Universidad del País Vasco Euskal Herriko Unibertsitatea

NAZIOARTEKO BIKAINTASUN CAMPUSA
CAMPUS DE EXCELENCIA INTERNACIONAL

1,2,3-Triazoles as key frameworks in drug discovery & metal catalysis

Aitziber Irastorza Epelde

Doctoral Thesis

Supervised by Prof. Jesus Mª Aizpurua Iparraguirre and Dr.Arkaitz Correa Navarro

Department of Organic Chemistry I

Donostia, July 2017

Ackowledgements

Orain dela 5 urte laborategiko ateak iriki, eta doktoretza-tesi hau egiteko aukera eman zenidalako zure pazientzi eta denbora eskainiz, eskerrikasko Txusmari. Naiz eta tesia hasita egon, erronka onartzeagatik, eta zure ezagutzak nirekin erkarbanatzeagataik, eskerrikasko Arkaitz. Urte hauek pertsonalki naiz profesionalki haztea bultzatu naute eta ez dut inoiz ahaztuko emen pasatako denbora. Eskerrikasko Eusko Jaurlaritzari ere, diru laguntzagatik (PRE_2013_1_447).

Me gustaría agradecer a mis compañeros de laboratorio con los cuales he crecido, he llorado, me he reído y he disfrutado casi de cada momento. Nunca olvidaré aquellos primeros meses cuando me encontraba tan perdida y tuvisteis tanta paciencia de enseñarme una y otra vez como se hacían o dejaban de hacer las cosas. O cuando me engañasteis para ser torpe del mes, y pagaros una croqueta (y ponerme la banda hasta que Txusmari os llamó la atención, jajaja). Eskerrikasko Maialen, Elena, Nerea y Zaira. En especial agradecer a Nerea, por aguantarme a mí y a mis altibajos (ya sé que soy una montaña rusa) así como a Zaira por su apoyo y sus locuras (que ya sabemos que no eres tan recatada como pareces!!).

Por haber aceptado formar parte de esta tesis y enseñarme tanto a trabajar como a pensar, eskerrikasko Arkaitz. Ya sé que no ha sido fácil para ti (ni para mí) el rol de esta tesis. El hecho de tener que lidiar conmigo y con mi cabezonería tiene su mérito, y aunque han caído algunas bronkas, lo que nunca olvidaré serán todos los momentos que hemos pasado, riendonos con nuestras anécdotas o las ajenas (velociraptor), las noches interminables en el burunda, o las clases de spinning.

Aunque no he pasado tanto tiempo con vosotros por circunstancias de la vida, ya sea porque estabais en el "otro lado" o porque yo estaba en un bunquer de aislamiento, eskerrikasko Xabi, Itziar, Markos eta Maite. Me lo he pasado muy bien con vosotros, y espero que volvamos a coincidir en algún momento de la vida.

Nola ez, eskerrikasko bizilagunei, Cossio's group!! Por ser la alegría del pasillo, y una desconexión necesaria. Bereziki eskerrikasko Maddalen ta Mikel, zeaten bezelakok izateagatik, dos trozos de pan. Nere, zurire eskerrikasko autobuseko txarla guztingatik, eta emandako kontsejungatik. A la gente que nos aguanta todos los días, eskerrikasko J.I., Santos y Celsi.

For giving me the oportunity to visit that awesome country named Australia as well as his fantastic research group, thanks Michael! A special hug for Geraud for his big heart and all the help provided.

Ezin eskertu gabe utzi ardi galdu bat bezela iritxi ta besoak irekita lagun taldean onartu ninduzuten lagunei. Naiz eta azkenaldian juntatzea erreza ez izan, elkartzean gauzak berdin jarraitu dezaketela erakusteagatik, eskerrikasko Eneko, Nerea, Itziar, June eta Irati. Aintzane, denborak elkartzea egin gintuelako, eskerrikasko zure indarragatik.

Munduan zehar bananduta egon arren, koadrilako lagunei, nire txapa guztiak entzuteagatik ezertaz enteratu gabe, eskerrikasko. Batez ere azken aldian inguruan ibili direnei, Perez, Mozo, Ainhoa ta Mary. Baita tesiari kolorea ematen lagundu didanari ere, eskerrikasko Xabi.

Bigarren koadrilari, azkeneko urte hauetan asko lagundu didazuelako, eskerrikasko zuen artea horren ondo sentiarazteagatik. Asko pozten naiz zuek ezagutu izanaz. Batez ere Irati, Joseba eta Amaia, beti animoak emateko prest zaudetelako, eta behin ta berriz nei entzun ta aurpegi txarra inoiz jartzen ez diazuelako, eskerrikasko.

Ostegunei argitasun berezi bat eman eta transmititzen diazun energia positibo guztiangatik, eskerrikasko Alaitz. Oaindik pintxo-pote asko dauzkeu aurretik!!!

Familiakoei, zuek jakin ez arren zerikusi handia daukezuelako lan honetan ere, lengusu, izeba-osaba, eta amama, muxu handi bat!! Naiz eta gure artean ez egon, beti alboan sentitu zaitudalako, eskerrikasko aittitte.

Lehen egunetik familiakoa izango banintz bezela tratatu nauzuelako, zuen alaitasuna eta maitasuna emanez, millesker Arantxa, Alberto, Kepa, Eli, Txirri ta Idoia. Haritz, muxu handi bat zutzakore bihurri!! Baita zurire Txope, irrifarrea ateratzeagatik. Muxu handi bana!!!

Etxekoiei. Aita, ama eta Igor, zuengatik naiz gaur naizena, eskerrikasko emandako guztiagatik, momentu on naiz zailenetan ondoan egoteagatik, nigandik eta netzako egindako sakrifizio guztiagatik, eta nola ez eman diazuen maitasunagatik. Netaz arro eotea espero det. Pilloa maite dizuet.

Eskerrikasko Eloi, nere indarra ta ausardia izateagatik. Negan nik neuk baino gehiago sinisteagatik eta momentuoro nire alboan izateagatik. Eskerrikasko urte hauetan nerekin eduki dezun pazientziagatik eta emandako maitasunagatik. Izugarri maitte dizut txiki. Tesi hau nerea bezain zurea da.

Bihotz-bihotzez

Nire familia eta Eloiri

List of Publications

1. *Triazole-Directed Pd-Catalyzed C(sp^2)–H Oxygenation of Arenes and Alkenes.* Irastorza, A.; Aizpurua, J. M.; Correa, A. *Org. Lett.* **2016**, *18*, 1080.

2. *Site-Selective N‑Dealkylation of 1,2,3-Triazolium Salts: A Metal-Free Route to 1,5-Substituted 1,2,3-Triazoles and Related Bistriazoles.* Monasterio, Z.; Irastorza, A.; Miranda, J. I.; Aizpurua, J. M. *Org. Lett.* **2016**, *18*, 2511.

3. *Triazoles for muscle contraction regulation.* Vallejo, A.; López de Munain, A. J.; Toral, I.; Aldanondo, G.; Aizpurua, J. M.; Irastorza, A.; Ferrón, P.; Miranda, J. I. Solicitud Pat ES : P201630670, **2016.**

4. *Triazolium cations: from "click" pool to multipurpose applications.* Aizpurua, J. M.; Fratila, R. M.; Monasterio, Z.; Pérez-Esnaola, N.; Andreieff, E.; Irastorza, A.; Sagartzazu-Aizpurua, M. *New J. Chem.* **2014**, *38*, 474.

Scientific presentations:

1. XIII Simposio de Investigadores Jóvenes RSEQ-Sigma Aldrich. *"Triazoles for muscle contraction regulation via Ryanodine (RYR1) receptors."* Irastorza, A.; Miranda, J. I.; Aizpurua, J. M.; Aldanondo, G.; Vallejo, A.; López de Munain, A. Logroño, November **2016** (**Poster**).

2. 11th Spanish-Italian Symposium on Organic Chemistry SISOC XI. *"Site-selective N-dealkylation of 1,2,3-triazolium salts: a metal free route to 1,5-substituted 1,2,3-triazoles and related bistriazoles."* Irastorza, A.; Monasterio, Z.; Aizpurua, J. M. Donostia, July **2016** (**Flash communication**).

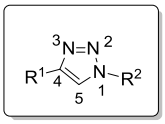
3. XII Simposium of Young Researchers RSQE-Sigma Aldrich. *"Palladium-catalyzed C(sp^2)–H acetoxylation directed by 1,2,3-triazoles."* Irastorza, A.; Aizpurua, J. M.; Correa. A. Barcelona, November **2015** (**Oral Communication**).

4. XI Simposium of Young Researchers RSQE-Sigma Aldrich. *"One-Pot Synthesis of Halo-Imidazolium and Halo-Triazolium Salts by Neutral and Selective Reagents."* Irastorza, A.; Monasterio, Z.; Perez-Esnaola, N.; Fernandez, F. J.; Sagartzazu-Aizpurua, M.; Aizpurua. J. M. Bilbao, November **2014** (**Poster**).

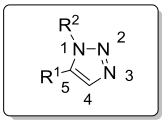
5. 4th Brazil-Spain Workshop on Organic Chemistry 4-BSWOC. *"Halocyanogens as Neutral and Selective Reagents for the C-Halogenation of Alkynes, Imidazolium Salts and Triazolium Salts"*. Fernandez, F. J.; Irastorza, A.; Monasterio,Z.; Perez-Esnaola, N.; Sagartzazu-Aizpurua, M.; Aizpurua, J. M. Donostia-San Sebastian, July **2014** (**Poster**).

Resumen

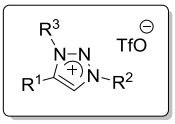
Los 1*H*-1,2,3-triazoles son compuestos heterocíclicos que durante los últimos 15 años han atraído un enorme interés debido a sus crecientes aplicaciones en campos tales como la química farmacéutica o la ciencia de materiales, así como por su fácil preparación a través de cicloadiciones "click" azida-alquino catalizadas por Cu(I) o Ru(II) y mediante organocatálisis a partir de compuestos carbonílicos y azidas. Además, su *N*3-alquilación regioselectiva proporciona sales de 1,2,3-triazolio cuya química, menos estudiada, posee aplicaciones más específicas.



1,2,3-Triazol
(1,4-disustituido)



1,2,3-Triazol
(1,5-disustituido)



Sal de 1,2,3-triazolio
(1,3,4-trisustituido)

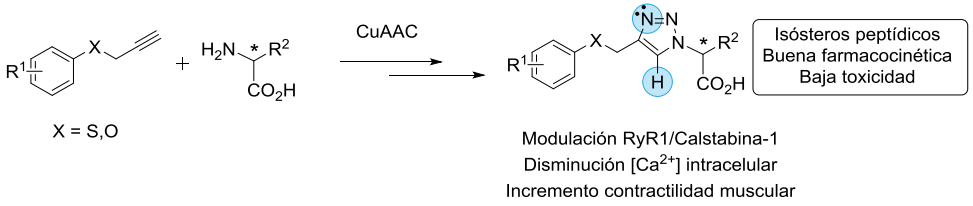
El propósito general de esta Tesis Doctoral es identificar ámbitos poco explorados de la química de los 1,2,3-triazoles y demostrar que sus propiedades estructurales y electrónicas así como las de sus sales de *N*-alquil triazolio pueden aprovecharse para llevar a cabo transformaciones, tanto estequiométricas como catalíticas, que permitan acceder a nuevos compuestos heterocíclicos. Para ello, se han planteado los siguientes objetivos:

1. Diseñar y sintetizar 1*H*-1,2,3-triazoles como plantillas moleculares de fármacos reguladores de [Ca^{2+}] intraplasmático en músculo esquelético.
2. Crear una metodología para la transformación de triazoles 1,4-disustituidos en 1,5-disustituidos *via N*-desalquilación regiocontrolada de sales de triazolio.
3. Estudiar la utilidad de los 1,2,3-triazoles como agentes directores en reacciones de funcionalización C−H catalizadas por metales de transición.

Seguidamente se resumen los principales resultados alcanzados durante la realización del trabajo experimental.

1. <u>1*H*-1,2,3-triazoles como plantillas moleculares de fármacos reguladores de [Ca^{2+}] intraplasmático en músculo esquelético.</u>

Para alcanzar el primer objetivo, se llevó a cabo un estudio de docking computacional con estructuras triazólicas sobre una zona de contacto entre el canal de calcio receptor de rianodina RyR1 y la Calstabina-1, su proteína reguladora. Ello permitió identificar varios 1*H*-1,2,3-triazoles 1,4-disustituidos con grupos 1-carboxialquilo y 4-ariltiometilo, adecuados para el diseño de moduladores de la interacción alostérica RyR1/Calstabina-1 que regula la concentración de ión calcio en músculo esquelético.



La síntesis de los triazoles carboxílicos enantiopuros se llevó a cabo con rendimientos globales del 45-85% a partir de α-aminoácidos en una transformación "one-pot" que incluyó la combinación de una reacción de *N*-diazotación y otra de cicloadición CuAAC de los α-azidoácidos intermedios con alquinos de tipo 3-ariloxipropargilo o 3-ariltioprogargilo. Alternativamente, se emplearon α-azidoésteres metílicos quirales (p.ej. HPheOMe, HValOMe) como compuestos de partida, pero los ésteres triazólicos resultantes sufrieron una racemización parcial cuando se saponificaron para dar los α-aminoácidos finales.

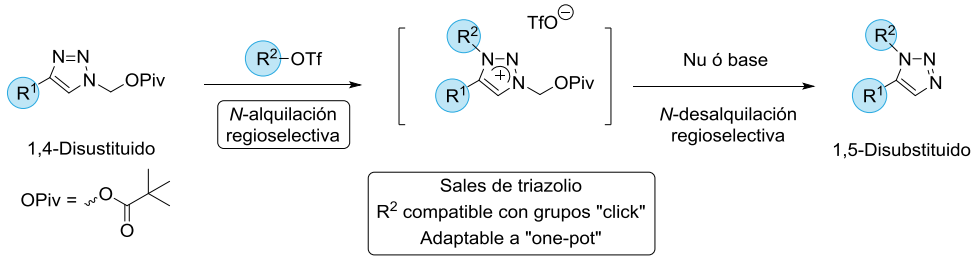
La evaluación biológica de los 11 triazoles carboxílicos sintetizados indicó que ninguno de ellos presenta citotoxicidad *in vitro* frente a cultivos de mioblastos murinos (C2C12) ni humanos (LHCN-M2) hasta el rango milimolar. También se demostró que el compuesto 1-carboximetil-4-[3-(metoxi)-feniltiometil]-1,2,3-triazol (**15**) es capaz de disminuir en un 75% la concentración de Ca^{2+} intraplasmático en miocitos distróficos, disminuye un 30% el número de núcleos centrales en miotubos tras la administración oral durante 5 semanas a dosis 0.8 mM e incrementar en un 40% la fuerza de agarre muscular *in vivo* en ratones *mdx*, modelos de la distrofia muscular de Duchenne.

De cara a favorecer la capacidad de los nuevos triazoles carboxílicos moduladores de RyR1 para atravesar la barrera hematoencefálica (BBB), se ha estudiado mediante

técnicas de RMN su complejación con β-ciclodextrina (β-CD) en agua a 25ºC. La correlación entre la variación de desplazamientos químicos (Δδi) y la fracción molar de cada componente en series de experimentos ^{1}H-RMN permitió confirmar la formación de un complejo de inclusión β-CD/Trz **15** de estequiometría 1:1 y una constante de asociación Ka=428 M^{-1}. Además, la topología de la interacción indicó que el compuesto **15** interacciona con la cavidad hidrofóbica de la β-CD a través de su fragmento aromático y no por el anillo triazólico.

2. Transformación de triazoles 1,4-disustituidos en 1,5-disustituidos *via* *N*-desalquilación regiocontrolada de sales de triazolio.

En la segunda parte de la Tesis se ha desarrollado una metodología para preparar nuevos 1,2,3-triazoles 1,5-disustituidos que incorporan grupos funcionales tales como azidas o alquinos terminales, a partir de 1-pivaloiloximetil-1,2,3-triazoles y alcoholes funcionalizados siguiendo una estrategia "one-pot" basada en una secuencia de *N*-alquilación / *N*-desalquilación regiocontrolada.



La secuencia comenzó con la formación de triflatos de alquilo a partir de alcoholes y anhídrido trifluorometanosulfónico en condiciones heterogéneas empleando $KHCO_3$ como base. La *N*3-alquilación de 1-pivaloiloximetil-1,2,3-triazoles con dichos triflatos de alquilo en ausencia de disolvente proporcionó las correspondientes sales de 1,2,3-triazolio *N*1, *N*3, C4-trisustituidas con rendimientos prácticamente cuantitativos. Por su parte, la reacción de *N*-desalquilación del grupo pivaloiloximetilo transcurrió *in situ* en condiciones básicas suaves (K_2CO_3, MeOH) proporcionando una variedad de 1,2,3-triazoles 1,5-disustituidos y 1,4,5-trisustituidos funcionalizados con grupos de reactividad latente (azida, alquino terminal) en ausencia de metales y con rendimientos globales del 55-74%.

Un estudio computacional *Ab initio* (B3LYP/6-31G*) permitió cuantificar una carga formal NBO de +0.08 para el carbono metilénico en el grupo pivaloiloximetilo enlazado a un

catión triazolio, mientras que un grupo metilo equivalente mostró una carga de -0.48. Este incremento de electrofilia se confirmó en los perfiles de energía libre de la reacción SN_2 entre el 3,4-dimetil-1-pivaloiloximetil 1,2,3-triazol y el anión hidróxido a través de un estado de transición de $\Delta G^{\ddagger}$ = 4.6 kcal/mol en el que el anillo de triazolio 1,5-disustituido actúa como grupo saliente.

La reactividad latente de varios 1,5-triazoles con sustituyentes conteniendo un grupo azido terminal se aprovechó para realizar cicloadiciones CuAAC con alquinos a través del mismo. De este modo se obtuvieron sistemas triazólicos dobles 1,4- y 1,5-sustituidos de forma no simétrica y enlazados entre sí por cadenas alifáticas.

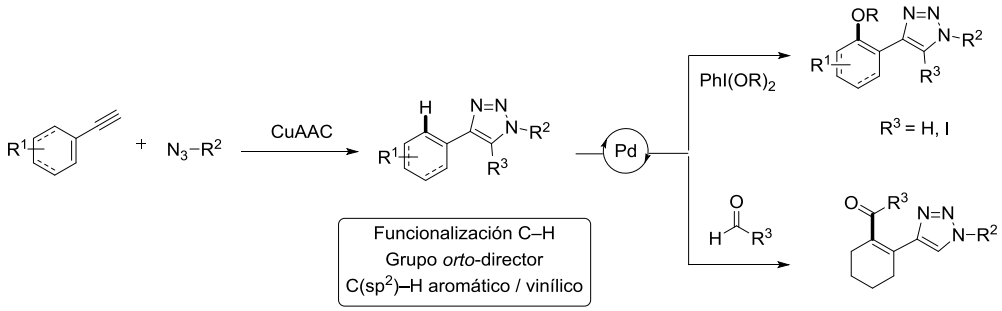
Por último, la metodología de *N*-alquilación / *N*-desalquilación también se aplicó a la obtención de bis(1,2,3-triazoles) enlazados directamente por las posiciones C5-C4' y C5-C5' mediante la reacción del 1,3-butadiíno con pivalato de azidometilo, seguida de una reacción CuAAC con azidas. Los bistriazoles así obtenidos constituyen sendas familias de anillos heterocíclicos inéditos hasta la fecha.

3. <u>Empleo de 1,2,3-triazoles como grupos directores en funcionalizaciones de enlaces C−H catalizadas por metales de transición</u>

En la tercera parte de la Tesis Doctoral se demostró que los 1,2,3-triazoles provenientes de reacciones "click" pueden actúar como eficientes grupos directores en reacciones de funcionalización de enlaces $C(sp^2)$−H catalizadas por metales de transición.

En primer lugar se llevó a cabo la reacción de acetoxilación y pivaloilación catalizada por sales de paladio de anillos aromáticos situados en la posición C4 de diversos 1,2,3-triazoles. De este modo, se obtuvieron los correspondientes derivados de *orto*-aciloxiarilo como mezclas de productos mono- y difuncionalizados con rendimientos que oscilaron entre 50-90 %. Es importante remarcar que la monofuncionalización selectiva se pudo obtener utilizando 5-yodo 1,2,3-triazoles como grupo director así como empleando sustratos con patrón de sustitución *orto*- y *meta*- que impiden la doble funcionalización.

Los productos resultantes de las funcionalizaciones comentadas, pudieron transformarse en otros compuestos de mayor complejidad estructural empleando reacciones de acoplamiento cruzado (Sonogashira y Heck).



Seguidamente, el alcance de la reacción de funcionalización se extendió con éxito a enlaces C(sp^2)−H vinilicos. Concretamente, se logró introducir tanto el grupo acetoxilo como el pivaloílo en anillos 1-ciclohexenilo con rendimientos del 72-77% asistidos por grupos 1,2,3-triazol.

Desafortunadamente, cuando en las reacciones anteriores se intentó sustituir el catalizador de paladio por otros más asequibles como el cobre reemplazando simultáneamente el grupo director por otro triazol bidentado (TAM), no se pudo conseguir la transformación deseada.

Por último, también se ensayó la acilación catalizada por sales de paladio de enlaces C(sp^2)−H vinílicos con aldehídos. Tras la optimización de diferentes variables de la reacción, sólo pudieron obtenerse rendimientos moderados (30-57%).

List of abbreviations, Acronyms and Symbols

Asp	Aspartic acid
Arg	Arginine
ATP	Adenosine triphosphate
Aq.	Aqueous
BBB	Blood Brain Barrier
Boc	*tert*-Butoxycarbonyl
BPO	Benzoyl peroxide
Cav1.1	Calcium channel, voltage-dependent
CCDC	The Cambridge Crystallographic Data Centre
CD	Cyclodextrin
CHP	Cumene hydroperoxide
CNS	Central Nerve System
COD	1,5-Cyclooctadiene
Cp*	Pentamethylcyclopentadiene
CuAAC	Copper-catalyzed azide alkyne cycloaddition
d	Doublet (NMR)
dd	Doublet of doublets (NMR)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCP	Dicumyl peroxide
DFT	Density Functional Theory
DG	Directing Group
DIPEA	*N*,*N*-Diisopropylethylamine
DMD	Duchenne Muscular Dystrophy
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DNA	Deoxyribonucleic acid
DTBP	Di-*tert*-butyl peroxide
δ	Chemical shift (NMR)
$\Delta E^{\ddagger}$	Activation Energy
E-C	Excitation-contraction
EDG	Electron-donating group
ESI	Electrospray ionization (Mass spectrometry)

Equiv.	Equivalent(s)
EWG	Electron-withdrawing group
FDA	Food and Drug Administration
FG	Functionalized group
FKBP12	FK506 binding protein 12
FMO	Frontier Molecular Orbital
Glu	Glutamic acid
$\Delta G^{\ddagger}$	Activation Gibbs energy
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz
IR	Infrared
J	Coupling constant (NMR)
Ka	Affinity constant or stability constant
Leu	Leucine
LUMO	Lowest Unoccupied Molecular Orbital
Lys	Lysine
M	Metal
m	Multiplet (NMR)
mdx	Duchenne muscular dystrophy mouse model
MCPBA	3-Chloroperbenzoic acid
MD	Muscular Dystrophy
mp	Melting point
MS	Mass Spectrometry
NBO	Natural Bonding Orbital
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
n.d.	Not determined
NHC	*N*-Heterocyclic carbene
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
Phe	Phenylalanine
PIDA	(Diacetoxyiodo)benzene
PTSA	*p*-Toluenesulfonic acid

q	Quartet (NMR)
RyR1	Ryanodine receptor channel
r.t.	Room temperature
ROESY	Rotating-frame nuclear Overhauser effect correlation spectroscopy
RuAAC	Ruthenium-catalyzed azide alkyne cycloaddition
SPAAC	Strain-promoted azide alkyne cycloaddition
SERCA	Sarco/endoplasmic reticulum Ca^{2+}-ATPase
SR	Sarcoplasmic reticulum
t	Triplet (NMR)
T	Temperature
TBTA	Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine
TBHP	*tert*-Butyl hydroperoxide
TBPB	*tert*-Butyl peroxybenzoate
TEA	Triethylamine
TFA	Trifluoroacetic acid
TfN_3	Trifluoromethanesulfonyl azide
TIP	2,4,6-Triiodophenoxy
TON	Turnover number
Trp	Tryptophan
Trz	Triazole
Tyr	Tyrosine
Val	Valine

Index

1

General introduction and objectives

1. General introduction and objectives

1.1 1,2,3-Triazoles

Despite the 1,2,3-triazole ring does not occur in Nature, organic compounds that contain this heterocyclic motif have shown an inordinate interest in the last decades. As a result, the 1,2,3-triazole core stands out as a privileged structure of wide presence in a vast array of relevant compounds in different research areas such as medicinal chemistry,[1] material science,[2] optoelectronics,[3] crop protection[4] and pharmacology.[5] Their unique molecular architecture plays an important role in the development of new disease treatments and is thus attractive for designing numerous specific molecules with important biological activities such as anticancer,[6] antimalarial[7] and antimicrobial[8] (Figure 1.1).

---

1 a) Ustyugov, A. A.; Aliev, G. M. *Russ. Chem. Bull.* **2016**, *65*, 1151. b) Alfonso, M.; Tárraga, A.; Molina, P. *Tetrahedron Lett.* **2016**, *57*, 3053. c) El-Sagheer, A. H.; Brown, T. *Chem. Soc. Rev.* **2010**, *39*, 1388.

2 a) Xiaosong, C.; Yi, S.; Haifeng, G. *Synlett* **2017**, *28*, 391. b) Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. *Chem. Rev.* **2016**, *116*, 5689. c) Flood, A. H. *Beilstein J. Org. Chem.* **2016**, *12*, 611. d) Qin, A.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2010**, *39*, 2522.

3 a) Marrocchi, A.; Facchetti, A.; Lanari, D.; Santoro, S.; Vaccaro, L. *Chem. Sci.* **2016**, *7*, 6298. b) Dou, L.; Liu, Y.; Hong, Z.; Li, G.; Yang, Y. *Chem. Rev.* **2015**, *115*, 12633.

4 Gonçalves, S. S.; Souza, A. C. R.; Chowdhary, A.; Meis, J. F.; Colombo, A. L. *Mycoses* **2016**, *59*, 198.

5 a) Akhtar, J.; Khan, A. A.; Ali, Z.; Haider, R.; Yar, M. S. *Eur. J. Med. Chem.* **2017**, *125*, 143. b) Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. *Chem. Rev.* **2016**, *116*, 3086.

6 Yadav, P.; Lal, K.; Kumar, A.; Guru, S. K.; Jaglan, S.; Bhushan, S. *Eur. J. Med. Chem.* **2017**, *126*, 944.

7 a) Singh, A.; Gut, J.; Rosenthal, P. J.; Kumar, V. *Eur. J. Med. Chem.* **2017**, *125*, 269. b) Santos, J.; Pereira, G. R.; Brandão, G. C.; Borgati, T. F.; Arantes, L. M.; de Paula, R. C.; Soares, L. F.; do Nascimento, M. F. A.; Ferreira, M. R. C.; Taranto, A. G.; Varotti, F. P.; de Oliveira, A. B. *J. Braz. Chem. Soc.* **2016**, *27*, 551.

8 Abdel-Wahab, B. F.; Khidre, R. E.; Awad, G. E. A. *J. Heterocyclic. Chem.* **2017**, *54*, 489.

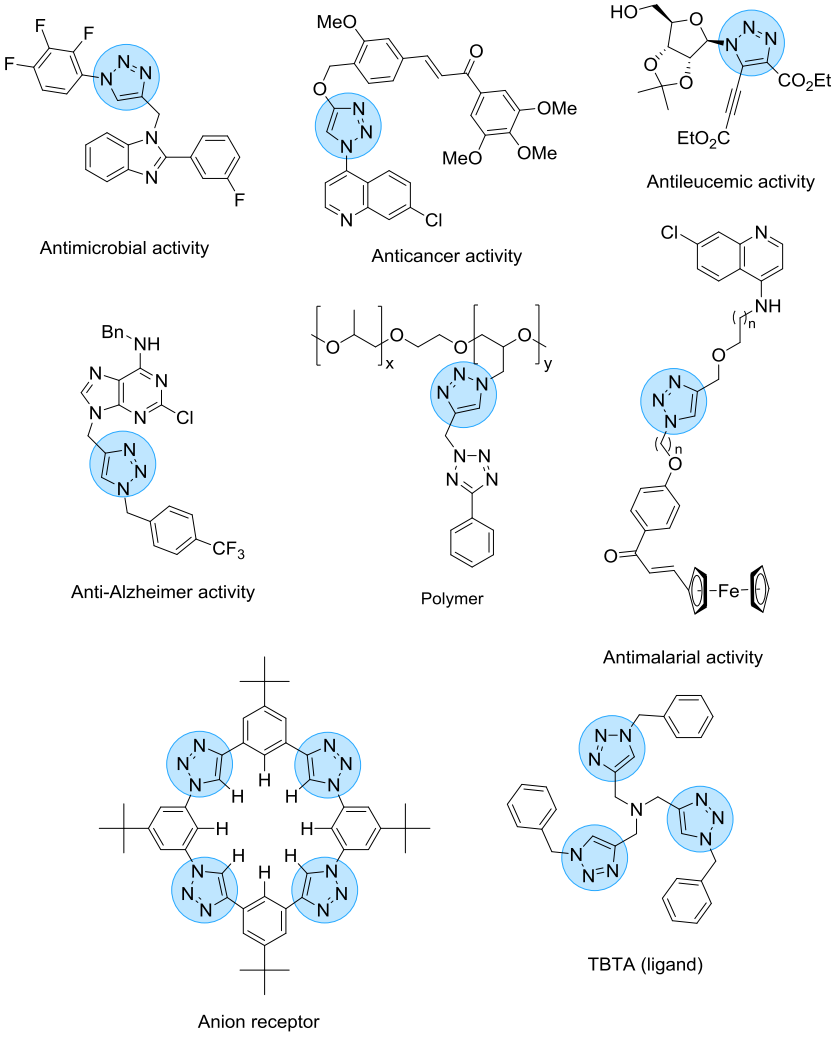


Figure 1.1. Illustrative examples of 1,2,3-triazoles with therapeutic and scientific applications.

Importantly, the 1,2,3-triazole scaffold is chemically inert against oxidation, reduction and hydrolysis both in acidic and basic environment, which makes it an excellent mimetic for hydrogen, amide or disulfide bonds thus stabilizing the resulting drugs[9] or

[9] a) Dheer, D.; Singh, V.; Shankar, R. *Bioorg. Chem.* **2017**, *71*, 30. b) Sum, T. H.; Sum, T. J.; Galloway, W. R. J. D.; Collins, S.; Twigg, D. G.; Hollfelder, F.; Spring, D. R. *Molecules* **2016**, *21*, 1230. c) Whiting, M.; Muldoon, J.; Lin, Y.-C.; Silverman, S. M.; Lindstrom, W.; Olson, A. J.; Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 1435.

pharmacophores.[10] Furthermore, they are highly promising moieties for supramolecular interactions[11] upon coordination to the metal centers either by the nitrogen atoms or by carbanionic and mesoionic carbenes, with useful applications in metal catalysis.[12]

In a short period of time the use of triazoles has had a dramatic and diverse impact in chemistry and molecular biology. However, although this area of expertise is gaining attention exponentially, the powerful and unique properties of 1,2,3-triazoles have not yet been fully exploited.

1.2 Synthesis of 1,2,3-triazoles

The very first triazole was synthesized in 1893 by Michael;[13] however, such a finding did not attract interest until some years later, when Huisgen[14] described the cycloaddition reaction between organic azides[15] and internal alkynes named as [3+2] 1,3-dipolar cycloaddition. Despite the versatility of this technique, its practicality is rather limited due to the formation of mixtures of 1,4- and 1,5-regioisomers and the low efficiency even at high temperatures. In this respect, a variety of synthetic methods for the assembly of 1,2,3-triazoles has been widely investigated during the last decade. In 2002, Meldal[16] and Sharpless[17] independently implemented the use of *in situ* generated Cu(I) species as efficient catalysts to perform the cycloaddition of alkynes and azides in a regioselective fashion toward the formation of 1,4-disubstituted 1,2,3-triazoles. This Cu-catalyzed Huisgen 1,3-dipolar cycloaddition represents one of the early examples of a "click" process and owing to

---

10 a) Kaushik, R.; Kushwaha, K.; Chand, M.; Vashist, M.; Jain, S. C. *J. Heterocyclic Chem.* **2017**, *54*, 1042. b) Kaushik, R.; Kushwaha, K.; Chand, M.; Vashist, M.; Jain, S. C. *J. Heterocyclic Chem.* **2017**, *54*, 1042. c) Surineni, G.; Yogeeswari, P.; Sriram, D.; Kantevari, S. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3684.

11 a) Lim, J. Y. C.; Marques, I.; Thompson, A. L.; Christensen, K. E.; Félix, V.; Beer, P. D. *J. Am. Chem. Soc.* **2017**, *139*, 3122. b) Lehn, J. M. *Science* **1993**, *260*, 1762.

12 a) Gazvoda, M.; Virant, M.; Pevec, A.; Urankar, D.; Bolje, A.; Kočevar, M.; Košmrlj, J. *Chem. Commun.* **2016**, *52*, 1571. b) Hollering, M.; Albrecht, M.; Kühn, F. E. *Organometallics* **2016**, *35*, 2980. c) Qureshi, Z.; Kim, J. Y.; Bruun, T.; Lam, H.; Lautens, M. *ACS Catal.* **2016**, *6*, 4946. d) Huang, D.; Zhao, P.; Astruc, D. *Coord. Chem. Rev.* **2014**, *272*, 145.

13 Michael, A. *J. Prakt. Chem.* **1893**, *48*, 94.

14 Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565.

15 Huanga, D.; Yan, G. *Adv. Synth. Catal.* **2017**, *359*, 1600.

16 Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

17 Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2002**, *41*, 2596.

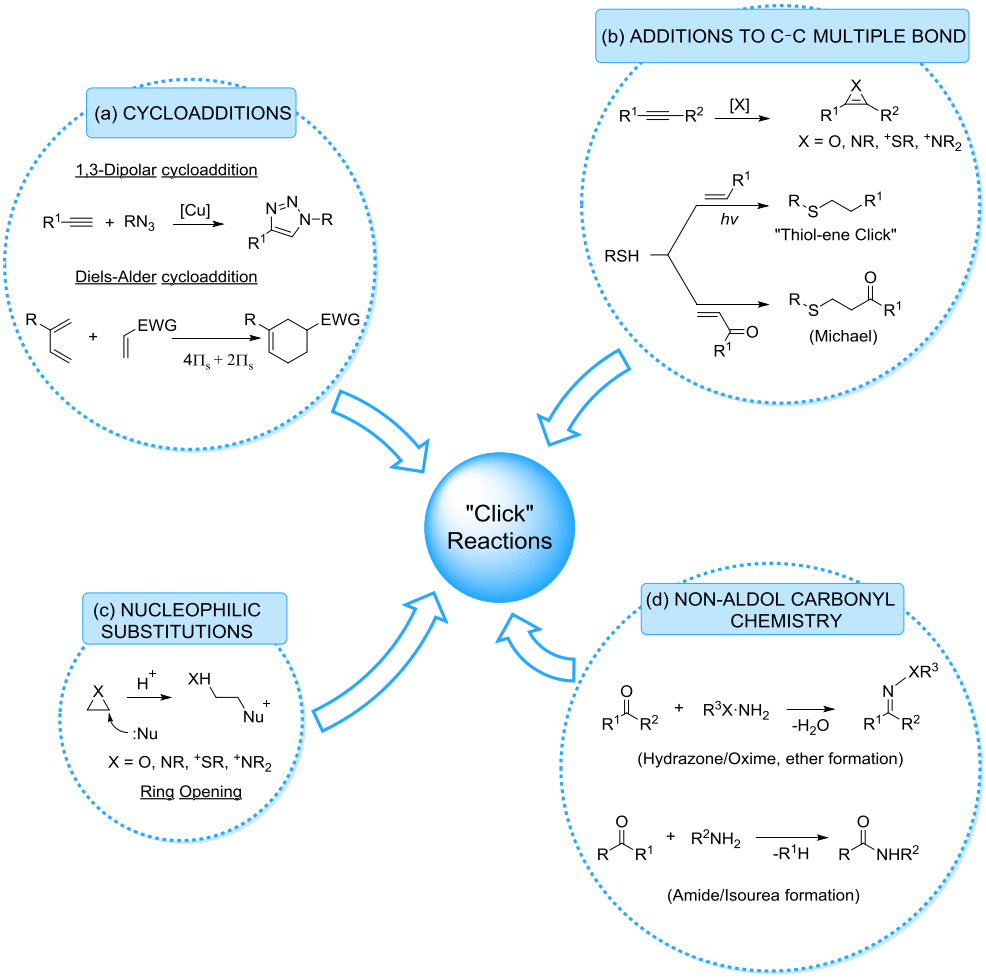
its impressive popularity is often erroneously considered as the "click" chemistry concept itself.

The "click chemistry" concept was introduced by the group of Sharpless and is based on the rapid assembly of relevant compounds under specific reaction conditions.[18] They defined a "click" transformation as a reaction easy to perform, modular, wide in scope and high-yielding. The required features for those events involve:

- ✓ Simple reaction conditions.
- ✓ Readily available starting materials and reagents.
- ✓ Easily removable solvents with particular emphasis on aqueous solvents.
- ✓ Usually exotermic reactions.
- ✓ Most of them include the formation of carbon-heteroatom bonds.
- ✓ In general, they are highly tolerant to the presence of oxygen and water, which represents a practical bonus in terms of operational simplicity.

In this regard, numerous methodologies fulfill the latter criteria and can be referred to as a "click" process. They can be classified into four categories including (a) *cycloadditions*, such as Huisgen's cycloadditions or Diels-Alder reactions, (b) *additions to multiple carbon-carbon bonds*, including epoxidations, aziridinations or Michael additions, (c) *nucleophilic substitutions* like nucleophilic ring opening reactions of strained heterocycles and (d) *carbonyl chemistry* of non-aldol type transformations (Scheme 1.1).

[18] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

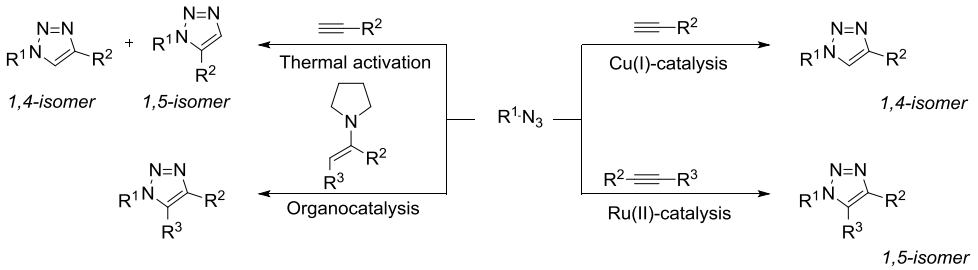


Scheme 1.1. General classification of "click" reactions.

The copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction meets the requirements of the Sharpless "click" chemistry concept, as the reaction is easy to perform, wide in scope, regiospecific, high yielding, involves readily available alkynes/azides as starting materials and copper salts as cost-efficient catalysts, and it is performed in benign solvents such as water.

Some years later, Fokin and Jia introduced the alternative use of Ru(II) catalysts in 1,3-dipolar cycloadditions which resulted in the regioselective formation of 1,5-substituted 1,2,3-triazoles (Scheme 1.2).[19] Importantly, unlike CuAAC, the parent Ru-catalyzed azide-alkyne cycloaddition (RuAAC) could be extended to internal alkynes.

Despite the advances realized, the toxicity of the transition metals to living cells and biomolecules like DNA is a limiting factor for the applications of metal-catalyzed "click" processes in the field of biomaterial chemistry and chemical biology.[20] As a result, more environmentally friendly protocols are highly desired and significant efforts have been directed to the development of metal-free methods to synthetize 1,2,3-triazoles. In 2004, Bertozzi and his group reported a pioneering metal-free cycloaddition reaction[21] between an azide and a strained cyclooctyne, also known as strain-promoted azide alkyne cycloaddition (SPAAC).



Scheme 1.2. Common approaches for the assembly of 1*H*-1,2,3-triazoles.

More recently, the significance of organocatalyzed reactions to synthesize 1,2,3-triazoles has received an impressive attention. Many of those methods are ingenious extensions of previously reported Dimroth reaction, which was first published in 1971 by L'abbé[22] and described as "*the condensation of organic azides with active methylene compounds in the presence of an equimolar amount of organic or inorganic base leading to highly substituted 1,2,3-triazoles in a regioselective manner*" (Scheme 1.3).

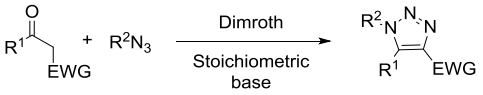
---

19 Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

20 a) Gaetke, L. M.; Chow, C. K. *Toxicology* **2003**, *189*, 147. b) Jomova, K.; Valko, M. *Toxicology* **2011**, *283*, 65.

21 a) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16793. b) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046.

22 L'abbé, G. *Ind. Chim. Belge* **1971**, *36*, 3.



Scheme 1.3. Dimroth reaction for the synthesis of 1,2,3-triazoles.

Nevertheless, these procedures usually suffer from modest functional group tolerance as well as narrow substrate scope which can be overcome by recent advancements based on methodologies such as enamine and dienamine/azide [3+2]-cycloaddition or the use of enolates as dipolarophiles, among others.[23] In the following section, some of the most widely utilized procedures for the preparation of 1,2,3-triazoles mentioned before will be discussed.

1.2.1 1,3-Dipolar cycloaddition

The [3+2] Huisgen 1,3-dipolar cycloaddition reaction or the concerted addition of a 1,3-dipole to a multiple bond is the most direct route to 1,2,3-triazoles, and provides fast access to an enormous variety of heterocycles. However, it has a high activation energy (ca. 24-26 kcal/mol) and elevated temperatures are needed for the process to occur, thus giving place to mixtures of 1,4- and 1,5-regioisomers which are often difficult to separate.

The azide taking part in a 1,3-dipolar cycloaddition reaction is characterized by the presence of an electrophilic nitrogen atom with an electron sextet and a formal positive charge, as well as a nucleophilic nitrogen atom with an electron octet and a formal negative charge placed at 1- and 3-positions respectively (Figure 1.2).

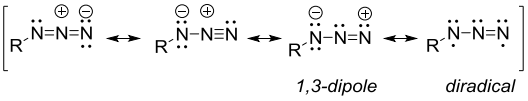


Figure 1.2. Selected contributing resonance structures of an organic azide.

The cycloaddition process was classified by Woodward and Hofmann as an example of pericyclic cycloaddition which is thermally allowed due to symmetrically and geometrically favorable [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] molecular orbital interactions.[24] Nevertheless, not until

---

[23] For a recent review, see: Lima, C. G. S.; Ali, A.; van Berkel, S. S.; Westermann, B.; Paixão, M. W. *Chem. Commun.* **2015**, *51*, 10784.

[24] Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.

Sustmann[25] and Houk[26] did apply the frontier molecular orbital (FMO) model to this process, the reaction rates and regisolectivity were rather difficult to predict.[27] In a few words, this computational model suggests that the reaction between the 1,3-dipole (azide) and the 1,3-dipolarophile (alkyne) proceeds upon interaction of the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of the other reactant, being the reaction rate dependent on the corresponding energy gap between them.

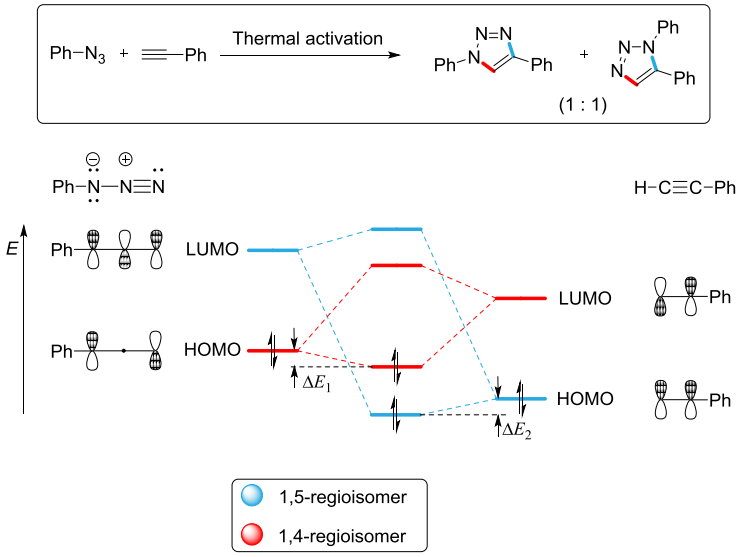


Figure 1.3. FMO interaction diagram for the 1,3-dipolar cycloaddition of phenyl azide and phenyl acetylene.

On the one hand, when the azide dipole has a high-lying HOMO which overlaps with the LUMO of the alkyne, it is referred to as HOMO-*controlled dipole* or nucleophilic dipole. In this case, the azide HOMO-raising electron-donating groups (EDG) as well as alkyne LUMO-lowering electron-withdrawing groups (EWG) will increase the reaction rate

---

25 a) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717. b) Sustmann, R.; Trill, H. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 838. c) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569.

26 a) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. b) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. c) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

27 a) Dewar, M. J. S. *Theochem* **1989**, *200*, 301. b) Fukui, K. *Science* **1982**, *218*, 747. c) Herndon, W. C. *Chem. Rev.* **1972**, *72*, 157. d) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223. e) Salem, L. *J. Am. Chem. Soc.* **1968**, *90*, 553. f) Fukui, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722.

favoring the formation of the 1,4-isomer. On the other hand, an inverse demand FMO interaction is possible when the azide dipole has a low-lying LUMO (LUMO-*controlled dipole* or electronic dipole). Figure 1.3 illustrates a typical azide-alkyne FMO interaction for the cycloaddition between phenyl azide and phenylacetylene which yields a mixture of 1,4- and 1,5-substituted 1,2,3-triazoles in roughly 1:1 ratio.[28] If the interaction energies ΔE_1 and ΔE_2 are similar, the cycloaddition is said to be synchronous. The presence of EDG or EWG substituents in the azide or alkyne reagents usually favors asynchronous FMO interactions, resulting in the preferred formation of one of the 1,2,3-triazole regioisomers.

In general, the quantitative Huisgen reaction rate change is well-predicted by the FMO model as a function of the azide and alkyne substituents. However, the observed regioselectivity is usually the opposite based on the FMO model, in particular for varying azide substituents. With the development of more sophisticated computational methods, new approaches have been proposed[29] such as the distortion/interaction[30] energy model for 1,3-dipolar cycloaddition reactivity. According to this model, the reactivity is controlled by the stability of the dipolarophile and, in particular, of the 1,3-dipole.

1.2.2 Copper-catalyzed azide-alkyne cycloaddition

The copper-catalyzed azide alkyne cycloaddition (CuAAC)[31] reaction efficiently transforms organic azides and terminal alkynes exclusively into the corresponding 1,4-disubstituted 1,2,3-triazoles, in contrast to the uncatalyzed process which provides mixtures of regioisomers. Moreover, the use of copper salts as practical catalysts of the reaction increases the rate by a factor of 10^7 in comparison with the thermal process, even at room temperature.

From the huge number of publications reporting the use of Cu(I) species on these "click" processes two main experimental methods have emerged as the most widely used.

---

28 Kirmse, W.; Horner, L. *Liebigs Ann. Chem.* **1958**, *614*, 1.

29 Heravi, M. M.; Tamimi, M.; Yahyavi, H.; Hosseinnejad, T. *Curr. Org. Chem.* **2016**, *20*, 1591.

30 a) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187. b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646.

31 For selected reviews see: a) Singh, M. S.; Chowdhury, S.; Koley, C. *Tetrahedron* **2016**, *72*, 5257. b) Haldon, E.; Nicasio, M. C.; Pérez, P. J. *Org. Biomol. Chem.* **2015**, *13*, 9528. c) Schulze, B.; Schubert, U. S. *Chem. Soc. Rev.* **2014**, *43*, 2522. d) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302.

The first one involves the direct use of Cu(I) salts under strict exclusion of oxygen in order to prevent their oxidation to Cu(II) species. In these cases, the addition of supporting ligands have been found to have a beneficial impact on the reaction outcome since they are assumed to prevent the degradation of Cu(I) species by oxidation or disproportionation.[32] In particular, the tetradentate ligand tris(benzyltriazolylmethyl) amine (TBTA) has shown to be very efficient in increasing the rate of CuAAC reactions.[33] Apart from these nitrogen-based compounds, other ligands containing oxygen, phosphorous,[34] carbon,[35] and sulfur[36] as donor atoms have also been reported. The use of preformed Cu(I) pre-catalysts is not so extended, but it seems to be increasing in the last years.[37] Metallic copper (wire or turning) also catalyzes the CuAAC reaction, although higher catalyst loadings and prolonged reaction times are needed in comparison with Cu(II) salts.[38]

The second common procedure relies on the *in situ* reduction of Cu(II) salts such as $CuSO_4 \cdot 5H_2O$ to Cu(I) species with a 3- to 10- fold excess of a reducing agent. Undoubtedly, sodium ascorbate is the most utilized reductant but other alternatives have been described such as hydrazine,[39] tris(2-carboxyethyl)phospine[40] or thiol-grafted cellulose paper,[41] among others. From a practical standpoint, the latter strategy is by far the preferred one since it can be performed in water, does not require inert atmosphere, and gives very reliable results, hence posing ideal in the field of chemical biology. Besides, it is compatible with the use of other Cu(II) salts such as $Cu(OAc)_2$, which can be used even without external reductant. In those cases, the formation of Cu(I) species was suggested to be facilitated by either the oxidation of alcohols or alkyne homocoupling.[42]

---

32 Díez-González, S. *Catal. Sci. Technol.* **2011**, *1*, 166.
33 Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.
34 Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951
35 Díez-Gonzalez, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558.
36 Wang, F.; Fu, H.; Jiang, Y.; Zhao, Y. F. *Green Chem.* **2008**, *10*, 452.
37 Lal, S.; Díez-González, S. *J. Org. Chem.* **2011**, *76*, 2367.
38 Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223.
39 Pathigoolla, A.; Pola, R. P.; Sureshan, K. M. *Appl. Cat. A* **2013**, *453*, 151.
40 Samantaray, M. K.; Alauzun, J.; Gajan, D.; Kavitake, S.; Mehdi, A.; Veyre, L.; Lelli, M.; Lesage, A.; Emsley, L.; Copéret, C.; Thieuleux, C. *J. Am. Chem. Soc.* **2013**, *135*, 3193.
41 Rull-Barrull, J.; d'Halluin, M.; Le Grognec, E.; Felpin, F.-X. *Angew. Chem. Int. Ed.* **2016**, *55*, 1.
42 Brotherton, W. S.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Dalal, N. S.; Zhu, L. *Org. Lett.* **2009**, *11*, 4954.

Since the initial mechanistic proposal by Fokin and Sharpless, where mononuclear Cu-intermediates were assumed as the key species of the process, subsequent in-depth kinetic experiments[43] and computational modeling[44] evidenced that the intermediacy of dinuclear species would be a more plausible scenario. In Scheme 1.4 the up-to-date understanding of the CuAAC reaction is depicted.[45] The reaction begins with the coordination of the Cu(I) species to the corresponding alkyne to form intermediate **A**, which increases the CH-acidity of the terminal alkyne allowing thus the subsequent formation of σ, π-di (copper) acetylide **B**.[46] In the next step, the acetylide picks up the azide to form the azide/alkyne/copper(I) ternary complex **C**.[47] Further oxidative coupling afforded metallacycle **D**, in which one Cu(I) center is oxidized to Cu(III) and the metallacycle is stabilized by a bimetallic coordination which alleviates the ring strain. The resulting six-membered metallacycle undergoes reductive elimination in a highly exothermic process, thus affording the Cu(I)-bound triazolide **E** which further undergoes protonolysis with the alkyne, hence liberating the triazole and allowing to complete the catalytic cycle. If there is some Cu(II) in the media generated *via* oxidation or disprotonation of Cu(I) species, bis(triazoles)[48] could be formed. This side-process could be prevented by using for example additional reducing agents such as sodium ascorbate, and in the absence of oxygen. The triazolide **E** could also give other type of side-reactions, like transmetallations[49] or halogenation events.[50] Among the Cu-intermediates depicted in the catalytic cycle, both σ, π-di(copper)acetylide **B** and the Cu(I)-triazolide **E** have been fully characterized and verified as viable intermediates within the process. Importantly, Fokin and co-workers found that the metallacyle **D** was involved in a rapid equilibrium to scramble the two Cu-centers.

---

43 a) Presolski, S. I.; Hong, V.; Cho, S.-H.; Finn, M. G. *J. Am. Chem. Soc.* **2010**, *132*, 14570. b) Rodionov, V. O.; Presolski, S. I.; Díaz, D. D.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12705. c) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 2210.

44 a) Ahlquist, M.; Fokin, V. V. *Organometallics* **2007**, *26*, 4389. b) Straub, B. F. *Chem. Commun.* **2007**, 3868.

45 Zhu, L.; Brassard, C. J.; Zhang, X.; Guha, P. M.; Clark, R. J. *Chem. Rec.* **2016**, *16*, 1501.

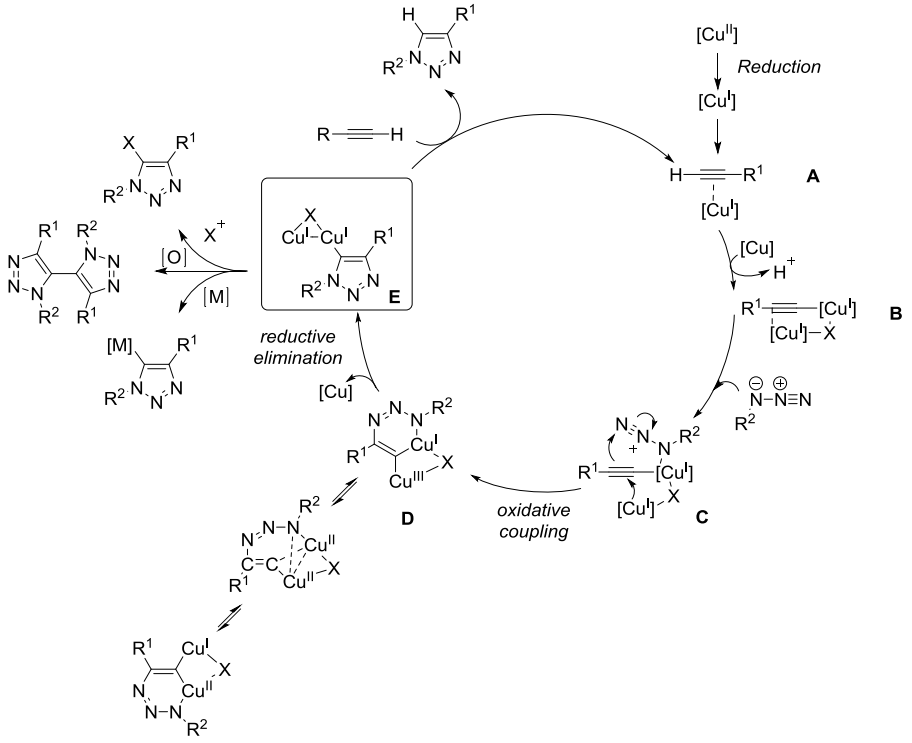
46 Jin, L.; Tolentino, D. R.; Melaimi, M.; Bertrand, G. *Sci. Adv.* **2015**, *1*, e1500304.

47 a) Nolte, C.; Mayer, P.; Straub, B. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 2101. b) Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457.

48 a) González, J.; Pérez, V. M.; Jiménez, D. O.; Lopez-Valdez, G.; Corona, D.; Cuevas-Yañez, E. *Tetrahedron Lett.* **2011**, *52*, 3514. b) Angell, Y.; Burgess, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3649.

49 Liu, S.; Müller, P.; Takase, M. K.; Swager, T. M. *Inorg. Chem.* **2011**, *50*, 7598.

50 Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503.



Scheme 1.4. CuAAC proposed mechanism.

Increasing amount of data have shown that the deprotonation of alkyne to afford the target triazole is in fact the turnover-limiting step. It must be mentioned that the copper(I)/acetylide/azide complex **C** have been captured once in mass spectrometric studies as a fleeting intermediate.[51] Additionally, the kinetic significance of alkyne deprotonation in the CuAAC reaction leads to the conclusion that alkynes with relatively low pK_a values undergo faster reactions. This statement can be verified by using alkynes containing electron-withdrawing substituents, such as 4-nitrophenylacetylene,[52] ethyl propiolate[53] and 4-ethynyl 1,2,3-triazolium salts,[54] which react very fast in CuAAc reactions.

---

51 Iacobucci, C.; Reale, S.; Gal, J. F.; De Angelis, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 3065.

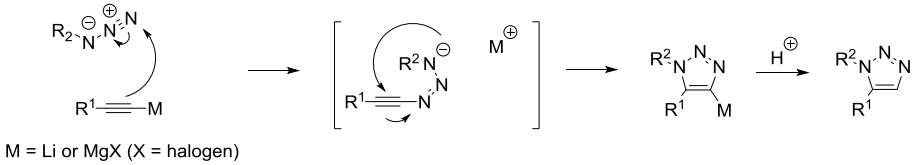
52 Kuang, G.-C.; Guha, P. M.; Brotherton, W. S.; Simmons, J. T.; Stankee, L. A.; Nguyen, B. T.; Clark, R. J., Zhu, L. *J. Am. Chem. Soc.* **2011**, *133*, 13984.

53 Berg, R.; Straub, J.; Schreiner, E.; Mader, S.; Rominger, F.; Straub, B. F. *Adv. Synth. Catal.* **2012**, *354*, 3445.

54 Monasterio, Z.; Sagartzazu-Aizpurua, M.; Miranda, J. I.; Reyes, Y.; Aizpurua, J. M. *Org. Lett.* **2016**, *18*, 788.

1.2.3 Ruthenium-catalyzed azide-alkyne cycloaddition

As highlighted before, the use of Ru-catalysts affords the parent 1,5-disubstituted 1,2,3-triazole derivatives hence complementing the more established CuAAC which provides the corresponding 1,4-isomers. Early examples of preparing 1,5-triazole isomers involved the use of various metal acetylides (Sn, Ge, Si and Na),[55] and subsequent studies by Akimova in the 1960s[56] extended the process to the use of highly reactive lithium and magnesium acetylides. Those processes are proposed to occur via nucleophilic attack of the metal acetylide to the azide followed by ring closure to form the corresponding metallotriazole, which upon acidic work-up furnished the corresponding 1,5-disubstituted compounds (Scheme 1.5).



Scheme 1.5. Proposed mechanism for triazole formation using Li and Mg acetylides.

Owing to the undesirable use of stochiometric amounts of metals, the latter procedures were incompatible with a wide variety of functional groups. Accordingly, a catalytic alternative was actively studied and indeed in 2005 Fokin and Jia solved the problem by introducing the use of Ru(II) catalysts in azide-alkyne cycloadditions.[19]

A typical RuAAC involves the reaction of an organic azide with an alkyne in the presence of catalytic amounts of a Ru(II) complex containing a [Cp*RuCl] unit in a nonprotic solvent.[57] In general, the more suitable catalyst complexes have the general formula Cp*Ru(L)X in which L = phospine or NHC, and X = Cl or OCH_2CF_3. Although heating is often utilized to enshort reaction times, RuAACs at room temperature have been also reported when using a very reactive catalyst such as [Cp*RuCl(COD)]. As mentioned

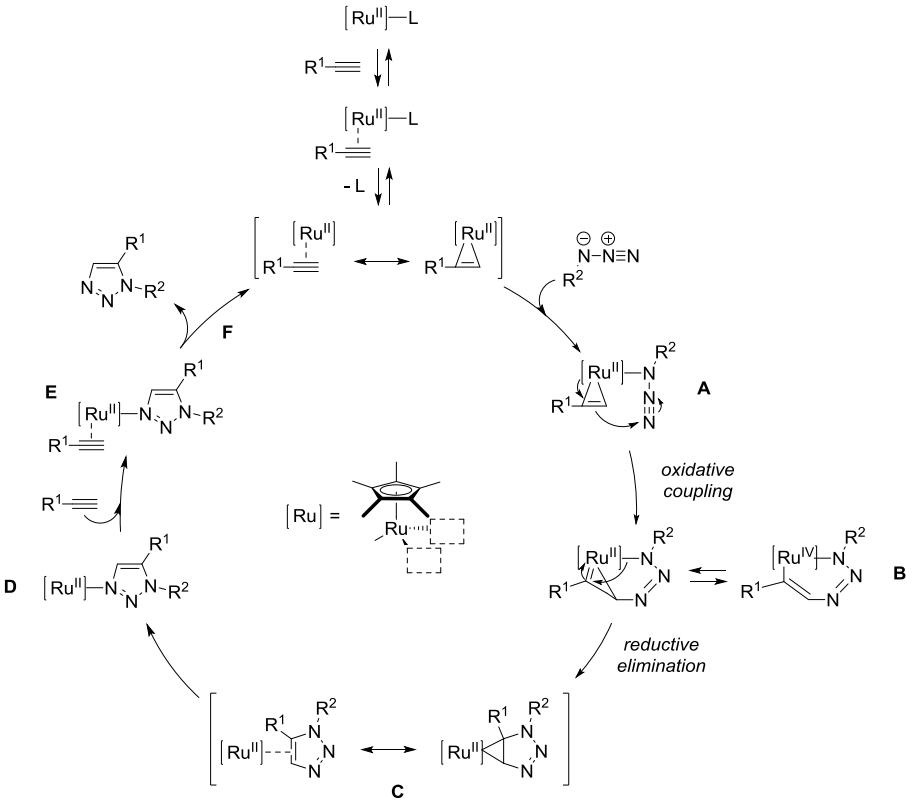
---

55 a) Himbert, G.; Frank, D.; Regit, M. *Chem. Ber.* **1976**, *109*, 370. b) Boyer, N.; Mack, C.; Goebel, N.; Morgan, L. *J. Org. Chem.* **1958**, *23*, 1051.

56 a) Akimova, G.; Chistokletov, V.; Petrov, A. *Zh. Obshch. Khim.* **1968**, *4*, 389. b) Akimova, G.; Chistokletov, V.; Petrov, A. *Zh. Obshch. Khim.* **1967**, *3*, 968. c) Akimova, G.; Chistokletov, V.; Petrov, A. *Zh. Obshch. Khim.* **1967**, *3*, 2241.

57 a) Johansson, J. R.; Beke-Somfai, T.; Stålsmeden, A. S.; Kann, N. *Chem. Rev.* **2016**, *116*, 14726. b) Wang, C. L.; Ikhlef, D.; Kahlal, S.; Saillard, J. Y.; Astruc, D. *Coord. Chem. Rev.* **2016**, *316*, 1. c) Heravi, M. M.; Tamimi, M.; Yahyavi, H.; Hosseinnejad, T. *Curr. Org. Chem.* **2016**, *20*, 1591.

before, one of the significant features of RuAAC in comparison with CuAAC is the tolerance to a variety of internal alkynes, which facilitates the assembly of 1,4,5-trisubstituted heterocycles.



Scheme 1.6. Catalytic cycle of the RuAAC for a terminal alkyne.

Although the mechanism of RuAAC has not been extensively studied, a general mechanistic picture is disclosed in Scheme 1.6.[58] The accepted mechanism is based on the well-known cyclotrimerization of alkynes catalyzed by [Cp*RuCl] and similar complexes, which is assumed to proceed *via* ruthenacyclopentadiene intermediates.[59]

---

58 a) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923. b) Lamberti, M.; Fortman, G. C.; Poater, A.; Broggi, J.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P. *Organometallics* **2012**, *31*, 756. c) Boz, E.; Tüzün, N. Ş. *J. Organomet. Chem.* **2013**, *724*, 167.

59 Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721.

The reaction would start with the generation of a 16-electron Ru complex upon ligand dissociation of the precatalyst in the presence of the corresponding alkyne, to form the catalytically active π-coordinated complex. Further ligation with the azide through the internal nitrogen produces intermediate **A**, which upon subsequent nucleophilic attack provides the six-membered ruthenacycle **B**. The latter is prone to undergo reductive elimination to furnish the triazole-complex **C,** which further isomerizes to intermediate **D**. Eventually, substitution with the alkyne delivers the target triazole derivative and closes the catalytic cycle. It is important to emphasize that the oxidative coupling entirely controls the regioselectivity of the overall process. Therefore, the new C−N bond is formed between the more electronegative and less sterically-demanding carbon atom of the alkyne and the terminal nitrogen atom of the corresponding azide.

1.2.4 Organocatalytic cycloadditions

The organocatalytic cycloaddition[23,60] has recently emerged as a consequence of the existing demand towards the development of metal-free selective syntheses of the 1,2,3-triazole core. These alternative techniques have certain advantages over the metal-catalyzed versions, as they are often insensitive to oxygen, eco-friendly, more sustainable, and are considered nontoxic in the realm of Biology. Notably, due to the limited availability of structurally diverse alkynes, organocatalytic approaches focus on the use of carbonyl compounds as versatile coupling counterparts.

The pioneering work in the field of metal-free cycloaddition reactions came from Bertozzi's lab, where they demonstrated that a strain-promoted azide alkyne cycloaddition reaction (SPAAC) resulted in a rapid triazole formation.[21] While the first discoveries suffered from a narrow substrate scope and modest functional group tolerance, the recent advancements in the field[61] can overcome these limitations and also offer an easy access to diversely functionalized triazoles that are inaccessible by other means. The significance of organocatalyzed events has recently reached an impressive level of performance and

---

[60] For reviews, see: a) Jalani, H. B.; Karagöz, A. Ç.; Tsogoeva, S. B. *Synthesis* **2017**, *49*, 29. b) John, J.; Thomas, J.; Dehaen, W. *Chem. Commun.* **2015**, *51*, 10797.

[61] a) Codelli, J. A.; Baskin, J. M.; Agard, N. J.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 11486. b) Laughlin, S. T.; Baskin, J. M.; Amacher, S. L.; Bertozzi, C. R. *Science* **2008**, *320*, 664. c) Sletten, E. M.; Bertozzi, C. R. *Org. Lett.* **2008**, *10*, 3097.

versatility, and the synthesis of functionalized 1,2,3-triazoles through organocatalytic reactions is extended in the lines below.

1.2.4.1 1,2,3-Triazoles *via* enamine intermediates

The 1,3-dipolar cycloaddition between enamines and azides constitutes a highly regioselective procedure for the assembly of 1,2,3-triazoles. The required enamines that act as dipolarophiles are generated from the corresponding carbonyl compounds which can be divided into two categories: a) activated carbonyl derivatives including Hagemann's esters, ß-ketoesters, and β-oxo-amines, and b) unactivated carbonyl moieties such as alkyl/allyl ketones and aldehydes.[62]

In 2008 Ramachary and his group reported for the first time a proline-catalyzed synthesis of fused triazoles starting from Hagemann's esters.[63] In 2011 Wong and co-workers implemented the use of diethylamine as organocatalyst for the reaction of aryl ketones and keto esters with a variety of azides.[64] Since these early discoveries numerous approaches consisting of an organocatalytic enamine-azide [3+2]-cycloaddition have been developed,[65] but a comprehensive discussion of those methods is beyond the scope of this section. In this respect, a general mechanism to rationalize this type of cycloadditions is depicted on Scheme 1.7.

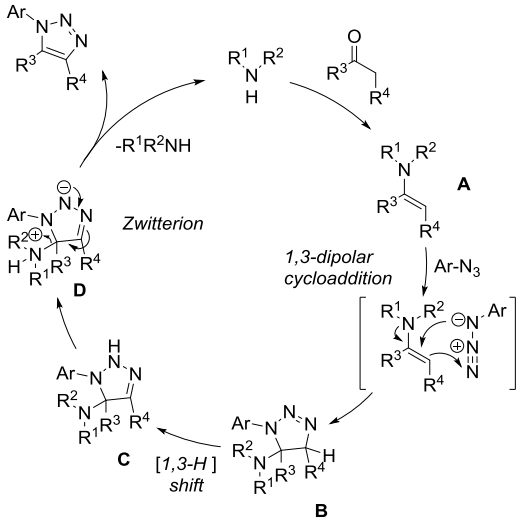
---

62 Dehaen, W.; Bakulev, V. A. *Chemistry of 1,2,3-triazoles*, Springer International Publishing, New York, 1st edn, **2014.**

63 Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem. Eur. J.* **2008**, *14*, 9143.

64 Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem. Eur. J.* **2011**, *17*, 3584.

65 a) Thomas, J.; Jana, S.; John, J.; Liekens, S.; Dehaen, W. *Chem. Commun.* **2016**, *52*, 2885. b) Wan, J.-P.; Cao, S.; Liu, Y. *J. Org. Chem.* **2015**, *80*, 9028. c) Li, W.; Du, Z.; Huang, J.; Jia, Q.; Zhang, K.; Wang, J. *Green Chem.* **2014**, *16*, 3003. d) Ramachary, D. B.; Shashank, A. B. *Chem. Eur. J.* **2013**, *19*, 13175. e) Li, W.; Jia, Q.; Du, Z.; Wang, J. *Chem. Commun.* **2013**, *49*, 10187. f) Yeung, D. K. J.; Gao, T.; Huang, J.; Sun, S.; Guo, H.; Wang, J. *Green Chem.* **2013**, *15*, 2384. g) Belkheira, M.; Abed, D. E.; Pons, J.-M.; Bressy, C. *Chem. Eur. J.* **2011**, *17*, 12917.



Scheme 1.7. General mechanism for the enamine-mediated 1,2,3-triazole synthesis.

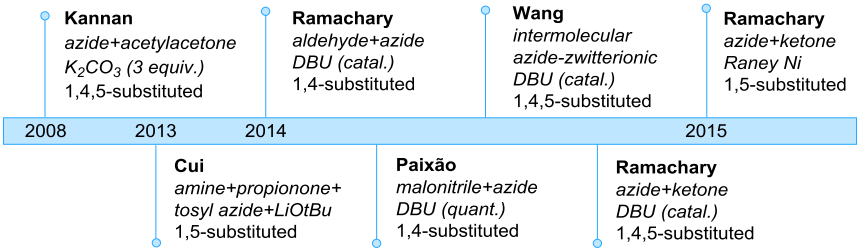
The mechanism for the enamine-based triazole synthesis begins with the condensation of the organocatalyst with the corresponding carbonyl compound to generate the enamine intermediate **A**. This enamine compound acts as an electron-rich olefinic partner thus reacting with the aryl azide to form the cycloaddition adduct **B**. The latter undergoes a 1,3-hydride shift to generate the triazoline intermediate **C**, which is then converted into the zwitterion **D**. Eventually, the 1,2,3-triazole is obtained upon elimination of the corresponding organocatalyst.

1.2.4.2 1,2,3-Triazoles *via* enolate intermediates

In a similar, yet complementary, approach enolates have been successfully employed as dipolarophiles in the metal-free synthesis of triazoles. The first reported synthesis in 2008 by Kannan and co-workers[66] provided 1,4,5-trisubstituted 1,2,3-triazoles from aromatic azides and acetylacetone utilizing potassium carbonate in excessive amounts. Some years later, in 2013 Cui[67] described the synthesis of 1,5-disubstituted 1,2,3-triazoles in a cascade process involving a Michael addition of primary amines to alkynes, followed by the addition of tosyl azide and a final deacylative diazo transfer step, which results in the

[66] Kamalraj, V. R.; Senthil, S.; Kannan, P. *J. Mol. Struct.* **2008**, *892*, 210.
[67] Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 13265.

cyclization to triazoles. In that process, lithium *tert*-butoxide is used as the base, and remarkably enables the preparation of chiral triazoles when using chiral amines.



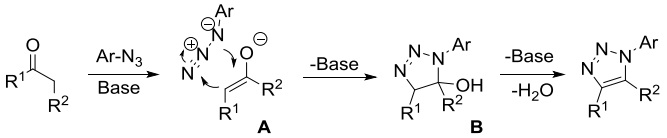
Scheme 1.8. Evolution of enolate-mediated triazole synthesis.

In 2014 Ramachary[68] described an azide-alkyne [3+2] cycloaddition organo"click" reaction between enolizable aldehydes and aryl azides utilizing DBU as catalyst. As illustrated in Scheme 1.8, more approaches were discovered along the same year. The formation of 1,4-disubstituted 1,2,3-triazoles was described by Paixão,[69] applying a 1,3-dipolar cycloaddition strategy which involves the use of alkylidene-malonitriles and aromatic azides in the presence of quantitative amounts of DBU. Shortly thereafter, Wang's group[70] developed an intermolecular azide-zwitterionic reaction catalyzed by DBU for the assembly of fully substituted 1,2,3-triazoles, and Ramachary[71] described an azide ketone [3+2] cycloaddition. Likewise, in 2015 the same group[72] reported an azide-ketone [3+2] cycloaddition reaction, which followed by treatment with Raney nickel provided 1,5-disubstituted 1,2,3-triazoles.

The proposed general mechanism for the enolate mediated synthesis of 1,2,3-triazoles from active methylene compounds such as enolizable aldehydes or ketones, and substituted acetonitriles is illustrated in the Scheme 1.9. In the first step, the base reacts with the acidic C−H bond and the resulting enolate **A**, upon *in situ* treatment with Ar-N_3, selectively furnished the adduct 1,2,3-triazoline **B** through a concerted [3+2] cycloaddition reaction. Eventually, dehydration of adduct **B** gives access to the corresponding triazole.

---

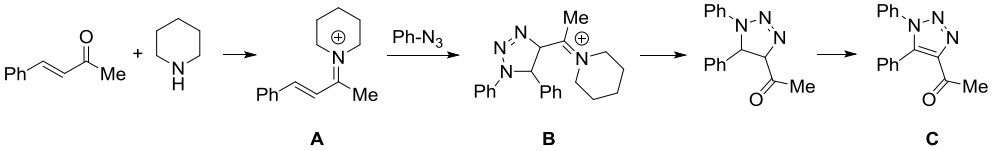
68 Ramachary, D. B.; Shashank, A. B.; Karthik, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 10420.
69 Ali, A.; Corrêa, A. G.; Alves, D.; Zukerman-Schpector, J.; Westermann, B.; Ferreira, M. A. B.; Paixão, W. P. *Chem. Commun.* **2014**, *50*, 11926.
70 Li, W.; Wang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 14186.
71 Shashank, A. B.; Karthik, S.; Madhavachary, R.; Ramachary, D. B. *Chem. Eur. J.* **2014**, *20*, 16877.
72 Ramachary, D. B.; Krishna, P. M.; Gujral, J.; Reddy, G. S. *Chem. Eur. J.* **2015**, *21*,16775.



Scheme 1.9. General mechanism for base-catalyzed 1,2,3-triazole synthesis *via* enolate intermediates.

1.2.4.3 1,2,3-Triazoles *via* iminium intermediates

The synthesis of trisubstituted triazoles starting from α,β-unsaturated ketones was recently reported by Wang.[73] As shown in Scheme 1.10, piperidine was used as catalyst to activate unsaturated ketones and promote their reaction with azides.



