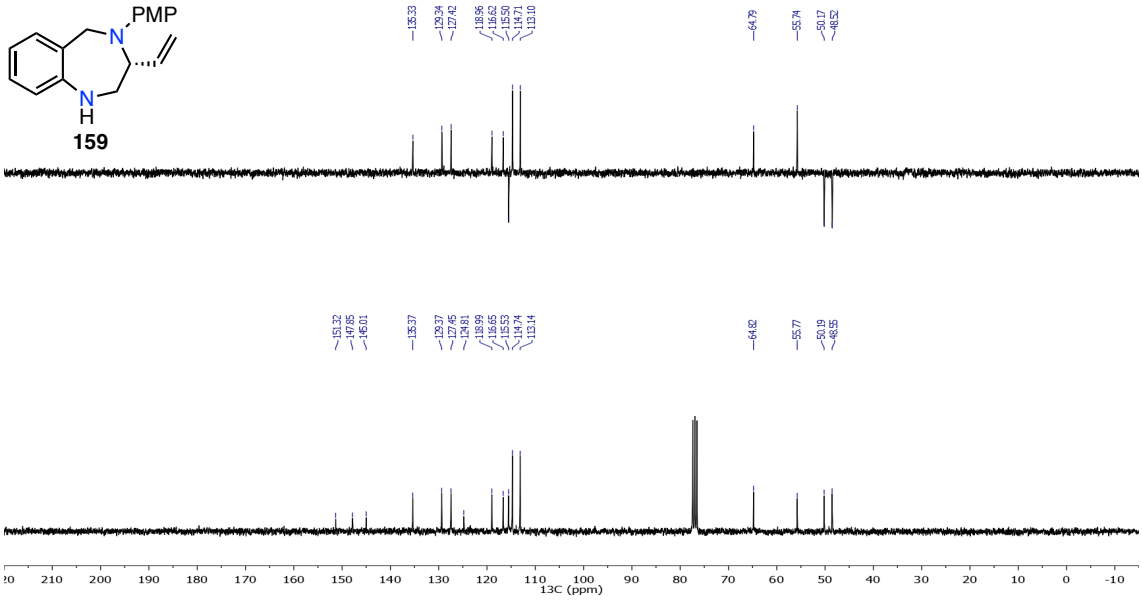



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

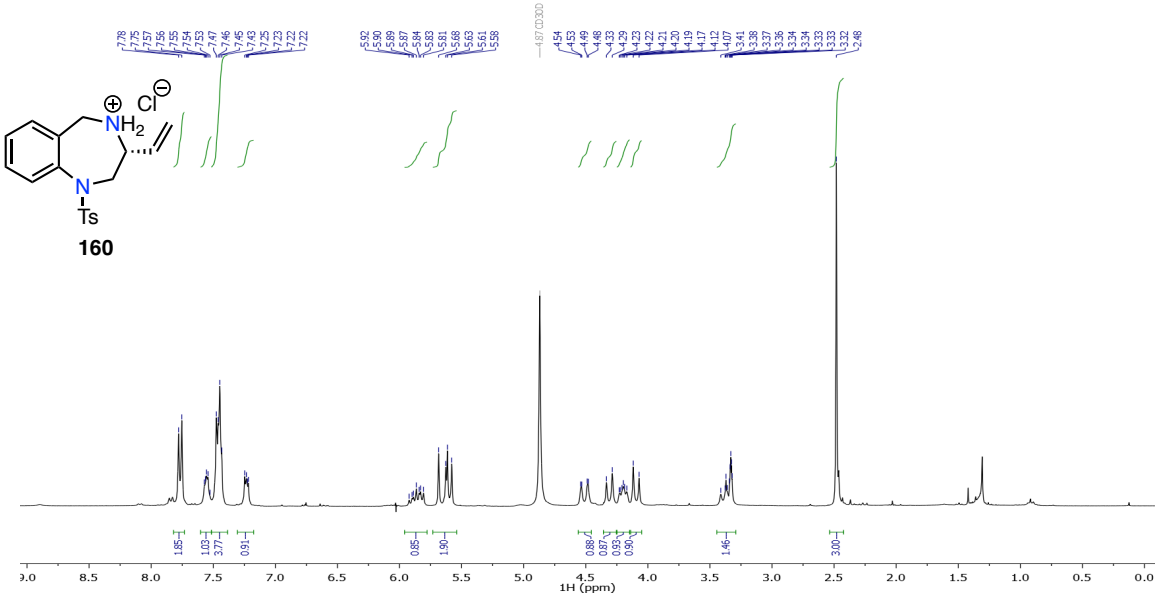



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

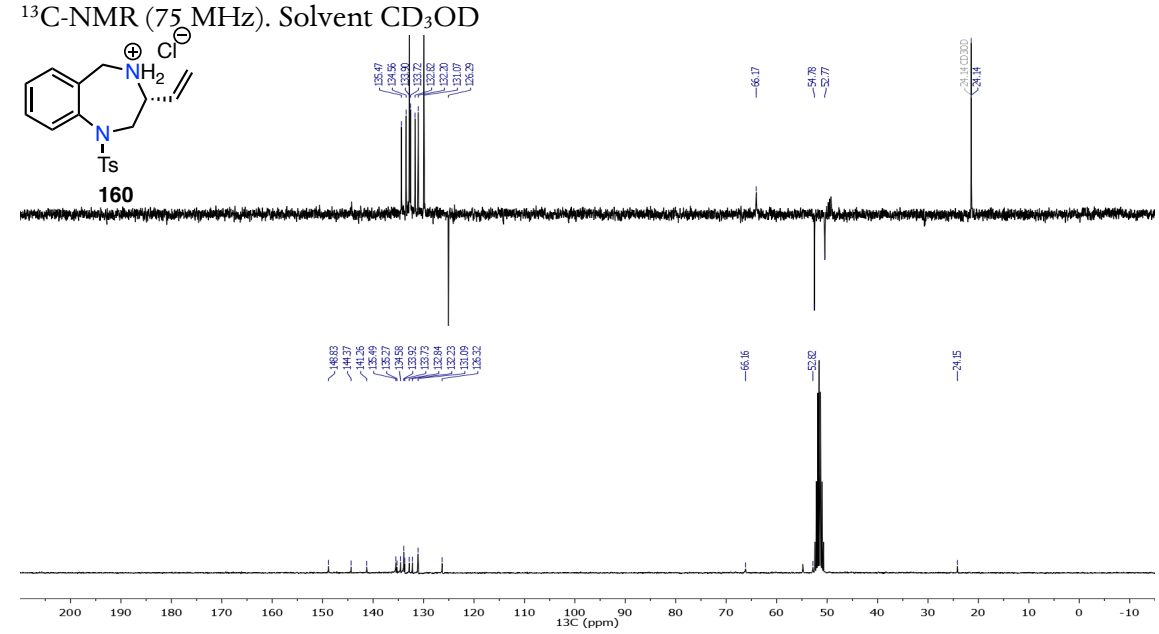



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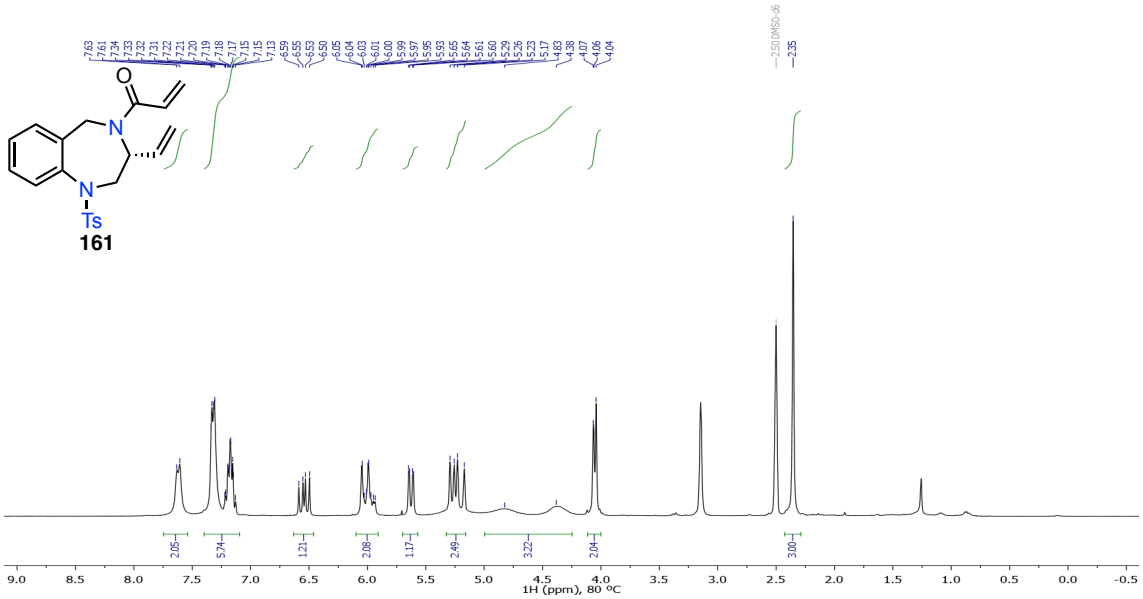
$^{1}$H-NMR (300 MHz). Solvent $CD_3OD$