Scheme 1.10. 1,2,3-Triazole formation *via* iminium intermediate.

The proposed mechanism begins with the formation of the iminium intermediate **A** by reaction of the unsaturated ketone and the catalyst. Then, a cycloaddition reaction takes place between the iminium species **A** and the corresponding azide to generate the triazoline intermediate **B**, which upon hydrolysis of the iminium center and subsequent air oxidation is converted into the target triazole **C**.

1.2.4.4 Miscellaneous reactions towards substituted 1,2,3-triazoles

In 1986 Rossi and co-workers[74] published the synthesis of 1,4,5-trisubstituted triazoles utilizing enediamines and aryl azides. In the same year, Sakai and his group[75] reported the reaction between ketones and amines for the assembly of 1,4-disubstituted 1,2,3-triazoles, which Westermann[76] later improved into a cascade reaction utilizing DIPEA.

---

73 Li, W.; Du, Z.; Zhang, K.; Wang, J. *Green Chem.* **2015**, *17*, 781.
74 Grassivaro, N.; Rossi, E.; Stradi, R. *Synthesis* **1986**, 1010.
75 Sakai, K.; Hida, N.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179.
76 Berkel, S. S.; Brauch, S.; Gabriel, L.; Henze, M.; Stark, S.; Vasilev, D.; Wessjohann, L. A.; Abbas, M.; Westermann, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 5343.

The synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from aldehydes, nitroalkanes and azides in a one-pot reaction was first described by Dehaen in 2014.[77] Later on, Wang, Ji and co-workers[78] reported a novel synthetic approach for the assembly of 1,4- and 1,5-disubstituted 1,2,3-triazoles starting from arylamines.

In 2016, the synthesis of fully substituted triazoles using a reaction between aldehydes, amines and the Bestmann-Ohira reagent was reported by the group of Mohanan.[79] In the same year, Li and co-workers[80] developed a reaction of ketoamines with azides catalyzed by DBU to generate 1,5-disubstituted 1,2,3-triazoles.

On balance, organocatalytic reactions have led to the generation of highly functionalized/fused triazoles which were not possible to obtain by classical or metal-catalyzed approaches. These green methods use easily accessible starting materials such as carbonyl compounds which render rather advantageous procedures in terms of economics and sustainability. However, most of the organocatalytic reactions are rather limited to the use of aromatic azides, and their application to aliphatic derivatives is still under development. Besides, in-depth mechanistic studies are still required for the better understanding of those processes from a fundamental point of view.

1.3 General objectives of this PhD thesis

As disclosed in the preceding Section 1.2, a wide variety of strategies have been developed for the efficient preparation of 1,2,3-triazole derivatives, which are prevalent backbones of paramount medicinal significance. Despite these successful developments, there are still some aspects of the chemistry of 1,2,3-triazoles that remain scarcely explored and will constitute the main subject of research of this PhD thesis. In particular, our work will focus on studying the following topics:

---

77 Thomas, J.; John, J.; Parekh, N.; Dehaen, W. *Angew. Chem. Int. Ed.* **2014**, *53*, 10155.
78 Bai, H.-W.; Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2015**, *17*, 2898.
79 Ahamad, S.; Kant, R.; Mohanan, K. *Org. Lett.* **2016**, *18*, 280.
80 Zhou, X.; Xu, X.; Liu, K.; Gao, H.; Wang, W.; Li, W. *Eur. J. Org. Chem.* **2016**, *1886*.

1.3.1 1*H*-1,2,3-Triazoles as drug scaffolds: intracellular Ca^{2+} regulation in muscle cells (Chapter 2)

As outlined above, 1,2,3-triazoles are becoming increasingly popular scaffolds for drug design in many pharmaceutical areas. Their electronic and structural characteristics are similar to the peptide bond but, unlike peptides, they possess excellent pharmacokinetic properties. Furthermore, the 1*H*-1,2,3-triazole ring is inherently nontoxic and stable to hydrolytic enzymes. (Figure 1.4).

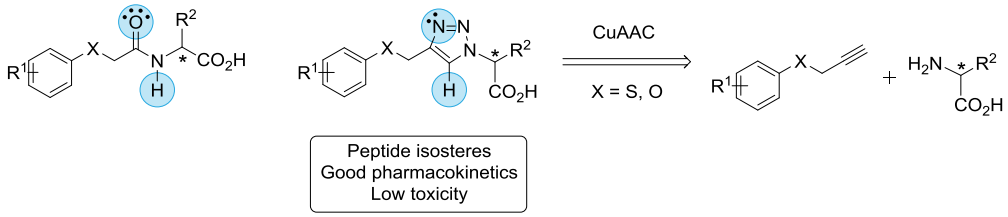
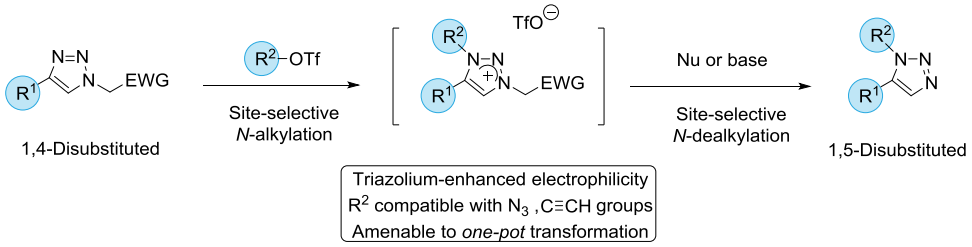


Figure 1.4. Design, synthesis and biological evaluation of 1,2,3-triazoles derived from α-amino acids as RyR1/Calstabin-1 interaction modulators.

Few low molecular weight 1,2,3-triazoles have been developed to modulate protein-protein interactions with therapeutic purposes. In the first part of our work, we will disclose the synthesis of a new family of 1,4-disubstituted triazoles derived from natural α-amino acids specifically designed to stabilize the interaction between the ryanodine receptor channel (RyR1) and its allosteric modulator Calstabin-1. This interaction is crucial to control the [Ca^{2+}] homeostasis inside skeletal muscle cells (myocytes) and its deregulation is involved in the development of some important muscular diseases, like the Duchenne muscular dystrophy.

1.3.2 *N*-Dealkylation of 1,2,3-triazolium salts. A metal-free route to 1,5-disubstituted 1,2,3-triazoles and related bistriazoles (Chapter 3)

In connexion with previous results reported by our group on the alkylation of 1,2,3-triazoles, we will evaluate the development of a novel procedure for the assembly of less common 1,5-disubstituted 1,2,3-triazoles. In particular, we will face the synthesis of triazolium salts with a pendant group which can be easily removed and thus render the corresponding 1,5-disubstituted heterocycles upon a metal-free process.

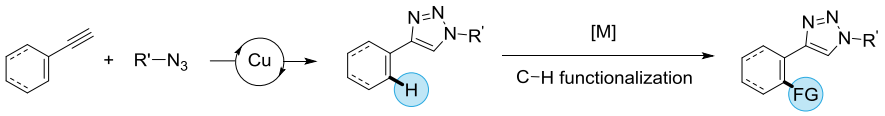


Scheme 1.11. Synthesis of 1,5-disubstituted 1,2,3-triazoles.

Furthermore, the practical introduction of azido and terminal alkyne groups with latent "click" reactivity along these alkylation processes would facilitate the assembly of new bistriazole derivatives of high structural complexity.

1.3.3 Triazoles as directing groups in C−H functionalization reactions (Chapter 4)

The use of 1,2,3-triazole units easily prepared upon CuAAC as directing groups (DGs) in the field of C−H functionalization has been rarely explored and is still in its infancy. In this respect, we will explore the development of practical metal-catalyzed C−H functionalization reactions featuring an unconventional role of 1,2,3-triazoles as versatile DGs.



Scheme 1.12. Evaluation of "click" triazoles as DGs in C−H functionalization reactions.

Our procedures will complement existing methodologies for the functionalization of C(sp^2)−H bonds and will represent novel late-stage functionalization procedures of "click" compounds. In particular, we will study Pd-catalyzed C−H oxygenation and acylation reactions which would afford fully decorated triazole derivatives of general structure **A** and **B**.

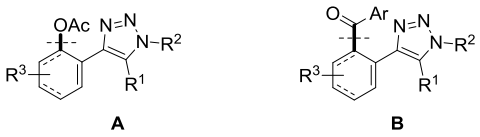


Figure 1.5. General structures of fully decorated triazole derivatives.

2

1H-1,2,3-Triazoles as drug scaffolds: intracellular Ca^{2+} regulation in muscle cells

2 1*H*-1,2,3-Triazoles as drug scaffolds: intracellular Ca^{2+} regulation in muscle cells

2.1 Introduction

Muscular dystrophies (MDs) were characterized as a family of illnesses in the 19th century. The progressive weakening of the musculoskeletal system, previously attributed to tuberculosis, was comprehensively accounted by the neurologist Guillaume Duchenne, which also described an etiology including progressive loss for walking ability and early age death. Nowadays, the most common form of such diseases is named "Duchenne muscular dystrophy" (DMD)[81] after his discoverer.

In general, muscular dystrophies (MD) refer to a group of more than 30 genetic diseases, either inherited or arising from spontaneous mutations, that cause progressive weakness and degeneration of skeletal muscles used for voluntary movement. The age the disease appears as well as the intensity is variable, depending on the type of muscle that is affected. Some dystrophies affect other parts of the body than skeletal muscle, such as the heart, gastrointestinal system, respiratory system, eyes, brain and other organs.

MDs involve mutations in at least one of the genes[82] encoding proteins that are crucial for the integrity of muscles. When a protein is altered, not produced in the adequate quantity or missing, the muscles' cells (myocytes) do not work in the appropriate way. Furthermore, MDs-related gene mutations often occur in sex-determining chromosomes and, therefore, are transmitted following a sex pattern. For example, the Duchenne muscular dystrophy DMD involves a single mutation of the X chromosome that skips the biosynthesis of the dystrophin protein and affects exclusively to male animals.

---

81 For an updated Duchenne Muscular Dystrophy overview and current therapeutic approaches, see: a) https://www.mda.org/disease/duchenne-muscular-dystrophy. b) Rao, M. V.; Sindhav, G. M.; Mehta, J. J. *Ann. Indian Acad. Neur.* **2014**, *17*, 303. c) Mercuri, E.; Muntoni, F. *Lancet* **2013**, *381*, 845. d) Flanigan, K. M. *Semin. Neurol.* **2012**, *32*, 255. e) Bushby, K.; Finkel, R.; Birnkrant, D. J.; Case, L. E.; Clemens, P. R.; Cripe, L.; Kaul, A.; Kinnett, K.; McDonald, C.; Pandya, S.; Poysky, J.; Shapiro, F.; Tomezsko, J.; Constantin, C. *Lancet* **2010**, *9*, 77. f) Emery, A. E. *Lancet* **2002**, *359*, 687.

82 Koenig, M.; Hoffman, E. P.; Bertelson, C. J.; Monaco, A. F.; Feener, C.; Kunkel, L. M. *Cell* **1987**, *50*, 509.

In humans, DMD is the most common muscular dystrophy affecting approximately 1 in every 3.500-6.000 male births each year in the United States.[83] It usually becomes apparent during the toddler years, progressing rapidly, it causes inability to walk to the affected boys around the early age of 12 and, some years later, they need a respirator to breathe. Expected lifetime is under 25 years for most DMD patients.[84] No effective therapeutic treatment for DMD is available at present.[85]

To understand more in detail the structural and molecular basis of the DMD, it is necessary to briefly explain how the skeletal muscle is constituted, and how it works under normal and pathological conditions.

2.1.1 Skeletal muscle and Duchenne muscular dystrophy (DMD)

Skeletal muscles[86] are formed by muscle fibers[87] containing myocytes or muscle cells (Figure 2.1). Myocytes can contain more than one nucleus and include in their structure the myofibrils, which are long protein filaments composed of actin (thin filament) and myosin (thick filament). Repeated units of actin and myosin gathered together are called sarcomeres, which are the basic functional units of the muscle fiber.

---

83 Monaco, A. P.; Neve, R. L.; Colletti-Feener, C.; Bertelson, C. J.; Kurnit, D. M.; Kunkel, L. M. *Nature* **1986**, *323*, 646.

84 a) Bushby, K. M.; Goodship, J. A.; Nicholson, L. V.; Johnson, M. A.; Haggerty, I. D.; Gardner-Medwin, D. *Neuromusc. Disord.* **1993**, *3*, 57. b) Hoffman, E. P.; Arahata, K.; Minetti, C.; Bonilla, E.; Rowland, L. P. *Neurology* **1992**, *42*, 967. c) Richards, C. S.; Watkins, S. C.; Hoffman, E. P.; Schneider, N. R.; Milsark, I. W.; Katz, K. S.; Cook, J. D.; Kunkel, L. M.; Cortada, J. M. *Am. J. Hum. Genet.* **1990**, *46*, 672.

85 Fairclough, R. J.; Wood, M. J.; Davies, K. E. *Nat. Rev. Genet.* **2013**, *14*, 373.

86 Birbrair, A.; Zhang, T.; Wang, Z.-M.; Messi, M. L.; Enikolopov, G. N.; Mintz, A.; Delbono, O. *Stem Cells Dev.* **2012**, *22*, 2298.

87 Zammit, P. S.; Partridge, T. A.; Yablonka-Reuveni, Z. *J. Histochem. Cytochem.* **2006**, *54*, 1177.

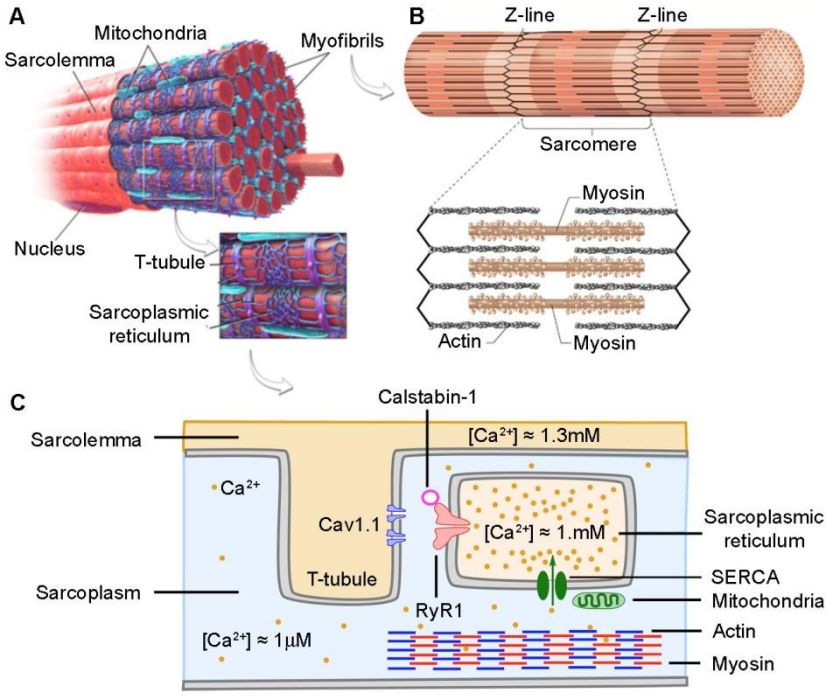


Figure 2.1. Structure of skeletal muscles and myocytes (**A**) Myofibrils are embedded by the sarcolemma; they have peripheral nuclei and internal mitochondria to provide energy for contraction (**B**) Sarcomeres are the contractile units of myofibrils. Their length is shortened upon calcium ion activated actin/myosin interaction (**C**) Schematic view of myocyte membrane main calcium channels: dihydropyridine receptors channels (Cav1.1), ryanodine receptor channels (RyR1) and SERCA channels (ATPase-active calcium ion pumps).

The interaction between myosin and actin is triggered and modulated by a periodical change in the Ca^{2+} ion concentration inside the myocyte's sarcoplasm fluid and is the ultimate responsible for the muscle contraction (high Ca^{2+} concentration) and relaxation (low Ca^{2+} concentration). Under resting conditions, the calcium ion is accumulated inside the sarcoplasmic reticulum (SR), a membrane complex that forms a tubular network of cisternae around each individual myofibril (Figure 2.2).

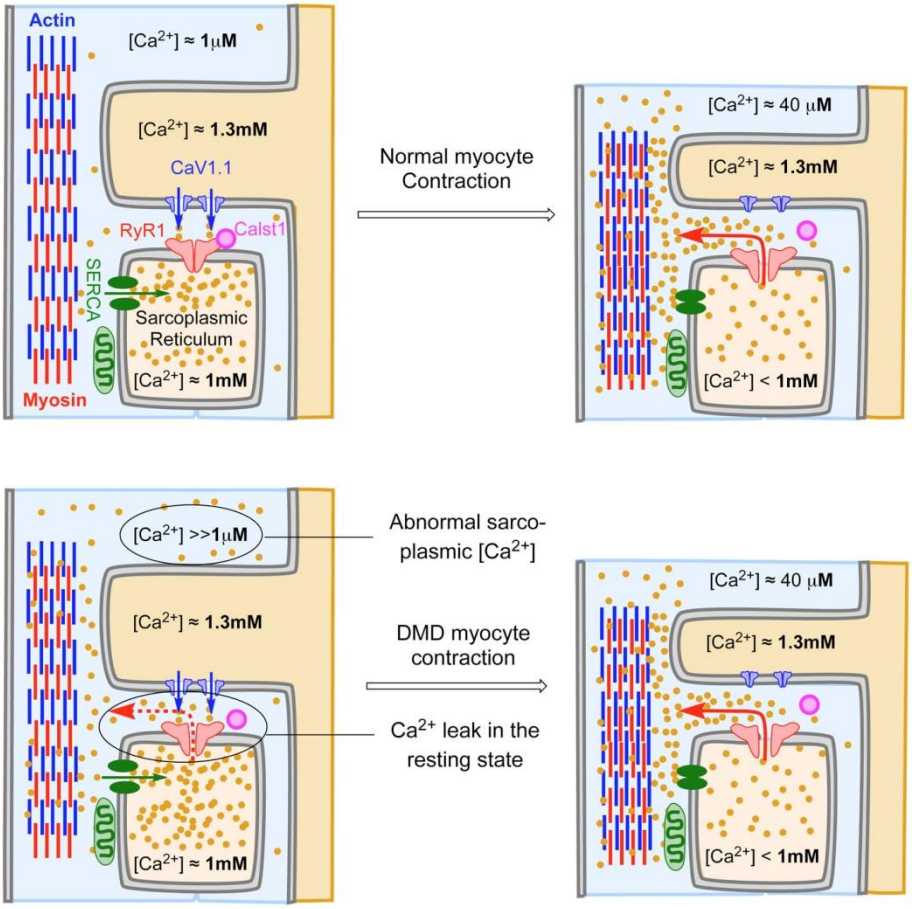


Figure 2.2. Schematic comparison of the excitation-contraction coupling of skeletal muscle in normal myocytes (top) and dystrophic DMD myocytes (bottom). A defective RyR1/Calstabin1 coupling (bottom-left) results in "Ca^{+2}-leaky RyR1 channels". In the resting state, DMD myocytes have abnormally high sarcoplasmic Ca^{+2} concentrations, which provokes a poor muscle contractility and, in the long term, the cell stress and death.

In a normal skeletal muscle, the excitation-contraction (E-C) coupling process begins in the brain where the signal for the contraction is sent to the T-tubule membrane causing the depolarization and activation (opening) of Cav1.1 channels (dihydropyridine receptor voltage sensors). This triggers at the same time the large ryanodine receptor channels (RyR1),[88] opens the sarcoplasmic reticulum (SR), and releases large amounts of

[88] a) Witherspoon, J. W.; Meilleur, K. G. *Acta. Neuropathol. Commun.* **2016**, *4*, 121. b) Fill, M.; Copello, J. A. *Physiol. Rev.* **2002**, *82*, 893.

Ca^{2+} to the sarcoplasm leading ultimately to the muscle contraction.[89] When the contraction is completed, Cav1.1 and RyR1 channels are closed and the intracellular Ca^{2+} is re-uptaken to the SR, by an ATPase-active calcium pump (sarco-endoplasmatic reticulum Ca, SERCA1a) which results in muscle relaxation [90] and preparation for the next excitation-contraction.[91]

As mentioned above, the Duchenne's muscular dystrophy is caused by the absence of dystrophin,[92] which keeps connected the sarcolemma membrane and the actin-myosin complex in myocytes. The absence of this protein causes the malfunction of the skeletal muscle during the excitation-contraction coupling. In particular, the RyR1 channels are hyper-nitrosylated and/or hyper-phosphorylated leading to poor RyR1/Calstabin-1 interactions. In turn, this results in a failure in the complete closing of the channel during the resting step of the E-C coupling, which causes a permanent Ca^{2+} "leak" and, therefore, a perturbation in the intracellular Ca^{2+} concentration changes.[93] In the long term, the incomplete calcium ion cycling compromises the contractility of the myocytes (muscle performance) makes the cells permanently stressed and, finally, provokes their death by apoptosis.

Although genetic therapeutic approaches are being studied intensively to restore dystrophin production in DMD patients, a more profound understanding of the molecular basis of the disease is necessary to attain such goal. Alternatively, some therapeutic strategies are being actively developed in animal models[94] seeking to mitigate the pathological alterations[95] caused by the disease. More particularly, the use of low molecular weight

---

89 a) Petrof, B. J.; Shrager, J. B.; Stedman, H. H.; Kelly, A. M.; Sweeney, H. L. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 3710. b) Sandow, A. *Yale J. Biol. Med.* **1952**, *25*, 176.

90 Saladin, K. S. *Anat. Physiol.* **2010**, *405*.

91 Hernandez-Ochoa, E. O.; Pratt, S. J. P.; Garcia-Pelagio, K. P.; Schneider, M. F.; Lovering, R. M. *Physiol. Rep.* **2015**, *3*, e12366.

92 Lapidos, K. A.; Kakkar, R.; McNally, E. M. *Circ. Res.* **2004**, *94*, 1023.

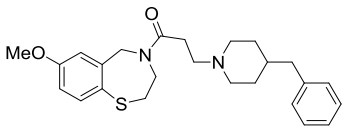
93 a) Bellinger, A. M.; Mongillo, M.; Marks, A. R. *J. Clin. Invest.* **2008**, *118*, 445. b) Gillis, J. M. *J. Muscle Res. Cell Motil.* **1999**, *20*, 605. c) Michalak, M.; Fu, S.; Milner, R.; Bussan, J.; Hance, J. *Biochem. Cell Biol.* **1996**, *74*, 431.

94 a) Bellinger, A. M.; Reiken, S.; Carlson, C.; Mongillo, M.; Liu, X.; Rothman, L.; Matecki, S.; Lacampagne, A.; Marks, A. R. *Nat. Med.* **2009**, *15*, 325. b) Muntoni, F.; Wells, D. *Curr. Opin. Neurol*. **2007**, *20*, 590.

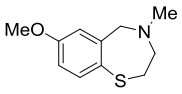
95 a) Pratt, S. J.; Valencia, A. P.; Le, G. K.; Shah, S. B.; Lovering, R. M. *Front. Physiol.* **2015**, *6*, 252. b) Mazala, D. A.; Pratt, S. J.; Chen, D.; Molkentin, J. D.; Lovering, R. M.; Chin, E. R. *Am. J. Physiol. Cell Physiol.* **2015**, *308*, C699. c) Lovering, R. M.; Shah, S. B.; Pratt, S. J. P.; Gong, W.; Chen, Y. *Muscle Nerve* **2013**, *47*, 588. d) Lovering, R. M.; Michaelson, L.; Ward, C. W. *Am. J.*

compounds to restore the intracellular Ca^{2+} homeostasis and to recover normal skeletal muscle function seems very promising.

Different studies have demonstrated the beneficial effects of RyR1 channel stabilizers on animal models of muscular dystrophy.[94a] In particular, the treatment of Duchenne mice models (*mdx*) with the benzothiazepines JTV-519[96] and S-107 has shown to partially improve the calcium homeostasis by reducing the RyR1 channel leaking, and to improve the muscle function and exercise performance *in vivo* (Figure 2.3).[94,97] However, they have failed to reach a proper preclinical profile and, currently, there is no FDA-approved treatment for RyR1-related congenital myopathies.



JTV-519



S-107

Figure 2.3. Benzothiazepines with sarcoplasmic Ca^{2+} concentration modulation activity.

Finally, it should be mentioned that RyR1 channels do not exclusively occur in the skeletal muscle tissue, but also in the brain and central nerve system (CNS) of mammals. Various authors have reported that alterations of the intracellular Ca^{2+} homeostasis in neurons caused by RyR1 channels leaking can be involved in several neurodegenerative conditions. Interestingly, some simple 4-chlorophenol-derived compounds, such as 4-chloro-*m*-cresol or 4-chloro-3-ethylphenol, have been claimed to consolidate the long-term memory stage in young chicks by RyR1 activation and control of the intracellular calcium release.[98]

Physiol. Cell Physiol. **2009**, *297*, C571. e) Berchtold, M. W.; Brinkmeier, H.; Muntener, M. *Physiol. Rev.* **2000**, *80*, 1215. f) Tutdibi, O.; Brinkmeier, H.; Rudel, R.; Fohr, K. J. *J. Physiol.* **1999**, *515*, 859. g) McArdle, A.; Edwards, R. J.; Jackson, M. J. *Neuromuscul. Disord.* **1995**, *5*, 445. h) Florence, J. M.; Fox, P. T.; Planer, G. J.; Brooke, M. H. *Neurology* **1985**, *35*, 758.

96 Wehrens, X. H. T.; Lehnart, S. E.; Reiken, S.; Van der Nagel, R.; Morales, R.; Sun, J.; Cheng, Z.; Deng, S.-X.; Windt, L. J.; Landry, D. W.; Marks, A. R. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 9607.

97 a) Kreko-Pierce, T.; Azpurua, J.; Mahoney, R. E.; Eaton, B. A. *J. Biol. Chem.* **2016**, *291*, 26045. b) Bellinger, A. M.; Reiken, S.; Dura, M.; Murphy, P. W.; Deng, S.-X.; Landry, D. W.; Nieman, D.; Lehnart, S. E.; Samaru, M.; LaCampagne, A.; Marks, A. R. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 2198.

98 Baker, K. D.; Edwards, T. M.; Reiken, S.; Rickard, N. *Behav. Brain Res.* **2010**, *206*, 143.

Within this context, the research group of Neuromuscular Diseases at the BioDonostia Research Institute (San Sebastián, Spain) led by Prof. Adolfo López de Munain and Dr. Ainara Vallejo,[99] established a scientific collaboration with our research group to explore the synthesis of novel molecules based on 1*H*-1,2,3-triazole scaffolds **I** designed to modulate the activity of RyR1 channels in myocytes.

2.2 Hypothesis

To the best of our knowledge, the rational design of molecules to stabilize the RyR1/Calstabin-1 protein interface has not been studied previously using a combination of computational modeling and designed synthesis. This could be attributed to the lack of reliable and high-resolution crystallographic information regarding the 3D-structure of the huge RyR1 565 kDa-channel, which has been only partially unveiled by Marks in 2015.[100] In contrast, the precise 3D-structure of the 12 kDa-protein Calstabin-1, also named FKBP12, was reported more than two decades ago,[101] establishing that there are four Calstabin-1 subunits binding the homotetrameric RyR1 protein in a 1:1 manner.

It is thought that Calstabin-1 promotes the RyR1 channel closure by means of a long-range allosteric effect[102] involving a cascade of conformational changes altering most of the domains of the large RyR1 protein (Figure 2.4). Recently, Girgenrath *et al*[103] have used site-directed fluorescence resonance energy transfer (FRET) techniques to identify two segments of RyR1 comprising the amino acids residues 76-619 and 2157-2777, respectively, which are likely involved in the interaction with Calstabin-1. Finally, and more importantly, Calstabin-1 systematic mutation studies conducted by Galfre *et al* [104] have revealed that Trp-59 residue modification efficiently cancels the interaction with RyR1.

---

99 a) Hernandez-Ochoa, E. O.; Pratt, S. J. P.; Lovering, R. M.; Schneider, M. F. *Front. Physiol.* **2016**, *6*, 1. b) Vallejo-Ilarramendi, A.; Toral-Ojeda, I.; Aldanondo, G.; López de Munain, A. *Expert Rev. Mol. Med.* **2014**, *16*, e16.

100 Zalk, R.; Clarke, O. B.; des Georges, A.; Grassucci, R. A.; Reiken, S.; Mancia, F.; Hendrickson, W.A.; Frank, J.; Marks, A. R. *Nature* **2015**, *517*, 507.

101 Griffith, J. P.; Kim, J. L.; Kim, E. E.; Sintchak, M. D.; Thomson, J. A.; Fitzgibbon, M. J.; Fleming, M. A.; Caron, P. R.; Hsiao, K.; Navia, M. A. *Cell* **1995**, *82*, 507.

102 Bai, X-Ch.; Yan, Z.; Wu, J.; Li, Z.; Yan, N. *Cell. Res.* **2016**, *26*, 995.

103 Girgenrath, T.; Mahalingam, M.; Svensson, B.; Nitu, F. R.; Cornea, R. L.; Fessenden, J. D. *J. Biol. Chem.* **2013**, *288*, 16073.

104 Galfre, E.; Venturi, E.; Pitt, S. J.; Bellamy, S.; Sessions, R. B.; Sitsapesan, R. *Biophys. J.* **2013**, *104*, 443a.

On the basis of these observations, we reasoned that 1*H*-1,2,3-triazole-containing analogues could be designed to modulate the protein-protein interaction at the RyR1/Calstabin-1 interface around the key Trp-59 Calstabin-1 residue. More particularly, we selected triazoles **I** comprising the combination of a hydrophobic aromatic ring and a polar α-amino acid residue to favor the solubilization in physiological media.

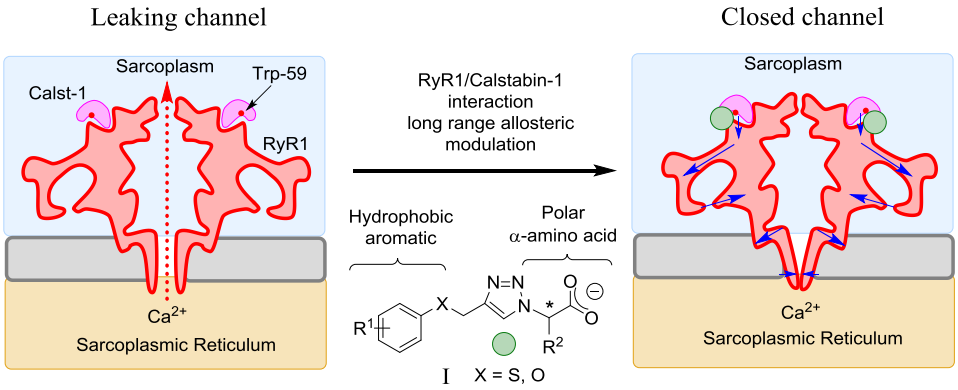


Figure 2.4. Schematic representation of the modulation of the long-range allosteric effect of the RyR1/Calstabin-1 interaction by triazole compounds **I**. Only two of four homomers are represented.

As mentioned above, some RyR1 channels occur in the CNS. Consequently drug candidates aimed to modulate the RyR1/Calstabin-1 interaction inside the brain have to cross the blood brain barrier (BBB).[105] Carboxylic acid-containing small molecules often fail to traverse the BBB because they form carboxylate anions in the blood plasma, which are repealed by the negatively charged membrane of the cerebral endothellium. As a possible solution to this problem, we considered the formation of inclusion complexes of triazoles **I** with cyclodextrins (CD), which have recently shown to have the ability to cross the BBB.[106]

[105] Mensh, J.; Oyarzabal, J.; Mackie, C.; Augustijns, P. *J. Pharm. Sci.* **2009**, *98*, 4429.

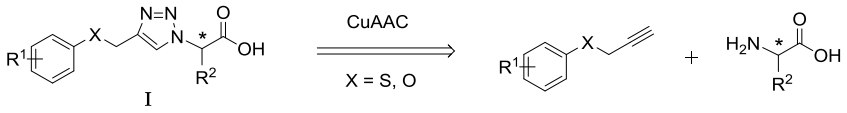
[106] a) Shityalov, S.; Salmas, R. E.; Salvador, E.; Roewer, N.; Broscheit, J.; Foerster, C. *J. Toxicol. Sci.* **2016**, *41*, 175. b) Gil, E. S.; Wu, L.; Xu, L.; Lowe, T. L. *Biomacromolecules* **2012**, *13*, 3533.

2.3 Objectives

In order to test the hypotheses disclosed above, the first part of this doctoral thesis will be focused on the following activities:

1. A docking computational study of several 1*H*-1,2,3-triazoles **I** at the RyR1/Calstabin-1 interface close to the Trp-59 residue using the Autodock FR package and the CCDC X-ray data available for Calstabin-1.[101] The resulting virtual library of triazole modulators will be used to select the best candidates to be synthesized.

2. The synthesis of a representative series of 1*H*-1,2,3-triazoles **I** starting from phenols, thiophenols and natural α-amino acids, by following standard CuAAC "click" procedures or adapted versions developed in our research group.[107]



   Some of the compounds synthesized will be tested at BioDonostia Research Institute to establish their toxicity profile, the effect on intracellular calcium ion concentration in myocytes, and "in vivo" effect on *mdx* mice models of Duchenne muscular dystrophy.

3. The formation of inclusion complexes of some selected 1*H*-1,2,3-triazoles **I** with β-cyclodextrin in water solution will be investigated using NMR techniques to measure the corresponding association constants (Ka) and propose a plausible interaction model.

---

[107] a) Aizpurua, J. M.; Fratila, R. M.; Monasterio, Z.; Pérez-Esnaola, N.; Andreieff, E.; Irastorza, A.; Sagartzazu-Aizpurua, M. *New J. Chem.* **2014**, *38*, 474. b) Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Azcune, I.; Miranda, J. I.; Monasterio, Z.; García-Lecina, E.; Fratila, R. M. *Synthesis* **2011**, *17*, 2737. c) Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Sagartzazu-Aizpurua, M.; Miranda, J. I. *Org. Lett.* **2010**, *12*, 1584.

2.4 Results and discussion

2.4.1 Preliminary computational docking studies

To address the first objective, a computational docking study was conducted in collaboration with Dr. Jose Ignacio Miranda from SGIker (General Research Services of the University of the Basque Country) using the Autodock FR[108] software package. Structures of the RyR1/Calstabin-1 tetramer complex (code 3J8H)[109] were obtained from the Protein Data Bank. Only one monomeric RyR1/Calstabin-1 pair was used for the calculations. Triazole ligand structures **Ia-c**, formally derived from substituted thiophenols and glycine, were selected to confirm their binding ability with the RyR1/Calstabin-1 complex and to estimate the effect of electron-donating and electron-withdrawing groups on such interactions. Proteins and triazole ligands **Ia-c** were prepared following the standard protocols using the AutoDock Tools 1.5.7 software. Selection of the docking area and mobile side-chains in the Calstabin-1 was achieved using the AutoGrid FR software and was limited to the residues Tyr-26, Asp-37, Arg-42, Lys-44, Lys-47, Phe-48, Lys-52 and Glu-54, which were all surrounding the key Trp-59 amino acid placed in the center of a characteristic groove-like structure (see Figure 2.5 D). Likewise, the RyR1 protein docking surface was limited to the 1778-1784 residues comprising a peptide loop interacting with the Calstabin-1 groove. Each ligand was docked 5 times to give an average interaction energy.

As shown in Figure 2.5, an excellent matching of the triazoles **Ia-c** and the RyR1/Calstabin-1 complex in the expected interface region was anticipated by the docking results. The ligand repeatedly docked inside the Calstabin-1 groove and placed itself in front of the RyR1 loop segment after each docking run. In view of this result and the docking energy range (≈12-13 kcal/mol), we reasonably presumed that triazole ligands **I** could modulate the long-range allosteric effect elicited by Calstabin-1 on the activation/closure of the RyR1 channel and, therefore, we expected to have a significant activity on the control of the sarcoplasmic calcium ion concentration in myocytes. Finally, the presence of an electron-

---

[108] a) Ravindranath, P. A.; Forli, S.; Goodsell, D. S.; Olson, A. J.; Sanner, M. F. *PLOS Comput. Biol.* **2015**, *11*, e1004586. b) Zhao, Y.; Stoffler, D.; Sanner, M. *Bioinformatics* **2006**, *22*, 2768.

[109] Yan, Z.; Bai, X.-C.; Yan, C.; Wu, J.; Li1, Z.; Xie, T.; Peng, W.; Yin, C.-C.; Li, X.; Scheres, S. H. W.; Shi, Y.; Yan, N. *Nature* **2015**, *517*, 50.

donating substituent (MeO) at the aromatic ring appeared to exert a sizeable enhancing effect on the docking energy, when compared to electron-withdrawing substituents (F).

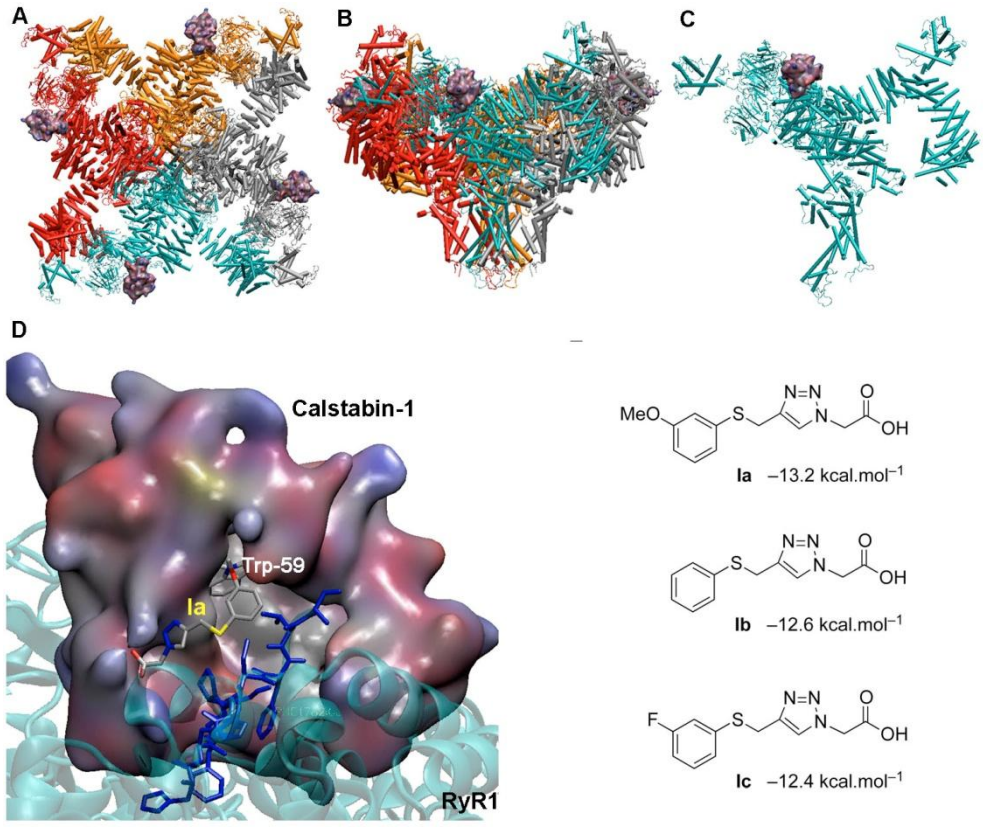
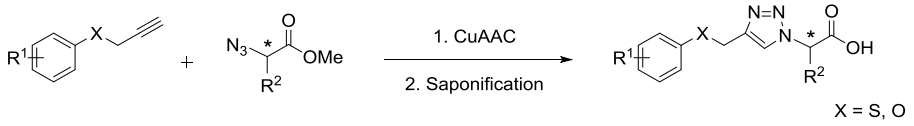


Figure 2.5. RyR1/Calstabin-1 tetramer complex, (**A**) top view; (**B**) side view. (**C**) Monomer complex RyR1 (blue)/Calstabin-1 (purple). (**D**) Structure of the triazole ligand **I-a** docked at the RyR1/Calstabin-1 complex; deep-blue side-chains correspond to the RyR1 segment of residues 1778-1784; purple surface corresponds to Calstabin-1.

2.4.2 Synthesis of 1,4-disubstituted 1*H*-1,2,3-triazole ligands for RyR1 modulation

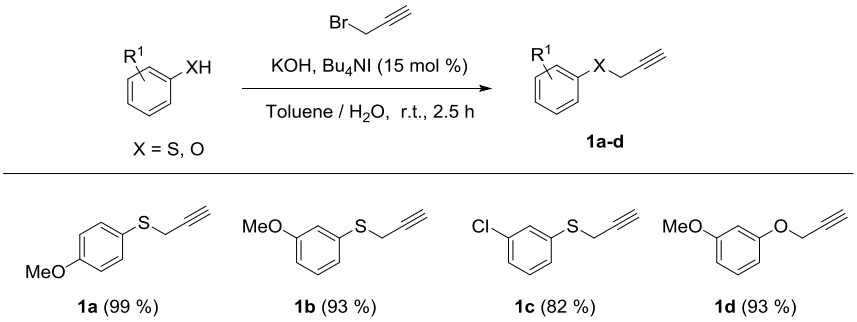
To get a library of representative carboxylic triazole RyR1 ligands, we planned a simple two-step reaction sequence comprising a standard CuAAC "click" reaction of alkynes and α-azido esters, followed by the saponification of the intermediate triazole esters under basic conditions (Scheme 2.1).



Scheme 2.1. "Click" synthetic approach to carboxylic 1*H*-1,2,3-triazole RyR1 ligands.

First, we prepared a set of alkynes **1a-d** containing either electron-donating or electron-withdrawing groups at the aromatic moiety by reacting a few commercially available thiophenols and phenols with propargyl bromide under phase transfer reaction conditions (Table 2.1). The aryl ethers or thioether products were obtained in high yields and were pure enough to be used directly in the next CuAAC cycloaddition reactions.

Table 2.1. Preparation of alkynes **1** from thiophenols and phenols.



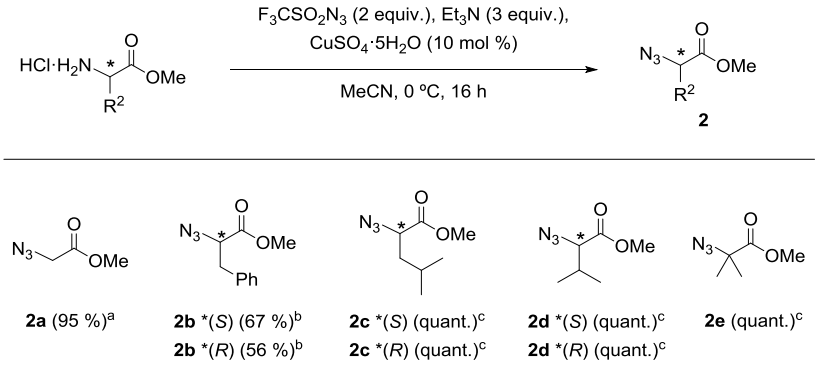
Next, a set of α-azido esters **2** was readily synthesized from α-amino acid ester hydrochlorides following the *N*-diazotation method described by Pelletier[110] (Table 2.2). Accordingly, the α-amino ester was liberated *in situ* with triethylamine and reacted at room temperature in dichloromethane with a solution of triflyl azide (TfN_3), freshly prepared from sodium azide and Tf_2O. The *N*-diazotation was efficiently catalyzed by Cu(II) salts to provide practically quantitative yields of the corresponding α-azido esters **2** without appreciable epimerization when enantiopure starting α-amino esters were used.

Attempted isolation and purification of some of the azido compounds (e.g. (*S*)-**2c** and (*R*)-**2c**) resulted in a significant yield lowering, probably due to partial decomposition during the purification by column chromatography. For this reason, we decided to avoid such operation and use immediately the crude α-azido esters **2** in the subsequent cycloaddition

[110] Lundquist, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781.

reactions with alkynes **1**. Finally, it should be mentioned that the achiral methyl azidoglycinate **2a** was more conveniently prepared using a different method. Thus, reacting methyl bromoacetate with NaN_3 in DMF at room temperature followed by extraction with diethyl ether and careful evaporation provided the azido ester **2a** in 95 % yield.

Table 2.2. Preparation of α-azido esters by *N*-diazotation of α-amino esters.

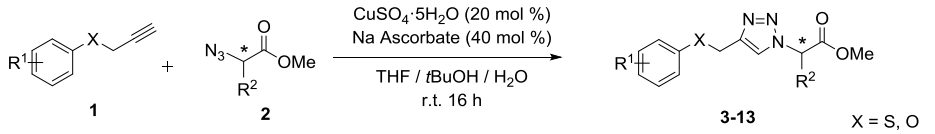


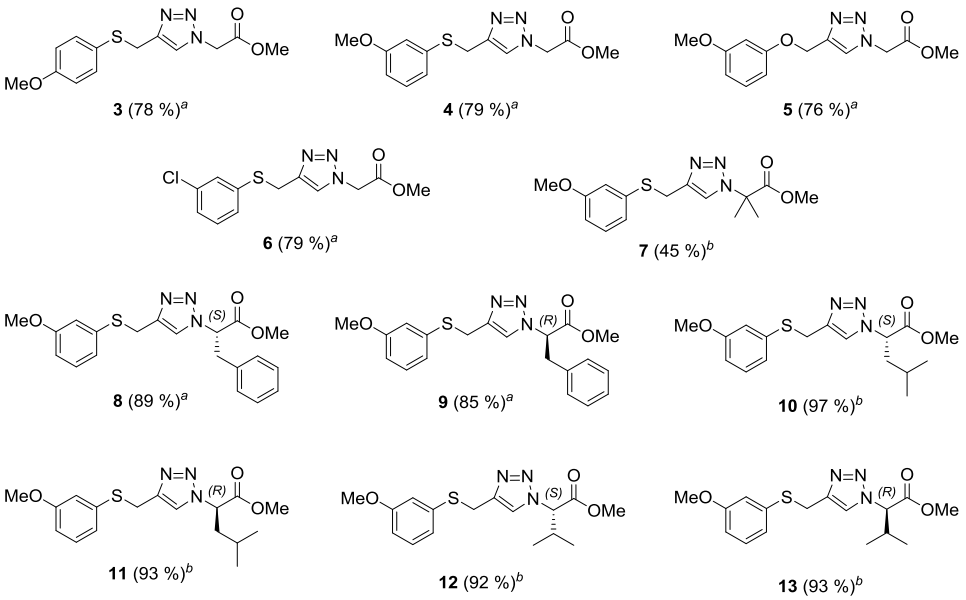
2a (95 %)[a] | **2b** *(*S*) (67 %)[b] **2b** *(*R*) (56 %)[b] | **2c** *(*S*) (quant.)[c] **2c** *(*R*) (quant.)[c] | **2d** *(*S*) (quant.)[c] **2d** *(*R*) (quant.)[c] | **2e** (quant.)[c]

[a]Azidoglycinate **2a** was obtained from $BrCH_2CO_2Me$ and NaN_3 in DMF, r.t. 2h. [b]Yield of isolated compounds after column chromatography. [c]Compound not purified, used *in situ* in CuAAC reaction with alkynes **1**.

With alkynes **1** and α-azido esters **2** in hand, we studied their CuAAC coupling reaction using the Sharpless standard reaction conditions (Table 2.3). Thus, when equimolar quantities of both compounds were reacted in the presence of 0.2 equivalents of copper(II) sulfate and 0.4 equivalents of sodium ascorbate in a mixture of THF, *t*BuOH and water, the desired triazoles **3-13** were obtained in good to excellent yields after chromatographic purification. Interestingly, a one-pot cycloaddition procedure using *in situ* generated chiral α-azido esters **2c-d** proved to be particularly efficient to prepare the triazoles **8-13**, which were assumed to undergo no racemization owing to the mild and neutral reaction conditions used.

Table 2.3. "Click" synthesis of 1-(methoxycarbonylalkyl) 1,2,3-triazoles **3-13**.





[a]From pure azidoglycinates **2a** and **2b**. [b]One-pot procedure was followed from *in situ* generated α-azido esters **2c-e**.

Triazole ring formation was easily assessed in all instances by ^{1}H-NMR analysis. For example, Figure 2.6 shows the spectrum of the reaction crude product of compound **3**, which exhibits a characteristic 1*H*-1,2,3-triazole C5−H peak at 7.38 ppm. Similarly, consistent sets of spectroscopic data were found for all the synthesized triazole esters.

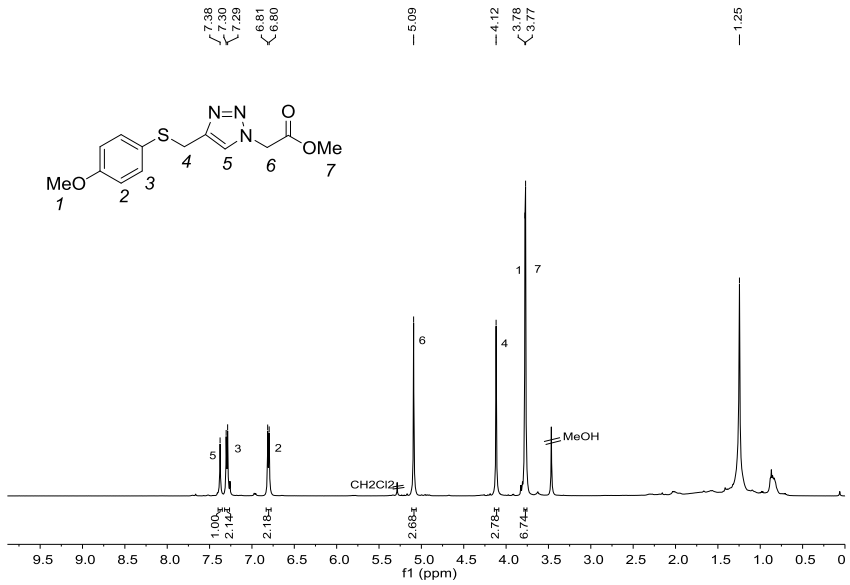


Figure 2.6. ^{1}H-NMR (500MHz, $CDCl_3$) spectrum of the crude product triazole ester **3**.

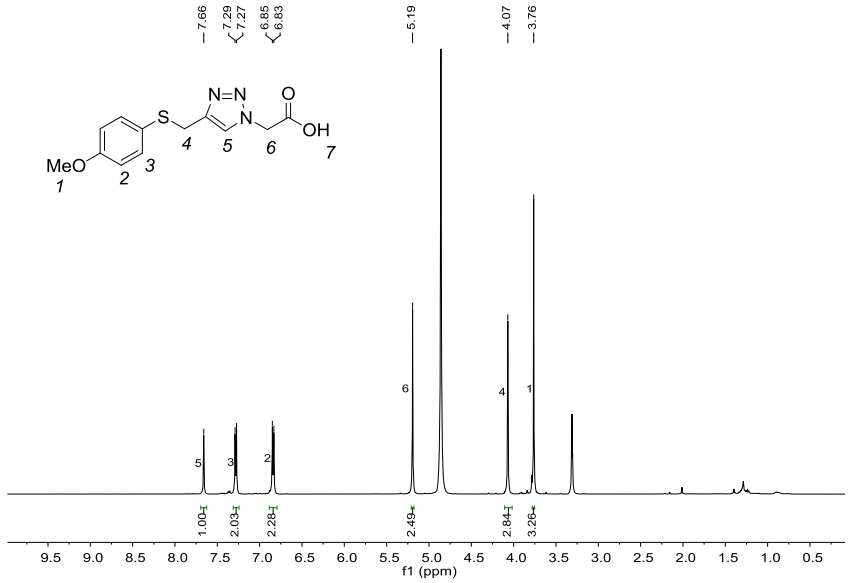
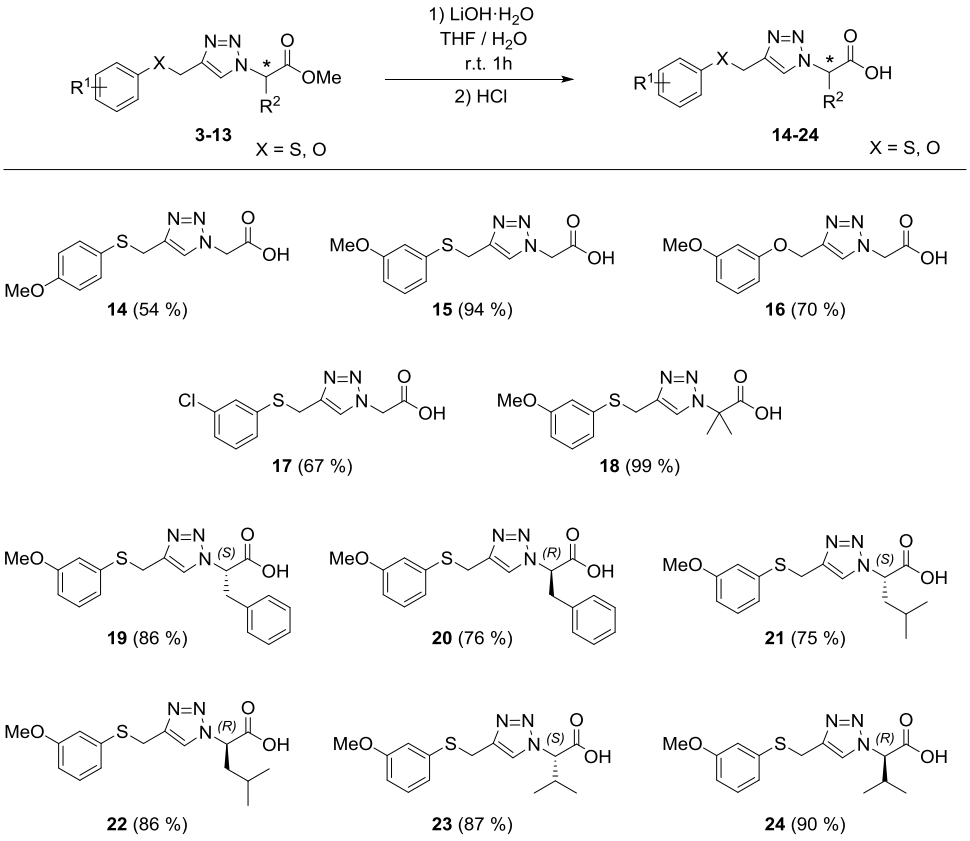


Figure 2.7. ^{1}H-NMR (500MHz, MeOH-d_4) spectrum of carboxylic triazole compound **14**.

The final synthetic step to get the desired RyR1 triazole modulators consisted in the saponification of triazolic methyl esters **3-13**. This transformation was achieved treating each compound with $LiOH \cdot H_2O$ in a mixture of THF and water at room temperature. An acidic extraction of the aqueous solution afforded the triazolic carboxylic acids **14-24** in 54-94 % isolated yields (Table 2.4). Again, the saponification reaction was confirmed by the comparison of the ^{1}H-NMR spectra of the methyl esters **3-13** and the free carboxylic acids **14-24**. For example, the spectra in Figures 2.6 and 2.7 correspond to the saponification of **4** to **14**, and show how the signal at 3.78 ppm vanished completely after the reaction.

Table 2.4. Synthesis of 1-(carboxylalkyl)-1,2,3-triazoles **14-24**.



In order to use chiral carboxylic triazoles **19-24** (Table 2.4) as RyR1 ligands, it was essential to determine their enantiomeric purity arising from the degree of preservation of the chiral integrity during the *N*-diazotation/CuAAC cycloaddition/saponification sequences described above. To achieve this purpose, we first repeated these reactions starting from

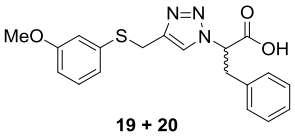
racemic mixtures of (±)-H-Phe-OMe, (±)-H-Leu-OMe and (±)-H-Val-OMe, to prepare the corresponding pairs of triazoles (**19**+**20**), (**21**+**22**) and (**23**+**24**), respectively. Neat separation of all the racemic carboxylic triazole pairs was confirmed using HPLC chromatography on chiral stationary phase (Figure 2.8, left columns). The optimized conditions were achieved using a Chiracel IC50 column together with an eluent mixture composed of hexane (80 %), isopropanol (20 %) and trifluoroacetic acid (0.1 %).

Next, we injected compounds **19**-**24** and compared the chromatograms with the respective racemic mixtures. In the case of the phenylalanine-derived carboxylic triazoles **19** and **20** (Figure 2.8, row **A**), a similarly low enantiomeric purity (e.e. ≈ 40 %) was measured for each compound, which clearly suggested a partial racemization reaction at one or several of the synthetic steps leading to the final products. A very similar behavior was observed for the valine-derived carboxylic triazoles **23**-**24** (Figure 2.8, row **C**), which yielded an even lower enantiomeric purity (e.e. ≈ 20 %).

To our surprise, however, no racemization at all was observed for the leucine-derived carboxylic triazoles **21**-**22** (Figure 2.8, row **B**). In this case, 98 % e.e. purity values were recorded for each enantiomer, precluding the occurrence of the racemization reactions in any of the synthetic steps.

The above results clearly suggested that the observed racemization was strongly dependent on the nature of the substituent group at the α-amino acid moiety, but it did not explained at which particular reaction step of the synthesis the racemization actually took place. In order to clarify this point, we first tried to confirm the enantiomeric purity of the precursor triazole esters **8**-**9** and **12**-**13** (Table 2.3) using the same chiral HPLC techniques described above for the carboxylic analogues. Unfortunately, none of the racemic triazole ester pairs derived from H-Phe-OMe and H-Val-OMe could be separated under a variety of chromatographic conditions.

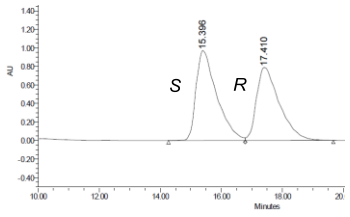
A



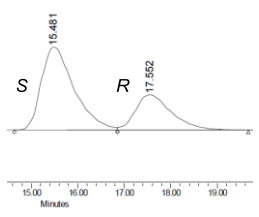
19 + 20

19

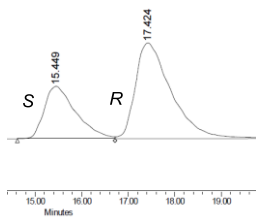
20



	RT	Area	% Area	Height	% Height
1	15.396	45413544	52.69	969096	55.20
2	17.410	40783433	47.31	786601	44.80

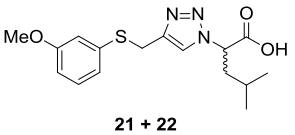


	RT	Area	% Area	Height	% Height
1	15.481	39253604	68.34	798852	70.15
2	17.552	18183532	31.66	339876	29.85



	RT	Area	% Area	Height	% Height
1	15.449	23827602	32.37	506557	35.38
2	17.424	49785997	67.63	925117	64.62

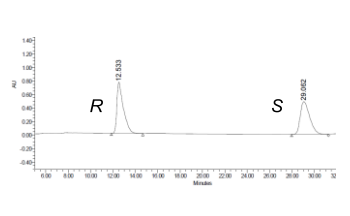
B



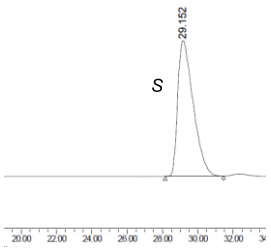
21 + 22

21

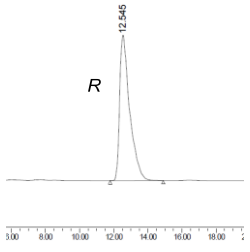
22



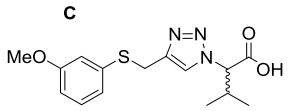
	RT	Area	% Area	Height	% Height
1	12.533	30345585	51.87	755773	60.99
2	29.062	28159078	48.13	483441	39.01



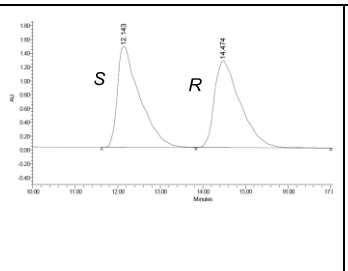
	RT	Area	% Area	Height	% Height
1	29.152	80233678	100.00	1314953	100.00



	RT	Area	% Area	Height	% Height
1	12.545	63655618	100.00	1562128	100.00

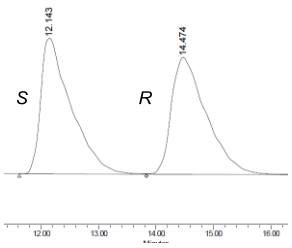


23 + 24



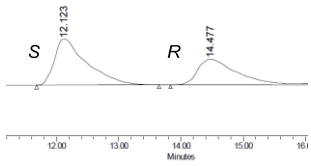
	RT	Area	% Area	Height	% Height
1	12.092	11264134	39.88	288102	41.94
2	14.421	16979122	60.12	398798	58.06

23



	RT	Area	% Area	Height	% Height
1	12.143	53649909	50.26	1460248	53.70
2	14.474	53085080	49.74	1258868	46.30

24

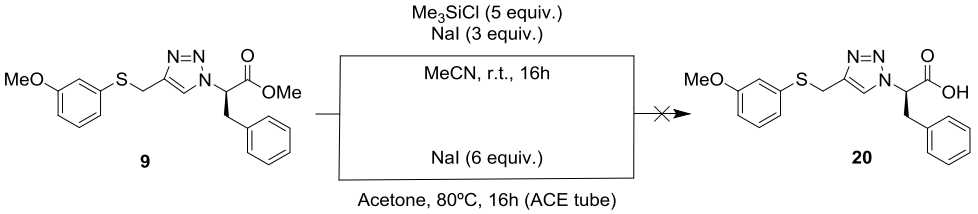


	RT	Area	% Area	Height	% Height
1	12.123	16502529	58.73	456874	64.00
2	14.477	11597371	41.27	257024	36.00

Figure 2.8. HPLC chromatograms of chiral carboxylic triazoles obtained from HPheOMe (**A**), HLeuOMe (**B**) and HValOMe (**C**). Left column: racemic mixtures. Center: *S* major isomers. Right: *R* major isomers. Conditions: Chiracel IC50 column, eluent: hexane (80 %), isopropanol (20 %), trifluoroacetic acid (0.1 %), wavelength $\lambda = 210$ nm.

Owing to the strong basic conditions needed to conduct the saponification step, we assumed that this reaction was more likely responsible for the racemization observed for phenylanine- and valine-derived chiral triazoles. In an attempt to avoid such base-induced racemization, we tried to perform the methyl ester deprotection of compound **9** under neutral conditions (Scheme 2.2). Unfortunately, neither the *in situ* generated iodotrimethylsilane[111] nor the iodide anion[112] was able to promote the desired demethylation reaction (Scheme 2.2). In the first case, an extensive degradation of the starting material was observed under a variety of conditions, while in the second case the ester **9** remained unreactive.

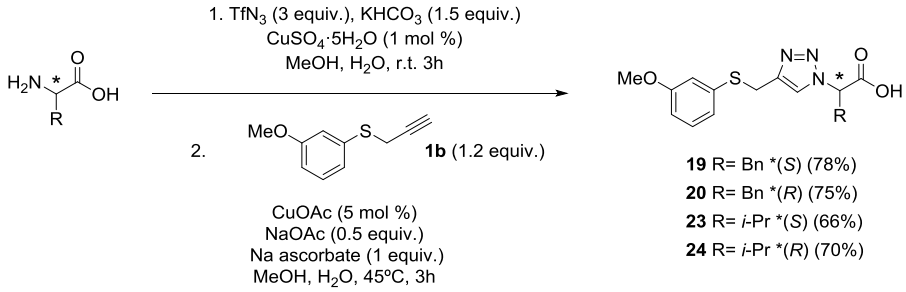
[111] Miller, A. R. *J. Org. Chem.* **1979**, *44*, 889.
[112] Bentley, T. W.; Carter, G. E.; Harris, H. C. *J. Chem. Soc., Chem. Commun.* **1984**, 387.



Scheme 2.2. Attempted deprotection of compound **9** under non-basic conditions.

At this point, we decided to modify the original synthetic approach by replacing the methyl ester groups of the starting materials by free-carboxylic acid groups. Wittmann and co-workers[113] have demonstrated that free α-amino acids can be directly transformed into α-azido acids with triflyl azide under slightly basic conditions using a mixture of methanol and water to solubilize the substrates. Furthermore, the authors proved that such transformation was totally racemization-free for a large array of α-amino acids.

As shown in the examples of Scheme 2.3, the *N*-diazotation reaction of the free phenylalanine and valine α-amino acids provided α-azido acid intermediates which were reacted *in situ* with the alkyne **1b** under CuAAC conditions to afford the desired carboxylic triazoles in a one-pot operation. The overall yields were excellent and the whole transformation, including the purification of the final products, could be performed in a single working day.

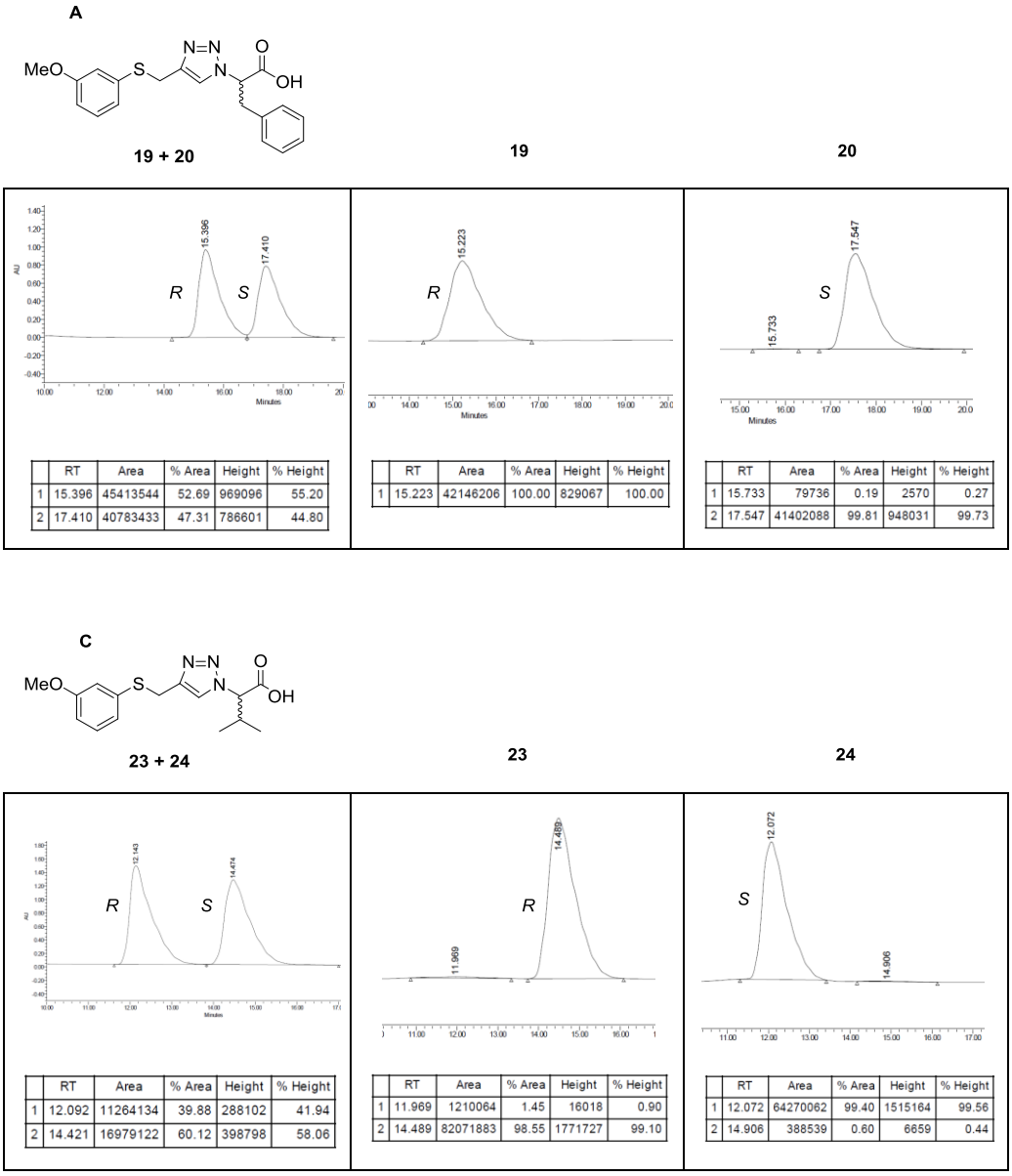


Scheme 2.3. Two-step one-pot synthesis of carboxylic triazoles **19**, **20**, **23** and **24**.

To our delight, the HPLC analysis on chiral stationary phase revealed a total preservation of the stereogenic integrity in all the instances tested (Figure 2.9). For each pair of enantiomers analyzed, the measured enantiomeric purities gave e.e. values above 99 %.

---

[113] Beckmann, H. S. G.; Wittmann, V. *Org. Lett.* **2007**, *9*, 1.



	RT	Area	% Area	Height	% Height
1	15.396	45413544	52.69	969096	55.20
2	17.410	40783433	47.31	786601	44.80

	RT	Area	% Area	Height	% Height
1	15.223	42146206	100.00	829067	100.00

	RT	Area	% Area	Height	% Height
1	15.733	79736	0.19	2570	0.27
2	17.547	41402088	99.81	948031	99.73

	RT	Area	% Area	Height	% Height
1	12.092	11264134	39.88	288102	41.94
2	14.421	16979122	60.12	398798	58.06

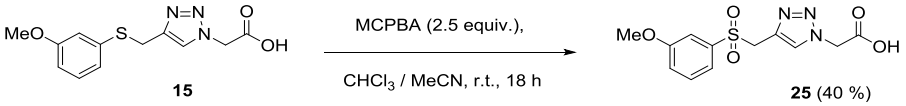
	RT	Area	% Area	Height	% Height
1	11.969	1210064	1.45	16018	0.90
2	14.489	82071883	98.55	1771727	99.10

	RT	Area	% Area	Height	% Height
1	12.072	64270062	99.40	1515164	99.56
2	14.906	388539	0.60	6659	0.44

Figure 2.9. HPLC chromatograms of chiral carboxylic triazoles obtained from HPheOH (top), and HValOH (bottom). Left column: racemic mixtures. Center: *S* major isomers. Right: *R* major isomers. Conditions: Chiracel IC50 column, eluent: hexane (80 %), isopropanol (20 %), trifluoroacetic acid (0.1 %), wavelength $\lambda = 210$ nm.

Finally, we decided to demonstrate that carboxylic triazoles designed to be RyR1 channel modulator ligands could be easily modified into related compounds with potential

pharmacological interest. More particularly, we tested the *S*-oxidation reaction of the sulfide moiety using MCPBA reagent (Scheme 2.4).



Scheme 2.4. *S*-oxidation of compound **15.**

In a preliminary experiment, we were pleased to confirm that a clear oxidation of compounds **15** to the corresponding sulfone **25** could be achieved under standard conditions in a nonoptimized yield of 40 %. These oxidation reactions are currently being studied in our laboratory to prepare novel families of calcium channel modulator candidates.

2.4.3 Biological activity of carboxylic triazoles as RyR1 channel modulators in myocytes and *mdx* mouse models

Samples of the carboxylic triazoles **14-24** were provided to the BioDonostia Research Institute to establish their toxicity profile, the effect on intracellular calcium ion concentration in myocytes, and *in vivo* effect on *mdx* mouse model of Duchenne muscular dystrophy. Nevertheless, due to the long time necessary to grow *mdx* mice colonies large enough to provide statistically significant results *in vivo*, it was decided to conduct the initial trials using only the ligand **16**. This task was achieved by Dr. Garazi Aldanondo as part of her PhD thesis work.[114] Similar evaluations are now underway for all the remaining carboxylic triazole samples and the results will be discussed elsewhere.

As mentioned previously (see Section 2.1.1), benzothiazepine S-107 is one of the most active RyR1 modulator known at present. For this reason, we decided to synthesize such compound following the procedure described by Villeneuve *et al.*[115] (Figure 2.10).

[114] Aldanondo, G. *PhD Thesis UPV-EHU* **2017** "Effect of novel ryanodine receptor modulators in mouse and human models of Duchenne muscular dystrophy."

[115] Yan, J.; Belvedere, S.; Webb, Y.; Bertrand, M.; Villeneuve, N. *Patent* WO-2013156505 A1. 2013.

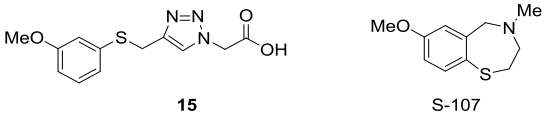


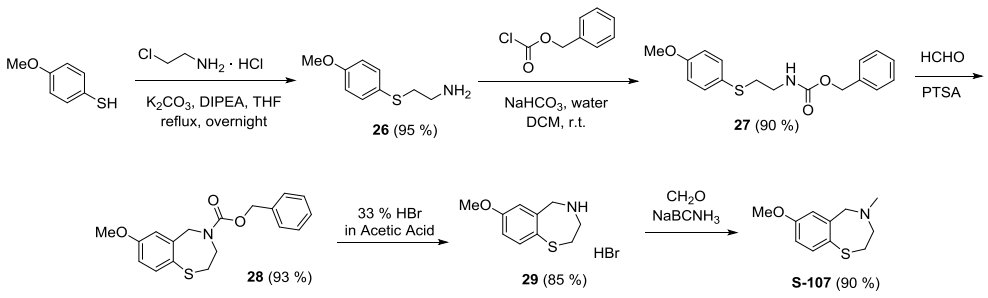
Figure 2.10. Chemical structures of triazole **15** and S-107 used in the biological evaluations conducted in this work.[114]

Figures 2.11-2.13 collect the main results obtained after the completion of 4 representative biological assays. Brief comments of the nature of such assays and the conclusions that can be drawn from these results follow:

1. Triazole **15** shows very low or undetectable *in vitro* toxicity towards mouse C2C12 myoblast and human LHCN-M2 myoblast cultures, whereas compound S107 is strongly cytotoxic to both types of myoblasts at concentrations above 1 mM (Figure 2.11). Triazole compounds **14** and **16**-**24** were also essentially not toxic in the same concentration range.

2. Intracellular Ca^{2+} concentrations are determined using the calcium ratiometric red color dye Fura-2AM in combination with a computer-assisted pseudocolor image analysis. Compound **15** or compound S107 normalize up to 75 % the resting intracellular sarcoplasmic Ca^{2+} levels of isolated muscle fibers from dystrophic *mdx* mice after *in vivo* treatment (Figure 2.12).

3. In *mdx* mice, 5-week treatments with compounds **15** as well as S107 reduce histopathological and biochemical evidence of muscle damage and ameliorate overall muscle weakness. In contrast, these RyR1 modulators do not have any obvious effect in wild-type mice. This effect can be evidenced by the reduction of the pathologic central nuclei proportion after the drug treatment (Figure 2.13).



4. After a 5-week treatment with compound **15** as well as S107 at oral doses of 0.8 mM, *mdx* mice increase the *in vivo* grip strength in up to 40 % when they are submitted to controlled exercise (Figure 2.14).

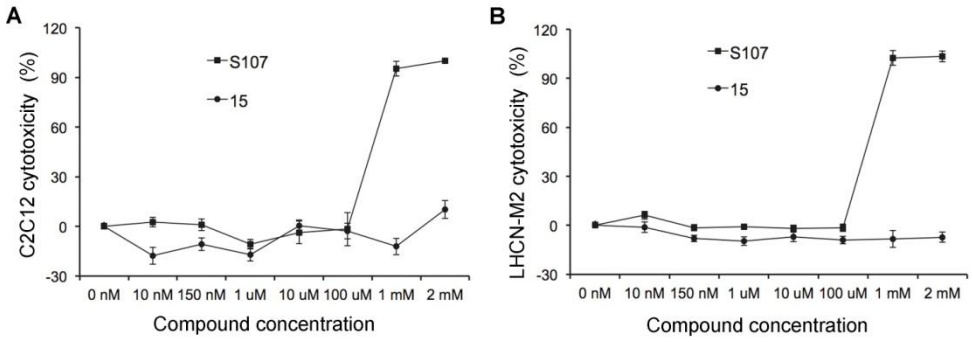


Figure 2.11. Concentration dependent 24 hours *in vitro* cytotoxicity of compounds **15** and S107 in: (**A**) 7 days-old C2C12 mouse myoblasts and (**B**) LHCN-M2 immortalized human myoblasts. Data are represented as average of the percentage of cell death ± SEM, n = quadruplicates per condition in 3 independent cultures.[114]

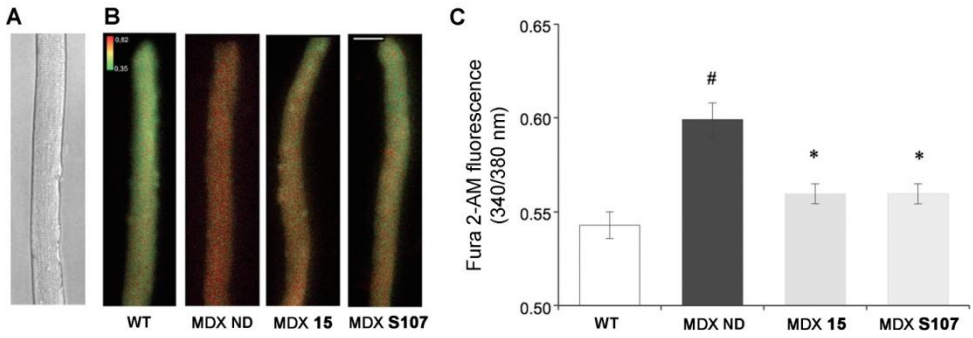


Figure 2.12. Intracellular Ca^{2+} basal levels measured *in vitro* in mouse muscle fibers using the calcium ratiometric red color dye Fura-2AM. (**A**) Single fiber isolated from *flexor digitorum brevis* muscle, showing characteristic striation pattern. (**B**) Representative pseudocolor images of Fura-2AM loaded fibers from: control wild-type (WT), non-treated *mdx* (MDX ND), *mdx* treated with compound **15** (MDX **15**), and *mdx* treated with S-107 (MDX S107); a deeper red color corresponds to a higher intracellular Ca^{2+} concentration. (**C**) Relative intracellular calcium levels in resting myocyte muscle fibers. A lower intracellular Ca^{2+} level indicates a more normalized activity.[114]

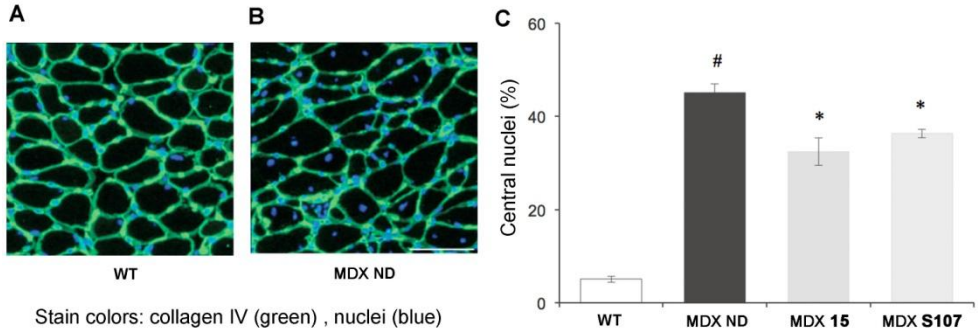


Figure 2.13. Muscle histopathology: representative cryostat sections from control and dystrophic diaphragms stained with DAPI for collagen IV (green) and to show nuclei (blue). (**A**) Diaphragm cryostat sections from wild-type (WT) and (**B**) *mdx* mice (MDX) stained for collagen IV (green) and nuclei (blue) showing central nucleation in dystrophic muscle. Scale bar 100 µm. (**C**) Quantification of myofiber central nucleation in diaphragm muscles from wild-type (WT), non-treated *mdx* (MDX ND), **15**-treated *mdx* (MDX **15**) and S107-treated *mdx* (MDX S107) mice after 5 weeks of treatment. Data are represented as average ± SEM, n = 3 WT, n = 9 MDX ND, n = 7 MDX 15, and n = 6 MDX S107. P <0.05 (one-way ANOVA, Tukey´s Post hoc test). [DAPI: 4',6-Diamidine-2'-phenylindole hydrochloride].[114]

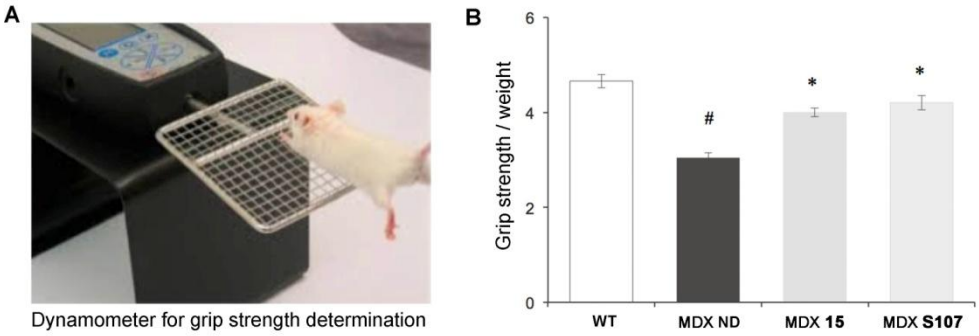


Figure 2.14. Protective *in vivo* effect of triazole ligands **15** and S-107 on muscle function in dystrophic *mdx* mice after 5 weeks of oral administration (0.25 mg/mL). (**A**) Dynamometric grip strength determination apparatus. (**B**) Forelimb grip strength of wild-type (WT), non-treated *mdx* (MDX ND), **15**-treated *mdx* (MDX **15**) and S107-treated *mdx* (MDX S107) mice after 5 weeks of treatment. Data are represented as average ± SEM, n = 10 WT, n = 11 MDX ND, n = 10 MDX 15, and n = 6 MDX S107. P <0.05 (one-way ANOVA, Tukey´s Post hoc test).[114]

In conclusion, the novel carboxylic triazole **15** has proved to be a highly efficient intracellular calcium homeostasis regulator in skeletal muscle upon oral administration to dystrophic *mdx* mice. The efficacy of **15** is comparable to S107, but the former is

significantly less toxic. Accordingly, these novel carboxylic triazoles[116] are promising candidates to develop protective therapies for Duchenne muscular dystrophy and other related diseases.

2.4.4 Inclusion complexes of 1-(carboxyalkyl)-1,2,3-triazoles and β-cyclodextrin

As discussed previously in this chapter (Section 2.2), some cyclodextrins have been used to enhance carboxylic drug transportation across the blood-brain barrier. In order to complete the third objective of this chapter, we studied the supramolecular interaction of a model cyclodextrin with the carboxylic triazole **15** in aqueous solution.

Cyclodextrins[117] (CD) are cyclic oligosaccharides produced by enzymatic degradation of starch and they are constituted of 6 (α), 7 (β) or 8 (γ) glucopyranose units connected by α-[1,4]-linkages. They present a truncated cone structure, in which the internal cavity diameter increases as a function of the number of glucopyranose units from 5.7 to 7.8 and 9.5 Å, when the height of the truncated cone is 7.8 Å.

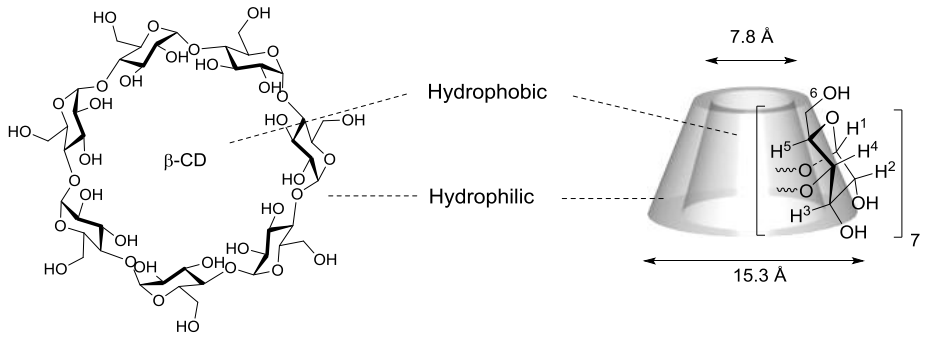


Figure 2.15. Chemical structure and approximate dimensions of β-cyclodextrin (β-CD).

[116] Vallejo, A.; López de Munain, A. J.; Toral, I.; Aldanondo, G.; Aizpurua, J. M.; Irastorza, A.; Ferrón, P.; Miranda, J. I. *Spanish Patent Application* ES : P201630671, 2016.

[117] a) Duchêne, D.; Bochot, A. *Int. J. Pharm.* **2016**, *514*, 58. b) Wang, X.; Luo, Z.; Xiao, Z. *Carbohydr. Polym.* **2014**, *101*, 1027. c) Benk, M.; Király, Z. *J. Chem. Therm.* **2012**, *54*, 212. d) Challa, R.; Ahuja, A.; Ali, J.; Khar, R. K. *Aaps Pharmscitech* **2005**, *6*, E329. e) Huang, D.; Ou, B.; Hampsch-Woodill, M.; Flanagan, J. A.; Deemer, E. K. *J. Agric. Food Chem.* **2002**, *50*, 1815. f) Szejtli, *J. Chem. Rev.* **1998**, *98*, 1743. g) Wenz, G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803. h) Saenger, W. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 344.

The hydroxyl groups of the glucopyranose ring are located on the outside of the molecular cavity, which renders the CDs hydrophilic and soluble in water. In contrast, the internal cavity is hydrophilic and can reversibly trap apolar molecules (or part of molecules), leading to an inclusion complex.[118] The inclusion complex (host-guest complex) results from the chemical equilibrium between the cyclodextrin host and the inclusion molecules to form typically 1:1, 1:2 or 2:1 clusters depending on the molecules involved. The equilibrium constant Ka is also known as affinity constant or stability constant. It must be mentioned that cyclodextrin complexes are routinely used in food,[119] cosmetics[120] and chemical industries,[121] agriculture and environmental engineering[122] and also in pharmaceutical technology.[123]

Triazoles have been extensively used for the chemical modification of cyclodextrins *via* CuAAC reactions, facilitated by the higher reactivity of the primary hydroxyl groups, which can be easily turned into "clickable" azido or alkyne groups.[124] However, the ability of 1*H*-1,2,3-triazoles to act as "aromatic-like" heterocyclic guest molecules of cyclodextrins has been only partially investigated.[125] In this respect, we decided to study the supramolecular interaction of the RyR1 regulator carboxylic triazole **15** and β-cyclodextrin (β-CD), which has been recognized as the more suitable to the purpose of controlling drug delivery.[126]

---

[118] a) Kumar, A. R.; Ashok, K.; Brahmaiah, B.; Nama, S.; Baburano, C. *Int. J. Pharm. Res. Bio-sci.* **2013**, *2*, 291. b) Brinker, U. H.; Mieusset, J.-L. *John Willey & Sons, Chichester, UK* **2010**. c) Duchêne, D. *John Willey & Sons, Hobboken, USA* **2001**, 3.

[119] a) Cheng, J.; Hu, Y.; Luo, Z.; Chen, W.; Chen, H.; Peng, X. *Food Chem.* **2017**, *218*, 116. b) Fenyvesia, É.; Vikmona, M. A.; Szente, L. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, 1981. c) Nazi, M.; Malek, R. M. A.; Kotek, R. *Carbohydr. Polym.* **2012**, *88*, 950. d) Inoue, M.; Hashizaki, K.; Taguchi, H.; Saito, Y. *Chem. Pharm. Bull.* **2008**, *56*, 668. e) Huang, D.; Ou, B.; Hampsch-Woodill, M.; Flanagan, J. A.; Deemer, E. K. *J. Agric. Food Chem.* **2002**, *50*, 1815.

[120] Wang, C. X.; Chen, S. L. *J. Ind. Text.* **2005**, *34*, 157.

[121] Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743.

[122] a) Li, Y.; Zhao, Y.; Chan, W.; Wang, Y.; You, Q.; Liu, C.; Zheng, J.; Li, J.; Yang, S.; Yang, R. *Anal. Chem.* **2015**, *87*, 584. b) Soheilmoghaddam, M.; Sharifzadeh, G.; Pour, R. H.; Wahit, M. U.; Whye, W. T.; Lee, X. Y. *Mater. Lett.* **2014**, *135*, 210.

[123] a) Menuela, S.; Jolyb, J.-P.; Courcotc, B.; Elyséec, J.; Ghermanid, N.-E.; Marsuraa, A. *Tetrahedron* **2007**, *63*, 1706. b) Loftsson, T.; Masson, M. *Int. J. Pharm.* **2001**, *225*, 15. c) Tabushi, *I. Acc. Chem. Res.* **1982**, *15*, 66.

[124] a) Legros, V.; Vanhaverbeke, C.; Souard, F.; Len, C.; Desire, J. *Eur. J. Org. Chem.* **2013**, 2583. b) Hänni, K. D.; Leigh, D. A. *Chem. Soc. Rev.* **2010**, *39*, 1240.

[125] a) Farcas, A.; Fifere, A.; Stoica, I.; Farcas, F.; Resmerita, A. M. *Chem. Phys. Lett.* **2013**, *514*, 74. b) Menuel, S.; Azaroual, N.; Landy, D.; Six, N.; Hapiot, F.; Monflier, E. *Chem. Eur. J.* **2011**, *17*, 3954.

[126] Cheong, A. M.; Tan, K. W.; Tan, C. P.; Nyam, K. L. *Food Hydrocoll.* **2016**, *52*, 934.

2.4.4.1 NMR study on the β-CD/triazole 15 host-guest complexation

NMR is the technique of choice to investigate the supramolecular interactions of cyclodextrins with organic molecules.[127] Standardized titration ^{1}H-NMR experiments on series of samples with different concentrations of the host β-CD and guest compounds, allows the accurate measurement of variations of the chemical shift (Δδi) of the protons of both molecules involved in the interaction. From this data, three valuable kinds of information can be obtained: a) the stoichiometry of the interaction, b) the association constant (Ka) and, in some cases, c) the topology of the binding, revealing which side of the guest molecule is interacting with the β-cyclodextrin inner moiety.

To implement these titration experiments, we selected the method described by C. Jaime.[128] Accordingly, we prepared a set of 11 NMR sample tubes containing β-CD/**15** mixtures of variable molar fractions ($X_{\beta\text{-CD}}$ and X_{14}) ranging from 0 to 1 at 0.1 intervals (Table 2.5).

Table 2.5. NMR sampling of β-CD and triazole **15** mixtures in D_2O.[a]

Tube (nº)	1	2	3	4	5	6	7	8	9	10	11
$V_{\beta\text{-CD}}$ (mL)	0.5	0.45	0.4	0.35	0.3	0.25	0.2	0.15	0.1	0.05	0
V_{Trz} (mL)	0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
$X_{\mathbf{15}}$	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
$X_{\beta\text{-CD}}$	1.0	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0

[a]Two 5 mM mother solutions of β-CD and triazole **15** were prepared in D_2O. Then, different volumes from each mother solution were mixed at 0.05 mL volume intervals to give 11 samples with a total volume of 0.5 mL in each case and ($X_{\beta\text{-CD}}$) molar fractions ranging from 1 to 0 at 0.1 intervals.

Next, we recorded the ^{1}H NMR spectra of the 11 samples, which are collected in Figure 2.16 in a stacked representation. Evidences of a strong interaction between the triazole **15** and β-CD were apparent from the significant variations of the chemical shift (Δδi)

[127] a) Fielding, L.; McKellar, S. M.; Florence, A. J. *Magn. Reson. Chem.* **2011**, *49*, 405. b) Pean, C.; Cheminon, C.; Grassi, J.; Pradelles, P.; Perly, B.; Djedaini-Pilard, F. J. *Inclusion Phenom. Macrocycl. Chem.* **1999**, *33*, 307.

[128] Salvatierra, D.; Díez, C.; Jaime, C. *J. Inclusion Phenom.* **1997**, *27*, 215.

observed both for the Hg proton of the triazole ring and the β-CD protons H3 and H5 located at the inner hydrophobic hole of the β-cyclodextrin. Proton Hg shifted to lower fields as the β-CD concentration was increased in the mixture, whereas H3 and specially H5 shifted to higher fields.

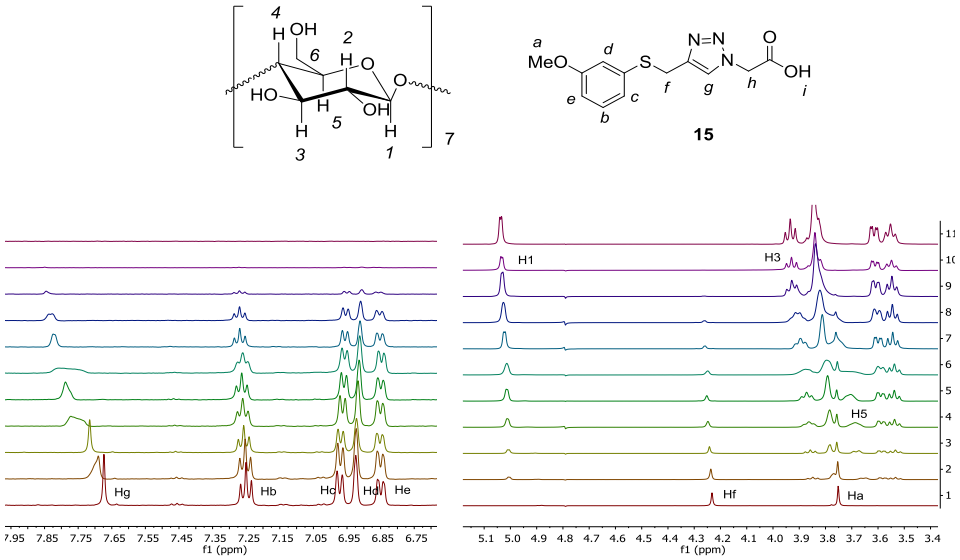


Figure 2.16. ^{1}H-NMR (500 MHz, D_2O) proton-assigned spectra of mixtures of β-CD and triazole **15** registered at 25ºC. Spectrum n=1 ($X_{\beta\text{-CD}}$ = 0, bottom). Spectrum n=11 ($X_{\beta\text{-CD}}$ = 1, top).

The stoichiometry of the β-CD/**15** complex was easily determined from the ^{1}H-NMR chemical shift values at different molar fractions by representing a Job's plot.[129] Figure 2.17 shows the variations of the chemical shifts (Δδi) for all the protons of the β-CD (left) and the triazole **15** (right) as a function of $X_{\beta\text{-CD}}$ and $X_{\mathbf{14}}$, respectively. In both cases, the maximum chemical shift variation occurs at $X_{\beta\text{-CD}} \approx X_{\mathbf{14}} \approx 0.5$ for the protons Hg and H5 directly involved in the supramolecular interaction, which means a 1:1 complex stoichiometry.

[129] Fielding, L. *Tetrahedron* **2000**, *56*, 6151.

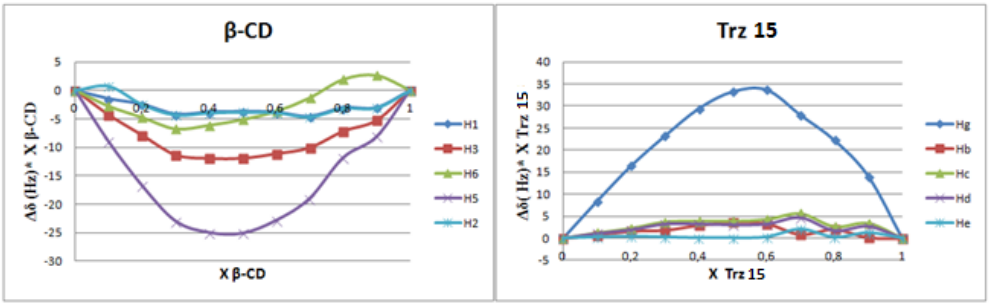


Figure 2.17. Job's plot of the β-CD/**15** complex measured in D_2O at 25 ºC.

Next, we measured the Ka association constant for the β-CD/**15** complex, according to the formation equilibrium quoted below. Given the 1:1 stoichiometry determined experimentally, such constant can be expressed as a function of the initial concentrations of β-CD and triazole Trz**15** and their molar fractions as follows:

β-CD + Trz **15** ⇄ β-CD / Trz **15**

$$K_a = \frac{X_{Trz}}{([\beta CD] - X_{Trz}[Trz])(1 - X_{Trz})}$$

The same equation can be re-written as a function of the variations of the chemical shifts of the interaction protons at the triazole (Δδi) and at the inclusion complex (Δδc):[129]

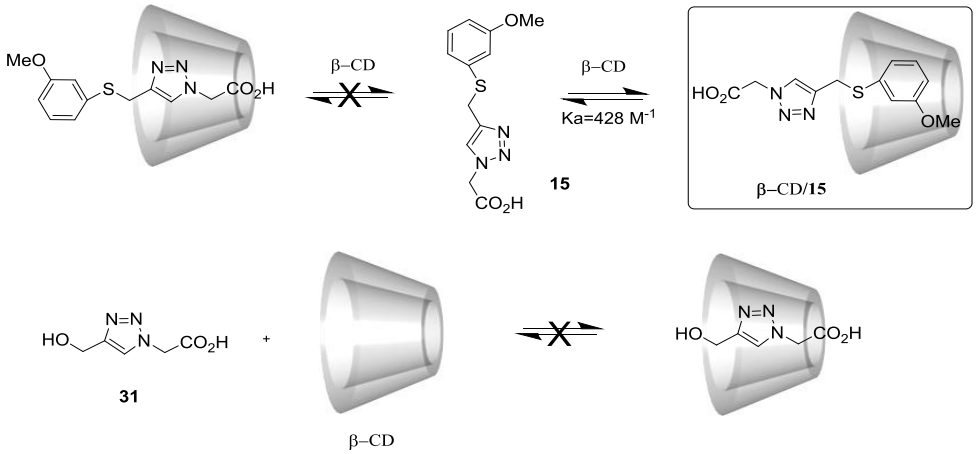
$$K_a = \frac{\Delta\delta_i/\Delta\delta_c}{([\beta CD] - \Delta\delta_i/\Delta\delta_c\,[Trz])(1 - \Delta\delta_i/\Delta\delta_c)}$$

Application of the curve fitting method to the equation using the CLAK algorithm software[128] allowed a good assessment of Ka (428 M^{-1}) for the β-CD/**15** complex, which can be considered an interaction of medium stability.

After the confirmation of the stability of the inclusion complex β-CD/**15** in water, we investigated its structure assuming two possible topologies of 1:1 stoichiometry with the β-CD inner hole interacting with: a) the triazole moiety or, b) the thioaryl moiety (Scheme 2.5, top). The striking variation of the chemical shift of the triazole C5-H proton in the titration experiments (Hg in Figure 2.15) suggested a direct interaction of the β-CD

hydrophobic protons and the triazole ring. Unfortunately, several attempts to get long range 2D ROESY[130] cross-peaks between the triazole Hg proton and β-CD met with failure.

At this point, we reasoned that studying the complexation of β-CD with the triazole **31**,[131] which is similar to **15** but lacking the aromatic moiety, could provide interesting information on the inherent ability of 1-carboxymethyl-1,2,3-triazoles to form inclusion complexes with β-cyclodextrin (Scheme 2.5, bottom). Unfortunately, when ^{1}H-NMR titration experiments were conducted with mixtures of β-CD and triazole **31** in D_2O at 25 ºC, no chemical shift variation of the triazole C5-H proton was observed at all. Therefore, we concluded that a typical cyclodextrin/thioaryl hydrophobic interaction would likely account for the stability and structural topology of the β-CD/**15** complex.



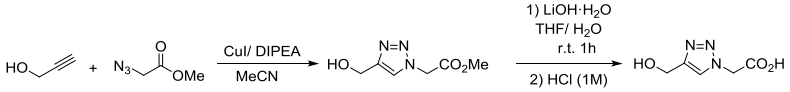
Scheme 2.5. Likely structure of the β-CD/ **15** inclusion complex in D_2O at 25 ºC.

Next, we extended the β-CD complexation studies to the three pair of enantiomers **19-24** (Figure 2.19) to investigate the effect of chirality on their supramolecular diastereoisomeric interactions with β-cyclodextrin. According to the recorded Job's plots

---

130 Bax, A.; Davies, D. G. *J. Magn. Reson.* **1985**, *65*, 355.

131 a) Buckley, B. R.; Dann, S. E.; Heaney, H.; Stubbs, E. C. *Eur. J. Org. Chem.* **2011**, 770. b) Carmo, A. M. L.; Stroppa, P. H. F.; Corrales, R. C. N. R.; Barroso, A. B. N.; Ferreira-Leitãob, V. S.; Silva, A. D. *J. Braz. Chem. Soc.* **2014**, *25*, 2088.



(see experimental section for details), all of them formed stable 1:1 β-CD/Trz inclusion complexes. In all instances, the titration experiments resulted in a significant variation of the chemical shift of the triazole C5-H proton (Hg) and the β-CD inner protons H3 and H5. An inspection of the Ka association constants of the chiral carboxylic triazoles gathered in Figure 2.18 seems to discard the existence of a general correlation between their configuration and the Ka values.

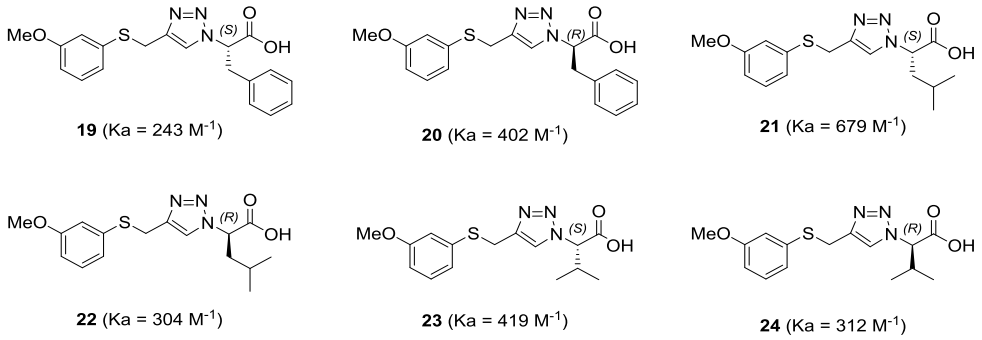
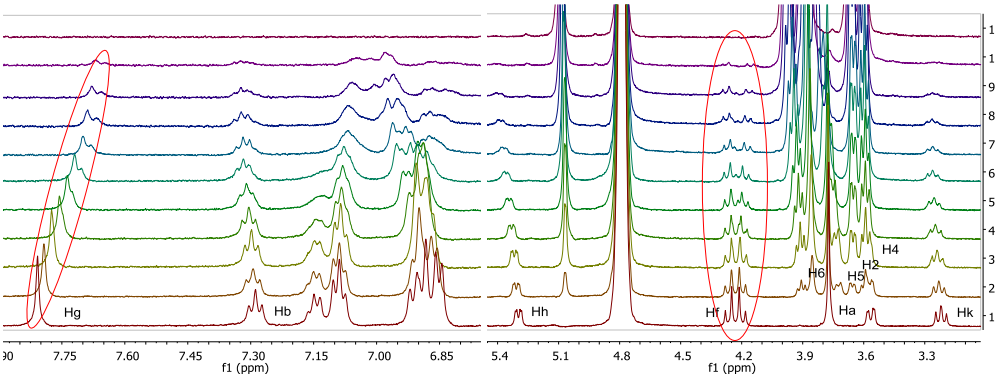


Figure 2.18. Association constants (Ka) of β-CD/triazole complexes measured in D_2O at 25 ºC.

Finally, it is worth mentioning that a careful inspection of the titration spectra of these chiral compounds revealed some β-CD concentration dependent signal coalescence and splittings, which could be tentatively attributed to the emergence of conformational barriers near the triazole ring groups. For example (Figure 2.20), the C5-H proton (Hg) of triazole **20** experienced a splitting into two signals as the β-CD concentration increases, and the diastereotopic Hf protons shift at different rates. This phenomenon could be rationalized as a gradual blocking of the rotation around the methylene group linked to the triazole ring.



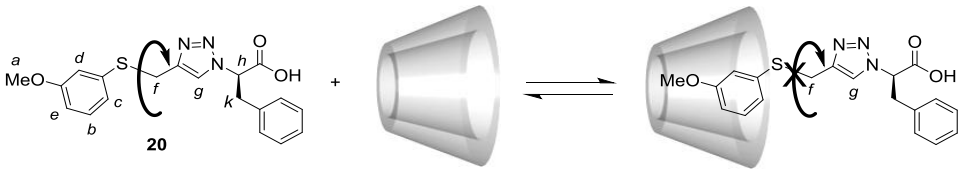


Figure 2.19. ^{1}H-NMR titration spectra of β-CD/**20** in D_2O at 25ºC showing β-CD-dependent peak coalescence (Top). Molecular interpretation of the β-CD-induced conformational barrier.

In summary, the cyclodextrin/carboxylic triazole supramolecular strategy seems practicable to provide novel inclusion complexes designed to interact with the blood-brain barrier. Nevertheless, the triazole interaction topology observed for the β-CD complexes in aqueous media is likely to keep the negatively charged carboxylate moiety exposed to the hydrophilic region in physiological media and, therefore, in an unsuitable configuration to cross the negatively charged blood brain barrier.

2.5 Conclusion

1. 1,4-Disubstituted 1*H*-1,2,3-triazoles comprising 1-carboxyalkyl- and 4-arylthiomethyl- groups are effective templates for the design of modulators of the RyR1/Calstabin-1 interface.

2. Certain triazoles (**19**,**20**,**23** and **24**) can be synthesized in enantiopure form and high overall yields from α-amino acids in a one-pot operation comprising the combination of an *N*-diazotation reaction and a "click" CuAAC cycloaddition with a 3-aryloxypropargyl or a 3-arylthiopropargyl alkyne.

3. 1-Carboxymethyl-4-[3-(methoxy)phenylthiomethyl]-1,2,3-triazole (compound **15**) is a non cytotoxic molecule which efficiently lowers the intracellular sarcoplasmatic calcium ion concentration in dystrophic myocytes *in vitro*. It also enhances *in vivo* the muscle performance on *mdx* mice models of Duchenne muscular dystrophy.

4. Compound **15** forms an inclusion complex with β-cyclodextrin in water solutions at 25 ºC, likely through a hydrophobic interaction of the cyclodextrin with the aromatic ring, but not with the triazole moiety.

Experimental

Experimental

General

All reagents and solvents were obtained from commercial sources (Aldrich, Acros, Alfa Aesar, Merck and Fluka) and were used without further purification unless stated otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried through PS-MD-2columns. Extra pure dichloromethane (CH_2Cl_2), acetonitrile (MeCN), hexane (Hex) and ethyl acetate (EtOAc) were bought from Sharlau.

Moisture sensitive reactions were carried out under an atmosphere of nitrogen in oven or flame-dried glassware with magnetic stirring.

The solvents produced in reactions or chromatography were evaporated in *Büchi* R-210 rotapavors under reduced pressure.

Purification of reaction products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates and visualization was accomplished with UV light (λ = 254 nm) or $KMnO_4$ as TLC stain.

^{1}H NMR spectra were recorded on Bruker avance spectrometers operated at 500 and 400 MHz; and ^{13}C NMR spectra were recorded at 125 and 101 MHz. The chemical shifts are reported as δ values (ppm) relative to residual deuterated solvent as internal standards: for $CDCl_3$ δH (7.26 ppm) and δC (77.16 ppm), respectively; for MeOH-d_4 δH (3.31 ppm) and δC (49.0 ppm), respectively; for MeCN-d_3 δH (1.94 ppm) and δC (118.26 ppm, 1.32 ppm), respectively; for DMSO-d_6 δH (2.50 ppm) and δC (39.52 ppm), respectively.

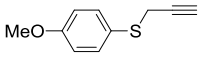
High resolution mass spectra were performed by SGIker and were acquired on a time of flight (TOF) mass spectrometer (SYNAPT G2 HDMS from Waters, Milford, MA, USA) equipped with an electrospray source in positive mode (ESI^+). Melting points were measured with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a *Bruker Alpha P*. Optical rotations were measured on an *Jasco P-200* polarimeter using a sodium lamp (589 nm, D line) at 25 ± 0.2 °C and concentrations are reported in g/100mL units.

Analytical HPLC was performed on a Waters 1525 Binary HPLC pump (dual wavelength detector), using a Diacel Chiralpak IC 50 column. The mobile phase was iPrOH (% 0.1 TFA)/Hex 20:80 with a flow rate of 1 mL/min monitored by UV detection at 210 nm.

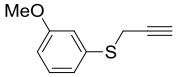
2.1 Synthesis of the starting materials

2.1.1 General procedure for the synthesis of alkynes

The corresponding thiophenol (10.00 mmol) was dissolved in H_2O (20 mL) and KOH (15.00 mmol, 840 mg) was added. The mixture was stirred at room temperature for 1 h. Then, it was cooled down to 0 ºC and a solution formed by propargyl bromide (15.00 mmol, 1.80 g), toluene (20 mL) and a catalytic amount of tetrabutylammonium iodide (1.50 mmol, 0.55 g) was added dropwise. Then, the reaction mixture was further stirred at room temperature for 2 h 30 min. The organic layer was separated, dried with $MgSO_4$ and the solvent was evaporated under reduced pressure.

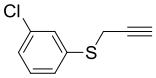


4-Methoxyphenyl propargyl sulfide (1a).[132] General procedure **2.1.1** was followed starting from 4-methoxybenzenethiol (10.0 mmol, 1.22 mL) to provide 1.95 g (99 % yield) of **1a** as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.22 (m, 1H), 7.07-6.99 (m, 2H), 6.81 (dd, J = 7.6, 2.4 Hz, 1H), 3.83 (s, 3H), 3.65 (s, 2H), 2.27 (t, J = 2.6 Hz, 1H).

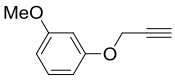


3-Methoxyphenyl propargyl sulfide (1b).[132] General procedure **2.1.1** was followed starting from 3-methoxybenzenethiol (10.0 mmol, 1.22 mL) to provide 1.66 g (93 % yield) of **1b** as an orange liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.49 (d, J = 2.6 Hz, 2H), 2.22 (s, 1H).

[132] Yadagiri, D.; Anbarasan, P. *Chem. Sci.* **2015**, *6*, 5847.

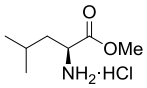


3-Clorophenyl propargyl sulfide (1c). General procedure **2.1.1** was followed starting from 3-clorobenzenethiol (4.68 mmol, 0.54 mL) to provide 0.70 g (82 % yield) of **1c** as a yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, J = 1.9 Hz, 1H), 7.31 (dt, J = 7.5, 1.7 Hz, 1H), 7.28-7.24 (m, 1H), 7.24-7.20 (m, 1H), 3.62 (d, J = 2.6 Hz, 2H), 2.26 (t, J = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.1, 134.7, 130.0, 129.3, 127.7, 127.0, 79.3, 72.1, 22.3. IR (cm^{-1}): 3295, 1576, 1460, 1407, 772, 636. MS (ESI^-) m/z (%) 180 (M-H). HRMS calcd. for (C_9H_6SCl): 180.9879, found 180.9886.



3-Methoxyphenyl propargyl ether (1d).[133] Propargyl bromide (30.00 mmol, 3.30 mL) was added to a suspension of 3-methoxyphenol (20.00 mmol, 2.20 mL) and K_2CO_3 (30.00 mmol, 4.17 g) in acetone (30 mL) at 0 ºC. The mixture was heated at 60 ºC and stirred over 17 h. Then the solvent was evaporated and extracted with EtOAc (15 mL x 3). The organic combined layer was washed with brine (15 mL x 2), dried over Mg_2SO_4 and concentrated under vacuum to provide 3.00 g (93 % yield) of **1d** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J = 8.2 Hz, 1H), 6.75-6.45 (m, 3H), 4.68 (d, J = 1.7 Hz, 2H), 3.79 (s, 3H), 2.52 (s, 1H).

2.1.2 Typical procedure for the preparation of α-amino acid methyl ester hydrochlorides



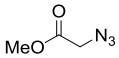
Methyl D-leucinate hydrochloride.[134] To a suspension of the D-leucine (5.00 mmol, 656 mg) in MeOH (14 mL) at 0 ºC under inert atmosphere, acetyl chloride (12.00 mmol, 0.85 mL) was dropwise added and the solution was heated to reflux during 2h. Then, the solution

[133] Nocentini, A.; Ferraroni, M.; Carta, F.; Ceruso, M.; Gratteri, P.; Lanzi, C.; Masini, E.; Supuran, C. T. *J. Med. Chem.* **2016**, *59*, 10692.

[134] Steinmetz, H.; Li, J.; Fu, C.; Zaburannyi, N.; Kunze, B.; Harmrolfs, K.; Schmitt, V.; Herrmann, J.; Reichenbach, H.; Höfle, G.; Kalesse, M.; Müller, R. *Angew. Chem. Int. Ed.* **2016**, *55*, 10113.

was cooled down to room temperature, and the solvent was evaporated under reduced pressure. The solid was washed with dry Et_2O and was stored in a desiccator as a white solid (91 mg, 99 % yield). ^{1}H NMR (500 MHz, D_2O): δ 4.17 (t, J = 6.5 Hz, 1H), 3.86 (s, 3H), 1.94-1.84 (m, 1H), 1.76 (tt, J = 14.5, 7.2 Hz, 2H), 0.98 (s, 6H).

2.1.3 Preparation of azides



Methyl azidoacetate (2a).[135]A solution of methyl bromoacetate (21.30 mmol, 3.20 g) and sodium azide (22.50 mmol, 1.50 g) in dry DMF (5 mL) was stirred at room temperature for 3 h. The solution was quenched with an equivalent quantity of water (21.30 mmol, 384 µL) and the resulting mixture was extracted with Et_2O (3 x 10 mL). The organic layer was washed three times with water and dried over $MgSO_4$. The solvent was carefully removed under reduced pressure to provide 2.32 g (95 % yield) of **2a** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 2H), 3.79 (s, 3H).

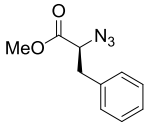
2.1.3.1 General procedure for the synthesis of α-azido esters

To a solution of the corresponding α-amino acid methyl ester hydrochloride (1.00 mmol) in MeCN (5 mL) at 0 ºC were added $CuSO_4 \cdot 5H_2O$ (0.01 mmol) and Et_3N (1.73 mmol) followed by the dropwise addition of freshly prepared solution of TfN_3 (1.50 mmol) in CH_2Cl_2. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the resulting product was purified by column chromatography.

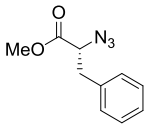
Triflyl azide.[136] Tf_2O (0.57 mmol, 0.10 mL) was added dropwise to a solution of sodium azide (2.80 mmol, 183 mg) in a mixture of H_2O:CH_2Cl_2 (1.5 mL:2.5 mL) at 0 ºC and the mixture was vigorously stirred for 2h. Then, the resulting mixture was extracted with CH_2Cl_2

[135] Bonacorsoa, H. G.; Liberoa, F. M.; Dal Fornoa, G. M.; Pittalugaa, E. P.; Backb, D. F.; Hörnerc, M.; Martinsa, M. A. P.; Zanattaa, N. *Tetrahedron Lett.* **2016**, *57*, 4568.
[136] Lundquist IV, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781.

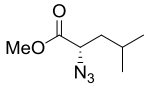
(2 mL x 2). The combined organic fraction was washed with a saturated aqueous solution of Na_2CO_3 and used directly in the next reaction without further purification.



Methyl (*S*)-2-azido-3-phenylpropanoate (2b*S).[137] General procedure **2.1.3.1.** was followed starting from methyl L-phenylalaninate hydrochloride (7.00 mmol, 1.50 g). The product was purified by column chromatography (Hex:EtOAc 3:1) to provide 0.96 g (67 % yield) of **2b*S** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.11 (dd, J = 8.7, 5.4 Hz, 1H), 3.80 (s, 3H), 3.21 (dd, J = 14.0, 5.4 Hz, 1H), 3.04 (dd, J = 14.0, 8.8 Hz, 1H).



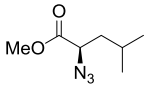
Methyl (*R*)-2-azido-3-phenylpropanoate (2b*R).[138] General procedure **2.1.3.1.** was followed starting from methyl D-phenylalaninate hydrochloride (7.00 mmol, 1.50 g). The product was purified by column chromatography (EtOAc:Hx 1:3) to provide 0.81 g (56 % yield) of **2b*R** as a yellow oil. The ^{1}H-NMR spectroscopic data were identical to those of the previous compound.



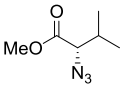
Methyl (*S*)-2-azido-4-methylpentanoate (2c*S).[139] General procedure **2.1.3.1.** was followed starting from methyl L-leucinate hydrochloride (5.74 mmol, 833 mg). The resulting crude product solution was used directly in the next step of the "click" reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.78 (s, 3H), 2.16 (s, 1H), 1.76 (dd, J = 13.4, 6.9 Hz, 1H), 1.66 (td, J = 13.6, 11.4, 7.0 Hz, 2H), 0.94 (dd, J = 10.6, 6.6 Hz, 6H).

---

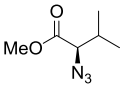
137 Stanleya, N. J.; Pedersenb, D. S.; Nielsenb, B.; Kvistb, T.; Mathiesenb, J. M.; Bräuner-Osborneb, H.; Taylorc, D. K.; Abella, A. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7512.
138 Paul, A.; Bittermann, H.; Gmeiner, P. *Tetrahedron* **2006**, *62*, 8919.
139 Hoffman, R. V.; Kim, H.-O. *Tetrahedron* **1992**, *48*, 3007.



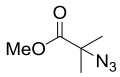
Methyl (*R*)-2-azido-4-methylpentanoate (2c*R).[139] General procedure **2.1.3.1.** was followed starting from methyl D-leucinate hydrochloride (7.00 mmol, 1.02 g). The solution was used directly in the next step of the "click" reaction. The ^{1}H-NMR spectroscopic data were identical to those of the previous compound.



Methyl (*S*)-2-azido-3-methylbutanoate (2d*S).[139] General procedure **2.1.3.1.** was followed starting from methyl L-valinate hydrochloride (7.00 mmol, 1.17g). The solution was used directly in the next step of the "click" reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.79 (s, 3H), 2.19 (dq, J = 13.2, 6.7 Hz, 1H), 0.98 (dd, J = 10.0, 6.8 Hz, 6H).



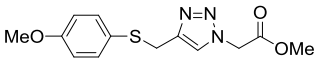
Methyl (*R*)-2-azido-3-methylbutanoate(2d*R).[139] General procedure **2.1.3.1.** was followed starting from methyl D-valinate hydrochloride (7.00 mmol, 1.17 g). The solution was used directly in the next step of the "click" reaction. The ^{1}H-NMR spectroscopic data were identical to those of the previous compound.



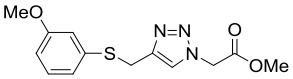
Methyl 2-azido-2-methylpropanoate (2e).[139] General procedure **2.1.3.1.** was followed starting from methyl α-aminoisobutyrate hydrochloride (2.00 mmol, 307 mg). The solution was used directly in the next step of the "click" reaction. ^{1}H NMR (400 MHz, MeOH-d_4): δ 3.09 (q, J = 7.1 Hz, 3H), 1.26 (t, J = 7.2 Hz, 6H).

2.2 General procedure for the synthesis of 1*H*-1,2,3-triazoles.[16]

To a solution of the corresponding alkyne (2.00 mmol, 356 mg) and azide (2.00 mmol, 230 mg) in a mixture of THF/tBuOH (1:1, 4 mL), $CuSO_4 \cdot 5H_2O$ (0.40 mmol, 63 mg) in H_2O (1 mL) were subsequently added and sodium ascorbate (0.80 mmol, 158 mg) in H_2O (1 mL) under inert atmosphere. The reaction mixture was stirred at room temperature overnight. Then, the solvent was partially evaporated under reduced pressure, sat. aq. NH_4OH (5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL) and washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude residue was purified by flash column chromatography.

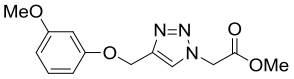


1-Methoxycarbonylmethyl-4-[4-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (3). The general procedure **2.2** was followed starting from 4-methoxyphenyl propargyl sulfide (2.00 mmol, 356 mg) and methyl 2-azidoacetate (2.00 mmol, 230 mg). The resulting product was purified by column chromatography (EtOAc:Hx 3:7) to provide 477 mg (78 % yield) of **3** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.30 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.09 (s, 2H), 4.12 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7, 159.4, 145.8, 134.0, 125.4, 123.5, 114.7, 55.4, 53.1, 50.8, 30.9. IR (cm^{-1}): 2953, 2837, 1750, 1219, 1174. MS (ESI^+) m/z (%) 294 (M+H). HRMS calcd. for ($C_{13}H_{16}N_3O_3S$): 294.0912, found 294.0916.

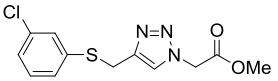


1-Methoxycarbonylmethyl-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (4). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl sulfide (6.00 mmol, 1.10 g) and methyl azidoacetate (6.43 mmol, 504 mg). The resulting crude product was purified by column chromatography (EtOAc:Hx 3:7) to provide 1.40 g (79 % yield) of **4** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.88 (t, J = 2.1, 1.5 Hz, 1H), 6.76-6.70 (m, 1H), 5.11 (s, 2H), 4.26 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7, 159.9, 145.7, 136.8, 129.9, 123.6, 121.5, 114.6, 112.5, 55.4, 53.1, 50.8, 28.7. IR (cm^{-1}): 2953, 2837, 1749, 1220, 1180.

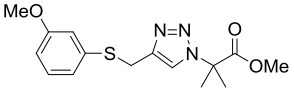
MS (ESI^+) m/z (%) 294 (M+H). HRMS calcd. for ($C_{13}H_{16}N_3O_3S$): 294.0912, found 294.0917.



1-Methoxycarbonyl-4-[3-(methoxy)phenoxymethyl]-1*H*-1,2,3-triazole (5). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl ether (4.34 mmol, 704 mg) and methyl azidoacetate (4.34 mg, 500 mg). The crude product was purified by column chromatography (EtOAc:Hx 1:1) to provide 0.91 g (76 % yield) of **5** as a white solid. Mp 71-75 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.19 (t, J = 8.2 Hz, 1H), 6.74-6.46 (m, 3H), 5.23 (s, 2H), 5.18 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.4, 155.6, 154.2, 139.4, 124.8, 118.9, 101.8, 101.6, 96.1, 56.7, 50.0, 47.8, 45.5. IR (cm^{-1}): 3156, 1747, 1591, 1493, 1200, 1152, 1015, 815. MS (ESI^+) m/z (%) 278 (M+H). HRMS calcd. for ($C_{13}H_{16}N_3O_4$): 278.1141, found 278.1148.

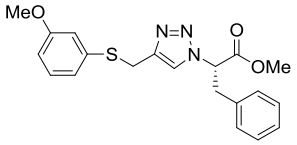


4-[3-(Chloro)phenylthiomethyl]-1-methoxycarbonylmethyl-1*H*-1,2,3-triazole (6). The general procedure **2.2** was followed starting from 3-clorophenyl propargyl sulfide (3.00 mmol, 535 mg) and methyl azidoacetate (3.00 mmol, 345 mg). The crude product was purified by column chromatography (EtOAc:Hx 1:3) to provide 0.71 g (79 % yield) of **6** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.34-7.10 (m, 4H), 5.12 (s, 2H), 4.26 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 145.2, 137.7, 134.8, 130.2, 129.0, 127.4, 126.7, 123.6, 53.2, 50.9, 28.7. IR (cm^{-1}): 3135, 1743, 1577, 1459, 1347, 1226, 774. MS (ESI^+) m/z (%) 298 (M+H). HRMS calcd. for ($C_{12}H_{13}N_3O_2SCl$): 298.0417, found 298.0416.

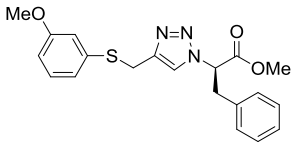


4-[3-(Methoxy)phenylthiomethyl]-1-(1-methyl-1-methoxycarbonylethyl)-1*H*-1,2,3-triazole (7). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl sulfide (2.00 mmol, 356 mg) and methyl 2-azido-2-methylpropanoate (2.00 mmol, 286 mg). The crude product was purified by column chromatography (EtOAc:Hx 2:6) to

provide 290 mg (45 % yield) of **7** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.11 (t, J = 7.7 Hz, 1H), 6.95-6.75 (m, 2H), 6.67 (d, J = 7.6 Hz, 1H), 4.17 (s, 2H), 3.69 (s, 3H), 3.62 (s, 3H), 1.82 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 159.9, 144.4, 136.9, 129.8, 121.8, 121.2, 114.9, 112.4, 64.4, 55.3, 53.2, 28.9, 25.7. IR (cm^{-1}): 2953, 1743, 1588, 1575, 1282, 1190, 1153, 1041. MS (ESI^+) m/z (%) 322 (M+H). HRMS calcd. for ($C_{15}H_{20}N_3O_3S$): 322.1225, found 322.1222.

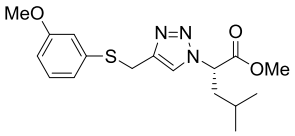


(*S*)-1-(1-Methoxycarbonyl-2-phenylethyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (8). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl sulfide (3.60 mmol, 642 mg) and methyl (*S*)-2-azido-3-phenylpropanoate (3.60 mmol, 740 mg). The crude product was purified by column chromatography (EtOAc:Hx 3:7) to provide 1.24 g (89 % yield) of **8** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.27-6.62 (m, 9H), 5.50 (dd, J = 8.5, 6.2 Hz, 1H), 4.12 (q, J = 14.9 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 3.46 (dd, J = 14.0, 5.8 Hz, 1H), 3.36 (dd, J = 13.9, 9.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 159.9, 145.1, 136.8, 134.7, 129.9, 128.9, 127.6, 122.4, 121.5, 114.5, 112.5, 64.3, 55.4, 53.2, 38.9, 28.7. IR (cm^{-1}): 2952, 2836, 1744, 1228, 1172. MS (ESI^+) m/z (%) 384 (M+H). HRMS calcd. for ($C_{20}H_{22}N_3O_3S$): 384.1382, found 384.1382. [α] = -56.11 (*c* 1.01, CH_2Cl_2).

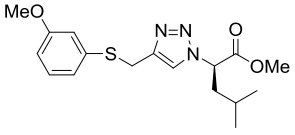


(*R*)-1-(1-Methoxycarbonyl-2-phenylethyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (9). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl sulfide (2.00 mmol, 384 mg) and methyl (*R*)-2-azido-3-phenylpropanoate (2.00 mmol, 358 mg). The crude product was purified by column chromatography (EtOAc:Hx 3:7) to provide 653 mg (85 % yield) of **9** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.27-6.62 (m, 9H), 5.50 (dd, J = 8.5, 6.2 Hz, 1H), 4.12 (q, J = 14.9 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 3.46 (dd, J = 14.0, 5.8 Hz, 1H), 3.36 (dd, J = 13.9, 9.2 Hz, 1H). ^{13}C NMR

(101 MHz, $CDCl_3$): δ 168.6, 159.9, 145.1, 136.8, 134.7, 129.9, 128.9, 127.6, 122.4, 121.5, 114.5, 112.5, 64.3, 55.4, 53.2, 38.9, 28.7. IR (cm^{-1}): 2952, 2836, 1744, 1228, 1172. MS (ESI^+) m/z (%) 384 (M+H). HRMS calcd. for ($C_{20}H_{22}N_3O_3S$): 384.1382, found 384.1382. [α] = +39.38 (*c* 2.71, CH_2Cl_2).

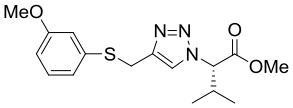


(*S*)-1-(1-Methoxycarbonyl-3-methyl-butyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (10). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl sulfide (2.00 mmol, 384 mg) and methyl (*S*)-2-azido-4-methylpentanoate (2.00 mmol, 342 mg). The crude product was purified by column chromatography (EtOAc:Hx 1:3) to provide 678 mg (97 % yield) of **10** as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.87 (s, 1H), 6.72 (dd, *J* = 8.2, 1.8 Hz, 1H), 5.38 (t, *J* = 8.0 Hz, 1H), 4.24 (q, *J* = 14.8 Hz, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 1.94 (t, *J* = 7.5 Hz, 2H), 1.19 (dt, *J* = 13.4, 6.7 Hz, 1H), 0.90 (d, *J* =6.5 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8, 159.9, 145.3, 136.6, 129.8, 122.1, 115.1, 112.7, 61.1, 55.3, 53.1, 41.4, 29.1, 24.7, 22.7, 21.3. IR (cm^{-1}): 2940, 2550, 1726, 1570, 1329, 967, 775, 550. MS (ESI^+) m/z (%) 350 (M+H). HRMS calcd. for ($C_{17}H_{24}N_3O_3S$): 350.1538, found 350.1550. [α] = +10.67 (*c* 1.00, CH_2Cl_2).

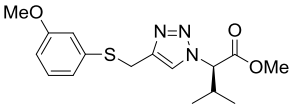


(*R*)-1-(1-Methoxycarbonyl-3-methyl-butyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (11). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl sulfide (4.50 mmol, 810 mg) and methyl (*R*)-2-azido-4-methylpentanoate (4.50 mmol, 793 mg). The crude product was purified by column chromatography (EtOAc:Hx 1:3) to provide 1.45 g (93 % yield) of **11** as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.87 (s, 1H), 6.72 (dd, *J* = 8.2, 1.8 Hz, 1H), 5.38 (t, *J* = 8.0 Hz, 1H), 4.24 (q, *J* = 14.8 Hz, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 1.94 (t, *J* = 7.5 Hz, 2H), 1.19 (dt, *J* = 13.4, 6.7 Hz, 1H), 0.90 (d, *J* =6.5 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8, 159.9, 145.3, 136.6, 129.8, 122.1, 115.1, 112.7,

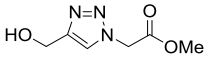
61.1, 55.3, 53.1, 41.4, 29.1, 24.7, 22.7, 21.3. IR (cm^{-1}): 2940, 2550, 1726, 1570, 1329, 967, 775, 550. MS (ESI^+) m/z (%) 350 (M+H). HRMS calcd. for ($C_{17}H_{24}N_3O_3S$): 350.1538, found 350.1550. [α] = -12.09 (*c* 1.03, CH_2Cl_2).



(*S*)-1-(1-Methoxycarbonyl-2-methyl-propyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (12). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl sulfide (4.70 mmol, 840 mg) and methyl (*S*)-2-azido-3-methylbutanoate (4.67 mmol, 734 mg). The crude product was purified by column chromatography (EtOAc:Hx 2:8) to provide 1.44 g (92 % yield) of **12** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.72 (d, *J* = 6.8, 1H), 5.06 (d, *J* = 8.7 Hz, 1H), 4.24 (q, *J* = 14.7 Hz, 2H), 3.76 (s, 6H), 2.44-2.30 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 159.6, 144.7, 136.3, 129.5, 121.9, 115.0, 112.3, 68.5, 55.0, 52.5, 32.0, 28.8, 18.9, 18.1. IR (cm^{-1}): 2940, 1865, 1501, 1365, 1210, 1020, 754. MS (ESI^+) m/z (%) 336 (M+H). HRMS calcd. for ($C_{16}H_{22}N_3O_3S$): 336.1382, found 336.1388. [α] = +21.49 (*c* 1.03, CH_2Cl_2).



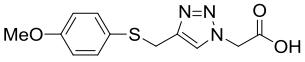
(*R*)-1-(1-Methoxycarbonyl-2-methyl-propyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (13). The general procedure **2.2** was followed starting from 3-methoxyphenyl propargyl sulfide (4.67 mmol, 832 mg) and methyl (*R*)-2-azido-3-methylbutanoate (4.67 mmol, 734 mg). The crude product was purified by column chromatography (EtOAc:Hx 2:8) to provide 1.45 g (93 % yield) of **13** as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.72 (d, *J* = 6.8, 1H), 5.06 (d, *J* = 8.7 Hz, 1H), 4.24 (q, *J* = 14.7 Hz, 2H), 3.76 (s, 6H), 2.44-2.30 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 159.6, 144.7, 136.3, 129.5, 121.9, 115.0, 112.3, 68.5, 55.0, 52.5, 32.0, 28.8, 18.8, 18.1. IR (cm^{-1}): 2940, 1865, 1501, 1365, 1210, 1020, 754. MS (ESI^+) m/z (%) 336 (M+H). HRMS calcd. for ($C_{16}H_{22}N_3O_3S$): 336.1382, found 336.1388. [α] = -19.47 (*c* 1.06, CH_2Cl_2).



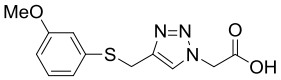
4-Hydroxymethyl-1-methoxycarbonylmethyl-1*H*-1,2,3-triazole (30).[131a] The reaction was carried out under nitrogen atmosphere in a flame-dried flask, with magnetical stirring. Propargyl alcohol (2.00 mmol, 112 mg), methyl azidoacetate (2.00 mmol, 230 mg) and CuI (2.00 mmol, 381 mg) were suspended in MeCN (10 mL). DIPEA (6.00 mmol, 1.04 mL) was added and the reaction mixture was stirred at room temperature for 5 h. The mixture was filtered through a pad of celite and the filtrate was dried with magnesium sulfate and evaporated under reduced pressure to provide 147 mg (86 % yield) of **30** as a yellow oil. ^{1}H NMR (500 MHz, MeOH-d_4): δ 7.95 (s, 1H), 5.33 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H).

2.3 General procedure for the synthesis of 1-(carboxyalkyl)-1*H*-1,2,3-triazoles

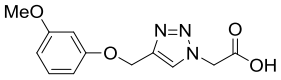
To a solution of the corresponding triazolic methyl ester (1.00 mmol) in THF/H_2O (1:1, 8 mL), LiOH·H_2O (2.00 mmol, 82 mg) was added and the mixture was stirred at room temperature for 1h. The solvent was evaporated, the resulting solution was acidified with 1M HCl, and it was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude products were purified by crystallization in a mixture of EtOAc:Hx.



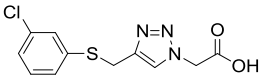
1-Carboxymethyl-4-[4-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (14). The general procedure **2.3** was followed starting from 1-methoxycarbonylmethyl-4-[4-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (1.70 mmol, 500 mg) to provide 0.42 g (88 % yield) of **14** as a white solid. Mp 168-170 ºC. ^{1}H NMR (500 MHz, MeOH-d_4): δ 7.66 (s, 1H), 7.28 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.19 (s, 2H), 4.07 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, MeOH-d_4): δ 169.7, 161.1, 146.3, 135.6, 126.3, 125.9, 115.7, 55.8, 51.6, 31.5. IR (cm^{-1}): 2923, 2848, 1730, 1223, 1188. MS (ESI^{+}) m/z (%) 280 (M+H). HRMS calcd. for ($C_{12}H_{14}N_3O_3S$): 280.0756, found 280.0760.



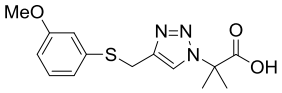
1-Carboxymethyl-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (15). The general procedure **2.3** was followed starting from 1-methoxycarbonylmethyl-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (2.22 mmol, 652 mg) to provide 0.58 g (94 % yield) of **15** as a white solid. Mp 118-119 ºC. ^{1}H NMR (500 MHz, MeOH-d_4): δ 7.80 (s, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.96-6.86 (m, 2H), 6.79-6.70 (m, 1H), 5.19 (s, 2H), 4.23 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, MeOH-d_4): δ 169.7, 161.4, 146.1, 138.0, 130.9, 125.9, 123.1, 116.1, 113.6, 55.7, 51.7, 29.3. IR (cm^{-1}): 2999, 2971, 1707, 1229. MS (ESI$^+$) m/z (%) 280 (M+H). HRMS calcd. for ($C_{12}H_{14}N_3O_3S$): 280.0756, found 280.0753.



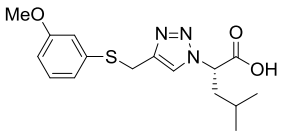
1-Carboxymethyl-4-[3-(methoxy)phenoxymethyl]-1*H*-1,2,3-triazole (16). The general procedure **2.3** was followed starting from 1-methoxycarbonylmethyl-4-[3-(methoxy)phenoxy methyl]-1*H*-1,2,3-triazole (1.90 mmol, 530 mg) to provide 0.35 g (70 % yield) of **16** as a white solid. Mp 108-110 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.20 (t, J = 8.5 Hz, 1H), 6.66-6.42 (m, 3H), 5.23 (s, 2H), 5.08 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 165.7, 164.6, 147.6, 135.2, 131.3, 112.1, 111.8, 106.2, 66.3, 60.3, 56.6. IR (cm^{-1}): 3411, 3184, 1666, 1589, 1491, 1415, 1196, 1152, 1040, 830. MS (ESI$^+$) m/z (%) 264 (M+H). HRMS calcd. for ($C_{12}H_{14}N_3O_4$): 264.0984, found 264.0980.



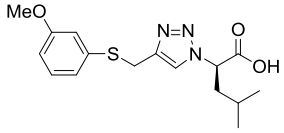
1-Carboxymethyl-4-[3-(chloro)phenylthiomethyl]-1*H*-1,2,3-triazole (17). The general procedure **2.3** was followed starting from 1-methoxycarbonylmethyl-4-[3-(chloro)phenylthiomethyl]-1*H*-1,2,3-triazole (0.53 mmol, 157 mg) to provide 0.19 g (67 % yield) of **17** as a white solid. Mp 146-148 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.38 (s, 1H), 7.27 (d, J = 6.8 Hz, 2H), 7.21 (d, J = 1.9 Hz, 1H), 5.22 (s, 2H), 4.28 (s, 2H). ^{13}C NMR (126 MHz, MeOH-d_4): δ 168.4, 144.2, 137.9, 134.4, 130.0, 128.8, 127.6, 126.3, 124.7, 50.4, 27.7. IR (cm^{-1}): 2928, 2850, 1731, 1224, 1184. MS (ESI$^+$) m/z (%) 284 (M+H). HRMS calcd. for ($C_{11}H_{10}ClN_3O_2S$): 284,0182, found 284,0190.



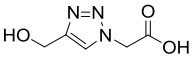
1-(1-Carboxy-1-methylethyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (18). The general procedure **2.3** was followed starting from 1-(1-methoxycarbonyl-1-methylethyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (0.45 mmol, 145 mg) to provide 138 mg (99 % yield) of **18** as a brown solid. Mp 119-121 ºC. ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.77 (s, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.90-6.73 (m, 2H), 6.67 (d, J = 7.7 Hz, 1H), 4.12 (s, 2H), 3.65 (s, 3H), 1.78 (s, 6H). ^{13}C NMR (101 MHz, MeOH-d_4): δ 174.2, 161.3, 145.3, 137.9, 130.8, 123.4, 116.5, 113.7, 65.9, 55.7, 29.5, 25.9. IR (cm^{-1}): 2931, 1589, 1573, 1283, 1229, 1178, 1030. MS (ESI$^+$) m/z (%) 308 (M+H). HRMS calcd. for ($C_{14}H_{18}N_3O_3S$): 308.1069, found 308.1074.



(*S*)-1-(1-Carboxy-3-methylbutyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (21). The general procedure **2.3** was followed starting from methyl (*S*)-1-(1-methoxycarbonyl-3-methylbutyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (1.44 mmol, 501 mg) to provide 0.36 g (77 % yield) of **21** as a white solid. Mp 103-105 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.88 (s, 1H), 7.54 (s, 1H), 7.12 (t, J = 7.9 Hz, 1H), 6.95-6.77 (m, 2H), 6.75-6.62 (m, 1H), 5.38 (dd, J = 10.7, 5.0 Hz, 1H), 4.35-4.15 (m, 2H), 3.70 (s, 3H), 2.33-1.75 (m, 2H), 1.17 (dq, J = 13.2, 6.5 Hz, 1H), 0.88 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 159.8, 144.7, 136.0, 129.8, 122.6, 122.4, 115.6, 112.9, 61.8, 55.3, 41.2, 28.5, 24.7, 22.7, 21.1. IR (cm^{-1}): 2958, 2513, 1726, 1588, 1478, 1229, 1037, 773, 685. MS (ESI$^+$) m/z (%) 336 (M+H). HRMS calcd. for ($C_{16}H_{22}N_3O_3S$): 336.1382, found 336.1389. [α] = +9.31 (*c* 1.11, CH_2Cl_2).



(*R*)-1-(1-Carboxy-3-methylbutyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (22). The general procedure **2.3** was followed starting from methyl (*R*)-1-(1-methoxycarbonyl-3-methylbutyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (1.00 mmol, 349 mg) to provide 301 mg (86 % yield) of **22** as a white solid. Mp 102-104 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.88 (s, 1H), 7.54 (s, 1H), 7.12 (t, J = 7.9 Hz, 1H), 6.95-6.77 (m, 2H), 6.75-6.62 (m, 1H), 5.38 (dd, J = 10.7, 5.0 Hz, 1H), 4.35-4.15 (m, 2H), 3.70 (s, 3H), 2.33-1.75 (m, 2H), 1.17 (dq, J = 13.2, 6.5 Hz, 1H), 0.88 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 159.8, 144.7, 136.0, 129.8, 122.6, 122.4, 115.6, 112.9, 61.8, 55.3, 41.2, 28.5, 24.7, 22.7, 21.1. IR (cm^{-1}): 2958, 2513, 1726, 1588, 1478, 1229, 1037, 773, 685. MS (ESI^+) m/z (%) 336 (M+H). HRMS calcd. for ($C_{16}H_{22}N_3O_3S$): 336.1382, found 336.1389. [α] = -12.06 (*c* 0.95, CH_2Cl_2).

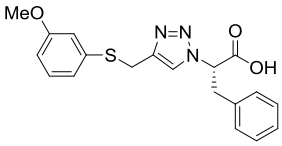


1-Carboxymethyl-4-hydroxymethyl-1*H*-1,2,3-triazole (31).[131b] The general procedure **2.3** was followed starting from 4-(hydroxymethyl)-1-methoxycarbonyl methyl-1*H*-1,2,3-triazol-1-yl) acetate (1.00 mmol, 171 mg) to provide 143 mg (99 % yield) of **31** as a white solid. ^{1}H NMR (500 MHz, MeOH-d_4): δ 8.05 (s, 1H), 5.32 (s, 2H), 4.73 (s, 2H).

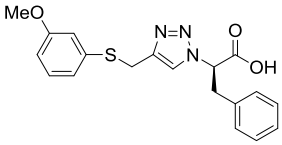
2.3.1 Synthesis of chiral 1*H*-1,2,3-triazoles.

To a solution of the corresponding α-aminoacid (1.00 mmol) in H_2O/MeOH (1:2, 9 mL), $KHCO_3$ (1.50 mmol, 197 mg) and $CuSO_4 \cdot 5H_2O$ (1 mol %, 2.5 mg) were added, followed by dropwise addition of freshly prepared TfN_3 (3.00 mmol) in CH_2Cl_2 (see page 68). The mixture was stirred at room temperature for 3 h. Then, the alkyne (1.2 mmol), CuOAc (5 mol %, 6 mg), NaOAc (5.00 mmol, 410 mg) and Na Ascorbate (1.00 mmol, 200 mg) were added to the reaction mixture and the solution was stirred at 45 ºC for 3h. The solvent was evaporated, the resulting mixture was basified with Na_2CO_3, and the aqueous solution was extracted with EtOAc (2 x 10 mL). The aqueous phase was acidified with HCl 3M and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over

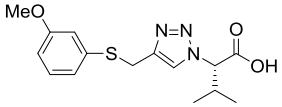
Na_2SO_4 and the solvents were evaporated under reduced pressure. The crude product was purified by crystallization in a mixture of CH_2Cl_2:Et_2O.



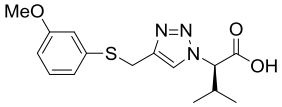
(*S*)-1-(1-Carboxy-2-phenylethyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (19). The general procedure **2.3.1.** was followed starting from L-phenylalanine (1.00 mmol, 165 mg) and 3-methoxyphenyl propargyl sulfide (1.20 mmol, 213 mg) to provide 270 mg (73 % yield) of **19** as a white solid. Mp 81-83 ºC. ^{1}H-NMR (500 MHz, MeOH-d_4): δ 7.77 (s, 1H), 7.20-6.71 (m, 9H), 5.56 (dd, J = 10.8, 4.6 Hz, 1H), 4.15 (s, 2H), 3.73 (s, 3H), 3.56 (dd, J = 14.3, 4.5 Hz, 1H), 3.40 (dd, J = 14.3, 10.9 Hz, 1H). ^{13}C NMR (126 MHz, MeOH-d_4): δ 171.1, 161.4, 145.9, 138.0, 137.2, 130.9, 129.9, 129.6, 128.1, 124.8, 122.9, 115.9, 113.5, 65.8, 55.7, 39.0, 29.1. IR (cm^{-1}): 2931, 1727, 1246, 1229. MS (ESI$^+$) m/z (%) 384 (M+H). HRMS calcd. for ($C_{19}H_{20}N_3O_3S$): 370.1147, found 370.1145. [α] = -23.31 (*c* 1.12, CH_2Cl_2).



(*R*)-1-(1-Carboxy-2-phenylethyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (20). The general procedure **2.3.1** was followed starting from D-phenylalanine (1.00 mmol, 165 mg) and 3-methoxyphenyl propargyl sulfide (1.20 mmol, 213 mg) to provide 280 mg (76 % yield) of **20** as a white solid. Mp 85-86 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.11 (s, 1H), 7.49 (s, 1H), 7.14 (d, J = 7.4 Hz, 4H), 6.89 (d, J = 6.6 Hz, 2H), 6.82 (d, J = 6.7 Hz, 2H), 6.72 (d, J = 7.4 Hz, 1H), 5.53 (dd, J = 9.4, 4.8 Hz, 1H), 4.31-4.08 (m, 2H), 3.70 (s, 3H), 3.52 (dd, J = 14.3, 4.6 Hz, 1H), 3.36 (dd, J = 14.1, 9.8 Hz, 1H). ^{13}C NMR (126 MHz, MeOH-d_4): δ 171.1, 161.4, 145.9, 138.0, 137.2, 130.9, 129.9, 129.6, 128.1, 124.8, 122.9, 115.9, 113.5, 65.8, 55.7, 39.0, 29.1. IR (cm^{-1}): 2930, 1727, 1246, 1230. MS (ESI$^+$) m/z (%) 384 (M+H). HRMS calcd. for ($C_{19}H_{20}N_3O_3S$): 370.1147, found 370.1145. [α] = +16.50 (*c* 0.98, CH_2Cl_2).

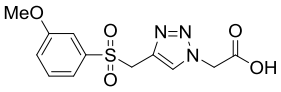


(*S*)-1-(1-Carboxy-3-methylpropyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (23). The general procedure **2.3.1** was followed starting from L-valine (1.00 mmol, 117 mg) and 3-methoxyphenyl propargyl sulfide (1.20 mmol, 213 mg) to provide 210 mg (65 % yield) of **23** as a white solid. Mp 119-121 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.53 (s, 1H), 7.68 (s, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.91-6.80 (m, 2H), 6.70 (d, J = 6.8 Hz, 1H), 5.13 (d, J = 7.6 Hz, 1H), 4.38-4.15 (m, 2H), 3.71 (s, 3H), 2.59-2.28 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H), 0.75 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.7, 159.9, 144.6, 136.1, 129.9, 123.0, 122.8, 115.8, 113.0, 69.3, 55.4, 32.2, 28.7, 19.3, 18.3. IR (cm^{-1}): 2966, 2461, 1907, 1591, 1573, 1479, 1281, 1228, 1206, 1037, 783, 721, 687. MS (ESI^{+}) m/z (%) 336 (M+H). HRMS calcd. for ($C_{15}H_{20}N_3O_3S$): 332.1227, found 332.1225. [α] = +4.52 (*c* 1.06, CH_2Cl_2).



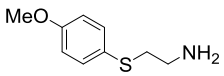
(*R*)-1-(1-Carboxy-3-methylpropyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (24). The general procedure **2.3.1.** was followed starting from D-valine (1.00 mmol, 117 mg) and 3-methoxyphenyl propargyl sulfide (1.20 mmol, 213 mg) to provide 220 mg (69 % yield) of **24** as a white solid. Mp 120-123 ºC. ^{1}H NMR (500 MHz, MeOH-d_4): δ 7.81 (s, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.03-6.82 (m, 2H), 6.82-6.66 (m, 1H), 5.06 (d, J = 8.1 Hz, 1H), 4.22 (s, 2H), 3.73 (s, 3H), 2.46 (dt, J = 13.5, 6.7 Hz, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.7, 159.9, 144.6, 136.1, 129.9, 123.0, 122.8, 115.8, 113.0, 69.3, 55.4, 32.2, 28.7, 19.3, 18.3. IR (cm^{-1}): 2966, 2461, 1907, 1591, 1573, 1479, 1281, 1228, 1206, 1037, 783, 721, 687. MS (ESI^{+}) m/z (%) 336 (M+H). HRMS calcd. for ($C_{15}H_{20}N_3O_3S$): 332.1227, found 332.1225. [α] = -6.68 (*c* 1.01, CH_2Cl_2).