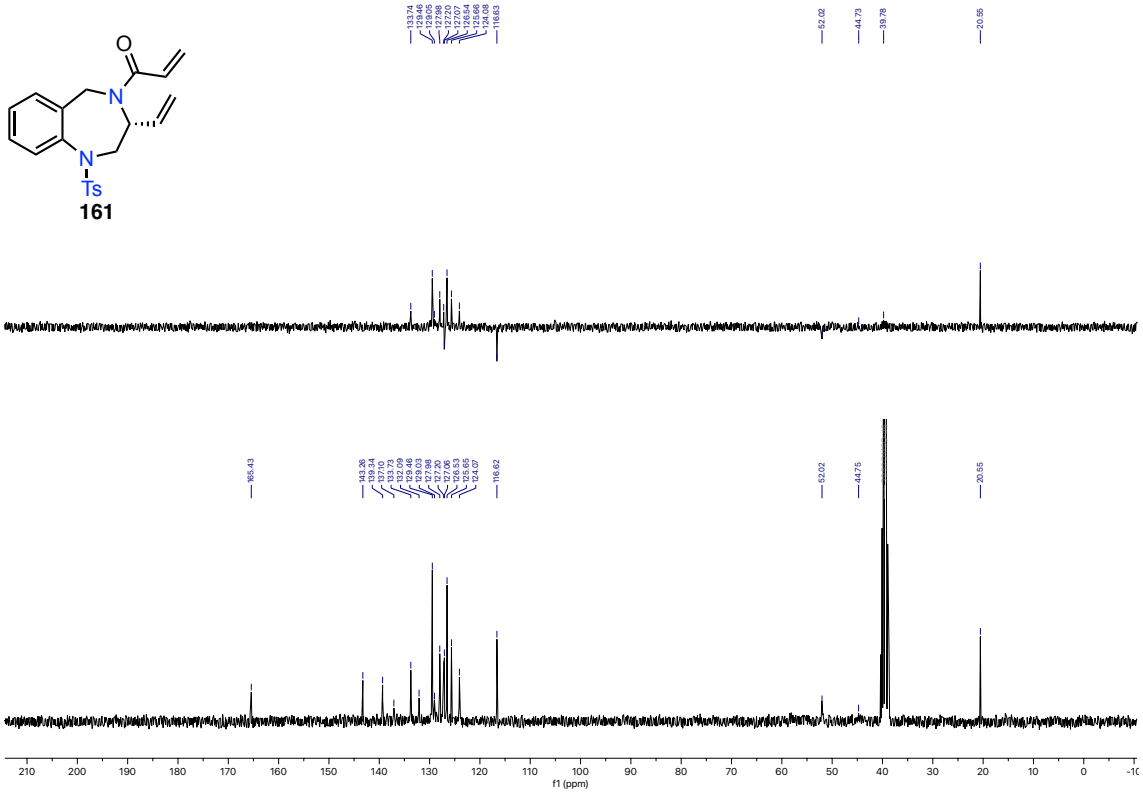

$^{13}$C-NMR (75 MHz). Solvent $CD_3OD$



$^{1}$H-NMR (300 MHz). Solvent DMSO-$d_6$

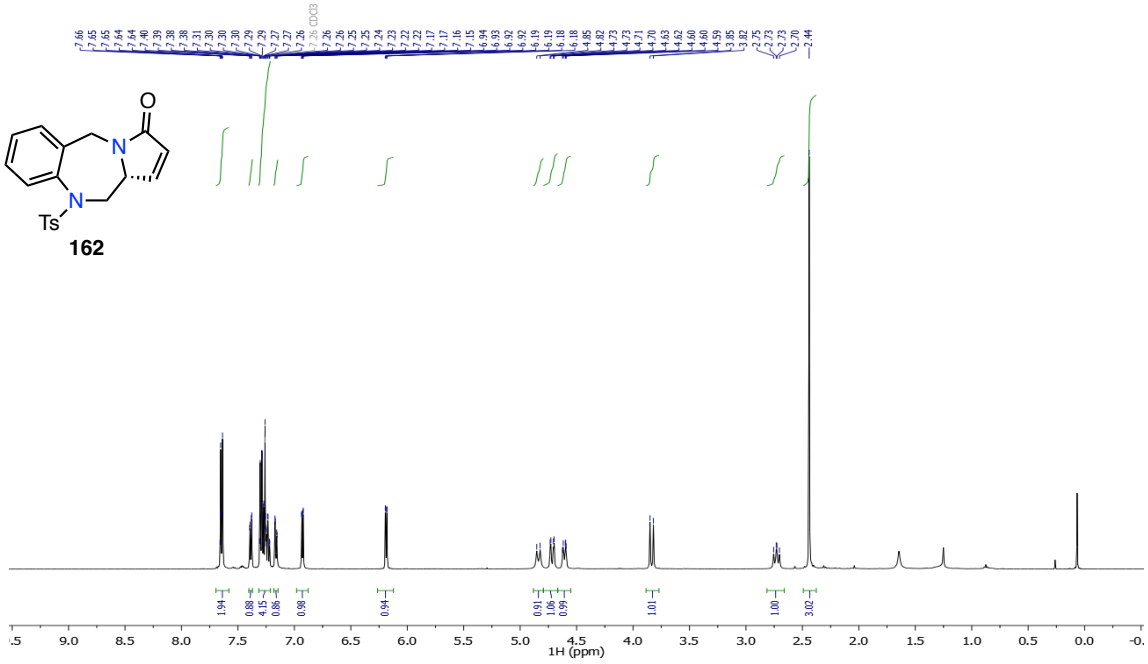



$^{13}$C-NMR (75 MHz). Solvent DMSO-$d_6$

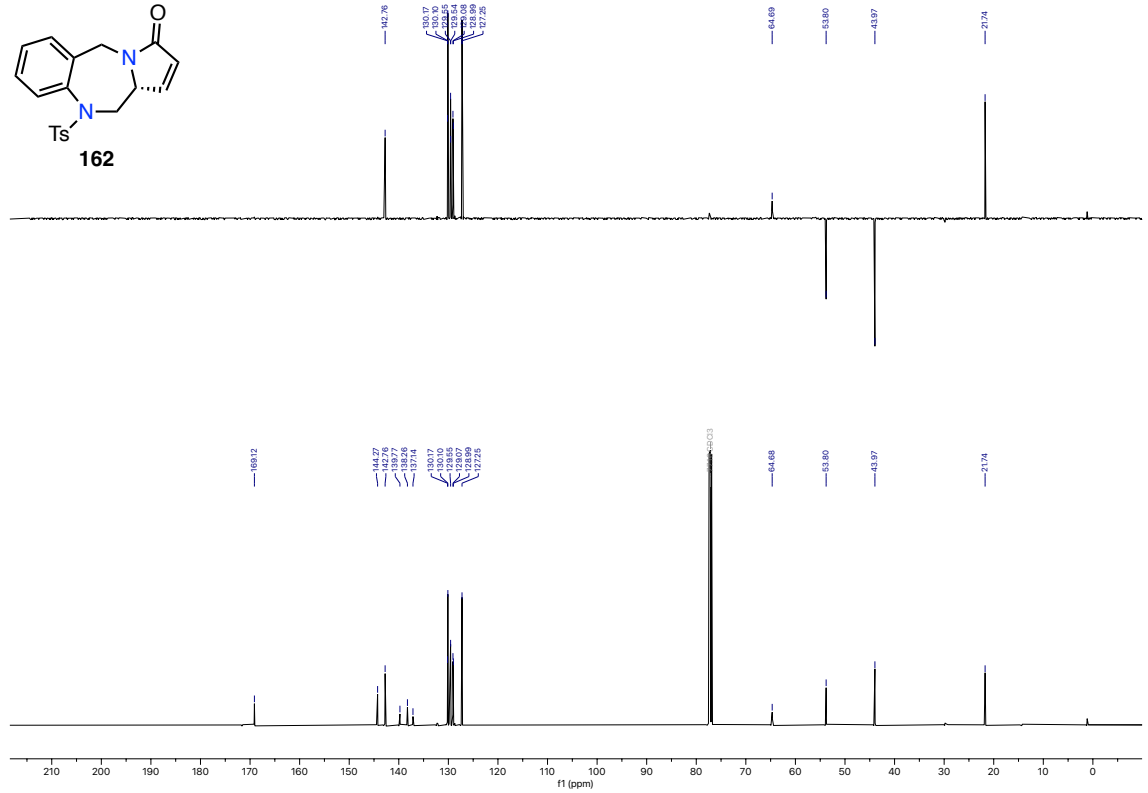



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

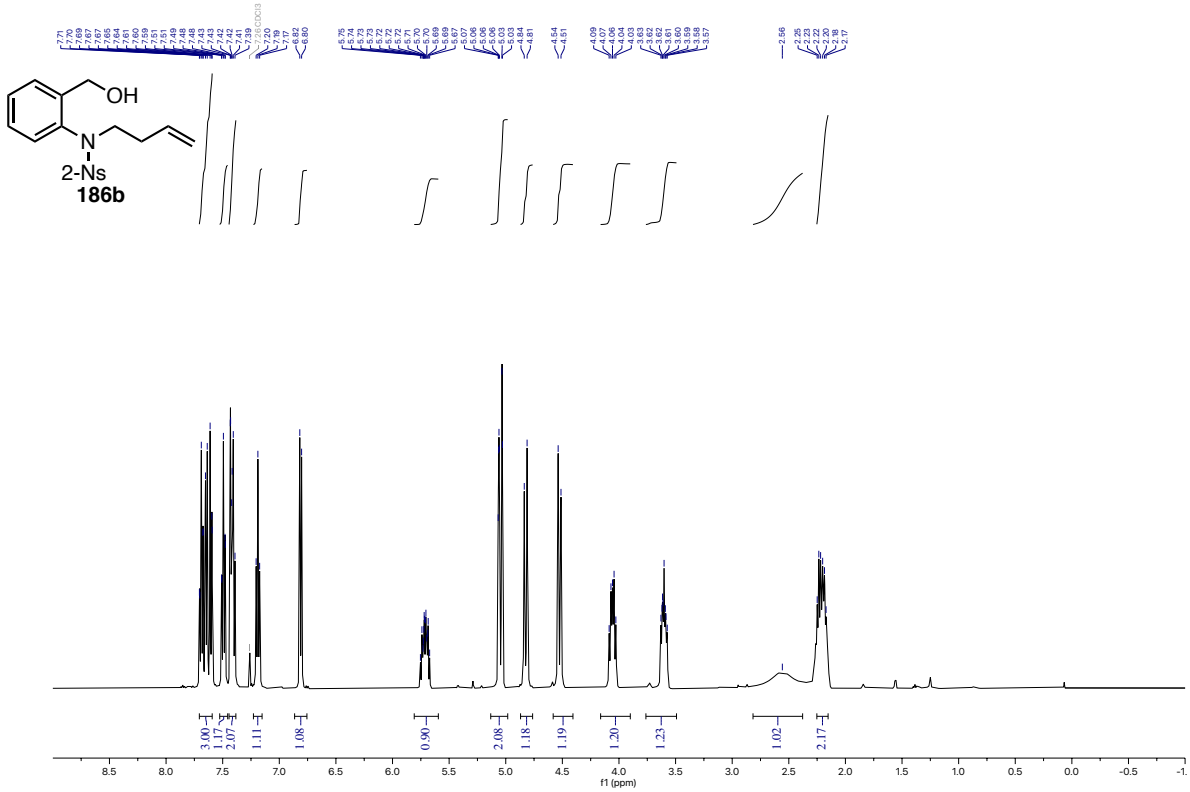



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

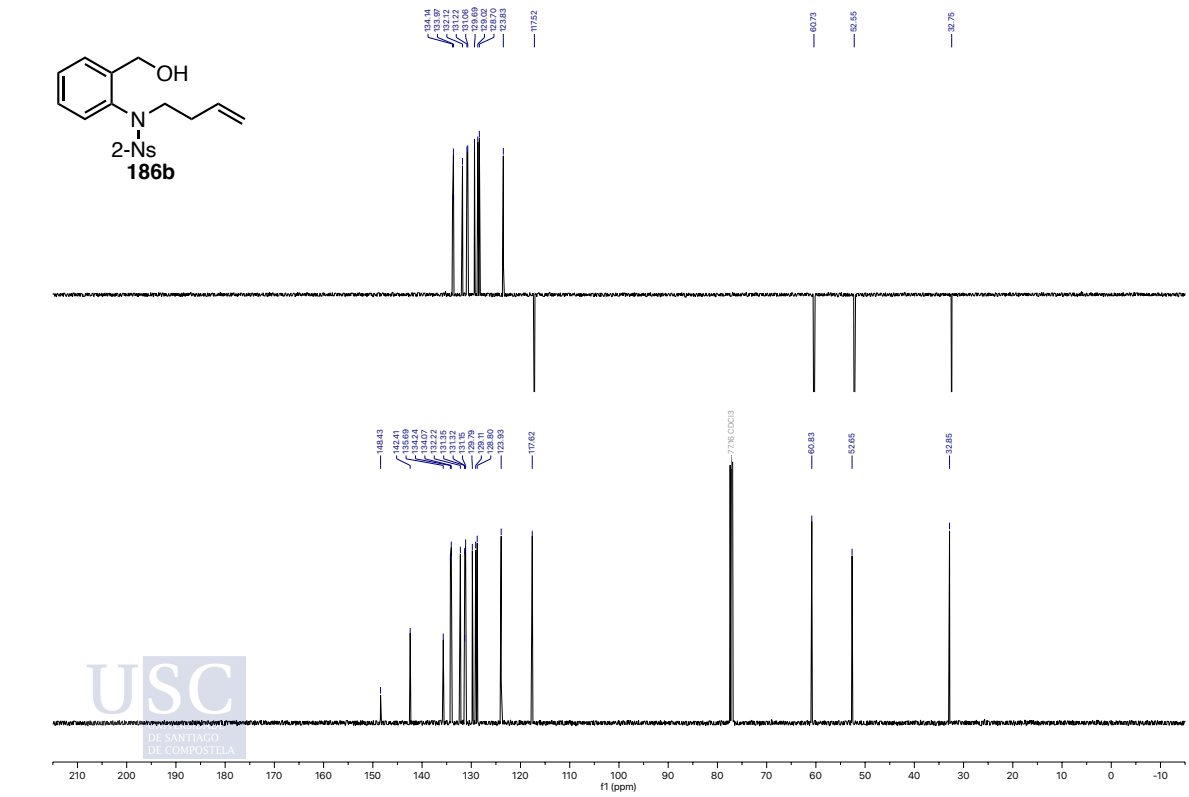



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

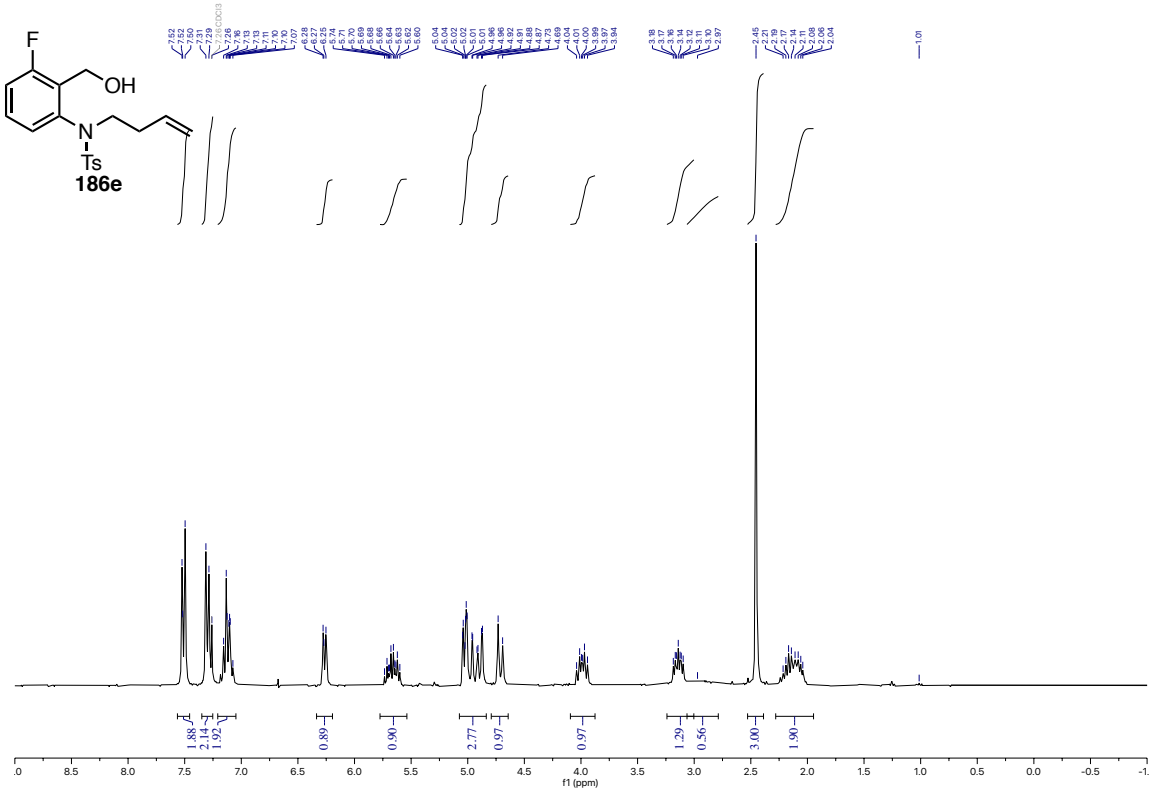



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

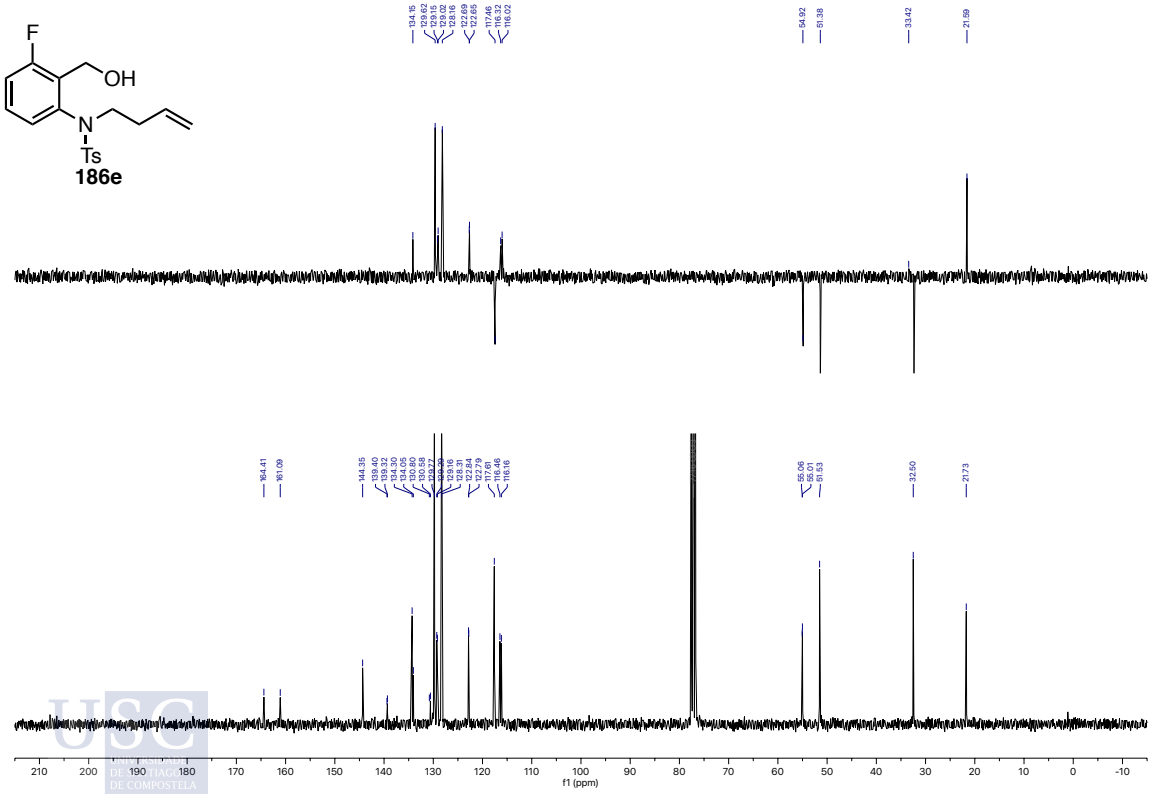



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

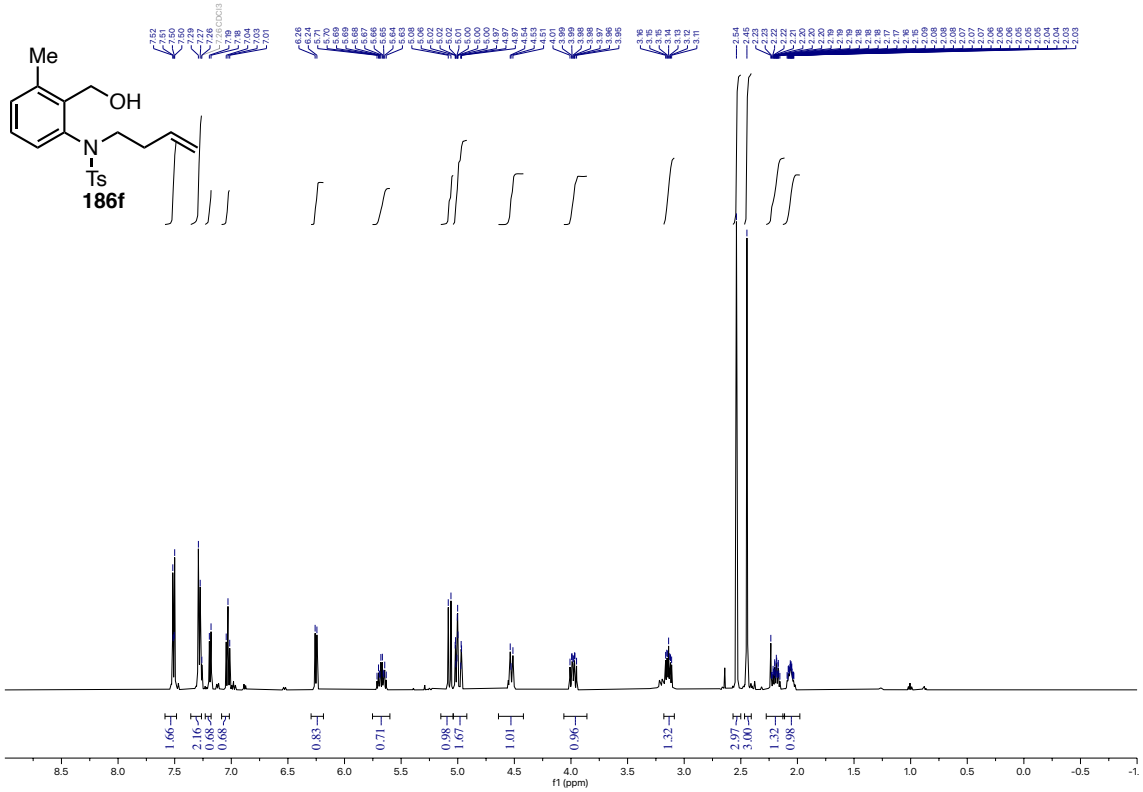



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

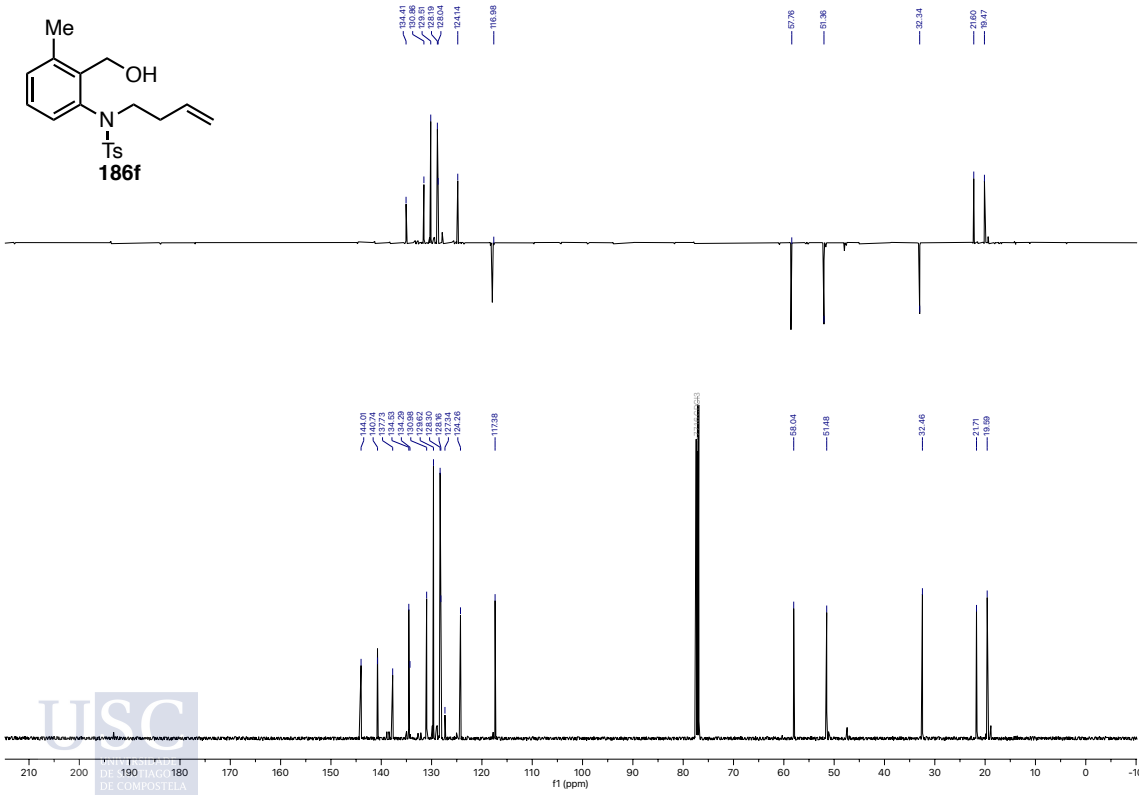



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

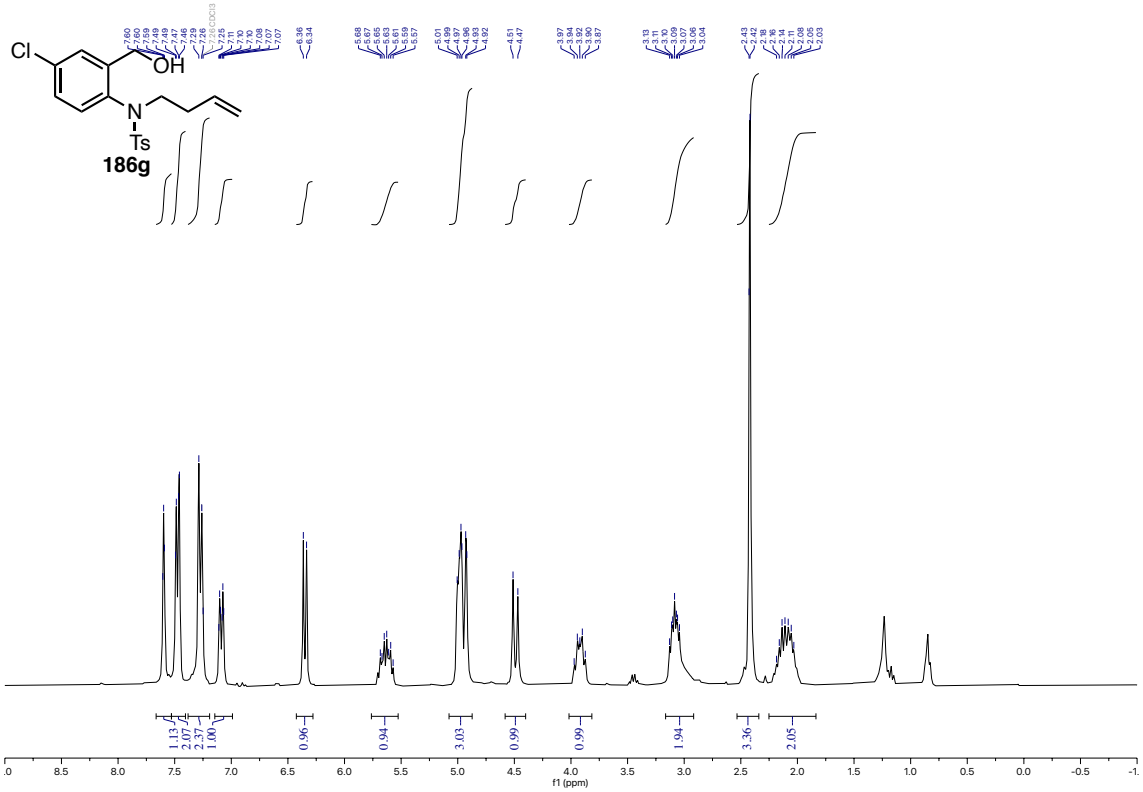



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

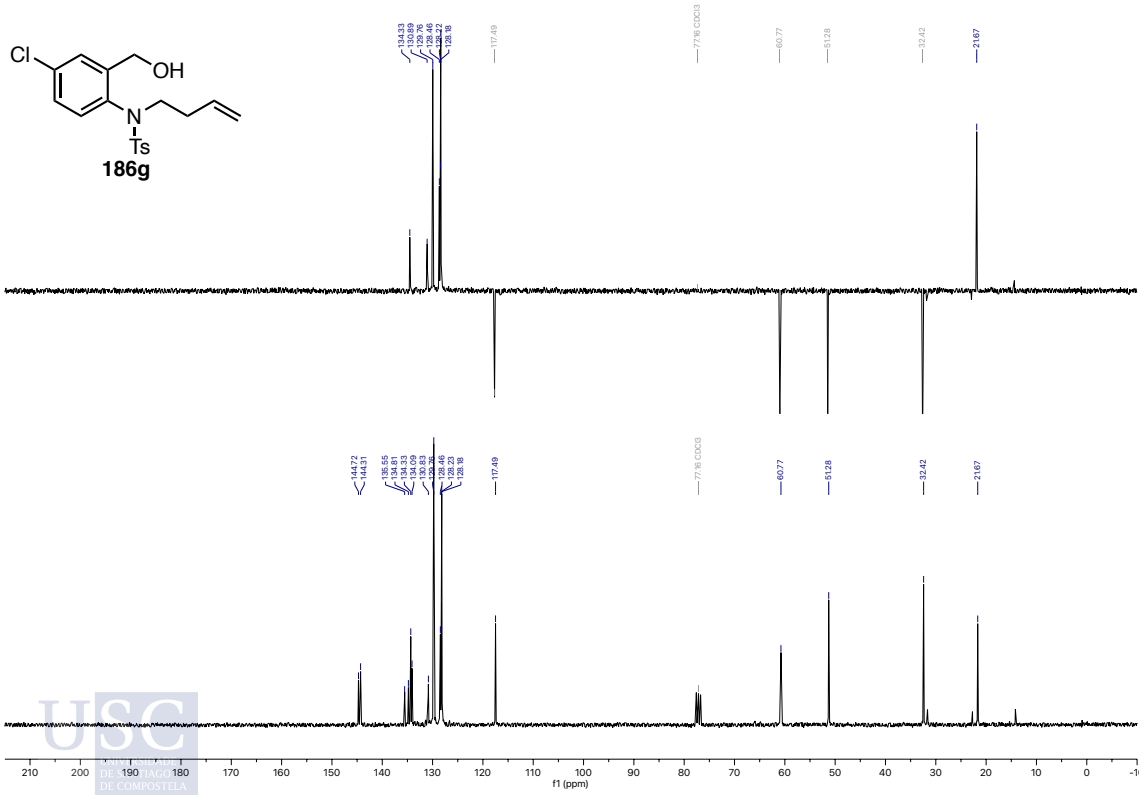



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

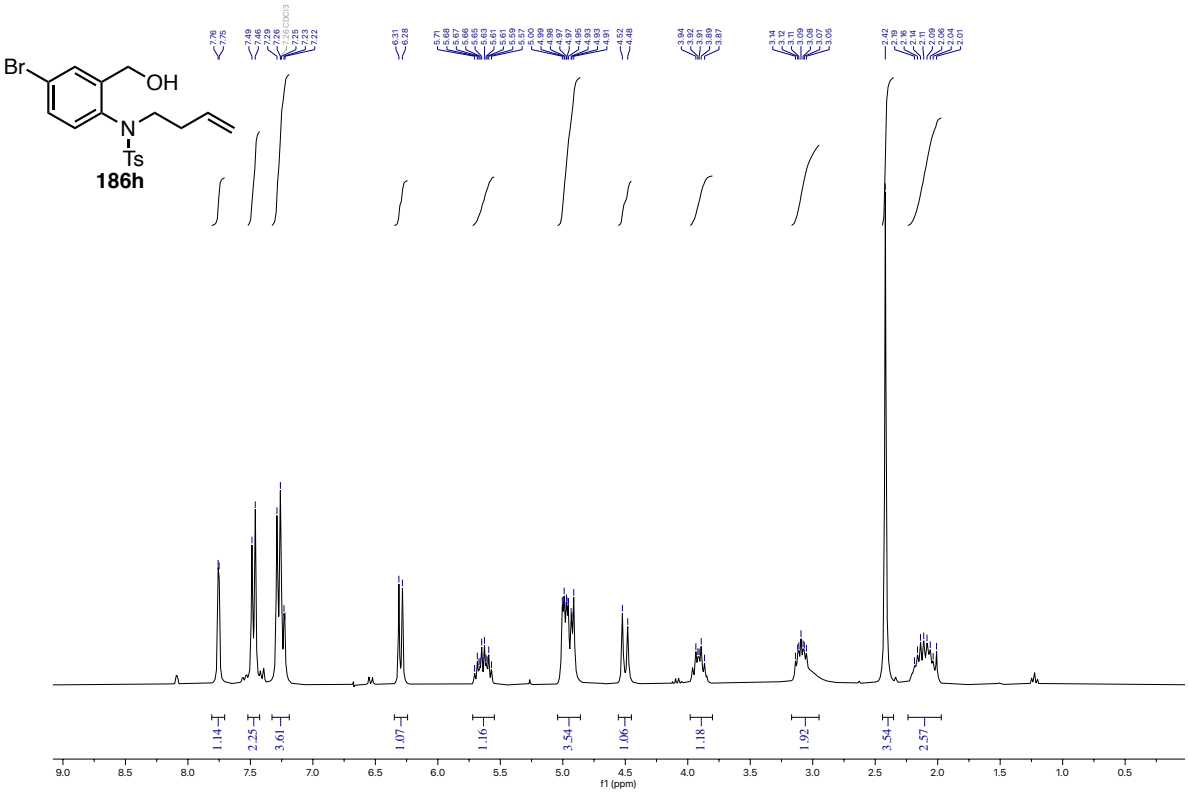



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

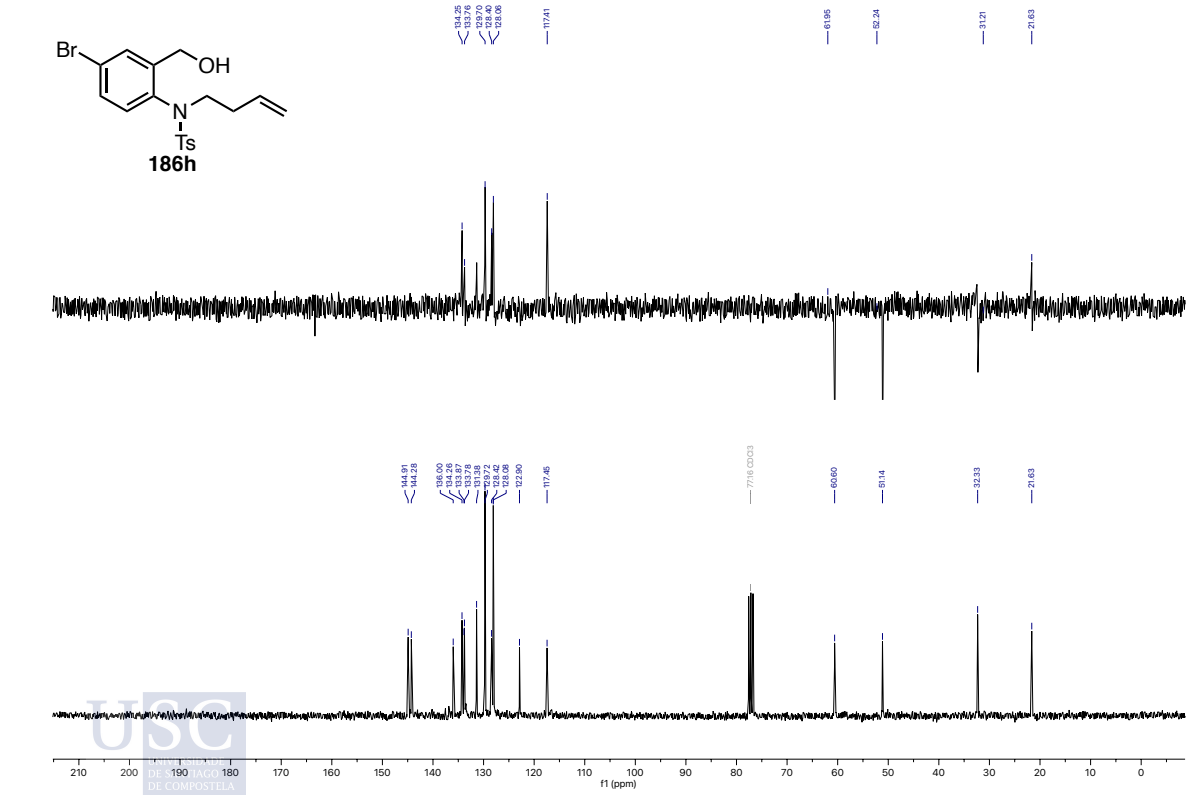



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

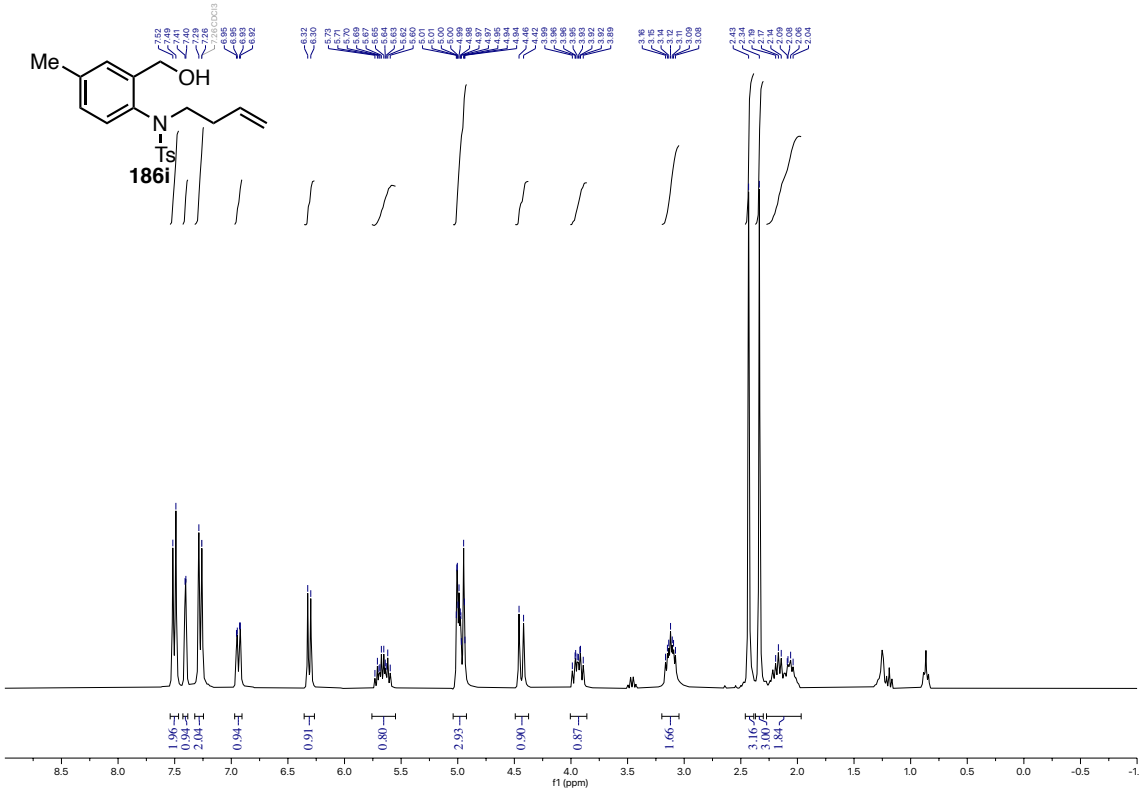