2.3.2 Synthesis of sulfonyl triazole

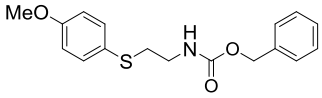


1-Carboxymethyl-4-[3-(methoxy)phenylsulfonylmethyl]-1*H*-1,2,3-triazole (25). To a solution of 1-(carboxymethyl)-4-[3-(methoxy)phenylthiomethyl]-1*H*-1,2,3-triazole (0.25 mmol, 70.7 mg) in a mixture of $CDCl_3$:MeCN (1:1, 1 mL), 3-chloroperbenzoic acid (0.63 mmol, 110 mg) was added. The reaction was stirred overnight at room temperature. The solvent was evaporated, and the product was purified by column chromatography DCM:MeOH (95:5) to provide 31 mg (40 % yield) of **25** as a white solid. Mp 113-115 ºC. ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.93 (s, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 7.4 Hz, 1H), 7.32-7.21 (m, 2H), 4.98 (s, 2H), 4.70 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, MeOH-d_4): δ 172.5, 161.4, 140.2, 136.5, 131.6, 128.2, 121.7, 121.5, 114.0, 56.3, 54.4, 54.0. IR (cm^{-1}): 2960, 2521, 1858, 1499, 1473, 1317, 1140, 1050, 780. MS (ESI$^+$) m/z (%) 312 (M+H). HRMS calcd. for ($C_{12}H_{14}N_3O_5S$): 312.0654, found 312.0662.

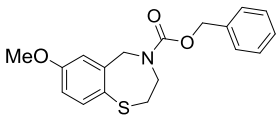
2.4 Synthesis of compound S107[115]



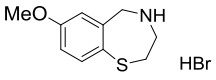
2-[(4-Methoxyphenyl)thio]ethan-1-amine (26).[115] 4-Methoxythiophenol (100.00 mmol, 14.00 g), 2-chloroethylamine monohydrochloride (96.00 mmol, 11.00 g) and diisopropyl ethylamine (0.05 mmol, 9.00 mL) were mixed in THF (55 mL), and after degasification the reaction was refluxed overnight under nitrogen. The solvent was evaporated, and water (85 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), and washed with a solution of NaOH 3M. The organic solution was dried over Na_2SO_4, and evaporated under reduced pressure to provide 16.8 g (95 % yield) of **26** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 2.88 (d, J = 5.8 Hz, 2H), 2.83 (d, J = 5.8 Hz, 2H).



Benzyl [2-(4-methoxyphenyl)thioethyl] carbamate (27).[115] To a flask containing 2-[(4-methoxyphenyl)thio]ethan-1-amine (92.00 mmol, 16.80 g), sodium bicarbonate (300.00 mmol, 25.00 g), water (200 mL) and CH_2Cl_2 (400 mL) were added. The mixture was cooled down to 0 ºC, and a solution of benzyl chloroformate (100.00 mmol, 14.00 mL) in dichloromethane (200 mL) was added dropwise. The mixture was stirred overnight at room temperature. The organic layer was collected and the aqueous solution was extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The resulting solid was triturated with 300 mL of THF/hexane (1:10), and then it was collected and dried to provide 26.2 g (90 % yield) of **27** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 9H), 6.84 (d, J = 8.2 Hz, 1H), 5.09 (s, 2H), 3.79 (s, 3H) 3.38-3.28 (m, 2H), 2.94 (t, J = 6.4 Hz, 2H).

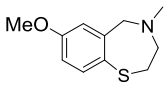


Benzyl 7-methoxy-2,3-dihydrobenzo[*f*][1,4]thiazepine-4(5*H*)-carboxylate (28).[115] A mixture of benzyl [2-(4-methoxyphenyl)thioethyl] carbamate (83.00 mmol, 26.20 g), paraformaldehyde (0.83 mmol, 25.00 g) and *p*-toluenesulfonic acid (27.00 mmol, 5.20 g) in toluene (600 mL) was stirred at 70 ºC overnight. After cooling to room temperature, it was filtered, and the resulting organic phase was cleaned with sat. sodium carbonate (200 mL), dried over anhydrous Na_2SO_4, and evaporated to provide 24.60 g (93 % yield) of **28** as an orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 8.3 Hz, 1H), 7.36-7.30 (m, 5H), 6.75-6.66 (m, 2H), 5.07 (d, J = 2.8 Hz, 2H), 4.58 (s, 2H), 3.57 (s, 3H), 2.78 (t, J = 4.9 Hz, 2H), 2.72 (t, J = 4.9 Hz, 2H).



7-Methoxy-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine hydrobromide (29).[115] A solution of HBr (33 % in acetic acid, 60 mL) was added to benzyl 7-methoxy-2,3-dihydrobenzo[*f*][1,4] thiazepine-4(5*H*)-carboxylate. After the addition, carbon dioxide was

generated and a white solid formed. The resulting mixture was stirred for 2 h at room temperature. Then, diethyl ether (500 mL) was added to the mixture and stirred for 30 min. The resulting solid was collected by filtration, washed with diethyl ether and dried under vacuum to provide 18.00 g (85 % yield) of **29** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.26 (s, 1H), 6.94 (dd, J = 8.4, 3.0 Hz, 1H), 4.41 (s, 2H), 3.78 (s, 3H), 3.50 (s, 2H), 2.96 (s, 2H).



7-Methoxy-4-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (S-107).[115] To 7-methoxy-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine hydrobromide (65.00 mmol, 18.00 g) in MeOH (600 mL) a solution of 30 % CH_2O (100 mL), and sodium cyanoborohydride ($NaBH_3CN$) (450 mmol, 28.30 g) were added. The reaction mixture was stirred at room temperature, maintaining the pH of the solution at around pH 4-5 by addition of a few drops of 1N HCl. After 3 hours, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (300 mL) and washed with H_2O and saturated $NaHCO_3$ (2 x 200 mL). The solvent was removed and the product purified by column chromatography to provide 12.30 g (90 % yield) of **S-107** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 8.5, 2.8 Hz, 1H), 4.75 (d, J = 13.7 Hz, 1H), 4.39 (dd, J = 13.7, 4.9 Hz, 1H), 3.79 (s, 3H), 3.72-3.64 (m, 1H), 3.53 (d, J = 11.6 Hz, 1H), 3.11-2.87 (m, 2H), 2.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.2, 134.8, 134.2, 127.2, 119.1, 115.6, 76.8, 58.6, 57.5, 55.8, 27.2.

2.5 NMR study of the inclusion complexes of triazoles 15-24 and β-cyclodextrin (β-CD).

Stock 5mM solutions of each triazole **15-24** and β-cyclodextrin (β-CD) were prepared in D_2O (5 mL) by dissolving 28.4 mg (0.025 mmol) of β-CD and 0.025 mmol of the corresponding triazole. Next, 10 solutions of 0.5 mL total volume were prepared for each triazole in 10 NMR test tubes in order to reach the molar fractions collected in Table 2.6. $V_{\beta\text{-}CD}$ and V_{Trz} represent the volumes of β-CD and triazole mother solutions, respectively. The molar fraction of β-CD ($X_{\beta\text{-}CD}$) is given by the ratio:

$$X_{\beta CD} = \frac{V_{\beta CD}}{V_{\beta CD} + V_{Trz}}$$

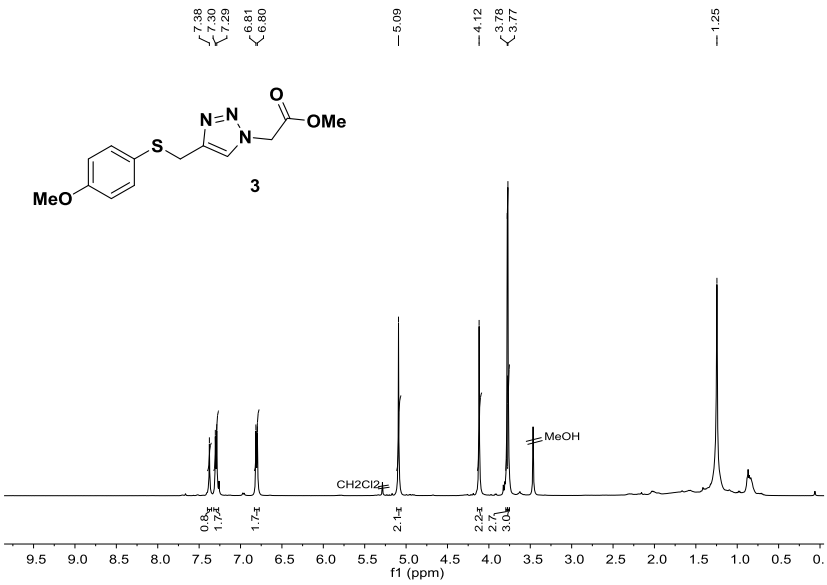
Table 2.6. Volume combinations of 5mM mother solutions of β-CD and triazoles **15-24** to get the different titration samples used in the NMR study.

Tube (nº)	1	2	3	4	5	6	7	8	9	10	11
$X_{\beta\text{-}CD}$	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
$V_{\beta\text{-}CD}$ (mL)	0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
V_{Trz} (mL)	0.5	0.45	0.4	0.35	0.3	0.25	0.2	0.15	0.1	0.05	0
X_{TRZ}	0	0.05	0.1	0.015	0.2	0.25	0.3	0.35	0.4	0.45	0.5

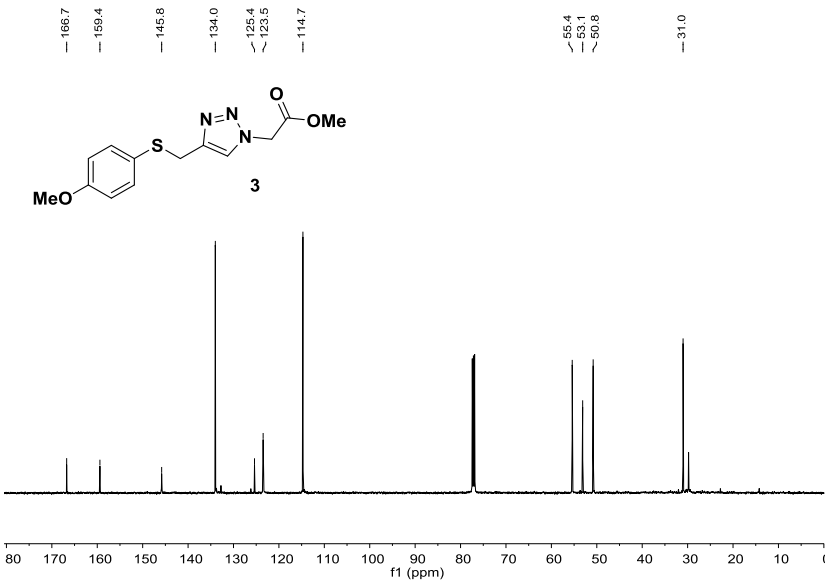
The ^{1}H-NMR spectra were registered at 500 MHz, in D_2O, and the association constants were determined with the method described by C. Jaime.[128]

Appendix

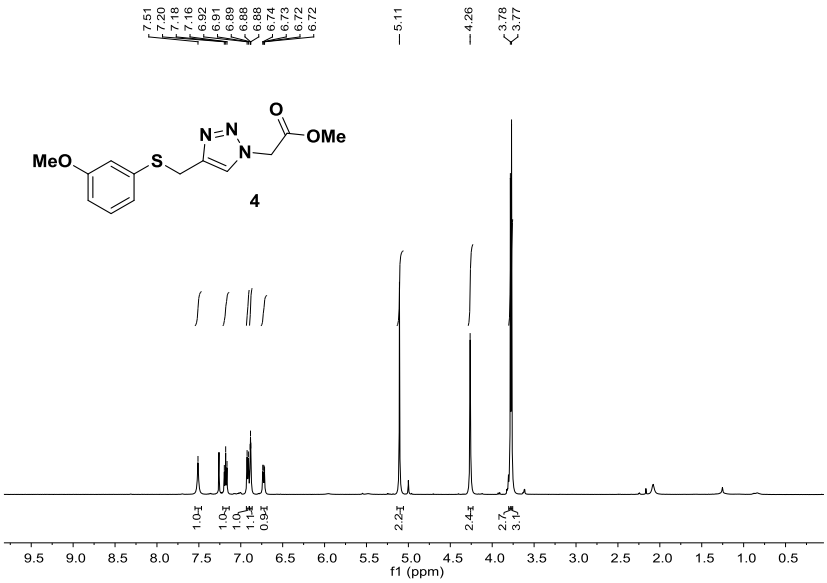
APPENDIX 1: ^{1}H NMR and ^{13}C NMR Spectra



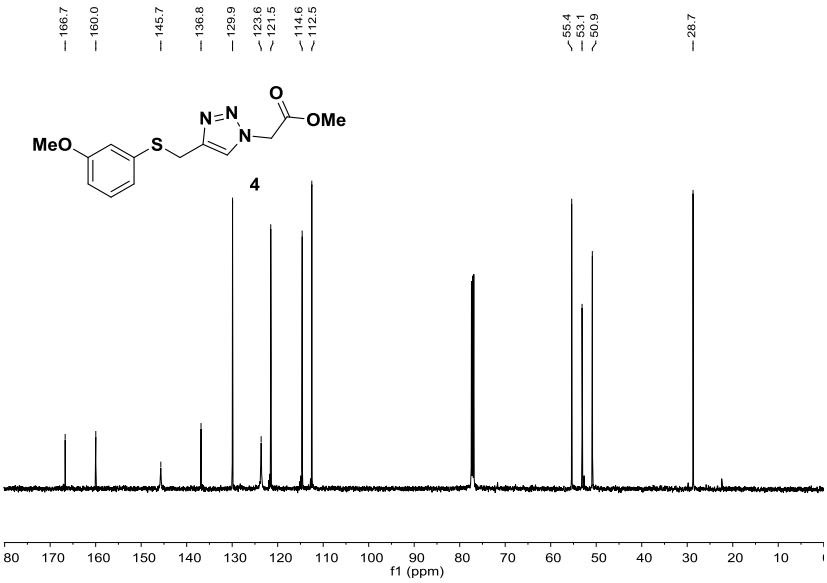
Spectrum 2.1. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3.**



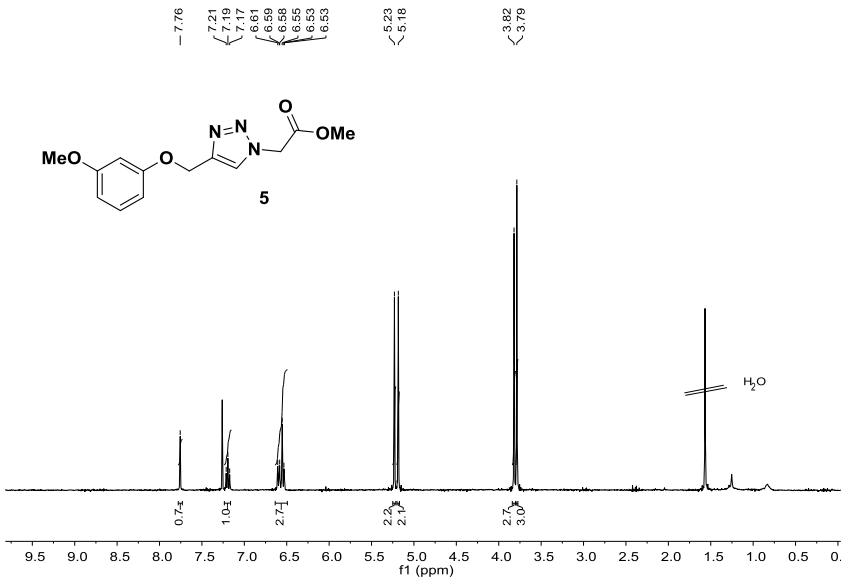
Spectrum 2.2. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **3**.



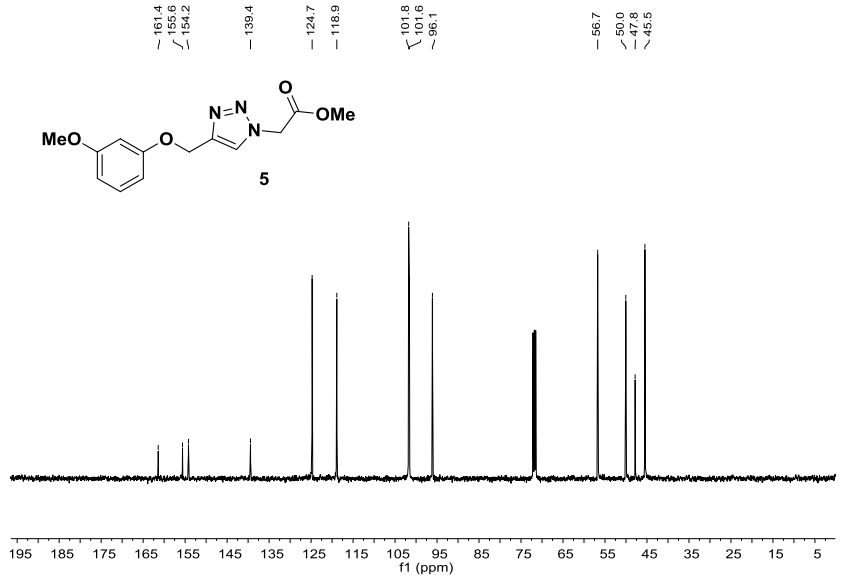
Spectrum 2.3. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4.**



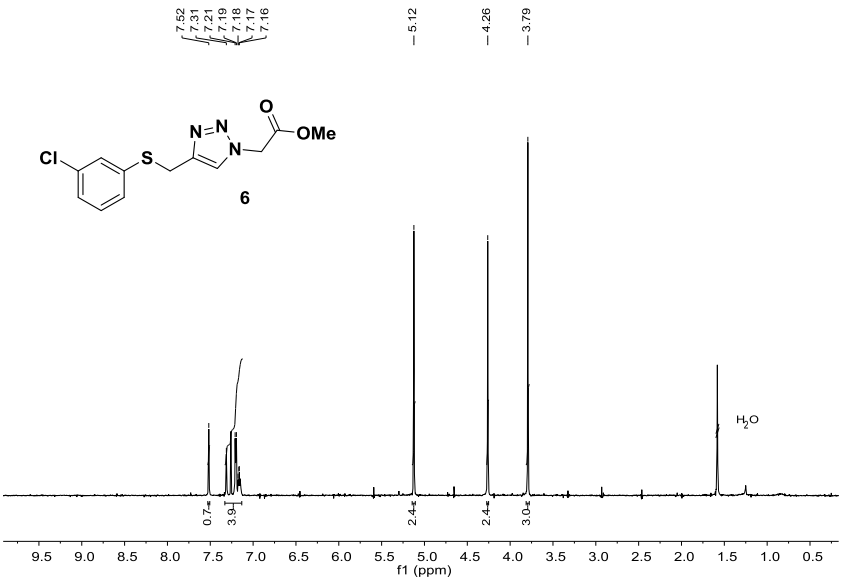
Spectrum 2.4. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **4**.



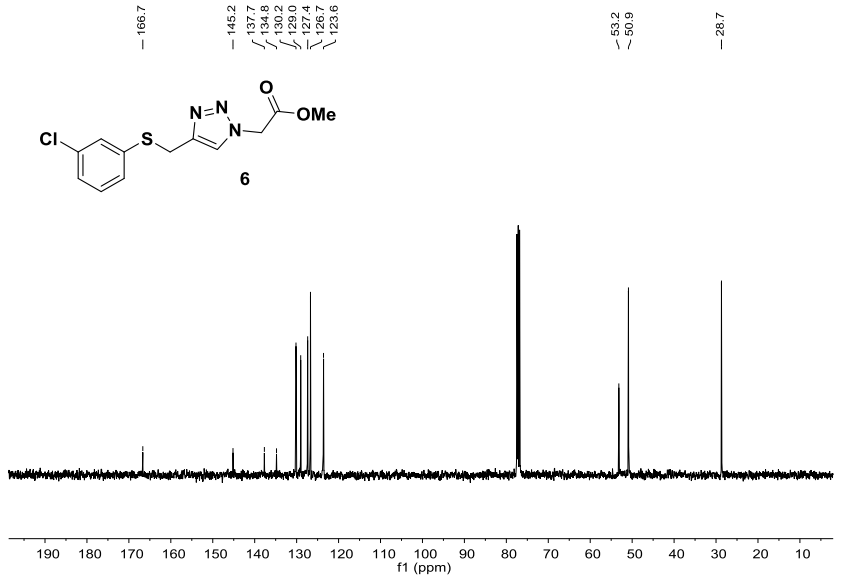
Spectrum 2.5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5.**



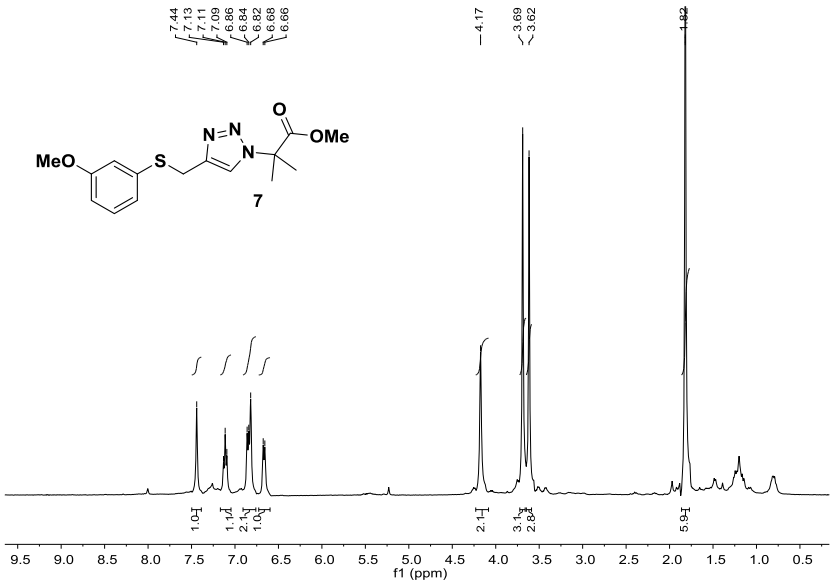
Spectrum 2.6. ^{13}C NMR (101 MHz, DMSO-d_6) spectrum of compound **5.**



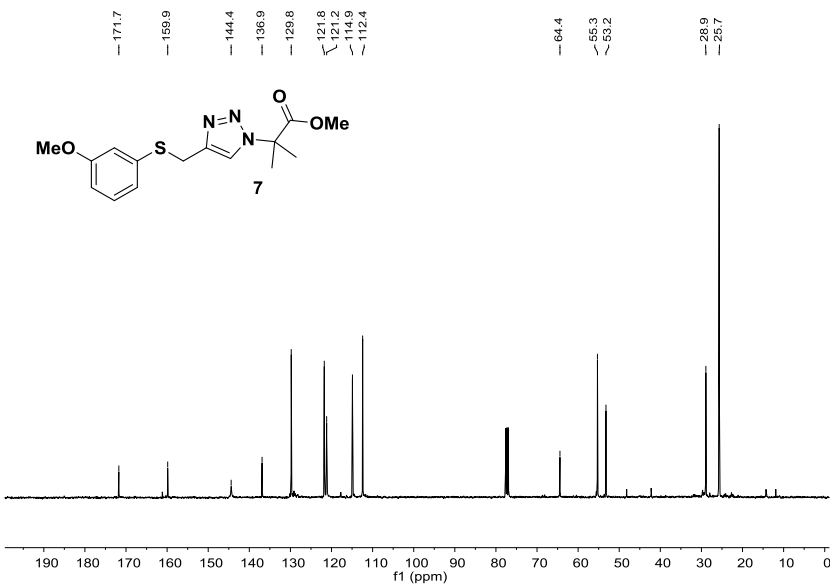
Spectrum 2.7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6.**



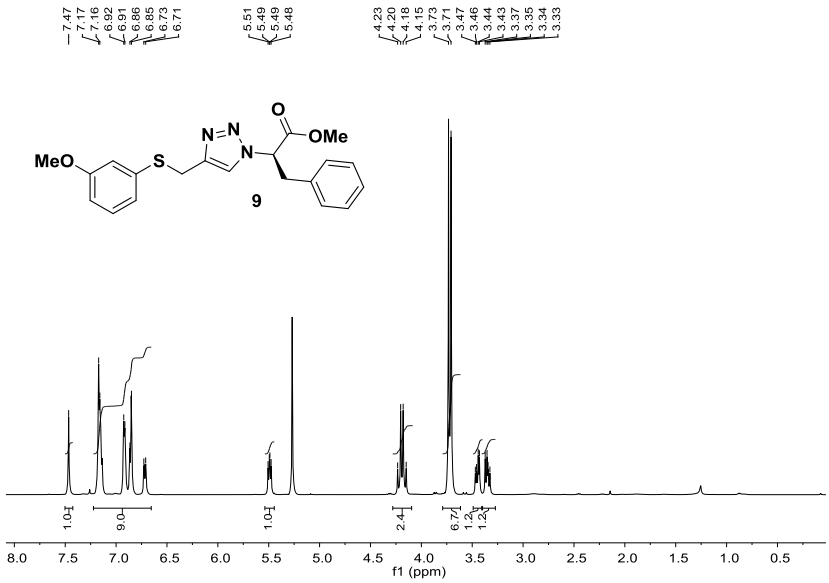
Spectrum 2.8. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **6**.



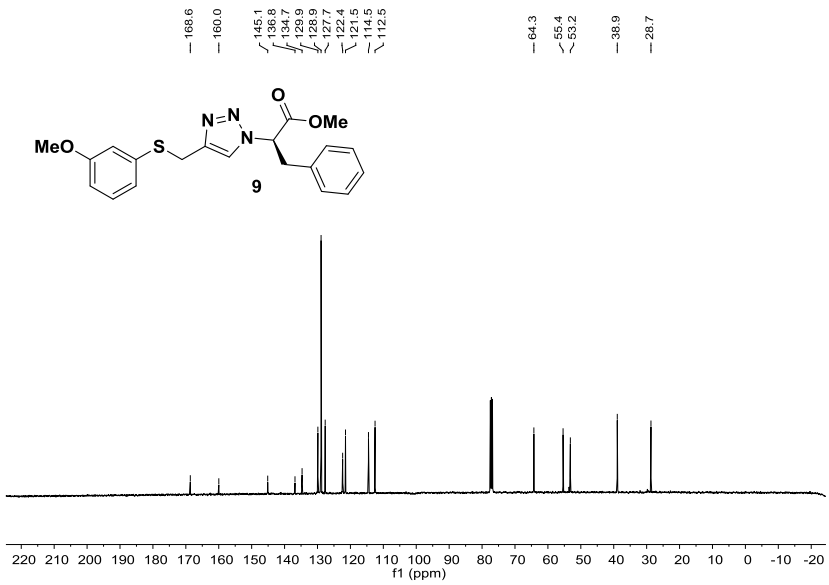
Spectrum 2.9. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **7.**



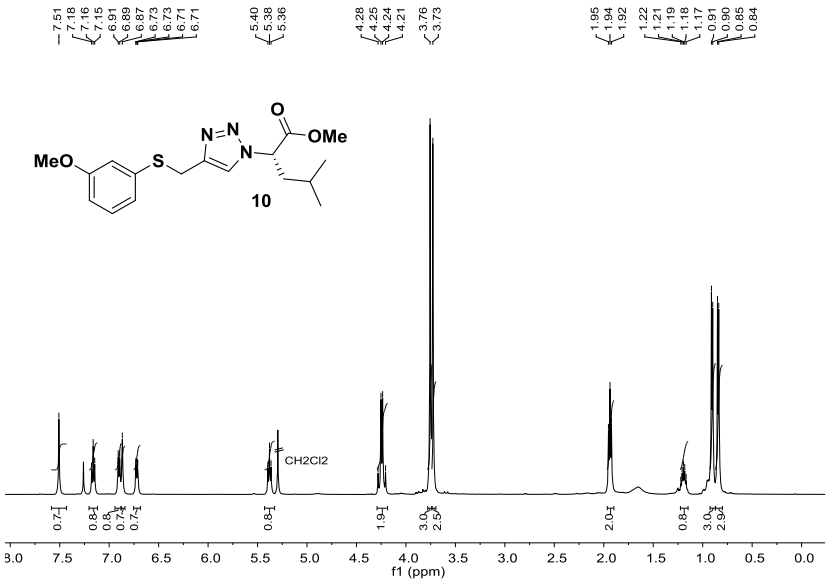
Spectrum 2.10. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **7.**



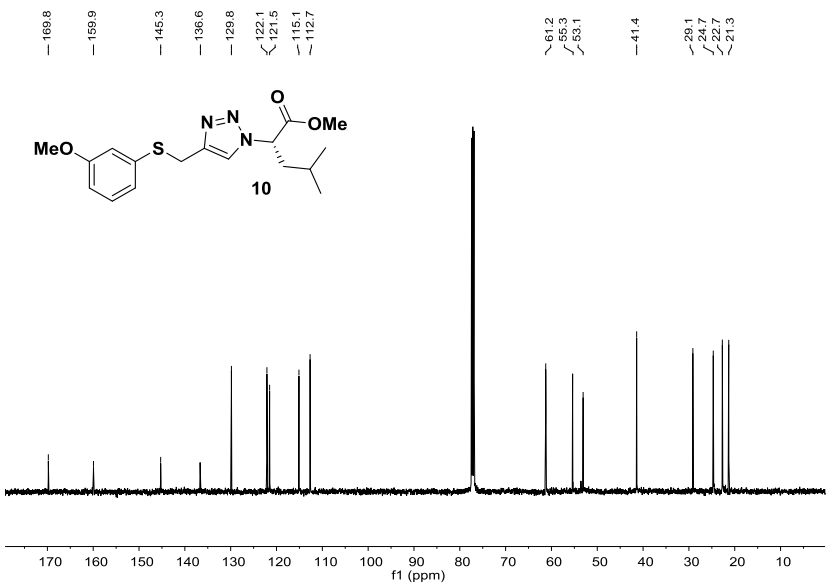
Spectrum 2.11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9.**



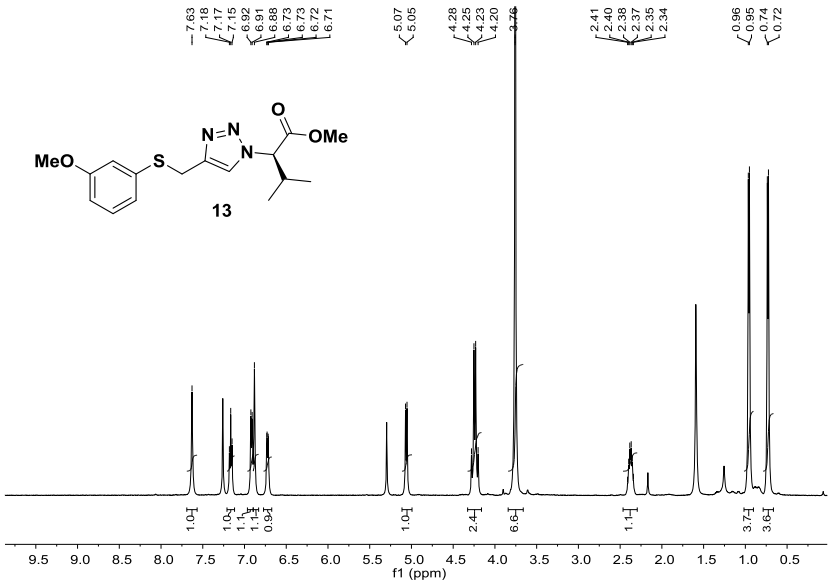
Spectrum 2.12. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9**.



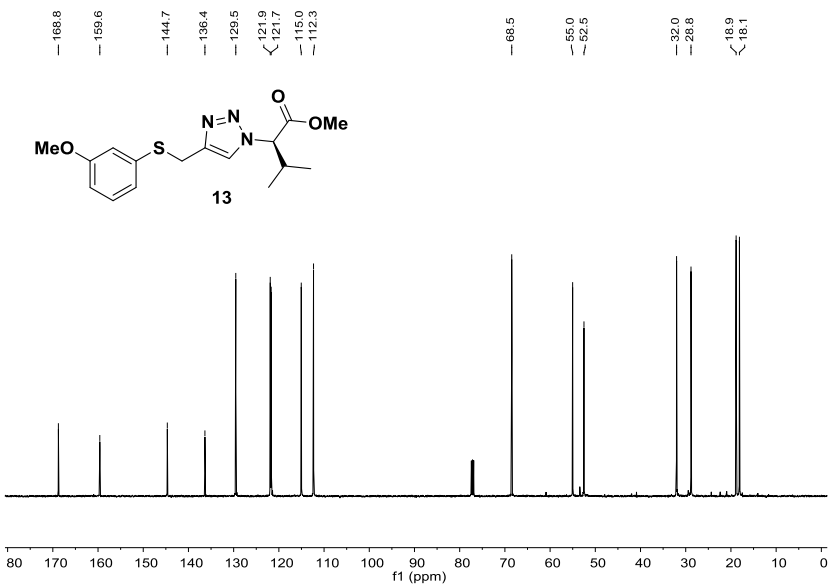
Spectrum 2.13. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **10.**



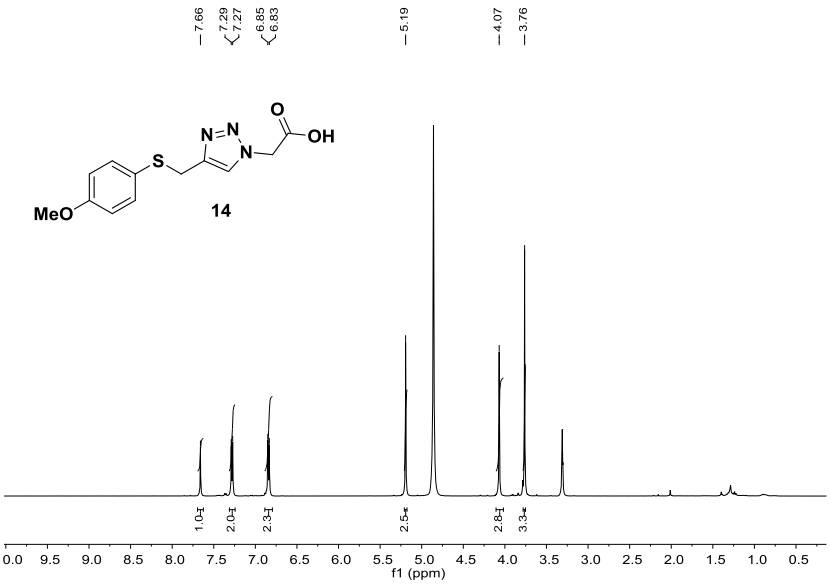
Spectrum 2.14. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **10**.



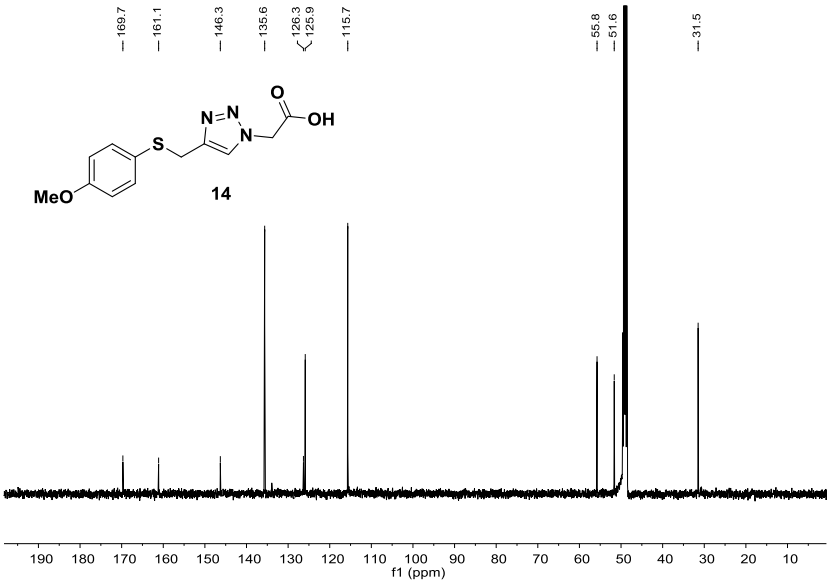
Spectrum 2.15. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **13.**



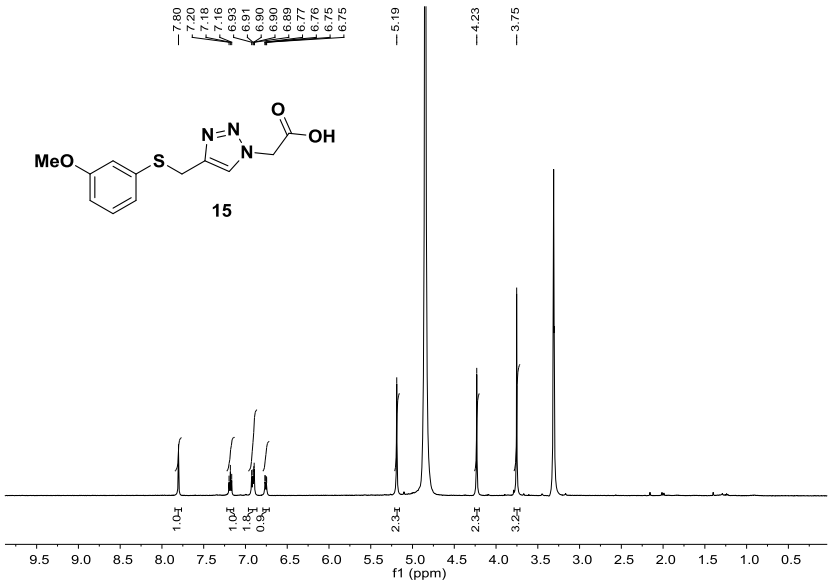
Spectrum 2.16. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **13.**



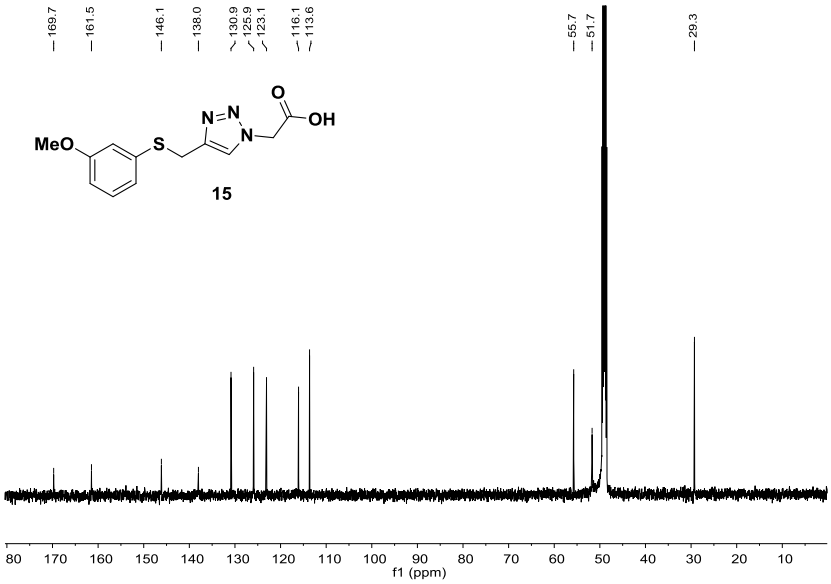
Spectrum 2.17. ^{1}H NMR (500 MHz, MeOH-d_4) spectrum of compound **14.**



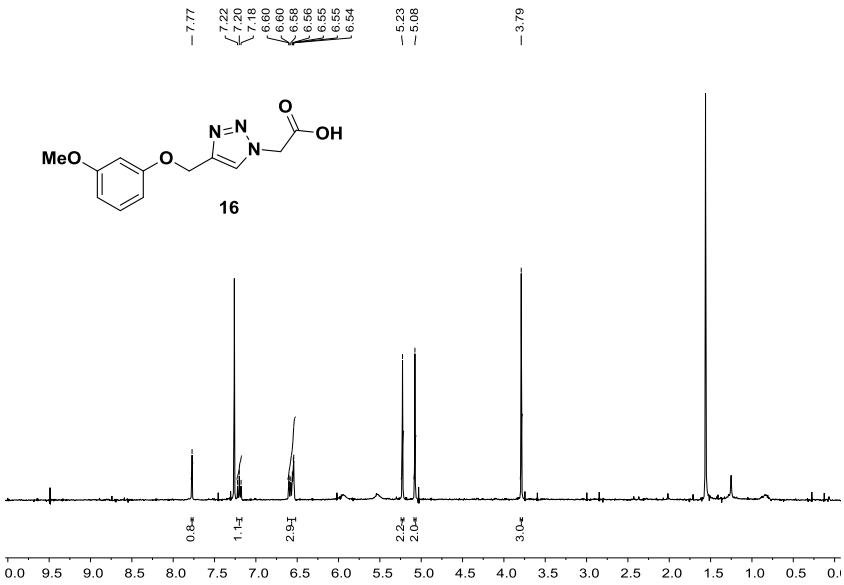
Spectrum 2.18. ^{13}C NMR (126 MHz, MeOH-d_4) spectrum of compound **14.**



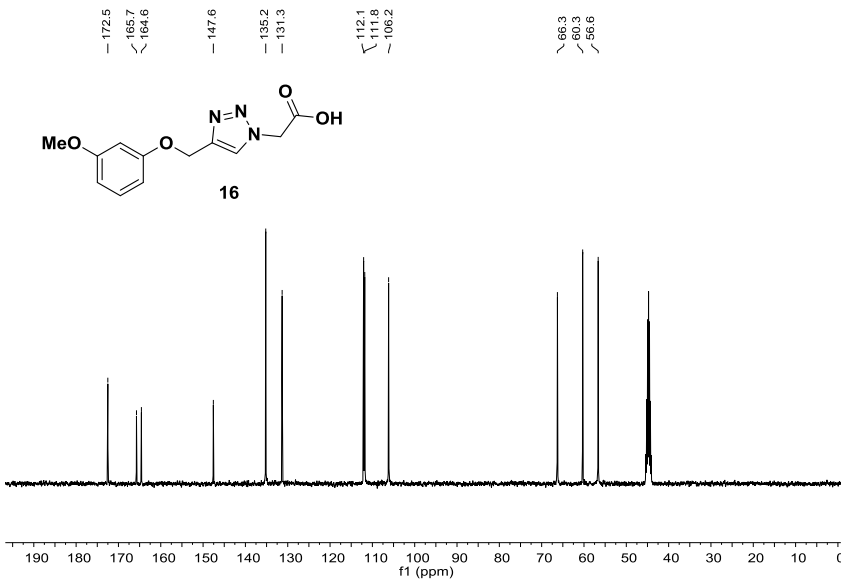
Spectrum 2.19. ^{1}H NMR (500 MHz, MeOH-d_4) spectrum of compound **15.**



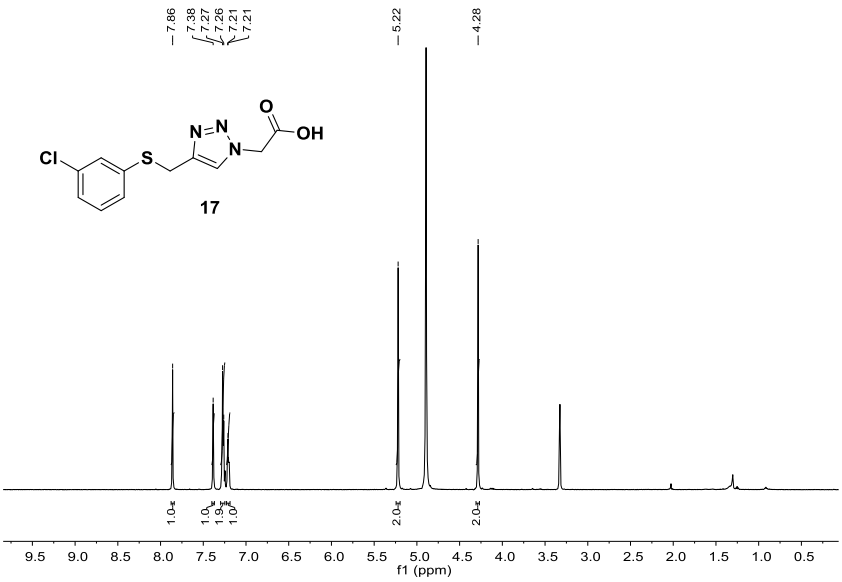
Spectrum 2.20. ^{13}C NMR (126 MHz, MeOH-d_4) spectrum of compound **15.**



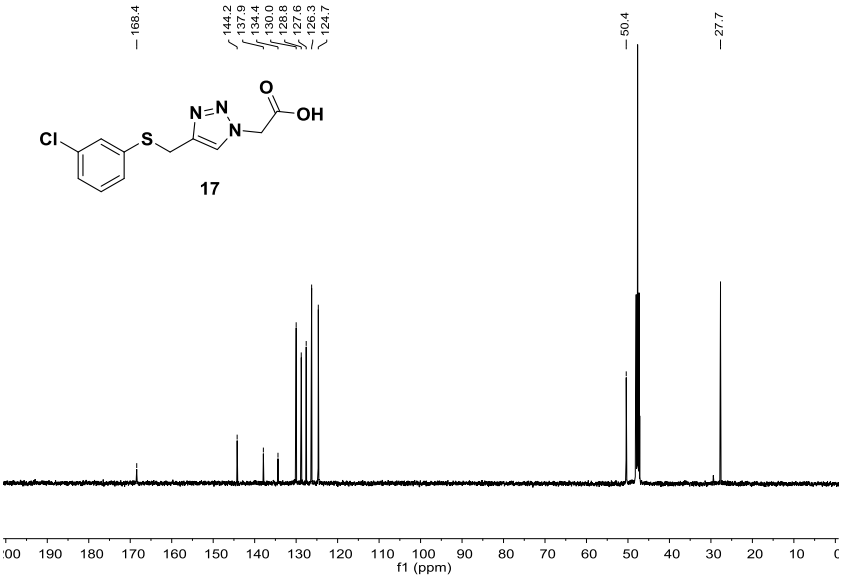
Spectrum 2.21. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **16.**



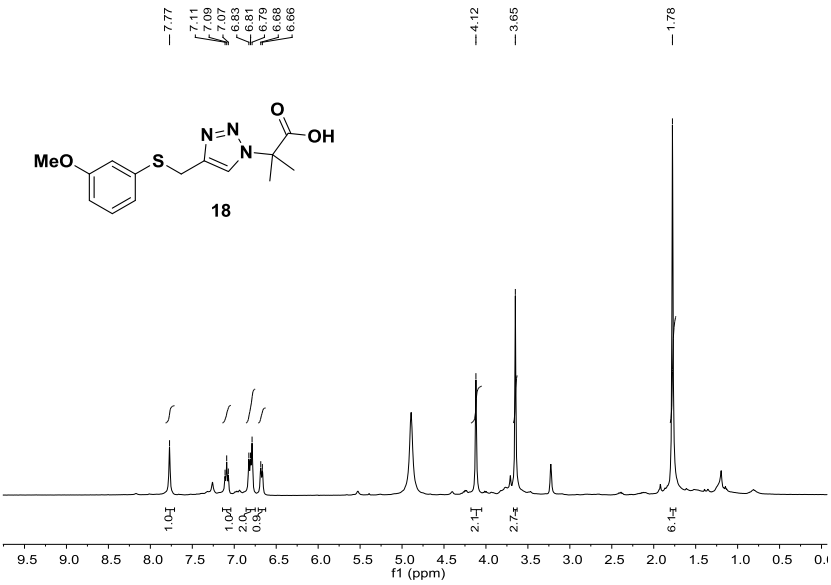
Spectrum 2.22. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **16.**



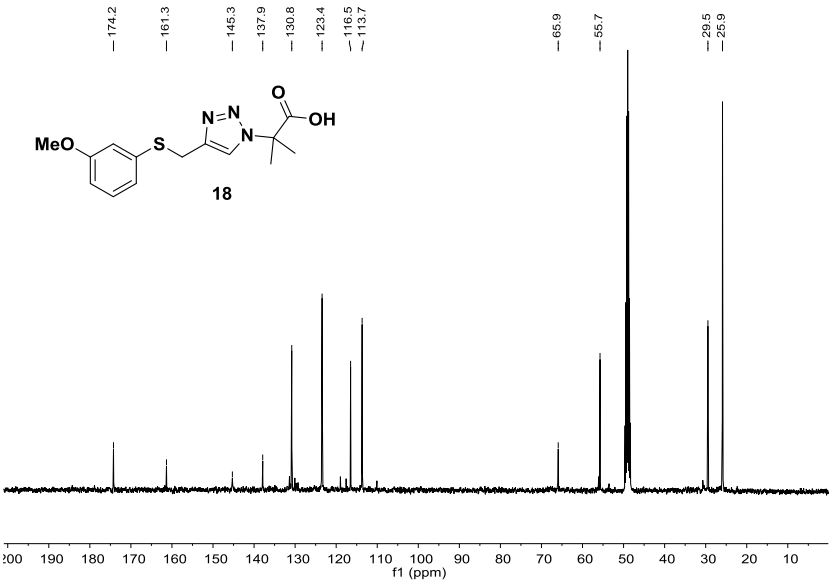
Spectrum 2.23. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **17.**



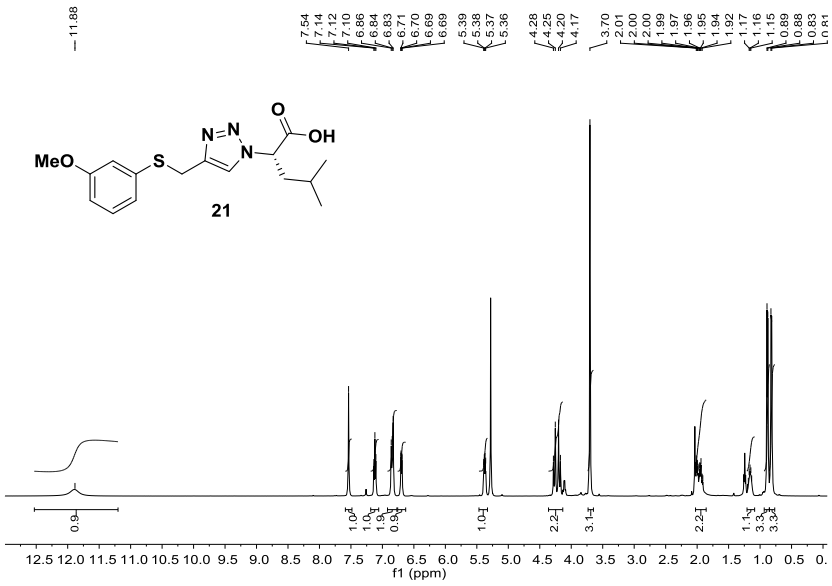
Spectrum 2.24. ^{13}C NMR (126 MHz, MeOH-d_4) spectrum of compound **17.**



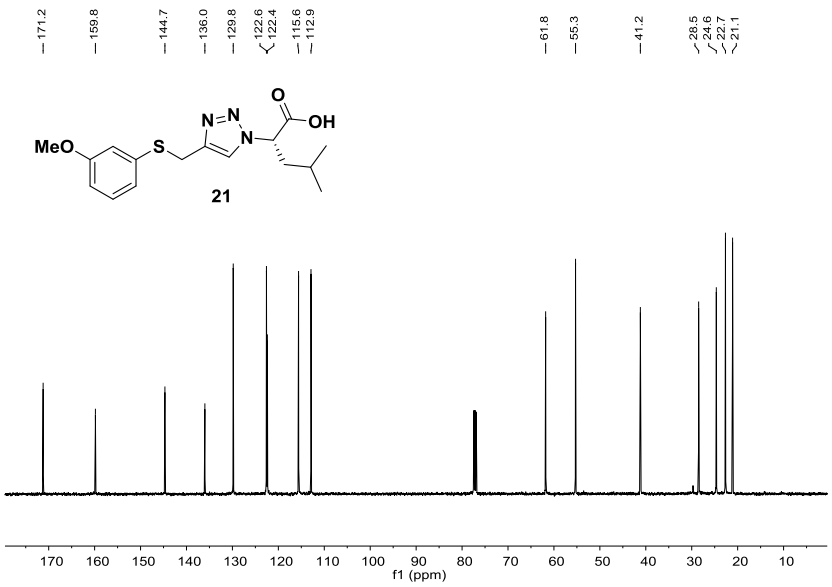
Spectrum 2.25. ^{1}H NMR (400 MHz, MeOH-d_4) spectrum of compound **18.**



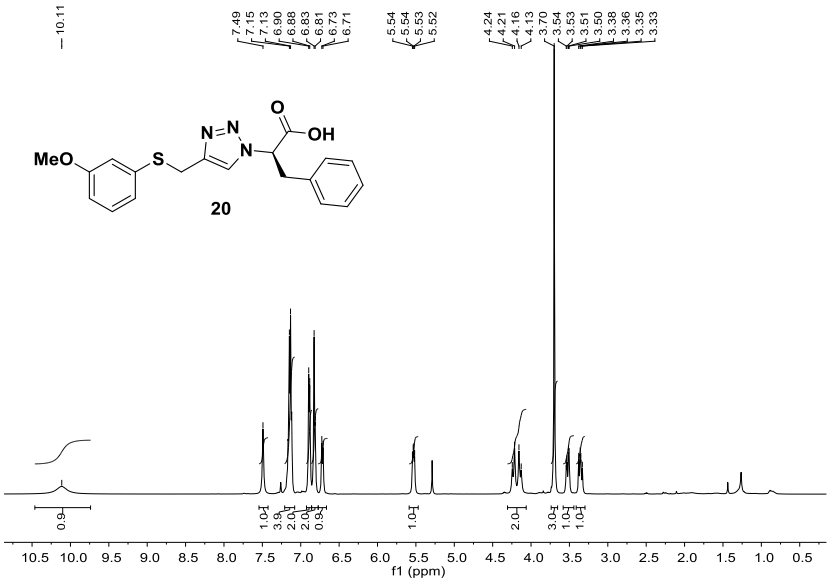
Spectrum 2.26. ^{13}C NMR (101 MHz, MeOH-d_4) spectrum of compound **18.**



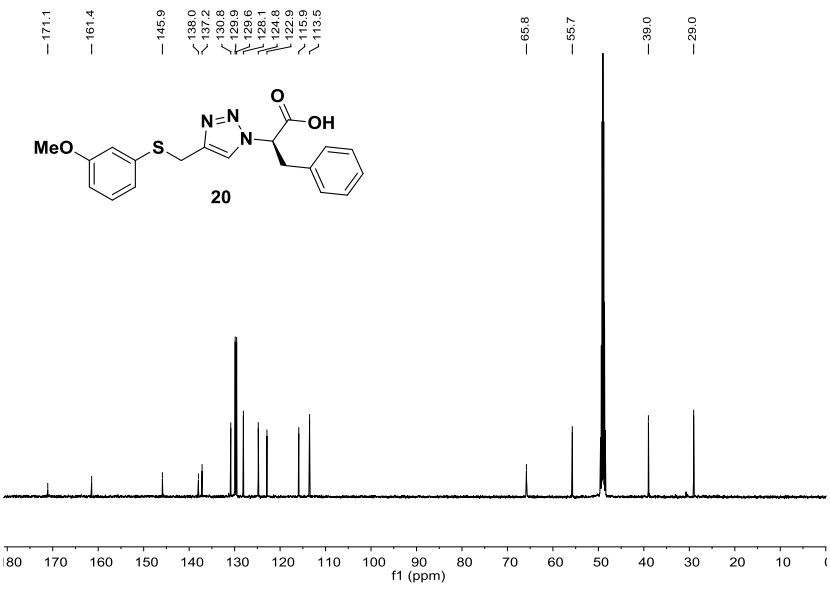
Spectrum 2.27. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **21.**



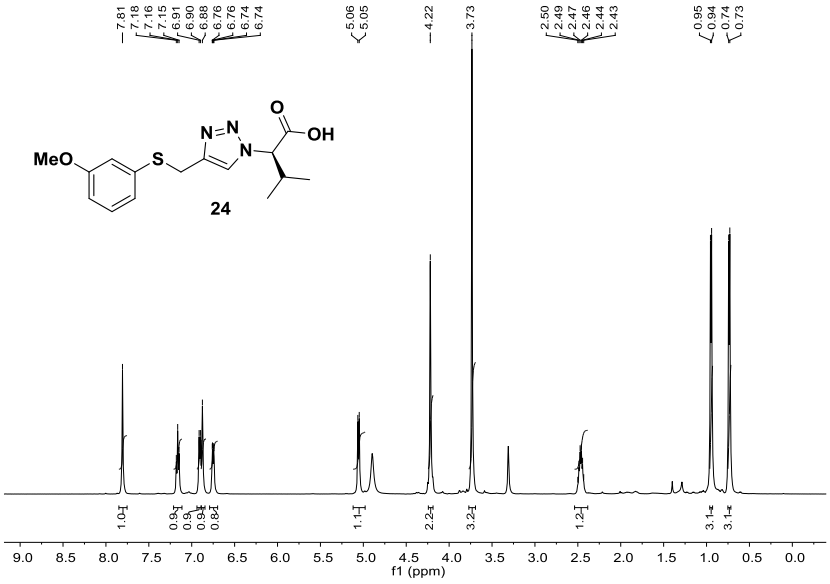
Spectrum 2.28. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **21.**



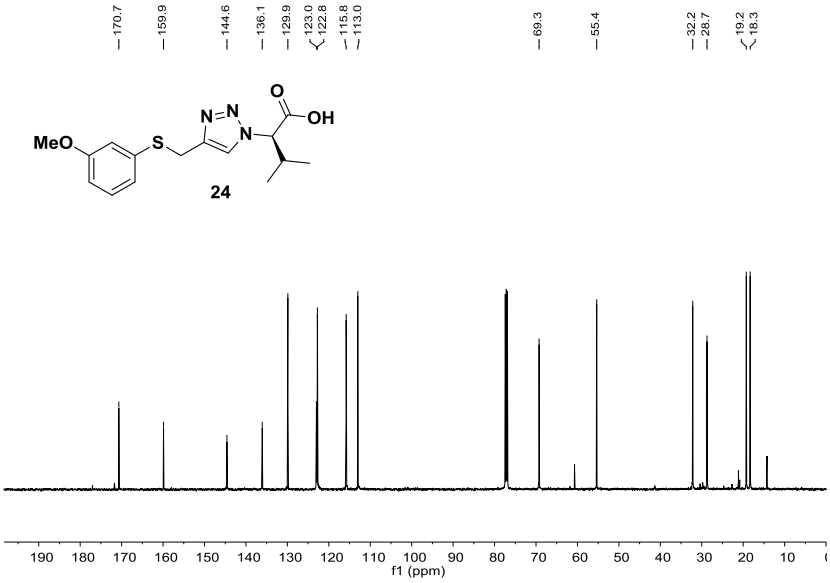
Spectrum 2.29. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **20.**



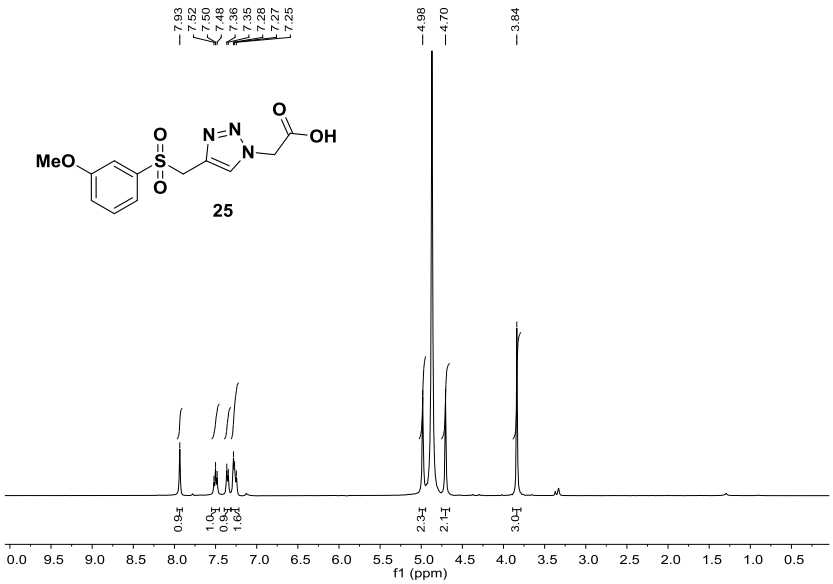
Spectrum 2.30. ^{13}C NMR (126 MHz, MeOH-d_4) spectrum of compound **20.**



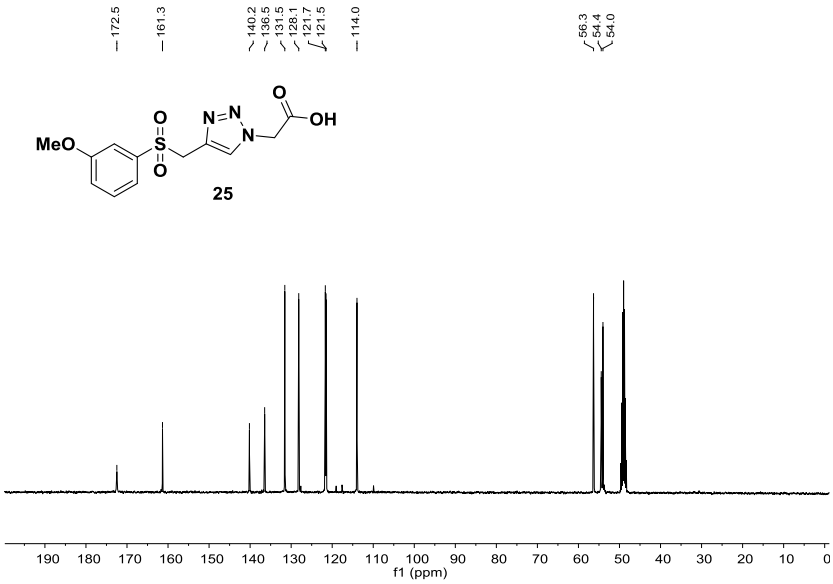
Spectrum 2.31. ^{1}H NMR (500 MHz, MeOH-d_4) spectrum of compound **24.**



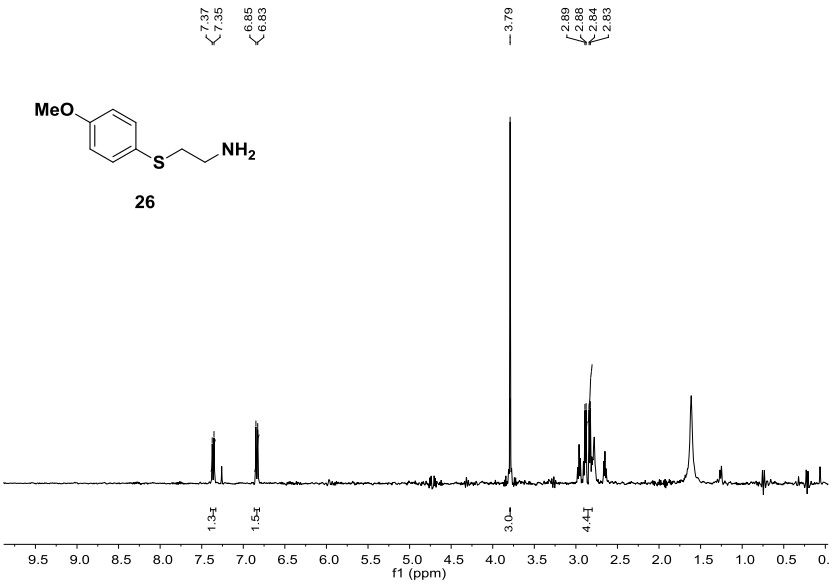
Spectrum 2.32. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **24.**



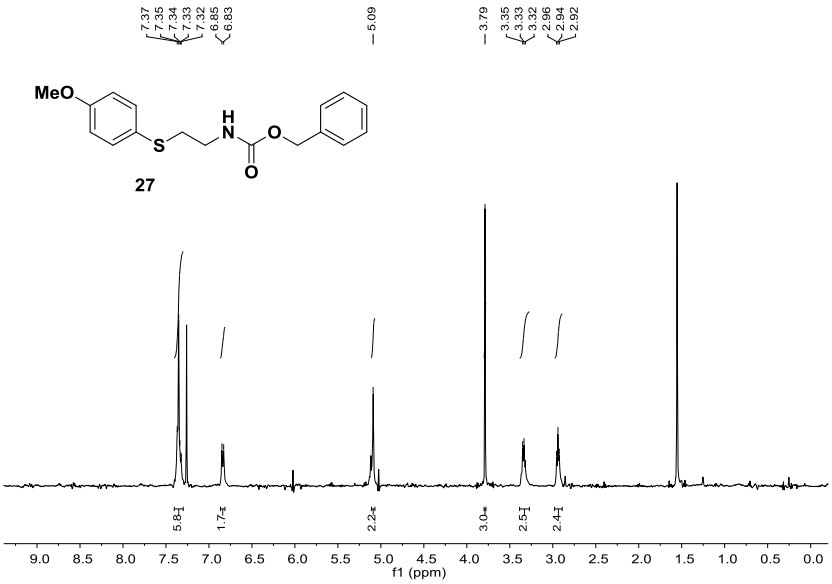
Spectrum 2.33. ^{1}H NMR (400 MHz, MeOH-d_4) spectrum of compound **25.**



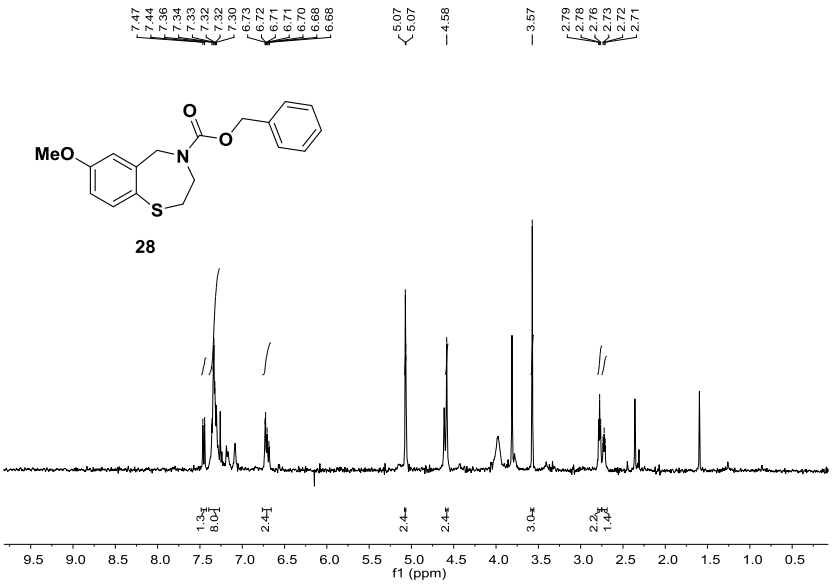
Spectrum 2.34. ^{13}C NMR (101 MHz, MeOH-d_4) spectrum of compound **25.**



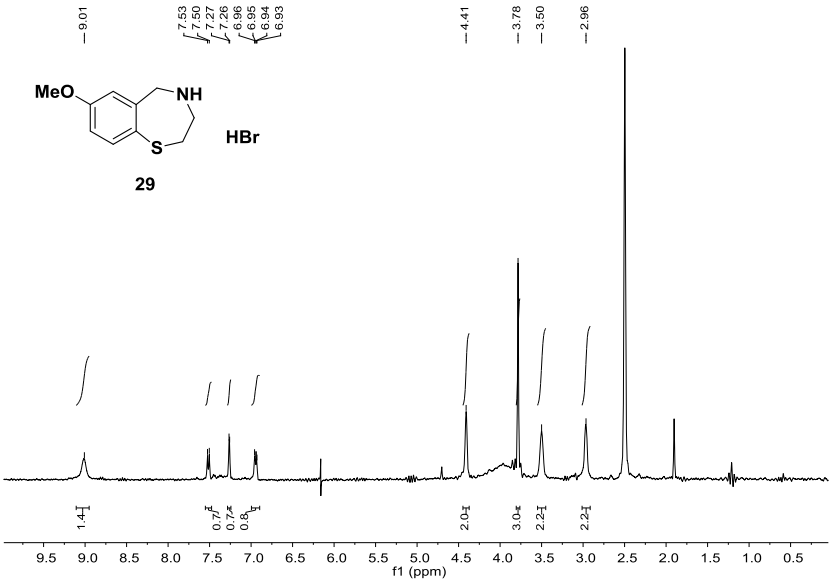
Spectrum 2.35. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26.**



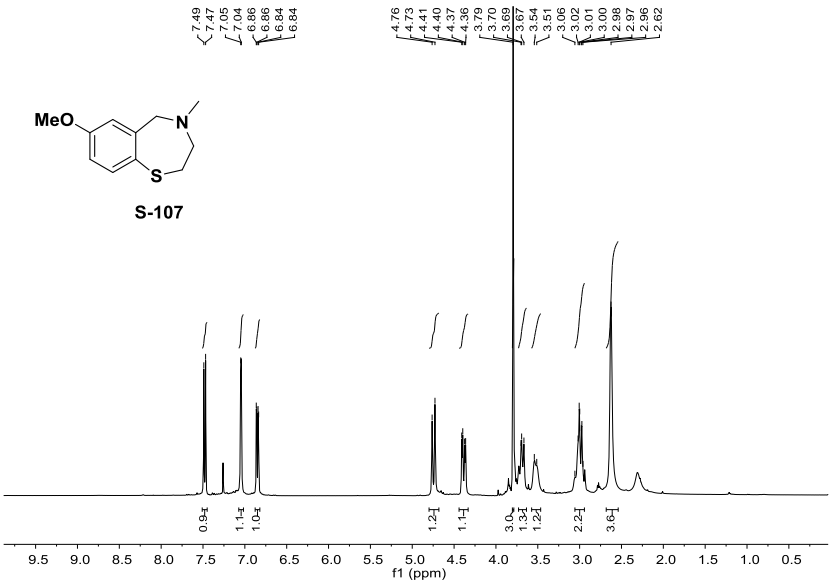
Spectrum 2.36. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **27.**



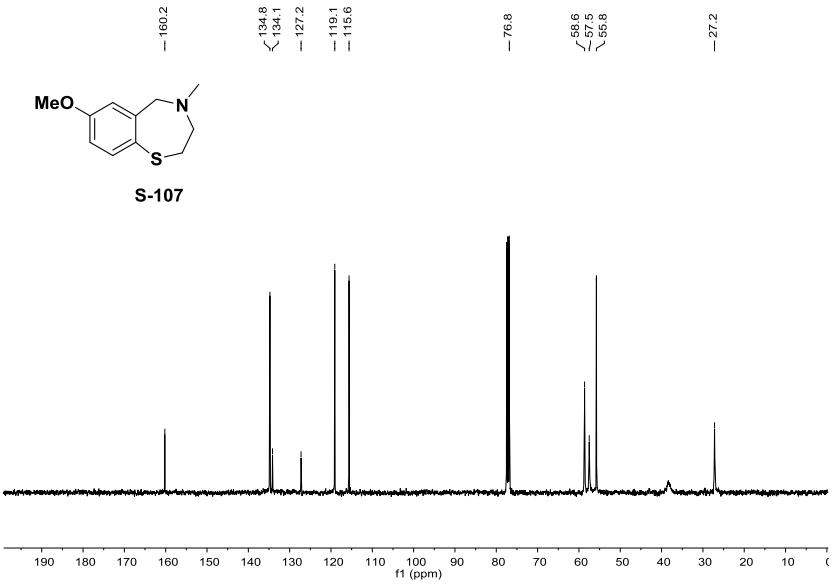
Spectrum 2.37. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **28.**



Spectrum 2.38. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **29.**

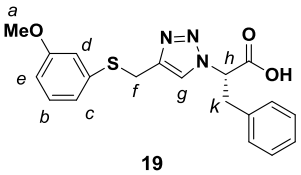


Spectrum 2.39. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **S-107.**

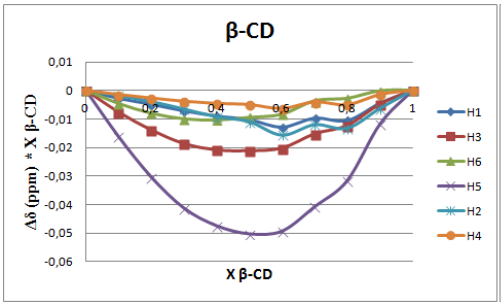


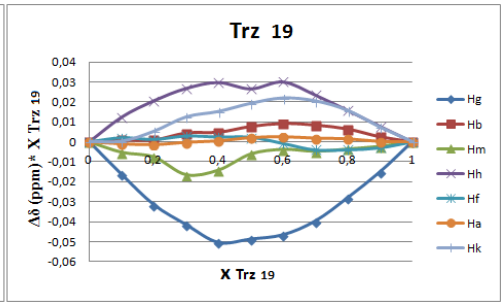
Spectrum 2.40. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **S-107.**

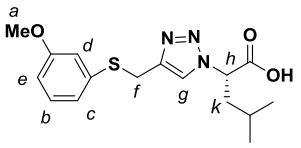
APPENDIX 2: Job Plots of Compounds 19-24 (D_2O, 25 ºC)



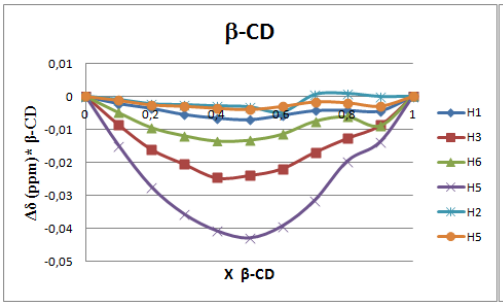
19

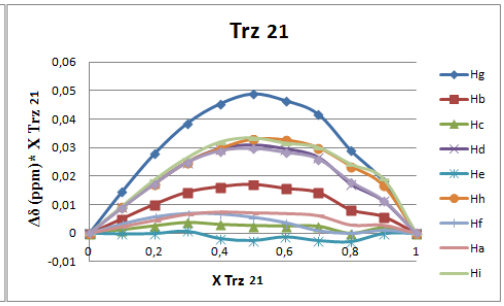


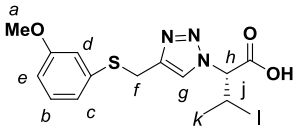




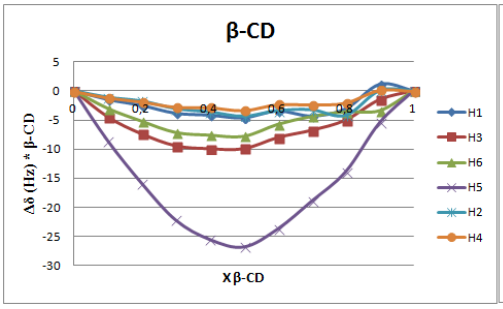
21

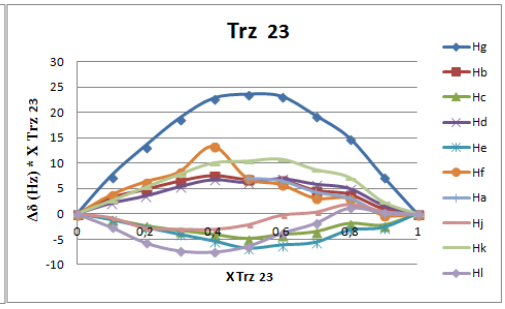


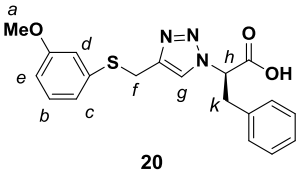




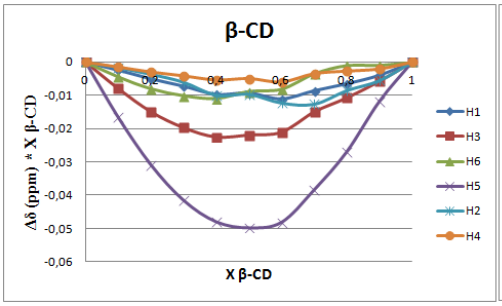
23

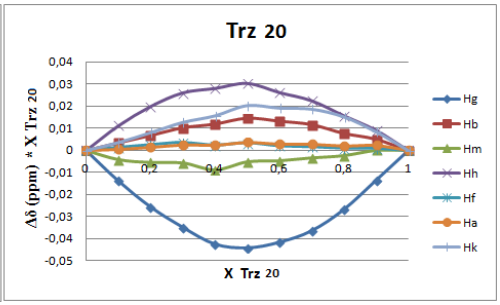


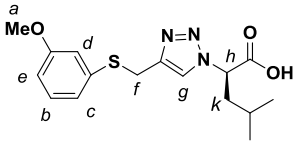



a
MeO
d
e
S
N=N
N
h
O
OH
f
g
k
b
c

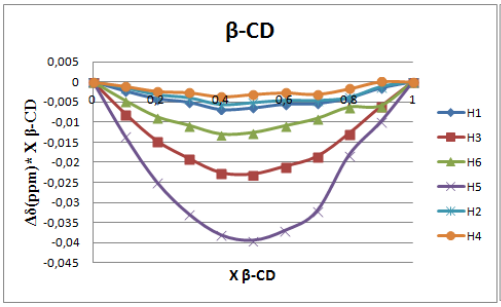
20

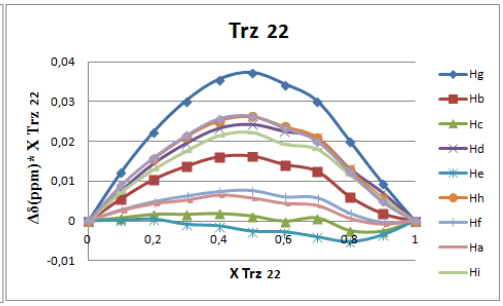

β-CD
Δδ (ppm) * X β-CD
X β-CD
H1
H3
H6
H5
H2
H4

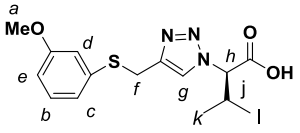

Trz 20
Δδ (ppm) * X Trz 20
X Trz 20
Hg
Hb
Hm
Hh
Hf
Ha
Hk


a
MeO
d
e
S
N=N
N
h
O
OH
f
g
k
b
c

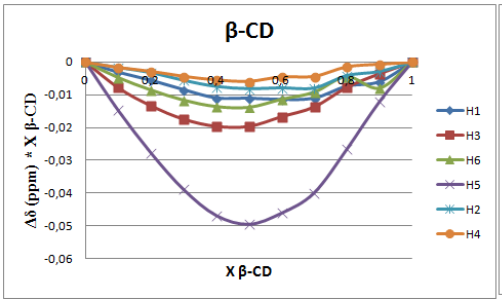
22

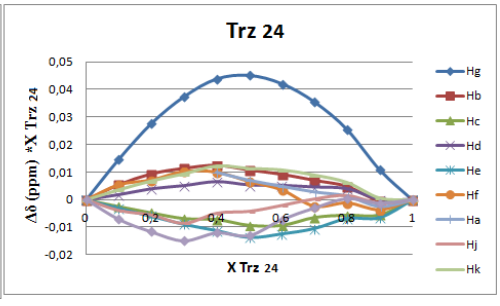

β-CD
Δδ(ppm)* X β-CD
X β-CD
H1
H3
H6
H5
H2
H4


Trz 22
Δδ(ppm)* X Trz 22
X Trz 22
Hg
Hb
Hc
Hd
He
Hh
Hf
Ha
Hi

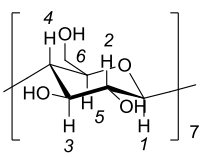

a
MeO
d
e
S
N=N
N
h
O
OH
f
g
j
k
l
b
c

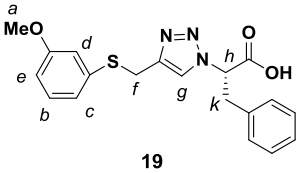
24


β-CD
Δδ (ppm) * X β-CD
X β-CD
H1
H3
H6
H5
H2
H4

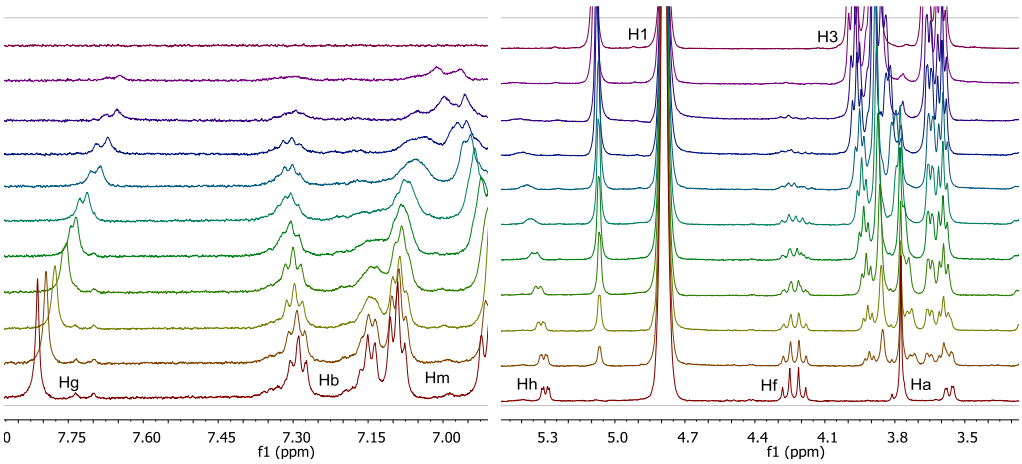

Trz 24
Δδ (ppm) *X Trz 24
X Trz 24
Hg
Hb
Hc
Hd
He
Hf
Ha
Hj
Hk

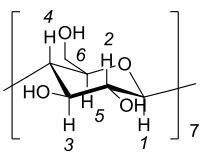
APPENDIX 3: Stacked ^{1}H NMR Titration Spectra of Compounds 19-24 (D_2O, 25 °C)

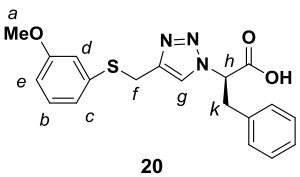




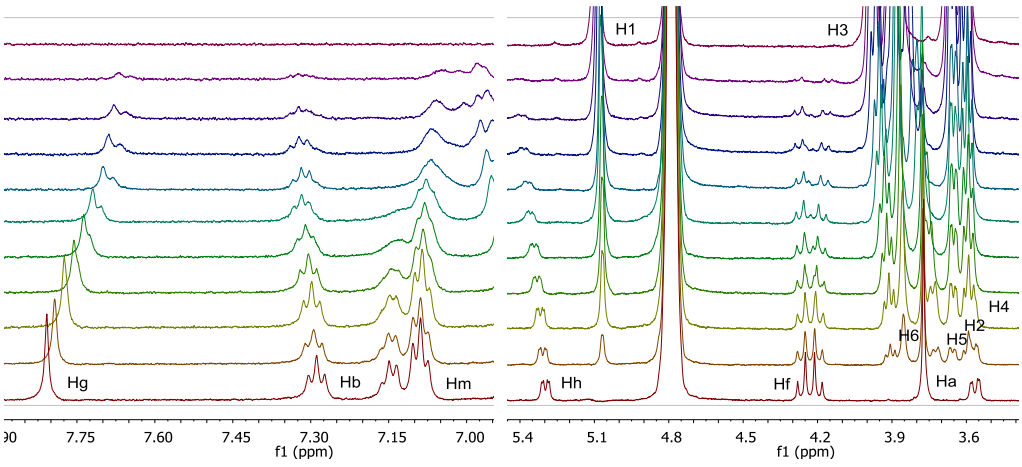
19

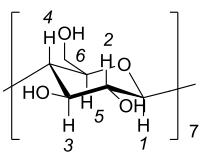


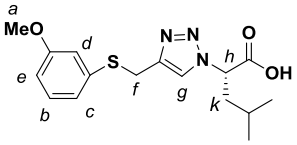




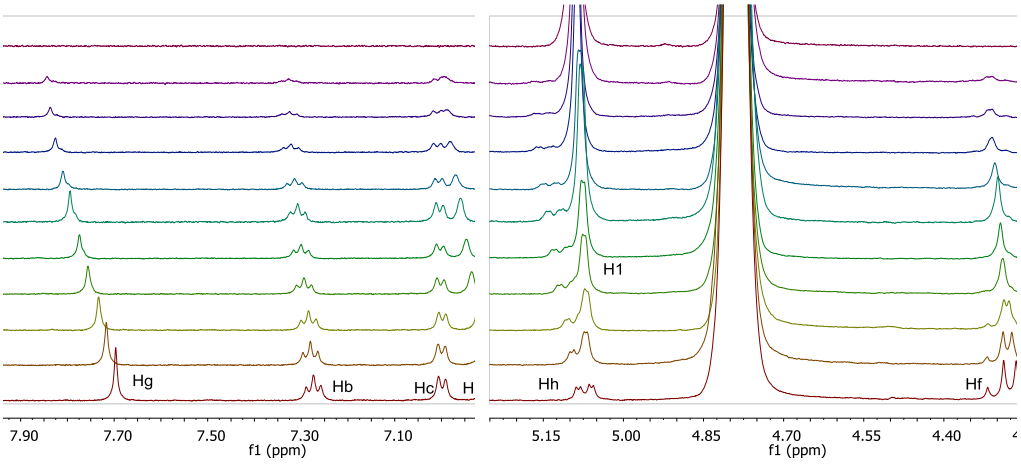
20

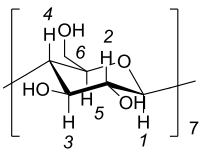


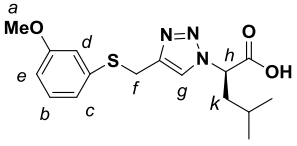

4
HOH
6
2
HO
HO
H
5
OH
H
3
H
1
7


a
MeO
d
e
S
N=N
N
h
O
OH
f
g
k
b
c

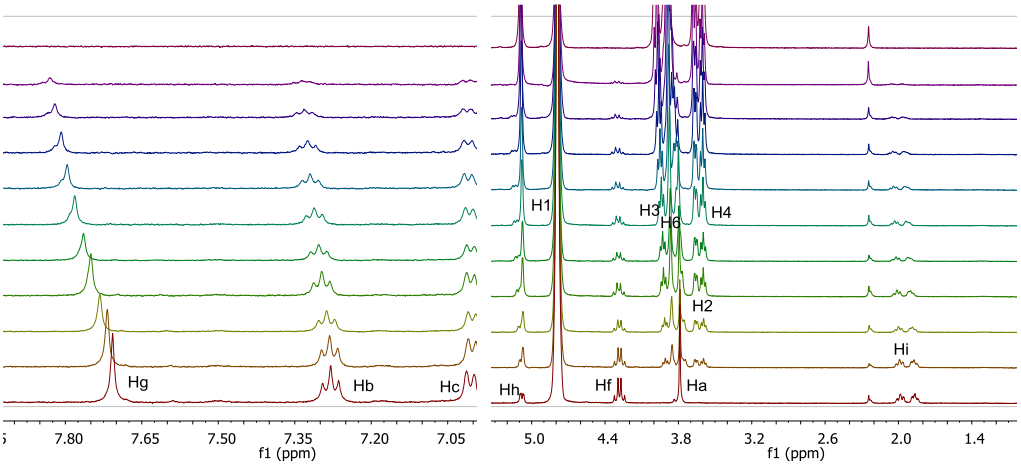
21

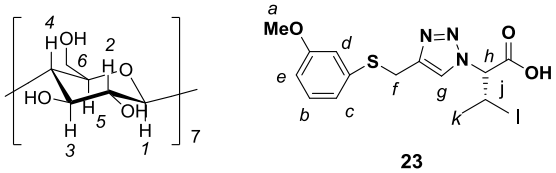

Hg
Hb
Hc
H
H1
Hh
Hf
7.90
7.70
7.50
7.30
7.10
f1 (ppm)
5.15
5.00
4.85
4.70
4.55
4.40
f1 (ppm)


4
HOH
6
2
HO
HO
H
5
OH
H
3
H
1
7

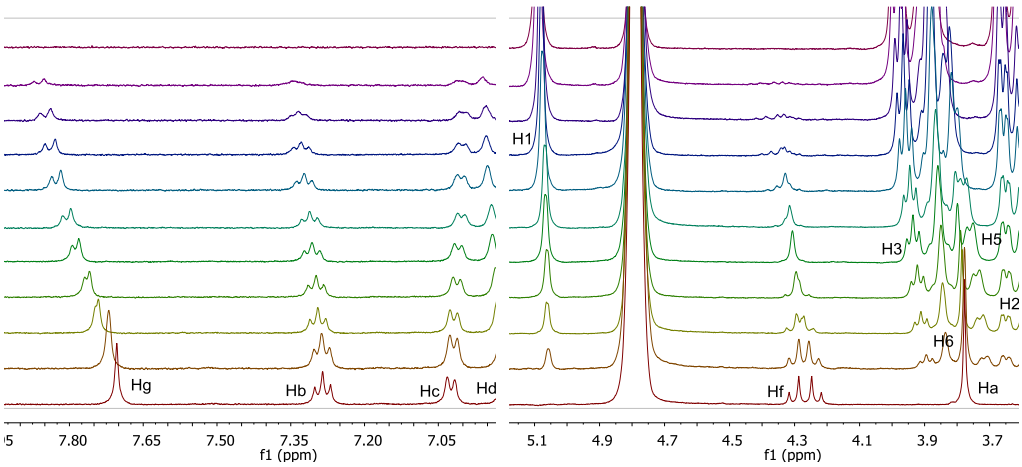

a
MeO
d
e
S
N=N
N
h
O
OH
f
g
k
b
c

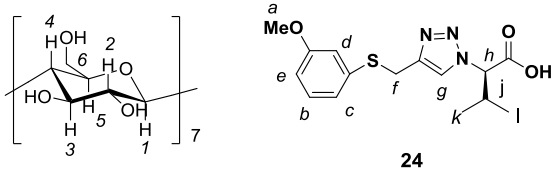
22


H1
H3
H6
H4
H2
Hi
Hh
Hf
Ha
Hg
Hb
Hc
7.80
7.65
7.50
7.35
7.20
7.05
f1 (ppm)
5.0
4.4
3.8
3.2
2.6
2.0
1.4
f1 (ppm)

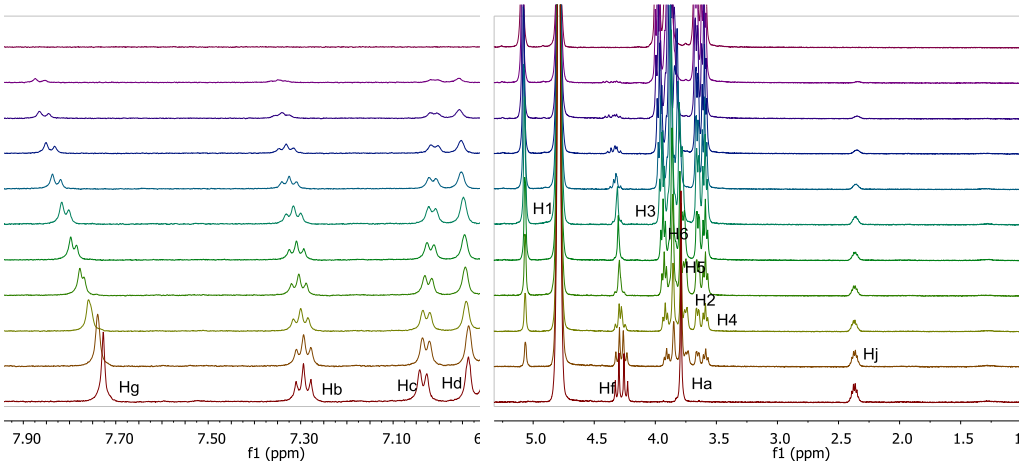

4
OH
2
6
O
HO
H
OH
5
H
3
H
1
7
a
MeO
d
N=N
O
S
h
OH
e
f
g
N
j
b
c
k
l

23


H1
H3
H5
H2
H6
Hg
Hb
Hc
Hd
Hf
Ha
7.80
7.65
7.50
7.35
7.20
7.05
5.1
4.9
4.7
4.5
4.3
4.1
3.9
3.7
f1 (ppm)


4
OH
2
6
O
HO
H
OH
5
H
3
H
1
7
a
MeO
d
N=N
O
S
h
OH
e
f
g
N
j
b
c
k
l

24


H1
H3
H5
H2
H4
Hj
Hg
Hb
Hc
Hd
Hf
Ha
7.90
7.70
7.50
7.30
7.10
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

3

N-Dealkylation of 1,2,3-triazolium salts. A Metal-free route to 1,5-disubstituted 1,2,3-triazoles and related bistriazoles.

3 *N*-Dealkylation of 1,2,3-triazolium salts. A metal-free route to 1,5-disubstituted 1,2,3-triazoles and related bistriazoles

3.1 Introduction

To address the second general objective of this PhD thesis consisting in the transformation of 1,4-disubstituted triazoles into their 1,5-disubstituted counterparts or related bistriazoles (Section 1.2.3), we selected to explore a synthetic route involving the use of triazolium cationic intermediates.

3.1.1 Synthesis of 1,5-disubstituted triazoles *via* 1,2,3-triazolium salts

During the past decade, 1,2,3-triazolium salts have attracted increasing interest as a result of their easy synthetic accessibility from the corresponding "click" 1,4-disubstituted 1,2,3-triazoles by *N*-alkylation. The alkylation process can be carried out using alkyl halides,[140] tosylates or triflates[141] (RX, ROTs or ROTf, respectively) or trimethyloxonium tetrafluoroborates (Meerwein's reagent, R_3OBF_4).[142] This transformation usually occurs with total *N*3-regioselectivity and quasi-quantitative yields for simple R alkyl groups.

As Figure 3.1 illustrates, 1,2,3-triazolium salts have been successfully used to design ionic liquids[143] by incorporating at least one flexible substituent (R^2) and a bulky hydrophobic anion (BF_4, TfO, PF_6, NTf_2) which makes the crystalline accommodation difficult. Additionally, the introduction of chiral substituents (R^1) also provides structures

---

[140] a) Cao, Q.-Y.; Pradhan, T.; Lee, M. H.; No, K.; Kim, J. S. *Analyst* **2012**, *137*, 4454. b) Chhatra, R. K.; Kumar, A.; Pandey, P. S. *J. Org. Chem.* **2011**, *76*, 9086. c) Schulze, B.; Friebe, C.; Hager, M. D.; Günther, W.; Köhn, U.; Jahn, B. O.; Görls, H.; Schubert, U. S. *Org. Lett.* **2010**, *12*, 2710. d) Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534. e) Kumar, A.; Pandey, P. S. *Org. Lett.* **2007**, *10*, 165.

[141] a) Sanghi, S.; Willett, E.; Versek, C.; Tuominenb, M.; Coughlin, E. B. *RSC Advances* **2012**, *2*, 848. b) Bernet, L.; Lalrempuia, R.; Ghattas, W.; Mueller-Bunz, H.; Vigara, L.; Llobet, A.; Albrecht, M. *Chem. Commun.* **2011**, *47*, 8058. c) Lalrempuia, R.; McDaniel, N. D.; Müller-Bunz, H.; Bernhard, S.; Albrecht, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9765.

[142] a) Cao, Q.-Y.; Wang, Z.-C.; Li, M.; Liu, J.-H. *Tetrahedron Lett.* **2013**, *54*, 3933. b) Spence, G. T.; Pitak, M. B.; Beer, P. D. *Chem. Eur. J.* **2012**, *18*, 7100. c) Mullen, K. M.; Mercurio, J.; Serpell, C. J.; Beer, P. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 4781.

[143] a) M'sahel, M.; Obadia, M. M.; Medimagh, R.; Serghei, A.; Zina, M. S.; Drockenmuller, E. *New J. Chem.* **2016**, *40*, 740. b) Li, H.-Y.; Chen, C.-Y.; Cheng, H.-T.; Chu, Y.-H. *Molecules* **2016**, *21*, 1355. c) Jeong, Y.; Ryu, J.-S. *J. Org. Chem.* **2010**, *75*, 4183. d) Hanelt, S.; Liebscher, J. *Synlett* **2008**, 1058. e) Yacob, Z.; Shah, J.; Leistner, J.; Liebscher, J. *Synlett* **2008**, 2342.

potentially suitable to promote asymmetric organocatalysis.[143e,144] Their acidic C5−H bond can be preserved to participate in supramolecular assemblies[145] or to prepare polymer electrolytes,[146] although its deprotonation can form mesoionic *N*-heterocyclic carbene ligands for transition metal complexes.[107c,147]

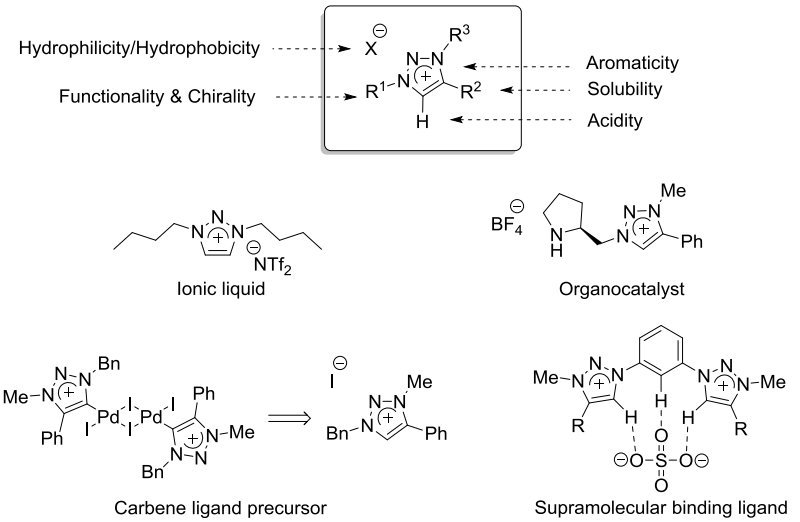


Figure 3.1. Some examples of 1,2,3-triazolium salts and their applications.

Despite the high potential of triazolium salts to participate in organic reactions as powerful and versatile electrophiles, they have received very limited attention as synthetic intermediates to prepare novel neutral 1,2,3-triazole derivatives. At the beginning of our work, the only example describing the use of 1,3,4-trisubstituted 1,2,3-triazolium cations to prepare 1,5-disubstituted 1,2,3-triazoles was reported by Koguchi[148] (Scheme 3.1). The

---

144 a) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* **2011**, *133*, 1307. b) Khan, S. S.; Shah, J.; Liebscher, J. *Tetrahedron* **2011**, *67*, 1812. c) Khan, S. S.; Shah, J.; Liebscher, J. *Tetrahedron* **2010**, *66*, 5082. d) Shah, J.; Khan, S. S.; Blumenthal, H.; Liebscher, J. *Synthesis* **2009**, 3975.

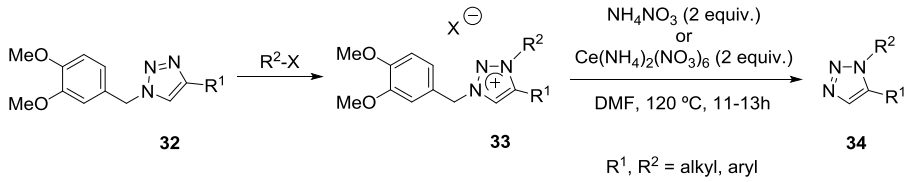
145 a) Clavel, C.; Romuald, C.; Brabet, E.; Coutrot, F. *Chem. Eur. J.* **2013**, *19*, 2982. b) Zhang, Z.-J.; Han, M.; Zhang, H.-Y.; Liu, Y. *Org. Lett.* **2013**, *15*, 1698. c) Gilday, L. C.; White, N. G.; Beer, P. D. *Dalton Trans.* **2012**, *41*, 7092. d) Coutrot, F.; Busseron, E. *Chem. Eur. J.* **2008**, *14*, 4784.

146 Obadia, M. M.; Drockenmuller, E. *Chem. Commun.* **2016**, *52*, 2433.

147 a) Mendoza-Espinosa, D.; González-Olvera, R.; Negrón-Silva, G. E.; Angeles-Beltrán, D.; Suárez-Castillo, O. R.; Álvarez-Hernández, A.; Santillan, R. *Organometallics* **2015**, *34*, 4529. b) Eisenberger, P.; Bestvater, B. P.; Keske, E. C.; Crudden, C. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 2467. c) Hettmanczyk, L.; Manck, S.; Hoyer, C.; Hohloch, S.; Sarkar, B. *Chem. Commun.* **2015**, *51*, 10949.

148 a) Koguchi, S.; Izawa, K. *ACS Comb. Sci.* **2014**, *16*, 381. b) Koguchi, S.; Izawa, K. *Synthesis* **2012**, *44*, 3603.

procedure involves a sacrificial 3,4-dimethoxybenzyl group (DMB) attached to the *N*1-position of triazoles **32**, which is cleaved from triazolium salts **33** upon treatment with either ammonium nitrate or ceric ammonium nitrate. This method provides 1,5-disubstituted 1,2,3-triazoles **34** in fair to good yields for simple alkyl or aryl substituents but, unfortunately, it requires relatively harsh DMB-deprotection oxidative conditions which are unsuitable for triazoles bearing sensitive functional groups.



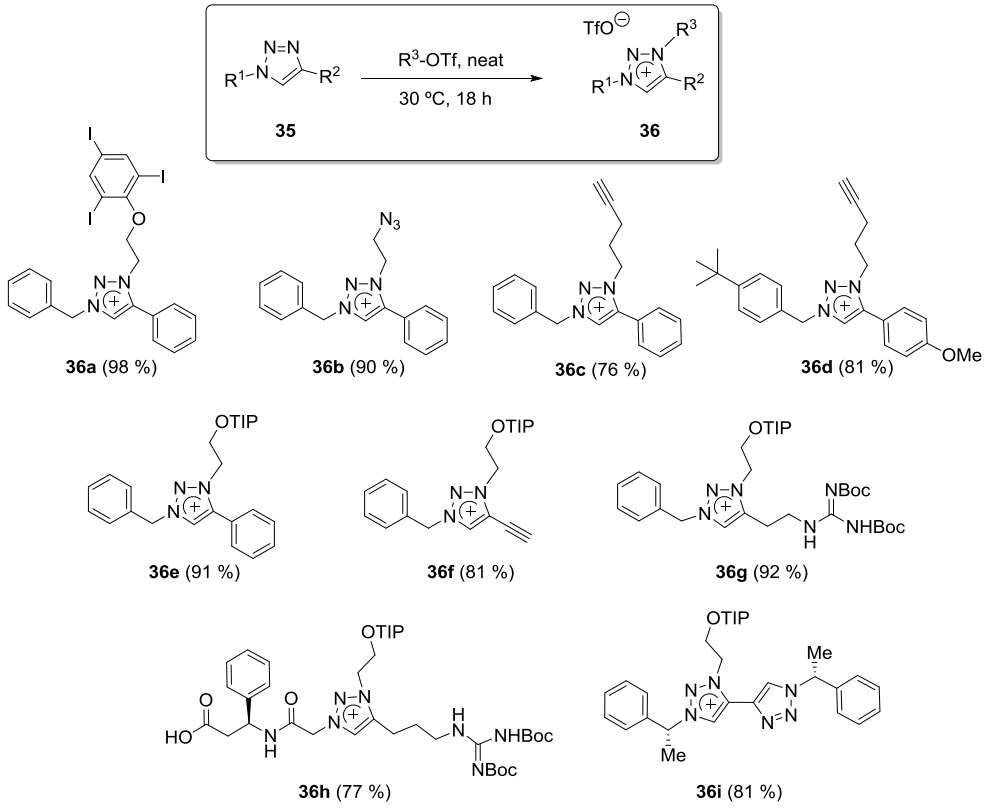
Scheme 3.1. Synthesis of 1,5-disubstituted 1,2,3-triazoles from *N*3-alkyl-1,2,3-triazolium salts.

Two critical aspects to make the above approach synthetically attractive are: a) the use of an alternative sacrificial group attached at the *N*1 position that can be removed under mild conditions and b) the extension of the *N*3-alkylation scope to a wider range of functionalized alkyl groups. It is worth mentioning that *N*3-alkylation of 1,2,3-triazoles is strongly dependent on the steric hindrance of the alkylating reagent and limited to primary alkyl groups, such as small groups (methyl, ethyl) or activated groups (allyl, benzyl). In general, a large excess of the alkylating agent is required to achieve acceptable yields. Importantly, a wide variety of functional groups such as ethers, amides,[143d] carbamates[149] and even sulfides[150] are well-accommodated at the *N*1 and C4 substituents of the 1,2,3-triazoles.

An improved method for the *N*3-alkylation of 1,4-disubstituted 1,2,3-triazoles with complex alkylating agents has been recently developed in our group by Dr. Zaira Monasterio.[151] It involves the use of alkyl triflates, freshly prepared from functionalized primary alcohols, to alkylate 1,2,3-triazoles **35** under solvent-free conditions (Scheme 3.2). In fact, the absence of solvent during the reaction turned out to be crucial to reach full conversion. As depicted in Scheme 3.2, "clickable" azide and terminal alkyne groups were

[149] Karthikeyan, T.; Sankararaman, S. *Tetrahedron Lett.* **2009**, *50*, 5834.
[150] Mendoza-Espinosa, D.; González-Olvera, R.; Osornio, C.; Negrón-Silva, G. E.; Santillan, R. *New J. Chem.* **2015**, *39*, 1587.
[151] Monasterio, Z. *PhD Thesis UPV-EHU* **2015** "Synthesis, applications and reactivity of 1,2,3-triazolium salts."

successfully incorporated into 1,2,3-triazolium salts **36** bearing numerous functional groups, such as ethers, esters, carboxylic acids or carbamates.



Scheme 3.2. *N*-alkylation of 1,2,3-triazoles with functionalized alkyl triflates. (TIP = 2,4,6-triiodophenoxy group).

3.1.2 Synthesis of bis(1,2,3-triazoles) containing 1,5-disubstituted triazole units

Bis(1,2,3-triazoles) have gained significant attention due to their potential application in supramolecular, pharmaceutical, biological and organometallic chemistry.[152] However, currently available bis(1,2,3-triazole) molecules share two common structural limitations: a) they are based almost exclusively on 1,4-disubstituted 1,2,3-triazoles units[153] and b) they invariably possess symmetrical substitution patterns.[154] This is not surprising

[152] Zheng, Z.-J.; Wang, D.; Xu, Z.; Xu, L.-W. *Beilstein J. Org. Chem.* **2015**, *11*, 2557.
[153] Damodiran, M.; Muralidharan, D.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3611.
[154] Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006**, *8*, 20.

because they all rely on CuAAC procedures which involve the use of α,ω-diazides[155] or α,ω-dialkynes and the performance of chemoselective "click" reactions over difunctionalized substrates towards the assembly of bis(1,2,3-triazoles) is still rather difficult.[156]

In recent years, few methods for the synthesis of nonsymmetrically substituted 4,4'-bitriazoles **37** (Figure 3.2) have been reported consisting in a "one-pot" sequential double CuAAC reactions of 1,3-butadiyne with different azides.[107c,157] Some nonsymmetrically 1,4-disubstituted bis(1,2,3-triazoles) 4,4'-tethered with short alkylene chains have also been prepared using alkyl azides bearing additional criptoazide groups.[158]

Since the seminal report by Burgess[48b] describing the formation of symmetrically substituted 5,5'-bistriazoles **38** (Figure 3.2) as byproducts in CuAAC reactions, numerous procedures to selectively prepare such heterocyclic products in good yields have been described.[48a,159] In particular, the combination of oxidative conditions with the use of a carbonate base and supporting ligands proposed by Zhu and coworkers[159a] has shown to be rather useful to give 5,5'-bistriazoles in high conversion, good selectivity and substrate scope extensible to aromatic azides.

---

155 Wang, Z.-X.; Zhao, Z.-G. *J. Heterocyclic Chem.* **2007**, *44*, 89.

156 Elamari, H.; Meganem, F.; Herscovici, J.; Girard, C. *Tetrahedron Lett.* **2011**, *52*, 658.

157 a) Doak, B. C.; Scanlon, M. J.; Simpson, J. S. *Org. Lett.* **2011**, *13*, 537. b) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzolo, F. *Tetrahedron* **2009**, *65*, 10573.

158 Guiard, J.; Fiege, B.; Kitov, P. I.; Peters, T.; Bundle, D. R. *Chem. Eur. J.* **2011**, *17*, 7438.

159 a) Brassard, C. J.; Zhang, X.; Brewer, C. R.; Liu, P.; Clark, R. J.; Zhu, L. *J. Org. Chem.* **2016**, *81*, 12091. b) del Hoyo, A. M.; Latorre, A.; Díaz, R.; Urbano, A.; Carreño, M. C. *Adv. Synth. Catal.* **2015**, *357*, 1154. c) Wang, C.-Y.; Zou, J.-F.; Zheng, Z.-J.; Huang, W.-S.; Lia, L.; Xu, L.-W. *RSC Adv.* **2014**, *4*, 54256. d) Li, L.; Fan, X.; Zhang, Y.; Zhu, A.; Zhang, G. *Tetrahedron* **2013**, *69*, 9939. e) Zheng, Z.-J.; Ye, F.; Zheng, L.-S.; Yang, K.-F.; Lai, G.-Q.; Xu, L.-W. *Chem. Eur. J.* **2012**, *18*, 14094. f) Oladeinde, O. A.; Hong, S. Y.; Holland, R. J.; Maciag, A. E.; Keefer, L. K.; Saavedra, J. E.; Nandurdikar, R. S. *Org. Lett.* **2010**, *12*, 4256.

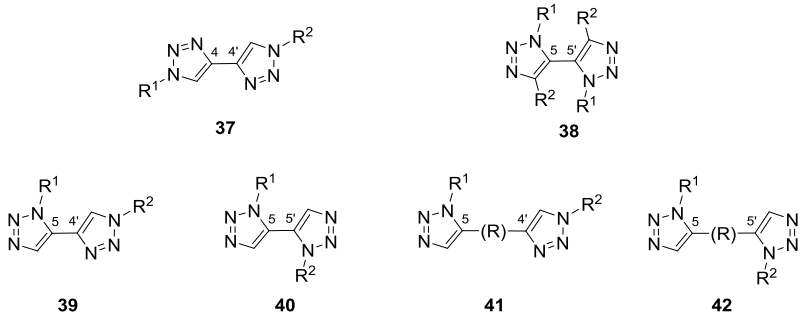
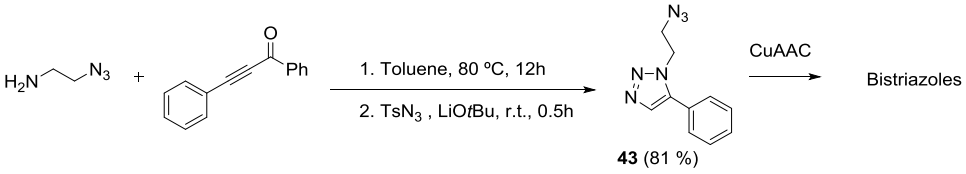


Figure 3.2. Bistriazole structures containing 1,4-disubstituted 1,2,3-triazole units (**37**-**38**) and 1,5-disubstituted 1,2,3-triazole units (**39**-**42**).

Despite the advancements disclosed above, the synthetic access to bis(1,2,3-triazoles) containing 1,5-disubstituted components **39**-**42** (Figure 3.2) remains challenging. In 2013 Cui[160] reported a single example of the preparation of triazole **43** containing simultaneously a 1,5-disubstitution pattern and a latent "clickable" azide group which could be further used to add the second triazole ring following a CuAAC methodology (Scheme 3.3). Unfortunately, the two-step procedure required the use of cumbersome starting materials and involved the diazotation of a preformed α-benzoyl-β-enamine intermediate with tosyl azide under strongly basic conditions.



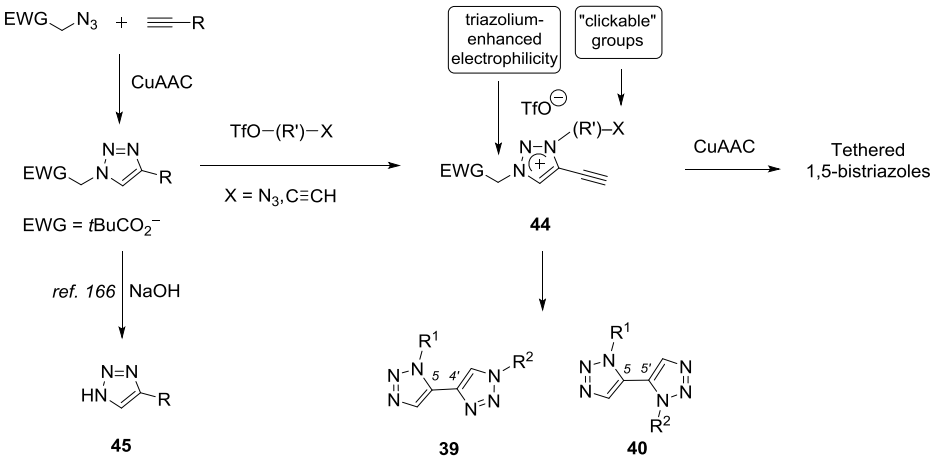
Scheme 3.3. Synthesis of a functionalized 1,5-disubstituted 1,2,3-triazole bearing a "clickable" *N*1-azidoalkyl group.

In view of the scarce precedents covering the synthesis of bis(1,2,3-triazoles) containing non-symmetrically substituted 1,5-triazole units, we decided to face the development of a novel and efficient protocol for the preparation of such appealing heterocyclic backbones.

[160] Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 13265.

3.2 Hypothesis

On the basis of the precedent discussion, we considered the use of the novel triazolium salts **44** (Scheme 3.4) as an interesting alternative to overcome the existing synthetic limitations to prepare bistriazoles comprising non-symmetrically substituted 1,5-substituted 1,2,3,-triazole units **39-42** (Figure 3.2). We surmised that the incorporation of "clickable" functionalized groups *via* *N*-alkylation with functionalized alkyl triflates as described by our research group[151] would overcome the above-mentioned limitations. Moreover, the subsequent *N*-dealkylation of triazolium salts **44** could be conducted in a totally site-selective manner if proper electronwithdrawing groups were used to enhance the electrophilicity of one of the *N*-alkyl substituents. In particular, we selected the *N*-pivaloyloxymethyl group described by Sharpless and Fokin[161] to prepare *N*-unsubstituted 1,2,3-triazoles **45** as a valuable candidate for our synthetic purposes.



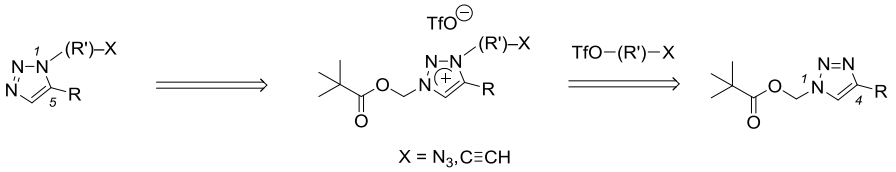
Scheme 3.4. Site-selective *N*3-alkylation / *N*1-dealkylation strategy to prepare 1,5-disubstituted triazoles and bistriazoles.

[161] a) Saftić, D.; Vianello, R.; Žinić, B. *Eur. J. Org. Chem.* **2015**, *7695*. b) Loren, J. C.; Krasi, A.; Fokin, V. V.; Sharpless, K. B. *Synlett* **2005**, 2847.

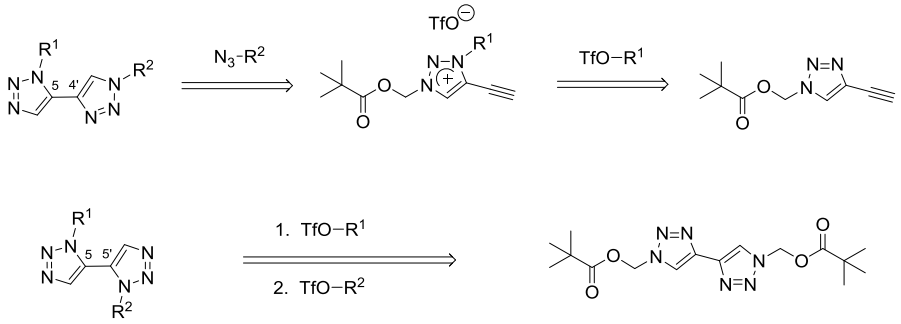
3.3 Objectives

To confirm the above hypotheses, we established two objectives consisting in the study of the following chemical transformations:

1. Conversion of 1-pivaloyloxymethyl 1,2,3-triazoles into 1,5-disubstituted triazoles, following a site-selective *N*3-alkylation / *N*1-dealkylation sequence.



2. Extension of the former methodology to the synthesis of unprecedented bistriazole systems involving 1,5-disubstituted 1,2,3-triazoles.



3.4 Results and discussion

To address the proposed objectives, we divided our working plan into four tasks. First, the preparation of alkyl triflates from primary alcohols bearing functionalized groups such as azide or terminal alkynes. Second, to use the resulting functionalized alkyl triflates to alkylate 1,4-disubstituted 1,2,3-triazoles. Then, to study the *N*-dealkylation of the resulting triazolium salts with different nucleophiles or bases to obtain 1,5-disubstituted 1,2,3-triazoles, and finally to perform the CuAAC reaction in order to obtain bistriazoles that are beyond reach by other methods.

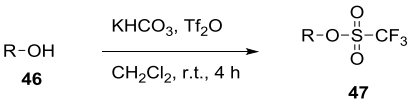
3.4.1 Synthesis of alkyl triflates

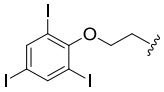
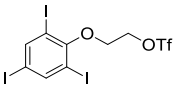
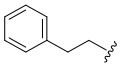
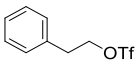
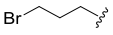
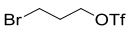
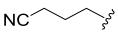
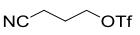
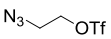
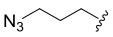
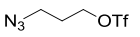
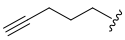
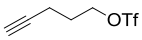
Alkyl triflates are excellent alkylating reagents, but their preparation and isolation as pure compounds is not trivial. They are often prepared from alcohols by reaction with triflic anhydride in the presence of sterically hindered organic bases like 2,6-di-*tert*-butyl-pyridine[162] or poly(vinylpyridine).[163] However, mild basic aqueous washing is required to separate the reaction byproducts, which often results in partial hydrolysis of alkyl triflates rendering their purification unpractical.

Hanack and Collins took advantage of using heterogeneous reaction conditions to prepare enol triflates from ketones.[164] Following this approach, we found that treating an alcohol with equimolar amounts of triflic anhydride and anhydrous $KHCO_3$ in CH_2Cl_2 resulted in quantitative conversion to the desired alkyl triflate (Table 3.1).

[162] Kramer, J. R.; Deming, T. J. *Biomacromolecules* **2012**, *13*, 1719.
[163] Ross, S. A.; Pitíe, M.; Meunier, B. *J. Chem. Soc., Perkin Trans.* **2000**, 571.
[164] Hanack, M.; Fuchs, K.-A.; Collins, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 4008.

Table 3.1. Synthesis of alkyl triflates from alcohols.



Entry	R	Product		Yield (%)
1[165]			**47a**	94[a]
2			**47b**	>95[b]
3			**47c**	>95[b]
4			**47d**	0
5[166]			**47e**	>95[b]
6[167]			**47f**	>95[b]
7			**47g**	>95[b]

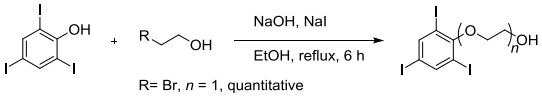
[a]Isolated yield. [b]Not isolated. Conversion determined by ^{1}H NMR.

After a simple filtration of the heterogeneous reaction mixture, solutions of practically pure alkyl triflates **47** were obtained ready for use in subsequent *N*-alkylation reactions as shown in Table 3.1. The method was useful to prepare not only simple alkyl triflates (entry 2), but also functionalized ones including groups such as azide (entries 5 and 6) or halogens (entry 3).

Although we tried to synthesize the alkyl triflate including a cyano group (entry 4), the reaction failed. Remarkably, alkyl triflate **47g** which incorporates the acid-sensitive alkynyl

---

[165] Radek, O.; Nemecek, O. *Czech Patent* CS 118450, 1966.



[166] Dowlut, M.; Hall, D. G.; Hindsgaul, O. *J. Org. Chem.* **2005**, *70*, 9809.

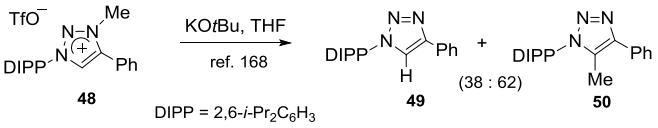
[167] Aucagne, V.; Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186.

group (entry 7) was also uneventfully prepared and the 2,4,6-triiodophenol derivative **47a** (entry 1) could be isolated and stored at -20 ºC for months without appreciable decomposition.

3.4.2 Metal-free synthesis of 1,5-disubstituted 1,2,3-triazoles through 1,3,4-trisubstituted triazolium intermediates

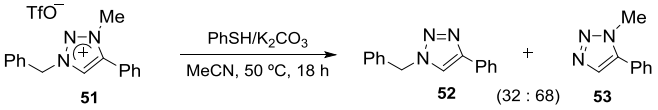
In order to select the most suitable 3-*N*-alkyl-1,2,3-triazolium salts to provide the target 1,5-disubstituted 1*H*-1,2,3-triazoles upon site-selective *N*-dealkylation, several test experiments and computational calculations were conducted. Accordingly, we studied the *N*3-demethylation reaction of several model 3-methyl-1,2,3-triazolium triflates under basic and nucleophilic substitution conditions.

Bertrand first established that the base-promoted *N*-demethylation of triazolium salt **48** to the C5-methylated triazole **50** likely occurred through the intermolecular nucleophilic attack of a mesoionic carbene formed by C5-H deprotonation of the triazolium salt (Scheme 3.5).[168]



Scheme 3.5. *N*-Dealkylation of a triazolium salt **48** under basic conditions.

To avoid the carbene formation, we tested several nucleophilic reagents and found that a much milder *N*-dealkylation of the *N*1-benzyl-*N*3-methyl-1,2,3-triazole **51** occurred using potassium thiophenoxide to cleave the C−N bond, albeit with very poor site-selectivity (Scheme 3.6).



Scheme 3.6. *N*-Dealkylation of 1,3-dialkyl-triazolium triflate **51** under nucleophile attack conditions.

[168] Bouffard, J.; Keitz, B. K.; Tonner, R.; Guisado-Barrios, G.; Frenking, G.; Grubbs, R. H.; Bertrand, G. *Organometallics* **2011**, *30*, 2617.

As shown in Figure 3.3, the assigned ^{1}H-NMR spectrum of the crude reaction mixture shows the signals of the dealkylated compound **52** and the 1,5-disubstituted triazole **53**, which is the major product in a 68 % yield.

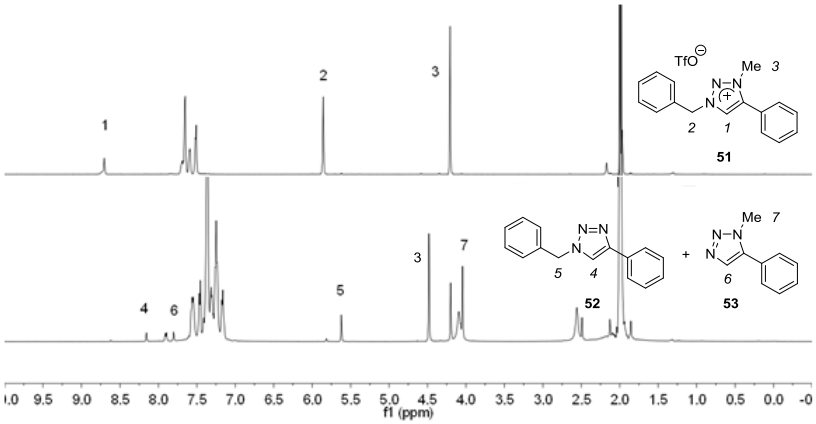


Figure 3.3. ^{1}H NMR (500 MHz, MeCN-d_3) spectra of the triazolium salt **51** (top) and the reaction crude of the non-selective *N*-dealkylation reaction of **51** with thiophenol and K_2CO_3 (bottom).

We concluded that the poor site-discrimination observed during the *N*-dealkylation reaction could be attributed to the similar electrophilicity of the two carbon substituents (Me and Bn groups) placed at the *N*1 and *N*3 positions of the 1,2,3-triazole ring, respectively.

As mentioned above[161] (see, section 3.2), the pivaloyloxymethyl group is particularly suitable for the *N*-protection of triazoles because it can be removed with nucleophilic or basic reagents. In order to get a quantitative estimation of the relative electrophilicity of the methyl, benzyl and pivaloyloxymethyl groups attached to triazolium rings, we decided to perform computational studies with triazolium cations **A** and **B** (Figure 3.4).[169] We also compared the mechanisms of the nucleophilic attack of the hydroxide ion to the pivaloyloxymethyl group of the cationic triazolium structure **B** and the neutral counterpart **C**. Each reaction was studied assuming two possible pathways involving the cleavage of the O−CH_2 bond [paths (1) and (3)] and the cleavage of the CH_2−N bond [paths (2) and (4)], respectively.

[169] Computational studies conducted by Dr. Jose Ignacio Miranda.

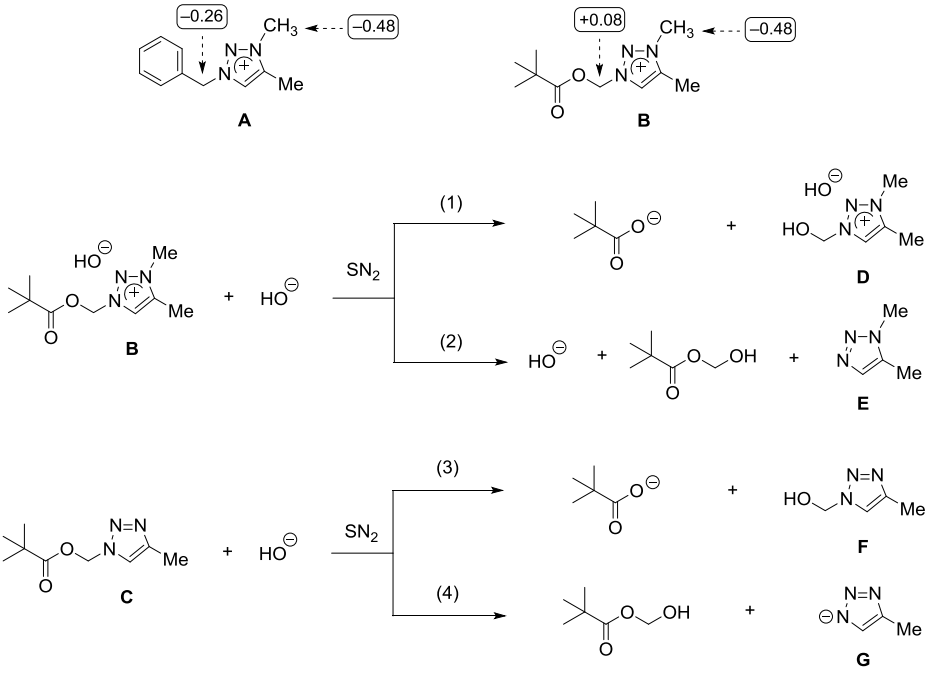


Figure 3.4. "*Ab initio*" natural bond orbital (NBO) charges of triazolium cations **A** and **B** (top). Comparison of the SN_2 reaction pathways (1)-(4) for the nucleophilic reaction of hydroxide anion with the pivaloyloxymethyl group of the triazolium cation **B** and the triazole **C** (bottom).

First, we computed the natural bonding (NBO)[170] charges of the *N*1-benzyl and *N*3-methyl carbon atoms of the triazolium structure **A**. We found negative formal charge values of -0.26 and -0.48, respectively, indicating a poor electrophilicity in both cases, but pointing at a higher reactivity for the benzyl methylene compared to the methyl group. Indeed, this result was in excellent agreement with the experimentally observed *N*-dealkylation ratio (Secheme 3.6).

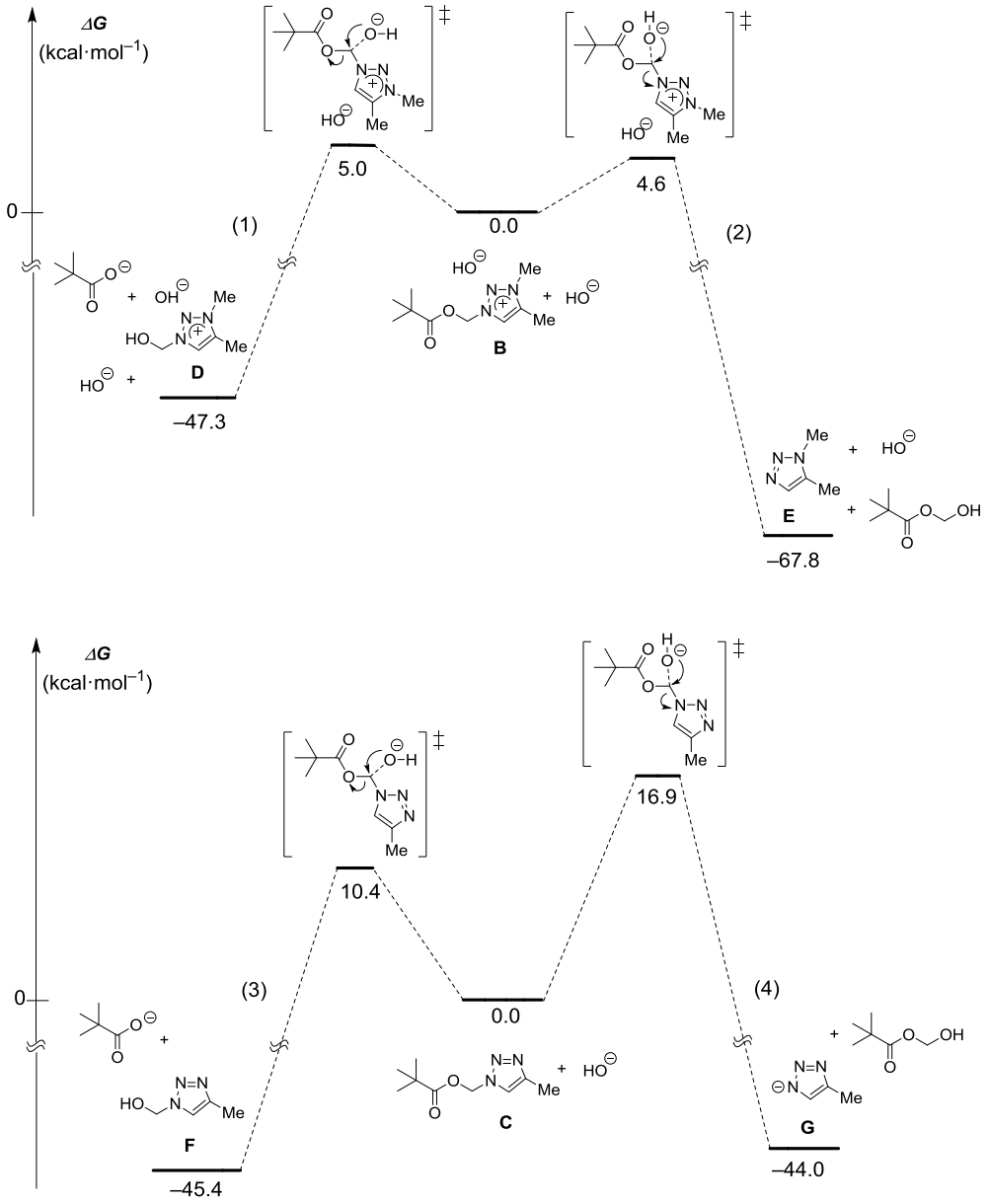
In contrast to benzyl and methyl groups, the pivaloyloxymethyl group in the triazolium structure **B** showed a positive formal charge of +0.08 at the methylene carbon. This result strongly suggested that *N*-pivaloyloxymethyl group could be clearly discriminated from other *N*-alkyl groups using site-selective nucleophilic *N*-dealkylation reactions. To confirm this

[170] NBO 6.0. Software: Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Landis, C. R.; Weinhold, F. Theoretical Chemistry Institute, University of Wisconsin, Madison, **2013**.

observation, we computed the SN_2 reaction pathways (1)-(4) to calculate the activation barriers ($\Delta G^{\ddagger}$) leading to the corresponding triazole four products **D**-**G**. The free energy profiles of the hydroxide-promoted *N*-dealkylation of the 1,2,3-triazolium salt **B** and the 1,2,3-triazole **C** are represented in Scheme 3.7.

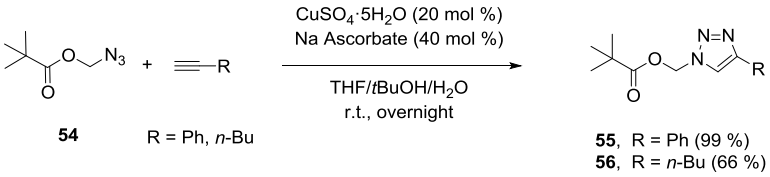
As expected, the SN_2 hydroxylation reaction was significantly more favored in the case of triazolium electrophile **B**, which could evolve through pathways (1) and (2) reaching computationally characterizable transition states of 5.0 kcal/mol and 4.6 kcal/mol activation barriers, respectively. In contrast, equivalent pathways (3) and (4) from the neutral triazole **C** involved transition states with comparatively higher activation barriers of 10.4 kcal/mol and 16.9 kcal/mol.

It should be mentioned that pathway (2), anticipated as the more likely by our computational study, involved the participation of a triazolium cation as the leaving group of the reaction to give rise to the uncharged 1,5-disubstituted triazole **E**. This transformation of charged reactants into neutral products, makes pathway (2) thermodynamically very favored ($\Delta G^{o}_{\mathbf{E}}$ = -67.8 kcal/mol) and could be considered the driving force of the reaction.



Scheme 3.7. Transition states and reaction products computed at B3LYP/6-31G* level of theory for the nucleophilic *N*-dealkylation of 1,2,3-triazolium salt **B** (top) and 1,2,3-triazole **C** (bottom) to the triazole products **D**-**G**. Relative $\Delta G^{\ddagger}$ energies in kcal/mol calculated at 25 ºC in MeOH.

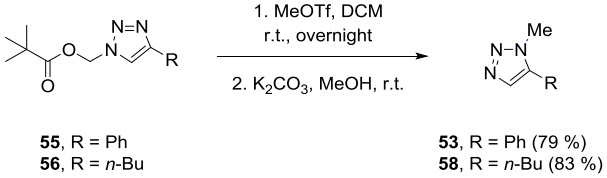
In agreement with these calculations, we further synthesized the 1-pivaloyloxymethyl substituted 1,2,3-triazoles **55** and **56** upon Cu-catalyzed cycloaddition of azidomethyl pivalate with phenylacetylene and 1-hexyne (Scheme 3.8).



Scheme 3.8. Preparation of model 1-pivaloyloxymethyl triazoles.

With the 1-pivaloyloxymethyl-1,2,3-triazoles in hand, we studied their alkylation reaction to form the intermediate 1,3,4-trisubstituted 1,2,3-triazolium triflates and submit them to the site-selective *N*-dealkylation reaction in order to obtain the desired 1,5-disubstituted 1,2,3-triazoles. In general, triazolium salts were not isolated and the products were obtained in a one-pot two-step reaction. Two different alkylating methods were used; the introduction of the methyl group was performed utilizing commercially available methyl trifluoromethanesulfonate in dichloromethane (Scheme 3.9), while the *N*3-alkylation with larger or functionalized groups was achieved employing previously synthesized alkyl triflates (Table 3.1) in the absence of solvent (Scheme 3.10).

As shown in the Scheme 3.9, 1,5-disubstituted 1,2,3-triazoles **53** and **57** were obtained in good overall yields, both from aromatic and aliphatic substituted triazoles. The operational simplicity of the method is worth mentioning, since practically pure products were obtained after a simple filtration of the final reaction mixture and evaporation of the solvent.



Scheme 3.9. One-pot two-step synthesis of 1-methyl-5-substituted-1,2,3-triazoles following a *N*3-alkylation / *N*1-dealkylation reaction sequence.

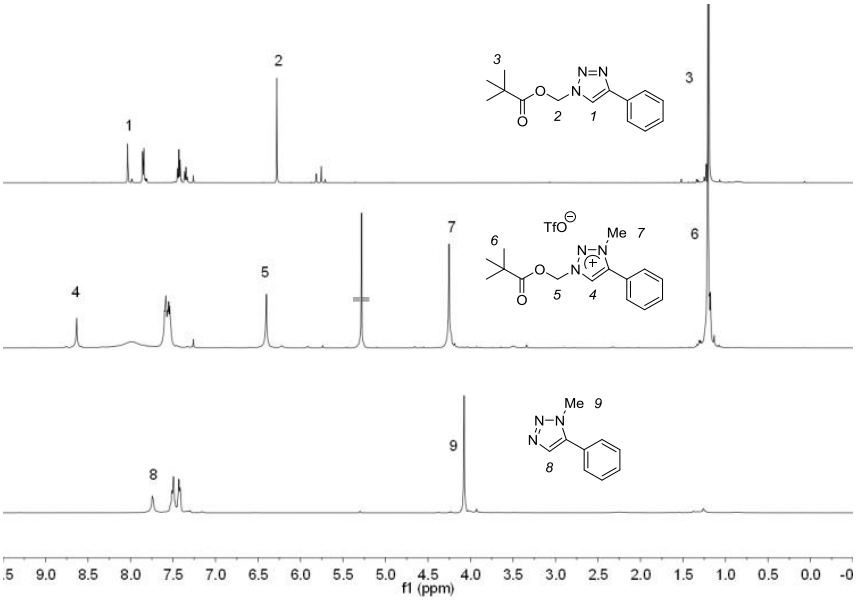
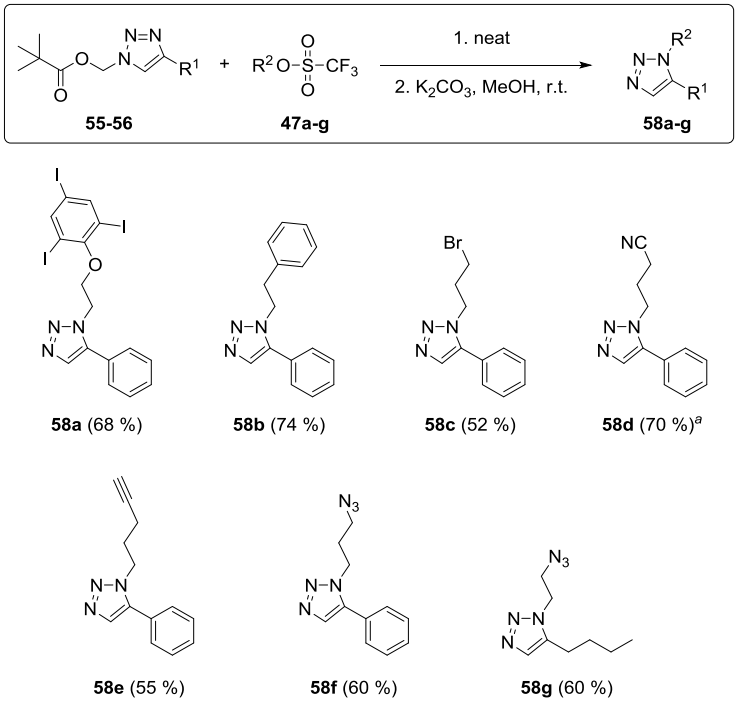


Figure 3.5. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of the *N*-methylation reaction of **55** with MeOTf followed by *N*-depivaloyloxymethylation reaction in the presence of K_2CO_3 and MeOH.

As depicted in Figure 3.5, upon methylation of triazole **55**, the signal corresponding to the heterocyclic proton *1* was shifted from 7.96 ppm to 8.52 ppm and a methyl group singlet appeared at 4.25 ppm. When the subsequent dealkylation took place, the pivaloyloxy group signal vanished and the 1,5-substituted triazole *8* proton shifted back to higher field as a result of the recovery of a neutral triazole nature.

Alternatively, to achieve equivalent transformations with more hindered or functionalized alkyl triflates, the alkylation step was conducted in neat conditions attained by the slow evaporation of an equimolar solution of the triflate and the triazole in dichloromethane under a very smooth nitrogen gas stream. The reaction was stirred at room temperature overnight and then it was dissolved in MeOH and K_2CO_3 was added to promote the dealkylation step.



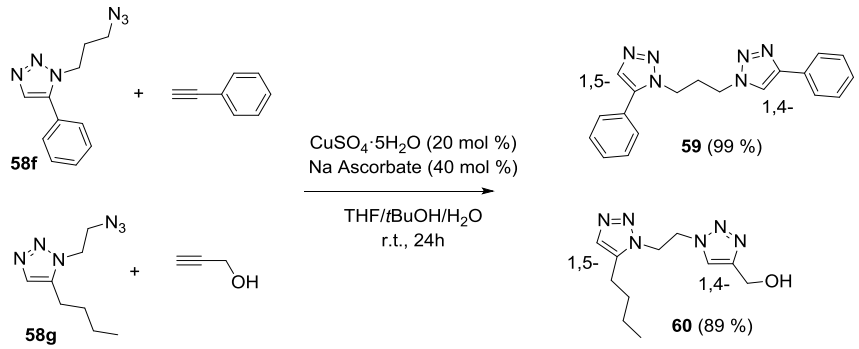
Scheme 3.10. 1,5-Disubstituted 1,2,3-triazoles prepared from 1-pivaloyloxy triazoles following a two-step "one-pot" *N*-alkylation / *N*-dealkylation sequence. [a]Obtained from **58c** by substitution with NaCN.

As depicted in Scheme 3.10, the method gave the corresponding 1,5-disubstituted 1,2,3-triazoles in moderate to good yields from functionalized alkyl triflates bearing halogen (compound **58c**), terminal alkyne (compound **58e**) and azide groups (compounds **58f** and **58g**). As mentioned before, we were unable to synthesize 3-cyanopropyl triflate (compound **4d** in Table 3.1) from the corresponding alcohol and therefore, compound **58d** could not be prepared directly from **55** using the alkylation/dealkylation method. Alternatively, the nitrile **58d** was obtained in 70 % yield from bromide **58c** by substitution reaction with sodium cyanide. It is worth noting that after the completion of our work, Page *et al.* reported the *N*-debenzylation reaction of triazolium salts bearing nonfunctionalized alkyl and aryl groups utilizing KO*t*Bu in THF at 0 ºC to provide 1,5-disubstituted 1,2,3-triazoles.[171]

[171] Page, P. C. B.; Stephenson, G. R.; Harveya, J.; Slawinb, A. M. Z. *Synlett* **2016**, *27*, 2500.

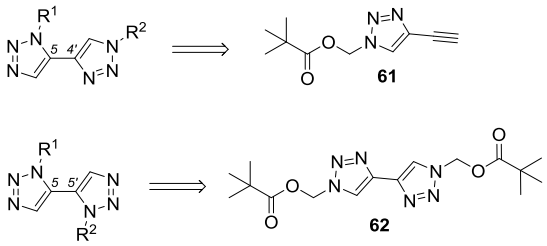
3.4.3 Synthesis of non-symmetrically substituted bistriazoles with full positional control.

Following our working plan, the previously synthesized 1,5-disubstituted 1,2,3-triazoles containing latent reactivity (compounds **58f** and **58g**) were further reacted with alkynes under CuAAC conditions as shown in Scheme 3.11. As expected, azide groups incorporated by *N*-alkylation reacted with phenylacetylene and propargyl alcohol to provide the corresponding 1,5- and 1,4-substituted bis(1,2,3-triazoles) **59** and **60** in excellent yields.



Scheme 3.11. Synthesis of 1,5- and 1,4-substituted bistriazoles linked by alkyl chains.

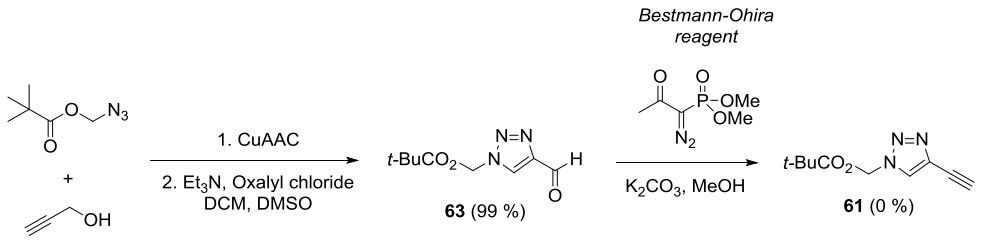
Encouraged by these results, we next explored the poorly studied, yet unknown, synthesis of, 4,5'- and 5,5'-tethered bistriazoles. To face this challenge, we began with the synthesis of the key triazole **61** containing the 4-alkyne group (Scheme 3.12).



Scheme 3.12. Synthesis of 5,4'-tethered and 5,5'-tethered bistriazoles from 1-pivaloyloxymethyl-1,2,3-triazole precursors.

We first tried to synthesize triazole **61** starting from a "click" reaction between the pivaloyloxymethyl azide and propargyl alcohol to obtain a 4-hydroxymethyl triazole intermediate which was immediately oxidized under Swern reaction conditions in nearly quantitative yield (Scheme 3.13). The resulting aldehyde derivative **63** was further treated with

the Bestmann-Ohira reagent but the desired 4-ethynyl compound was not obtained, regardless of the reaction conditions. In this respect, different types of bases as well as temperature and reaction time variations were tried with no evidence of the formation of **61**. As the initial product was consumed, the reaction was followed by ^{1}H-NMR and we observed that a competitive attack of the base to the pivaloyloxymethyl group occurred instead of the desired Bestmann-Ohira reaction. Therefore, we decided to evaluate the synthesis of triazole **67** using alternative routes.



Scheme 3.13. Attempted synthesis of 4-ethynyl-1,2,3-triazole **61** *via* Bestmann-Ohira reaction.

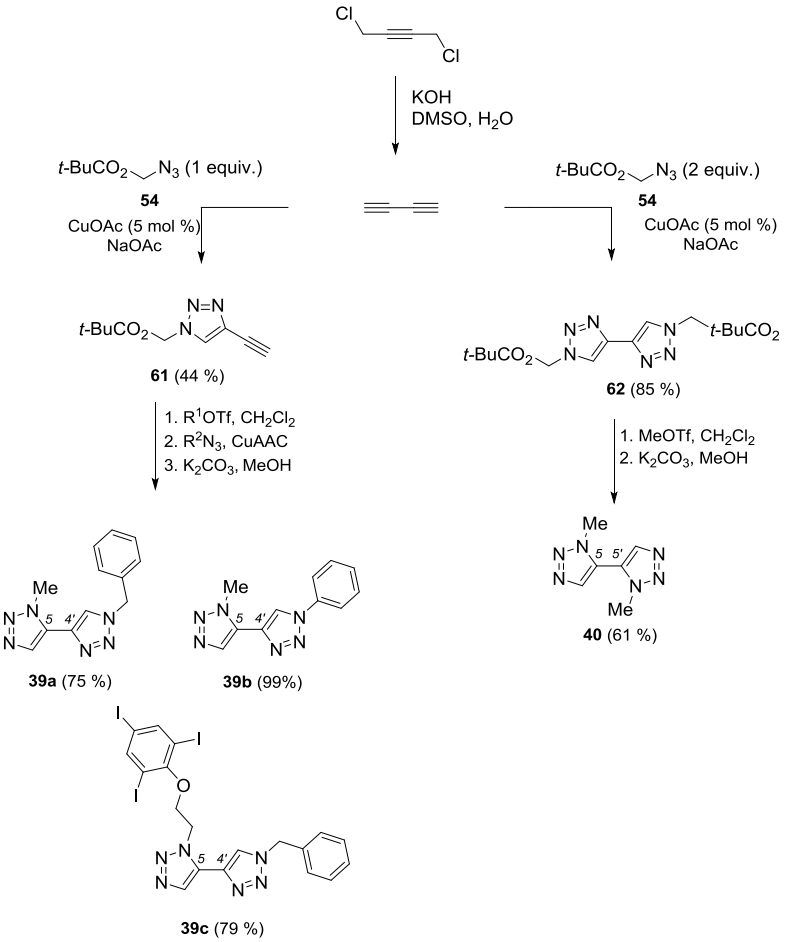
After a short literature survey, we decided to use butadyine as the starting material for the synthesis of ethynyl triazole **61**. Butadiyne is not commercially available, but it can be readily prepared by heating 1,4-dichlorobut-2-yne in a mixture of DMSO and water with potassium hydroxide at 70 ºC.[172] The resulting product evolved as a gas *via* cannula to a trap containing dry THF cooled at -78 ºC giving a solution that could be stored in the fridge.

Triazoles **61** and **62** were synthesized from pivaloyloxymethyl azide **54** *via* CuAAC reactions using an excess of butadiyne or stoichiometric amounts of reactants, respectively. In the former case, mixtures of mono- and bistriazole products were obtained, which were readily separated by column chromatography to give the major alkyne **61** in moderate yield (Scheme 3.14).

To demonstrate the usefulness of our methodology, we next prepared 5,4'-tethered bis(1,2,3-triazole) backbones through an alkylation/"click"/deprotection sequence. As shown in Scheme 3.14, nonsymmetrically substituted bis(1,2,3-triazoles) **39a**, **39b** and **39c** were obtained in overall yields ranging from good to excellent. To the best of our knowledge, this is the first time that these types of biheterocyclic systems have been prepared.

[172] Janka, M.; Anderson, G. K.; Rath, N. P. *Organometallics* **2004**, *23*, 4382.

Alternatively, to get 5,5'-tethered bis(1,2,3-triazoles), we performed the double methylation of the 4,4'-bistriazole **62** with methyl triflate, followed by *in situ N*-dealkylation with potassium carbonate to get the target product **40** in 61 % yield (Scheme 3.14).

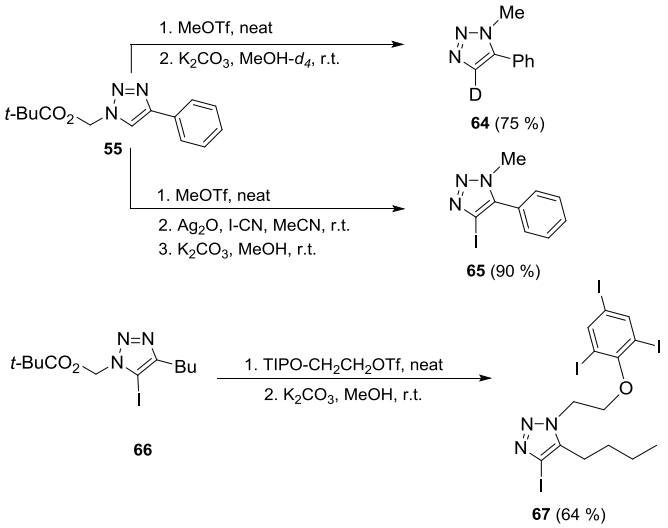


Scheme 3.14. Synthesis of 5,4'- and 5,5'-tethered bis(1,2,3-triazoles).