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

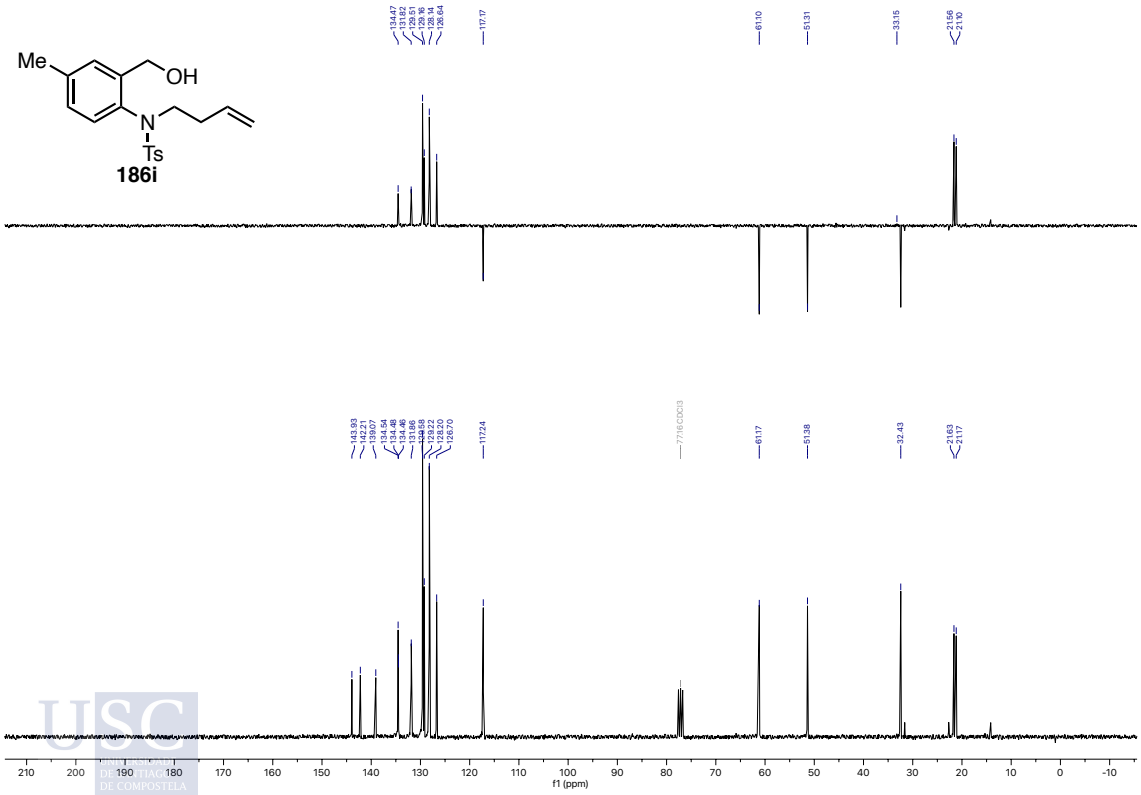



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

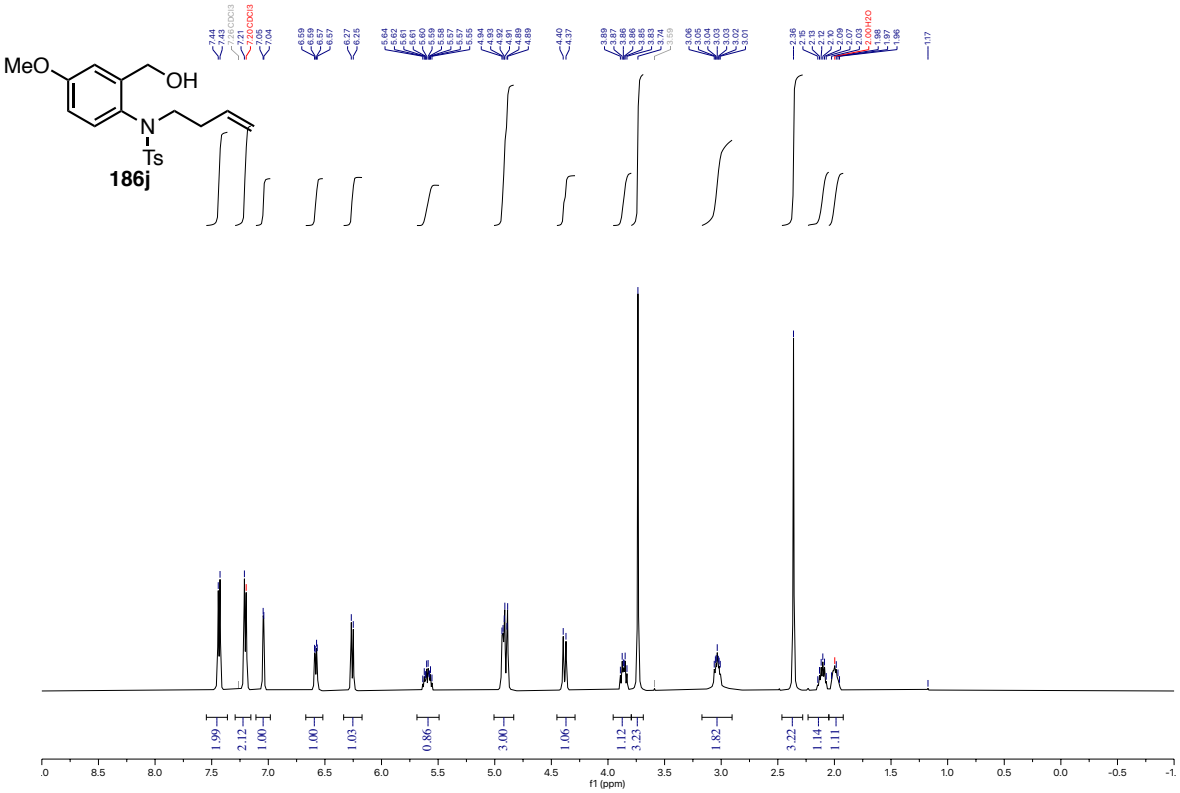



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

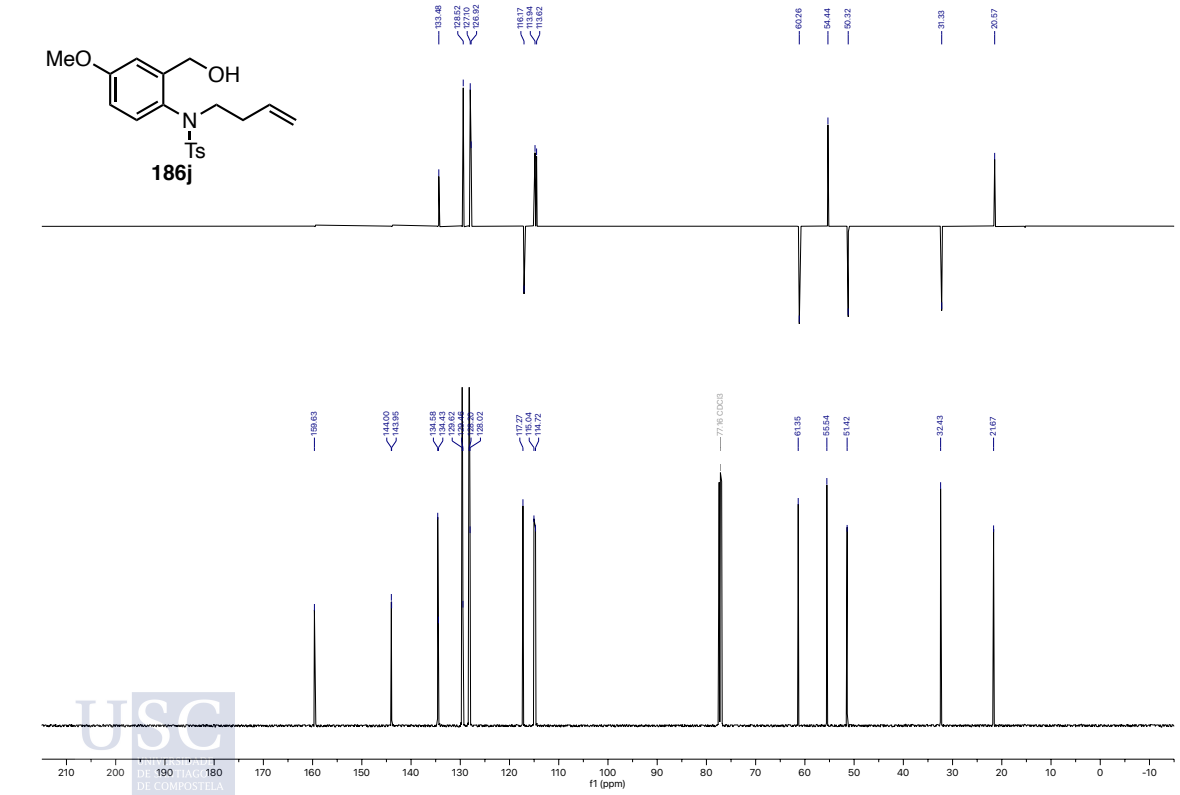



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

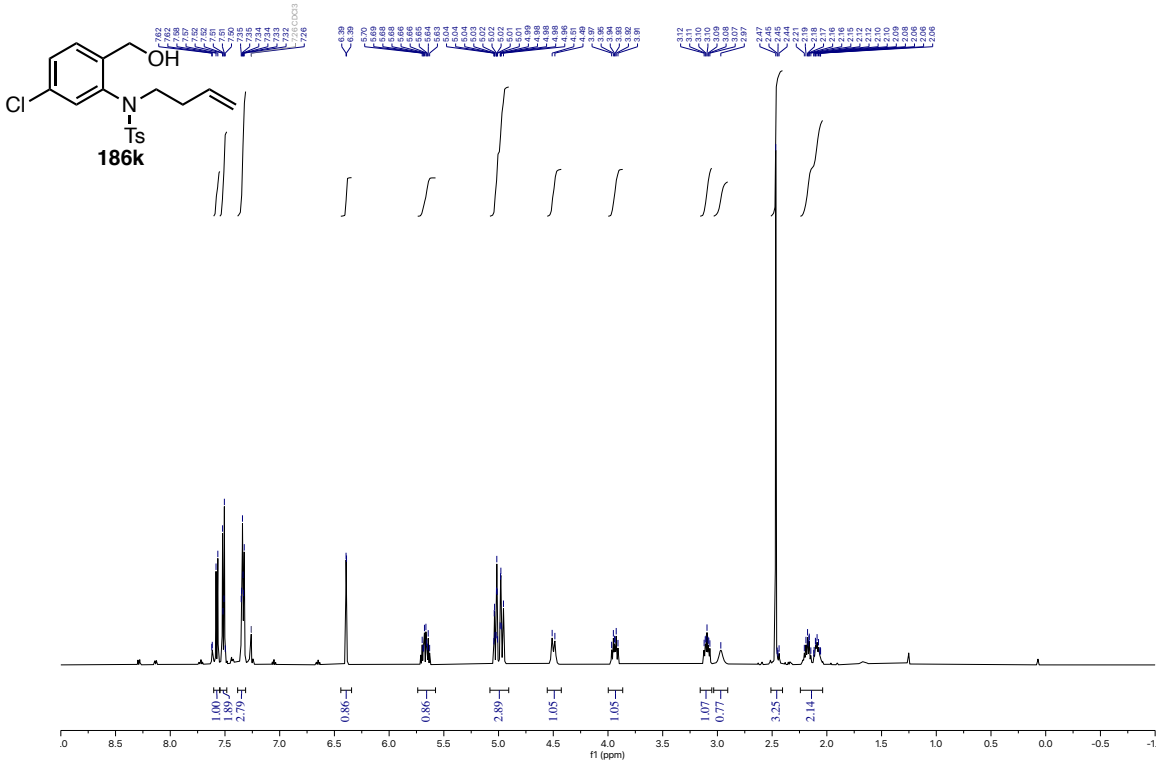



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

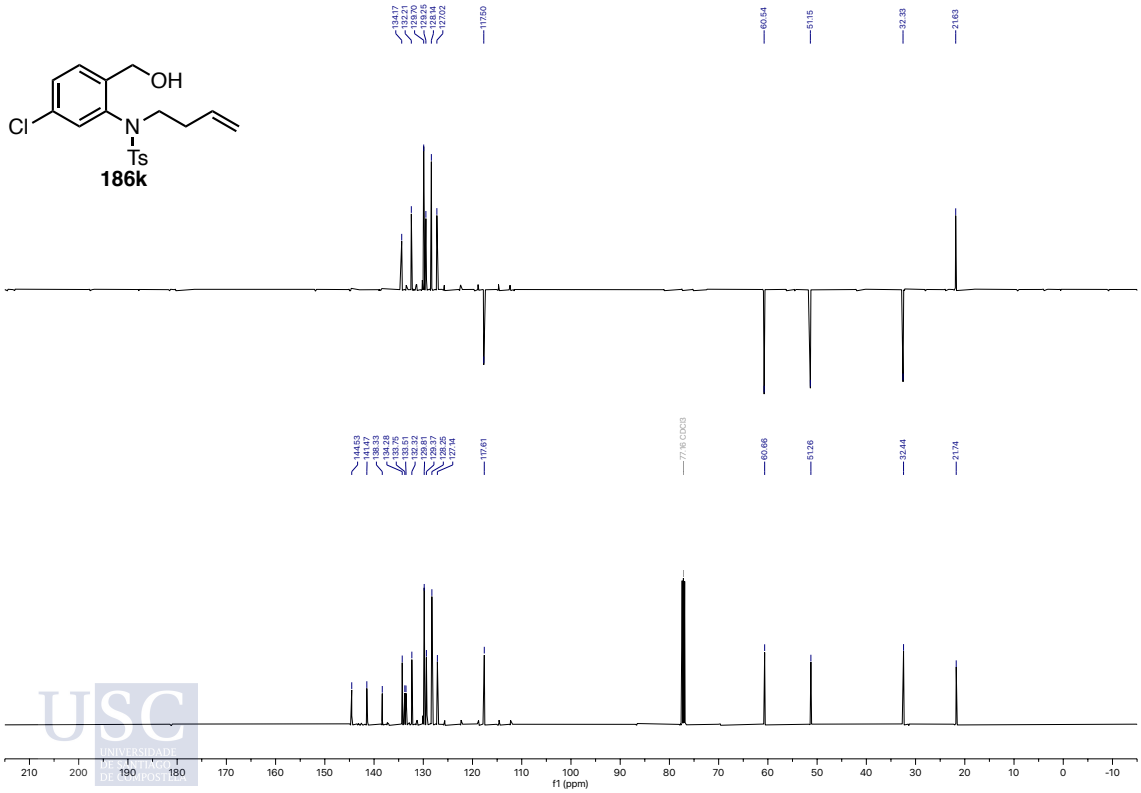



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

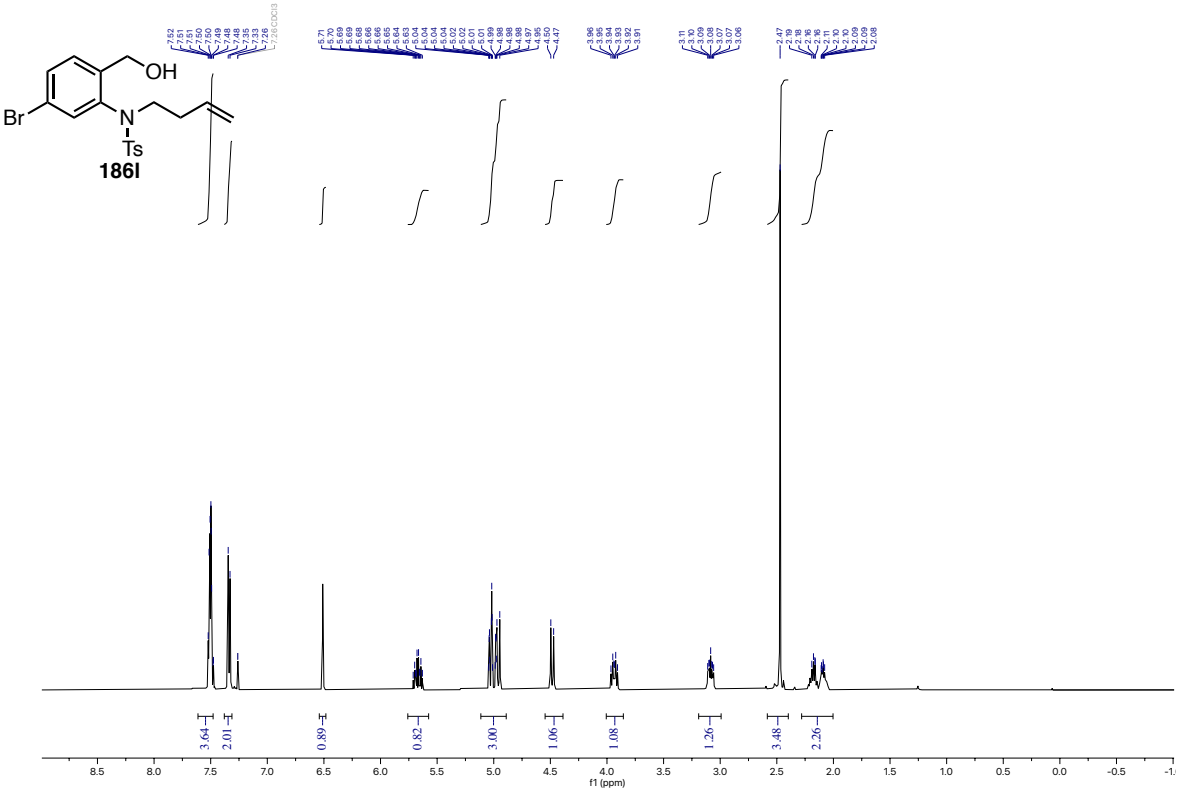



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

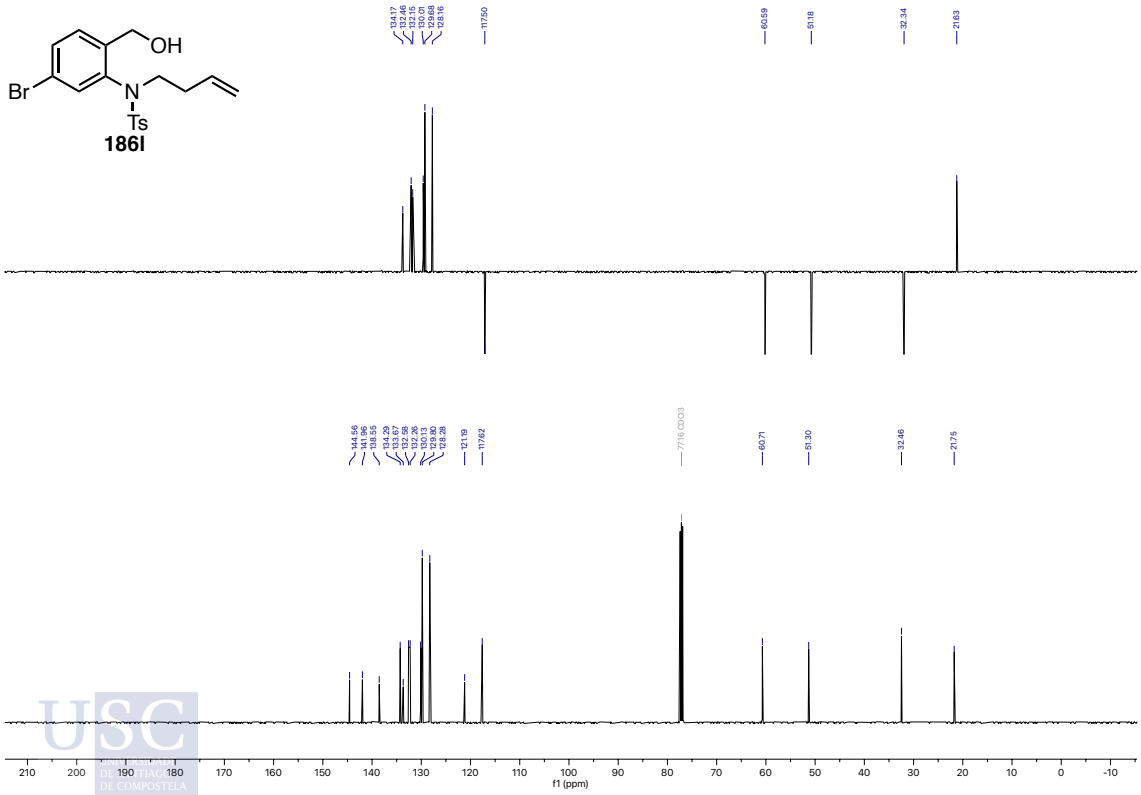



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

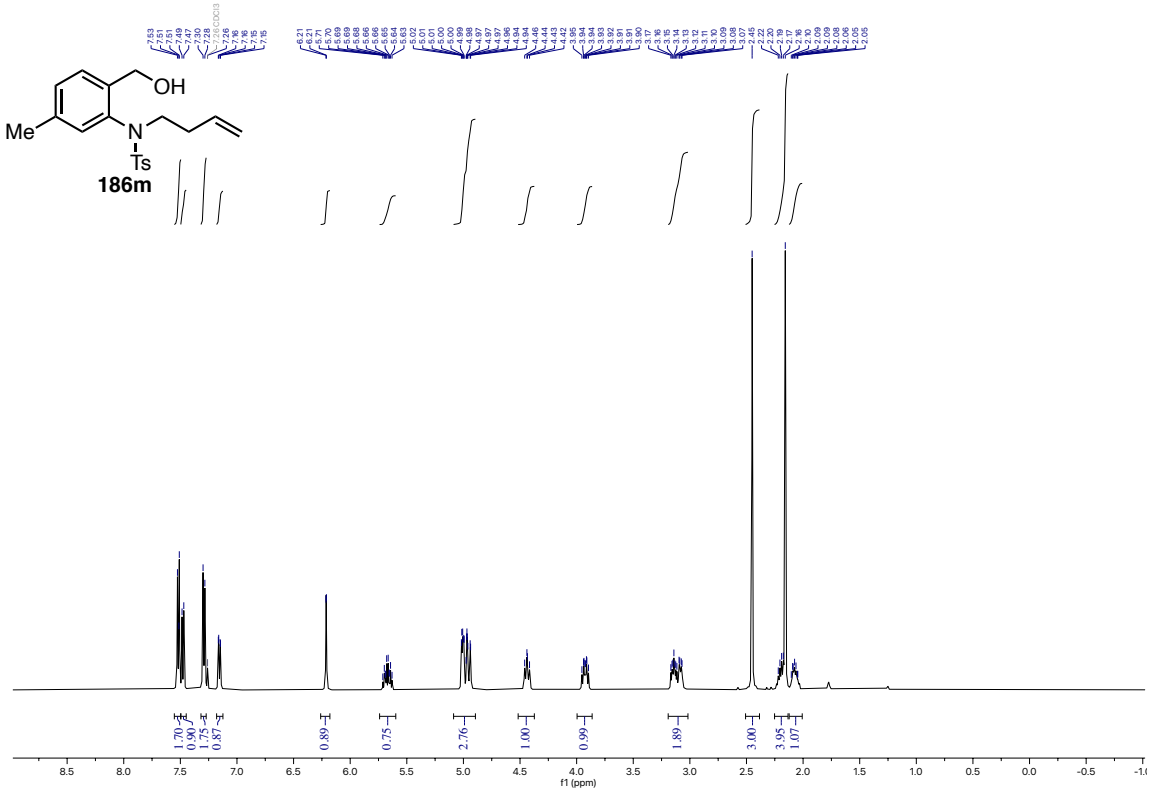



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

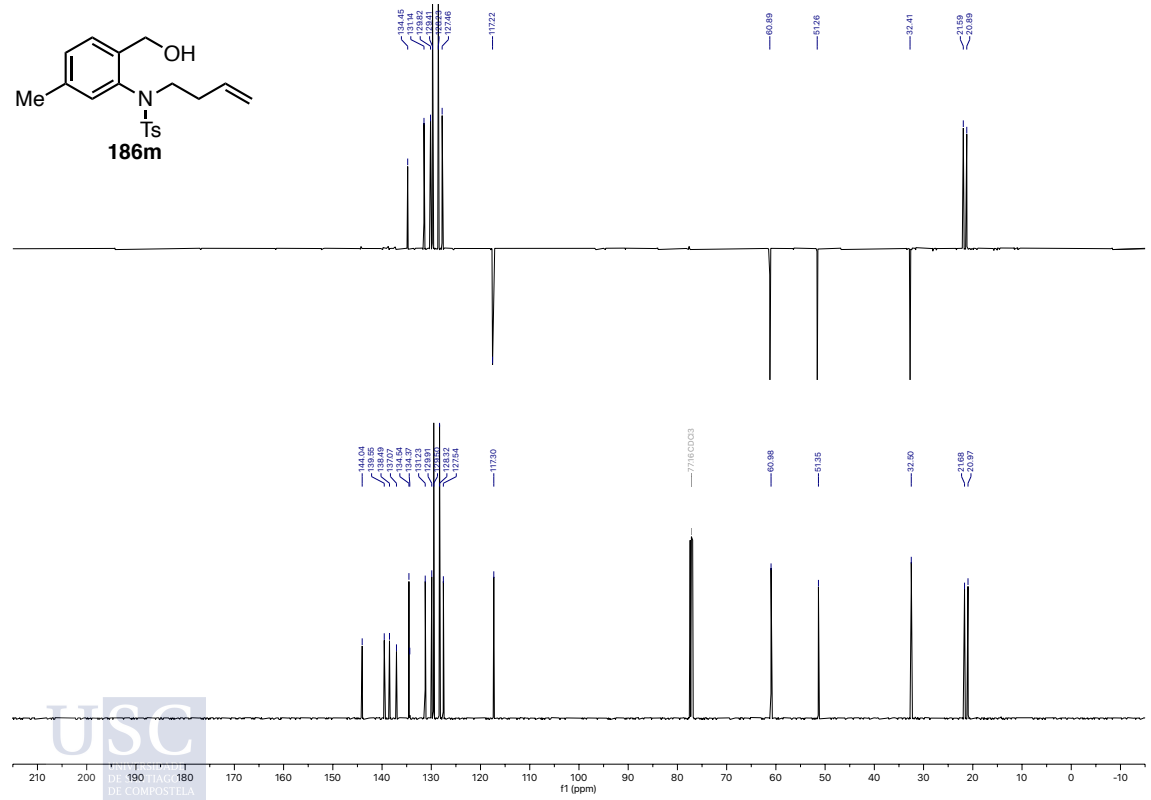



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

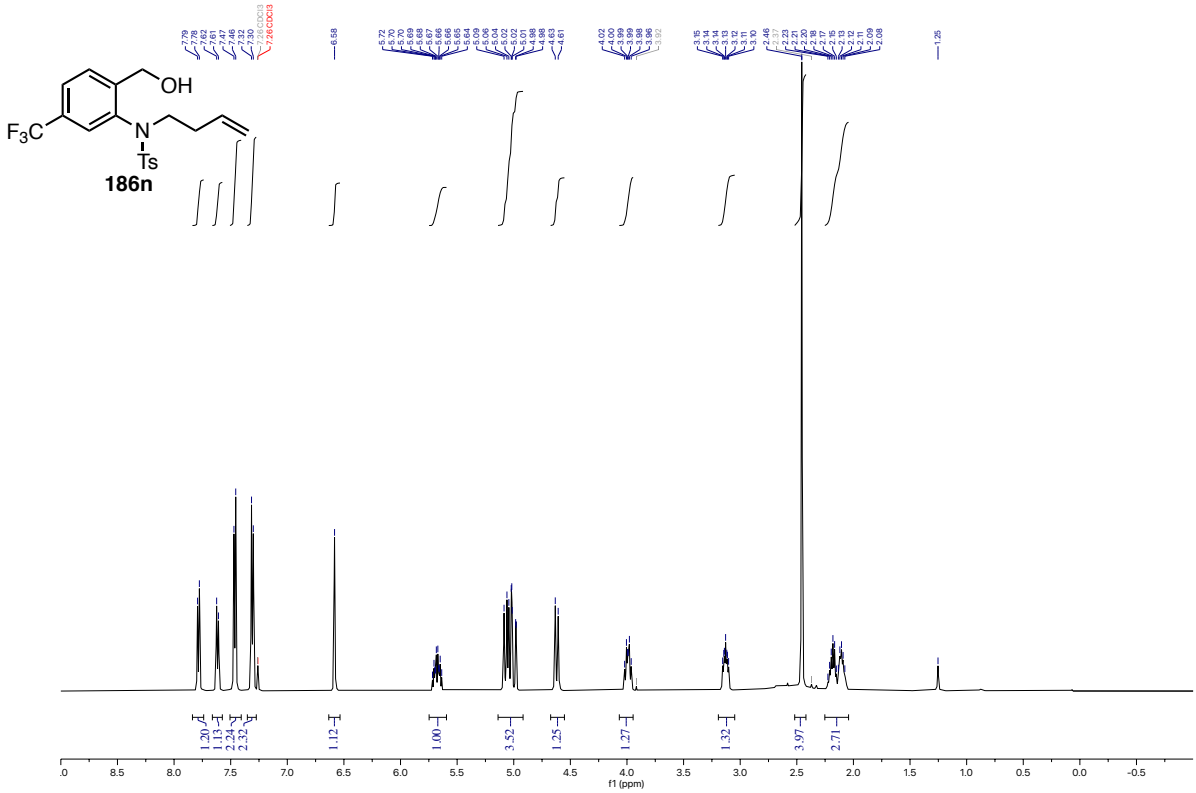



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

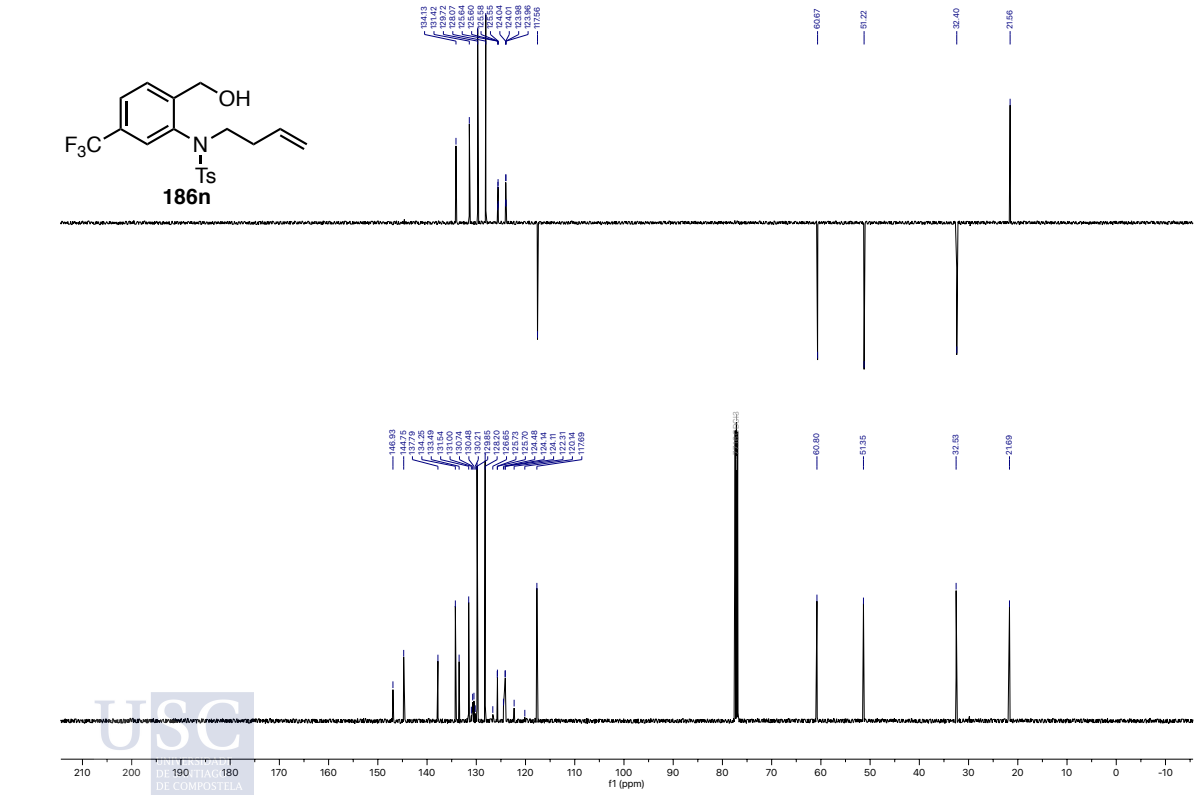



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

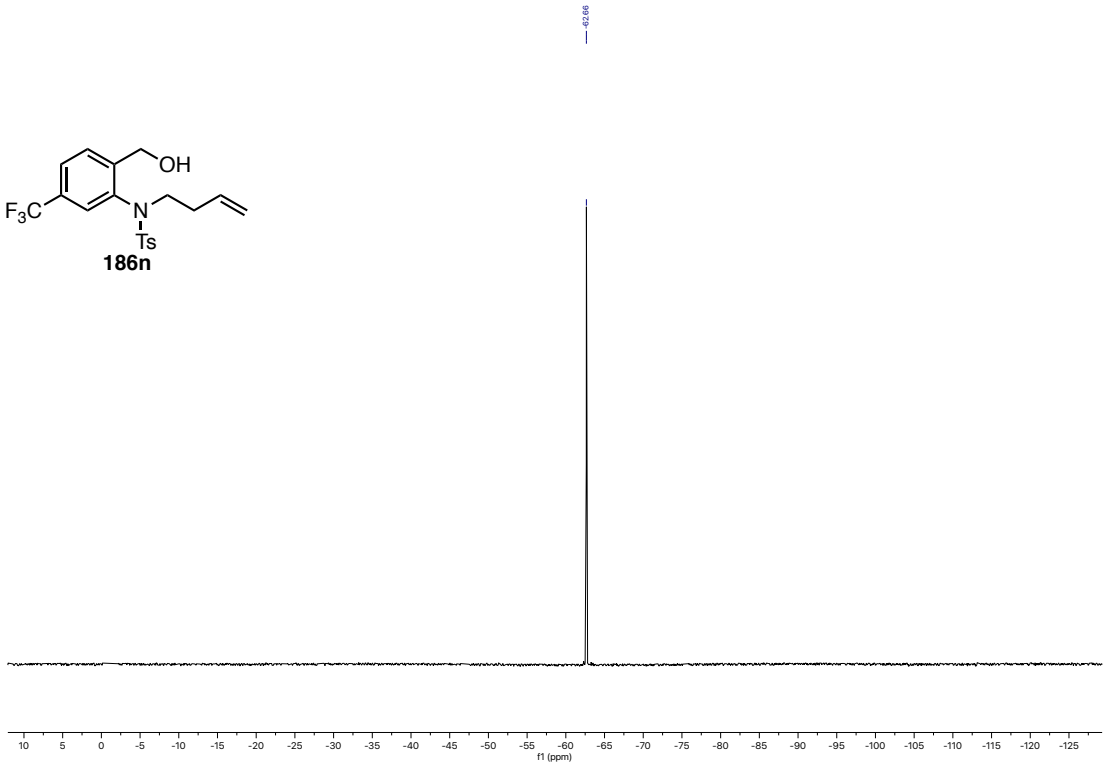



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$



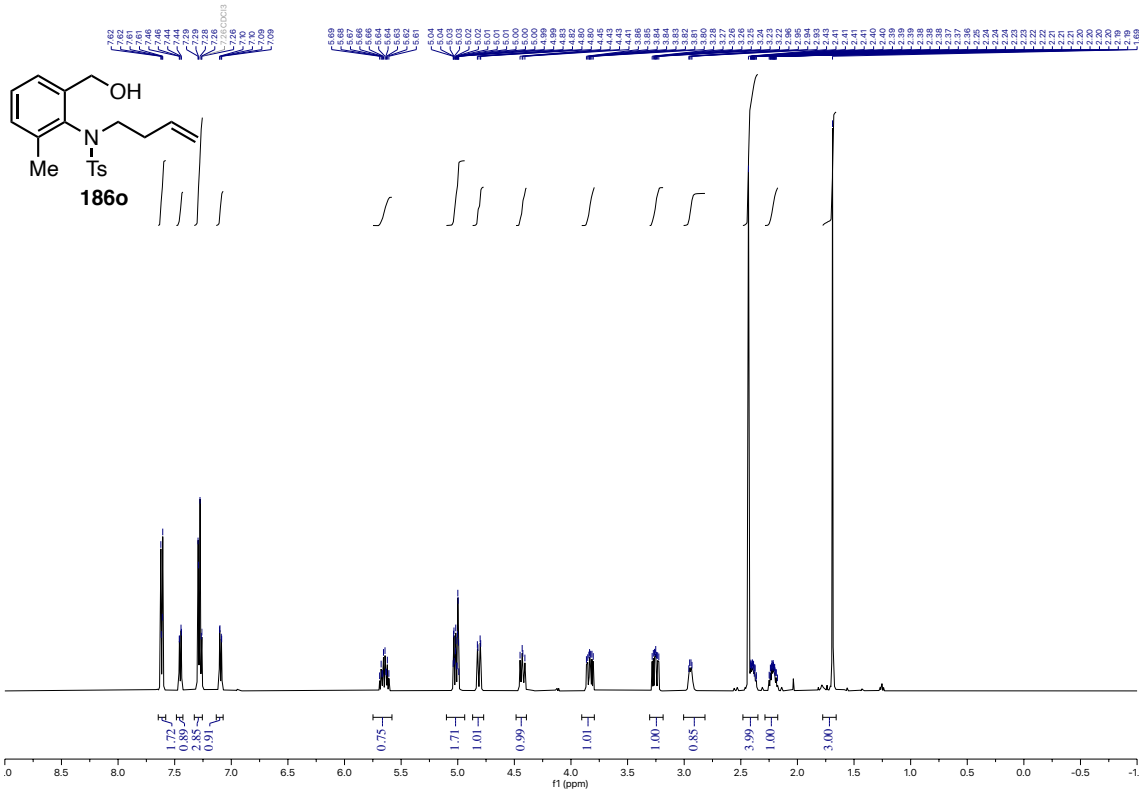

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$^{19}$F-NMR (282 MHz). Solvent $CDCl_3$