3.4.4 Synthesis of 1,4,5-trisubstituted 1,2,3-triazoles

We also extended the *N*-alkylation/activation methodology to the preparation of multisubstituted monocyclic triazoles. To accomplish this task, we studied the *in situ* deuteration and halogenation of the intermediate triazolium salts at the reactive C5-H position before the *N*-dealkylation of the pivaloyloxymethyl group.

As depicted in Scheme 3.15, triazole **55** could be easily converted into the C5-deuterated triazole **64** through an alkylation/deuteration sequence by simply replacing the regular methanol solvent with the deuterated analog. Although the reaction mechanism was not studied in detail, this outcome suggested the formation of a triazolydine carbene intermediate prior to the dealkylation reaction.



Scheme 3.15. Synthesis of fully substituted 1,2,3-triazoles. (TIP = 2,3,6-triiodophenyl).

In order to support the latter statement, we trapped the intermediate carbene from the *N*3-methyl-triazolium salt of **55** with silver oxide to form the corresponding silver carbene complex, which was reacted *in situ* with cyanogen iodide to iodinate the C5-H bond. The subsequent deprotection of the pivaloyloxymethyl group with potassium carbonate in methanol provided fully substituted 1,2,3-triazole **65** in good yields, in agreement with the suggested hypothesis.

Finally, we synthesized the C5-iodo derivative **66**, substituted with the pivaloyl group in the *N*1 position. In this case, the alkylation and deprotection processes were found compatible with the presence of a iodine atom as the reaction proceeded in good yield to give the product **67** in 64 % isolated yield.

3.5 Conclusions

The assembly of a variety of 1,5-disubstituted 1,2,3-triazoles incorporating "click" compatible functional groups has been easily conducted starting from 1-pivaloyloxymethyl-1,2,3-triazoles and functionalized alcohols, following a one-pot site-selective *N*-alkylation / *N*-dealkylation sequence.[173]

A two-step protocol consisting in the heterogeneous triflation of alcohols followed by a solvent-free *N*3-alkylation of 1,2,3-triazoles, provided *N*1, *N*3, C4-trisubstituted 1,2,3-triazolium salts in excellent yields and with great operational simplicity. The following *N*-dealkylation reaction of the pivaloyloxymethyl group provided a wide variety of 1,5-disubstituted 1,2,3-triazoles or 1,4,5-trisubstituted 1,2,3-triazoles following a metal-free protocol that takes advantage of the electrophilicity enhancement generated by the triazolium moiety on the 1-(pivaloxyloxymethyl)-1,2,3-triazolium intermediates.

The latent reactivity of some *N*3-azide-1,2,3-triazoles has been demonstrated by achieving their CuAAC coupling with alkynes to transform them into double 1,4- and 1,5-multisubstituted 1,2,3-triazoles.

Finally, 5,5'- and 5,4'-tethered-bistriazoles have been successfully prepared upon reaction of buta-1,3-diyne and azidomethyl pivalate and subsequent CuAAC processes. To the best of our knowledge, our approach represents the first straightforward access to those appealing bistriazoles.

[173] Monasterio, Z.; Irastorza, A.; Miranda, J. I.; Aizpurua, J. M. *Org. Lett.* **2016**, *18*, 2511.

Experimental

Experimental

General

All reagents and solvents were obtained from commercial sources (Aldrich, Acros, Alfa Aesar, Merck, and Fluka) and were used without further purification unless stated otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried through PS-MD-2columns. Extra pure dichloromethane (CH_2Cl_2), acetonitrile (MeCN), hexane (Hex) and ethyl acetate (EtOAc) were bought from Sharlau.

Moisture sensitive reactions were carried out under an atmosphere of nitrogen in oven or flame-dried glassware with magnetic stirring.

The solvents produced in reactions or chromatography were evaporated in *Büchi* R-210 rotapavors under reduced pressure.

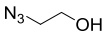
Purification of reaction products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates and visualization was accomplished with UV light (λ = 254 nm) or $KMnO_4$ as TLC stain.

^{1}H NMR spectra were recorded on Bruker avance spectrometers operated at 500 and 400 MHz; and ^{13}C NMR spectra were recorded at 125 and 101 MHz. The chemical shifts are reported as δ values (ppm) relative to residual deuterated solvent as internal standards: for $CDCl_3$ δH (7.26 ppm) and δC (77.16 ppm), respectively; for MeOH-d_4 δH (3.31 ppm) and δC (49.0 ppm), respectively; for MeCN-d_3 δH (1.94 ppm) and δC (118.26 ppm, 1.32 ppm), respectively; for DMSO-d_6 δH (2.50 ppm) and δC (39.52 ppm), respectively.

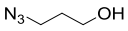
High resolution mass spectra were performed by SGIker and were acquired on a time of flight (TOF) mass spectrometer (SYNAPT G2 HDMS from Waters, Milford, MA, USA) equipped with an electrospray source in positive mode (ESI^+). Melting points were measured with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a *Bruker Alpha P*.

3.1 Synthesis of the starting materials

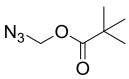
3.1.1 Synthesis of alkylazides



2-Azidoethan-1-ol (46e).[171] 2-Bromoethanol (3.00 mmol, 375 mg) was dissolved in H_2O (2 mL) and NaN_3 (3.30 mmol, 214 mg) was subsequently added. The mixture was stirred at 80 ºC for 8 h, then cooled down at room temperature and the solution was extracted with Et_2O (2 mL x 3). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to provide 222 mg (87 %) of **46e** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (q, J = 5.4 Hz, 2H), 3.48 (t, J = 5.1 Hz, 2H).



3-Azidopropan-1-ol (46f).[167] A mixture of 3-bromopropan-1-ol (7.19 mmol, 0.65 mL) and NaN_3 (14.38 mmol, 935 mg) in H_2O (20 mL) was stirred at 80 ºC for 18 h, then cooled down to room temperature and the solution was extracted with EtOAc (20 mL x 5). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to provide 698 mg (96 % yield) of **46f** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (t, J = 5.7 Hz, 2H), 3.45 (t, J = 6.3 Hz, 2H), 1.83 (p, J = 5.9 Hz, 2H).

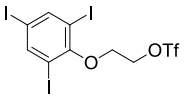


Azidomethyl pivalate (54).[174] A mixture of chloromethyl pivalate (1.33 mmol, 20 μL), NaN_3 (2.00 mmol, 130 mg) and NaI (10 mg) in H_2O (0.20 mL) was stirred at 90 ºC for 12h, then cooled down to room temperature and extracted with DCM (5 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to provide 174 mg (83 % yield) of **54** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (s, 2H), 1.25 (s, 9H).

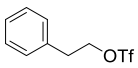
[174] Jogireddy, R.; Rullkötter, J.; Christoffers, J. *Synlett* **2007**, *18*, 2847.

3.1.2 General procedure for the preparation of alkyl trifluoromethanesulfonates

Trifluoromethanesulfonic anhydride Tf_2O (1.20 mmol) was added dropwise over a period of 5 min to a vigorously stirred solution of the corresponding alcohol (1.00 mmol) and anhydrous $KHCO_3$ (1.40 mmol) in dry CH_2Cl_2 (8.6 mL) cooled to 0 ºC and the reaction mixture was stirred for 5-18 hours at ambient temperature. The suspension was filtered through a 0.2 µm PTFE filter and the resulting alkyl trifluoromethanesulfonate solution was used in the next alkylation reactions without further purification. Alternatively, the pure product could be isolated by evaporating the solvent at reduced pressure.



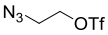
2-(2,4,6-Triiodophenoxy)ethyl trifluoromethanesulfonate (47a). The general procedure **3.1.2** was followed starting from 2-(2,4,6-triiodophenoxy)ethanol (0.58 mmol, 300 mg), $KHCO_3$ (0.81 mmol, 81 mg) and Tf_2O (0.70 mmol, 117 µL) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 18 hours and provided 355 mg (94 % yield) of **47a** as a white solid. Mp 62-63 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 2H), 4.95 (t, J = 4.2 Hz, 2H), 4.32 (t, J = 4.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 147.5, 118.6 (q, J = 320.5, 319.9 Hz), 91.5, 90.3, 74.5, 69.2. IR (cm^{-1}): 1238, 1200, 1141, 930, 863, 612.



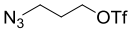
Phenethyl trifluoromethanesulfonate (47b).[175] The general procedure **3.1.2** was followed starting from 2-phenylethan-1-ol (0.14 mmol, 20 µL), $KHCO_3$ (0.20 mmol, 20 mg) and Tf_2O (0.17 mmol, 30 µL) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 18 hours to provide a solution of the product in practically quantitative yield, as checked from the ^{1}H-NMR analysis of a sample. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.19 (m, 5H), 3.86 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H). A freshly prepared solution of the alkyl triflate was directly used for the *N*-alkylation of triazoles.

[175] Dang, H.; Mailig, M.; Lalic, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 6473.

3-Bromopropyl trifluoromethanesulfonate (47c).[176] The general procedure **3.1.2** was followed starting from 3-bromopropan-1-ol (0.14 mmol, 13 µL), $KHCO_3$ (0.20 mmol, 20 mg) and Tf_2O (0.17 mmol, 30 µL) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 18 hours to provide a solution of the product in practically quantitative yield, as checked from the ^{1}H-NMR analysis of a sample. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (t, J = 7.1 Hz, 2H), 3.50 (t, J = 7.1 Hz, 2H), 1.90 (q, J = 7.1 Hz, 2H). A freshly prepared solution of the alkyl triflate was directly used for the *N*-alkylation of triazoles.

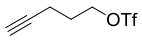


2-Azidoethyl trifluoromethanesulfonate (47e).[177] The general procedure **3.1.2** was followed starting from 2-azidoethan-1-ol (4.00 mmol, 360 mg), $KHCO_3$ (5.60 mmol, 560 mg) and Tf_2O (4.80 mmol, 0.80 mL) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 18 hours to provide a solution of the product in practically quantitative yield, as checked from the ^{1}H-NMR analysis of a sample. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (t, J = 7.6 Hz, 2H), 1.70 (t, J = 7.4 Hz, 2H). A freshly prepared solution of the alkyl triflate was directly used for the *N*-alkylation of triazoles.



3-Azidopropyl trifluoromethanesulfonate (47f).[162] The general procedure **3.1.2** was followed starting from 3-azidopropan-1-ol (0.14 mmol, 14 mg), $KHCO_3$ (0.20 mmol, 20 mg) and Tf_2O (0.17 mmol, 30 µL) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 18 hours to provide a solution of the product in practically quantitative yield, as checked from the ^{1}H-NMR analysis of a sample. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (t, J = 7.5 Hz, 2H), 1.52-1.48 (m, 6H). A freshly prepared solution of the alkyl triflate was directly used for the *N*-alkylation of triazoles.

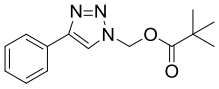
[176] Hugelshofer, C. L.; Mellem, K. T.; Myers, A. G. *Org. Lett.* **2013**, *15*, 3134.
[177] Vourloumis, D.; Winters, G. C.; Simonsen, K. B.; Takahashi, M.; Ayida, B. K.; Shandrick, S.; Zhao, Q.; Han, Q.; Hermann, T. *ChemBioChem* **2005**, *6*, 58.



Pent-4-yn-1-yl trifluoromethanesulfonate (47g).[178] The general procedure **3.1.2** was followed starting from pent-4-yn-1-ol (0.14 mmol, 13 μL), $KHCO_3$ (0.20 mmol, 20 mg) and Tf_2O (0.17 mmol, 30 μL) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 18 hours to provide a solution of the product in practically quantitative yield, as checked from the ^{1}H-NMR analysis of a sample. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (t, J = 7.1 Hz, 2H), 2.93 (t, J = 4.2, 1H), 2.51-2.44 (m, 2H), 1.65 (q, J = 7.6 Hz, 2H). A freshly prepared solution of the alkyl triflate was directly used for the *N*-alkylation of triazoles.

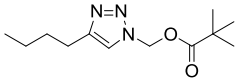
3.2 Synthesis of 1,4-disubstituted and 1,4,5-trisubstituted-1*H*-1,2,3-triazoles

General procedure : To a solution of the corresponding azide (1.00 mmol) and alkyne (1.10 mmol) in a mixture of deoxygenated ^{t}BuOH/THF 1:1 (1 mL/mmol), a deoxygenated aq. solution of $CuSO_4 \cdot 5H_2O$ (20 mol %, 1mL/mmol) followed by a deoxygenated aq. solution of sodium ascorbate (40 mol %, 1mL/mmol) was added. The resulting mixture was stirred under inert atmosphere at room temperature overnight. The solvent was partially evaporated under reduced pressure and the resulting solution was washed with aq. NH_3, extracted with EtOAc and washed with brine. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc 7/3) unless otherwise noted.

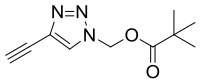


4-Phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole (55).[174] The general procedure **3.2** was followed starting from azidomethyl pivalate **54** (7.50 mmol, 1.18 g) and phenylacetylene (7.50 mmol, 0.82 mL) to provide 1.60 g (82 % yield) of **55** as a yellowish solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.78 (d, J = 7.4 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.4 Hz, 1H), 6.21 (s, 2H), 1.12 (s, 9H).

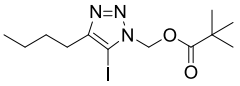
[178] Reyes-Gutiérrez, P. E.; Jirásek, M.; Severa, L.; Novotná, P.; Koval, D.; Sázelová, P.; Vávra, J.; Meyer, A.; Císařová, I.; Šaman, D.; Pohl, R.; Štěpánek, P.; Slavíček, P.; Coe, B. J.; Hájek, M.; Kašička, V.; Urbanová, M.; Teplý, F. *Chem. Commun.* **2015**, *51*, 1583.



4-Butyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole (56). The general procedure **3.2** was followed starting from azidomethyl pivalate **54** (12.3 mmol, 1.90 g) and hept-1-yne (13.50 mmol, 1.55 mL) to provide 1.90 g (66 % yield) of **56** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 6.10 (s, 2H), 2.60 (t, J = 7.7 Hz, 2H), 1.54 (p, J = 7.6 Hz, 2H), 1.25 (q, J = 7.6 Hz, 2H), 1.06 (s, 9H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.5, 148.7, 121.8, 69.5, 38.6, 31.2, 26.6, 25.0, 22.0, 13.6. IR (cm^{-1}): 2960, 1744, 1458, 1243, 1118, 1031, 776. MS (ESI^{+}) m/z (%) 240 (M+H). HRMS calcd. for $C_{12}H_{22}N_3O_2$: 240.1712; found: 240.1720.



4-Ethynyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole (61). A solution of KOH (65 mmol, 4.30 g) in water (10 mL) and DMSO (2.5 mL) was heated at 75 °C for 30 min in a three-necked flask equipped with a condenser and a dropping funnel. The top of the condenser was connected, via a tube to a trap containing dry THF, which was cooled at -20 °C. 1,4-dichloro-2-butyne (16 mmol, 1.60 mL) was added dropwise over a period of 30 min, while the temperature was maintained at 75 °C. A stream of argon was passed through the apparatus, which forced the butadiyne gas into the cold THF trap. The tube was extracted, and azidomethyl pivalate **54** (3.30 mmol, 512 mg), sodium acetate (9.90 mmol, 812 mg) and CuOAc (0.66 mmol, 120 mg) were added and the mixture was stirred at ambient temperature for 3-4 hours. Then, the solution was filtered through a celite pad, and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, Hex/EtOAc 7:3) to provide 301 mg (44 % yield) of **61** as a white solid. Mp 192-195 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 6.31 (s, 2H), 3.35 (s, 1H), 1.25 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.7, 140.3, 122.2, 75.6, 69.9, 38.9, 27.0. IR (cm^{-1}): 2976, 1730, 1279, 1144, 1089, 994, 829, 727. MS (ESI^{+}) m/z (%) 208 (M+H). HRMS calcd. for $C_{10}H_{14}N_3O_2$: 208.1086; found: 208.1096.



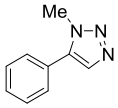
4-Butyl-5-iodo-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole (66). To a suspension of CuI (5.50 mmol, 1.10 g) in MeCN (15 mL) under argon at room temperature a solution of *N*-bromosuccinimide (6.00 mmol, 1.10 g) in MeCN (15 mL) was added and the mixture was stirred 5 min at room temperature. Later on, azidomethyl pivalate **54** (5.00 mmol, 786 mg), hept-1-yne (5.50 mmol, 0.63 mL) and DIPEA (5.50 mmol, 1 mL) were subsequently added and the resulting mixture was stirred at room temperature overnight. Next, the mixture was washed with HCl 10 %, aq. NH_3, extracted with EtOAc and washed with brine. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc 1/1) to provide 729 mg (40 % yield) of **66** as a yellowish solid. Mp 57-58 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 2H), 2.56 (t, J = 7.5 Hz, 2H), 1.57 (p, J = 7.5 Hz, 2H), 1.26 (h, J = 7.1 Hz, 2H), 1.09 (s, 9H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.1, 152.4, 78.8, 70.7, 38.5, 30.6, 26.6, 25.3, 21.9, 13.5. IR (cm-1): 2958, 2933, 1742, 1458, 1276, 1120, 1031, 985, 827. MS (ESI^+) m/z (%) 208 (M+H). HRMS calcd. for $C_{12}H_{21}N_3O_2I$: 366.0678; found: 366.0685.

3.3 Synthesis of 1,5-disubstituted-1*H*-1,2,3-triazoles

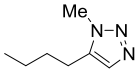
General Procedure A: A solution of the corresponding 1,2,3-triazole (1.00 mmol) and MeOTf (1.10 mmol) in anhydrous CH_2Cl_2 (5 mL) was stirred under nitrogen atmosphere at room temperature for 18 hours. The solvents were removed under reduced pressure. The crude was dissolved in MeOH (5 mL) and K_2CO_3 (2.00 mmol) was added. The mixture was stirred at ambient temperature for 5 hours. The solvents were removed under reduced pressure and the crude product was dissolved in CH_2Cl_2 and filtered using a PTFE filter.

General Procedure B: To a solution of the corresponding 1,2,3-triazole (1.00 mmol) in CH_2Cl_2 (8.6 mL) the selected alkyl trifluoromethanesulfonate (1.20 mmol) was added and the mixture was slowly evaporated by passing a slow stream of dry nitrogen through the solution. After 18 hours at 30 ºC the resulting viscous mixture was dissolved in MeOH (5 mL) and K_2CO_3 (2.00 mmol) was added. The mixture was stirred at ambient temperature for

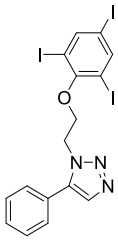
5 hours. The solvents were removed under reduced pressure and purified by column chromatography (silica gel, Hex/EtOAc 1:1).



1-Methyl-5-phenyl-1*H*-1,2,3-triazole (53). The general procedure **A** was followed starting from 4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **55** (0.60 mmol, 150 mg), MeOTf (0.64 mmol, 70 µL) and CH_2Cl_2 (2.50 mL) to provide 43 mg (79 % yield) of **53** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.47 (d, J = 7.4 Hz, 3H), 7.42-7.35 (m, 2H), 4.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.4, 133.3, 129.5, 129.1, 128.6, 127.0, 35.6. IR (cm^{-1}): 3423, 2917, 1749, 1483, 1244, 1016, 765, 696. MS (ESI$^+$) m/z (%) 160 (M+H). HRMS calcd. for $C_9H_{10}N_3$: 160.0875; found: 160.0869.

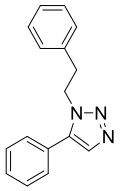


5-Butyl-1-methyl-1*H*-1,2,3-triazole (57). The general procedure **A** was followed starting from 4-butyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **56** (0.63 mmol, 150 mg), MeOTf (0.69 mmol, 80 µL) and CH_2Cl_2 (2.50 mL) to provide 73 mg (83 % yield) of **57** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1H), 3.87 (s, 3H), 2.54 (t, J = 7.8 Hz, 2H), 1.60-1.51 (m, 2H), 1.33 (q, J = 7.5 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.4, 131.9, 34.1, 29.9, 22.7, 22.1, 13.6. IR (cm^{-1}): 2956, 2872, 1749, 1458, 1238, 1031. MS (ESI$^+$) m/z (%) 140 (M+H). HRMS calcd. for $C_7H_{14}N_3$: 140.1188; found: 140.1173.

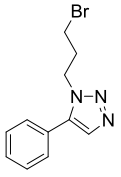


5-Phenyl-1-[2-(2,4,6-triiodophenoxy)ethyl]-1*H*-1,2,3-triazole (58a). The general procedure **B** was followed starting from 4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **55** (0.24 mmol, 60 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate **47a**

(0.29 mmol, 187 mg). The product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 95:5) to provide 105 mg (68 % yield) of **58a** as a white solid. Mp 141-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.73 (s, 2H), 7.60-7.53 (m, 2H), 7.48 (d, J = 5.7 Hz, 3H), 4.79 (t, J = 5.4 Hz, 2H), 4.41 (t, J = 5.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.8, 147.4, 139.3, 133.1, 129.7, 129.6, 129.1, 127.0, 91.8, 90.1, 70.9, 47.5. IR (cm^{-1}): 1421, 1234, 1024, 768, 697. MS (ESI$^+$) m/z (%) 644 (M+H). HRMS calcd. for $C_{16}H_{13}N_3OI_3$: 643.8193; found: 643.8207.

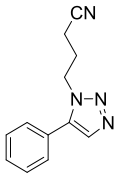


1-(2-Phenethyl)-5-phenyl-1*H*-1,2,3-triazole (58b). The general procedure **B** was followed starting from 4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **55** (0.12 mmol, 30 mg) and phenethyl trifluoromethanesulfonate **47b** (0.14 mmol, 35 mg). The product was purified by column chromatography (silica gel, Hex/EtOAc 7:3) to provide 22 mg (74 % yield) of **58b** as a white solid. Mp 110-112 ºC. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.15 (s, 1H), 7.83 (d, J = 7.6 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.30-7.09 (m, 6H), 3.74 (t, J = 7.2 Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, MeOH-d_4): δ 140.3, 131.2, 130.0, 130.0, 129.9, 129.5, 129.3, 127.1, 127.0, 64.3, 40.3. IR (cm^{-1}): 1450, 960, 768, 690. MS (ESI$^+$) m/z (%) 250 (M+H). HRMS calcd. for $C_{16}H_{16}N_3$: 250.1344; found: 250.1327.

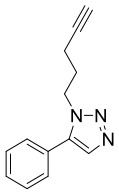


1-(3-Bromopropyl)-5-phenyl-1*H*-1,2,3-triazole (58c). The general procedure **B** was followed starting from 4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **55** (0.24 mmol, 60 mg) and 3-bromopropyl trifluoromethanesulfonate **47c** (0.28 mmol, 76 mg). The product was purified by column chromatography (silica gel, Hex/EtOAc 7:3) to provide 33 mg (52 % yield) of **58c** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.55-7.46 (m, 3H), 7.44-7.35 (m, 2H), 4.50 (t, J = 6.8 Hz, 2H), 3.36 (t, J = 6.3 Hz, 2H), 2.53-2.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.2, 133.2, 129.7, 129.3, 128.9, 126.9, 46.5, 32.7, 29.6. IR

(cm^{-1}): 2960, 1482, 1455, 1274, 1245, 1014, 959, 833, 763, 697. MS (ESI^+) m/z (%) 186 (M+H). HRMS calcd. for $C_{11}H_{12}N_3$: 186.1031; found: 186.1018.

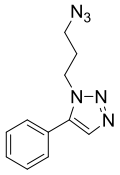


1-(4-Cyanopropyl)-5-phenyl-1*H*-1,2,3-triazole (58d). The general procedure **B** was followed starting from 4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **55** (0.50 mmol, 130 mg) and 3-bromopropyl trifluoromethanesulfonate **47c** (0.60 mmol, 163 mg). The product was purified by column chromatography (silica gel, Hex/EtOAc 7:3). After that, the resulting, 1-(3-bromopropyl)-5-phenyl-1*H*-1,2,3-triazole **58c** (0.24 mmol, 64 mg) was dissolved in EtOH/H_2O 7:3 (3 mL) and KCN (0.65 mmol, 43 mg) was added. The mixture was stirred for 45 min at 90 ºC, and then cooled down to room temperature and stirred overnight. The solvent was evaporated under reduced pressure, and the aqueous phase was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by column chromatography (silica gel, Hex/EtOAc 1:1) to provide 36 mg (70 % yield) of **64d** as a white solid. Mp 55-57 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.61-7.46 (m, 3H), 7.45-7.31 (m, 2H), 4.47 (t, J = 6.6 Hz, 2H), 2.41 (t, J = 7.1 Hz, 2H), 2.22 (p, J = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.2, 133.4, 129.9, 129.4, 128.8, 126.6, 118.3, 46.4, 25.8, 14.8. IR (cm^{-1}): 1738, 1483, 1233, 964, 840, 769, 696, 537. MS (ESI^+) m/z (%) 213 (M+H). HRMS calcd. for $C_{12}H_{13}N_4$: 213.1140; found: 213.1134.

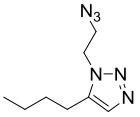


1-(Pent-4-yn-1-yl)-5-phenyl-1*H*-1,2,3-triazole (58e). The general procedure **B** was followed starting from 4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **55** (0.24 mmol, 60 mg) and pent-4-yn-1-yl trifluoromethanesulfonate **47g** (0.28 mmol, 61 mg). The product was purified by column chromatography (silica gel, Hex/EtOAc 7:3) to provide 14 mg (27 %

yield) of **58e** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.54-7.37 (m, 5H), 4.47 (t, J = 7.0 Hz, 2H), 2.21 (td, J = 6.9, 2.4 Hz, 2H), 2.09 (p, J = 6.9 Hz, 2H), 1.89 (t, J = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.2, 129.6, 129.2, 129.0, 127.2, 82.3, 69.8, 61.2, 47.0, 28.8, 15.9. IR (cm^{-1}): 3293, 2948, 1283, 1413, 1240, 1208, 965, 764, 697, 637. MS (ESI^+) m/z (%) 212 (M+H). HRMS calcd. for $C_{13}H_{14}N_3$: 212.1188; found: 212.1195.

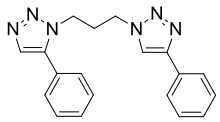


1-(3-Azidopropyl)-5-phenyl-1*H*-1,2,3-triazole (58f). The general procedure **B** was followed starting from 4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **55** (0.12 mmol, 30 mg) and 3-azidopropyl trifluoromethanesulfonate **47f** (0.14 mmol, 32.6 mg). The product was purified by column chromatography (silica gel, Hex/EtOAc 1:1) to provide 11 mg (40 % yield) of **58f** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.57-7.46 (m, 3H), 7.45-7.34 (m, 2H), 4.44 (t, J = 6.9 Hz, 2H), 3.34 (t, J = 6.4 Hz, 2H), 2.12 (p, J = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.3, 133.2, 129.8, 129.4, 128.9, 126.9, 48.3, 45.5, 29.3. IR (cm^{-1}): 2094, 1482, 1455, 1238, 964, 764, 697. MS (ESI^+) m/z (%) 229 (M+H). HRMS calcd. for $C_{11}H_{13}N_6$: 229.1202; found: 229.1187.

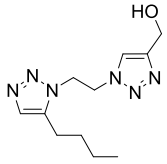


1-(3-Azidoethyl)-5-phenyl-1*H*-1,2,3-triazole (58g). The general procedure **B** was followed starting from 4-butyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **56** (1.70 mmol, 407 mg), and 2-azidoethyl trifluoromethanesulfonate **47e** (2.00 mmol, 438 mg). The product was purified by column chromatography (silica gel, Hex/EtOAc 1:1) to provide 198 mg (60 % yield) of **58g** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 4.36 (t, J = 5.9 Hz, 2H), 3.86 (t, J = 5.9 Hz, 2H), 2.71-2.62 (m, 2H), 1.67 (p, J = 7.5 Hz, 2H), 1.43 (dq, J = 14.6, 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.7, 131.2, 50.1, 46.0, 29.5, 22.1, 21.6, 13.1. IR (cm^{-1}): 2958, 2933, 2097, 1455, 1286, 1237, 827. MS (ESI^+) m/z (%) 195 (M+H). HRMS calcd. for $C_{18}H_{15}N_6$: 195.1358; found: 195.1360.

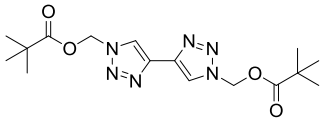
3.4 Synthesis of 1,4- and 1,5-substituted bistriazoles



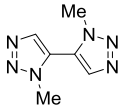
5-Phenyl-1-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl]-1*H*-1,2,3-triazole (59). The general procedure **3.2** was followed starting from 1-(3-azidopropyl)-5-phenyl-1*H*-1,2,3-triazole **58f** (0.07 mmol, 16.5 mg) and phenylacetylene (0.09 mmol, 10 µL) to provide 22 mg (99 % yield) of **59** as a white solid. Mp 113-115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.74 (m, 3H), 7.71 (s, 1H), 7.49-7.24 (m, 8H), 4.44 (t, J = 6.2 Hz, 2H), 4.41-4.33 (m, 2H), 2.59-2.42 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0, 147.8, 130.4, 129.9, 129.4, 128.9, 128.7, 128.3, 126.5, 125.8, 120.6, 47.1, 44.9, 30.3, 22.7. IR (cm^{-1}): 764, 696. MS (ESI^{+}) m/z (%) 331 (M+H). HRMS calcd. for $C_{19}H_{19}N_6$: 331.1671; found: 331.1664.



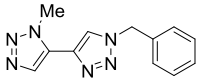
1-[2-(5-Butyl-1*H*-1,2,3-triazol-1-yl)ethyl]-4-hydroxymethyl-1*H*-1,2,3-triazole (60). The general procedure **3.2** was followed starting from 1-(2-azidoethyl)-5-butyl-1*H*-1,2,3-triazole **58g** (1.87 mmol, 364 mg) and propargyl alcohol (2.10 mmol, 0.12 mL) to provide 415 mg (89 % yield) of **60** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 1H), 7.26 (s, 1H), 5.03 (s, 1H), 4.85 (t, J = 5.9 Hz, 2H), 4.65 (t, J = 5.9 Hz, 2H), 4.56 (s, 2H), 2.21 (t, J = 7.8 Hz, 2H), 1.37 (p, J = 7.9, 7.3 Hz, 2H), 1.26-1.13 (m, 2H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.1, 138.3, 131.5, 123.1, 55.4, 49.0, 46.8, 29.5, 21.8, 21.8, 13.3. IR (cm^{-1}): 3346, 2931, 1667, 1455, 1236, 1039, 823, 765. MS (ESI^{+}) m/z (%) 251 (M+H). HRMS calcd. for $C_{11}H_{19}N_6O$: 251.1620; found: 251.1623.



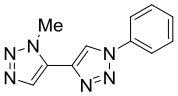
1,1'-[Di(pivaloyloxymethyl)]-4,4'-bis(1*H*-1,2,3-triazole) (62). KOH (4.30 g, 65.00 mmol), water (10 mL), and DMSO (2.5 mL) were heated to 75 °C for 30 min in a three-necked flask equipped with a condenser and a dropping funnel. The top of the condenser was connected via a tube to a trap containing dry THF, which was cooled to -20 °C. 1,4-dichloro-2-butyne (1.60 mL, 16 mmol) was added dropwise over a period of 30 min, while the temperature was maintained at 75 °C. A stream of argon was passed through the apparatus, which forced the butadiyne into the cold THF trap. The tube was extracted, and azidomethyl pivalate **54** (1.02 g, 6.60 mmol), sodium acetate (1.60 g, 19.80 mmol) and CuOAc (240 mg, 1.32 mmol) were added at ambient temperature for 4 hours. The solution was filtered through a celite pad, and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, Hex/EtOAc 7:3) to provide 1.06 g (85 % yield) of **62** as a white solid. Mp 201-203 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 6.26 (s, 4H), 1.20 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.6, 140.3, 122.2, 69.9, 38.9, 26.9. IR (cm-1): 2971, 1731, 1279, 1144, 1057, 828. MS (ESI^+) m/z (%) 365 (M+H). HRMS calcd. for $C_{16}H_{25}N_6O_4$: 365.1937; found: 365.1950.



1,1'-Dimethyl-5,5'-bis(1,2,3-triazole) (40). The general procedure **3.3.A** was followed starting from 1,1'-[di(pivaloyloxymethyl)]-4,4'-bis(1*H*-1,2,3-triazole) **62** (0.22 mmol, 80 mg) and MeOTf (1.2 mmol, 160 µL) to provide 22 mg (61 % yield) of **40** as a white solid. Mp 140-142 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 2H), 4.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 134.5, 124.7, 35.8. IR (cm-1): 3133, 1664, 1452, 1252, 1149, 1024, 954, 858, 679. MS (ESI^+) m/z (%) 165 (M+H). HRMS calcd. for $C_6H_9N_6$: 165.0889; found: 165.0892.

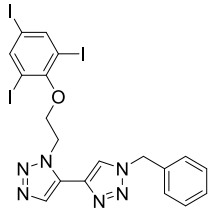


1-Benzyl-1'-methyl-4,5'-bis(1*H*-1,2,3-triazole) (39a). A solution of 4-ethynyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **61** (0.24 mmol, 50 mg) and MeOTf (0.36 mmol, 41 µL) in CH_2Cl_2 (2.50 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour and, on completion, the solvent was removed under reduced pressure. Then, benzylazide (0.24 mmol, 32 mg), $CuSO_4 \cdot 5H_2O$ (0.05 mmol, 12 mg), sodium ascorbate (0.10 mmol, 19 mg) and NaOAc (0.24 mmol, 20 mg) in THF/*t*BuOH/H_2O 1:1:1 (2 mL) were added and the mixture was stirred at ambient temperature for 18 hours. Finally, the volatiles were removed under reduced pressure, the crude product was dissolved in MeOH (2.50 mL) and K_2CO_3 (0.48 mmol, 66 mg) was added. The resulting mixture was stirred at ambient temperature for 3 hours. The solvents were removed under reduced pressure to provide 43.5 mg (75 % yield) of **39a** as a yellow solid. Mp 113-115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.75 (s, 1H), 7.46-7.23 (m, 5H), 5.58 (s, 2H), 4.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.1, 134.0, 132.5, 129.3, 129.2, 128.5, 128.3, 122.2, 54.5, 37.0. IR (cm^{-1}): 3079, 1426, 1243, 1025, 827, 731. MS (ESI^+) m/z (%) 241 (M+H). HRMS calcd. for $C_6H_9N_6$: 241.1202; found: 241.1203.



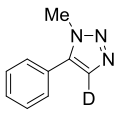
1-Methyl-1'-phenyl-5,4'-bis(1,2,3-triazole) (39b). A solution of 4-ethynyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **61** (0.24 mmol, 50 mg) and MeOTf (0.36 mmol, 41 µL) in CH_2Cl_2 (2.50 mL) was stirred under nitrogen atmosphere at ambient temperature for 1 hour. After that, the solvent was removed under reduced pressure. Then, phenylazide (0.24 mmol, 29 mg), $CuSO_4 \cdot 5H_2O$ (0.05 mmol, 12 mg), sodium ascorbate (0.10 mmol, 19 mg) and NaOAc (0.24 mmol, 20 mg) in THF/*t*BuOH/H_2O 1:1:1 (2 mL) were added and the mixture was stirred at ambient temperature for 18 hours. Finally, the volatiles were removed under reduced pressure, the crude product was dissolved in MeOH (2.50 mL) and K_2CO_3 (0.48 mmol, 66 mg) was added. The resulting mixture was stirred at ambient temperature for 3 hours. The solvents were removed under reduced pressure to provide 54 mg (99 % yield) of **39b** as a white solid. Mp 129-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.90 (s, 1H), 7.76 (d, J = 7.8 Hz, 2H), 7.52 (t, J = 7.7 Hz, 2H), 7.46 (d, J = 7.2 Hz, 1H), 4.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.1, 136.0, 129.5, 128.9, 120.7, 120.2, 116.4, 36.8. IR (cm^{-1}): 3119, 2962, 2920, 1599, 1509, 1458, 1418, 1248, 1176, 1030 749. MS (ESI^+) m/z (%) 227 (M+H). HRMS calcd. for $C_{11}H_{11}N_6$: 227.1045; found: 227.1040.



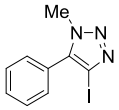
1-Benzyl-1'-[2-(2,4,6-triiodophenoxy)ethyl]-5,4'-bis(1,2,3-triazole) (39c). To a solution of 4-ethynyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **61** (0.29 mmol, 60 mg) in CH_2Cl_2 (0.50 mL), 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate **53a** (0.35 mmol, 225 mg) was added and evaporated under reduced pressure. After 18 hours at 30 ºC, benzylazide (0.29 mmol, 39 mg), $CuSO_4 \cdot 5H_2O$ (0.06 mmol, 14 mg), sodium ascorbate (0.12 mmol, 23 mg) and NaOAc (0.29 mmol, 24 mg) in THF/*t*BuOH/H_2O 1:1:1 (2 mL) were added and the mixture was stirred at ambient temperature for 18 hours. Finally, the volatiles were removed under reduced pressure, the crude product was dissolved in MeOH (3.00 mL) and K_2CO_3 (0.6 mmol, 80 mg) was added. The resulting mixture was stirred at ambient temperature for 3 hours. The solvents were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, Hex/EtOAc 7/3) to provide 166 mg (79 % yield) of **39c** as a white solid. Mp 75-76 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.90 (m, 3H), 7.85 (s, 1H), 7.35-7.23 (m, 5H), 5.57 (s, 2H), 5.13 (t, J = 5.2 Hz, 2H), 4.36 (t, J = 5.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 147.3, 135.9, 134.1, 132.8, 129.3, 129.1, 128.2, 122.9, 91.8, 90.0, 71.1, 54.5, 48.9. IR (cm^{-1}): 3123, 1425, 1229, 1045, 717, 695. MS (ESI^+) m/z (%) 725 (M+H). HRMS calcd. for $C_{19}H_{16}N_6OI_3$: 724.8520; found: 724.8529.

3.5 Synthesis of 1,4,5-trisubstituted-1*H*-1,2,3-triazoles



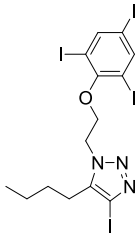
1-Methyl-5-phenyl-1*H*-1,2,3-triazole-4-*d* (64). To a solution of 4-phenyl-1-(pivaloyloxymethyl) 1*H*-1,2,3-triazole **55** (0.18 mmol, 48 mg) and MeOTf (0.20 mmol, 22

μL) in $CDCl_3$ (2.50 mL) was stirred under nitrogen atmosphere at ambient temperature for 18 hours. The volatiles were removed under reduced pressure. The crude was dissolved in MeOH-d_4 (2.50 mL) and K_2CO_3 (0.15 mmol, 21 mg) was added. The mixture was stirred at ambient temperature for 5 hours. The solvents were removed under reduced pressure and the crude product was dissolved in CH_2Cl_2 and filtered through a PTFE filter to provide 9 mg (75 % yield) of **64** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 5H), 4.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.9, 130.7, 130.2, 129.8, 127.9, 127.0, 36.1. IR (cm^{-1}): 2933, 1460, 1259, 1028, 772. MS (ESI$^+$) m/z (%) 161 (M+H). HRMS calcd. for $C_9H_9DN_3$: 161.0937; found: 161.0929.



4-Iodo-1-methyl-5-phenyl-1*H*-1,2,3-triazole (65). To a solution of 4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **55** (0.40 mmol, 104 mg) in CH_2Cl_2 (2 mL), MeOTf (0.44 mmol, 50 μL) was added and the mixture was stirred for 5 hours at ambient temperature. Then, triflate exchange was carried out by using an anion exchange resin (I^- form) following a procedure reported in the literature,[179] and using MeCN as solvent. After that, a mixture of 3-methyl-4-phenyl-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazolium iodide, Ag_2O (0.24 mmol, 48 mg) and cyanogen halide (0.80 mmol, 122 mg) in CH_2Cl_2/MeCN 1:1 (3 mL) was stirred at ambient temperature for 6 hours. The mixture was filtered through a celite/silice 1:1 pad which was successively washed with CH_2Cl_2 and MeCN. Finally, the product was dissolved in MeOH (2 mL) and K_2CO_3 (0.80 mmol, 110 mg) was added. The mixture was stirred at ambient temperature for 5 hours. The solvents were removed under reduced pressure and the product was purified by column chromatography (silica gel, Hex/EtOAc 1:1) to provide 114 mg (99 % yield) of **65** as a yellowish solid. Mp 122-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.47 (m, 3H), 7.40-7.33 (m, 2H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.2, 130.1, 129.6, 129.1, 126.0, 89.7, 36.3. IR (cm^{-1}): 2949, 1481, 1449, 1258, 1031, 980, 772, 697, 542. MS (ESI$^+$) m/z (%) 286 (M+H). HRMS calcd. for $C_9H_9N_3I$: 285.9841; found: 285.9833.

[179] Dinarès, I.; Mesquida, N.; Ibáñez, A.; Alcalde, E. *Arkivoc* **2014**, *ii*, 85.



5-Butyl-4-iodo-1-[2-(2,4,6-triiodophenoxy]ethyl-1*H*-1,2,3-triazole (67). The general procedure **3.3.B** was followed starting from 4-butyl-5-iodo-1-(pivaloyloxymethyl)-1*H*-1,2,3-triazole **66** (0.24 mmol, 60 mg) and 2-(2,4,6-triiodophenoxy)ethyl trifluoromethanesulfonate **47a** (0.29 mmol, 187 mg). The product was purified by column chromatography (silica gel, Hex/EtOAc 1:1) to provide 192 mg (64 % yield) of **67** as a white solid. Mp 123-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 2H), 4.76 (t, J = 5.2 Hz, 2H), 4.32 (t, J = 5.1 Hz, 2H), 2.85-2.76 (m, 2H), 1.61 (p, J = 7.7 Hz, 2H), 1.40 (q, J = 7.3 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.5, 147.4, 141.4, 91.8, 90.3, 89.4, 71.0, 48.4, 30.6, 23.4, 22.5. IR (cm^{-1}): 2923, 1524, 1462, 1423, 1377, 1220, 1028, 1005, 852, 651. MS (ESI^+) m/z (%) 750 (M+H). HRMS calcd. for $C_{14}H_{16}N_3OI_4$: 749.7472; found: 749.7486.

3.6 Computational calculations

3.6.1 Computational methods

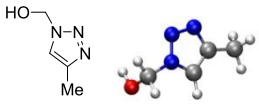
Density functional theory calculations were performed by use of Gamess 5 DEC 2014 (R1) from Iowa State University suite of programs.[180] Full geometry optimizations and harmonic analyses were carried out by use of the B3LYP hybrid functional [39] and the 6-31G* basis set. Solvent effects were computed by the C-PCM solvation model (MeCN, ε = 35.68) (MeOH ε = 32.63) and Grimme empirical dipersion DFTD3 v1.2[181] Free energies were computed at 298.15 K. The charges of compound D,E were obtained using NBO6.0 software.[182]

[180] Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus T. L.; Together with Dupuis, M.; Montgomery J. A. *J. Comput.Chem.* **1993**, *14*, 1347.

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

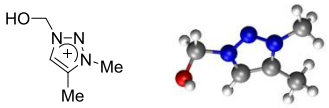
[182] NBO 6.0. Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Landis, C. R.; Weinhold F. *Theoretical Chemistry Institute* University of Wisconsin, Madison, WI, **2013**.

3.6.2 Electronic energies and cartesian coordinates for structures D and E NBO charges



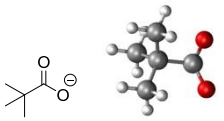
E(R-B3LYP)= -395.8693148

N	-3.52800	0.90638	1.87401
C	-3.85657	0.85272	0.54402
C	-4.93113	1.70737	-0.05106
H	-5.91839	1.43181	0.33867
H	-4.95377	1.60035	-1.13939
H	-4.76586	2.76402	0.18775
C	-3.04633	-0.09140	-0.05104
N	-2.27133	-0.56833	0.95692
N	-2.56603	0.05412	2.11937
H	-2.96325	-0.44897	-1.06631
C	-1.15900	-1.51408	0.88944
O	-0.01363	-0.95527	0.30064
H	-1.46134	-2.35383	0.26134
H	-0.99553	-1.85539	1.91677
H	0.35598	-0.30174	0.91838



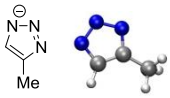
E(R-B3LYP)= -435.6024226

C	-4.56044	1.30706	2.96381
N	-3.76700	0.67755	1.90367
H	-4.47477	2.39078	2.86902
H	-4.15525	0.97898	3.91935
H	-5.60220	0.99501	2.86177
C	-3.91180	0.84224	0.55268
C	-4.92635	1.73797	-0.06704
H	-5.93787	1.47245	0.25852
H	-4.87778	1.65445	-1.15422
H	-4.74048	2.78188	0.20988
C	-2.92977	0.04507	0.00622
N	-2.29154	-0.52408	1.05982
N	-2.78656	-0.14939	2.21969
H	-2.64478	-0.13562	-1.01785
C	-1.15022	-1.49053	1.00459
O	-0.22247	-1.08314	0.06131
H	-1.56155	-2.44690	0.67772
H	-0.77862	-1.56128	2.03041
H	0.31934	-0.36279	0.42695



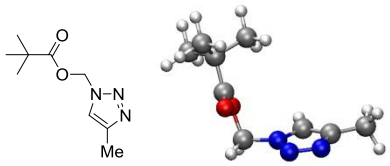
E(R-B3LYP)= -346.3516447

C	-3.43321	1.02169	-0.03115
C	-1.89356	0.99968	-0.03257
C	-3.91898	2.12996	0.92152
C	-3.97164	-0.33788	0.43133
C	-3.93344	1.37269	-1.47884
H	-3.57523	1.94985	1.95010
H	-5.01638	2.17946	0.94023
H	-3.54167	3.10174	0.58877
H	-1.49711	0.82134	0.97730
H	-1.50548	1.95449	-0.40022
H	-1.51129	0.20339	-0.68555
H	-3.61350	-0.58312	1.44145
H	-3.65338	-1.13066	-0.25373
H	-5.06668	-0.33893	0.44070
O	-4.70135	0.54877	-2.04592
O	-3.52873	2.47474	-1.94915



E(R-B3LYP)= -280.9080632

C	-8.03373	1.16105	-0.04309
C	-6.74744	0.68841	0.20185
C	-9.34640	0.43119	-0.02589
H	-9.76437	0.29747	-1.03412
H	-10.10230	0.96855	0.56179
H	-9.23091	-0.56662	0.41318
N	-7.92439	2.48157	-0.33173
N	-6.61562	2.79844	-0.25960
N	-5.87883	1.71987	0.06056
H	-6.41881	-0.31162	0.46556

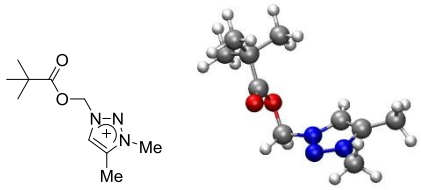


E(R-B3LYP)= -666.3245292

N	-3.61447	1.15351	1.68237
C	-3.94243	0.90750	0.37252
C	-5.06986	1.61110	-0.31456
H	-6.04014	1.27244	0.06852
H	-5.04653	1.42411	-1.39194
H	-5.00920	2.69240	-0.14985
C	-3.08065	-0.05673	-0.10129
N	-2.27242	-0.34618	0.95426
N	-2.60332	0.40476	2.03076
H	-2.97846	-0.54401	-1.05896
C	-1.14052	-1.24636	0.99429
O	-0.08555	-0.76819	0.15909
H	-1.42347	-2.21522	0.58558
H	-0.82501	-1.32960	2.03377
C	0.74815	0.17607	0.69694
O	0.65782	0.54120	1.84876
C	1.73644	0.70036	-0.34036
C	0.93120	1.53016	-1.36876
C	2.43955	-0.47722	-1.04954
C	2.76936	1.59031	0.36944
H	0.18173	0.91396	-1.87522
H	1.61639	1.93377	-2.12233
H	0.42187	2.37147	-0.88472
H	2.28504	2.43328	0.87133
H	3.48153	1.98382	-0.36384
H	3.32586	1.02160	1.12186
H	1.72287	-1.10960	-1.58074
H	2.98668	-1.10057	-0.33283
H	3.15871	-0.08323	-1.77599

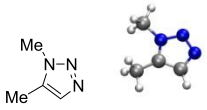
E(R-B3LYP)= -75.8256250

O	-6.46996	2.62939	0.00000
H	-5.49344	2.62939	0.00000



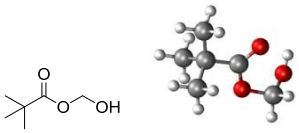
E(R-B3LYP)= -706.0548936

C	-4.44729	1.42405	2.90879
N	-3.74346	0.75165	1.81261
H	-4.23541	2.49442	2.85661
H	-4.07852	1.01091	3.84619
H	-5.51923	1.24621	2.80772
C	-3.96565	0.90804	0.46951
C	-5.02890	1.78291	-0.09499
H	-6.01645	1.48874	0.27646
H	-5.03209	1.70446	-1.18343
H	-4.85594	2.82973	0.17906
C	-3.01111	0.11392	-0.12595
N	-2.31166	-0.44669	0.89566
N	-2.74267	-0.06209	2.08046
H	-2.78680	-0.06388	-1.16588
C	-1.17336	-1.38007	0.79890
O	-0.15950	-0.81174	0.00409
H	-1.50834	-2.27927	0.28596
H	-0.85308	-1.58739	1.81971
C	0.62549	0.15077	0.61490
O	0.44008	0.47569	1.76412
C	1.67292	0.69765	-0.34508
C	0.95018	1.29289	-1.57576
C	2.59930	-0.45850	-0.78583
C	2.48095	1.78583	0.37911
H	0.39434	0.52511	-2.12167
H	1.69299	1.72719	-2.25370
H	0.25541	2.08811	-1.28174
H	1.83155	2.59854	0.71972
H	3.22684	2.20221	-0.30604
H	3.00133	1.37699	1.25107
H	2.04014	-1.24224	-1.30526
H	3.11045	-0.90641	0.07389
H	3.36067	-0.06565	-1.46869



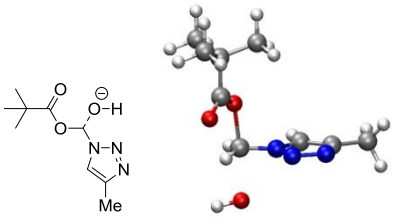
E(R-B3LYP)= -320.6871625

C	-8.02575	1.15772	0.07805
C	-6.73160	0.67121	0.09182
C	-9.35712	0.50156	0.23026
H	-9.98632	0.65762	-0.65464
H	-9.90242	0.89415	1.09753
H	-9.22758	-0.57455	0.36984
N	-7.85948	2.49224	-0.12226
N	-6.54881	2.81361	-0.22723
N	-5.86385	1.70315	-0.09589
H	-6.39464	-0.34781	0.22380
C	-8.88824	3.51617	-0.22786
H	-9.52098	3.32780	-1.09997
H	-8.38955	4.47931	-0.33824
H	-9.50542	3.52260	0.67478



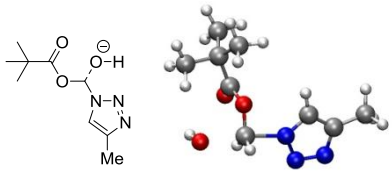
E(R-B3LYP)= -461.3095115

O	-4.90632	0.35947	-0.14724
C	-4.83780	1.59135	0.49083
O	-3.51795	2.19555	0.39692
H	-5.09854	1.53340	1.55316
H	-5.48894	2.28688	-0.03754
C	-2.54622	1.56311	1.08952
O	-2.75122	0.52378	1.69712
C	-1.20628	2.29268	1.00877
C	-1.38134	3.71187	1.59456
C	-0.78501	2.38587	-0.47502
C	-0.15846	1.50960	1.81301
H	-2.12143	4.28497	1.02859
H	-0.42464	4.24560	1.55596
H	-1.70328	3.67010	2.64189
H	-0.43765	1.44842	2.86985
H	0.81118	2.01478	1.74148
H	-0.04736	0.48946	1.43200
H	-1.52220	2.94198	-1.06135
H	-0.67070	1.38939	-0.91794
H	0.17892	2.90245	-0.54915
H	-4.42910	-0.27002	0.42288



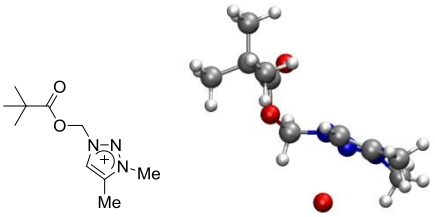
E(R-B3LYP)= -742.1496967
Freq= -564.970

N	-0.35275	2.09125	-1.65515
C	-0.93499	1.47305	-2.72832
C	-2.14591	2.02047	-3.41807
H	-3.04178	1.92231	-2.79225
H	-2.33034	1.48703	-4.35538
H	-2.01990	3.08479	-3.64658
C	-0.21621	0.32474	-2.99240
N	0.75980	0.30514	-2.05478
N	0.67686	1.38094	-1.25236
H	-0.31505	-0.44647	-3.74036
C	1.80677	-0.63270	-1.90024
O	2.97895	0.13847	-2.96170
H	1.73083	-1.53647	-2.47129
H	2.35756	-0.56857	-0.98162
C	4.00731	0.70755	-2.38347
O	4.26377	0.65776	-1.17679
C	4.91714	1.46207	-3.38294
C	4.07642	2.52962	-4.11363
C	5.46512	0.44543	-4.40641
C	6.07657	2.13130	-2.63133
H	3.23622	2.06876	-4.64004
H	4.69619	3.06393	-4.84465
H	3.67709	3.26691	-3.40661
H	5.70188	2.84628	-1.89195
H	6.72283	2.66671	-3.33777
H	6.68108	1.38928	-2.10040
H	4.64700	-0.05473	-4.93339
H	6.09654	0.95399	-5.14563
O	0.45386	-1.84423	-0.73324
H	6.07450	-0.32169	-3.91243
H	1.13375	-2.37718	-0.28288



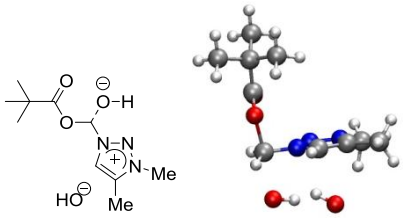
E(R-B3LYP)= -742.1393969
Freq= -584.592

O	-1.65442	2.73367	0.65321
N	1.65517	0.68671	0.24845
C	0.02627	1.55272	0.46757
C	3.37190	-0.65775	0.11352
C	4.32845	-1.81127	0.18329
H	4.91835	-1.88795	-0.73749
H	3.79267	-2.75605	0.32429
H	5.03689	-1.70564	1.01593
C	2.05135	-0.57202	0.53551
N	2.65577	1.35753	-0.32002
H	1.39136	-1.29357	0.99510
C	-1.41250	-0.08438	-0.39079
O	-1.18096	0.24535	-1.53710
C	-2.57330	-0.96931	0.04889
C	-3.74659	0.03739	0.21375
C	-2.29393	-1.67660	1.38665
C	-2.89133	-1.99870	-1.04620
H	-3.40514	0.92646	0.75784
H	-4.57613	-0.43881	0.74896
H	-4.10835	0.36446	-0.76786
H	-3.02594	-1.50828	-2.01444
H	-3.81413	-2.53281	-0.79362
H	-2.08516	-2.73589	-1.14303
H	-2.15780	-0.95898	2.19952
H	-3.14241	-2.32422	1.63643
H	-1.39571	-2.30264	1.32650
H	-2.01446	2.60706	-0.24064
N	3.71545	0.55006	-0.41069
H	0.31464	2.06812	1.36392
H	0.09807	1.99741	-0.50714
O	-0.73108	0.40570	0.67404



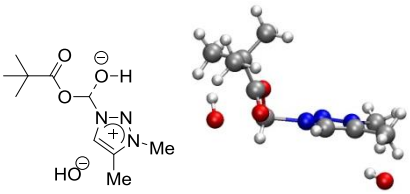
E(R-B3LYP)= -781.9102850

C	-5.23442	1.01341	2.69764
N	-3.99719	1.13000	1.93633
H	-5.99119	1.66410	2.26045
H	-5.05173	1.30280	3.73408
H	-5.50699	-0.04622	2.62699
C	-3.85838	1.45714	0.60262
C	-4.89203	2.18806	-0.18388
H	-5.82414	1.61436	-0.24180
H	-4.53073	2.35678	-1.20097
H	-5.11959	3.16090	0.26666
C	-2.62025	0.99404	0.25637
N	-2.09222	0.43941	1.39724
N	-2.98067	0.40487	2.37753
H	-2.07529	1.04037	-0.67216
C	-1.08452	-0.62397	1.45928
O	-0.13374	-0.44315	0.43204
H	-1.64942	-1.54616	1.28400
H	-0.63107	-0.60022	2.45083
C	0.86894	0.46670	0.67682
O	0.94031	1.07779	1.71887
C	1.80938	0.58643	-0.51722
C	0.99335	1.09825	-1.72745
C	2.40608	-0.80314	-0.83577
C	2.92497	1.58203	-0.16617
H	0.20509	0.39080	-2.00316
H	1.66013	1.22176	-2.58782
H	0.53417	2.07094	-1.51357
H	2.51381	2.56861	0.07014
H	3.60737	1.68514	-1.01691
H	3.50019	1.23846	0.69951
H	1.62312	-1.52369	-1.08792
H	2.97653	-1.19251	0.01538
H	3.08673	-0.71626	-1.69010
O	-3.89608	-1.66590	1.72784
H	-3.73674	-1.93041	2.64911



E(R-B3LYP)= -857.7509630
Freq= -569.53

C	-3.92947	1.87696	2.67785
N	-3.28536	1.11945	1.61120
H	-4.59647	2.61804	2.23654
H	-3.16096	2.37385	3.27352
H	-4.45975	1.06362	3.24701
C	-3.75295	0.87918	0.34907
C	-4.81732	1.68358	-0.31572
H	-5.78759	1.53913	0.17222
H	-4.91105	1.38037	-1.36101
H	-4.57808	2.75221	-0.28655
C	-3.02790	-0.20383	-0.09002
N	-2.21774	-0.54917	0.94514
N	-2.35542	0.24985	1.98228
H	-3.02925	-0.73532	-1.02733
C	-1.27181	-1.61570	0.98156
O	-0.03432	-0.87490	0.03083
H	-1.44011	-2.41970	0.29128
C	0.74043	-0.00878	0.65050
O	0.73894	0.18277	1.86630
C	1.66363	0.76906	-0.31351
C	0.79840	1.41431	-1.41612
C	2.65864	-0.22643	-0.94669
C	2.42189	1.85419	0.46359
H	0.26318	0.65121	-1.98741
H	1.43189	1.98946	-2.10266
H	0.05749	2.09976	-0.98561
H	1.72589	2.56535	0.92127
H	3.08778	2.40663	-0.21073
H	3.02545	1.41578	1.26441
H	2.12975	-1.01909	-1.48484
H	3.28917	-0.69284	-0.17967
H	3.31614	0.29520	-1.65337
O	-4.79002	-0.77999	3.46916
H	-3.86111	-0.93693	3.70348
O	-2.79651	-2.70420	1.95647
H	-3.47427	-2.06964	2.26145
H	-0.76966	-1.75116	1.91891

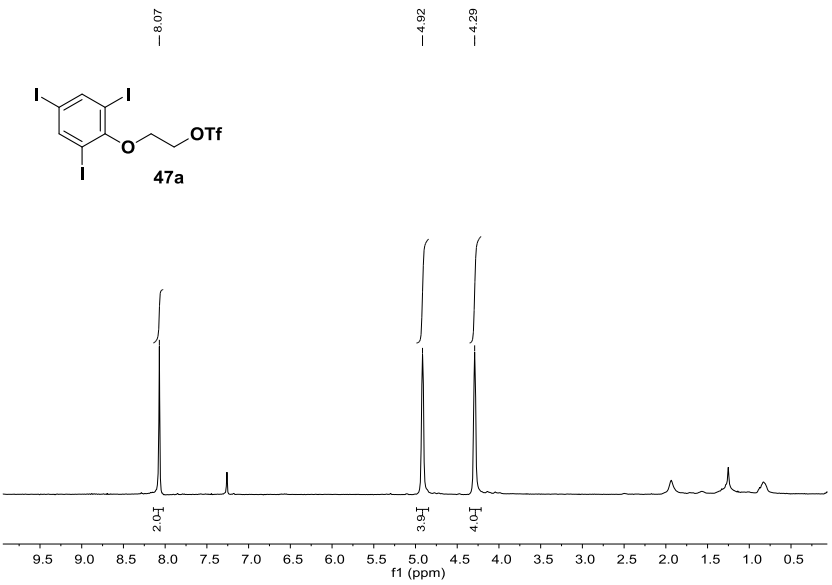


E(R-B3LYP)= -857.7460529
Freq= -576.08

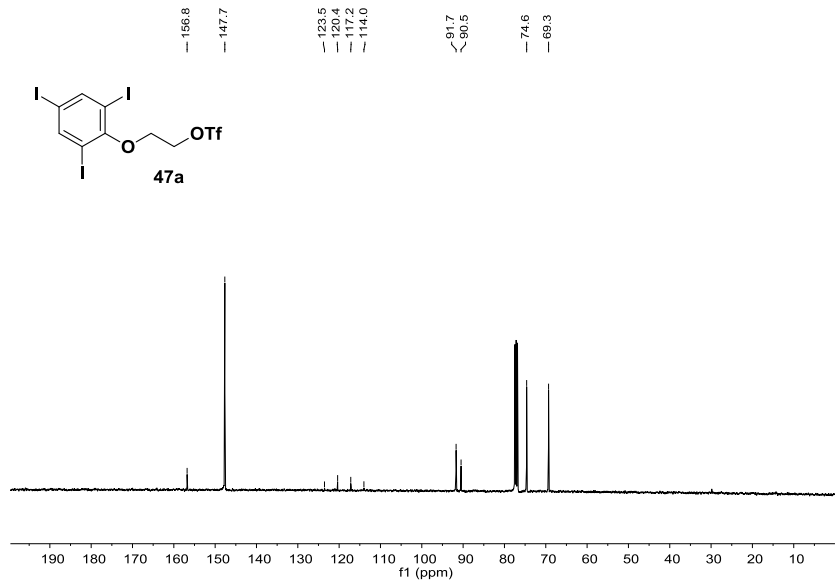
C	-4.64183	0.80303	3.27476
N	-3.77806	0.66853	2.10750
H	-4.87291	1.86412	3.40254
H	-4.06973	0.45735	4.13886
H	-5.61121	0.16439	3.16316
C	-3.85205	1.35684	0.93005
C	-4.79730	2.48450	0.68890
H	-5.83624	2.17246	0.83976
H	-4.68914	2.84636	-0.33642
H	-4.59616	3.32013	1.37029
C	-2.88718	0.77268	0.13054
N	-2.31232	-0.20684	0.86432
N	-2.84574	-0.28511	2.06403
H	-2.57141	0.98656	-0.87868
C	0.42315	0.04640	-0.80712
O	-0.32460	0.05965	-1.76305
C	1.85118	0.57565	-0.77206
C	2.21747	1.10862	-2.16518
C	2.77880	-0.59973	-0.37883
C	1.94822	1.70542	0.27725
H	2.17811	0.31161	-2.91475
H	3.23376	1.51711	-2.14665
H	1.52973	1.90111	-2.47730
H	1.30205	2.55047	0.01191
H	2.98111	2.06859	0.32699
H	1.66088	1.34707	1.27023
H	2.52576	-1.50175	-0.94547
H	2.66888	-0.84066	0.68288
H	3.82280	-0.32439	-0.56636
O	-6.91727	-0.84494	3.24762
H	-6.35391	-1.46759	3.74070
O	0.33229	-2.91078	-0.23370
H	1.04243	-2.69205	0.38991
C	-1.00750	-1.34740	0.39953
H	-1.43213	-1.64630	-0.54077
H	-1.08216	-1.96527	1.27598
O	0.05797	-0.46163	0.40519

Appendix

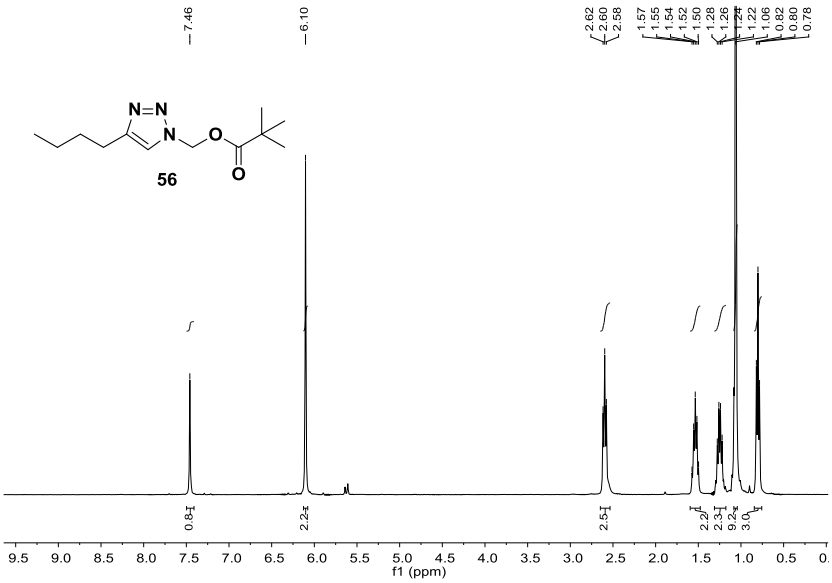
APPENDIX: ^{1}H NMR and ^{13}C NMR Spectra



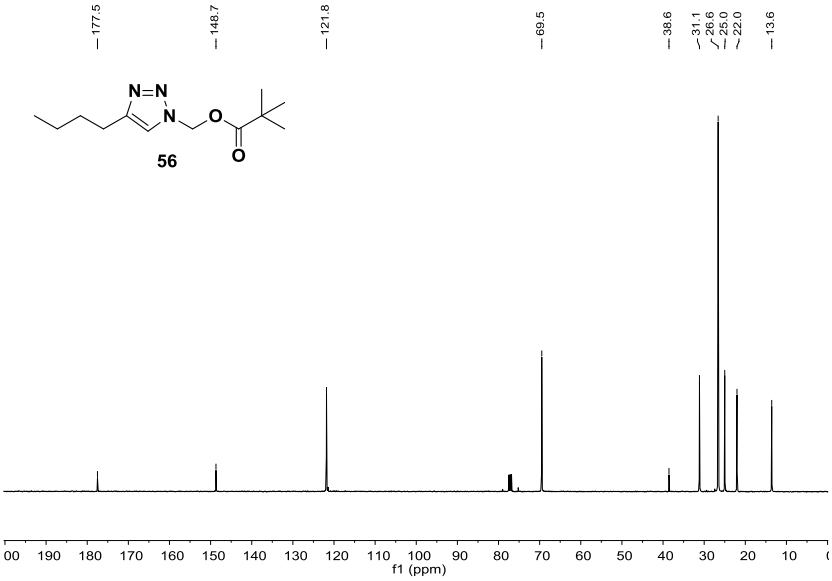
Spectrum 3.1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **47a**.



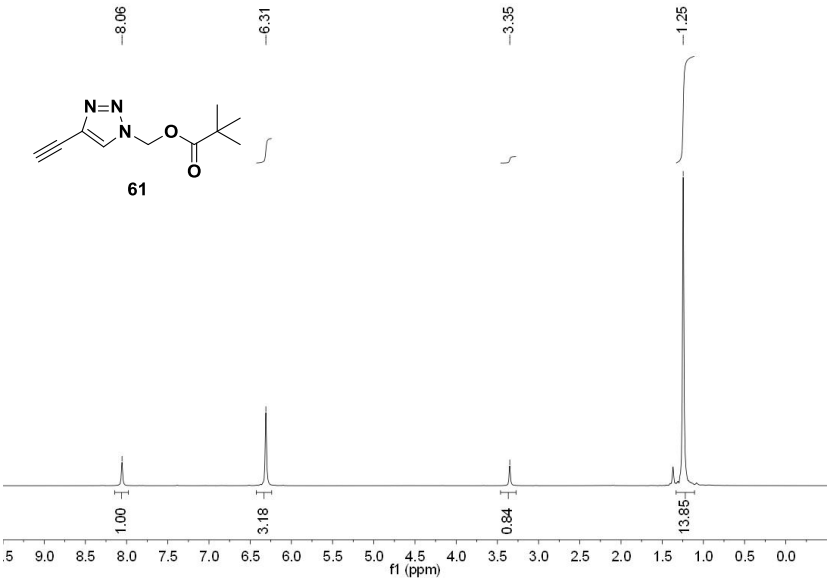
Spectrum 3.2. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **47a**.



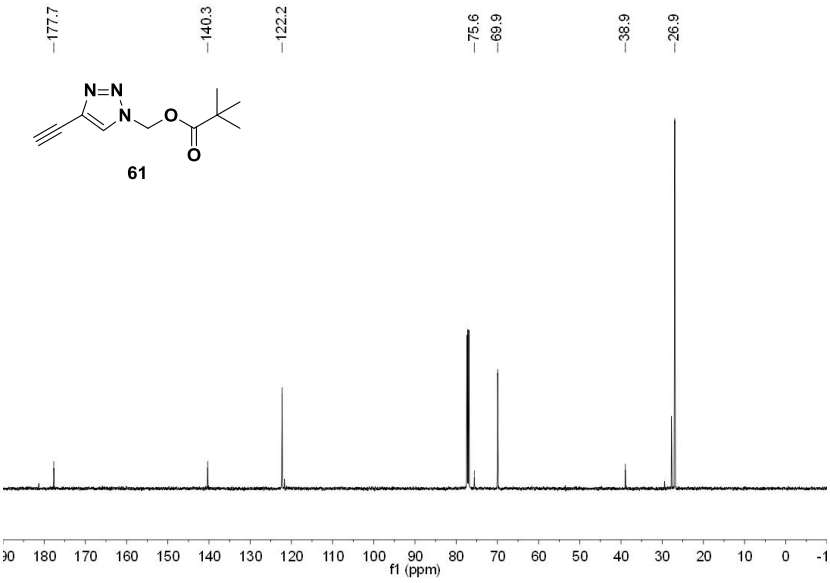
Spectrum 3.3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56**.



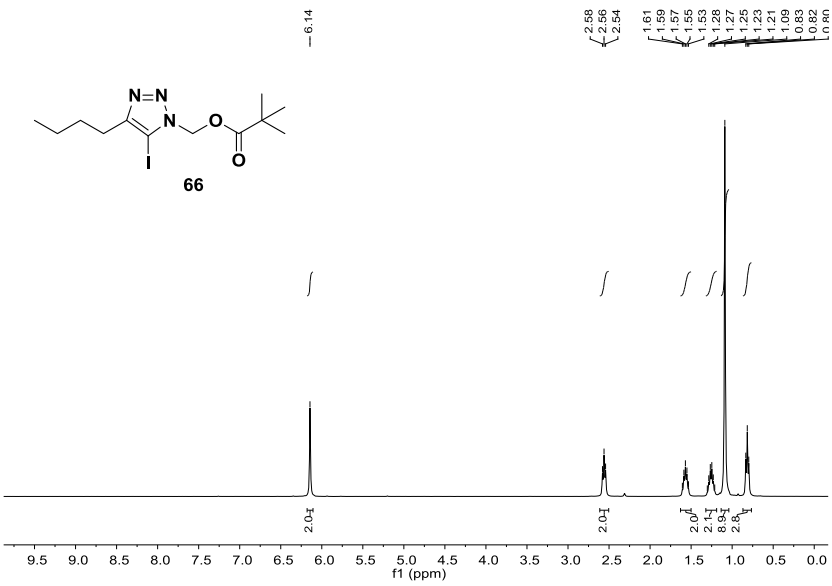
Spectrum 3.4. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **56**.



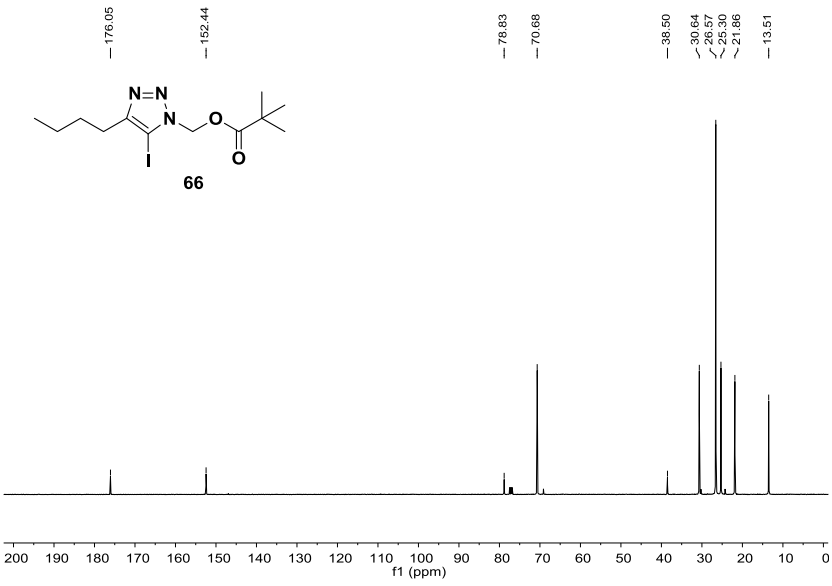
Spectrum 3.5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **61**.



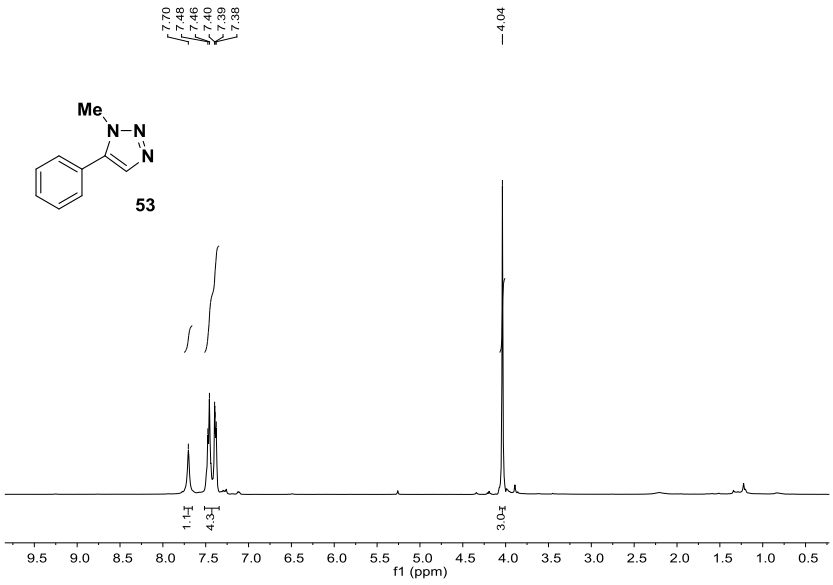
Spectrum 3.6. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **61**.



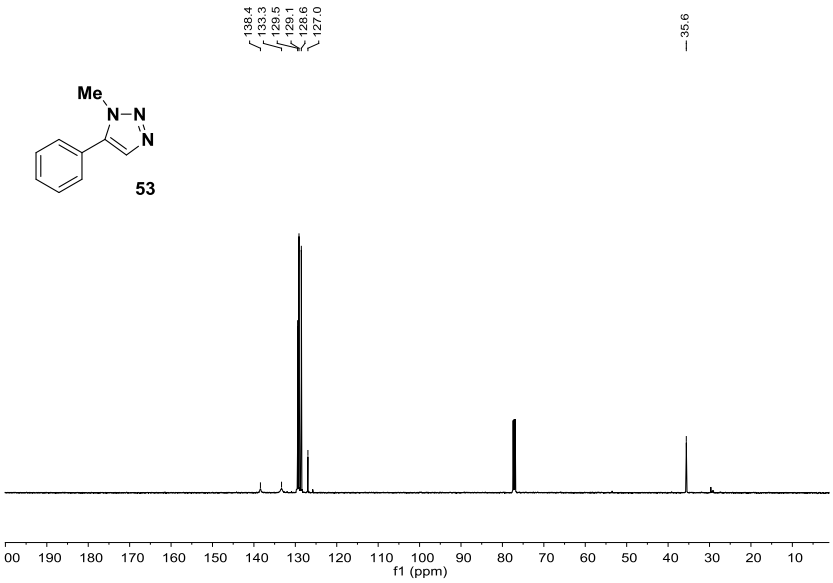
Spectrum 3.7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **66**.



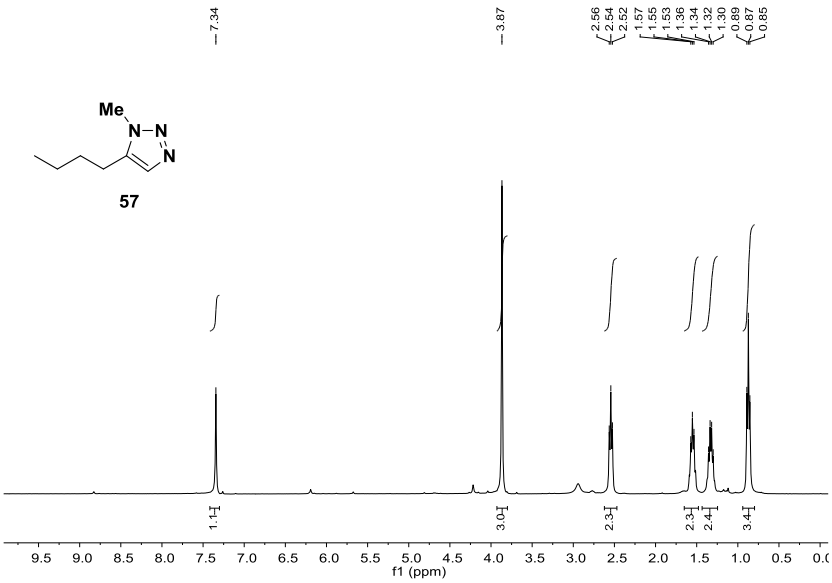
Spectrum 3.8. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **66**.



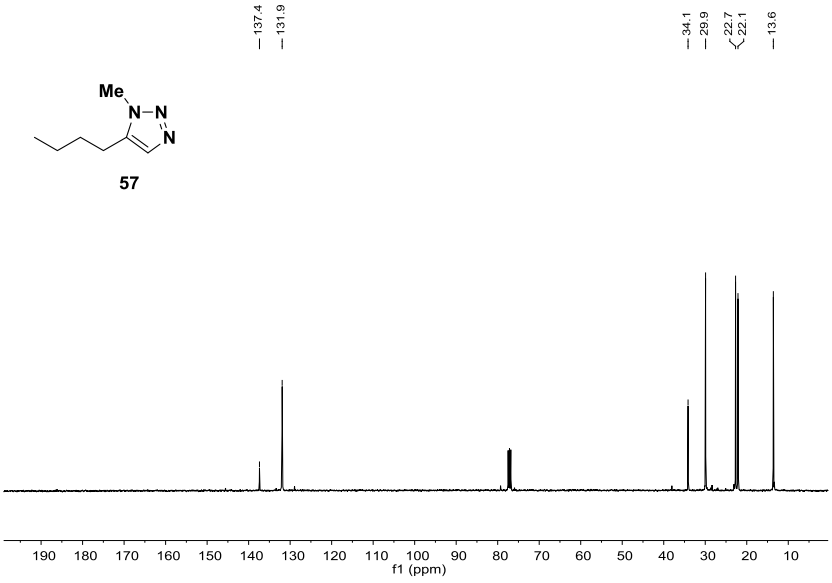
Spectrum 3.9. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **53**.



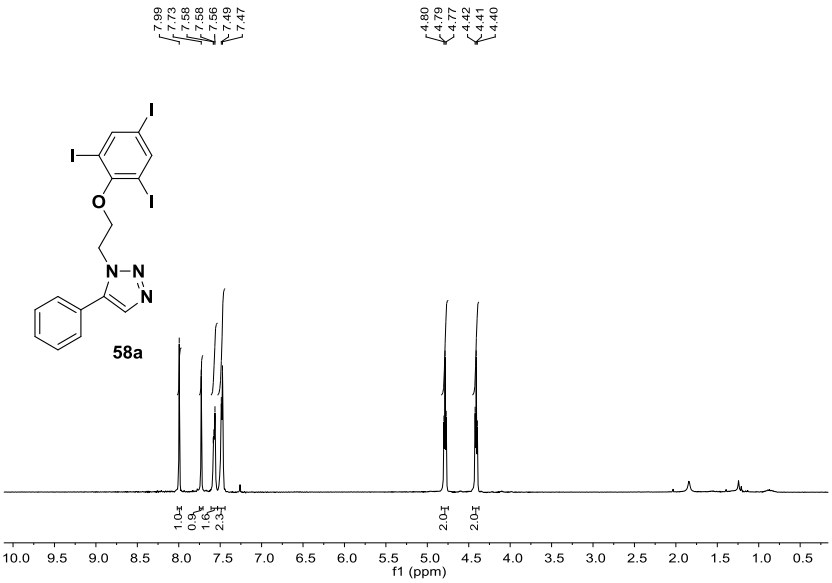
Spectrum 3.10. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **53**.



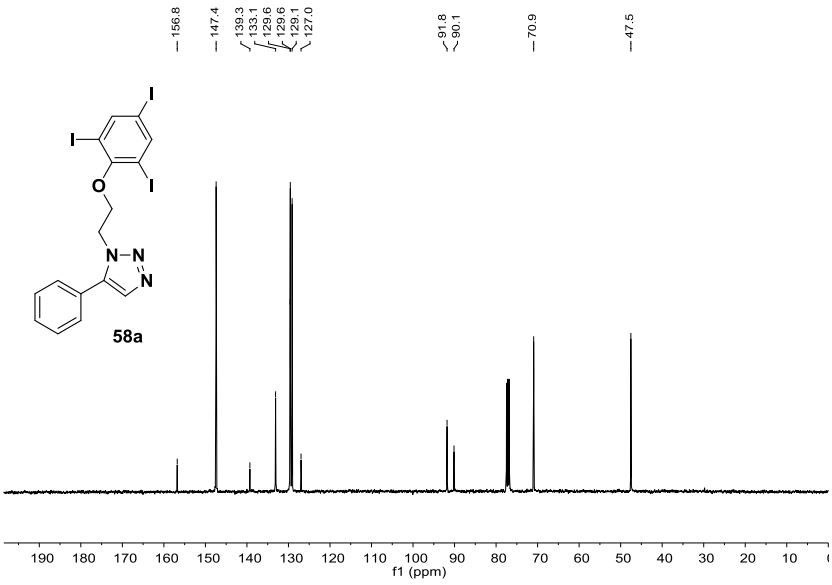
Spectrum 3.11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **57**.



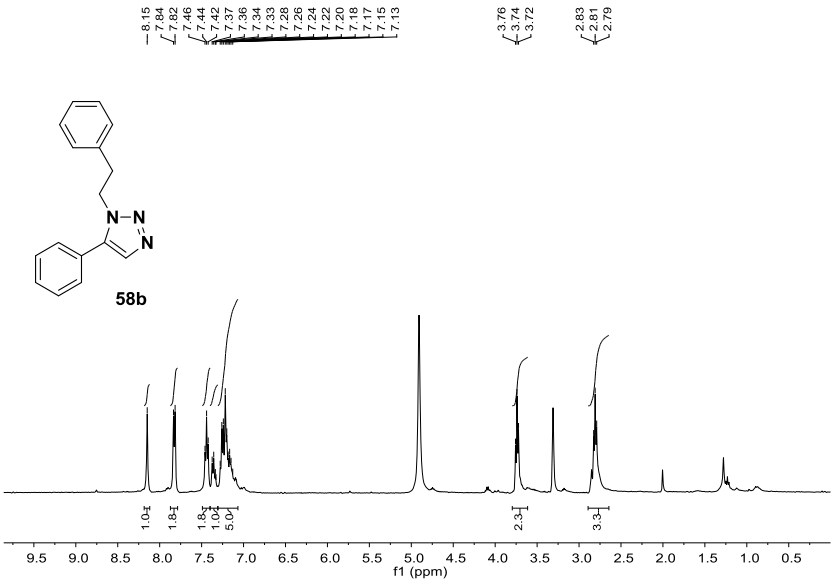
Spectrum 3.12. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **57**.



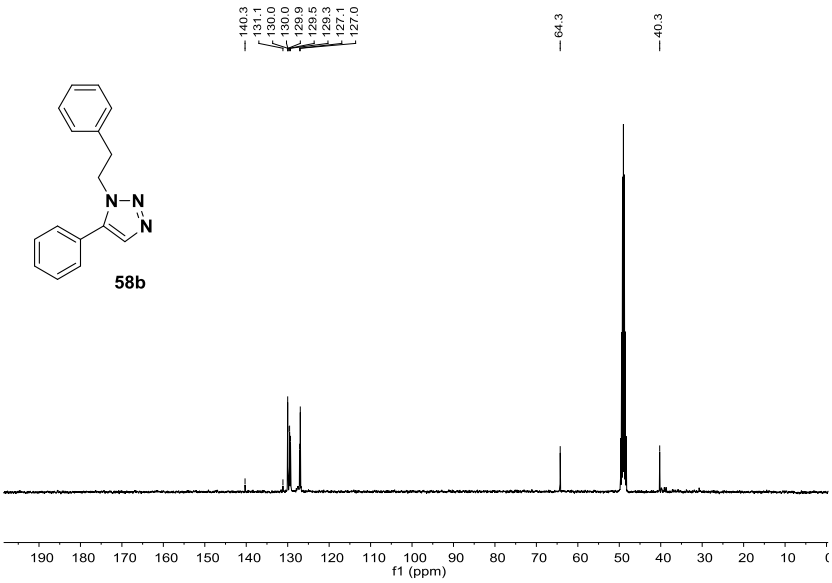
Spectrum 3.13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **58a**.



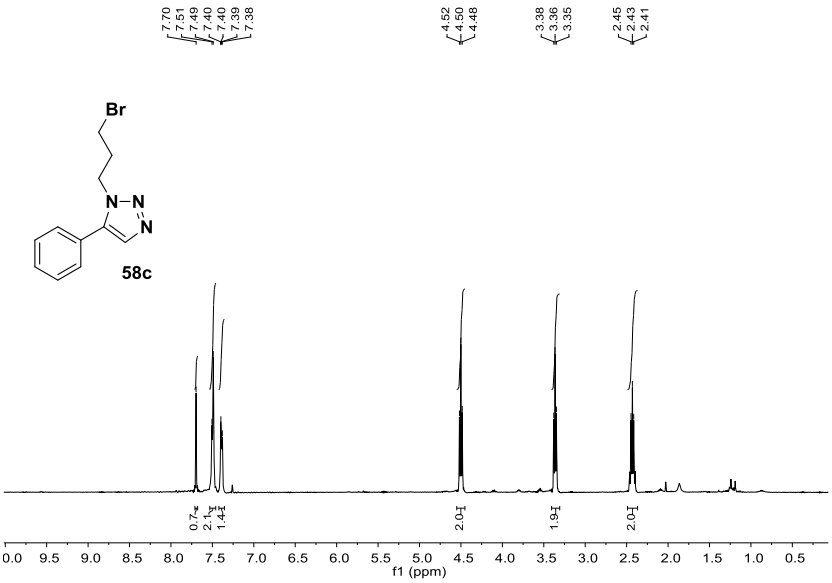
Spectrum 3.14. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **58a**.



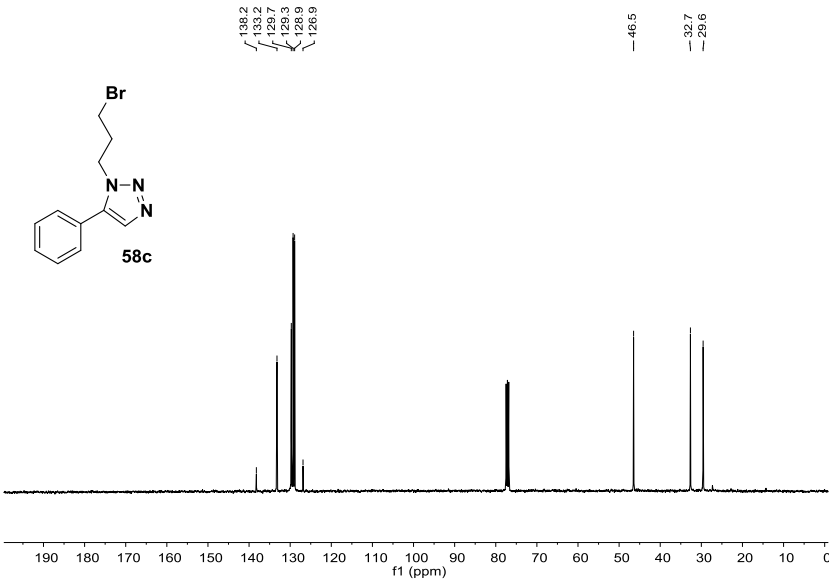
Spectrum 3.15. ^{1}H NMR (400 MHz, MeOH-d_4) spectrum of compound **58b**.



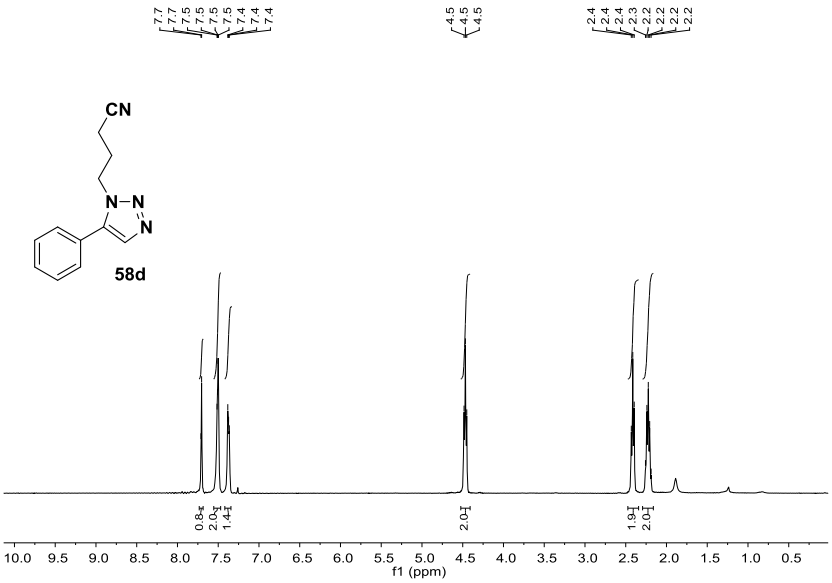
Spectrum 3.16. ^{13}C NMR (101 MHz, MeOH-d_4) spectrum of compound **58b**.



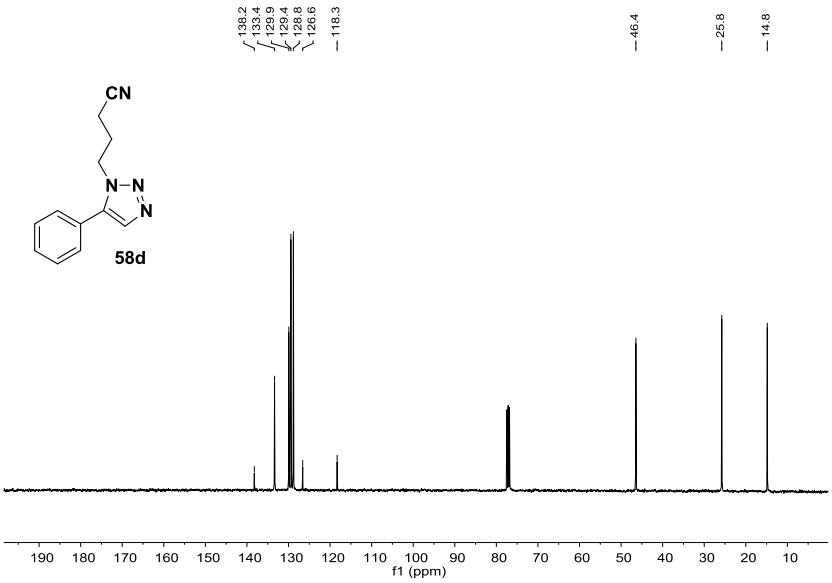
Spectrum 3.17. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **58c**.



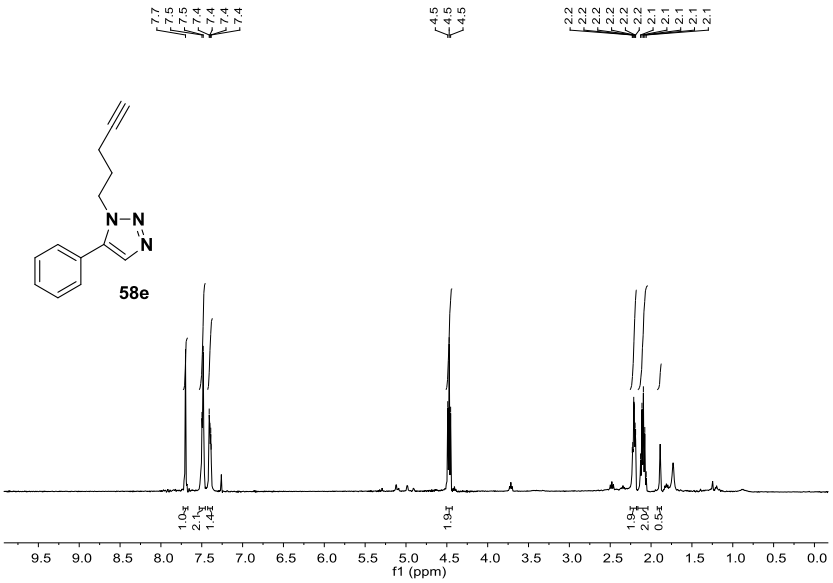
Spectrum 3.18. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **58c**.



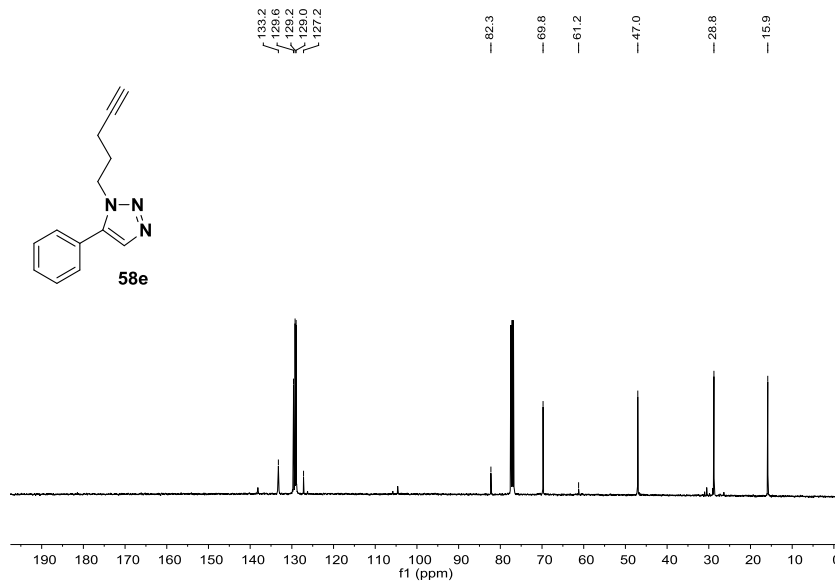
Spectrum 3.19. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **58d**.



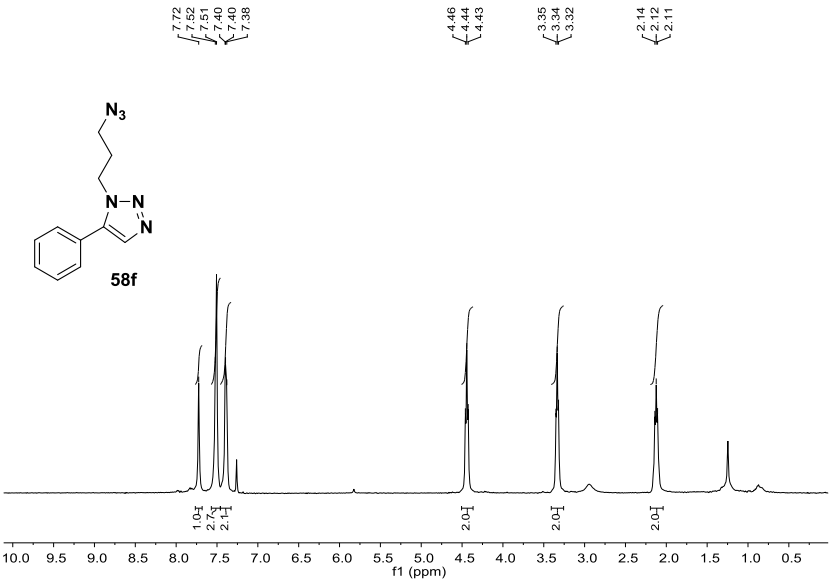
Spectrum 3.20. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **58d**.



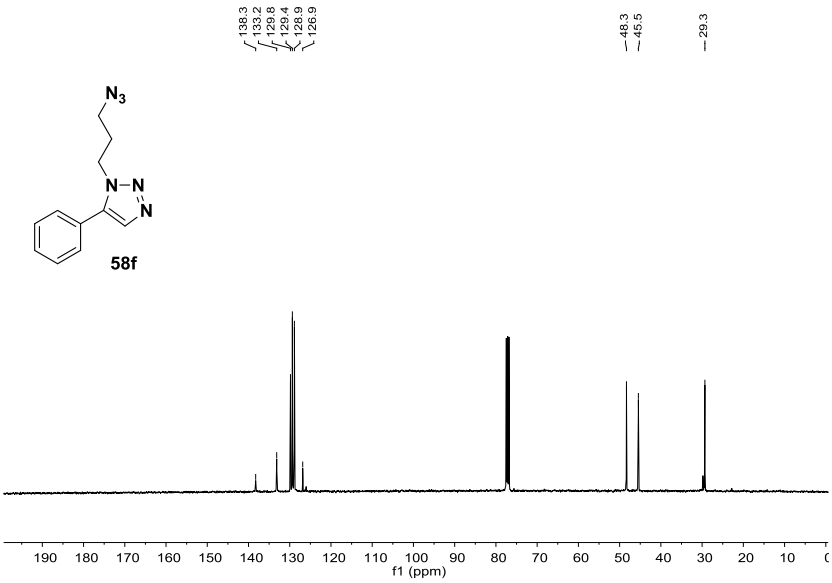
Spectrum 3.21. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **58e**.



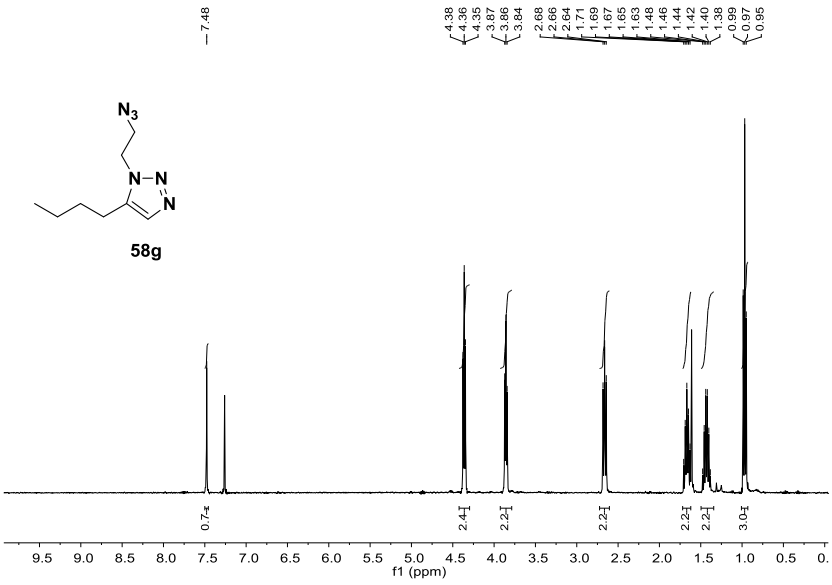
Spectrum 3.22. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **58e**.



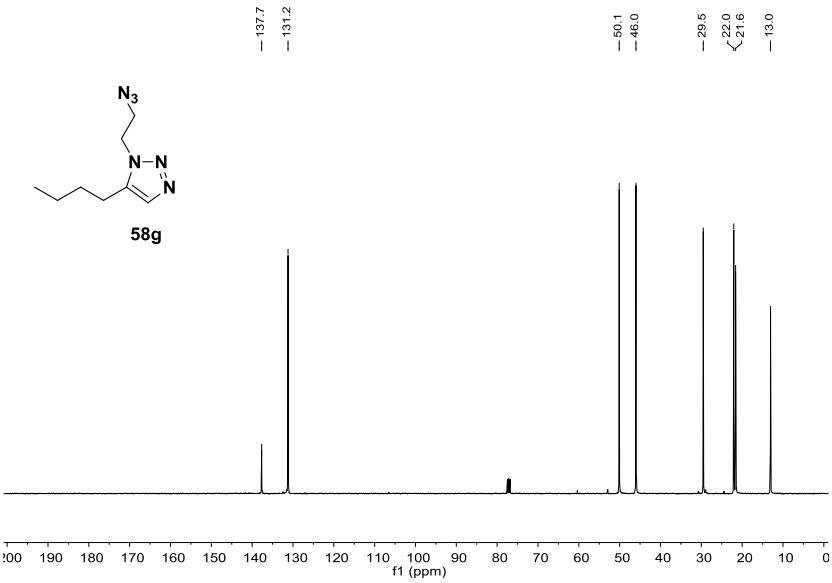
Spectrum 3.23. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **58f**.



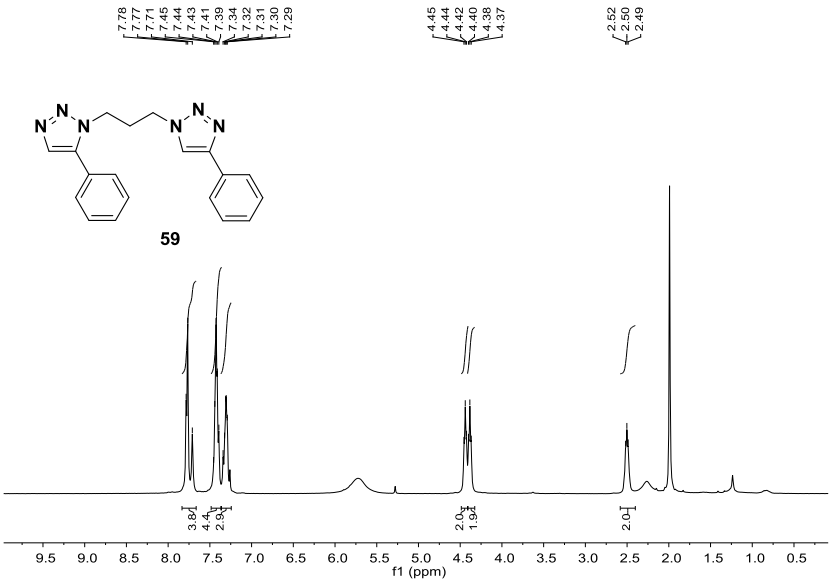
Spectrum 3.24. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **58f**.



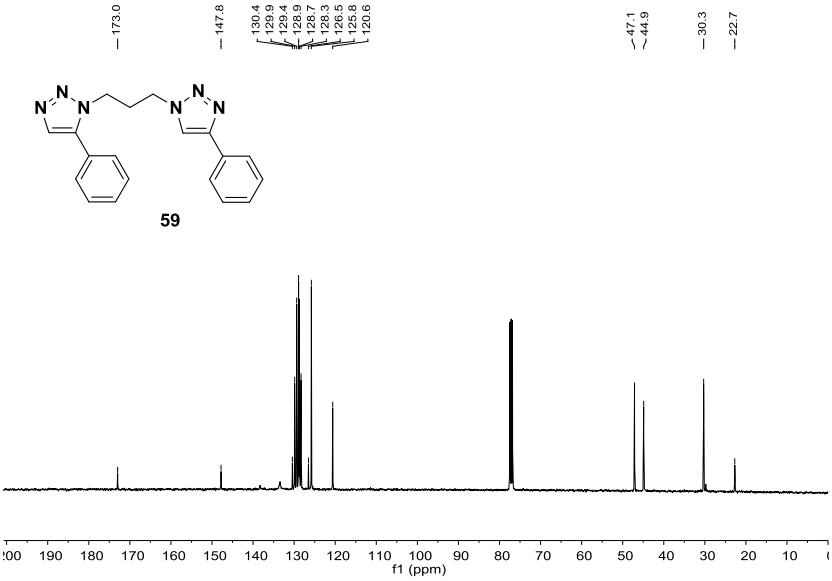
Spectrum 3.25. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **58g**.



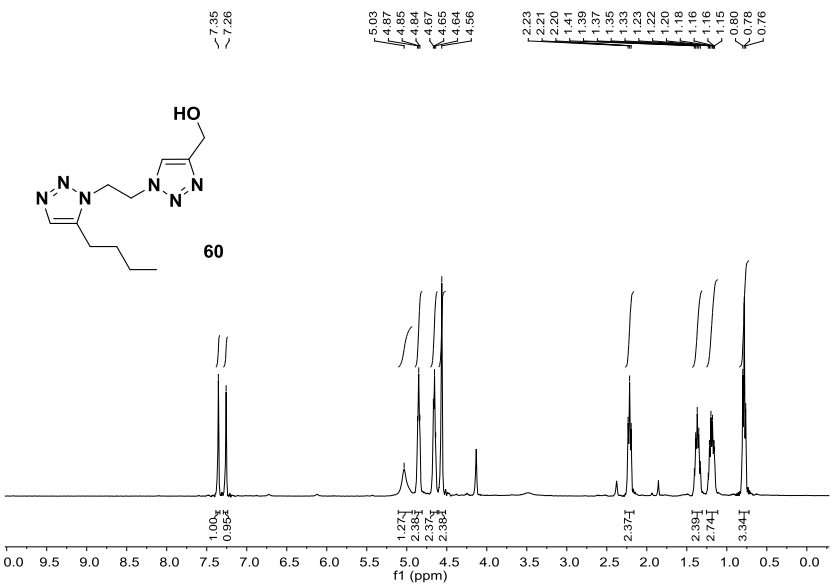
Spectrum 3.26. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **58g**.



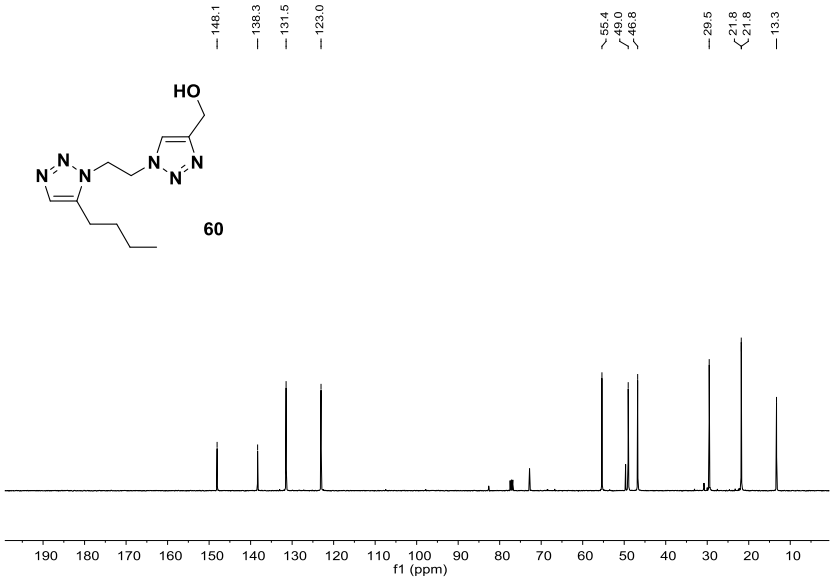
Spectrum 3.27. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **59**.



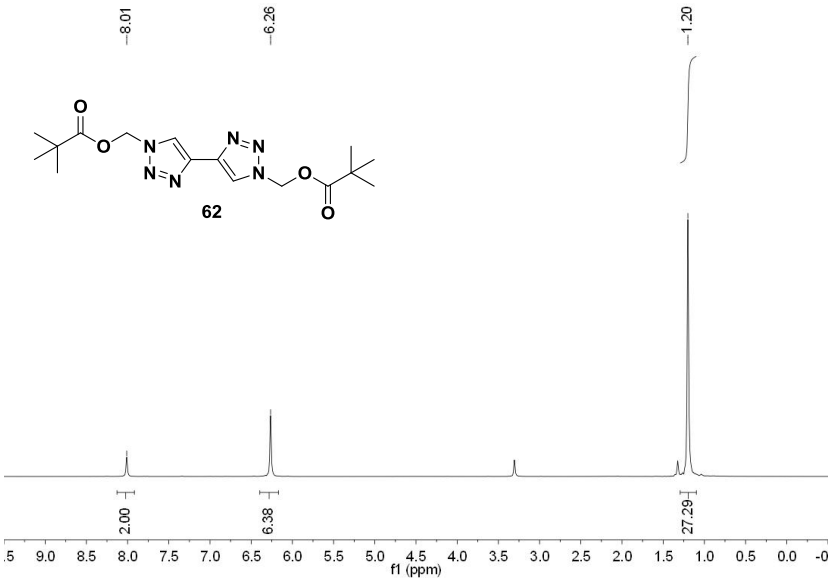
Spectrum 3.28. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **59**.



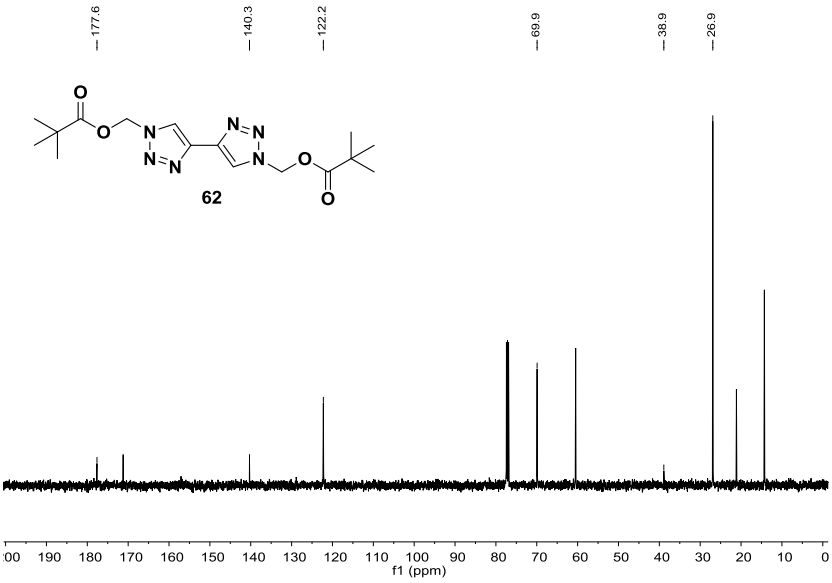
Spectrum 3.29. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **60**.



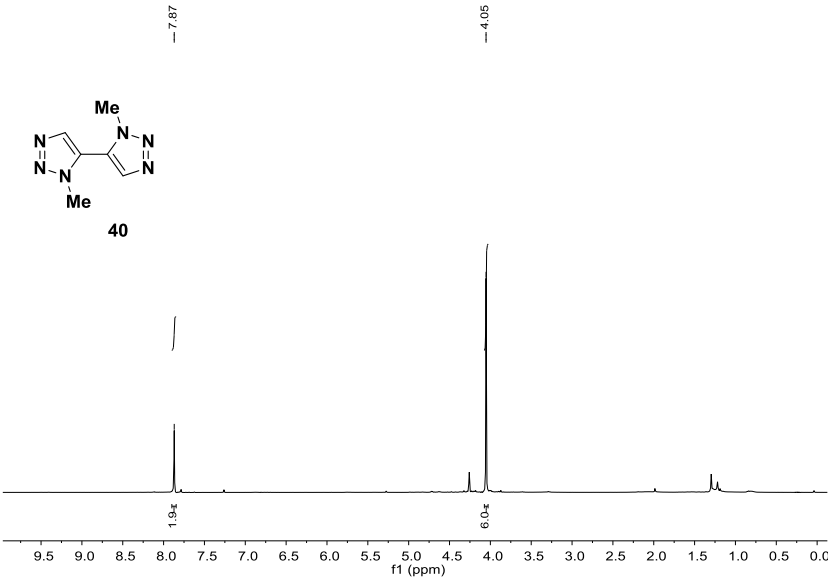
Spectrum 3.30. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **60**.



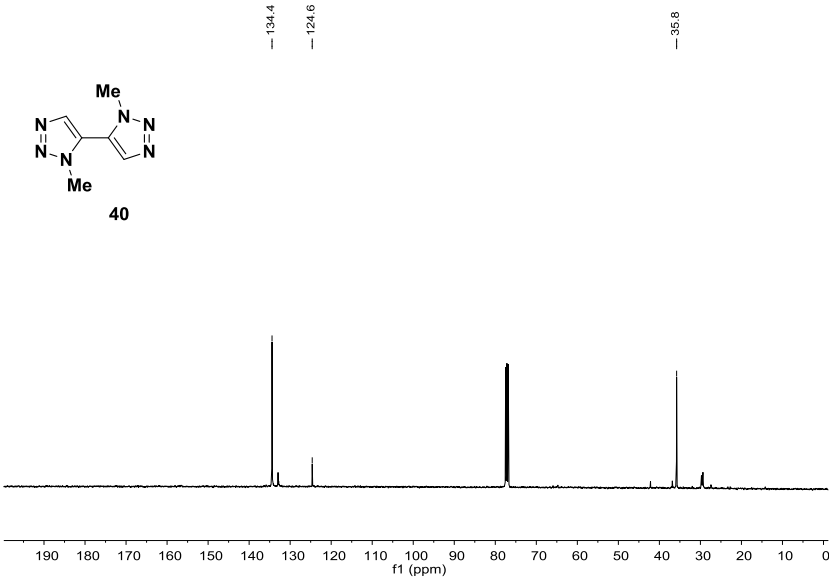
Spectrum 3.31. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **62**.



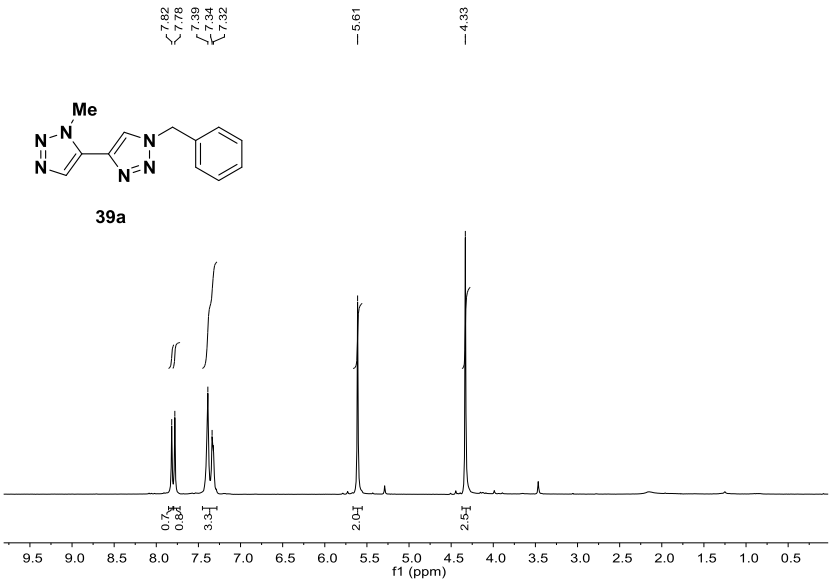
Spectrum 3.32. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **62**.



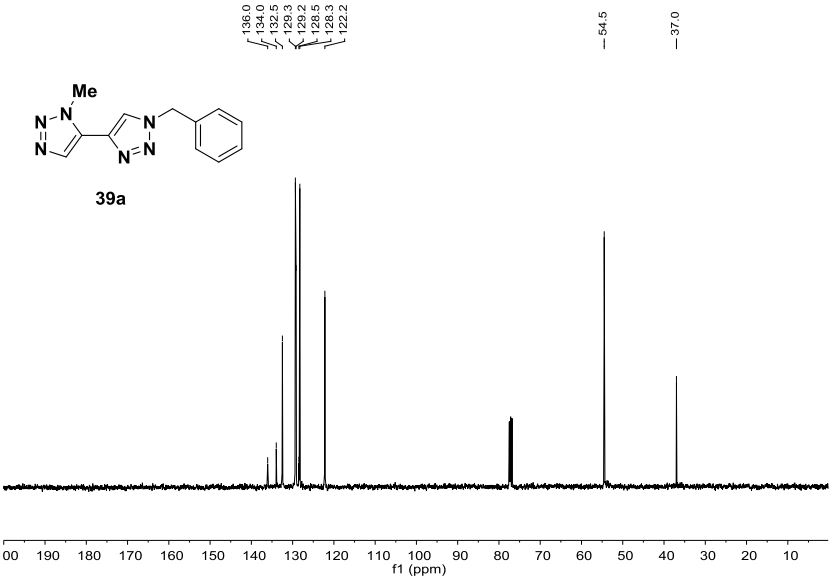
Spectrum 3.33. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **40**.



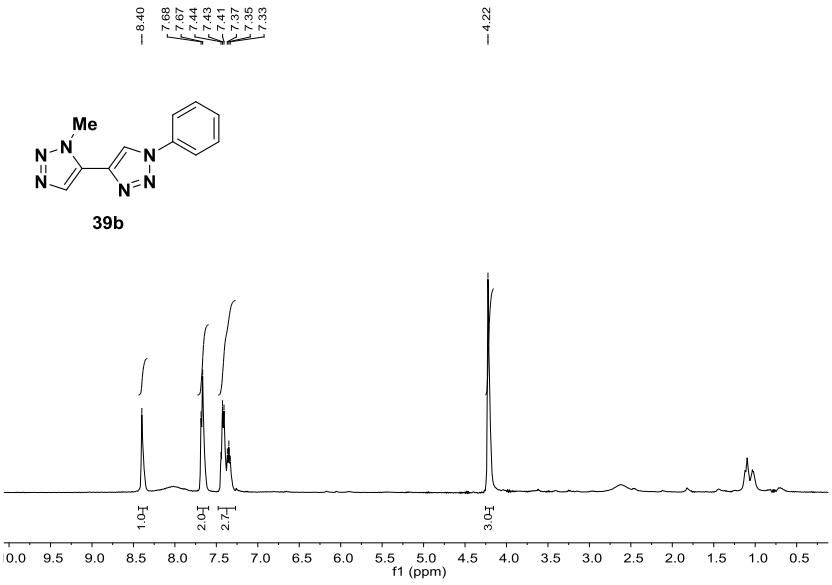
Spectrum 3.34. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **40**.



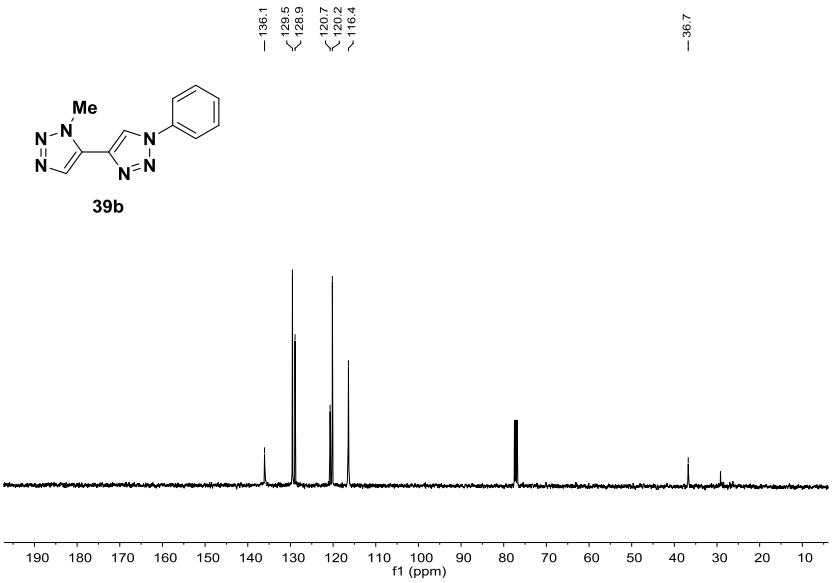
Spectrum 3.35. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **39a**.



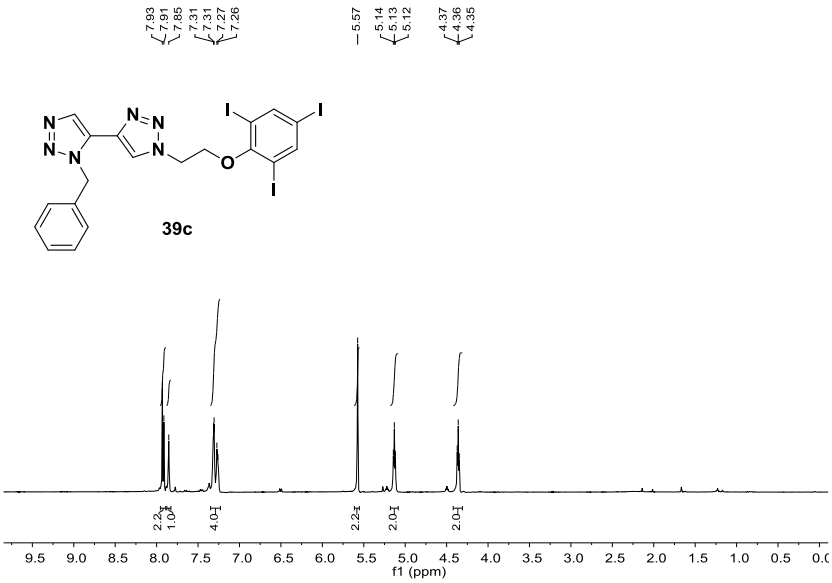
Spectrum 3.36. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **39a**.



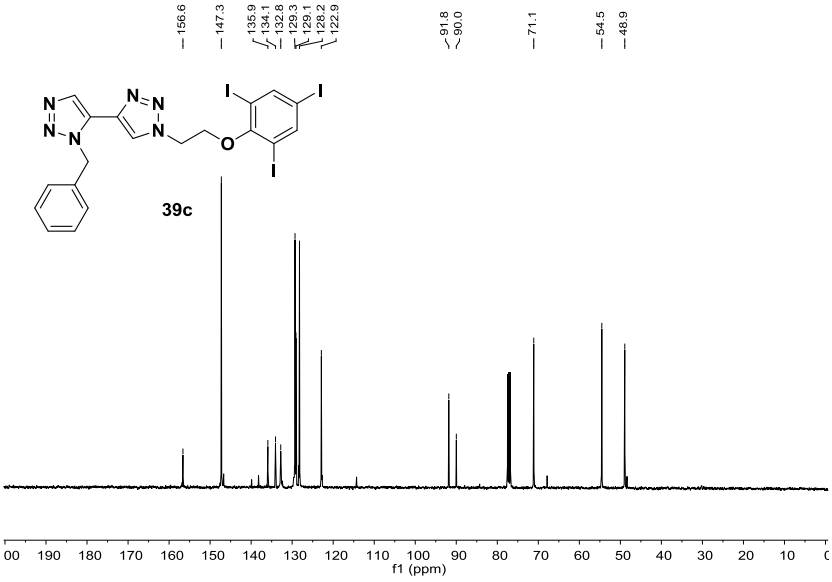
Spectrum 3.37. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **39b**.



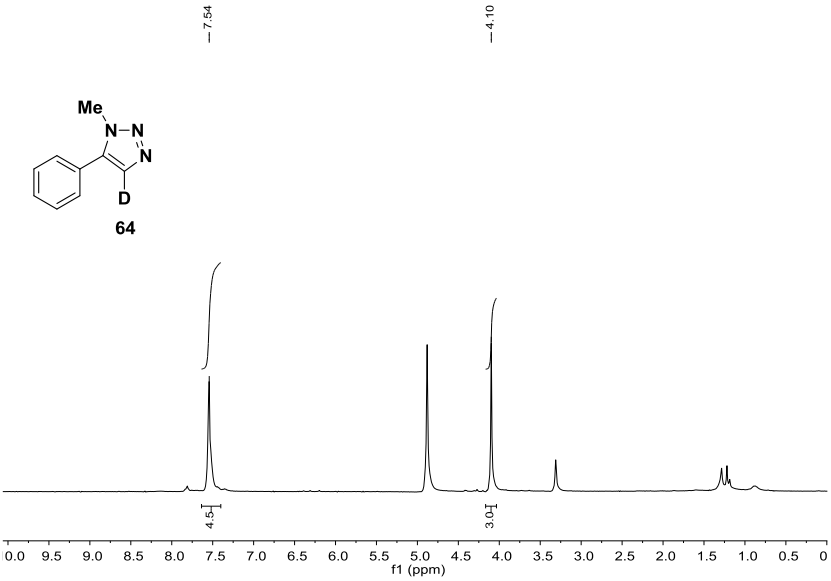
Spectrum 3.38. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **39b**.



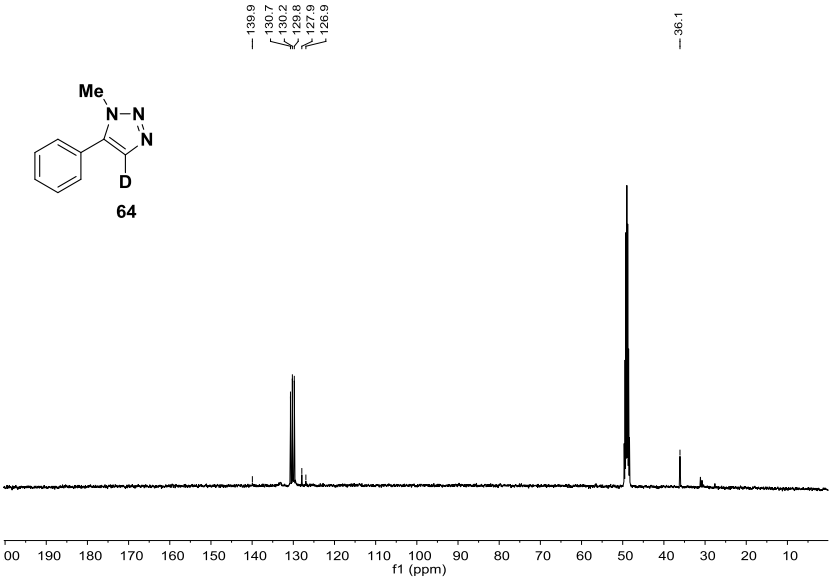
Spectrum 3.39. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **39c**.



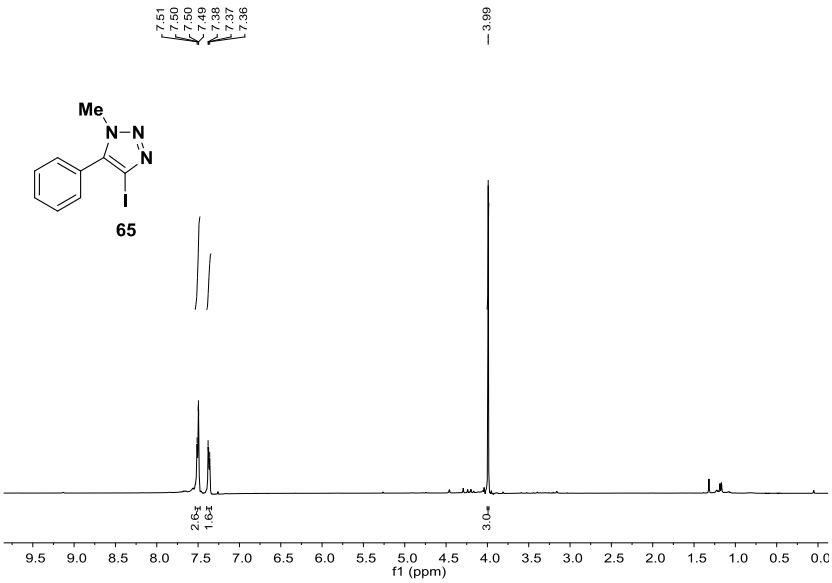
Spectrum 3.40. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **39c**.



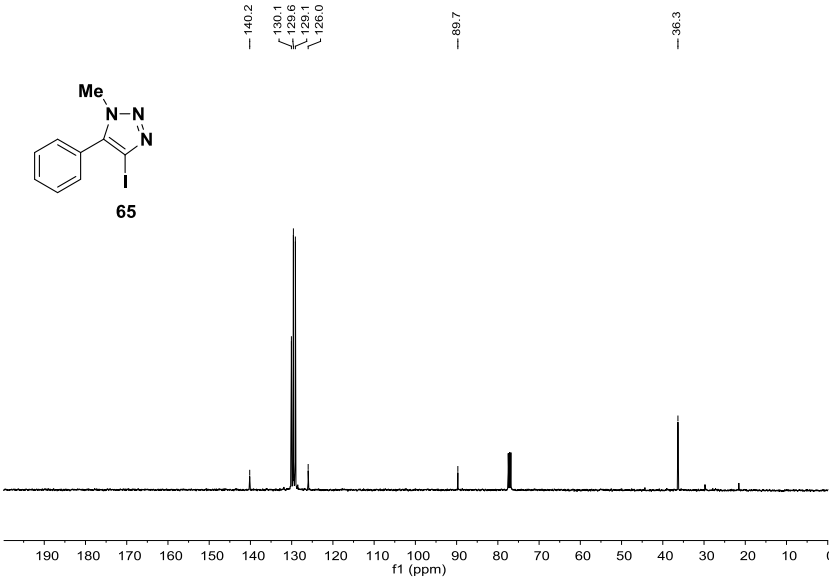
Spectrum 3.41. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **64**.



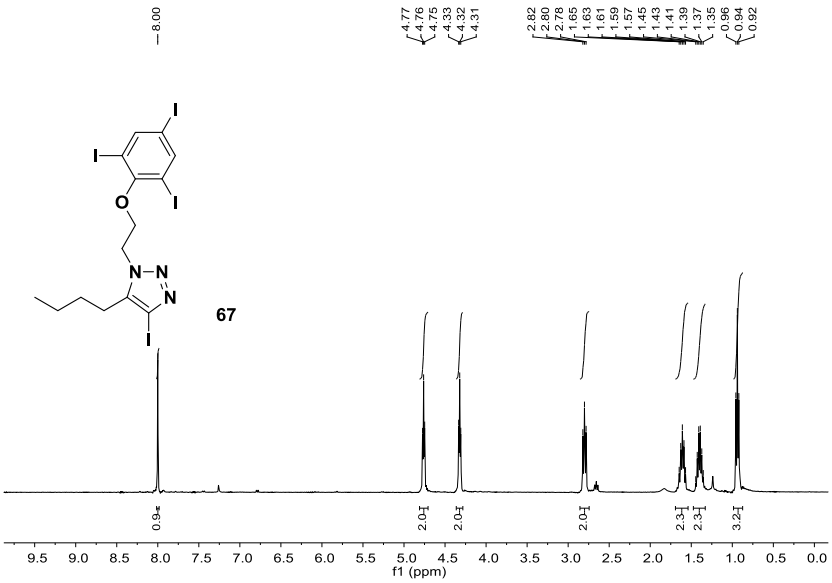
Spectrum 3.42. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **64**.



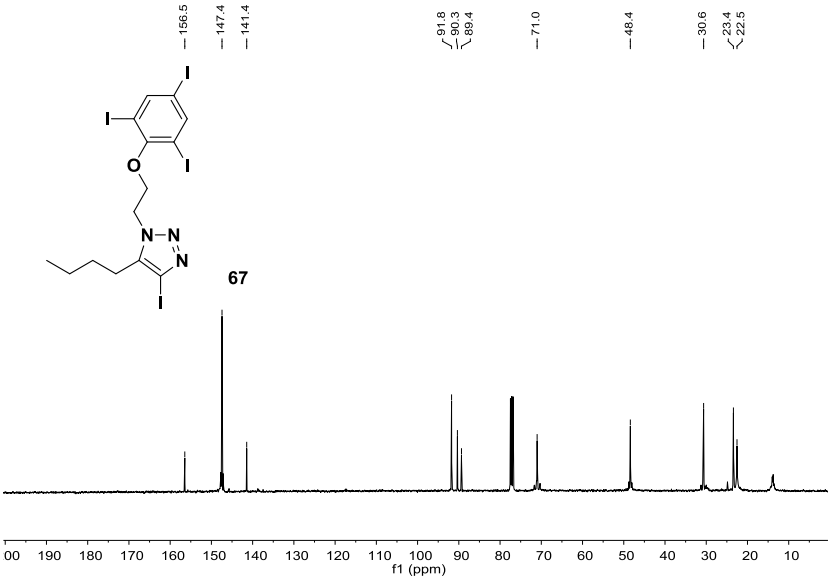
Spectrum 3.43. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **65**.



Spectrum 3.44. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **65**.



Spectrum 3.45. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **67**.



Spectrum 3.46. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **67**.

4

Triazoles as directing groups in C–H functionalization events

4. Triazoles as directing groups in C−H functionalization events

4.1 Introduction

Transition metal-catalyzed cross-coupling techniques are powerful tools in modern organic chemistry. Among the many strategies available, commonly used methods rely on the use of reactive functional groups, such as halides or unsaturated bonds, able to interact with a metal to form new C−M bonds which undergo a wide variety of chemical processes. In these cases, however, several steps are needed to synthesize the required substrates from readily available starting materials, and the production of a substantial amount of by-product waste often accompanies these reactions. During the last years a new dimension has been opened in the field of synthetic organic chemistry with the activation of carbon−hydrogen bonds utilizing transition metal catalysts.[183] The direct catalytic cleavage and transformation of C−H bonds, which are ubiquitous in organic molecules, avoids the need for preparing functionalized intermediates, allowing the assembly of the desired products in fewer steps and thus offering a virtually unlimited library of simple starting materials as well as new perspectives in retrosynthesis. Accordingly, the development of new synthetic strategies in which C−H bonds can be activated and further used as a simple functional group represents one of the most stimulating and promising areas of research in the field of organic chemistry.

Direct C−H bond functionalization reactions are limited by two fundamental challenges: (a) the inert nature of most carbon−hydrogen bonds and (b) the requirement to control site-selectivity in molecules that contain various C−H motifs. Numerous studies have addressed the first challenge by introducing transition metals which can react with C−H bonds to form new C−M bonds in a process known as "C−H activation".[184] The resulting C−M bonds are far more reactive than their C−H counterparts and they can be further

---

[183] For selected reviews, see: a) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* DOI: 10.1021/acs.chemrev.6b00574. b) Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Catal. A: Chem.* **2017**, *426*, 275. c) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. d) Santoro, S.; Kozhushkov, S. I.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2016**, *18*, 3471. e) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2. f) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74. g) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. h) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362. i) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. j) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

[184] a) Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. *Chem. Rev.* DOI: 10.1021/acs.chemrev.6b00664. b) Hartwig, J. F. *Nature* **2008**, *455*, 314.

converted into new functional groups. Given the large number and variety of C−H bonds that are usually present in an organic molecule, the ability to control the regioselectivity of the reaction is considered an ongoing challenge of high synthetic significance.

4.1.1 Transition metals in C−H functionalization

The introduction of transition metals in the field of C−H activation was described in the literature as early as the 1960s (Scheme 4.1). Some years later, Trofimenko[185] introduced the term "cyclometalation" to describe the activation reaction between the metal and the C−H bond in an intramolecular fashion. These reactions are known to proceed by different mechanisms depending on the metal species, kind of substrate, and the reaction conditions, including oxidative addition, electrophilic activation, concerted metalation/deprotonation, and σ-bond metathesis.[186] In 1963 Kleiman and Dubeck reported the first nickelacycle **I**.[187] Similar reactivity was discovered by Cope and Siekman when they used Pd(II) and Pt(II) salts to give complexes **II** and **III**, respectively.[188] Bennett and Milner observed that *ortho*-C−H bonds of triphenylphospine ligands underwent oxidative addition to give [Ir(III)-H] species **IV**,[189] and other metals were found to exhibit analogous reactivity with both phospines and phosphonites (**V** and **VI**).[190] Although different transition metals such as Ru,[191] Rh,[192] Pt[193] and Pd[194] have been used in a vast array of C−H activation reactions, the most widely used metal is by far Pd owing to its unique characteristics. Remarkably, having only three oxidation states facilitates the understanding of the reaction mechanisms, as well as the isolation ease of the corresponding intermediates in comparison with other metals.

---

185 Trofimenko, S. *Inorg. Chem.* **1973**, *12*, 1215.

186 Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

187 Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544.

188 Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272.

189 Bennett, M. A.; Milner, D. L. *Chem. Commun. (London)* **1967**, 581.

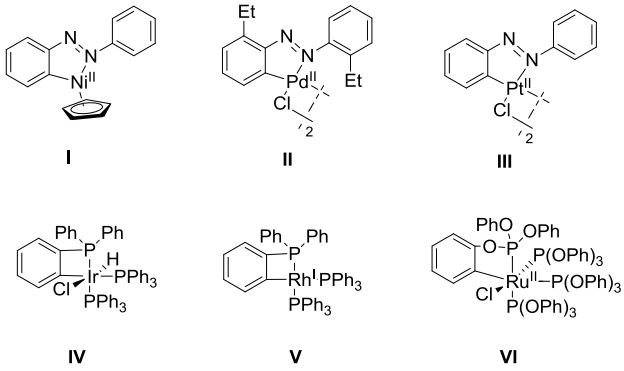
190 a) Keim, W. *J. Organomet. Chem.* **1968**, *14*, 179. b) Knoth, W. H.; Schunn, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 2400.

191 a) Ruiz, S.; Sayago, F. J.; Cativiela, C.; Urriolabeitia, E. P. *J. Mol. Catal. A: Chem.* **2017**, *426*, 407. b) Yamamoto, K.; Qureshi, Z.; Tsoung, J.; Pisella, G.; Lautens, M. *Org. Lett.* **2016**, *18*, 4954.

192 a) Nicolaou, K. C.; Pulukuri, K. K.; Yu, R.; Rigol, S.; Heretsch, P.; Grove, C. I.; Hale, C. R. H.; ElMarrouni, A. *Chem. Eur. J.* **2016**, *22*, 8559. b) Chidipudi, S. R.; Burns, D. J.; Khan, I.; Lam, H. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 13975.

193 a) Kumar, M. K.; Ramaprabhu, S. *J. Phys. Chem. B* **2006**, *110*, 11291. b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859.

194 a) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* DOI: 10.1021/acs.chemrev.6b00622. b) Jiang, H.; Zhang, Y.; Chen, D.; Zhou, B.; Zhang, Y. *Org. Lett.* **2016**, *18*, 2032.



Scheme 4.1. Some examples of metalacyles with different transition metals.

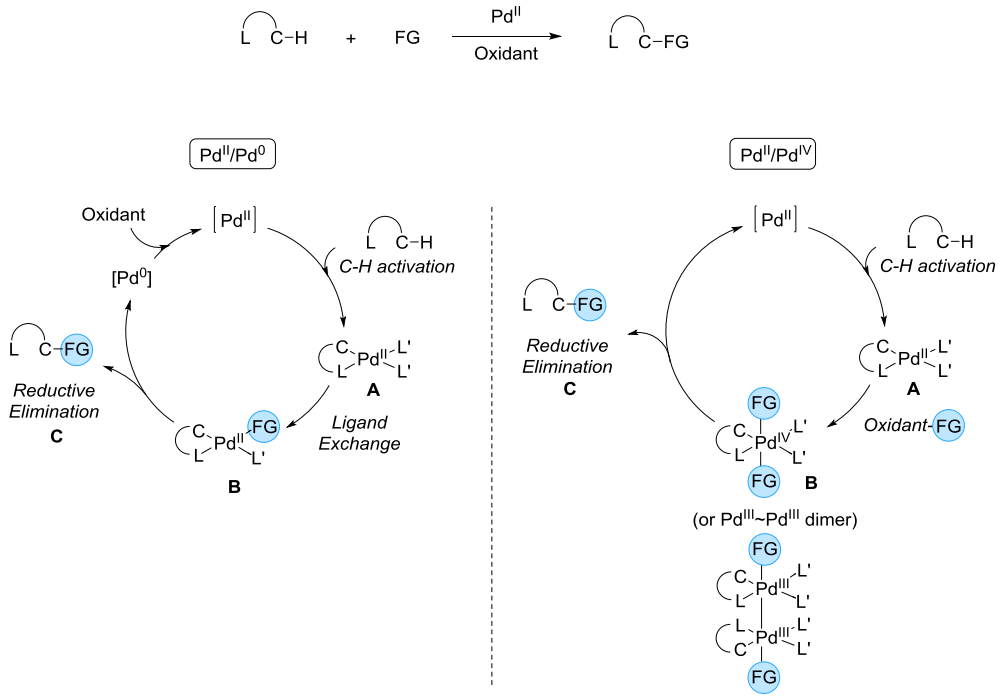
Palladium complexes are particularly attractive catalysts in the realm of C−H functionalization for several reasons. The first one, ligand-directed C−H functionalization at Pd centers can be utilized to build-up a vast array of different bonds, including carbon−oxygen, carbon−halogen, carbon−nitrogen, carbon−sulfur, and carbon−carbon unions. Few other catalysts allow such diverse bond constructions, and this versatility is predominantly the consequence of two main characteristics (a) the compatibility of many Pd^{II} catalysts with oxidants, and (b) the ability to selectively functionalize cyclopalladated intermediates. The second feature is that palladium can take part in the cyclometalation process with a wide variety of directing groups and, unlike many other transition metals, easily promotes C−H activation at both sp^2 and sp^3 C−H sites. At last but not least, Pd-catalyzed directed C−H functionalization processes can be usually carried out in the presence of air, making the reaction exceptionally practical for further applications in organic synthesis. The groups of Fujiwara,[195] Yu,[196] Sanford,[197] Gaunt,[198] and Shi,[199] among others, have contributed to the development of this area of expertise during the last decade.

Palladium-catalyzed C−H functionalization processes can proceed through either a Pd(0)/Pd(II) or Pd(II)/Pd(IV) catalytic cycle. The first one begins with the ligand-directed C−H activation, which takes place at Pd^{II} center to afford a cyclopalladated intermediate. Then, a ligand exchange followed by a reductive elimination process delivers the product.

---

[195] Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.
[196] Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.
[197] Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
[198] Beck, E. M.; Gaunt, M. J. *Top. Curr. Chem.* **2010**, *292*, 85.
[199] Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677.

The resulting Pd^0 species is subsequently oxidized to regenerate the active Pd^{II} catalyst (Scheme 4.2).



Scheme 4.2. Pd^{II}/Pd^0 and Pd^{II}/Pd^{IV} catalytic cycles.

The second pathway presumably starts with the C−H activation at Pd(II) center by electrophilic attack, followed by oxidation of the resulting Pd(II) intermediate and ligand transfer to afford a Pd(IV) complex or the corresponding Pd^{III}~Pd^{III} dimer.[200] Then, reductive elimination delivers the coupling product and regenerates the Pd(II) catalyst to facilitate the catalytic cycle (Scheme 4.2). The diversity of bond-forming reductive elimination processes from Pd(IV) complexes allows the installation of a wide range of functionalities starting from C−H bonds.

An oxidant is essential for both Pd^{II}/Pd^0 and Pd^{II}/Pd^{IV} catalysis.[201] In Pd^{II}/Pd^0 catalysis, the oxidant is used to regenerate the active Pd^{II} catalyst from the Pd^0 generated within the reaction and the most common oxidants include BQ/O_2, Ag^I salts and Cu^{II} salts. It

[200] a) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050. b) Campbell, M. G.; Zheng, S.-L.; Ritter, T. *Inorg. Chem.* **2013**, *52*, 13295.

[201] Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877.

is worth noting that many C−Y (Y = F, Cl, Br, I, O, N) bond-forming processes from the corresponding Pd^{II} centers are normally sluggish.[202] Conversely, in transformations involving Pd^{II}/Pd^{IV} catalysis, the oxidant is used to convert Pd^{II} to Pd^{IV} species. The oxidants utilized in these cases include $PhI(OAc)_2$, NCS, NBS, NIS, peroxide, Ce(IV), F^+, $K_2S_2O_8$ and oxone, among others.[203]

The second key issue in C−H functionalization is the control of the regioselectivity considering the wide variety of C−H bonds that are usually present in an organic molecule. This issue can be circumvented by employing molecules bearing C−H bonds of different reactivity, which has already been applied in the functionalization of various heterocycles that possess at least one position of special reactivity as a result of the presence of one or more heteroatoms.[204] However, in benzene derivatives, the discrepancy in reactivity between the C−H bonds is generally less pronounced and other regioselectivity-controlling elements are required. In this respect, the most common manner to achieve the regioselectivity of a single C−H bond involves the use of functional groups or atoms, often named directing groups (DGs).

4.1.2 DGs in C−H functionalization

Functional groups or commonly named directing groups (DGs) are able to coordinate or bind to a metal center and thus deliver the catalyst to a proximal C−H bond, in most cases *ortho* to the DG.[205] The stabilizing interaction formed between the π system of the

---

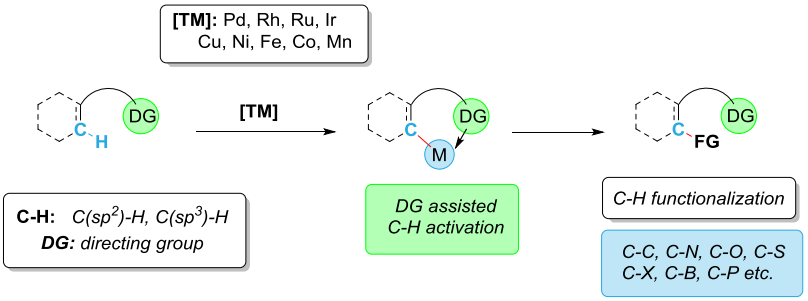
[202] a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. b) Muñiz, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9412.

[203] a) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. b) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712.

[204] a) Phillips, D.; France, D. J. *Asian J. Org. Chem.* **2017**, *6*, 27. b) Wilton, D. A. A. *C−H Bond Activation in Organic Synthesis, CRC Press* **2015**, *267*. c) Li, S.-S.; Qin, L.; Dong, L. *Org. Biomol. Chem.* **2016**, *14*, 4554. d) Zhang, Z.; Tanaka, K.; Yu, J.-Q. *Nature* **2017**, *543*, 538. e) Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 12968.

[205] For recent discoveries in remote *meta*- and *para*-C−H functionalization events, see: a) Bag, S.; Jayarajan, R.; Mondal, R.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 1. b) Wang, P.; Farmer, M. E.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2017**, *56*, 5125. c) Liang, S.; Bolte, M.; Manolikakes, G. *Chem. Eur. J.* **2017**, *23*, 96. d) Dey, A.; Maity, S.; Maiti, D. *Chem. Commun.* **2016**, *52*, 12398. e) Zhao, Y.; Yan, H.; Lu, H.; Huang, Z.; Lei, A. *Chem. Commun.* **2016**, *52*, 11366. f) Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 7751. g) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. *J. Am. Chem. Soc.* **2015**, *137*, 11888.

arene or alkene and the transition metal center is presumably a key factor for facilitating the activation of otherwise unreactive C−H bonds. In general, the process happens *via* the formation of a thermodynamically stable five- or six-membered metalacycle intermediate (Scheme 4.3).[206] One of the most important drawbacks is the additional synthetic steps which are required to both install and cleave the desired DG in the substrate and product, respectively. However, when the DG itself can play a key role in further applications of the resulting products practical and elegant late-stage functionalization approaches can be designed in the field of medicinal chemistry.



Scheme 4.3. DG-assisted C−H functionalization strategy.

The first example of a transition metal-catalyzed regioselective functionalization of a C−H bond was described in 1955 by Murahashi, which involved the insertion of carbon monoxide into C(sp^2)−H bonds catalyzed by cobalt.[207] However, the reaction mechanism was not defined until 1963, when Kleiman and Dubeck published the first characterization of a cyclometalated complex.[187] This complex, a five-membered *ortho*-nickelacycle, highlights the ability of some functional groups to promote the insertion of a transition metal into an *ortho*-C(sp^2)−H bond. Although important advances were achieved in the field in the next years, the main limitation came from using stoichiometric amounts of metal which rendered the process unpractical from a sustainable point of view.

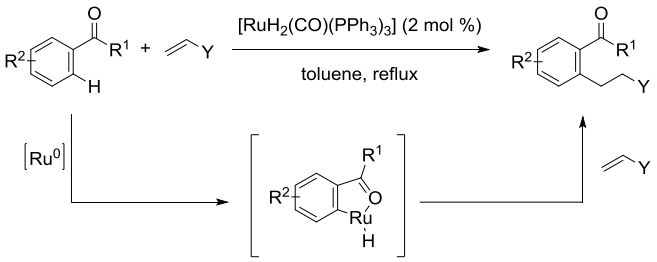
---

h) Wang, P.; Farmer, M. E.; Huo, X.; Jain, P., Shen, P.-X.; Ishoey, M.; Bradner, J. E.; Wisniewski, S. R.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 9269.

206 For selected reviews, see: a) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. b) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

207 Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403.

In 1993 a highly efficient and selective *ortho*-alkylation reaction of aromatic ketones with olefins catalyzed by ruthenium salts was reported by the group of Murai (Scheme 4.4).[208]



Scheme 4.4. Ruthenium-catalyzed *ortho*-alkylation of aromatic ketones with olefins.