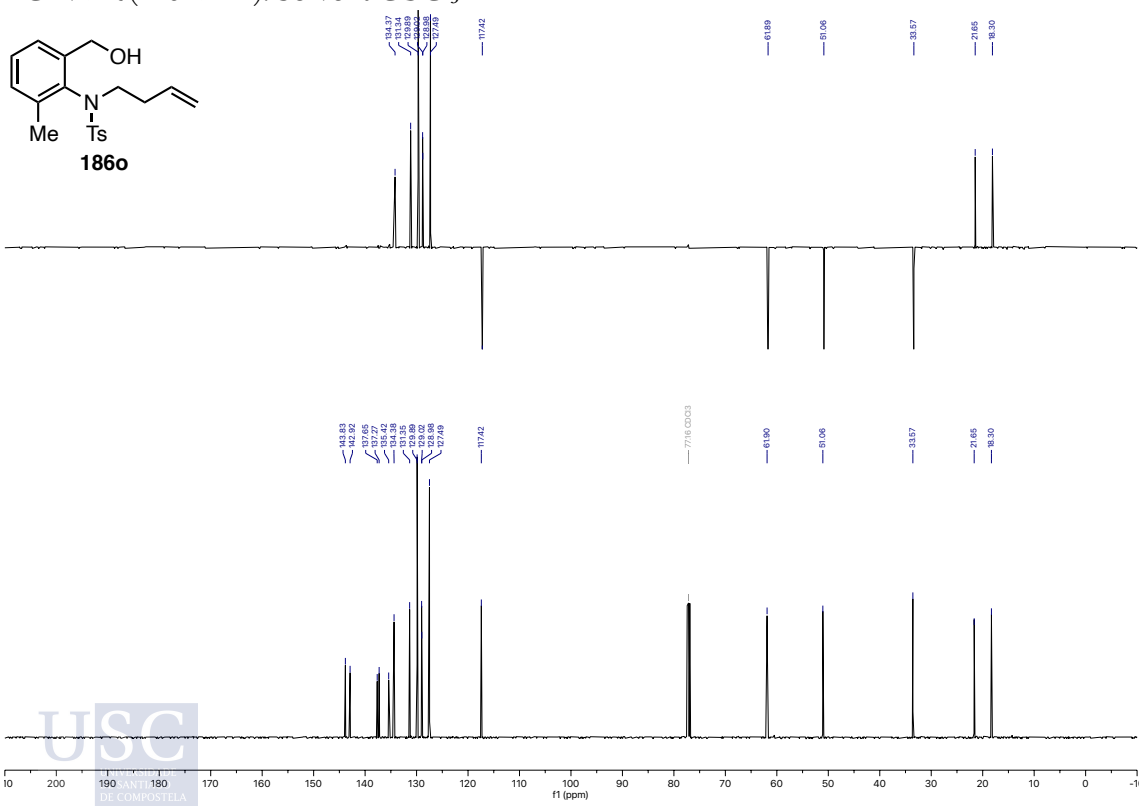



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

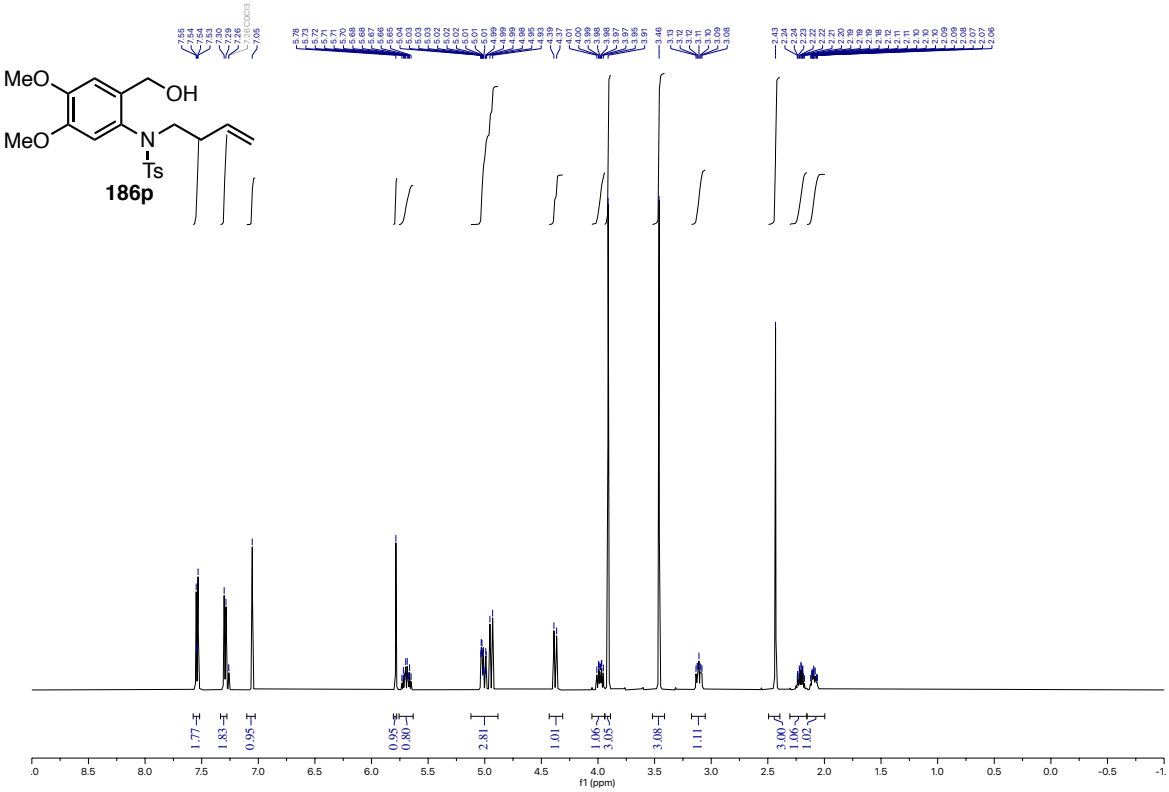



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

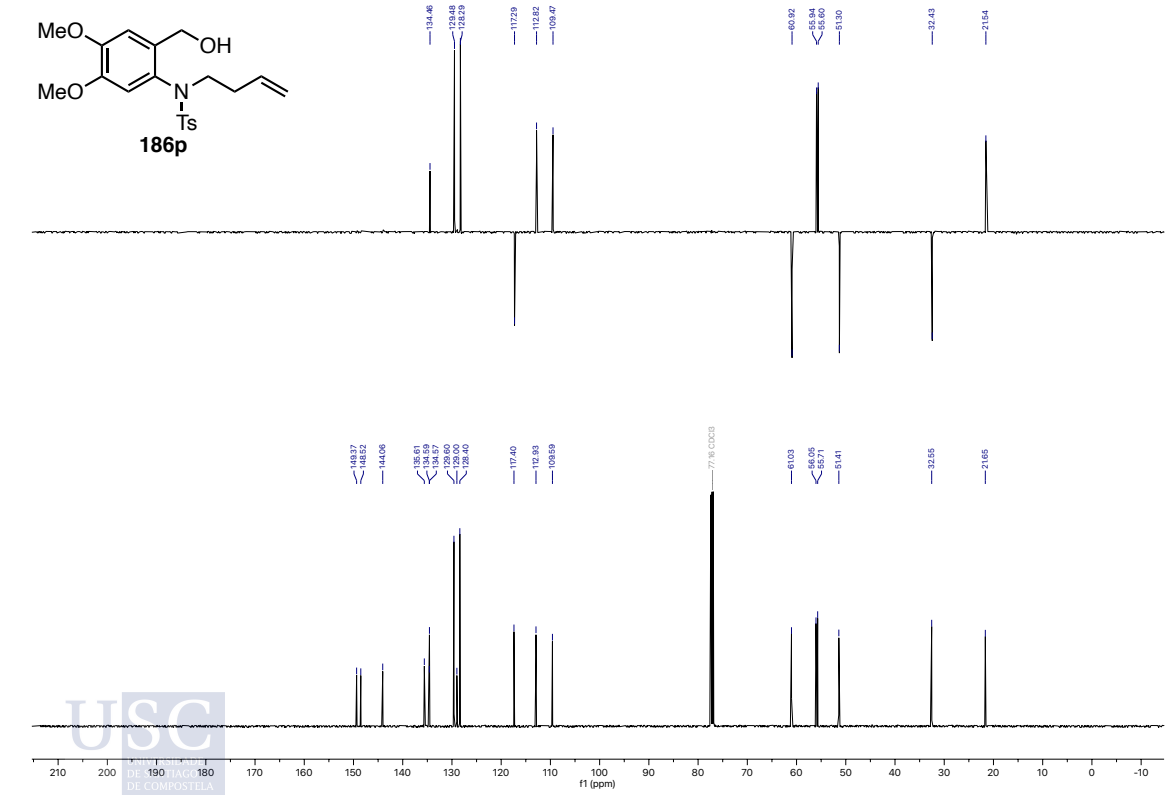



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

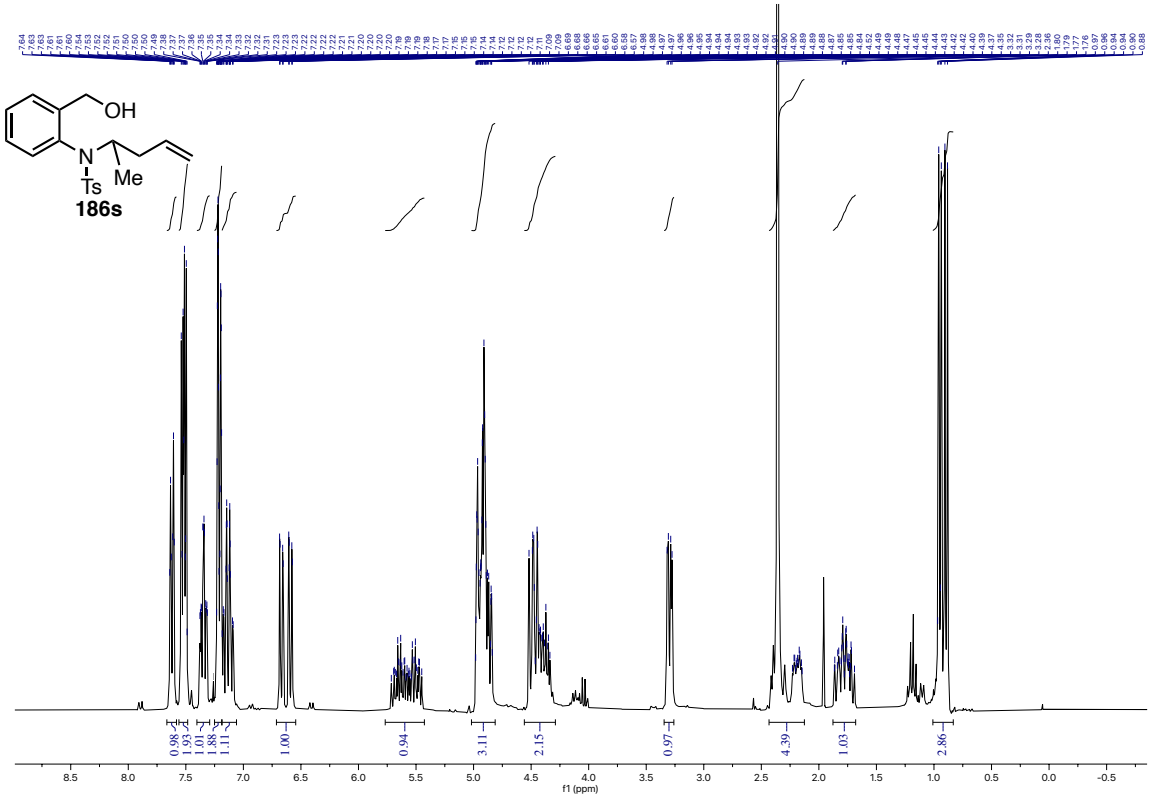



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

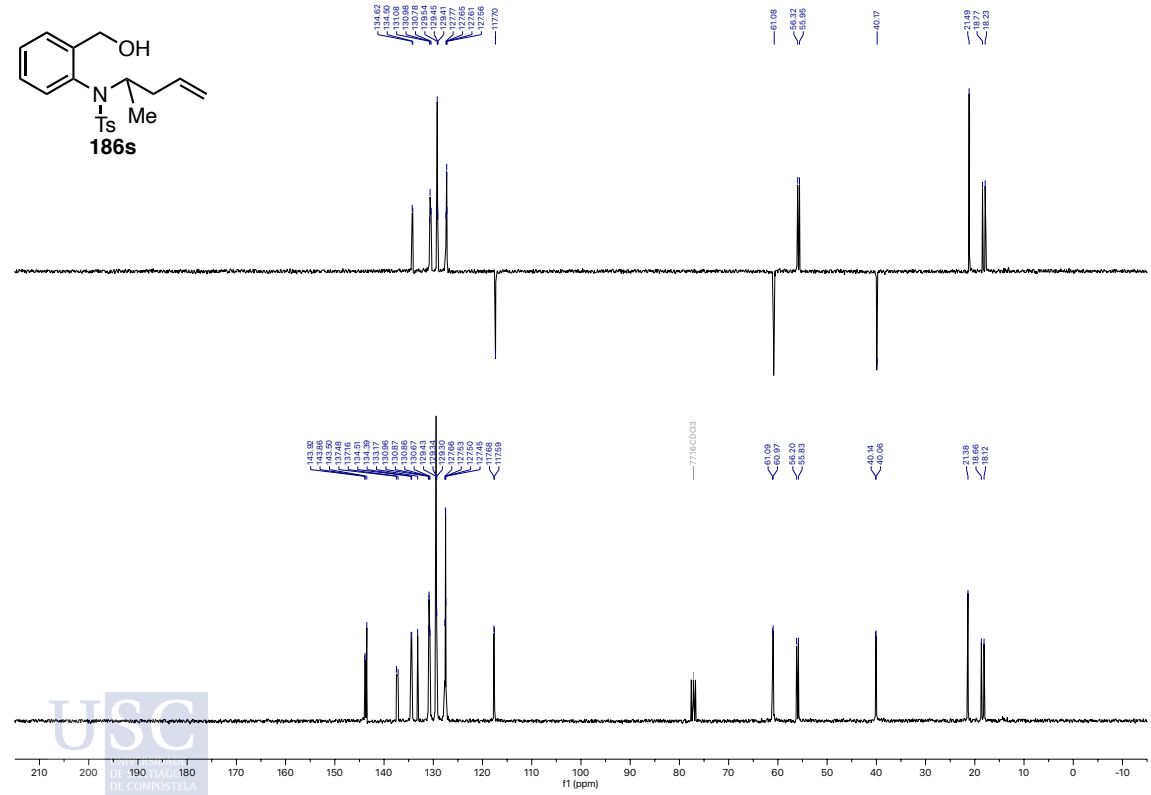



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

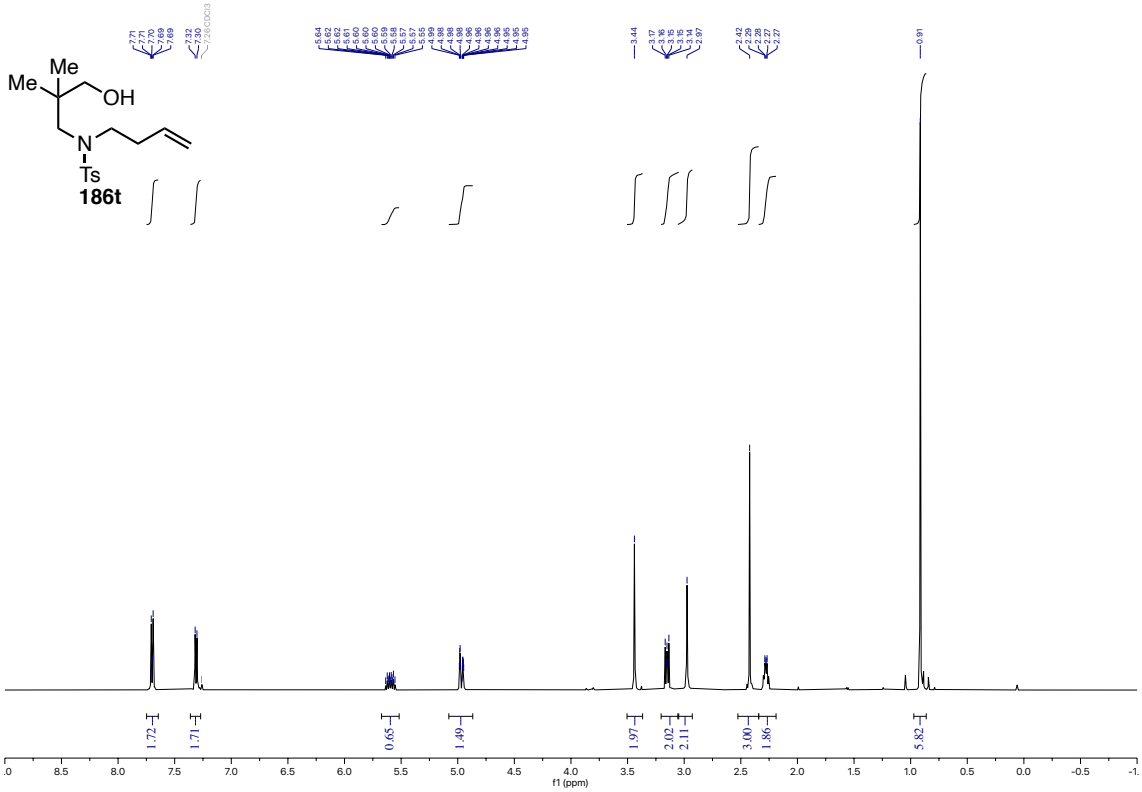



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

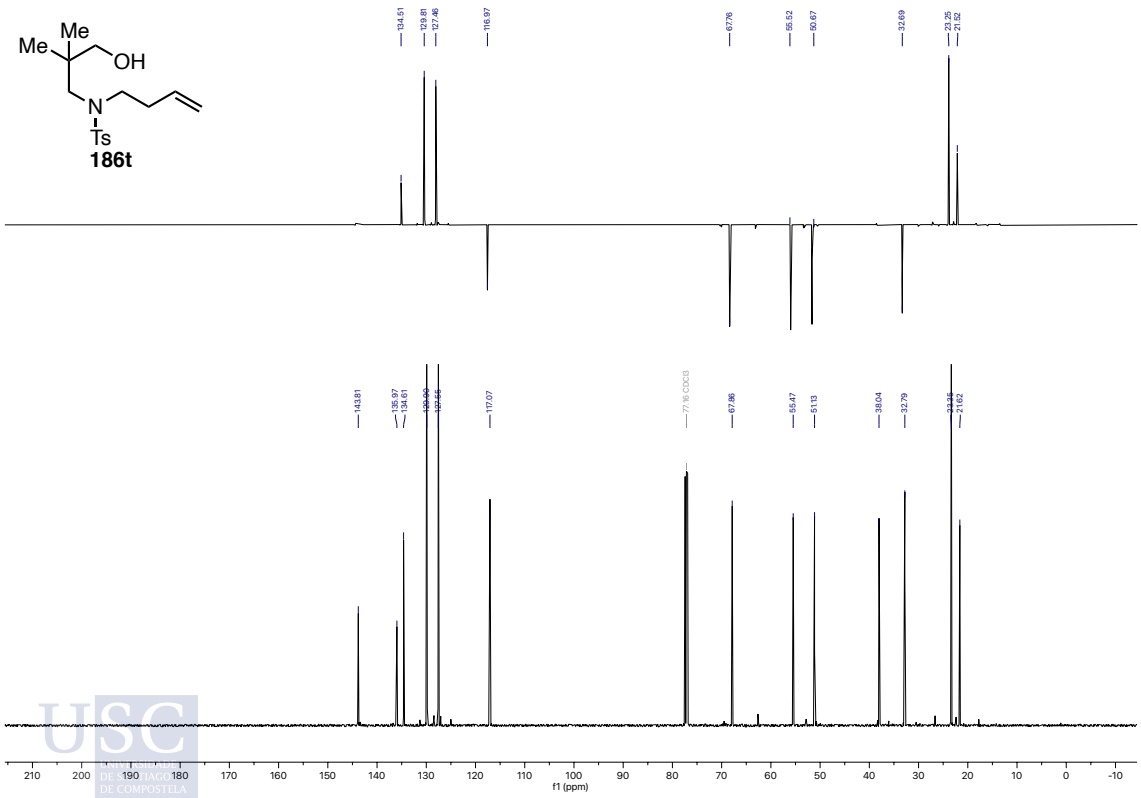



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

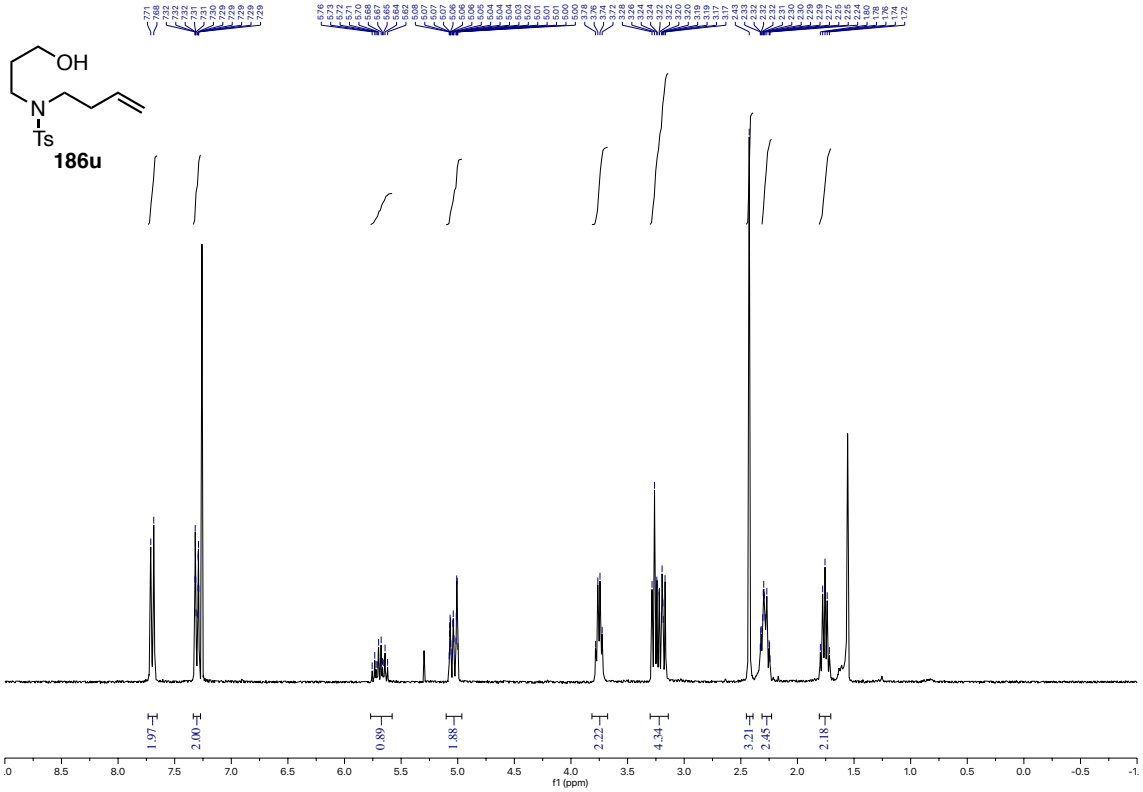



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

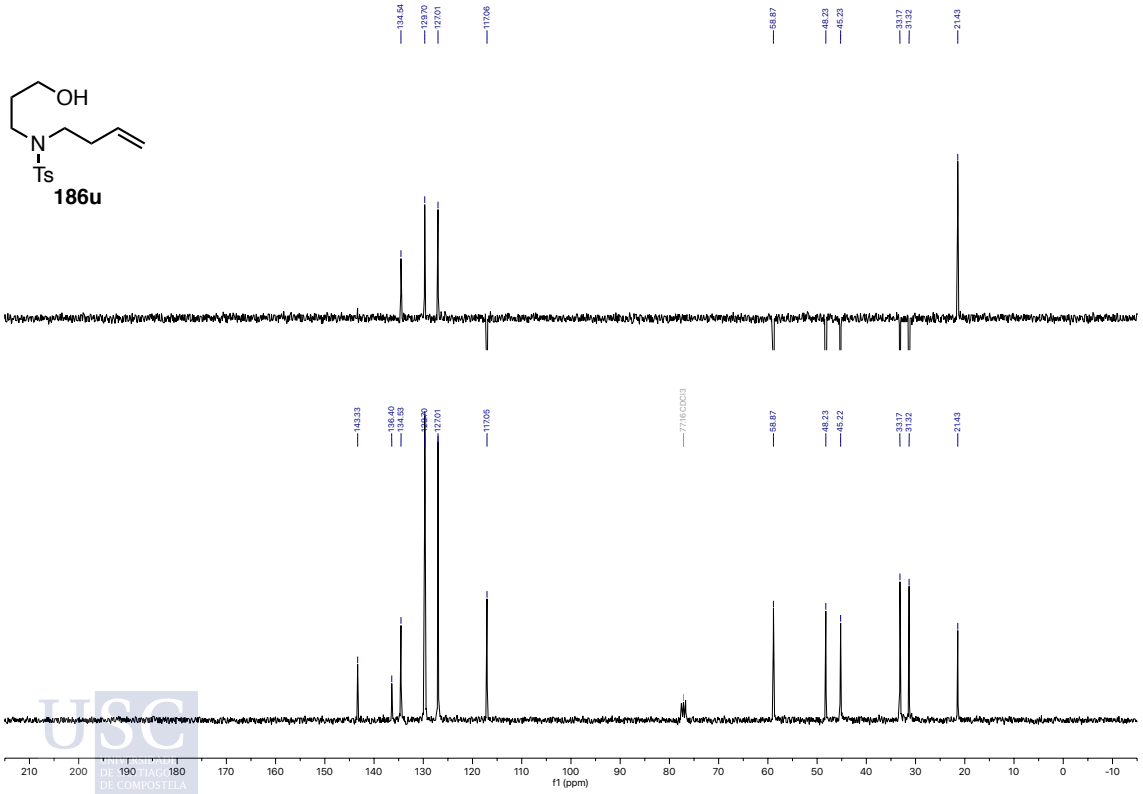



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

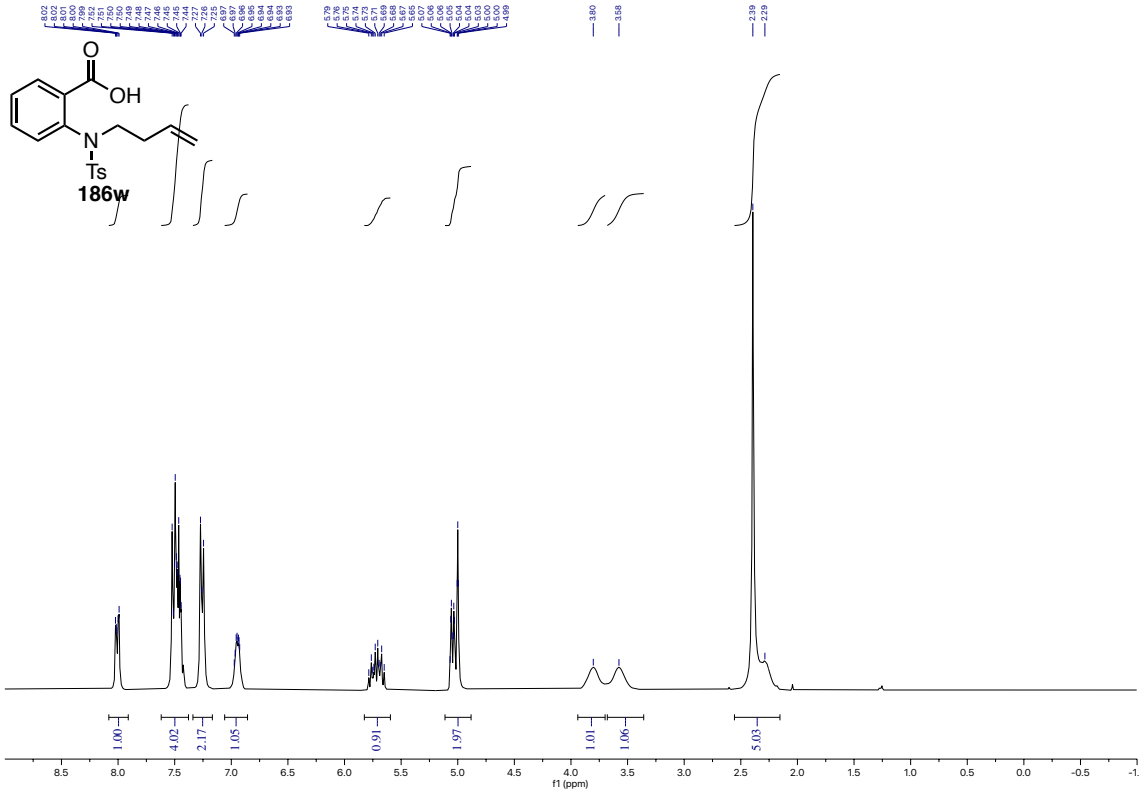



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

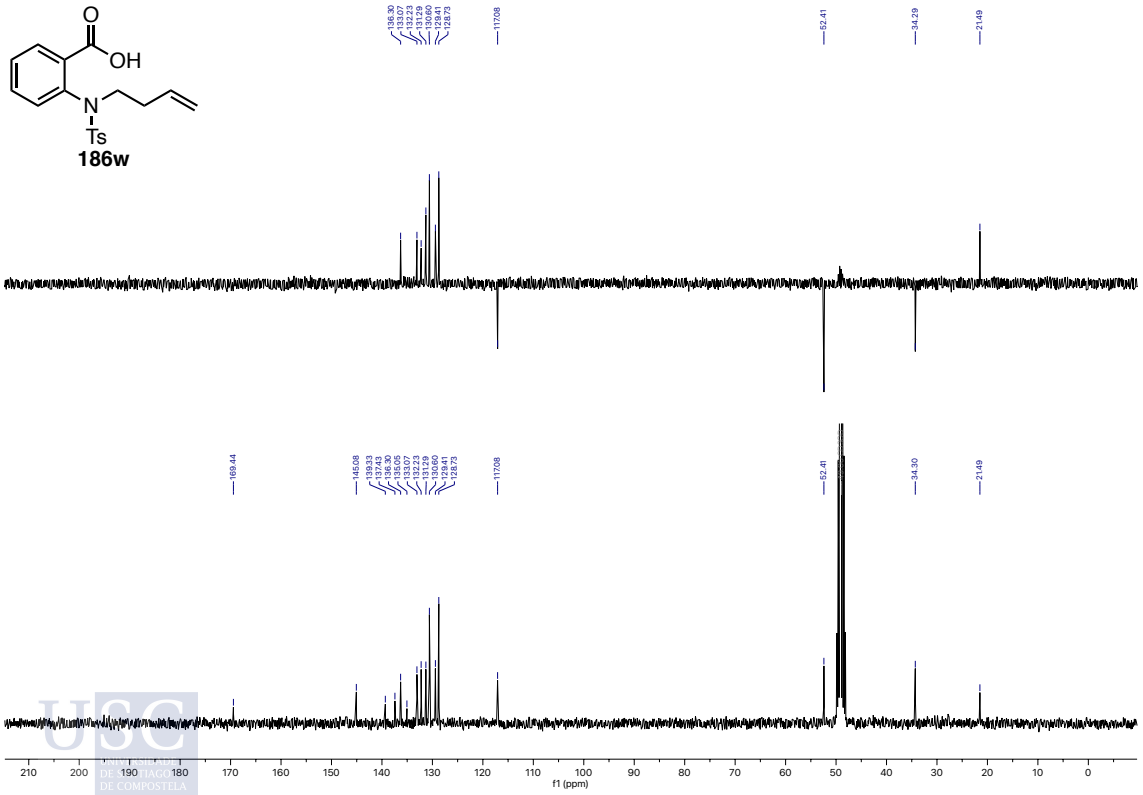



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

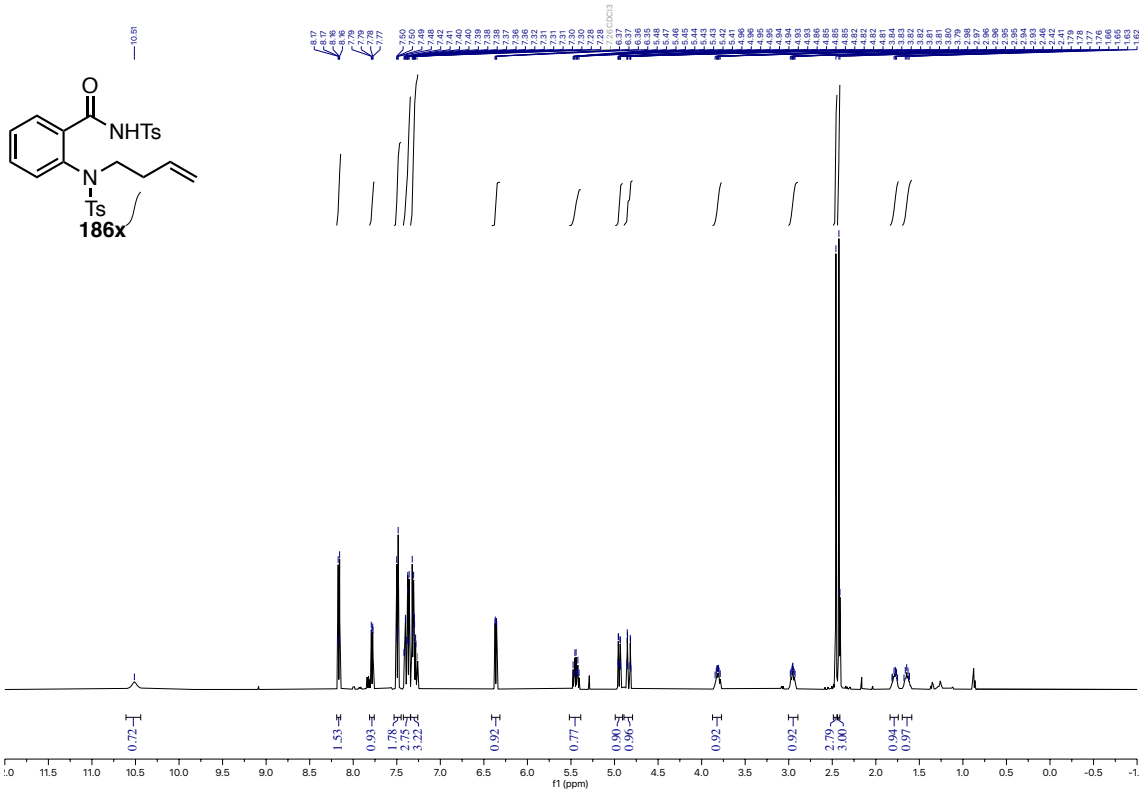



$^{13}$C-NMR (75 MHz). Solvent $CD_3OD$

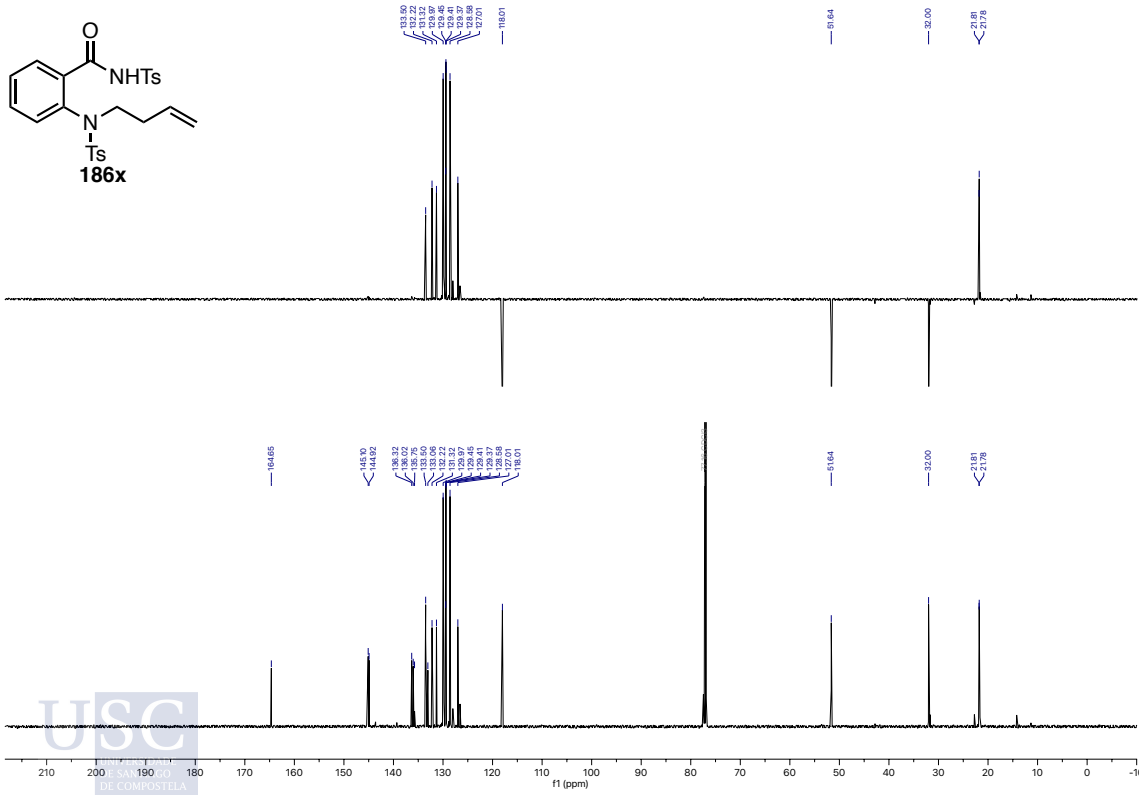



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

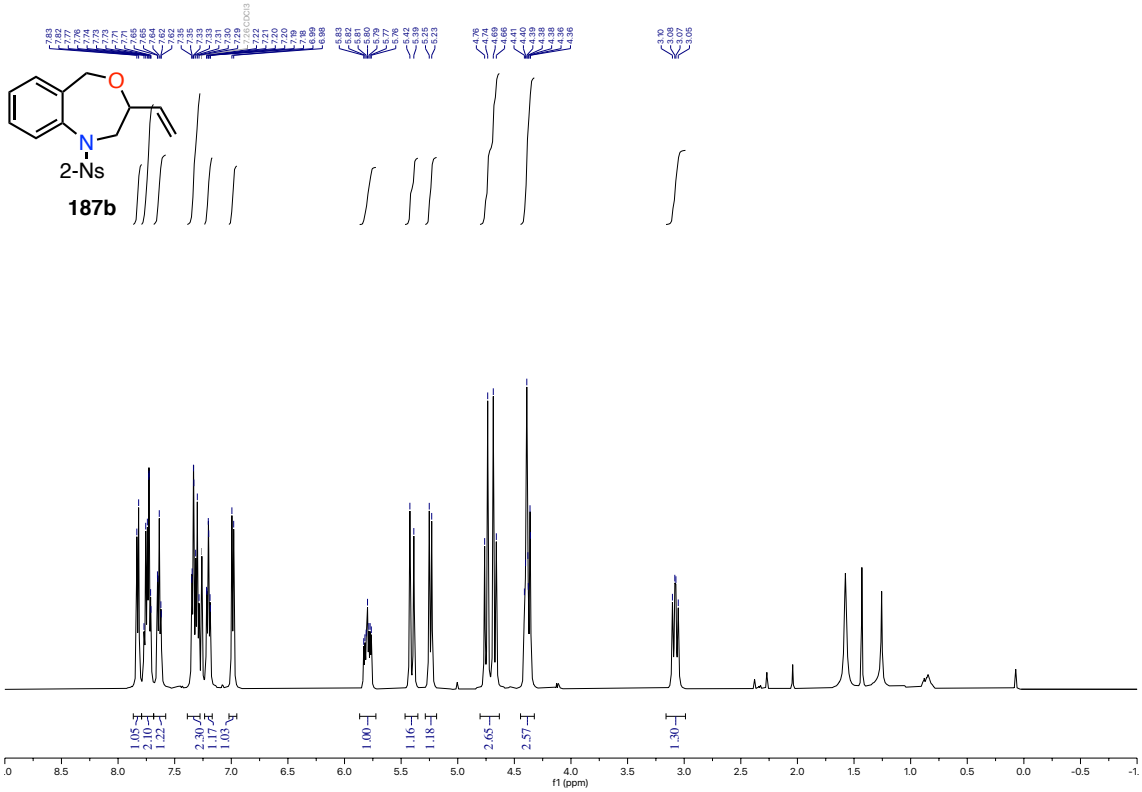



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

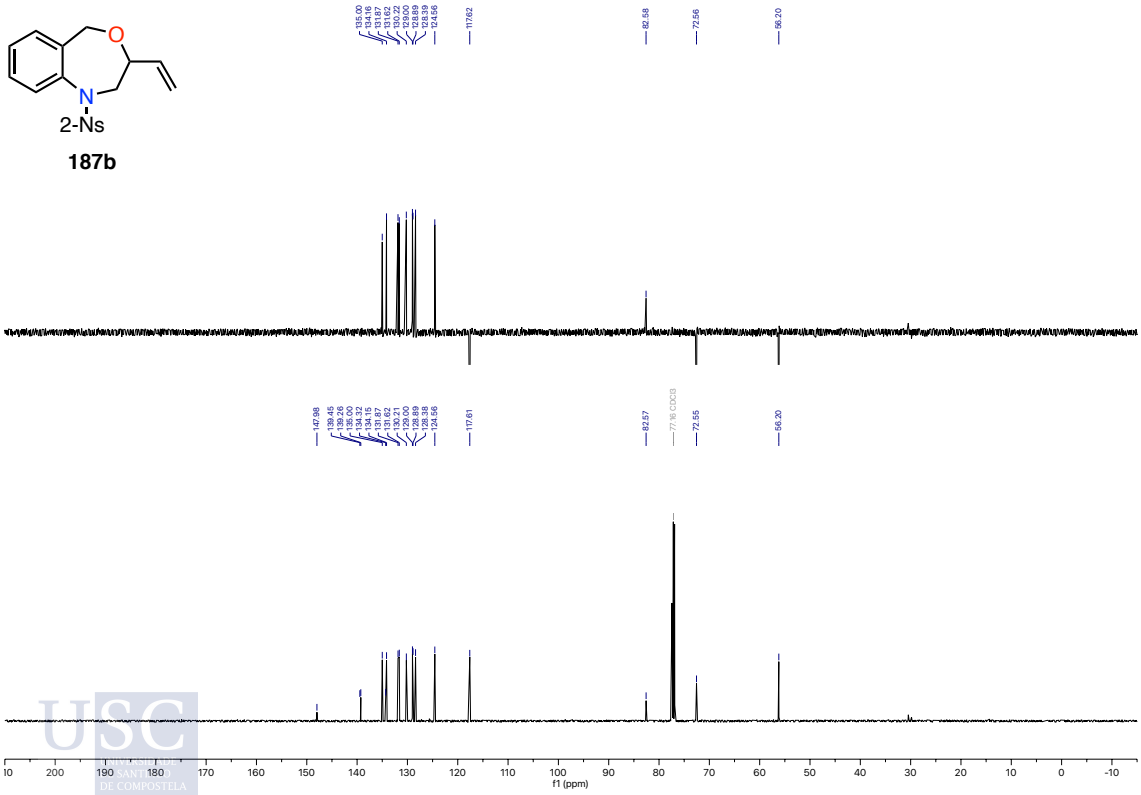



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

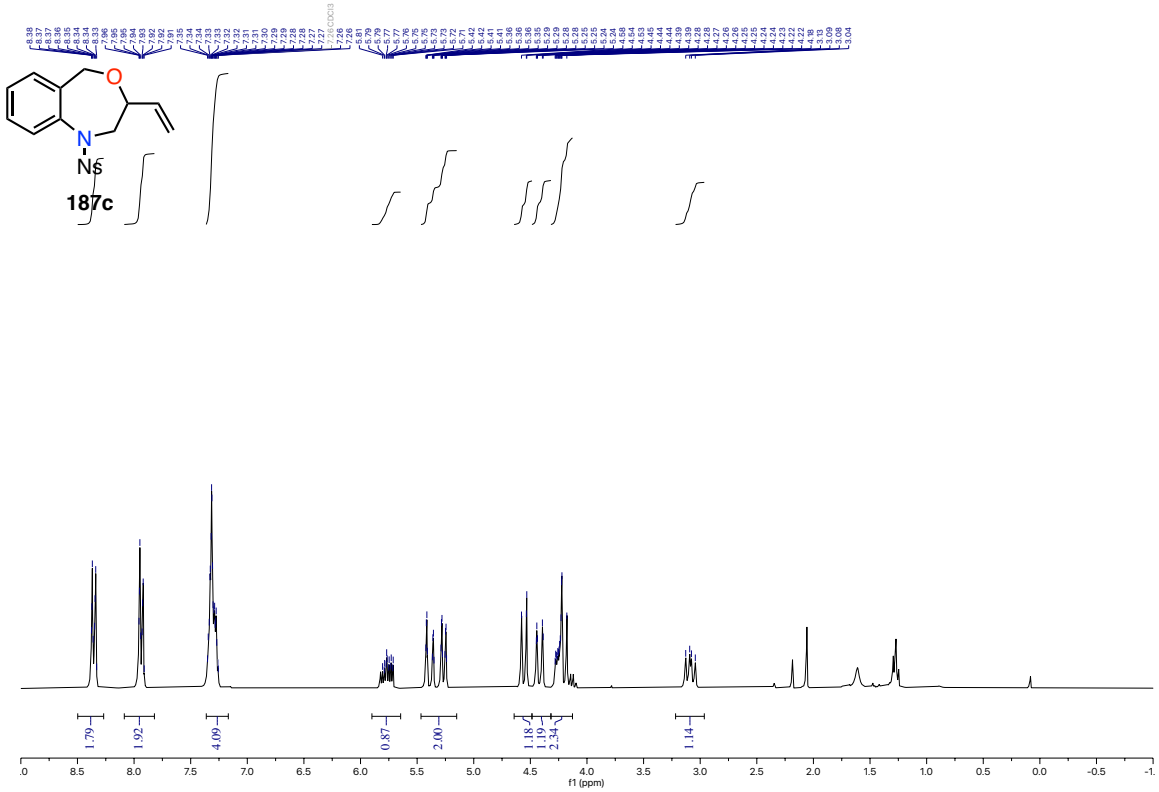



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

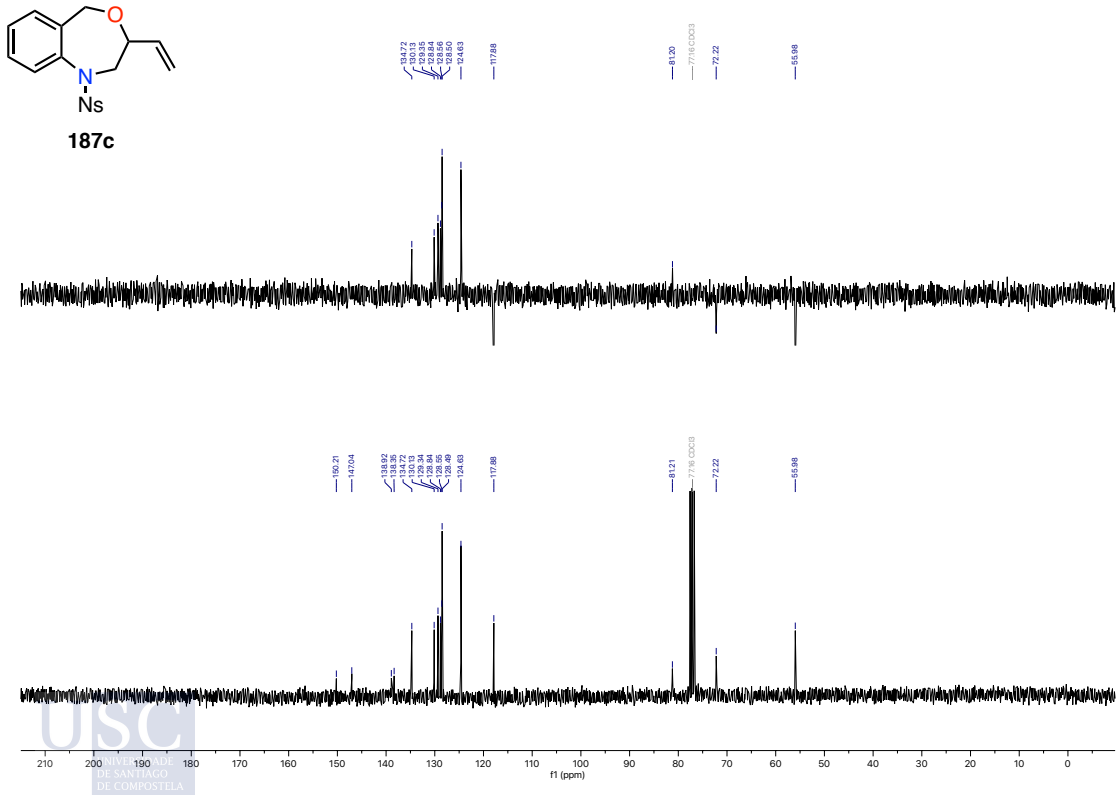



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

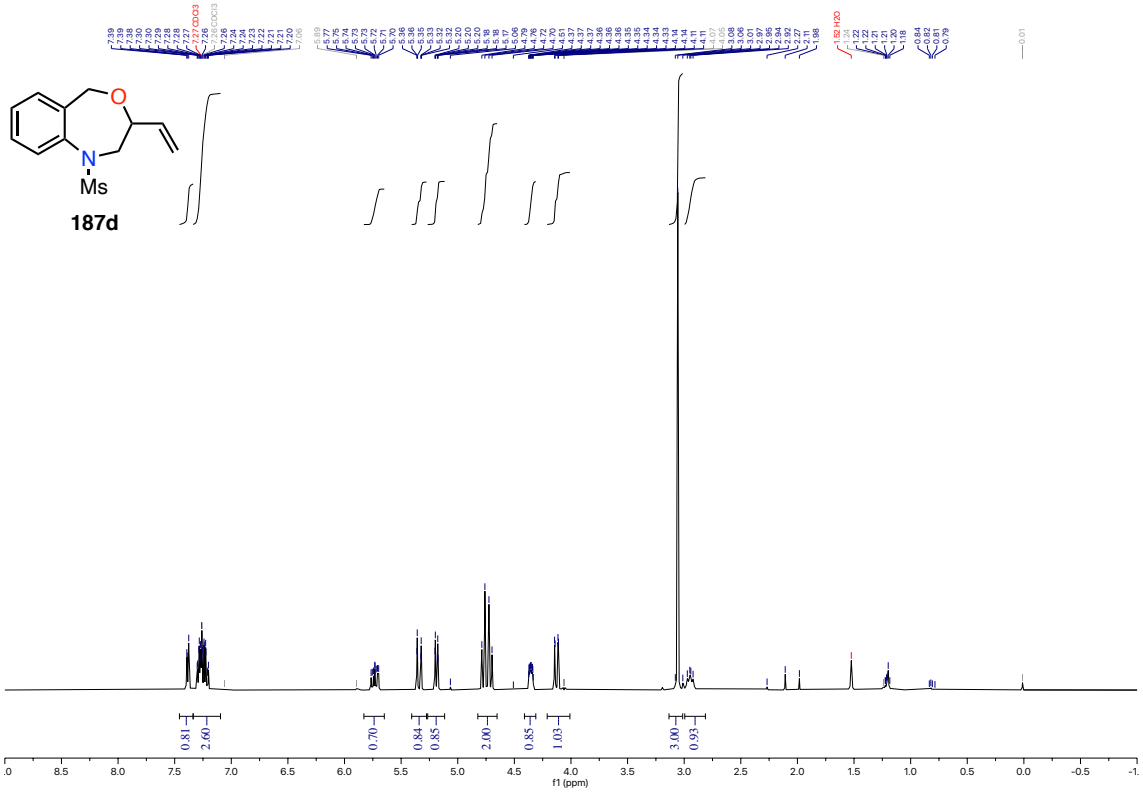



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

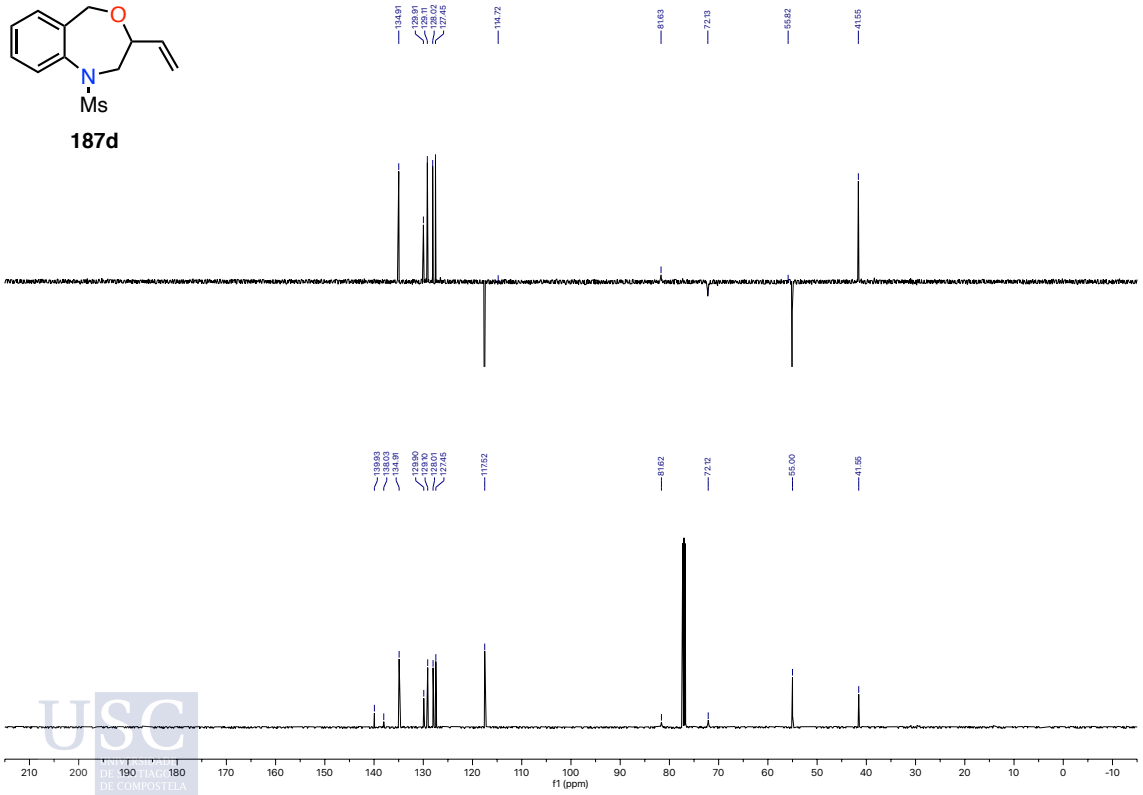



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

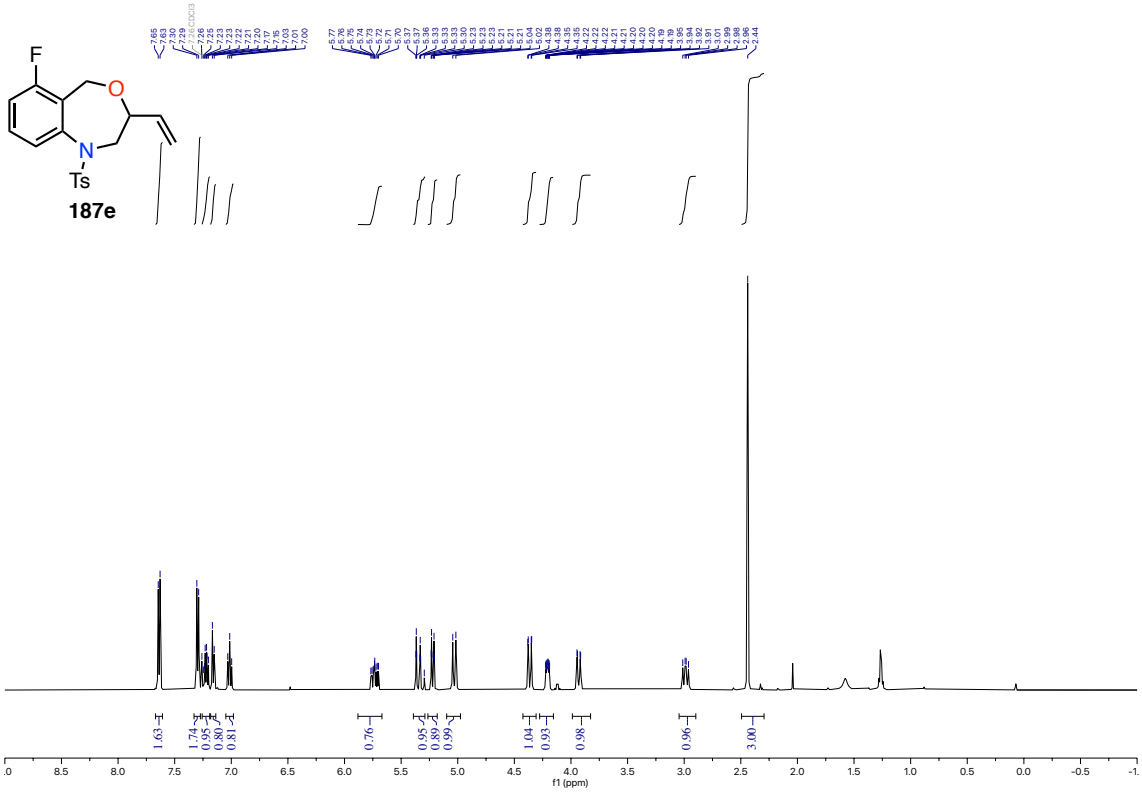



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

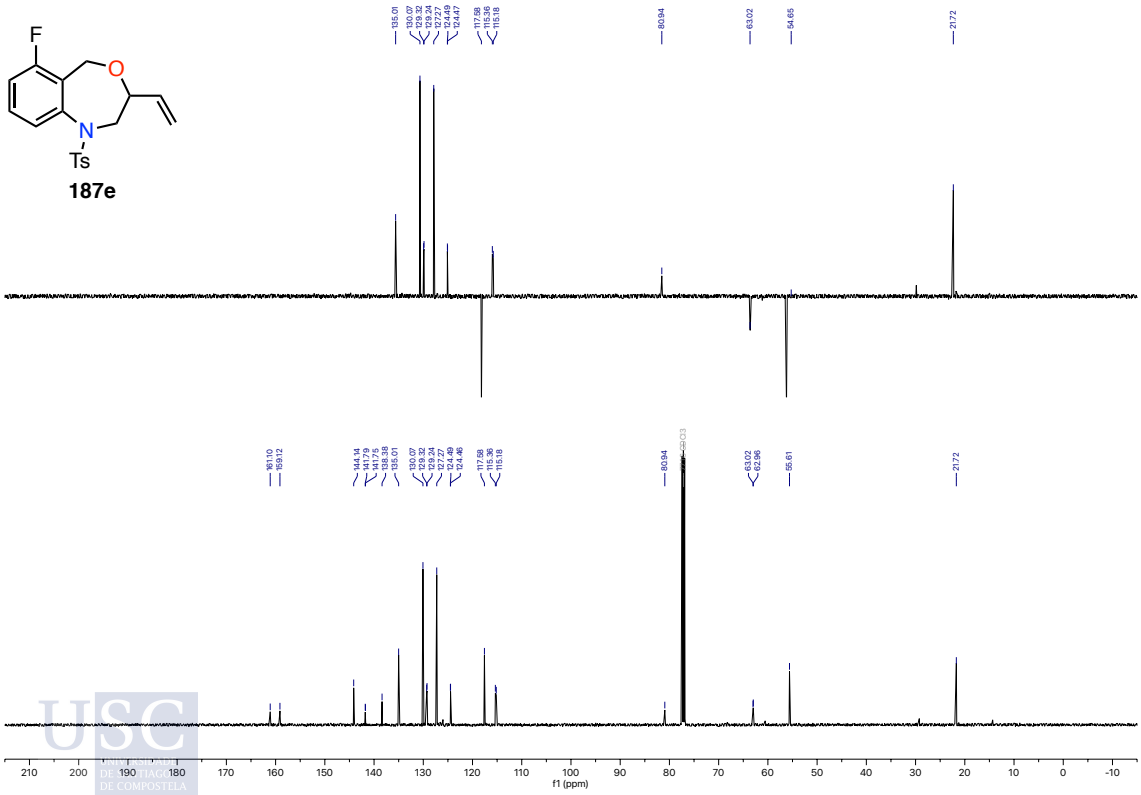



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$




$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

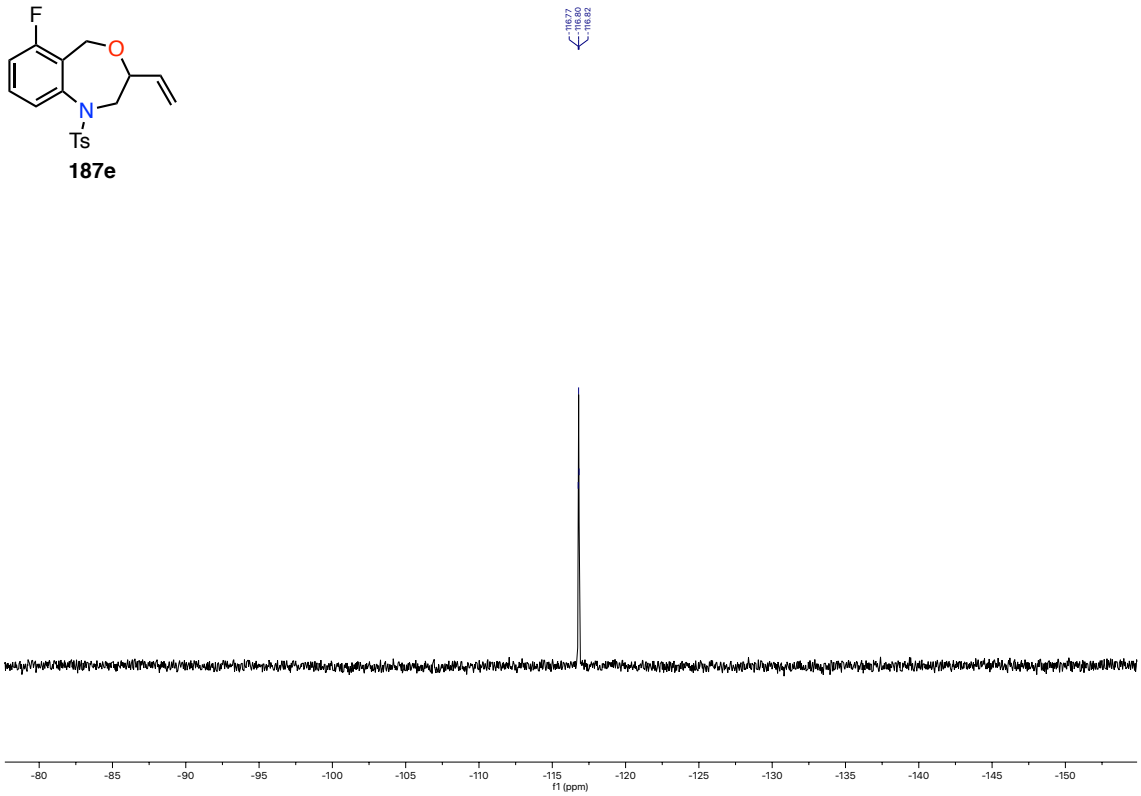



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$^{19}$F-NMR (282 MHz). Solvent $CDCl_3$

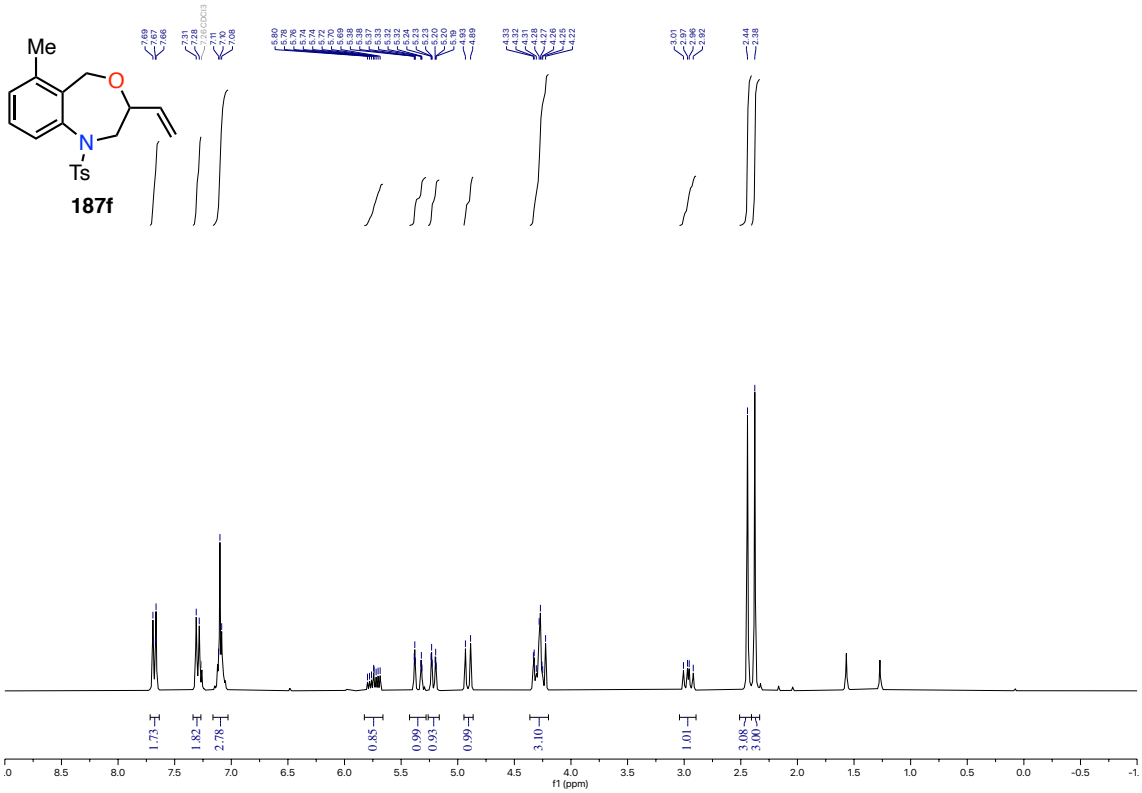



**187e**

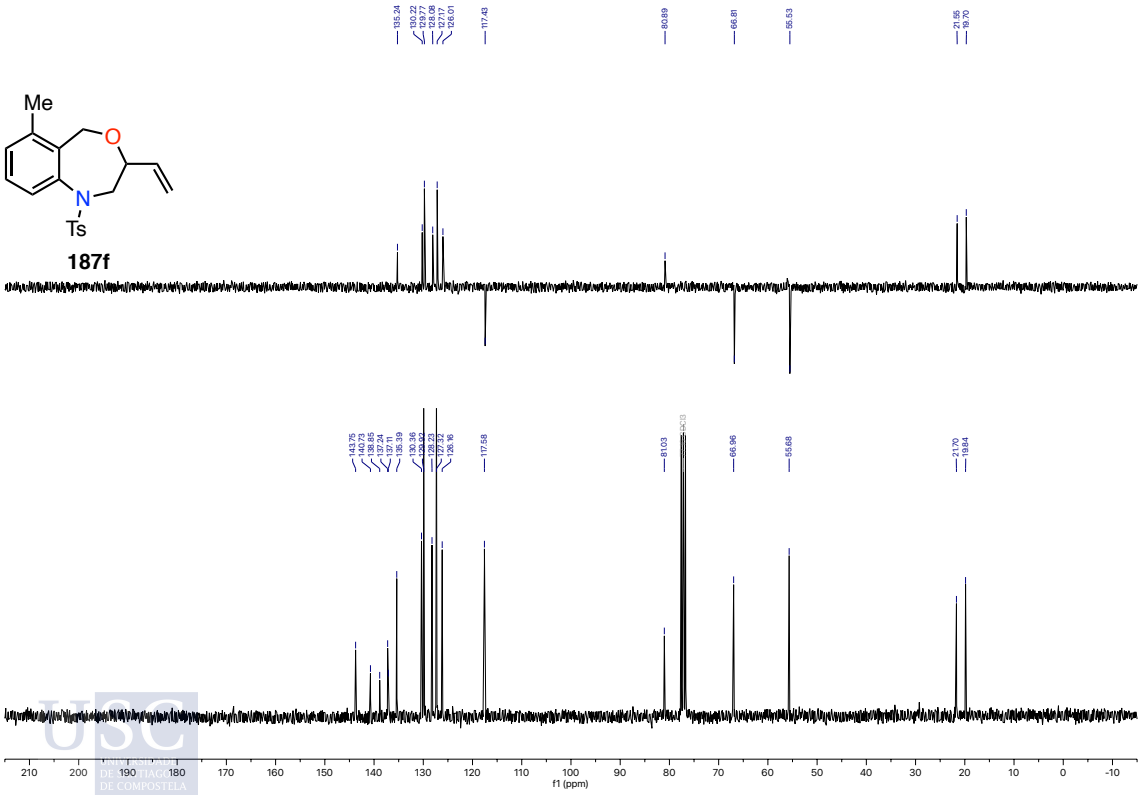



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

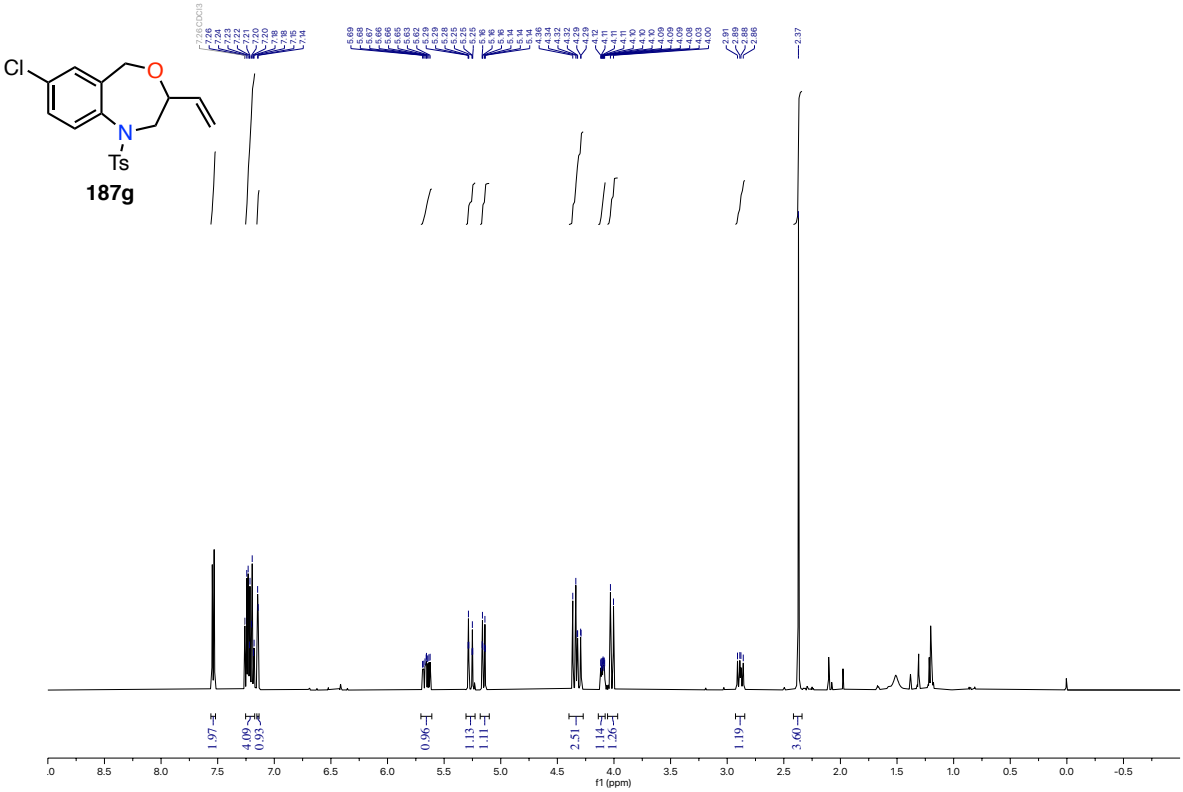



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

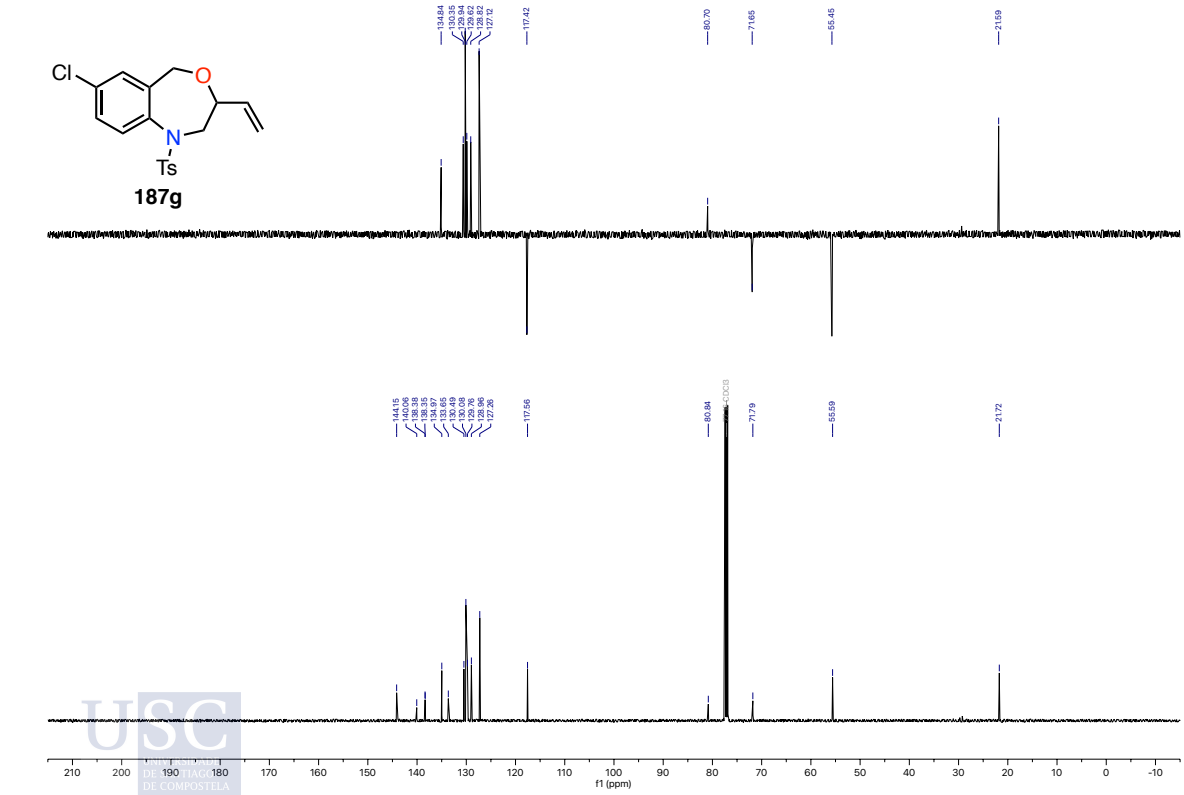



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

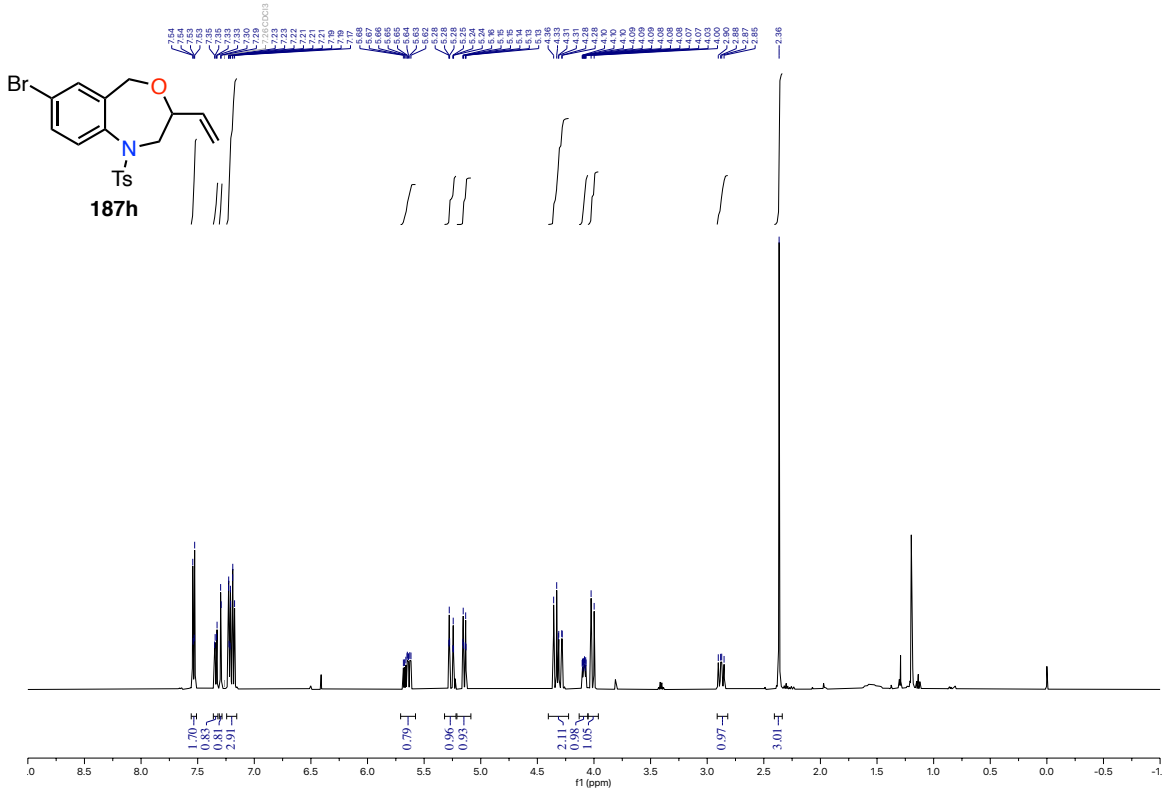



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

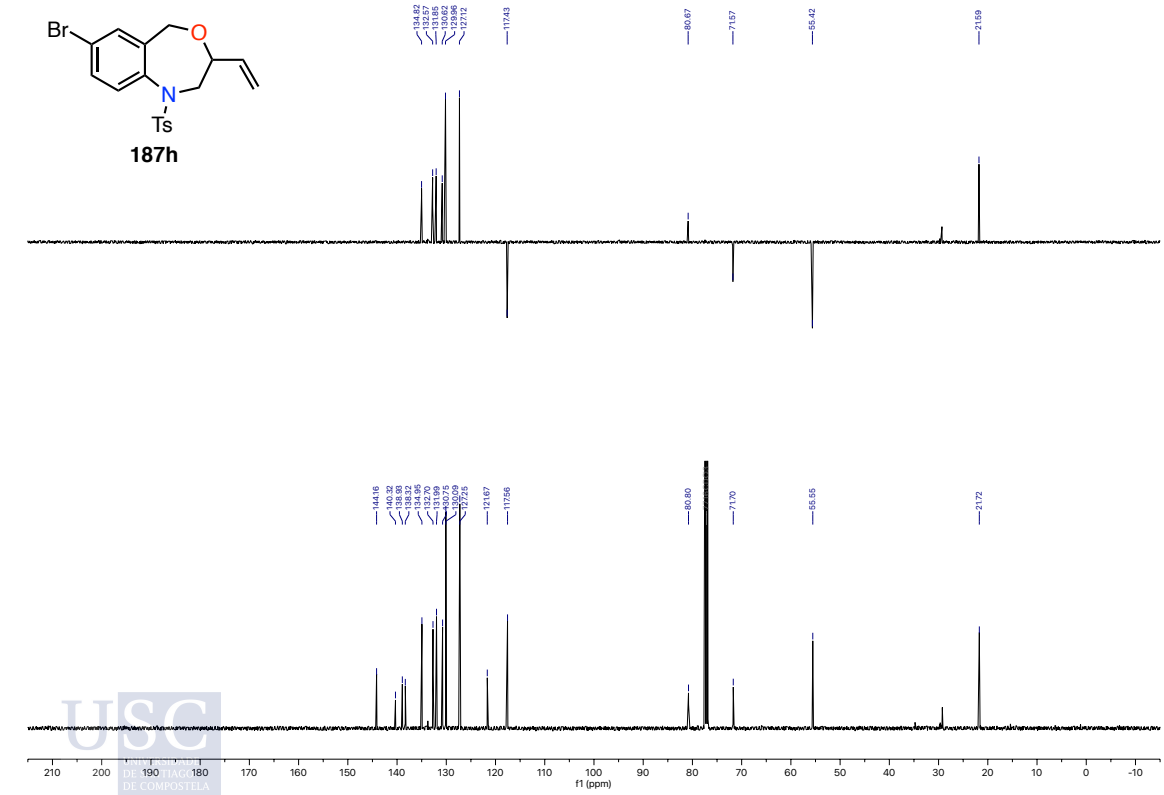



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

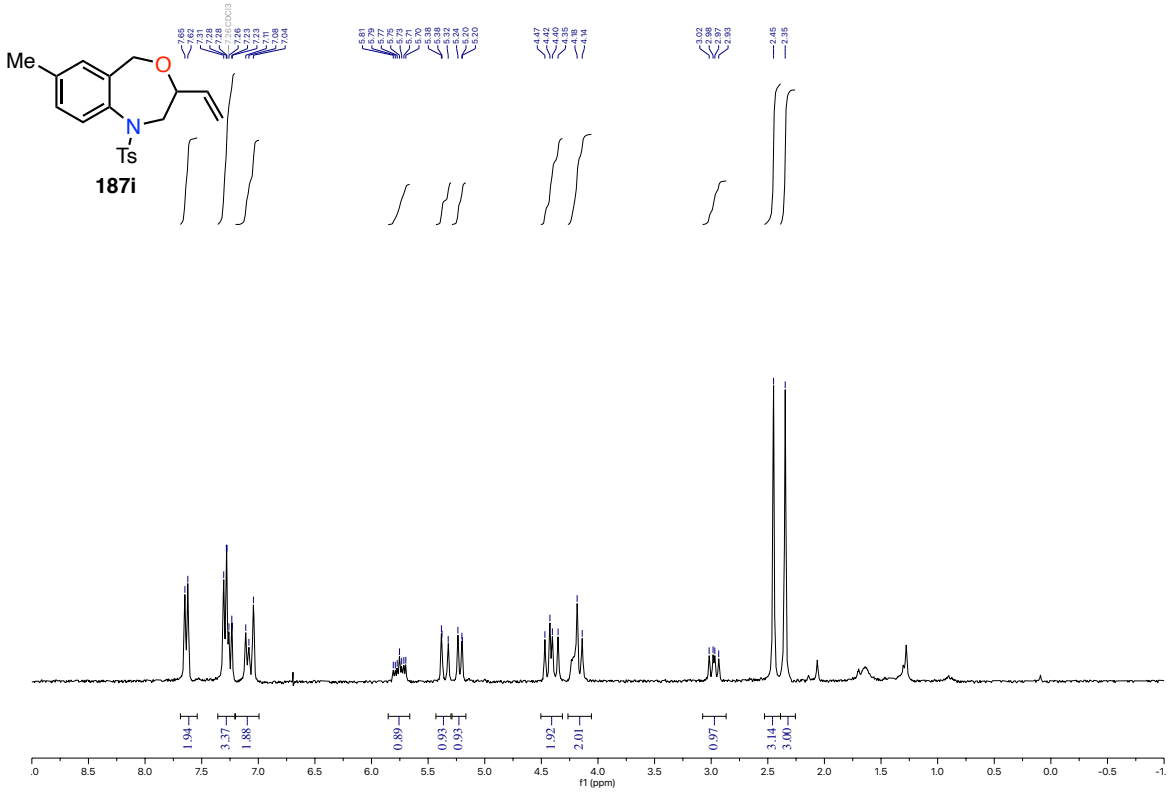



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

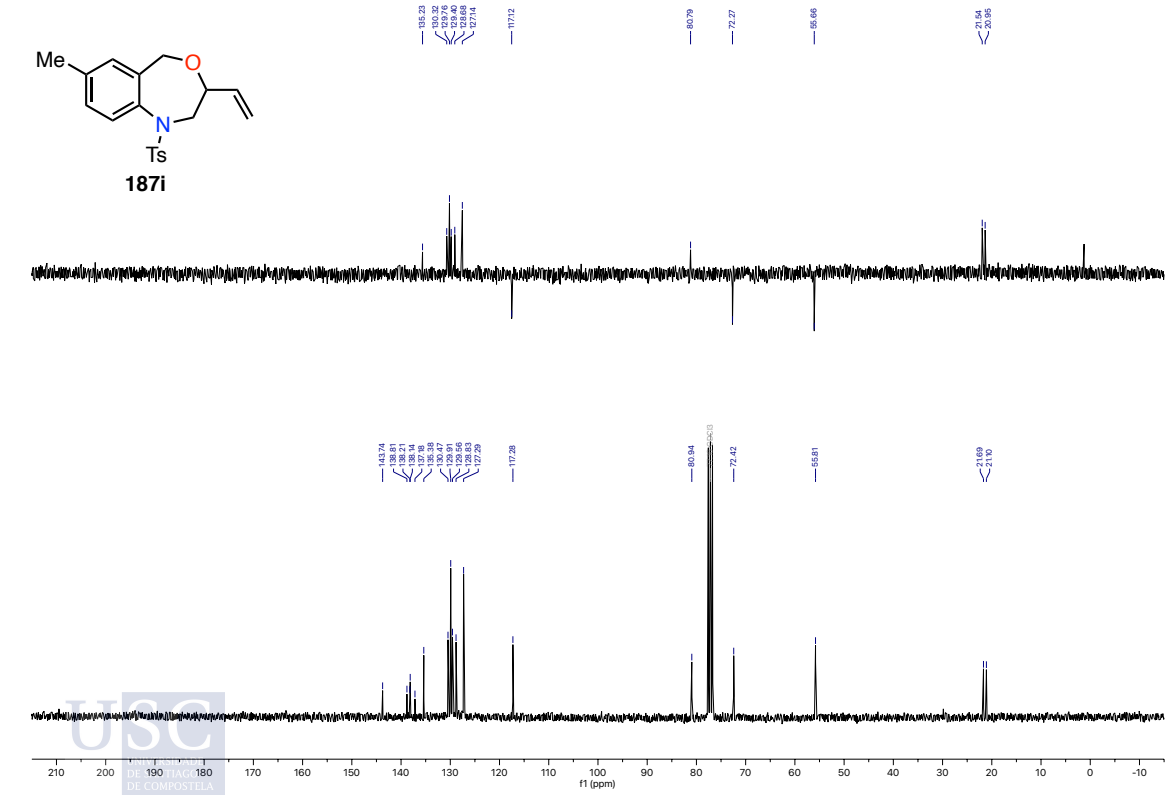



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

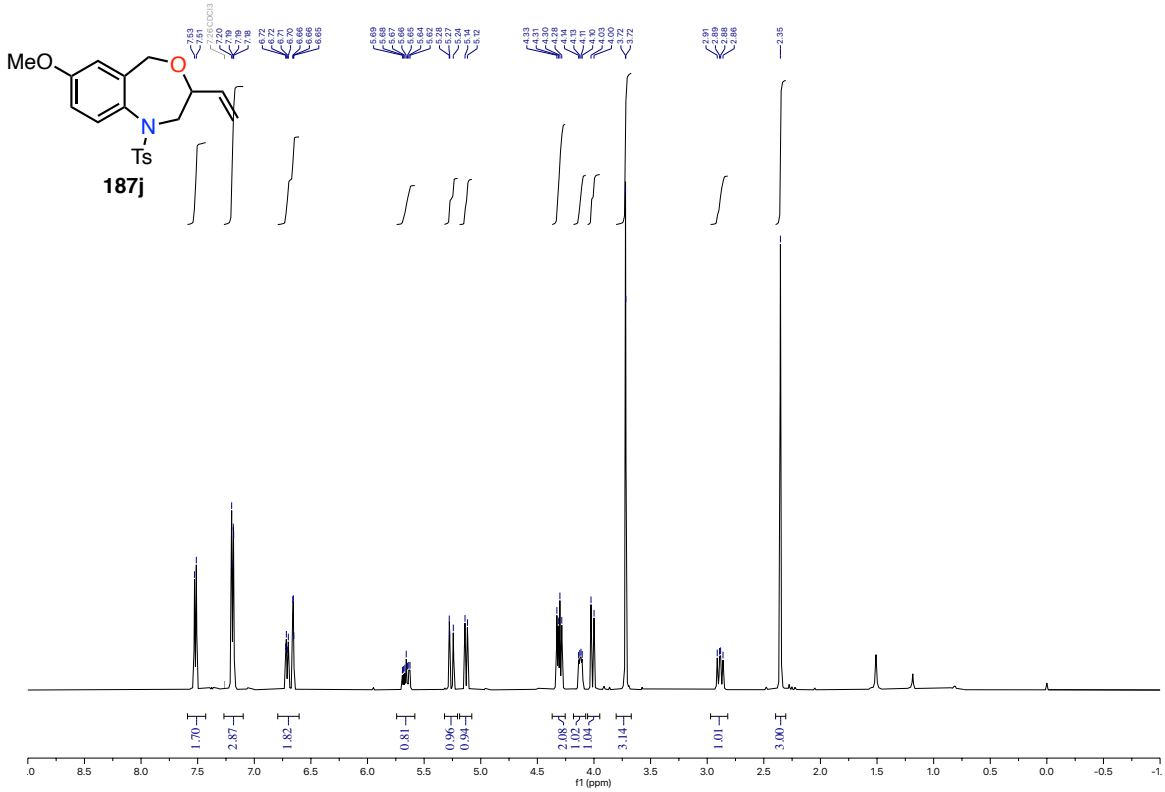



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

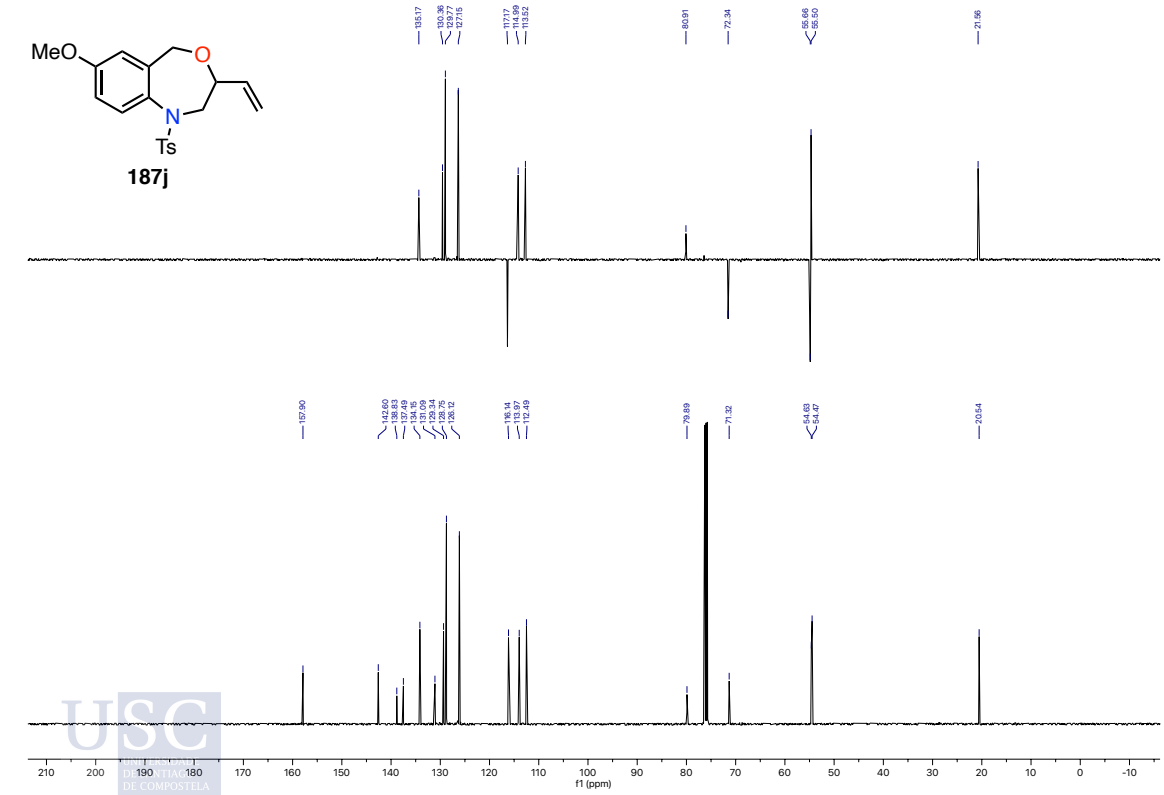



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

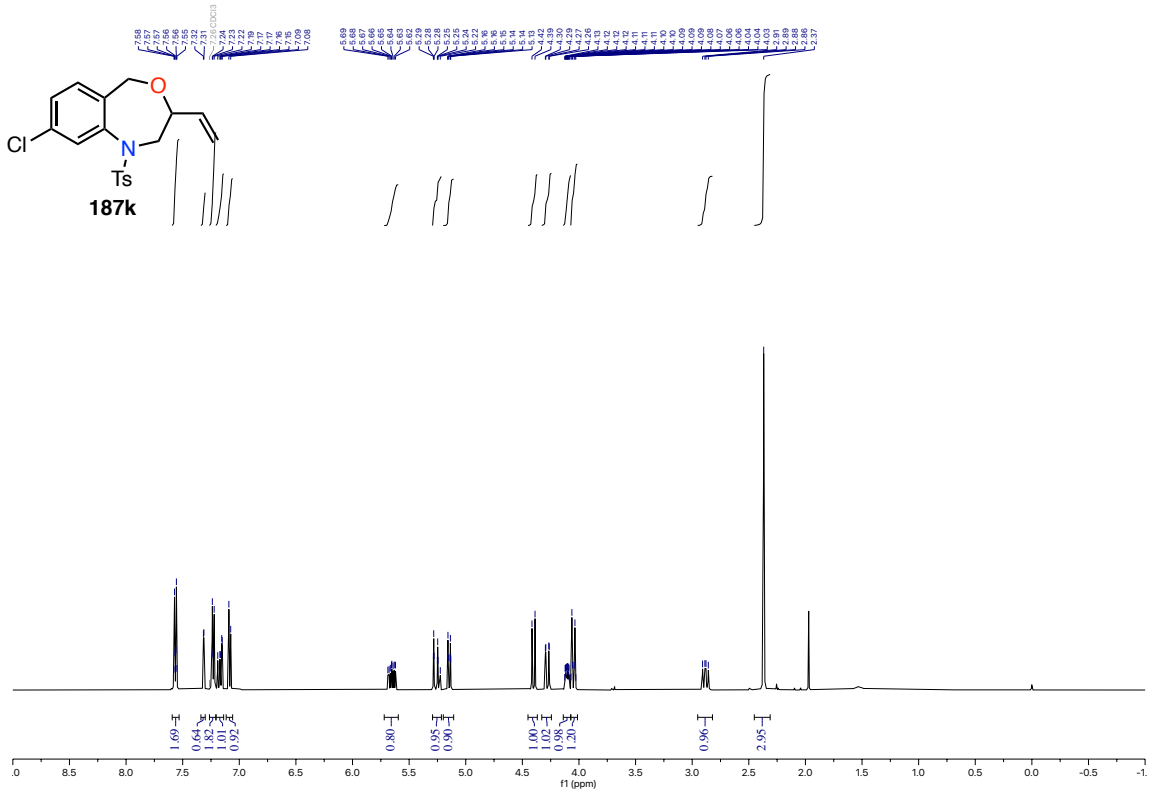



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

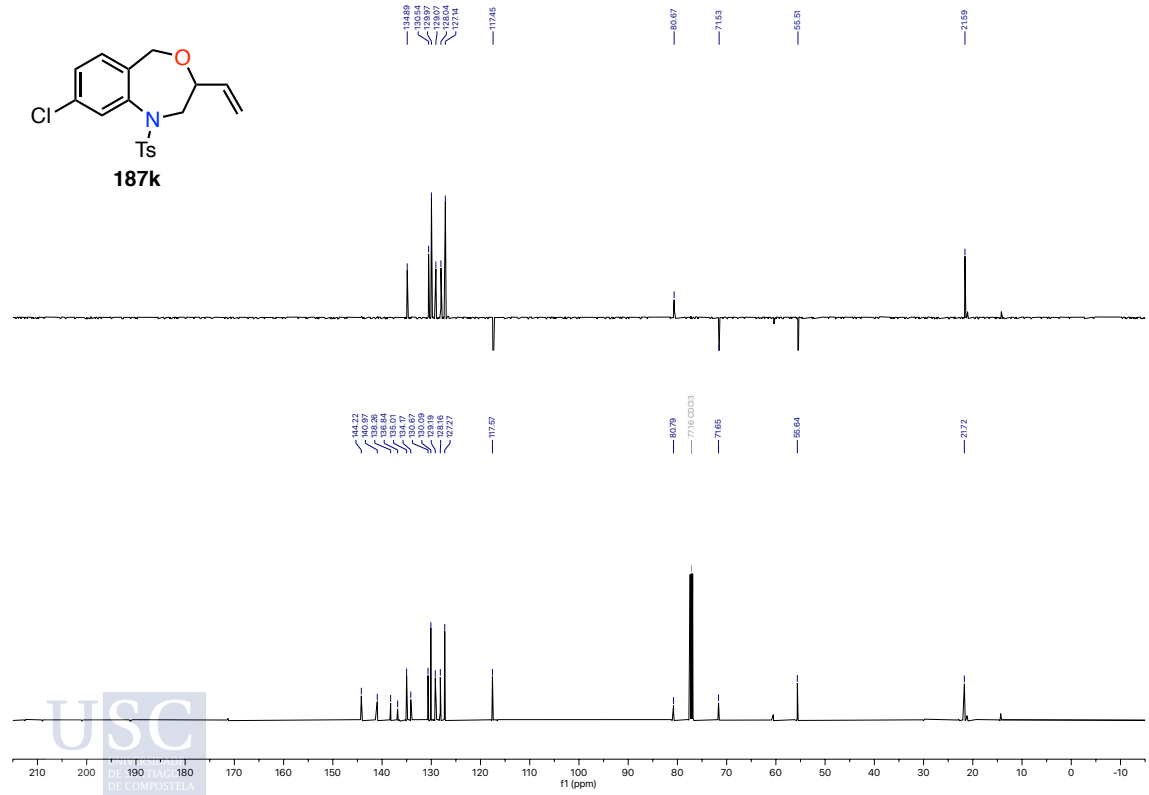



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

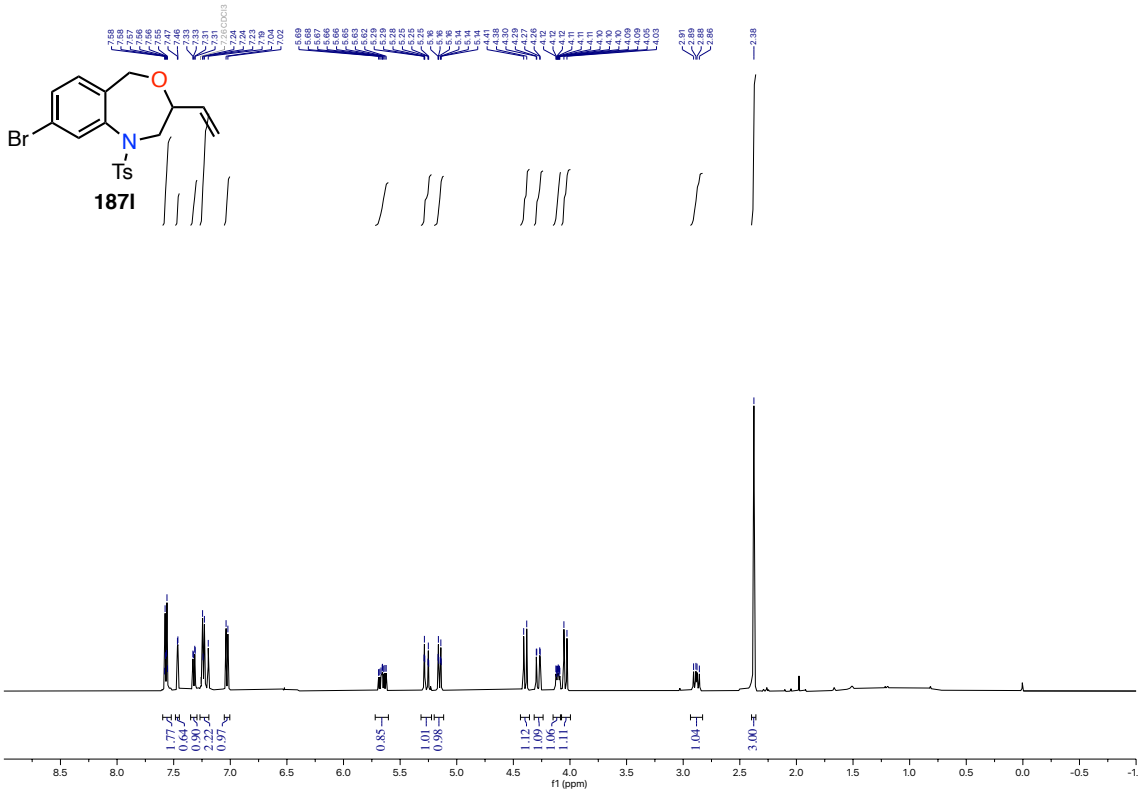



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

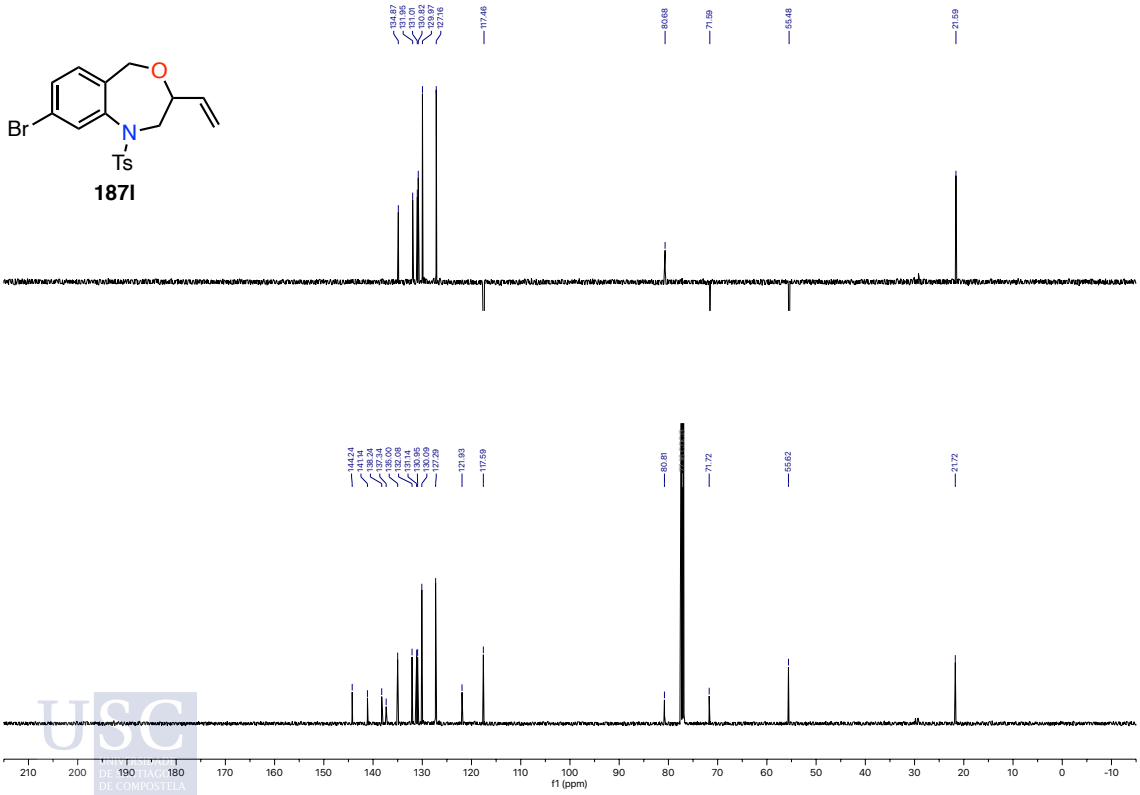



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

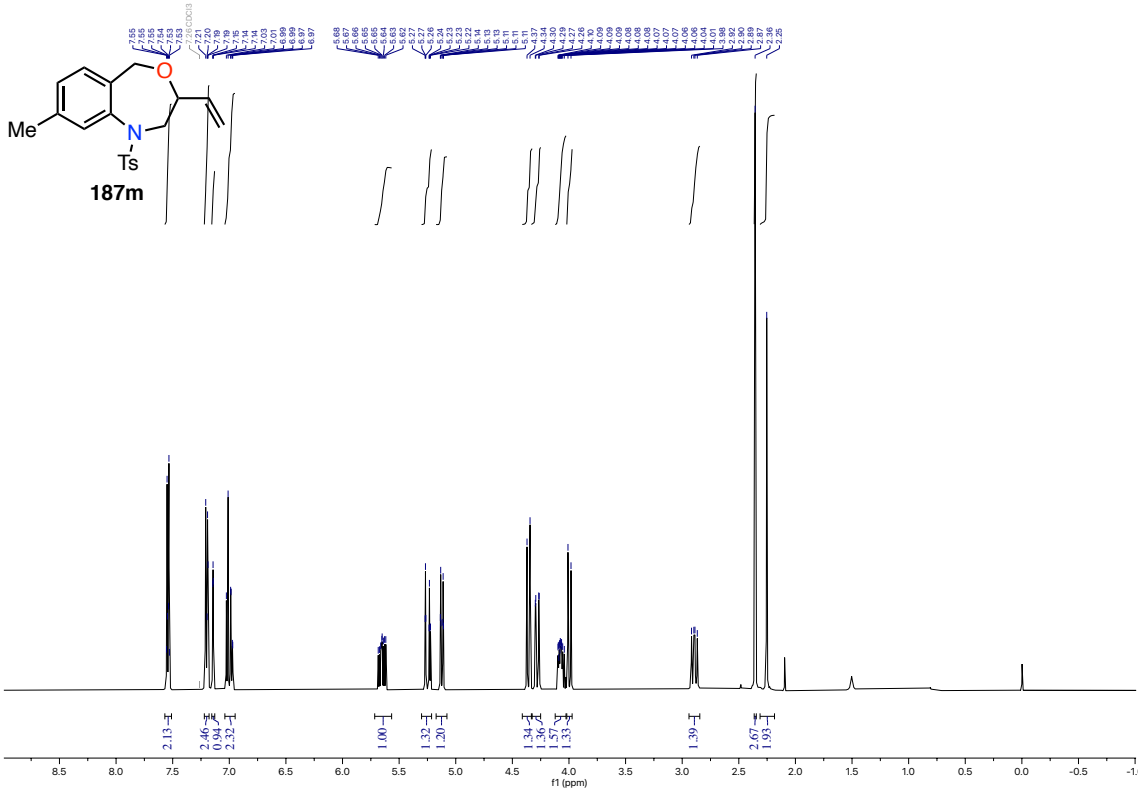



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

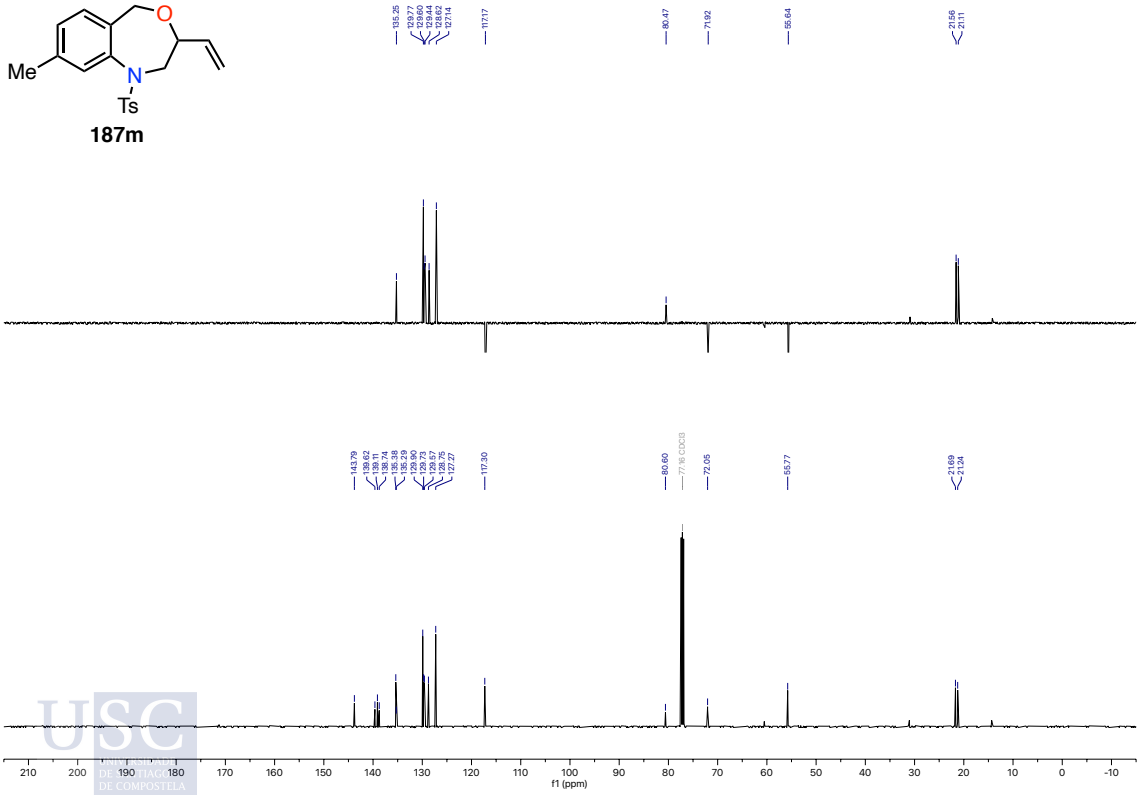



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

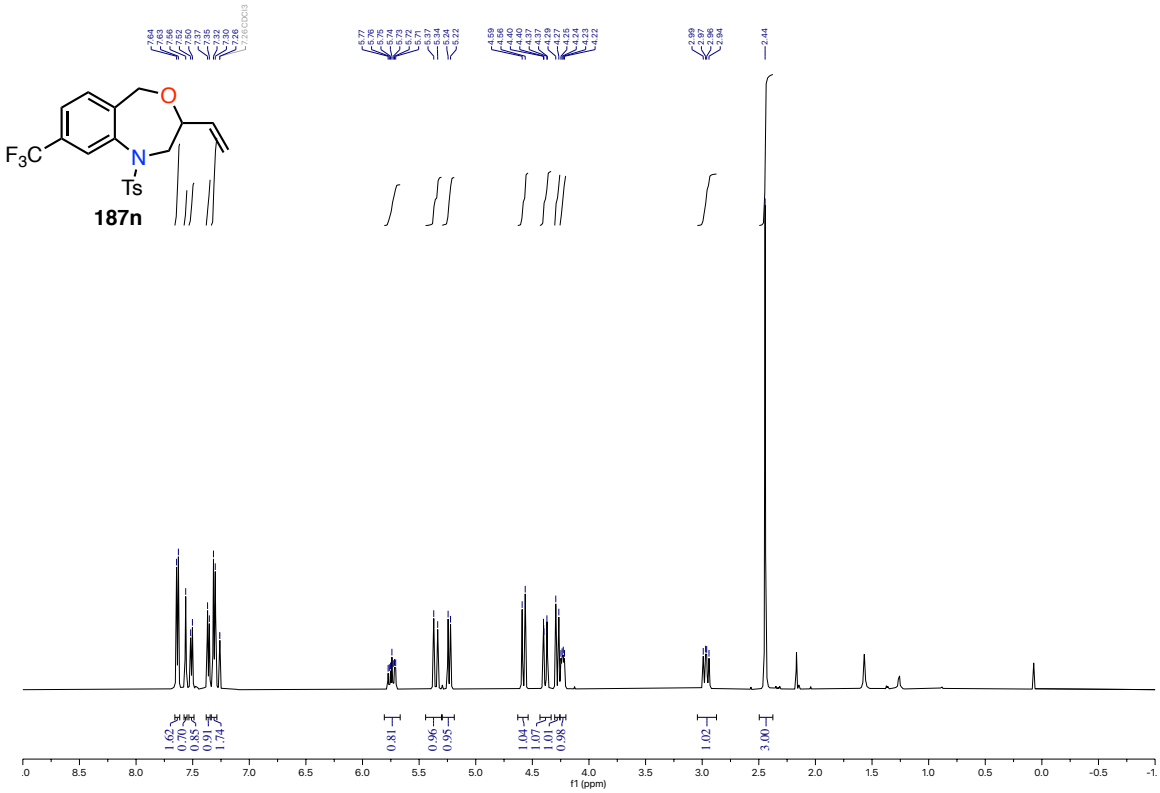



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

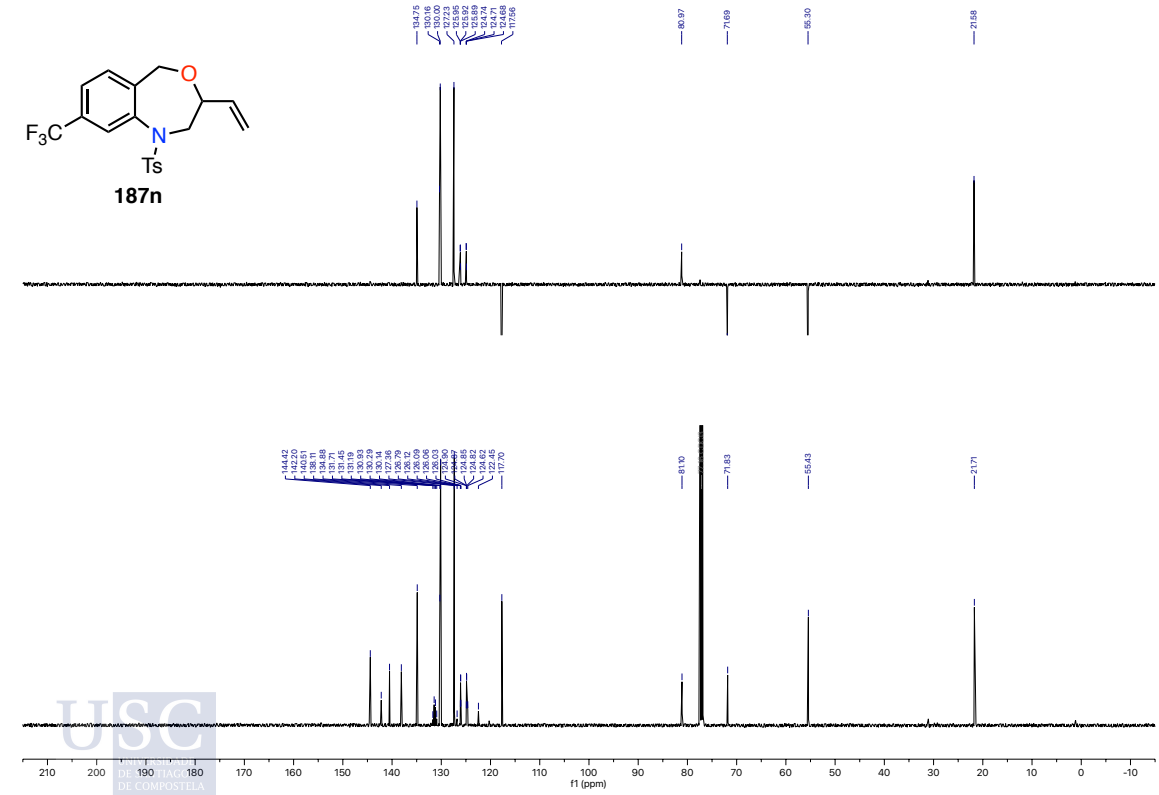



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

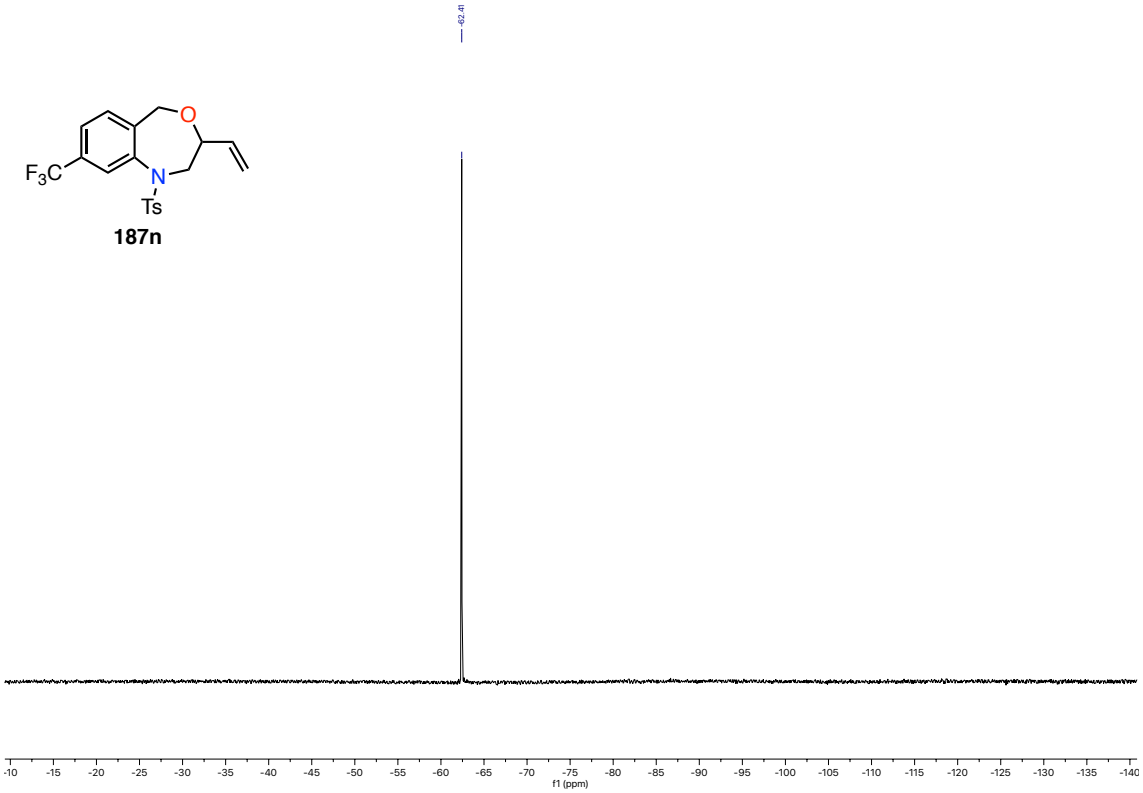



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$



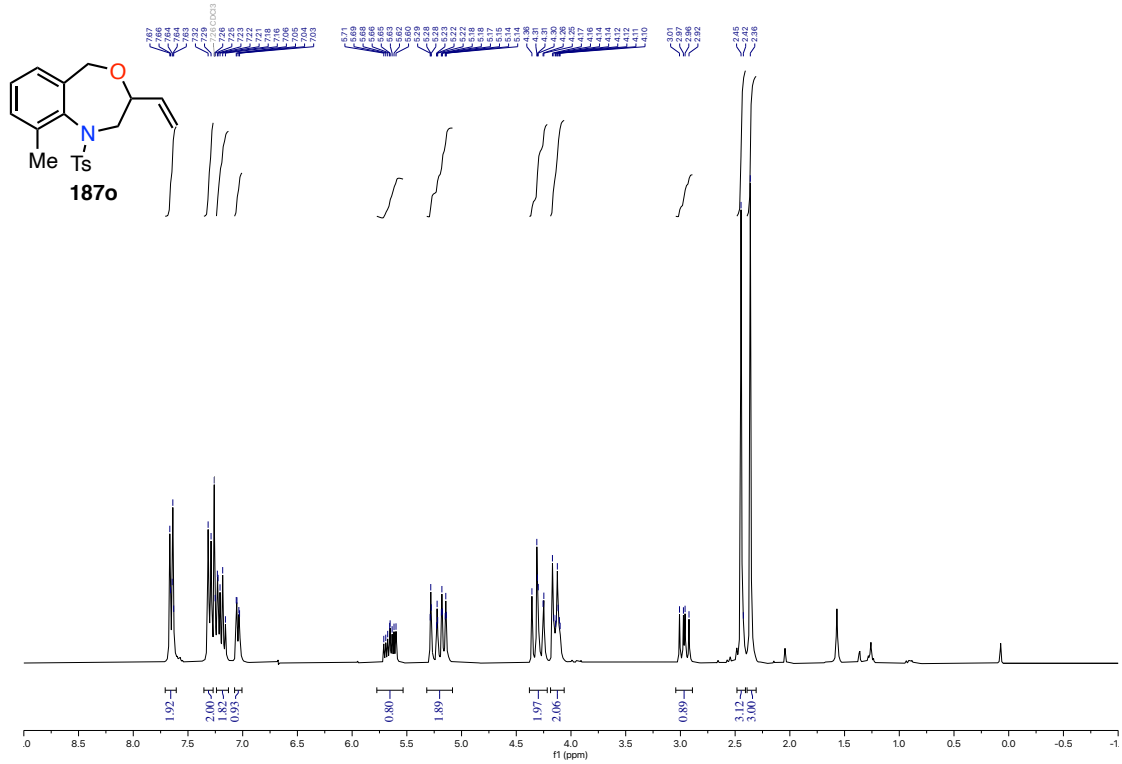

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$^{19}$F-NMR (282 MHz). Solvent $CDCl_3$

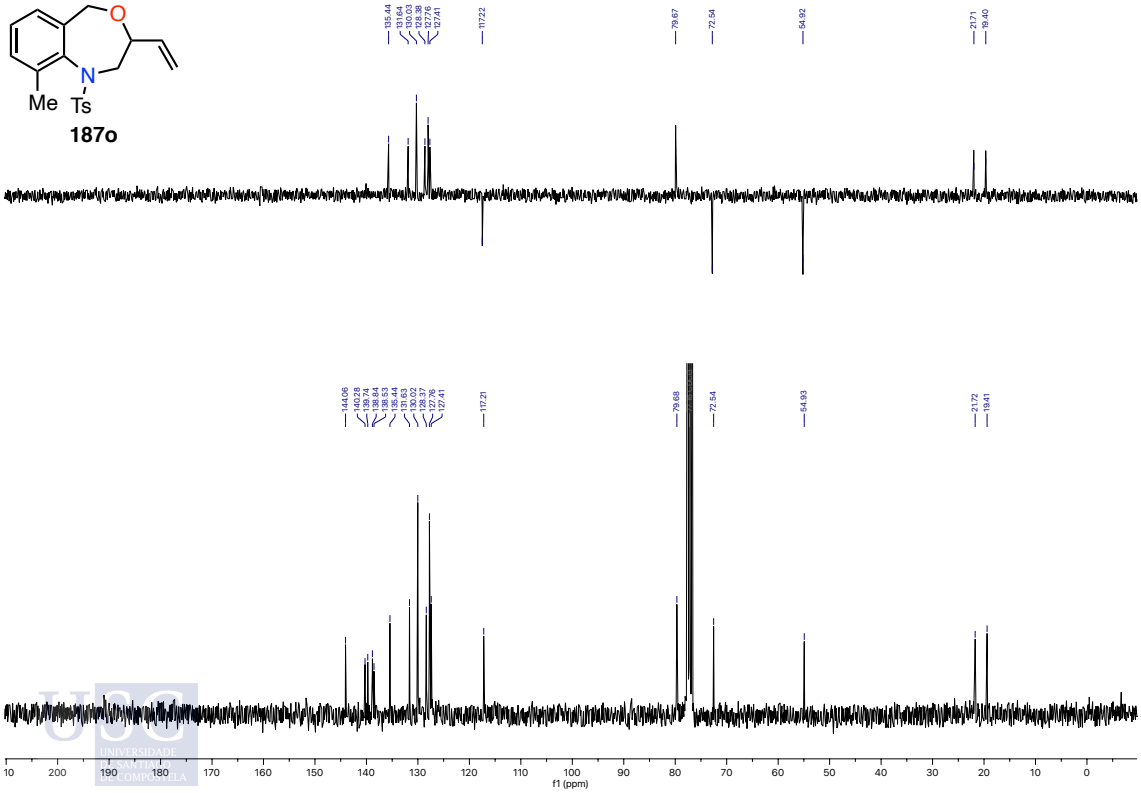



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

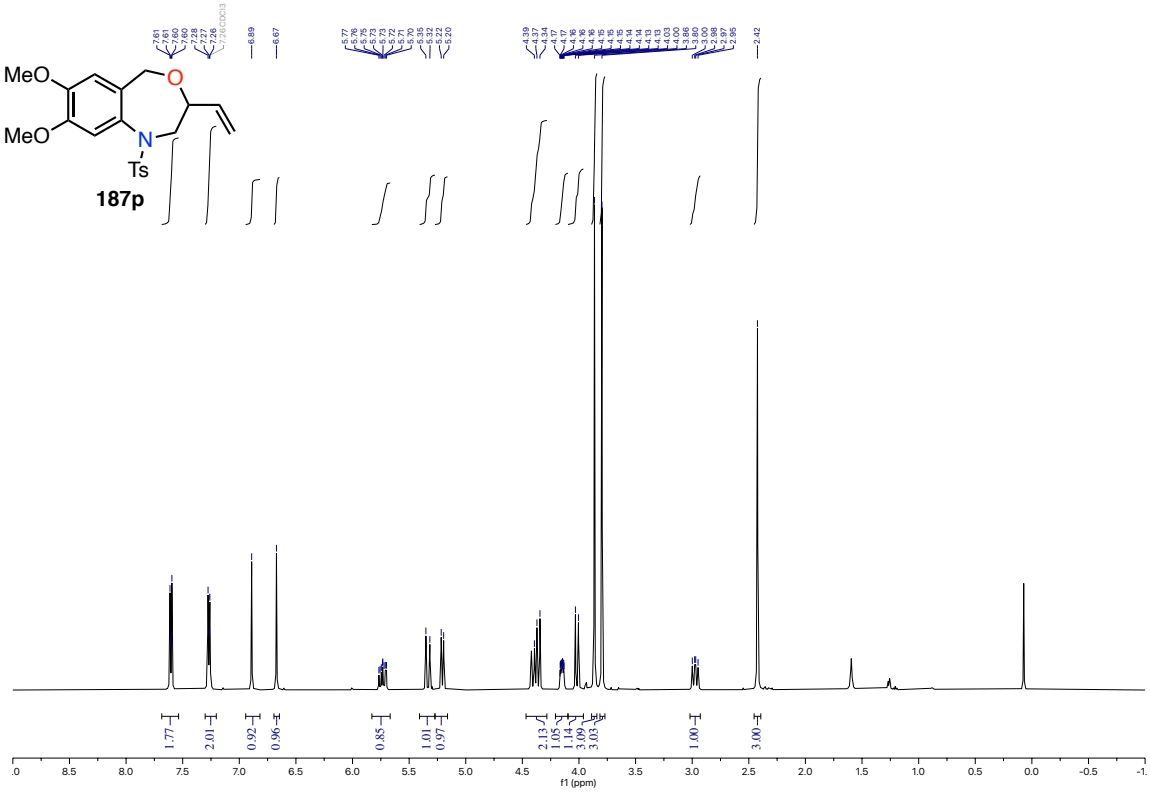
$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$



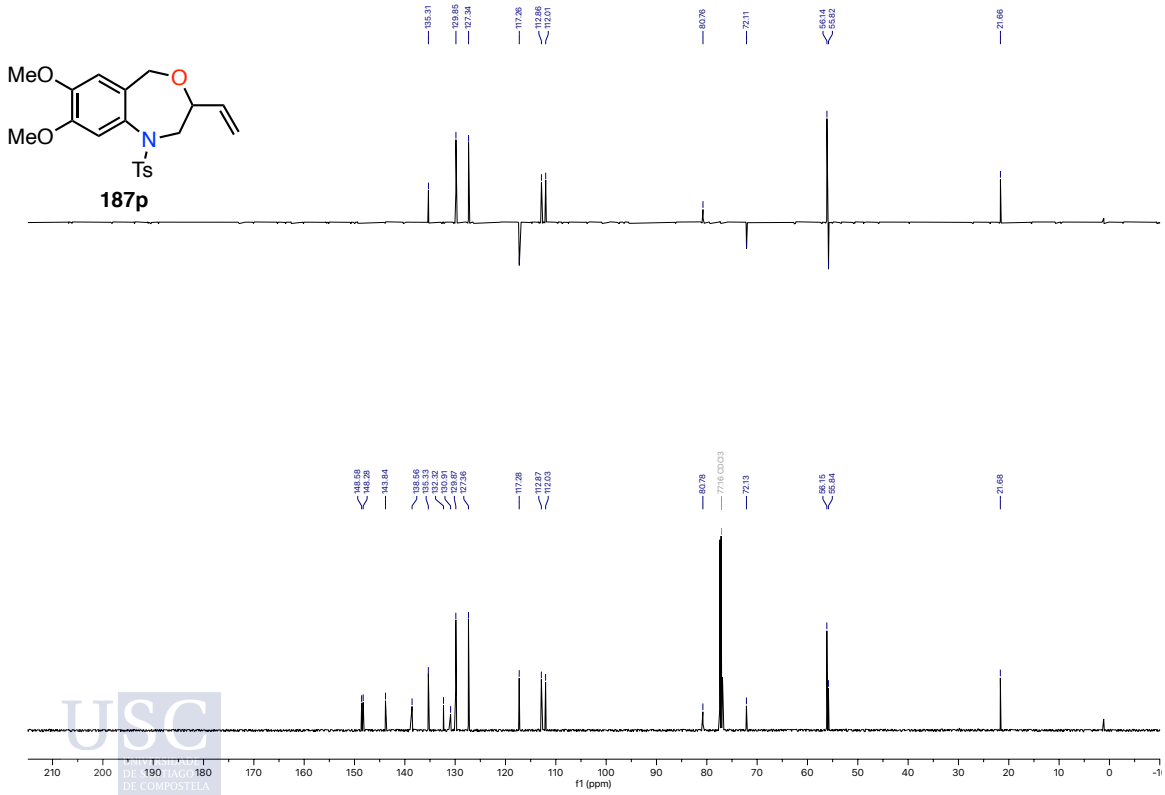

$^{13}$C-NMR (75MHz). Solvent $CDCl_3$



$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

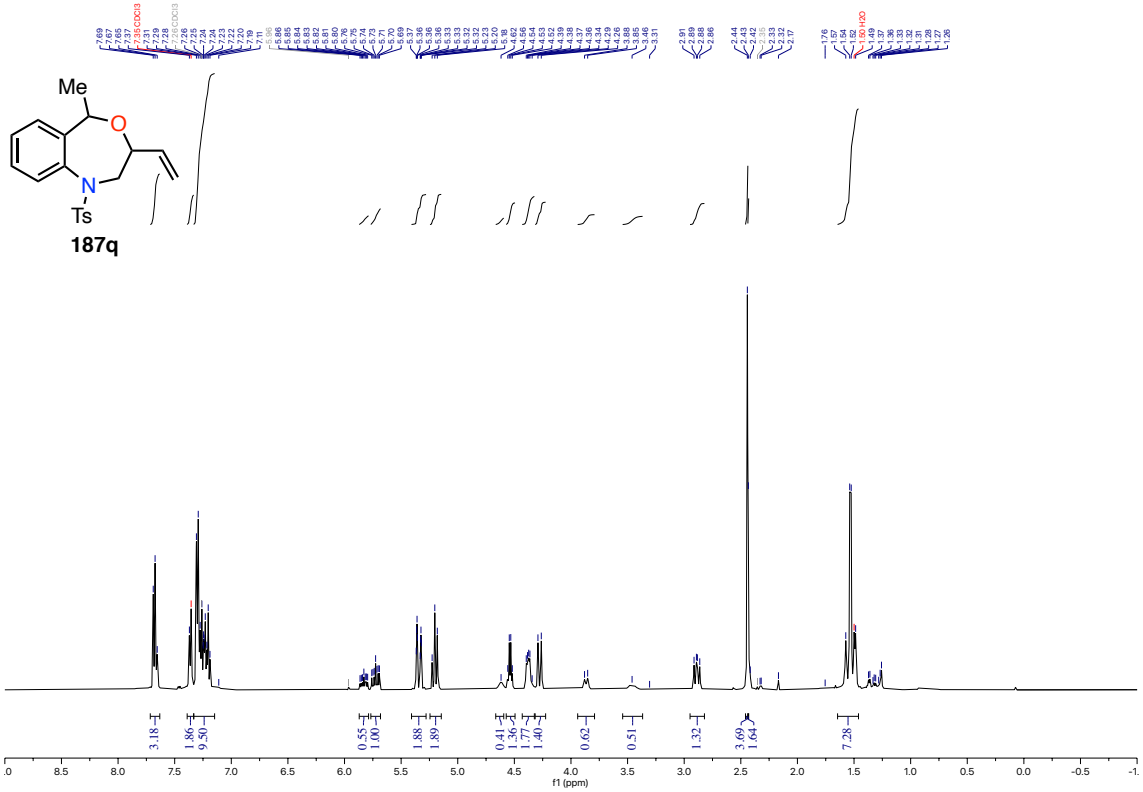



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

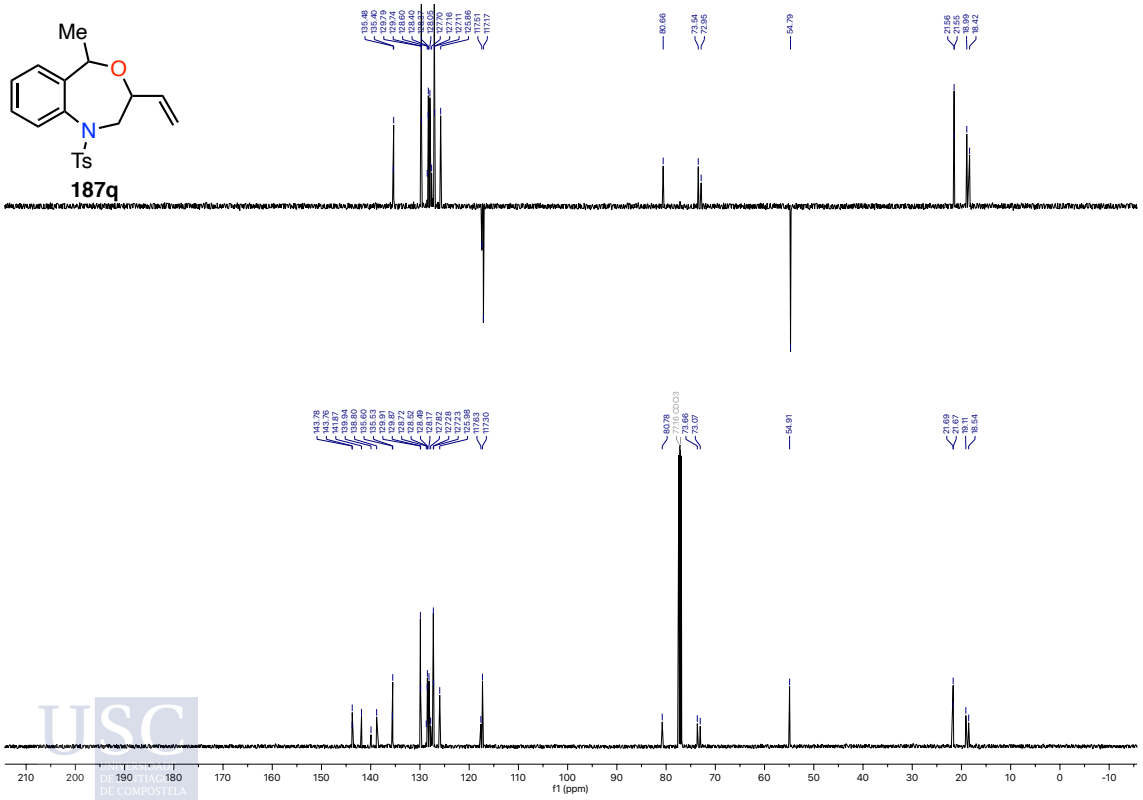



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

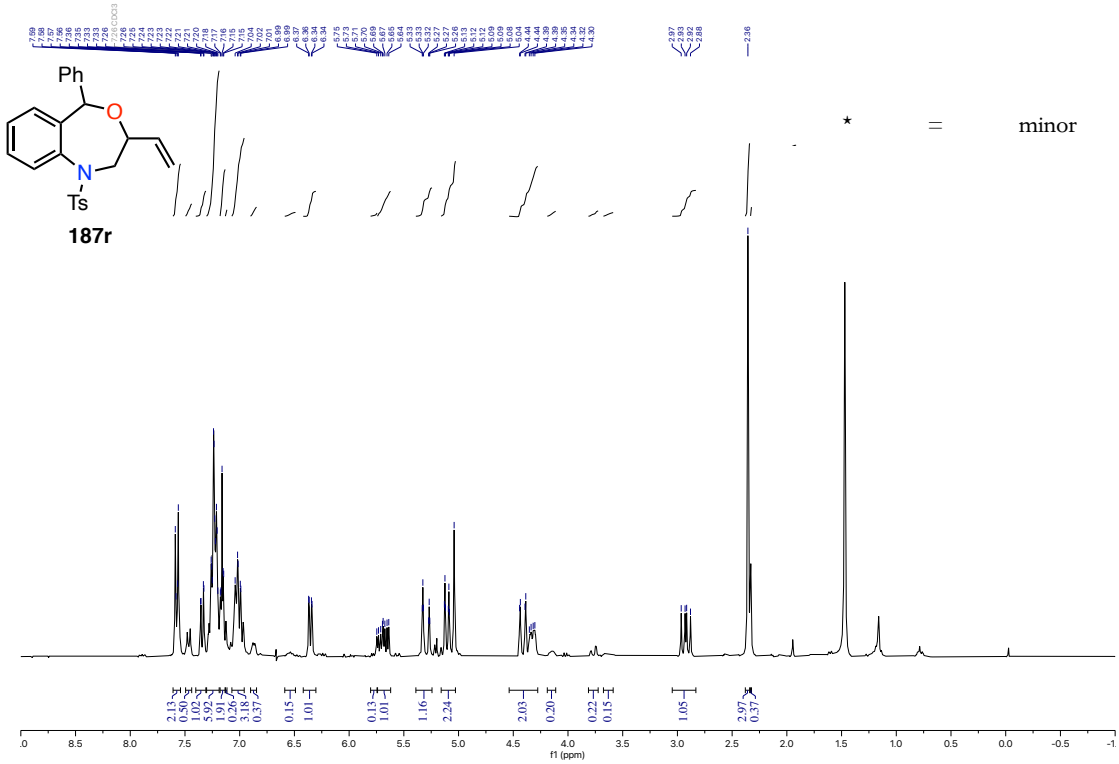



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

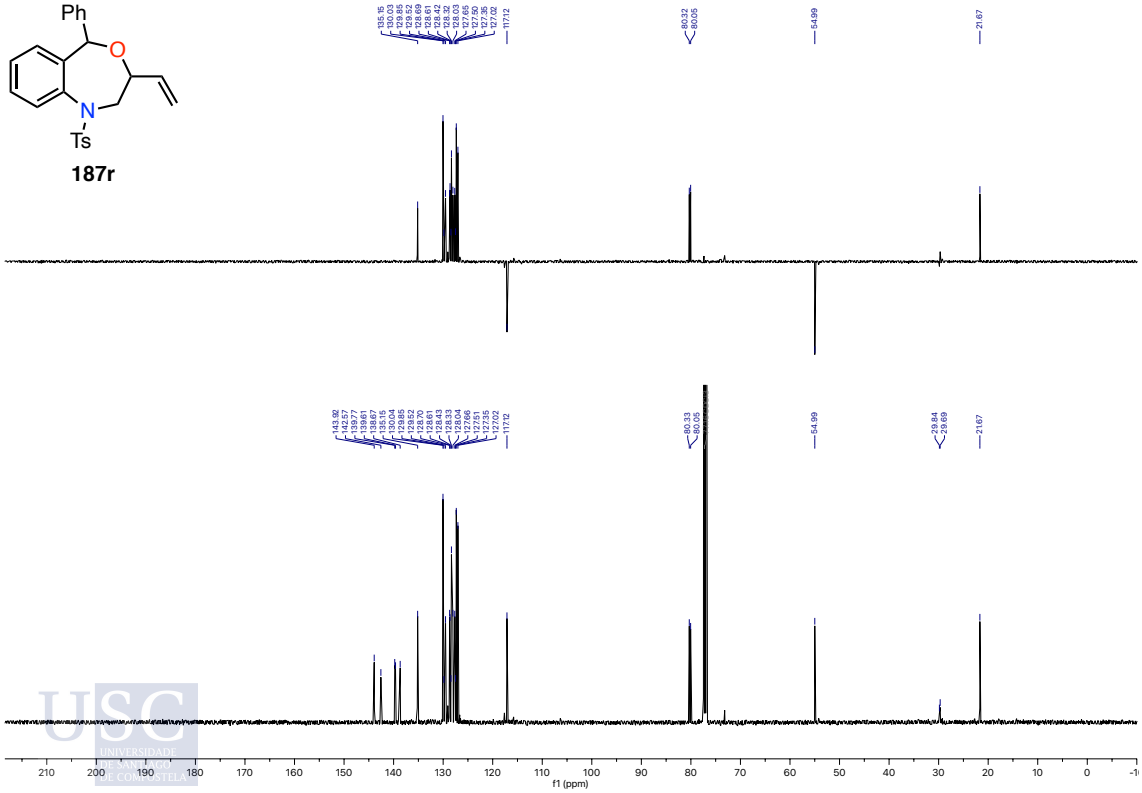



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

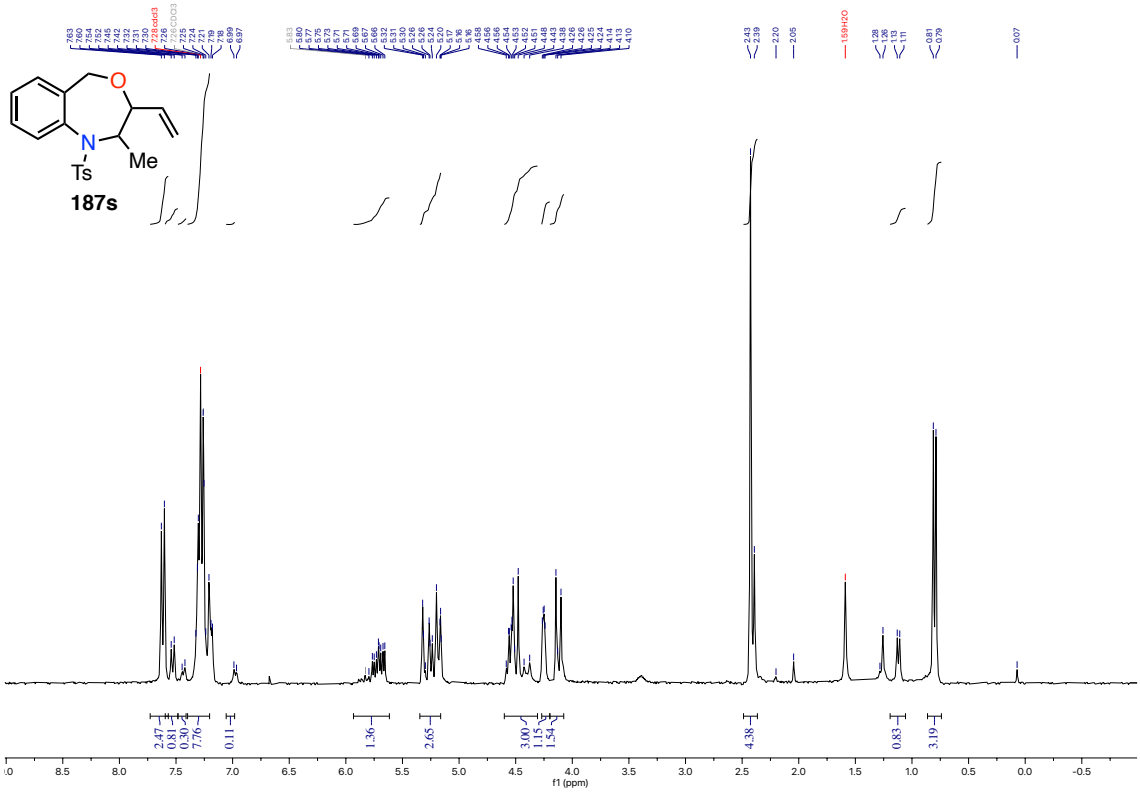
$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$



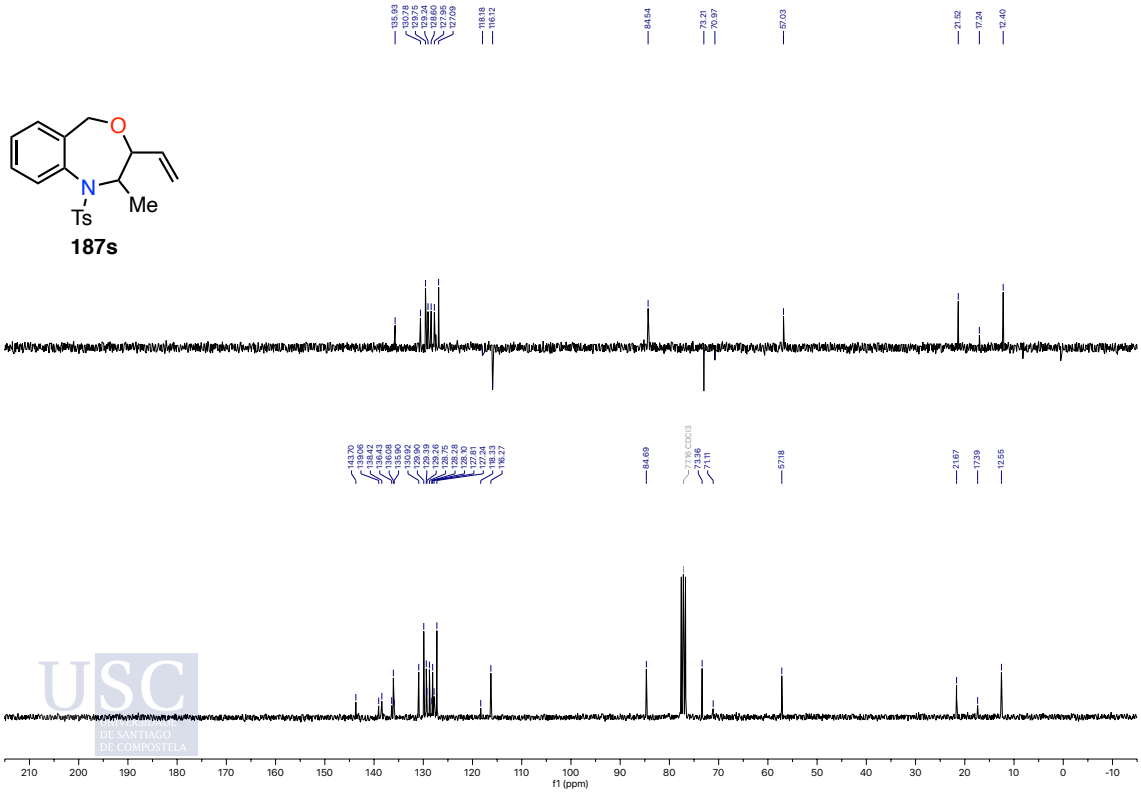

$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$



$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

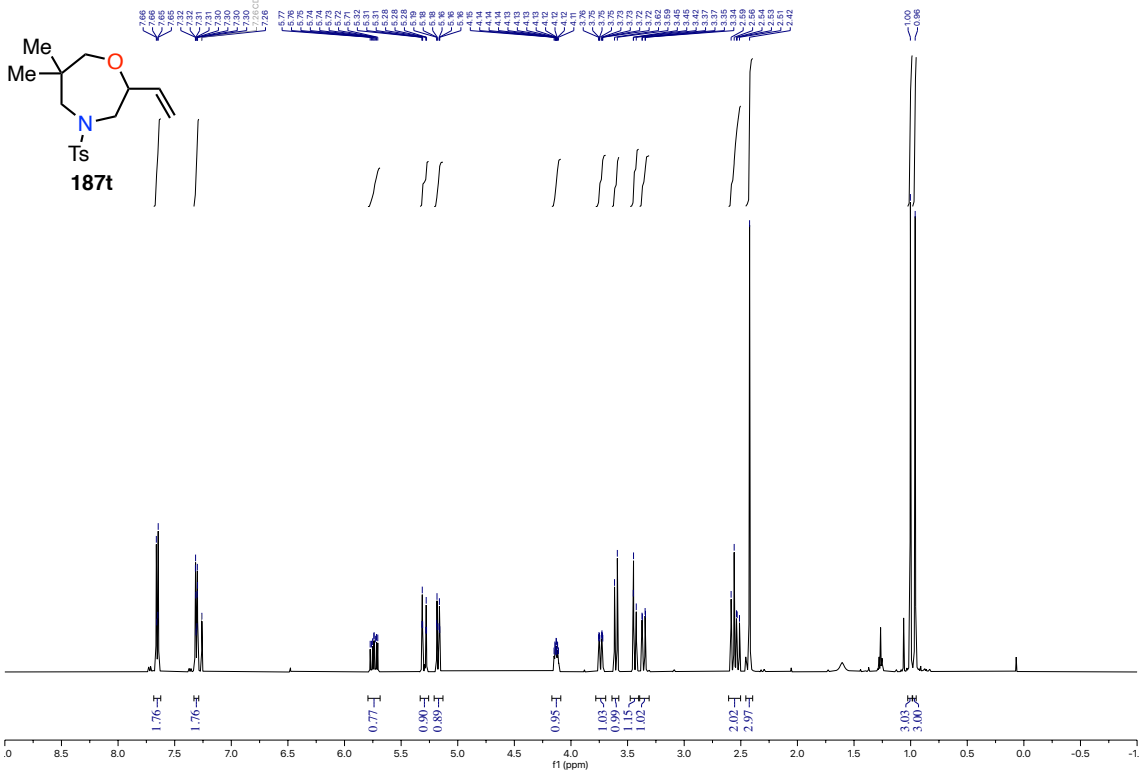



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

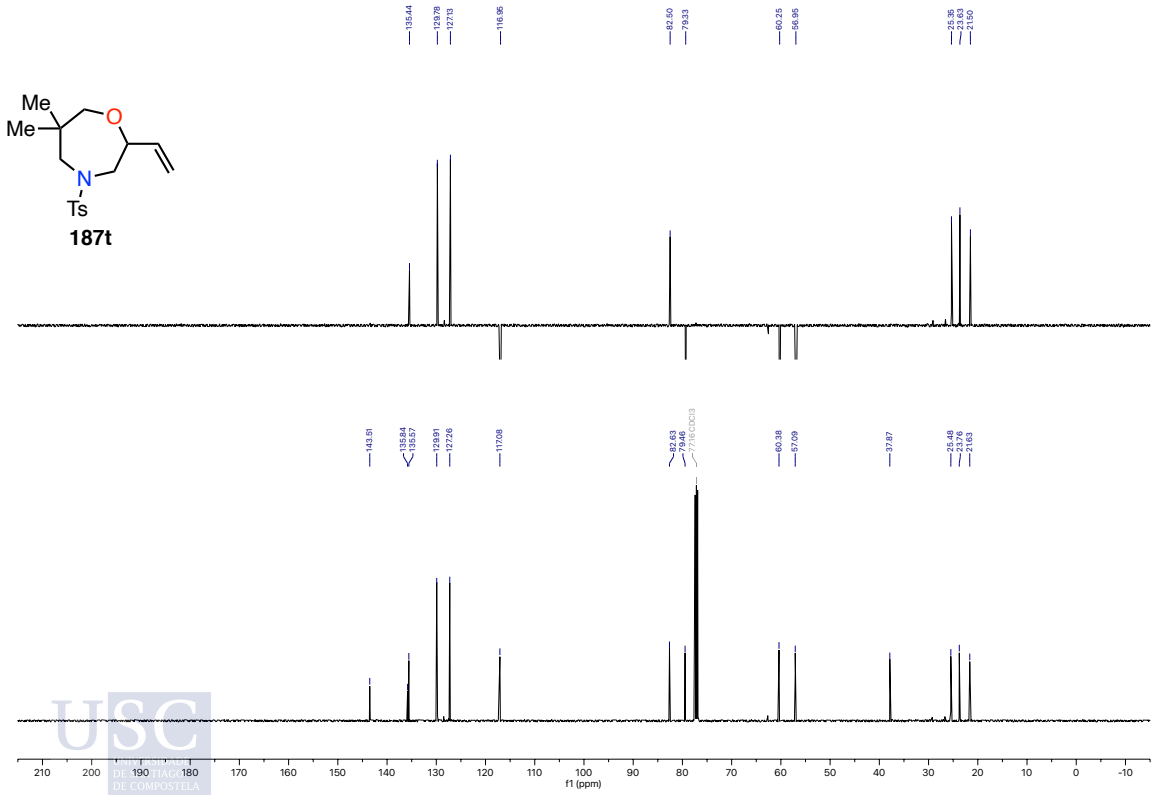



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

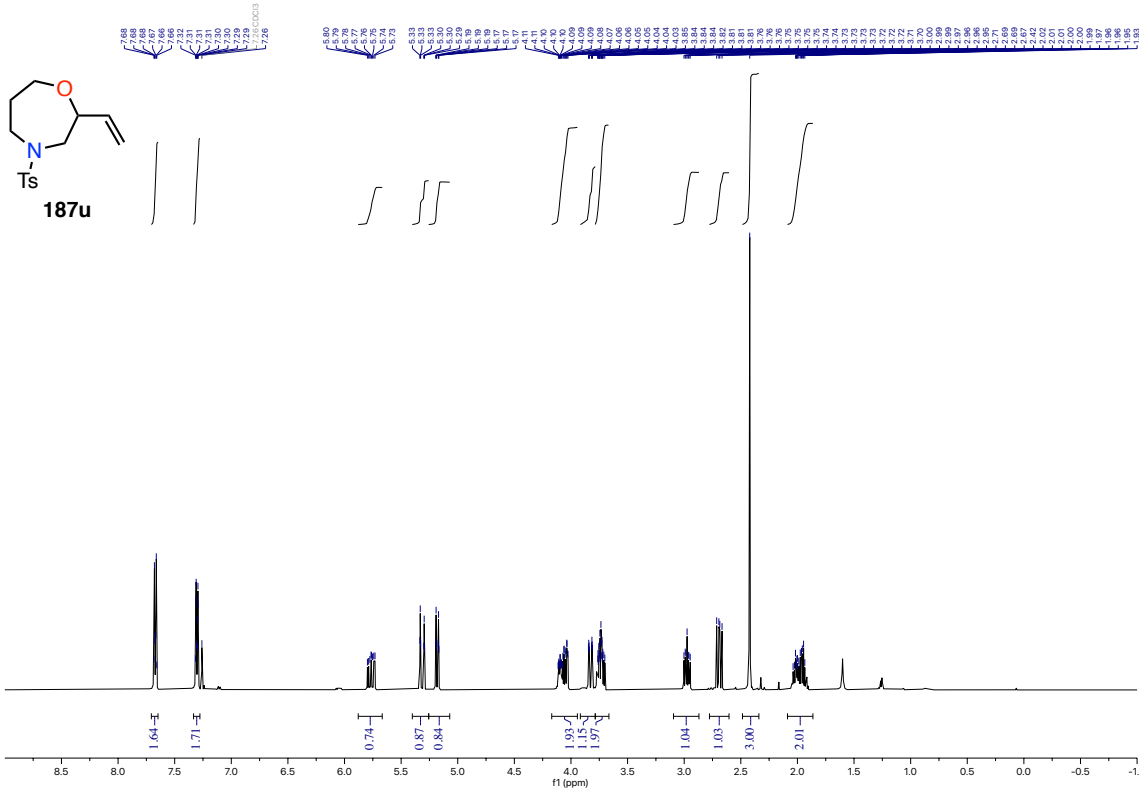



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

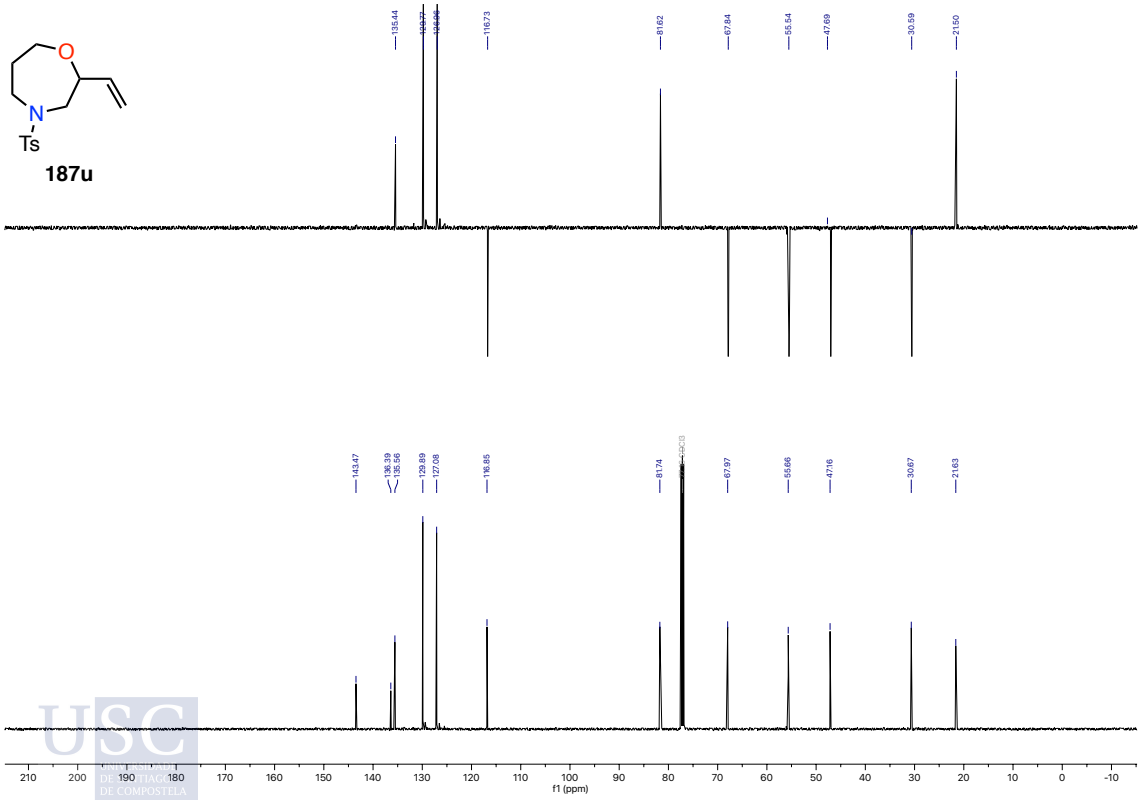



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

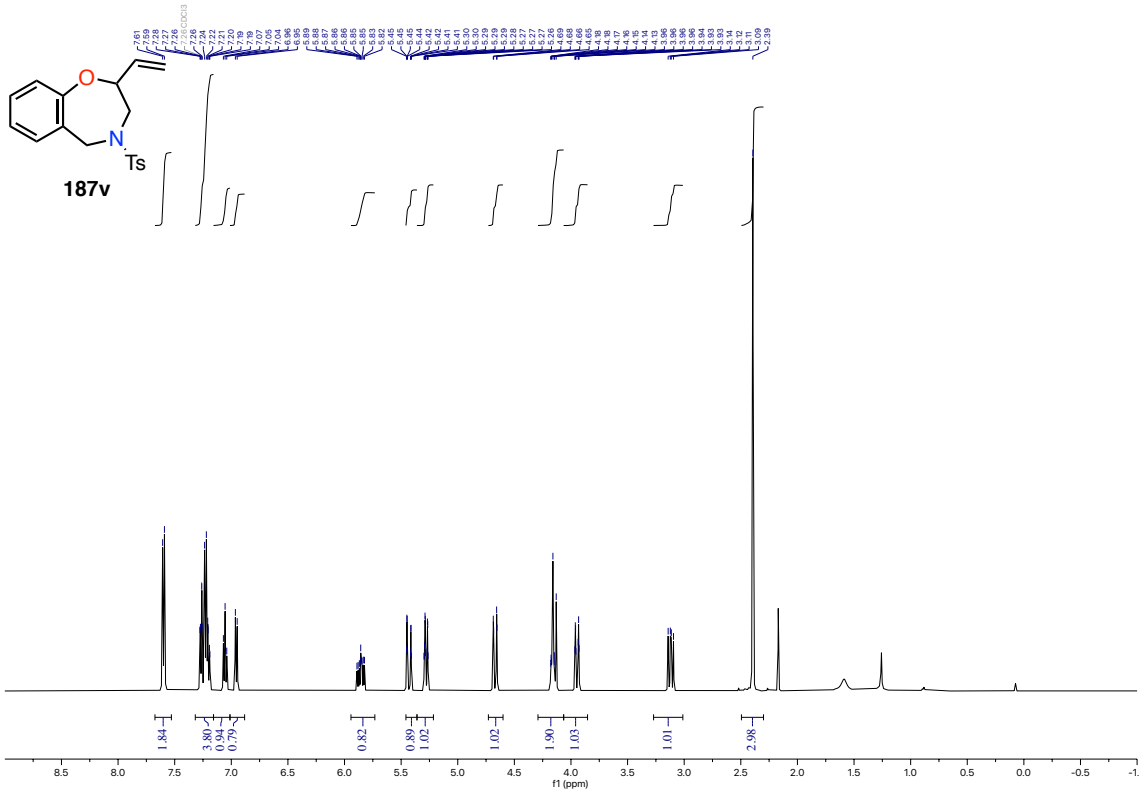



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

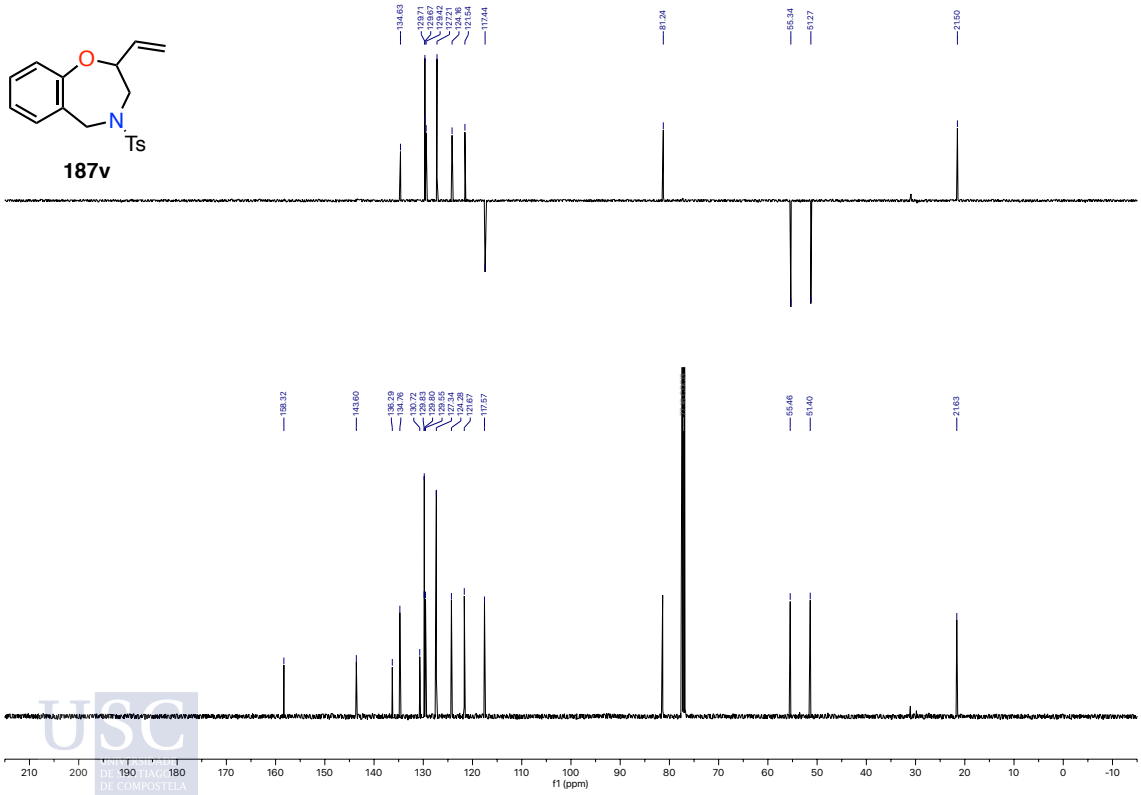



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$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

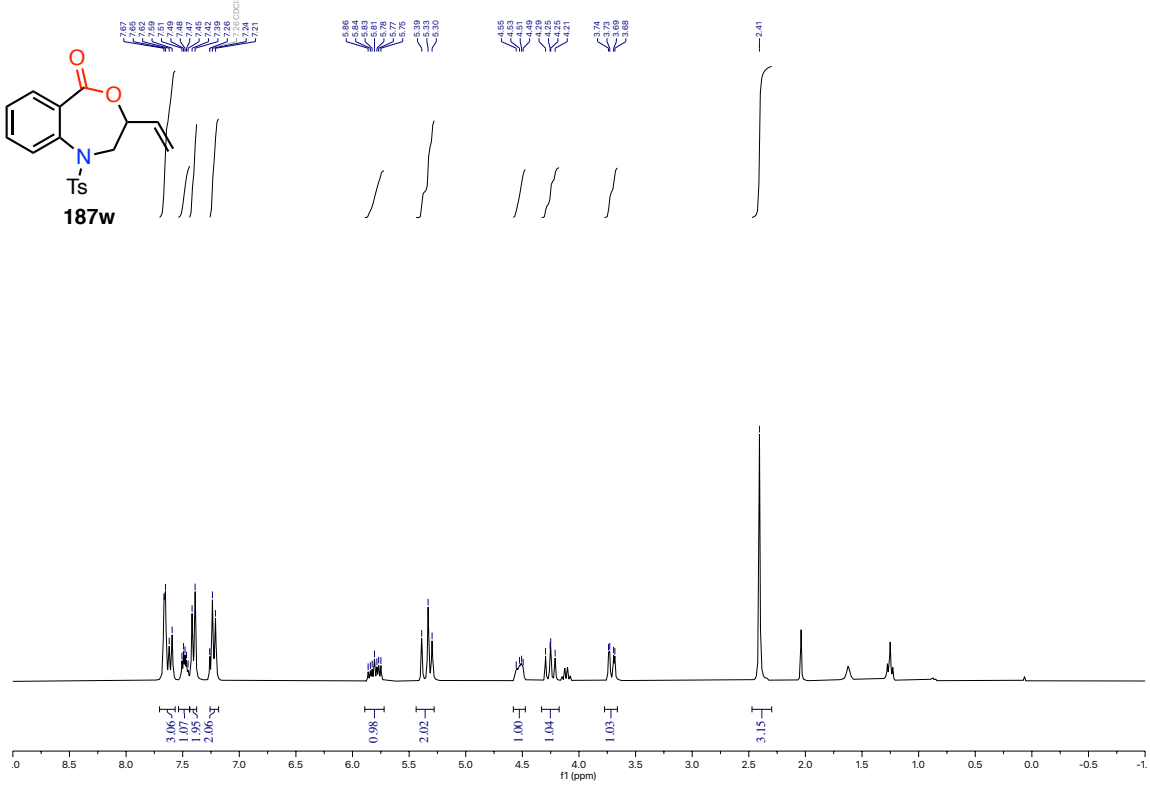



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

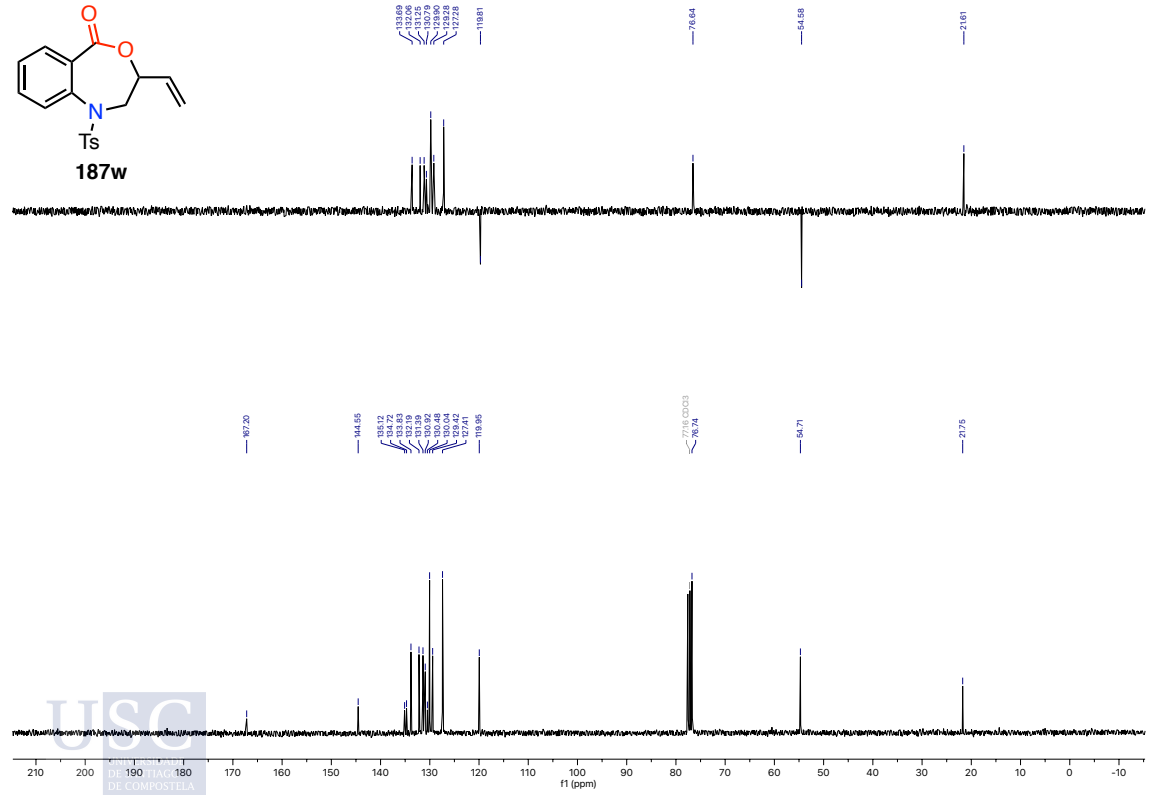



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

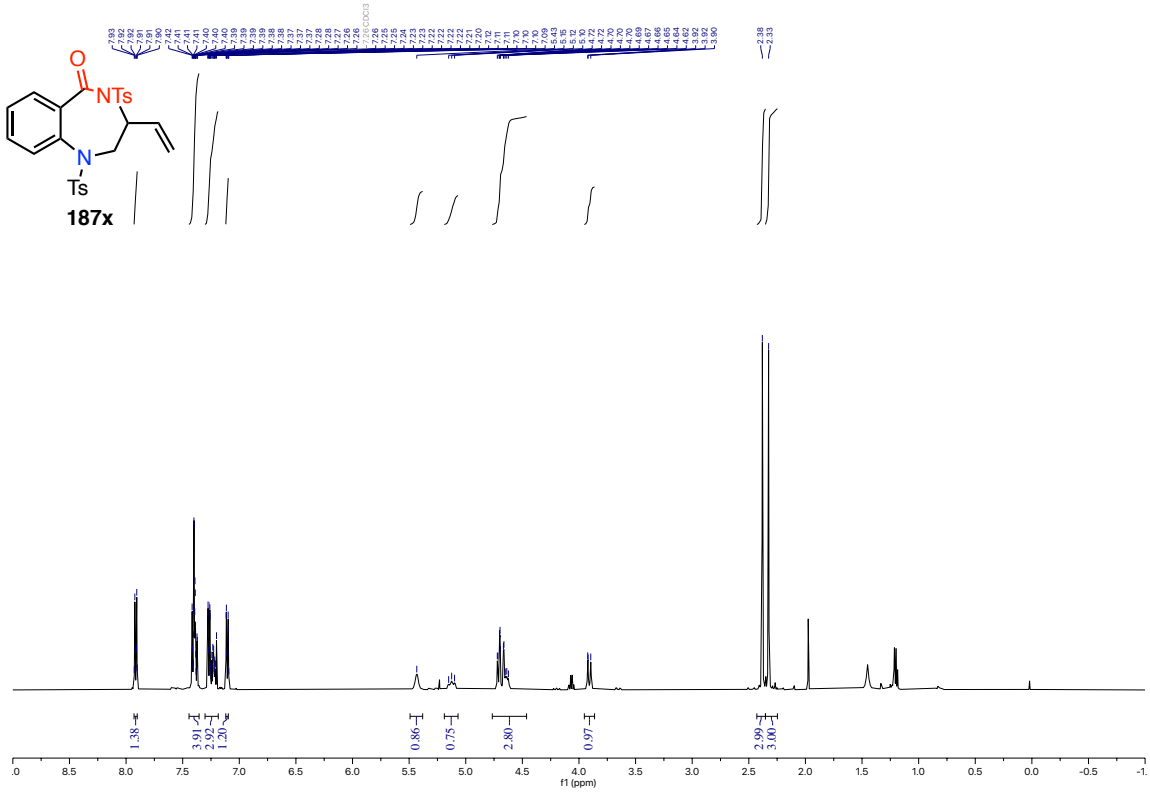



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

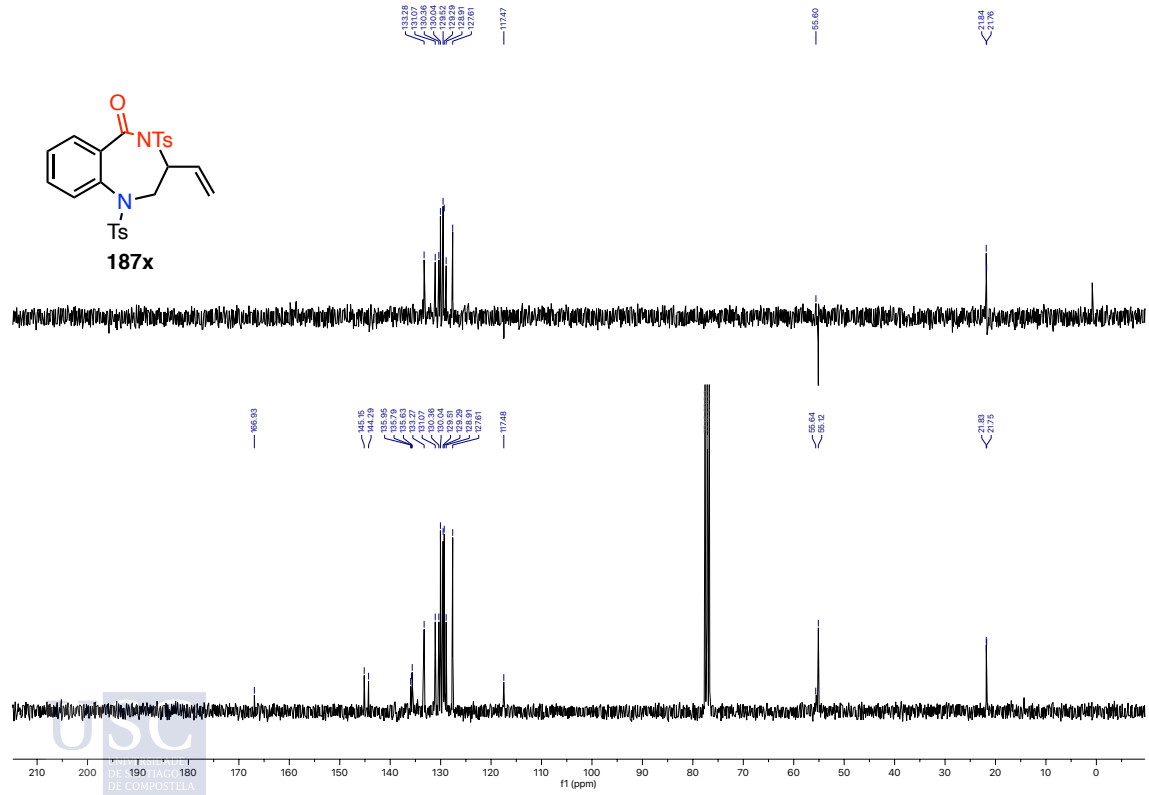



USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

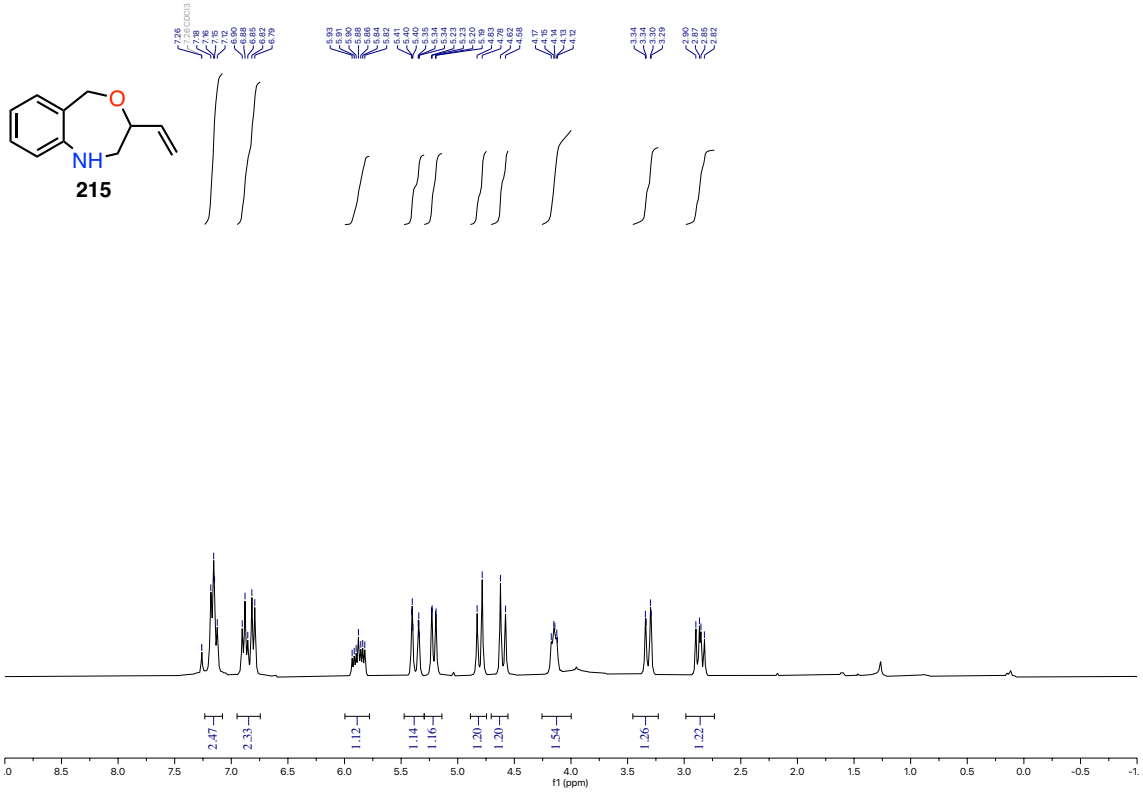



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

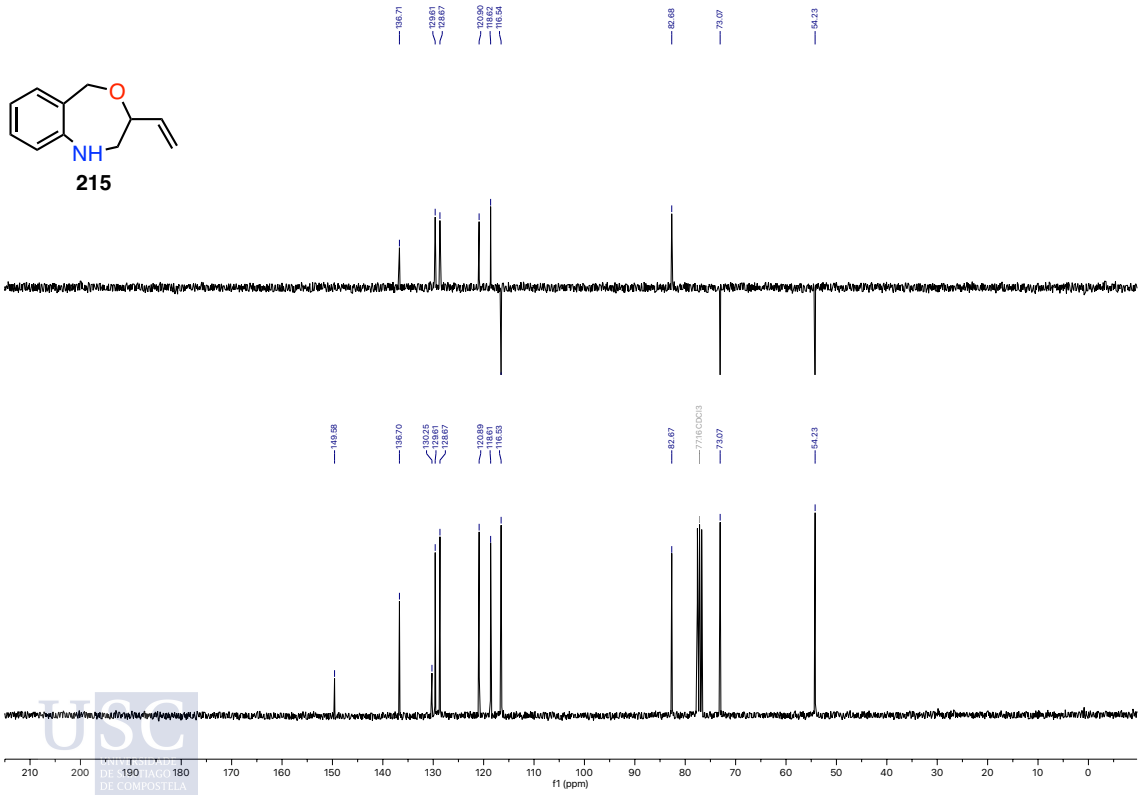



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$

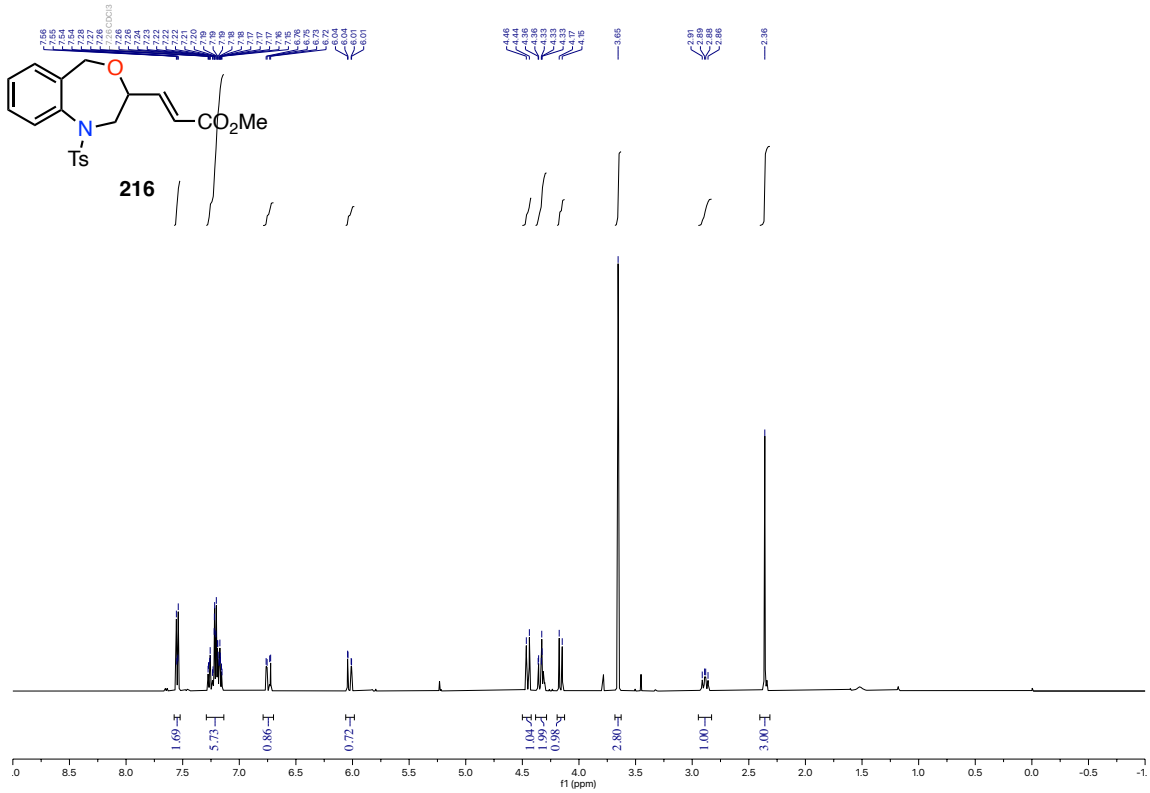



$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$

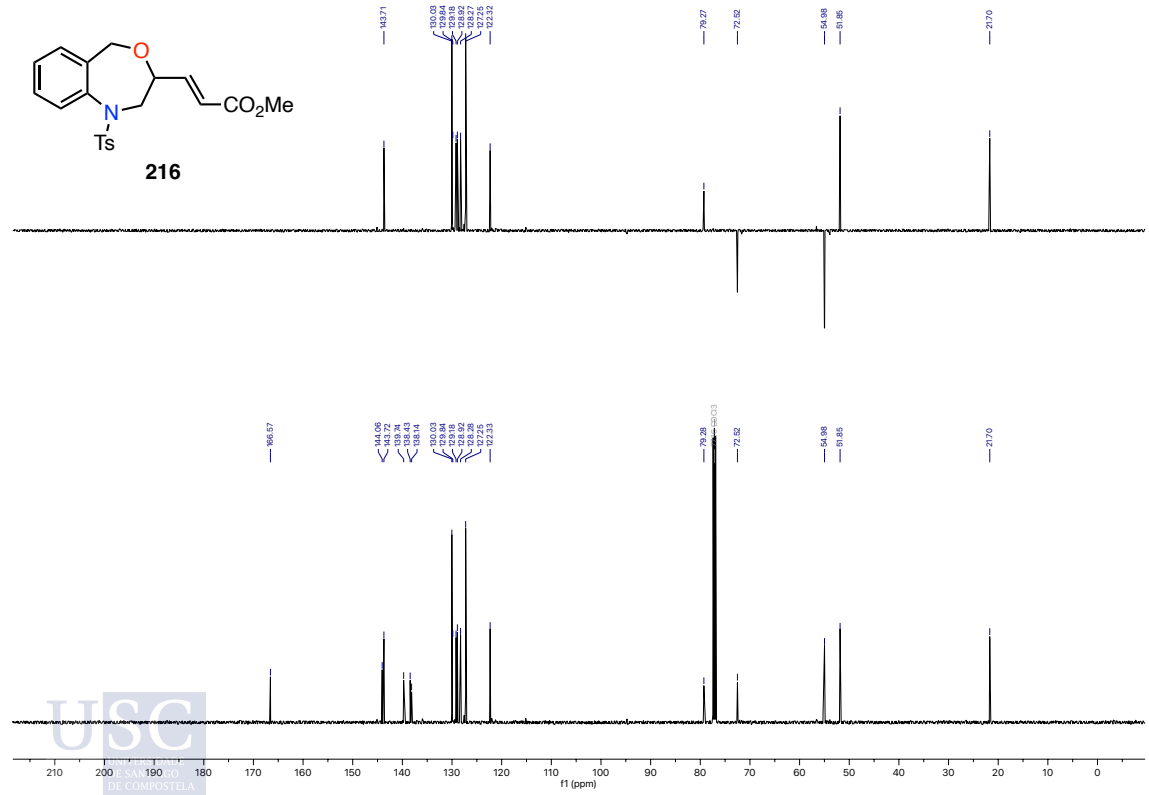



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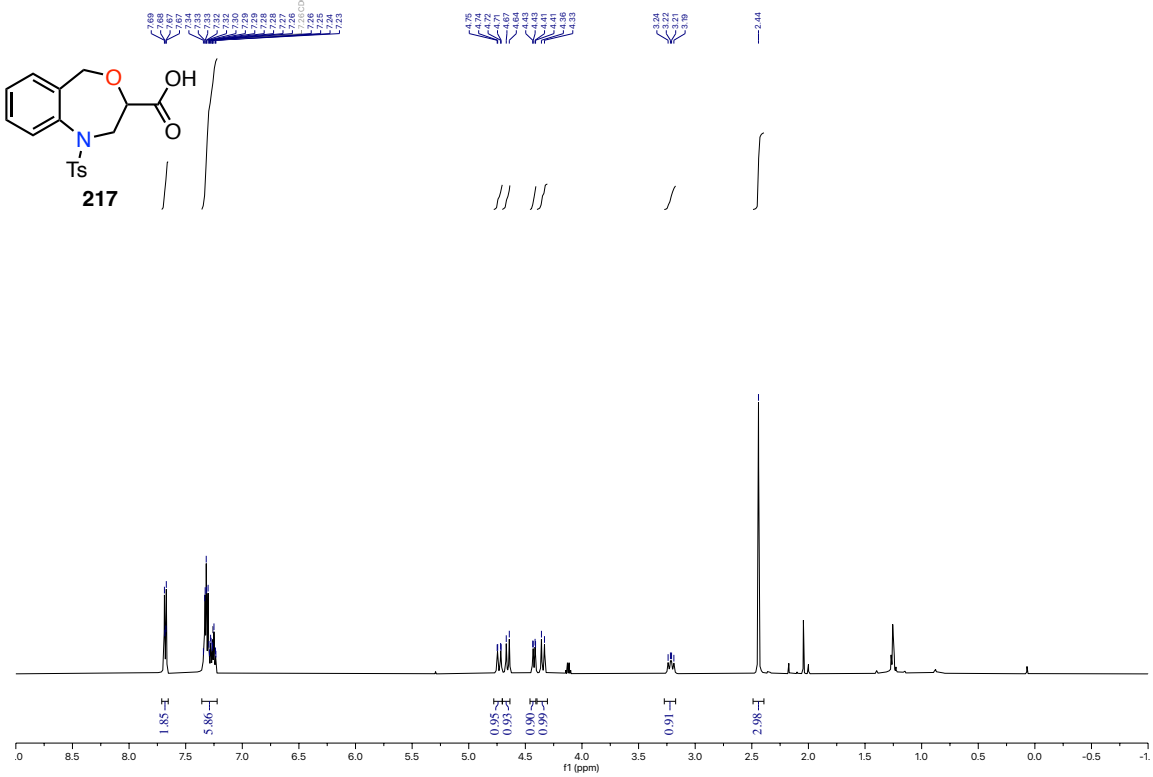
$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$



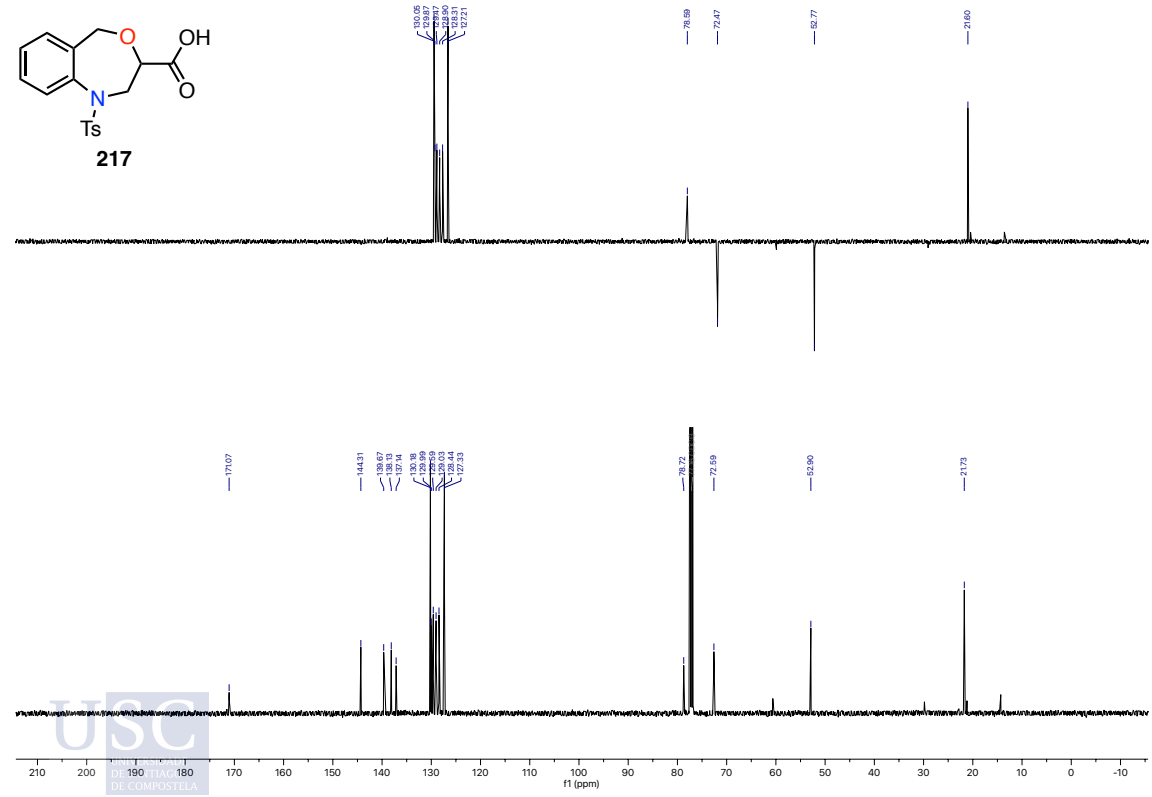

$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$



$^{1}$H-NMR (500 MHz). Solvent $CDCl_3$

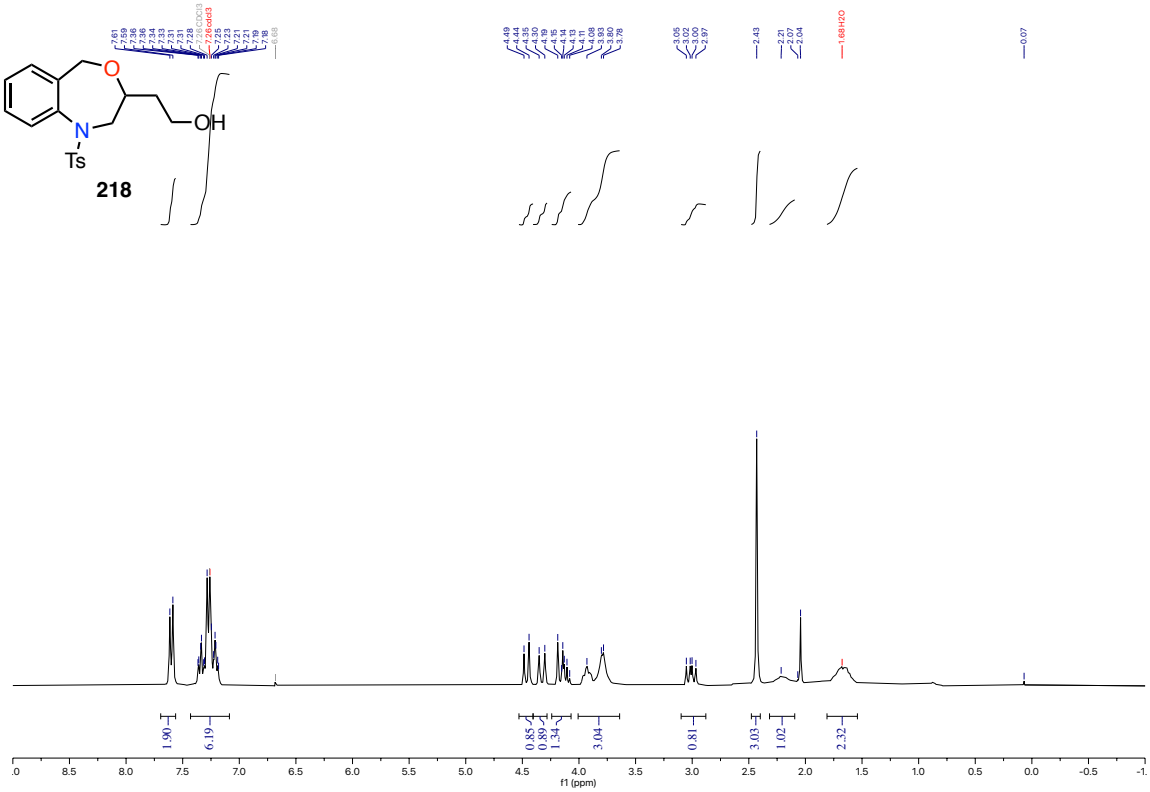



$^{13}$C-NMR (126 MHz). Solvent $CDCl_3$

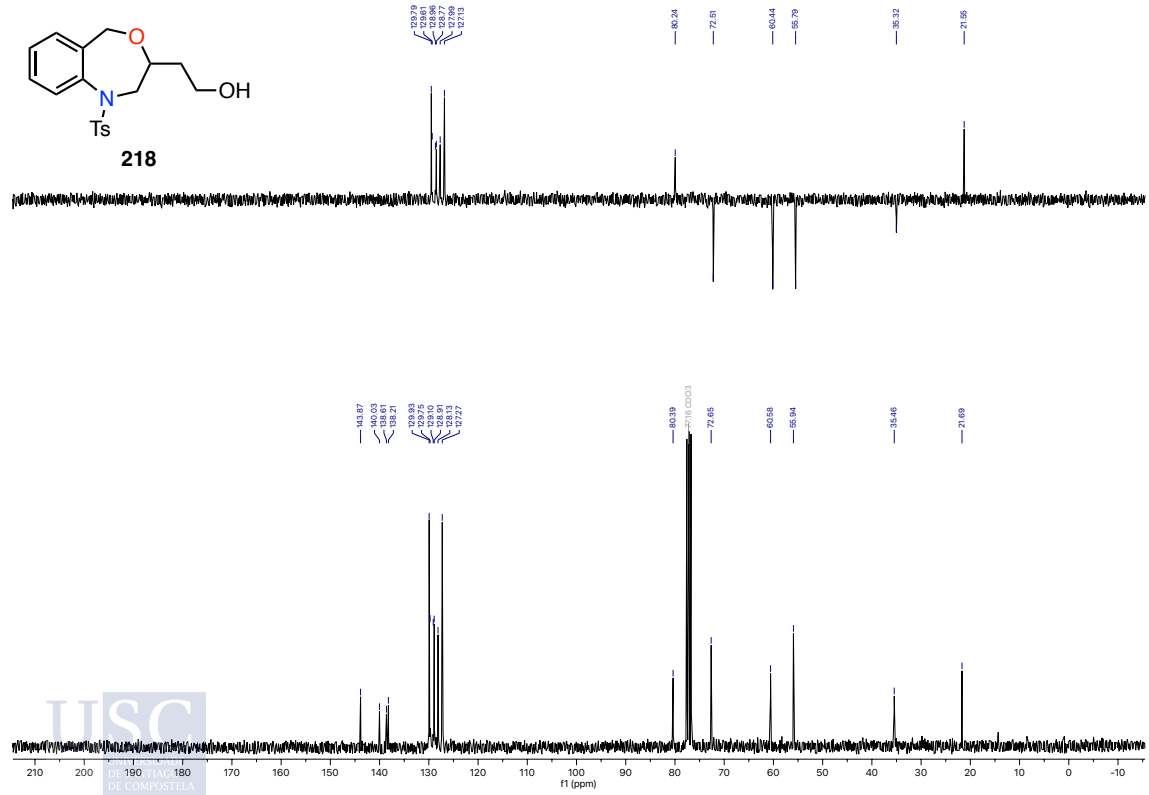



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$^{1}$H-NMR (300 MHz). Solvent $CDCl_3$




$^{13}$C-NMR (75 MHz). Solvent $CDCl_3$




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# General Conclusions

## Chapter 1

- The biological properties and the kinds of the benzofused seven-membered heterocycles are summarized in this chapter.
- Classic methodologies to synthesize benzofused seven-membered heterocycles are summarized.
- Transition-metal catalyzed reactions to synthesize benzofused seven-membered heterocycles are summarized.

## Chapter 2

- A sustainable, ecofriendly, atom- and step-economy methodology has been described to afford 3-benzazepines. The Pd-catalyzed [5+2] heteroannulation that requires a C-H activation step allowed the obtention of 2-substituted 3-benzazepines in moderate to good yields from commercially available starting materials.
- The use of $O_2$ allowed a reduction of the amount of metal oxidant needed and, therefore, the generation of waste amount.
- The diastereoselectivity of the reaction showed a high ratio when a substituent is located in the α-position (>20:1), whereas only gave a mixture 3:1 of diastereoisomers in β-position.
- Mechanistic studies suggested the key *cis*-$PdL_2X_2$ intermediates that were corroborated by the isolation and X-ray structural determination of **112a'** and **112h'**.
- DFT calculations shed light on the mechanism and the diastereoselectivity of the reaction. The 1,2-migratory insertion starts with a coordination of the less substituted olefin of the 1,3-diene. The key C-N bond formation occurs by an intramolecular $S_N2$-type reaction of the zwitterionic Pd-π-allyl intermediate **IV**.
- Unfortunately, despite the fact that a variety of chiral ligands were tested for the enantioselective Pd-catalyzed reaction, all of them failed either in the chemical yield or in the enantiomeric excess.
- An enantioselective Pd-catalyzed reaction of prochiral α-substituted phenethyltriflamides (desymmetrization reaction) using *L-p*Glu-OH (**L3**) was successfully developed. However, only moderate enantioselectivities were observed.
- In the enantioselective reaction, for the C-H activation step, a competition between two bases, the chiral ligand *L-p*Glu-OH (**L3**) and the acetate of the copper salt, was observed. As a rule of thumb, the higher enantioselectivities the lower yields were obtained.

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## Chapter 3

- An ecofriendly and asymmetric strategy to afford 1,4-BZDs **153** based on Rh-catalyzed hydroamination of alkynes **152** and allenes **158** has been successfully developed.

- *N*-Boc-protected alkyne **152a** and allene **158a** gave lower enantiomeric ratio of 1,4-BZD **153** than the corresponding *N*-Ts protected alkyne **152b** and allene **158b**. Thorpe-Ingold effect plays an important role in the cyclization.
- Alkyne **152b** was cyclized to the 1,4-BZD **153b** in a low 50% chemical yield with 80:20 enantiomeric ratio (Table 8, entry 7).
- Allene **158b** was cyclized to the 1,4-BZD **153b** with the best results, chemical yield 70% with 95:05 er (Table 10, entry 17). Substituted 1,4-BZDs **153c**-**153k** , bearing EDG and EWG groups in the aryl ring, were synthesized in good to excellent yields with excellent enantiomeric ratios.
- The nucleophile (nitrogenated *vs* oxygenated) plays an important role in the cyclization. Thus, 1,4-BZO **153l** was obtained in an excellent 90% yield but with moderate 78:22 er as compared to 1,4-BZD **153b** that was isolated in a fairly good 70% yield but with excellent 95:5 er. This might be explained because alcohols may follow an *"inner-sphere"* mechanism against the *"outer-sphere"* mechanism that might be operating with the NHPMP.
- *N*-Ts and *N*-PMP groups were orthogonally deprotected in fairly good yields under mild conditions.
- A straightforward derivatization of 1,4-BZD **153b** led to enantioenriched PBZD **162**, an advanced metabolite of the $V_2$-receptor antagonist of Lixivaptan®

## Chapter 4

- An efficient and ecofriendly, atom- and step-economy strategy to afford 1,4-benzoxazepines **187** based on Pd-catalyzed allylic C-H functionalization of alkenols **186** has been developed.
- Diastereoselectivity of the reaction ranged from low to good when the benzylic position of the alkenol **186** was substituted with Me or Ph substituents. In addition, a good diastereoselectivity was also observed when the homoallylic position of **186** was substituted with a Me group.
- Interestingly, the cyclization was not dramatically affected by the Thorpe-Ingold effect of the substrates and tolerates a range of heteronucleophiles. Non-benzofused alkenols and phenol, carboxylic acid and tosyl amide groups efficiently undergo the Pd-catalyzed allylic C-H functionalization.
- Asymmetric Pd-catalyzed allylic C-H activation was analyzed using two different families of chiral ligands, L-SOX and Matsunaga ligands. While a promising enantioselective Pd-catalyzed allylic C-H activation of 1,4-BZO **187a** was observed with L1-SOX ligand, no reaction with Matsunaga ligands was observed.
- Derivatization of the alkene unit of 1,4-BZO **187a** allows an easy entry to a variety of compounds in good to excellent yields, which highlights the methodology developed.

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