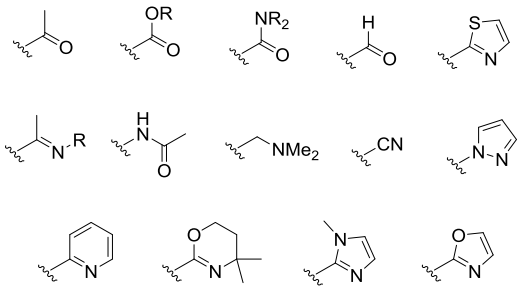
Inspired by this major breakthrough, a huge number of publications subsequently appeared involving related transformations such as arylations, vinylations or oxidations with a vast array of DGs. As shown in Scheme 4.5, nitrogen-based DGs including imines, pyridines, oxime ethers, azobenzene derivatives as well as some carbonyl containing DGs such as ketones, aldehydes and carboxylate derivatives were reported as efficient chelating mioeties. Moreover, it should be mentioned that some DGs, especially those derived from carboxylic acids and the carboxylic acids themselves, have been proven to be versatile functionalities for further transformations.[209] In addition, significant attention has been focused on the development of easily modifiable or removable DGs.[210]

---

208 Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

209 Drapeauand, M. P.; Gooßen, L. J. *Chem. Eur. J.* **2016**, *22*, 18654.

210 a) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450. b) Wang, C.; Huang, Y. *Synlett* **2013**, *24*, 145. c) Yadav, M. R.; Rit, R. K.; Shankar, M.; Sahoo, A. K. *Asian J. Org. Chem.* **2015**, *4*, 846.



Scheme 4.5. Some examples of monodentate DGs.

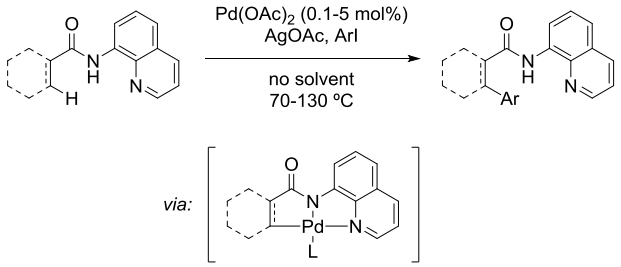
Considering the important advances that have been developed to date in a large variety of catalytic reactions involving C(sp^2)−H bonds of arenes, heteroarenes and alkenes, directed C−H bond functionalization can be considered a reliable strategy for the transformation of a C−H bond into a new C−X bond (X = C, O, N, F, Cl, Br, I, Si). In this manner, classical catalytic cross-coupling reactions involving the coupling of organohalides with organometallic species R−M (M = Li, MgX, ZnX, BR_2, SnR_3, SiR_3, etc.) can be replaced in certain cases by more atom-economical and sustainable C−H functionalization processes. Besides, benzylic or C(sp^3)−H bonds in α position to a heteroatom also undergo functionalization relatively easily, probably due to the lone pair of electrons which has stabilizing orbital interactions with the metal, or because of the influence of a proximal aromatic system.[194a,206c,211] However, directed functionalization of unactivated C(sp^3)−H bonds remains comparatively less explored. With the aim of extending the concept of directed C−H bond functionalization beyond its limits, the development of new types of DGs poses a promising strategy for achieving catalytic transformations that cannot be completed with the methods currently available.

In this regard, Daugulis introduced the utilization of novel bidentate DGs in 2005[212] which *via* the formation of a stable metalacycle C(sp^3)−H and C(sp^2)−H were elegantly functionalized. The DG of choice was 8-aminoquinoline, and its coordination to the metal center in a bidentate fashion during the formation of the corresponding intermediate was

[211] For selected reviews, see: a) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. *Synthesis* **2014**, *46*, 1421. b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654.

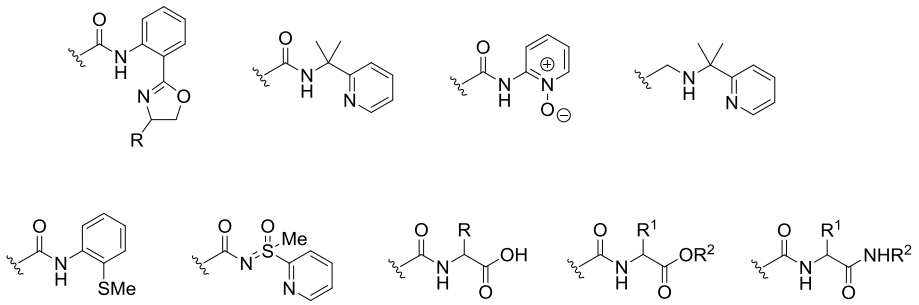
[212] Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

prepared within the Pd-catalyzed arylation of β-C−H bonds of various aliphatic and aromatic amides (Scheme 4.6).



Scheme 4.6. Palladium-catalyzed arylation of C−H bonds promoted by a bidentate DG.

In addition to 8-aminoquinoline DG, other bidentate DGs have been reported in the literature as well (Scheme 4.7).



Scheme 4.7. Some examples of bidentate DGs.

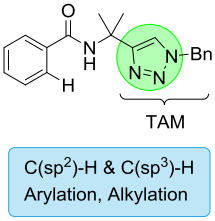
More recently, 1,2,3-triazole-containing bidentate DGs have been introduced by Ackermann,[213] Shi[214] and Ding,[215] and they have demonstrated the great potential that triazoles can offer as versatile DGs in the field of C−H functionalization. The group led by Ackermann reported iron- and ruthenium-catalyzed reactions, such as arylations and

[213] a) Cera, G.; Haven, T.; Ackermann, L. *Chem. Eur. J.* **2017**, *23*, 3577. b) Santrač, D.; Cella, S.; Wang, W.; Ackermann, L. *Eur. J. Org. Chem.* **2016**, 5429. c) Cera, G.; Haven, T.; Ackermann, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1484. d) Al Mamari, H. H.; Diers, E.; Ackermann, L. *Chem. Eur. J.* **2014**, *20*, 9739. e) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3868.

[214] a) Ye, X.; Shi, X. *Org. Lett.* **2014**, *16*, 4448. b) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712.

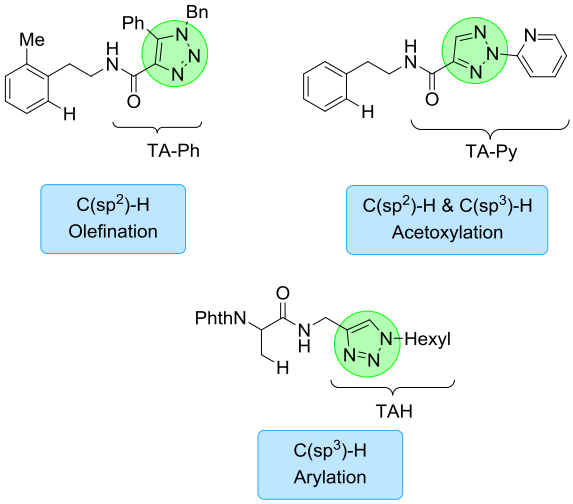
[215] Zhang, G.; Xie, X.; Zhu, J.; Li, S.; Ding, C.; Ding, P. *Org. Biomol. Chem.* **2015**, *13*, 5444.

alkylations of arenes, heteteroarenes and alkenes utilizing a bidentate DG containing a triazole scaffold named TAM (Scheme 4.8).



Scheme 4.8. TAM as DG in C−C bond formation.

Alternatively, Shi[214] and Ding[215] reported the Pd-catalyzed formation of new C−O and C−C bonds, respectively, assisted by other types of bidentate DGs. The group of Shi utilized DGs such as TA-Ph and TA-Py to perform olefination and acetoxylation reactions, and Ding achieved C(sp^3)−H arylations of aminoacid derivatives directed by the bidentate TAH moiety (Scheme 4.9).

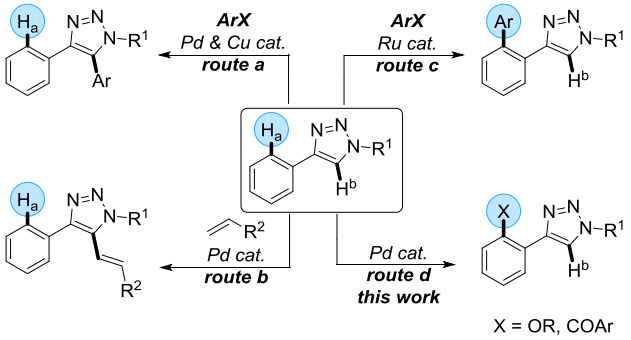


Scheme 4.9. Selected examples of triazole-containing DGs.

Despite the efficiency of those bidentate triazole-containing DGs, the mayor drawback relies on their structural complexity, which sometimes limited their synthetic scope. In this regard, the use of alternative and simple triazole derivatives easily installed within the arene ring in a straightforward fashion and acting as monodentate DGs would be of utmost synthetic practical value. In that sense, 4-aryl-1,2,3-triazoles resulting from the

atom economical CuAAC stand out as ideal substrates to develop novel C−H functionalization events. However, competitive functionalization of the heterocycle core poses a major limitation. Indeed, metal-catalyzed arylations and alkenylations selectively occurring at the acidic C−H bond are well-documented (Scheme 4.10, routes a and b).[216] On the one hand, C−H arylation processes generally involving Pd- and Cu-NHC systems promote the construction of C−C bonds from arenes or heteroarenes using aryl bromides and chlorides. On the other hand, alkenylation processes described by Jiang are carried out utilizing palladium salts and terminal conjugated alkenes in order to perform the corresponding C−H functionalization event in the C5 of the 1,2,3-triazole ring.

Our approach involves a distinct binding mode of the metal catalyst within the triazole and further activation of a specific C−H bond in the arene while leaving the C5−H bond intact (Scheme 4.10, route d). Whereas ruthenium complexes have allowed triazole-assisted direct arylations to selectively proceed at the arene (Scheme 4.10, route c),[217] at the time this work started Pd-catalyzed processes remained virtually unexplored.[218] In particular, we envisioned the use of triazoles as DG in challenging C−O bond-forming processes as well as in C−C bond-forming events such as acylation reactions.



Scheme 4.10. Metal-catalyzed C−H functionalization processes using 4-phenyl-1,2,3-triazoles.

---

[216] a) Lesieur, M.; Lazreg, F.; Cazin, C. S. J. *Chem. Commun.* **2014**, *50*, 8927. b) Tao, H.; Min, W.; Pinhua, L.; Lei, W. *Chin. J. Chem.* **2012**, *30*, 979. c) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922. d) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. e) Jiang, H.; Feng, Z.; Wang, A.; Liu, X.; Chen, Z. *Eur. J. Org. Chem.* **2010**, 1227.

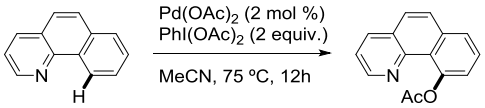
[217] Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. *Synthesis* **2010**, *13*, 2245.

[218] Very recently, other "click"-triazole directed C−H functionalization events have been reported, see for example: a) Zhao, F.; Chen, Z.; Ma, X.; Huang, S.; Jiang, Y. *Tetrahedron Lett.* **2017**, *58*, 614. b) Zhao, F.; Chen, Z.; Huang, S.; Jiang, Y. *Synthesis* **2016**, *48*, 2105.

4.2 Pd-catalyzed C(sp^2)−H oxygenations

4.2.1 Previous work

The field of Pd-catalyzed C−H functionalization has undergone an impressive development during the past decade and, in particular, C−H oxidations have received a great deal of attention. The C−H acetoxylation of benzene was first described in the presence of strong oxidants such as $K_2Cr_2O_7$ and $K_2S_2O_8$, albeit with low catalytic turnover and significant formation of the biphenyl product (homocoupling).[219] In 1996 Crabtree introduced a ligand-directed $Pd(OAc)_2$-catalyzed arene acetoxylation with $PhI(OAc)_2$ as the terminal oxidant.[220] The transformation proceeded with poor site-selectivity and both alkanes and electron-deficient arenes showed low reactivity. Although some efforts were done to improve the catalyst performance, in general it was found limited by harsh reaction conditions, low TON (turnover number), low functional group tolerance, significant formation of byproducts, and large excesses of substrate relative to oxidant were typically required.[221] In 2004 Sanford and co-workers circumvented some of the latter issues by describing a C−H acetoxylation protocol using a series of different nitrogen-containing DGs and $PhI(OAc)_2$ as the stoichiometric oxidant.[222]



Scheme 4.11. $Pd(OAc)_2$-catalyzed C(sp^2)−H acetoxylation with $PhI(OAc)_2$.

As depicted in scheme 4.11, they achieved the successful Pd-catalyzed C−H oxygenation of benzo[*h*]quinoline as a single isomer. The method was further extended at

---

[219] For Pd-catalyzed C−H acetoxylation of arenes using $K_2S_2O_8$ as oxidant, see: a) Eberson, L.; Jonsson, L. *J. Chem. Soc. Chem. Commun.* **1974**, 885. b) Eberson, L.; Jonsson, L. *Acta Chem. Scand. Ser. B* **1974**, *28*, 771. c) Eberson, L.; Jonsson, L. *Acta Chem. Scand. Ser. B* **1976**, *30*, 361. d) Eberson, L.; Jonsson, L. *Justus Liebigs Ann. Chem.* **1977**, 233. For Pd-catalyzed C−H acetoxylation of arenes using chromates as oxidant, see: e) Stock, L. M.; Tse, K.; Vorvick, L. J.; Walstrum, S. A. *J. Org. Chem.* **1981**, *46*, 1757. f) Henry, P. M. *J. Org. Chem.* **1971**, *36*, 1886.

[220] Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35.

[221] a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. b) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180. c) Mukhopadhyay, S.; Bell, A. T. *Angew. Chem. Int. Ed.* **2003**, *42*, 2990.

[222] Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

both sp^2 and sp^3 C−H bonds, as well as to the use of numerous DGs including pyridine, pyrimidine, pyrazine, pyrazole, azobenzene, imine, pyrrolidinone, oxime ether and acetate, isoxazole, amide and carbene derivatives.[223] Apart from the latter, other types of DGs have been reported including alcohols,[224] carboxylates[225] and sulfur derivatives such as sulfonyl,[226] silanol[227] or sulfoxide[228] groups, as well as alkene groups.[229] The reaction also proceeded in high yields with different types of oxidants such as oxone and $K_2S_2O_8$. Noteworthy, when employing protic solvents such as MeOH, ^{i}PrOH and CF_3CH_2OH, the corresponding ethers were obtained.

The generally accepted mechanism for this type of Pd-catalyzed C−H acetoxylation events starts with a site-selective C−H cleavage step to form palladacycle **I**. Then, such Pd(II) intermediate undergoes oxidation to provide the corresponding Pd(IV) intermediate **II**, which have been also proposed to exist as a Pd^{III}~Pd^{III} dimer.[200] Eventually, C−O bond forming reductive elimination furnishes the acetoxylated product and the active Pd(II) catalyst.[230]

---

223 a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. b) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. c) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. d) Kalberer, E. W.; Whitfield, S. R.; Sanford, M. S. *J. Mol. Catal. A* **2006**, *251*, 108. e) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. f) Neufeldt, S. R.; Sanford, M. S. *Org. Lett.* **2010**, *12*, 532. g) Gary, J. B.; Cook, A. K.; Sanford, M. S. *ACS Catal.* **2013**, *3*, 700. h) Tato, F.; García-Domínguez, A.; Cárdenas, D. J. *Organometallics* **2013**, *32*, 7487. i) Cook, A. K.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5428.

224 a) Ren, Z.; Schulz, J. E., Dong, G. *Org. Lett.* **2015**, *17*, 2696. b) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916.

225 Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315.

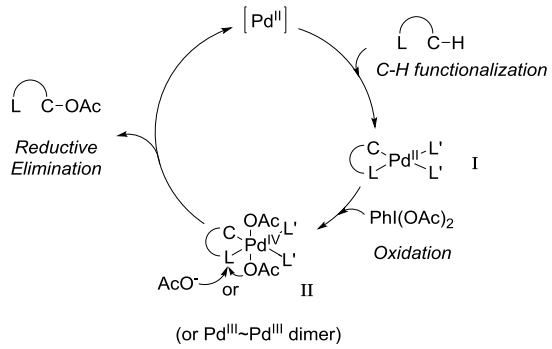
226 García-Rubia, A.; Fernández-Ibáñez, M. A.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Eur. J.* **2011**, *17*, 3567.

227 Wang, C.; Ge, H. *Chem. Eur. J.* **2011**, *17*, 14371.

228 Wang, B.; Shen, C.; Yao, J.; Yin, H.; Zhang, Y. *Org. Lett.* **2014**, *16*, 46.

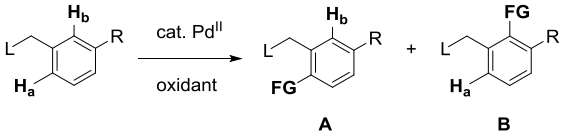
229 Gandeepan, P.; Cheng, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 5738.

230 For discussions of the intermediacy of monomeric Pd^{IV} or closely related dimeric Pd^{III}-Pd^{III}/ Pd^{IV}-Pd^{IV} intermediates in these reactions, see: a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2005**, *24*, 482. b) Racowski, J. R.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974. c) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. d) Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 14682. e) Ariafard, A.; Hyland, C. J. T.; Canty, A. J.; Sharma, M.; Yates, B. F. *Inorg. Chem.* **2011**, *50*, 6449. f) Ariafard, A.; Hyland, C. J. T.; Canty, A. J.; Sharma, M.; Brookes, N. J.; Yates, B. F. *Inorg. Chem.* **2010**, *49*, 11249. g) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840.



Scheme 4.12. Catalytic cycle for ligand-directed C−H acetoxylation

The selectivity of the acetoxylation reaction is dictated by more than one factor. In general, the C−H functionalization occurs *via* the formation of a five- or six-membered palladacycle, although reactions proceeding *via* seven-membered and even larger palladacyclic intermediates have been also reported.[231] Interestingly, multiple oxygenation processes can be performed when utilizing substrates with 2 or 3 identical C−H bonds in the presence of large amounts of oxidant. Remarkably, if two sterically distinct *ortho* C−H sites are available, high selectivity is typically observed for the functionalization in the less hindered position (Scheme 4.13, product **A**).

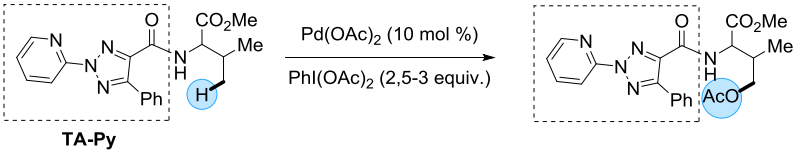


Scheme 4.13. Sterically inequivalent *ortho* C−H sites

As mentioned before, Shi and co-workers have recently reported the utilization of 1,2,3-triazole-containing DGs in Pd-catalyzed C−H oxygenations (Scheme 4.14).[214b] In particular, the use of TA-Py as DG facilitated the selective functionalization of both C(sp^2)−H and C(sp^3)−H bonds. Despite the remarkable importance of the method, the requirement of a structurally complex triazole-containing moiety as DG clearly limited the synthetic scope of the process. Inspired by their findings, we envisioned the alternate use of more simple triazoles as DGs in such C−H acetoxylation processes.

---

[231] Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008**, *64*, 6979.



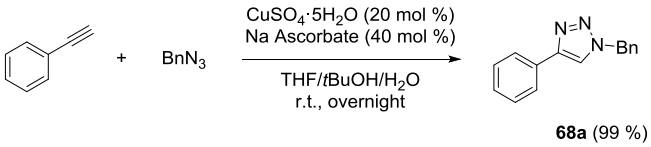
Scheme 4.14. TA-Py DG reported by Shi.

In this regard, the implementation of simple 1,2,3-triazoles as DGs prepared in a practical fashion upon "click" chemistry could open up new doors in this field of expertise. If successful, such procedures could complement existing methodologies for the assembly of acetoxylated arenes and represent likewise elegant late-stage functionalization events of "click" compounds.

4.2.2 Results and discussion

4.2.2.1 Screening of the reaction conditions

In order to test the feasibility of our approach, we first selected **68a** as the model substrate owing to its easy access in multi-gram scale following a reported CuAAC process from commercially available phenylacetylene and previously prepared benzyl azide. Thus, the desired 4-phenyl-1,2,3-triazole derivative **68a** was prepared in excellent yield (Scheme 4.15).

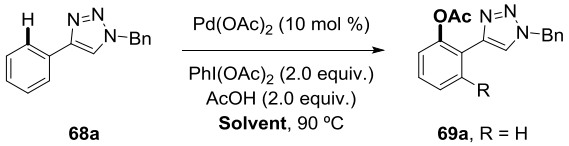


Scheme 4.15. Synthesis of triazole **68a** upon CuAAC.

With substantial amounts of **68a** in hand, we set out a systematic evaluation of the experimental variables such as metal, oxidant, solvent, additives and reaction temperatures. We started our screening process by varying the nature of the solvent and pleasingly found that $Pd(OAc)_2$ (10 mol %), PIDA (2.0 equiv.) and AcOH (2.0 equiv.) in THF (1 mL) at 90 ºC provided the desired acetoxylated product **69a** in 33 % yield (Table 4.1, entry 2). Although the oxygenated product was obtained in low yield, it demonstrated the viability of our hypothesis on the active role of "click" triazoles as DGs in C−H functionalization.

We next found out that the use of DCE as solvent provided the target product **69a** in slightly higher yield (entry 1), along with traces of diacetoxylated product. Other solvents such as PhCl, $PhCl_2$, C_2Cl_4, dioxane, DMF, DMA, MeCN and TFA were found unsuitable for the process to occur (entries 3-10). With the aim to improve the acetoxylation process,[222c] a co-solvent such as AcOH, DME and Ac_2O was added to the reaction mixture (entries 11-13). To our delight, the use of a mixture of DCE-Ac_2O in a 1:1 ratio favored the reaction obtaining 78 % yield of a mixture of mono- and diacetoxylated products (1.2:1 ratio) (Table 4.1, entry 13). This positive effect of Ac_2O has been justified by the presumable regeneration of the active catalyst.[223g,i,232]

Table 4.1. Screening of solvents.[a]



68a

69a, R = H
69a', R = OAc

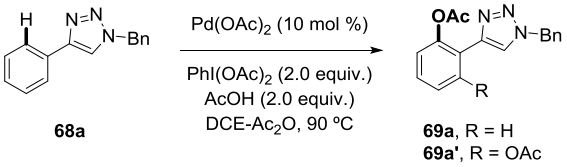
Entry	Solvent	Yield[b] (%)	Entry	Solvent	Yield[b] (%)
1	DCE	37	8	Dioxane	0
2	THF	33	9	MeCN	0
3	PhCl	0	10	TFA	0
4	$PhCl_2$	0	11	DCE-AcOH	n.d.
5	C_2Cl_4	0	12	DCE-DME	n.d.
6	DMF	n.d.	13	DCE-Ac_2O	78 (1.2:1)[c]
7	DMA	n.d.			

[a]Reaction conditions: **68a** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv.), AcOH (2.0 equiv.), DCE (1 mL) at 90 ºC for 24 h. [b]Yield of isolated product after column chromatography. [c]Ratio of mono- *vs* diacetoxylated product (**69a**/**69a'**).

Encouraged by these results, we further analyzed the influence of other Pd sources and oxidants, but we experimentally observed that $Pd(OAc)_2$ and $PhI(OAc)_2$, respectively, were the most efficient ones affording the target product in higher yields.

232 Cook, A. K.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 3109.

Table 4.2. Pd-catalyzed C(sp^2)−H acetoxylation of **68a**[a]



68a

69a, R = H
69a', R = OAc

Entry	Variation from standard conditions	Yield[b] (%)
1	none	78 (1.2:1)[c]
2	without $Pd(OAc)_2$	0
3	without $PhI(OAc)_2$	0
4	under air	60 (1.1:1)[c]
5	without Ac_2O	27 (1.1:1)[c]
6	*p*-TsOH·H_2O instead of AcOH	traces
7	$K_2S_2O_8$ instead of $PhI(OAc)_2$	traces
8	110 ºC instead of 90 ºC	79 (1.1:1)[c]
9	5 mol % of $Pd(OAc)_2$ instead of 10 mol %	61 (1.1:1)[c]

[a]Reaction conditions: **68a** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv.), AcOH (2.0 equiv.), AcOH (2.0 equiv.), DCE/Ac_2O (1:1, 1mL) at 90 ºC for 24 h. [b]Yield of isolated product after column chromatography. [c]Ratio of mono- *vs* diacetoxylated product (**69a**/**69a'**).

We further performed several control experiments (Table 4.2). As expected, the reaction did not proceed in the absence of either metal (entry 2) or oxidant (entry 3) and the addition of both AcOH and Ac_2O was crucial for the process to occur in high yields (entries 5-6).[203a,233] It is worth noting that the yield was not improved either at higher temperature (entry 8) or by adding pyridine derivatives which are known to enhance the rate of Pd-catalyzed C−H acetoxylations.[223g,i,232] Importantly, the process could take place in a remarkable 60 % yield even under air atmosphere (entry 4). Curiously, whereas the use of $K_2S_2O_8$ under the standard conditions resulted in the formation of just traces of the acetoxylated product (entry 7), Jiang and co-workers have recently reported related Pd-catalyzed acetoxylations of "click" triazoles using $K_2S_2O_8$ as oxidant instead of PIDA.[218a]

[233] Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 7420.

4.2.2.2 Synthesis of the starting triazoles

Having established the optimized reaction conditions, we continued our studies by preparing a wide range of 4-aryl-1,2,3,-triazoles to evaluate the influence of the nature of the heterocyclic motif on the *ortho*-acetoxylation. One of the most common strategies for the synthesis of triazoles is the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition between alkynes and azides (CuAAC), which has been previously described in chapter 1. This method provides exclusive regioselectivity toward the formation of 1,4-substituted 1,2,3-triazoles, and occurs under mild reaction conditions and very high yields, which constitutes a practical bonus for our synthetic goals. Accordingly, a variety of alkynes and azides were reacted in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate to provide the corresponding triazoles **68a-v** in moderate to good yields (Table 4.3).

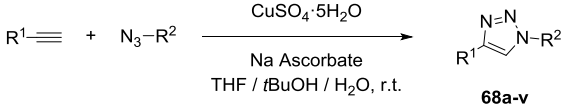
Similarly, another set of 1,2,3-triazoles **68w-zc** were obtained in a two-step sequence. Although organic azides are generally safe compounds, those of low molecular weight can be unstable and, therefore, difficult to handle. In those cases, we followed a one-pot, two-step procedure described in the literature,[234] where the alkyl azides were *in situ* generated and reacted with CuI and DIPEA to obtain the corresponding triazoles in overall good yields (Table 4.4).

Additionally, fully substituted 1,2,3-triazoles were synthesized in a different manner depending on the type of substituent in the C5 position. On the one hand, the 5-iodo-1,2,3-triazoles were synthesized in a one-pot, two-step procedure where the alkyl azides were generated *in situ* and reacted with CuI, NBS and DIPEA in MeCN to afford the corresponding triazoles in good yields (Table 4.5).[235] On the other hand, when the substituent was a phenyl group, the reaction was carried out through a metal-free Huisgen cycloaddition process which provided the target product **68zj** in low yield (Scheme 4.17).[236]

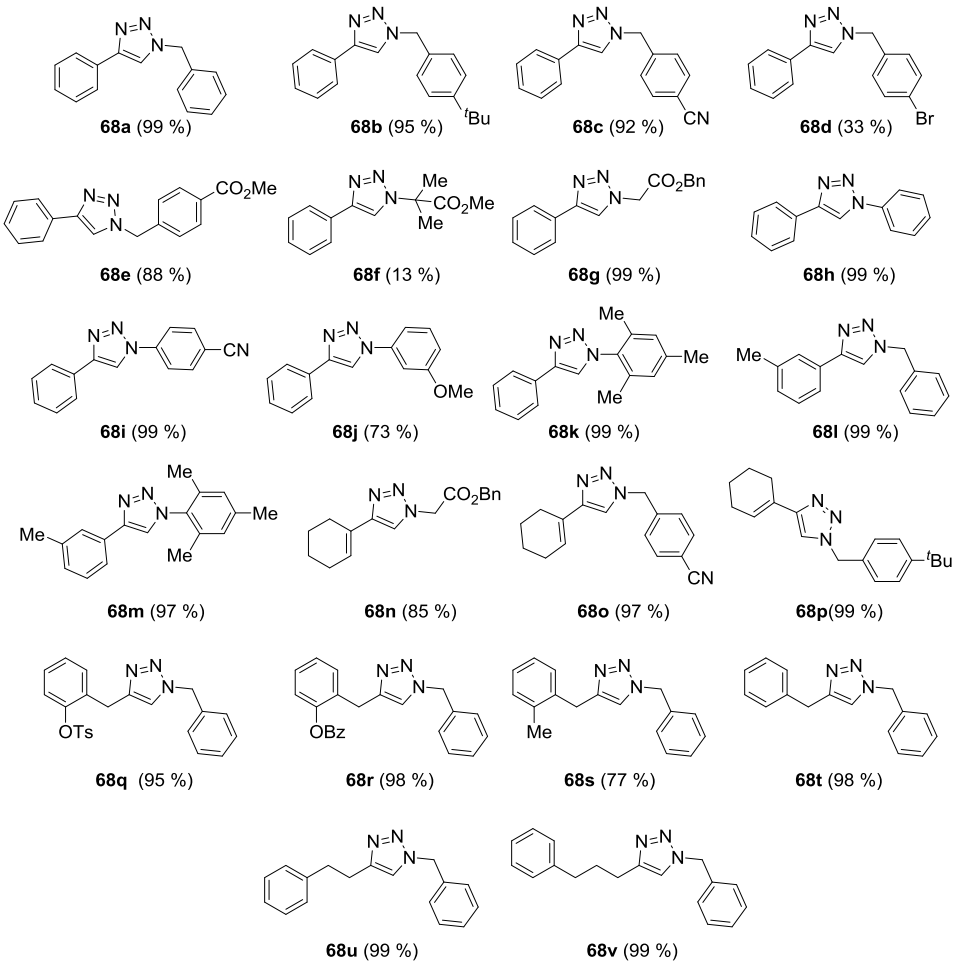
---

[234] Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897.
[235] Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, 1314.
[236] Wang, Z.-X.; Qin, H.-L. *Chem. Commun.* **2003**, 2450.

Table 4.3. Synthesis of 1,2,3-triazoles **68a-v**[a,b]

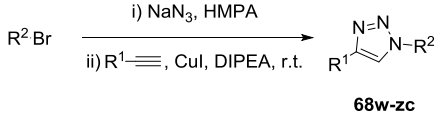


68a-v

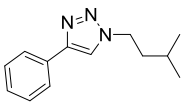


[a]Reaction conditions: alkyne (1.0 equiv.), R-N_3 (1.1 equiv.), $CuSO_4 \cdot 5H_2O$ (0.2 equiv.), Na Ascorbate (0.4 equiv.), THF/*t*BuOH (1:1, 30 mL) and H_2O (15 mL) under N_2 at room temperature. [b]Yield of isolated product after column chromathography.

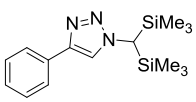
Table 4.4. Synthesis of 1,2,3-triazoles **68w-zc**[a,b]



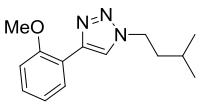
68w-zc



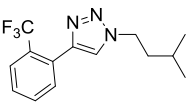
68w (85 %)



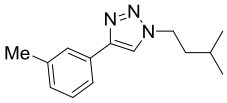
68x (87 %)



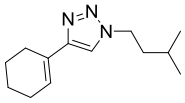
68y (69 %)



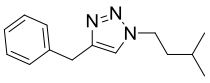
68z (50 %)



68za (86 %)



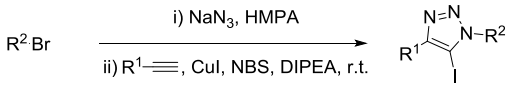
68zb (82 %)



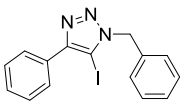
68zc (99 %)

[a]Reaction conditions: i) alkyl bromide (1.0 equiv.), R^2-N_3 (1.1 equiv.), HMPA (0.60 mL/mmol) under N_2, for 5h; ii) alkyne (1.0 equiv.), CuI (0.2 equiv.), DIPEA (5.0 equiv.), under N_2 overnight at room temperature. [b]Yield of isolated product after column chromathography.

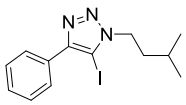
Table 4.5. Synthesis of 1,4,5-trisubstituted 1,2,3-triazoles[a,b]



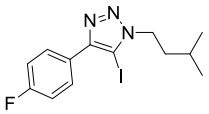
68zd-zi



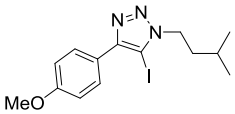
68zd (89 %)



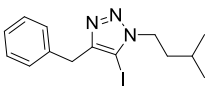
68ze (50 %)



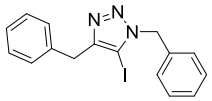
68zf (38 %)



68zg (43 %)

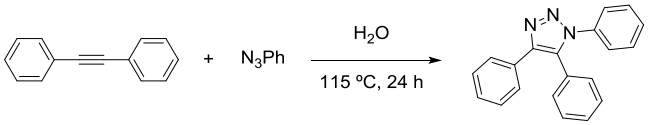


68zh (53 %)



68zi (30 %)

[a]Reaction conditions: i) alkyl bromide (1.0 equiv.), R^2-N_3 (1.1 equiv.), HMPA (0.60 mL/mmol) under N_2, for 5h; ii) CuI (1.0 equiv.) in MeCN (2.4 mL/mmol) and NBS (1.2 equiv.) in MeCN (2.4 mL/mmol) for 5min; azide (previously prepared), alkyne (1.0 equiv.) and DIPEA (1.1 equiv.), under N_2 overnight at room temperature. [b]Yield of isolated product after column chromathography.



68zj (38 %)

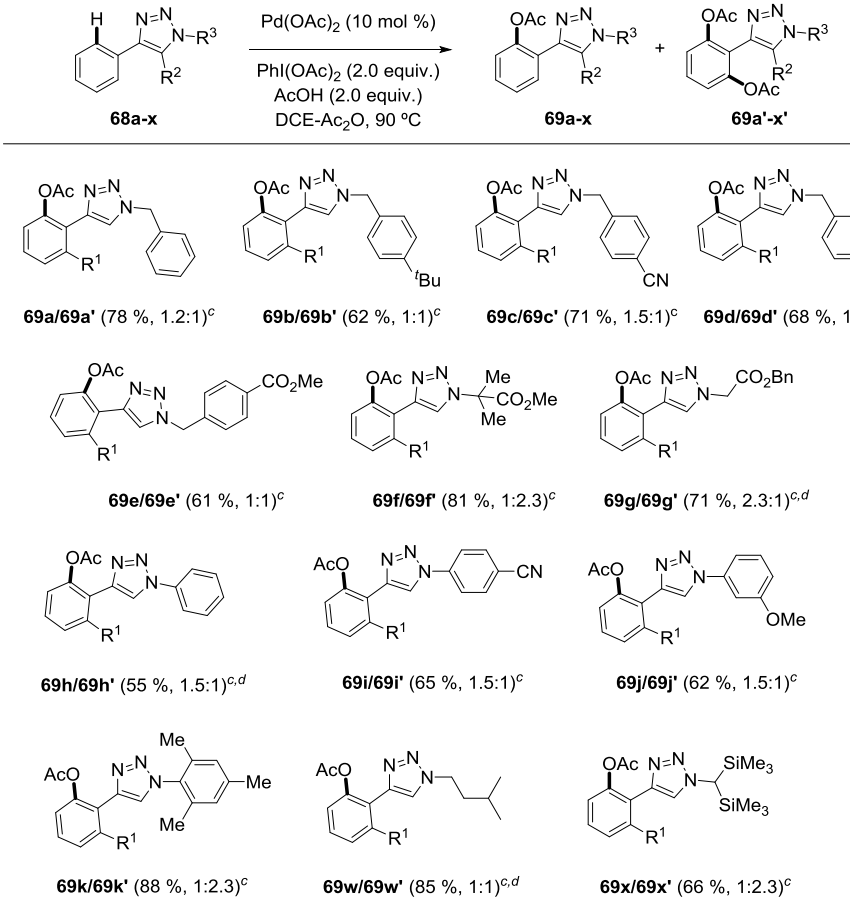
Scheme 4.16. Synthesis of 1,4,5-triphenyl-1*H*-1,2,3-triazole.

4.2.2.3 Pd-catalyzed C−H oxygenation of 4-aryl-1,2,3-triazoles

With a vast array of 1,2,3-triazoles in hand, we next explored the scope of the reaction evaluating the influence of differently substituted triazoles as DGs. As depicted in Table 4.6, a variety of triazoles including those bearing both aliphatic and aromatic motifs were found to be effective DGs to afford the corresponding oxygenated products as separable mixtures of mono- and diacetoxylated isomers in good to high yields (up to 88 % yield). Remarkably, a variety of functional groups such as cyano (**69c**,**i**), ester, (**69e**-**g**), bromide (**69d**) and ether (**69j**) were perfectly accommodated, as well as other bulky groups including silicon (**69x**) and mesityl (**69k**) groups.

As depicted in Table 4.6, when certain aliphatic chains were introduced in the *N*1 atom (**69f**,**g**,**w**) the yield was increased considerably. Additionally, we observed that sterical hindrance played a crucial role in selectivity and diacetoxylation was significantly enhanced when using triazoles bearing sterically demanding substituents on the *N*1 atom (**69f'**,**k'**,**x'**).

Table 4.6. Influence of the nature of triazole ring on the Pd-catalyzed C(sp^2)−H acetoxylation.[a,b]

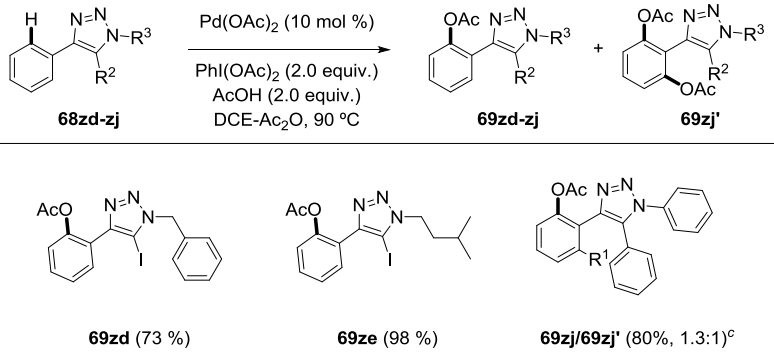


[a]Reaction conditions: **68** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv.), AcOH (2.0 equiv.), DCE/Ac_2O (1:1, 1 mL) at 90 ºC for 24 h. [b]Yield of isolated product after column chromatography, average of at least two independent runs. [c]Ratio of mono- *vs* diacetoxylated product (**69**/**69'**). [d]110 ºC.

Remarkably, in all the cases C(sp^2)−H acetoxylation exclusively occurred at the *ortho*-position of the arene moiety leaving the heterocyclic C(sp^2)−H bond intact. Although merely speculative, the regioselectivity toward the acetoxylation reaction may be related to the more feasible formation of the required palladacycle under acidic conditions, whereas C−H functionalization of the more acidic heterocyclic position generally occurs under basic conditions.[216]

Taking into account the crucial role that bulky groups can play within regioselectivity, we decided to prepare sterically demanding triazoles by introducing different substituents in the C5 of the triazole in order to evaluate their effect. To our surprise, iodinated compounds **68zd** and **ze** resulted in the exclusive formation of monoacetoxylated arenes **69zd** and **ze** in excellent yields. We tentatively hypothesized that the iodine atom could block the free-rotation of the arene thus positioning the directing triazole unit away from the second *ortho* C−H bond. In striking contrast, the introduction of a less sterically demanding phenyl group resulted in a total loss of selectivity towards the monoacetoxylation and the corresponding oxygenated product was obtained as a separable mixture of isomers (**69zj**/**zj'**) (Table 4.7).

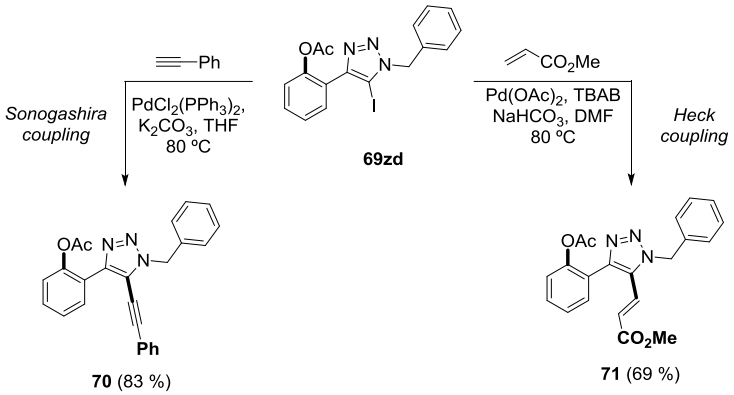
Table 4.7. Influence of C5-substituted triazoles on Pd-catalyzed C(sp^2)−H acetoxylation.[a,b]



[a]Reaction conditions: **68** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv.), AcOH (2.0 equiv.), DCE/Ac_2O (1:1, 1 mL) at 90 ºC for 24 h. [b]Yield of isolated product after column chromatography, average of at least two independent runs. [c]Ratio of mono- *vs* diacetoxylated product (**69**/**69'**).

Notably, an added benefit from using such 5-iodo-1,2,3-triazoles as DGs is that the resulting products constitute versatile synthetic intermediates in the cross-coupling arena. As shown in Scheme 4.17, when compound **69zd** was reacted with an alkyne in THF utilizing $PdCl_2(PPh_3)_2$ as catalyst and K_2CO_3 as base at 80 ºC, the corresponding Sonogashira reaction effectively yielded 1,4,5-trisubstituted 1,2,3-triazole **70** in high yield. Likewise, the Pd-

catalyzed Heck reaction on 5-iodo-1,2,3-triazole **69zd** with methyl acrylate afforded the corresponding product **71** in good yield.[237]



Scheme 4.17. Sonogashira and Heck couplings to 1,4,5-trisubstituted 1,2,3-triazoles.

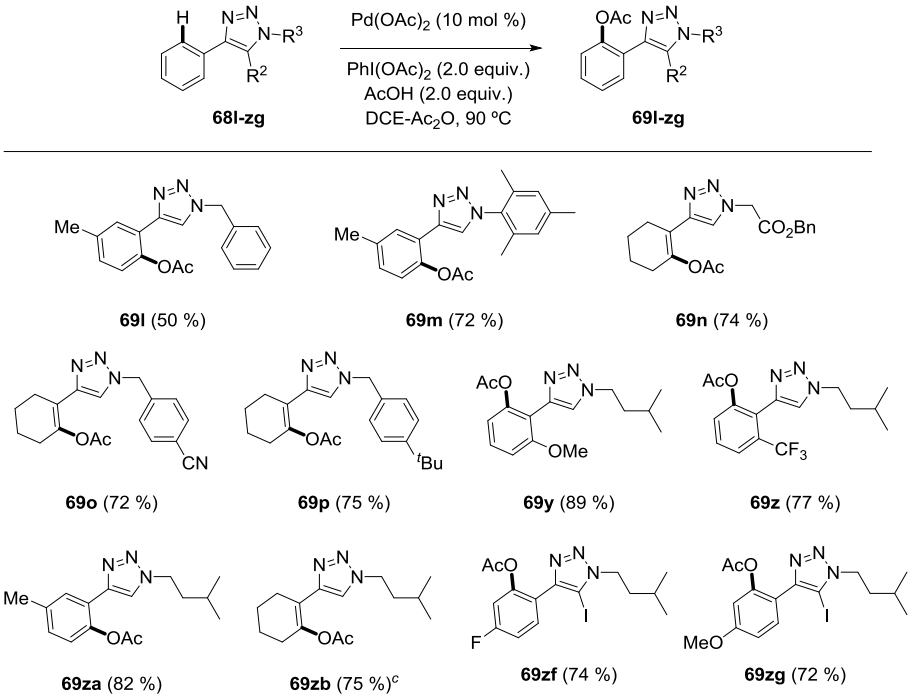
Having demonstrated the key role of 5-iodo-1,2,3-triazoles as efficient DGs, we next evaluated the synthetic scope of the process. To our delight, both DG-and substrate-controlled selectivity was achieved, and this transformation was found to be highly efficient for the exclusive monoacetoxylation of a wide range of substrates as depicted in Table 4.8. The use of 5-iodotriazoles facilitated the selective *ortho*-oxygenation of substituted arenes (**69zf**,**zg**) upon a DG-controlled reaction pathway. Notably, substrate-controlled selectivity was also observed even with simple triazoles (R^2=H); *ortho*-substituents did not hamper the process and indeed allowed the oxygenation to occur in high yields (**69y**,**z**). Conversely, in certain reported protocols the presence of *ortho*-substituents was found detrimental for the reaction to occur.[238] Likewise, *meta*-substituted substrates such as **69l**, **69m** and **69za** displayed excellent regioselectivity in the less hindered *ortho*-position producing the corresponding acetoxylated products as single regioisomers in 50 %, 72 % and 82 % yields, respectively. Remarkably, comparatively less explored vinylic C−H bonds smoothly underwent the acetoxylation process to furnish the desired products **69n**, **69o**, **69p** and **69zb** with high yields.

---

[237] a) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2009**, *48*, 8018. b) Deng, J.; Wu, Y.-M.; Chen, Q.-Y. *Synthesis* **2005**, 2730.

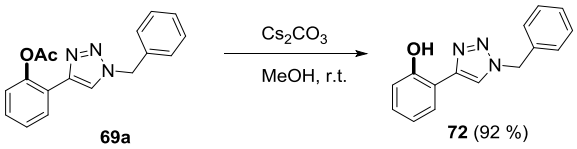
[238] a) Huang, C.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Adv. Synth. Catal.* **2011**, *353*, 1285. b) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270.

Table 4.8. Pd-catalyzed C(sp^2)−H *ortho*-acetoxylation of arenes and alkenes.[a,b]



[a]Reaction conditions: **68** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv.), AcOH (2.0 equiv.), DCE/Ac_2O (1:1, 1 mL) at 90 ºC for 24 h. [b]Yield of isolated product after column chromatography, average of at least two independent runs. [c]110 ºC.

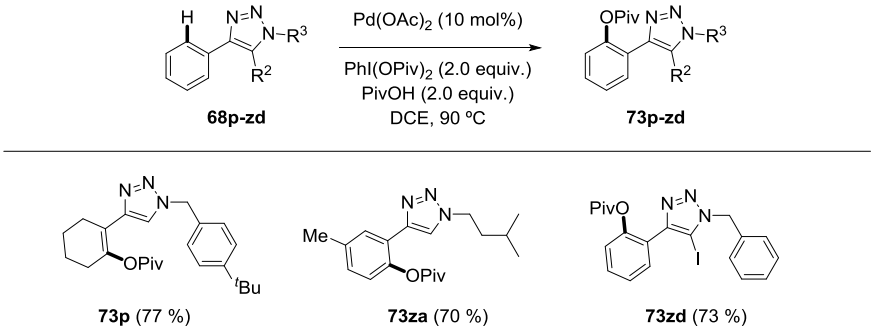
In an attempt to see the synthetic usefulness of the developed method, we tried to convert the acetoxylated product into a more versatile functionality. As depicted in Scheme 4.18, the acetoxylated product **69a** was easily hydrolyzed to produce the corresponding free-hydroxy derivative under mild reaction conditions.



Scheme 4.18. Mild hydrolysis of acetoxylated compound **69a**.

In order to study the feasibility of our protocol for the introduction of other related oxygenated moieties, we next performed the Pd-catalyzed C−H functionalization process utilizing $PhI(OPiv)_2$. After careful control experiments, we observed that AcOH had to be replaced by PivOH. Likewise, Ac_2O had to be removed from the reaction media to avoid competitive *ortho*-acetoxylation which could be attributed to the *in situ* formation of more reactive $PhI(OAc)_2$ by a reasonable ligand exchange on the hypervalent iodine species.[239] Gratifyingly, Pd-catalyzed *ortho*-pivaloxylation was successfully achieved to yield **73p**, **73za**, and **73zd** in 77 %, 70 % and 73 % yield, respectively (Table 4.9). It is worth highlighting that the selective introduction of pivaloxy group is of great synthetic importance owing to its broad opportunities in Ni-catalyzed cross-coupling events.[240]

Table 4.9. Pd-catalyzed $C(sp^2)$−H *ortho*-pivaloxylation of arenes and alkenes.[a,b]



[a]Reaction conditions: **68** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OPiv)_2$ (2.0 equiv.), PivOH (2.0 equiv.), DCE (1 mL) at 90 ºC for 24 h. [b]Yield of isolated product after column chromatography, average of at least two independent runs.

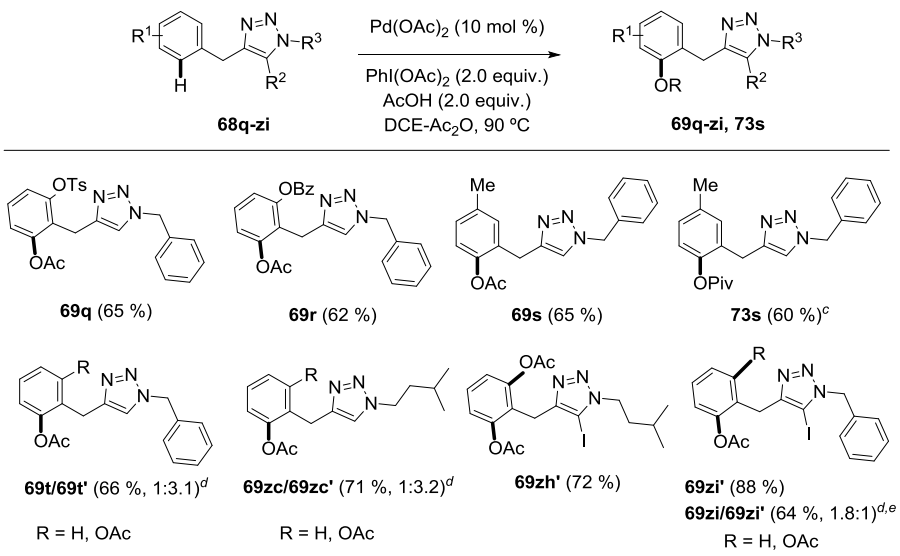
Next, we examined the feasibility of the Pd-catalyzed oxygenation process in substrates with a longer tether between the arene and the directing triazole. As depicted in Table 4.10, 4-benzyl-1,2,3-triazoles **68zc** and **68t** provided the corresponding acetoxylated products **69zc** and **69t**, respectively, as separable mixtures of mono- and difunctionalized products. Interestingly, whereas when using 4-phenyl-1,2,3-triazoles the corresponding monoacetoxylated products were obtained as the major isomers, in the latter cases the

239 a) Narayan, R.; Manna, S.; Antonchick, A. P. *Synlett* **2015**, *26*, 1785. b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.

240 See for example: a) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 7253. b) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.

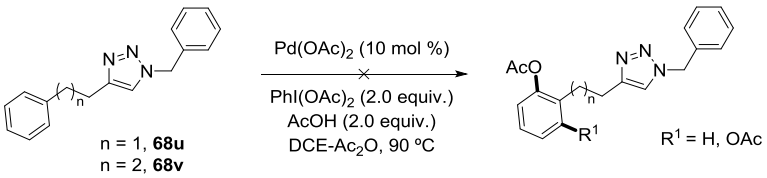
diacetoxylated products were mostly obtained, which could be tentatively attributed to the higher flexibility of the presumable formation of 6-membered palladacyclic intermediates. Remarkably, the introduction of both *ortho*- (**69q**, **69r**) and *meta*-substituents (**69s**) into the arene ring enabled the selective monooxygenation process to occur in good yields. Likewise, the monopivaloxylation of the arene bearing a *meta*- substituent **73s** was also achieved in good yield. Impressively, when 5-iodo derivatives **68zh** and **68zi** were utilized, an unexpected selectivity was achieved. Instead of the monoacetoxylated compounds, diacetoxylated products **69zh'** and **69zi'** were exclusively obtained in high yields. In an attempt to see if the monoacetoxylated product could be obtained, the amount of $PhI(OAc)_2$ was reduced providing the monosubstituted product **69zi** as the major compound. We hypothesized that the triazole motif could bind to the Pd center *via* the formation of a more flexible 6-membered palladacycle, and hence the iodine atom may not block the free rotation of the benzyl group as when a phenyl ring is used. As a result, previous selectivity toward monoacetoxylation (Table 4.7, **69zd**,**ze**) is not observed, and selective diacetoxylation is achieved instead, which remains unclear to rationalize at this stage.

Table 4.10. Pd-catalyzed C(sp^2)–H *ortho*-acetoxylation of arenes **68q-zi.**[a,b]



[a]Reaction conditions: **68** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv.), AcOH (2.0 equiv.), DCE/Ac_2O (1:1, 1 mL) at 90 ºC for 24 h. [b]Yield of isolated product after column chromatography, average of at least two independent runs. [c]$PhI(OPiv)_2$ (2.0 equiv), PivOH (2.0 equiv) in DCE (1 mL). [d]Ratio of mono- *vs* diacetoxylated product. [e]$PhI(OAc)_2$ (1.0 equiv).

Finally, in order to extend the synthetic scope of the process for the practical functionalization of arenes bearing the required DG in a longer distance to the corresponding C−H bond, triazoles **68u-v** were easily prepared through CuAAC. In those cases, the process would involve the formation of less common 7- and 8-membered palladacycles. Unfortunately, triazoles **68u-v** remained unreactive under the standard reaction conditions and not even traces of the target products were detected. Therefore, the process seems to be limited to the use of 4-phenyl and 4-benzyl triazole derivatives.

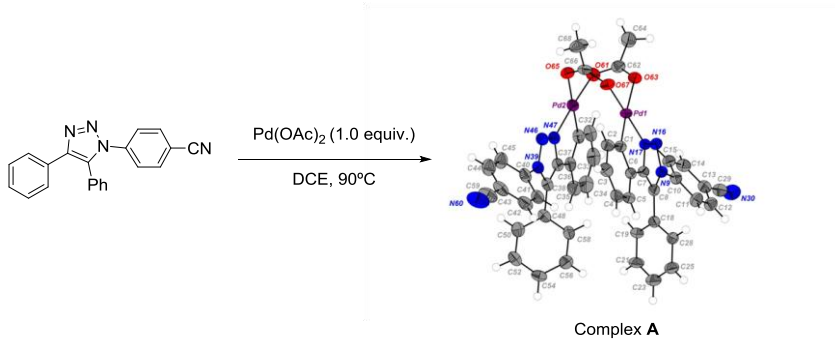


Scheme 4.19. Unsuccessful attempts with triazoles **68u-v**.

4.2.2.4 Reaction mechanism

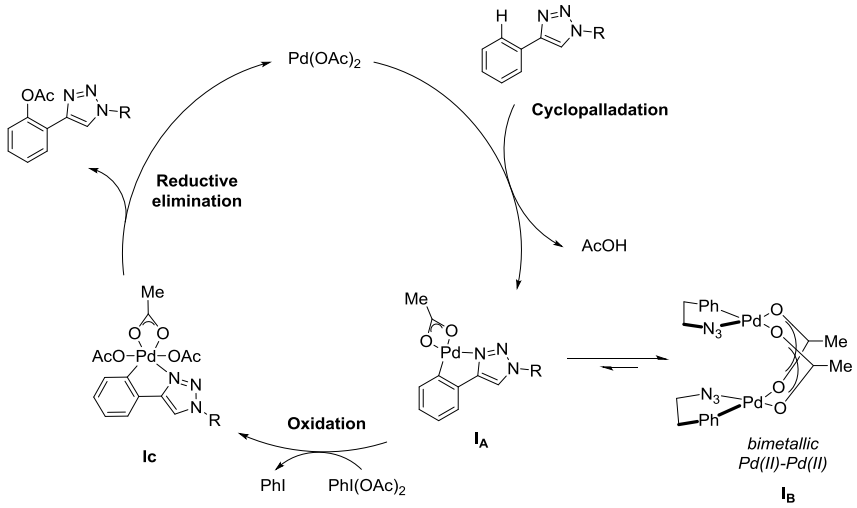
As mentioned in the introduction section, C−H functionalization reactions catalyzed by palladium salts are commonly proposed to proceed *via* either Pd(0)/Pd(II) or Pd(II)/Pd(IV) redox cycles.[241] Pd(IV) intermediates have been suggested in Pd-catalyzed aromatic C−H oxidation reactions since 1971,[242] and Pd(II)/Pd(IV) catalysis cycles have subsequently become generally accepted as the operative mechanisms for a large class of Pd-catalyzed oxidation reactions. In this regard, our group has recently reported a related Pd-catalyzed C−H bromination procedure assisted by "click" triazoles, where DFT studies supported the intermediacy of Pd(IV) species within the catalytic cycle. In particular, a palladacycle involving a "click"-triazole as DG was successfully characterized by X-Ray analysis verifying its bimetallic nature (Scheme 4.20).[243]

[241] Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041.
[242] Henry, P. M. *J. Org. Chem.* **1971**, *36*, 1886.
[243] Goitia, A.; Gómez-Bengoa, E.; Correa, A. *Org. Lett.* **2017**, *19*, 962.



Scheme 4.20. Synthesis of "click" 1,2,3-triazole complex **A**.

In-depth DFT studies demonstrated that the oxidation of the Pd(II)-intermediate was more energetically favored to occur under the monomeric species rather than the bimetallic one, and hence dissociation of the palladacycle is believed to proceed prior to the corresponding oxidation step. Accordingly, we reasonably assumed that a similar reaction mechanism for the present Pd-catalyzed C−H oxygenation procedure may be operative. In this regard, although further mechanistic studies are clearly required to confirm the mechanistic scenario, a plausible reaction pathway is proposed in Scheme 4.21.



Scheme 4.21. Proposed reaction mechanism.

The reaction would start by a cyclopalladation step to furnish the corresponding palladacyclic intermediate $\mathbf{I_A}$ which has been confirmed by DFT studies in related studies by our group to be more stable as its dimeric species $\mathbf{I_B}$. Based on DFT studies which revealed a

less favored oxidation step upon such bimetallic intermediate $\mathbf{I_B}$, a dissociation step was proposed to occur before its corresponding oxidation by treatment with a brominating agent. Accordingly, herein we also propose that the corresponding oxidation step would be more likely to happen on the monomeric palladacycle $\mathbf{I_A}$ to afford the corresponding Pd(IV) intermediate $\mathbf{I_C}$. Some reports support such Pd(IV) complexes as active intermediates in Pd-catalyzed C−H acetoxylations *via* oxidation of Pd(II) complexes with $PhI(OAc)_2$.[223b,244] Eventually, C−O bond-forming reductive elimination from the monomeric Pd(IV) species would deliver the target product and regenerate the active Pd catalyst.

4.2.2.5 Conclusions

1. "Click" triazoles have been demonstrated to act as versatile and practical DGs in Pd-catalyzed C−H oxygenation reactions. Both acetoxy and pivaloxy groups can be efficiently introduced in a wide variety of substituted arenes and alkenes by our protocol.

2. DG- and substrate-controlled selectivity towards monoacetoxylated products was achieved. The use of iodo-substituted DGs facilitated the *ortho*-oxygenation of $C(sp^2)$−H bonds upon a DG-controlled pathway. Additionally, substrate-controlled selectivity was performed employing *ortho*- and *meta*- substituted arenes as well as vinylic compounds.

3. The usefulness of the developed method was highlighted by the synthetically practical transformations that the prepared triazoles can undergo in cross-coupling reactions.[245]

4.2.3 Cu-catalyzed C−H functionalization directed by bidentate DGs

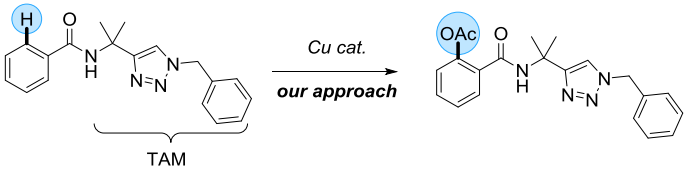
Despite the successful use of "click" triazoles as DGs in Pd-catalyzed C−H oxygenation reactions, the use of Pd salts has been replaced by other sustainable metals in the last years. In this respect, we faced the implementation of cost-efficient Cu-catalysts in these C−H oxidation processes. If successful, such procedures would be clearly more appealing in terms of economics and sustainability.

---

[244] a) Canty, A. J.; Denney, M. C.; van Koten, G.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 5432. b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

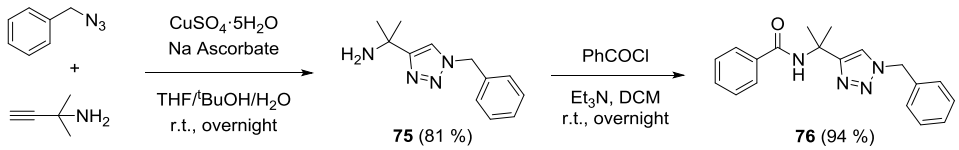
[245] Irastorza, A.; Aizpurua, J. M.; Correa, A. *Org. Lett.* **2016**, *18*, 1080.

In this respect, we hypothesized that the use of bidentate DGs would result in the formation of a more robust catalyst in combination with copper salts (Scheme 4.22). For that purposes, we decided to synthesize TAM-derivative **76**, which has been extensively utilized by Ackermann in a variety of C−C bond-forming processes,[213] but its use in C−H oxidation reactions remains unexplored.



Scheme 4.22. Cu-catalyzed C−H oxygenation strategy.

Accordingly, we chose **76** as our model substrate since it could be prepared in multi-gram scale in essentially two steps from commercially available 2-methylbut-3-yn-2-amine and freshly prepared benzyl azide under CuAAC conditions. The resulting triazole **75**, was then reacted with commercially available benzoyl chloride and triethylamine in DCM to obtain the desired compound **76** in 94 % yield.[213e]



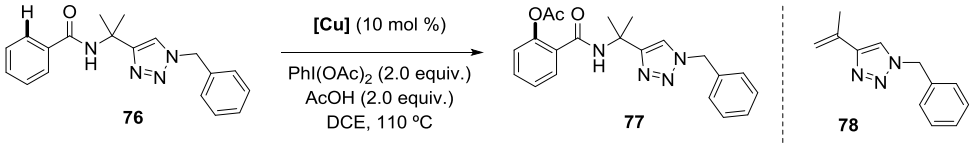
Scheme 4.23. Synthesis of compound **76**.

With substantial amounts of **76** in hand, we set out to investigate the viability of our hypothesis by testing a variety of experimental variables such as metals, ligands, additives, solvents and temperatures. Our initial reactions were performed using compound **76** in the presence of several copper catalysts such as $Cu(OTf)_2$, $Cu(OAc)_2$, $CuBr_2$, $CuCl_2$, CuF_2, CuBr, CuCl, $Cu(NO_3)_2{\cdot}H_2O$, CuO and $CuSO_4{\cdot}5H_2O$ utilizing PIDA as oxidant and AcOH as additive in DCE at 110 ºC. Taking into consideration the mechanism proposed by several authors,[246] both Cu(I) and Cu(II) are plausible for the reaction to occur.

---

[246] a) Bhadra, S.; Matheis, C.; Katayev, D.; Gooßen, L. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 9279. b) Khemnar, A. B.; Bhanage, B. M. *Org. Biomol. Chem.* **2014**, *12*, 9631. c) Kumar, S.; Guin, R. S.; Gogoi, A.; Majji, G.; Patel, B. K. *Org. Lett.* **2014**, *16*, 1614.

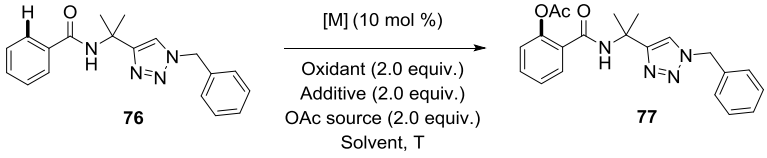
Table 4.11. Screening of different copper salts.



Entry	[Cu]	**77** (yield, %)	Entry	[Cu]	**77** (yield, %)
1	$Cu(OTf)_2$	**78** (60 %)	6	CuBr	0
2	$Cu(OAc)_2$	0	7	CuCl	0
3	$CuBr_2$	0	8	$Cu(NO_3)_2 \cdot H_2O$	0
4	$CuCl_2$	0	9	CuO	0
5	CuF_2	0	10	$CuSO_4 \cdot 5H_2O$	0

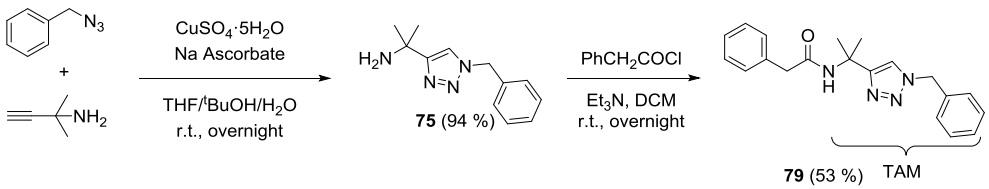
As shown in Table 4.11, the target acetoxylated product **77** was not detected and starting material was recovered instead, except when utilizing $Cu(OTf)_2$ as catalyst (entry 1) that compound **78** was obtained in 60 % yield. The formation of that olefinic derivative could be explained by first coordination of the hypervalent iodine reagent on the amide moiety and subsequent cleavage under acidic conditions.

In order to favor the formation of the acetoxylated product **77** over the undesired formation of **78** as side-product, we further conducted a careful screening process of several reaction parameters such as oxidants, acetate sources, solvents, chelating ligands and a wide variety of additives.



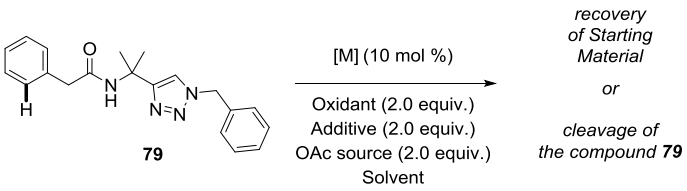
Scheme 2.24. Screening process with triazole **76**.

Unfortunately, all attempts were unfruitful and the target acetoxylation process was not favored under any tested reaction conditions. At this stage, we wondered whether the use of triazole derivative **79** bearing an extra methylene unit would render a more flexible system that could provide us more promising results. Accordingly, we successfully prepared triazole **79** following a similar CuAAC/*N*-protection sequence in good overall yield.



Scheme 4.25. Synthesis of compound **79**.

In this case, regardless of the reaction conditions utilized, we neither obtained the corresponding acetoxylated derivative and either the starting material **79** was recovered or the undesired cleavage of the starting material was observed instead (Scheme 4.26).



Scheme 4.26. Screening of reaction conditions for compound **79**.

At this stage, we concluded that whereas Pd salts were found to be efficient catalyst systems in C−H acetoxylations upon "click" triazoles, the use of more cost-efficient Cu-catalysts was found unsuccessful and the corresponding acetoxylation process was not achieved so far. Further studies are currently ongoing in our laboratories in order to develop more sustainable C−H acetoxylation procedures with "click" triazoles.

4.3 Pd-catalyzed C(sp^2)−acylations with aldehydes

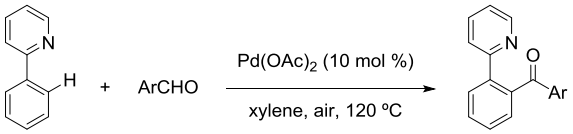
4.3.1 Previous work

Diaryl ketones are important motifs in the pharmaceutical, fragrance, dye, and agrochemical industries.[247] Among numerous known methodologies for diaryl and aryl alkyl ketone synthesis, the most accepted procedure is Friedel-Crafts acylation, which involves the use of a stoichiometric amount of a Lewis acid and has poor functional group compatibility

[247] a) Hruszkewycz, D. P.; Miles, K. C.; Thiel, O. R.; Stahl, S. S. *Chem. Sci.* **2017**, *8*, 1282. b) Benites, J.; Valderrama, J. A.; Ríos, D.; Lagos, R.; Monasterio, O.; Buc Calderon, P. *Mol. Cell Toxicol.* **2016**, *12*, 237. c) Kohtani, S.; Nishioka, S.; Yoshioka, E.; Miyabe, H. *Catal. Commun.* **2014**, *43*, 61.

and untenable regioselectivity.[248] The oxidation of a secondary alcohol is also a powerful tool to access ketones, but stoichiometric amounts of oxidant are generally required.[249] The reactions of carboxylic acid derivatives, such as nitriles, Weinreb amides, anhydrides, or acid chlorides with lithium, magnesium, or aluminum reagents are also important methods for the synthesis of the corresponding ketones.[250] However, these transformations require either highly basic and nucleophilic or acidic conditions, resulting in low compatibility with most functional groups. Thus, the construction of elaborated ketones generally involves further functionalization steps that are time-consuming and occur with low yields. To circumvent these drawbacks, various alternative methods have been developed including the hydroacylation of olefins,[251] acylation of aryl halides,[252] carbonylative coupling,[253] and arylboronate acylation with aldehydes.[254] However, the transition metal-catalyzed acylation of the C−H bond of arenes has emerged as a new approach which represents another direct and promising pathway for the synthesis of the desired target products.

In 2009, the Cheng group[255] reported for the first time the palladium-catalyzed regioselective acylation of aromatic C−H bonds utilizing aldehydes in the presence of air as ideal oxidant (Scheme 4.27).



Scheme 4.27. Direct acylation reaction with benzaldehyde

---

248 Olah, G. A. *Friedel-Crafts Chemistry;* Wiley. New York, **1973.**

249 a) Hudlicky, M. *Oxidation in Organic Chemistry*; American Chemical Society: Washington DC, **1990**. b) Tojo, G.; Fernandez, M. *In Oxidation of Alcohols to Aldehyde and Ketones: A Guide to Current Common Practice*; Tojo, G., Ed.; Springer: New York, **2006**.

250 a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, **1989**, 685. b) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, **1985**, 433 and 824.

251 a) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. b) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.

252 Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614.

253 a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. b) Sharma, P.; Rohilla, S.; Jain, N. *J. Org. Chem.* **2017**, *82*, 1105.

254 a) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356. b) Li, H.; Xu, Y.; Shi, E.; Wei, W.; Suo, X.; Wan, X. *Chem. Commun.* **2011**, *47*, 7880.

255 Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120.

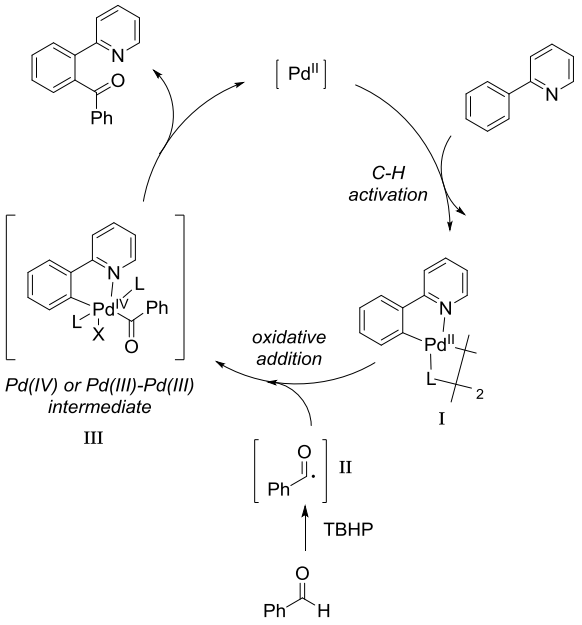
Shortly afterwards, Li and co-workers[256] developed an efficient palladium-catalyzed pyridine-directed oxidative acylation of sp^2 C−H bonds with aldehydes utilizing *tert*-butyl hydroperoxide as oxidant under neat conditions. In contrast to the previous synthetic method, this methodology enabled cross-couplings with both aromatic and aliphatic aldehydes. Subsequently, Deng and co-workers reported the practical acylation of arene C−H bonds using benzylic and aliphatic alcohols, which were *in situ* oxidized to the corresponding aldehydes and used as acylation reagents.[257] In 2010, Yu and co-workers[258] utilized oximes as DGs for the direct C−H bond acylation between aromatic oximes and aldehydes using *tert*-butyl hydroperoxide as oxidant. At almost the same time, the groups of Wang,[259] Kwong,[260] and Yu[261] developed the palladium-catalyzed *ortho*-acylation of acetanilides with aldehydes. Thereafter, aldehydes,[262] α-oxocarboxylic acids,[263] alcohols,[264] toluene,[265] and benzylic ethers[266] were used as acylating reagents in direct *ortho*-acylations of aromatic C−H bonds.

Taking palladium-catalyzed acylation of 2-phenylpyridine as a model example, a plausible reaction mechanism is depicted in Scheme 4.28. The reaction would be initiated by *ortho*-C−H activation/cyclopalladation of 2-phenylpyridine with palladium to form a bimetallic Pd^{II} complex **I**. The aldehyde would undergo its transformation to the radical **II** in the presence of the oxidant (TBHP in this case). Then, intermediate **I** would capture the acyl radical through an oxidative addition step to give intermediate **III**, which might be a Pd(IV)

---

256 Baslé, O.; Bidange, J.; Shuai, Q.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1145.
257 Xiao, F.; Shuai, Q.; Zhao, F.; Baslé, O.; Deng, G.; Li, C.-J. *Org. Lett.* **2011**, *13*, 1614.
258 Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 3926.
259 Li, C.; Wang, L.; Li, P.; Zhou, W. *Chem. Eur. J.* **2011**, *17*, 10208.
260 Wu, Y.; Li, B.; Mao, F.; Li, X.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 3528.
261 Chan, C.-W.; Zhou, Z.; Yu, W.-Y. *Adv. Synth. Catal.* **2011**, *353*, 2999.
262 a) Xiao, F.; Chen, S.; Huang, H.; Deng, G. *Eur. J. Org. Chem.* **2015**, 7919. b) Basle, O.; Bidange, J.; Shuai, Q.; Li, C. *Adv. Synth. Catal.* **2010**, *352*, 1145.
263 a) Wang, H.; Guo, L. N.; Duan, X. H. *Org. Lett.* **2012**, *14*, 4358. b) Miao, J.; Ge, H. *Org. Lett.* **2013**, *15*, 2930. c) Chen, X.; Cui, X.; Wu, Y. *Org. Lett.* **2016**, *18*, 3722. d) Wu, Y.; Sun, L.; Chen, Y.; Zhou, Q.; Huang, J.; Miao, H.; Luo, H. *J. Org. Chem.* **2016**, *81*, 1244.
264 a) Yuan, Y.; Chen, D.; Wang, X. *Adv. Synth. Catal.* **2011**, *353*, 3373. b) Park, J.; Kim, A.; Sharma, S.; Kim, M.; Park, E.; Jeon, Y.; Lee, Y.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Biomol. Chem.* **2013**, *11*, 2766. c) Hou, L.; Chen, X.; Li, S.; Cai, S.; Zhao, Y.; Sun, M.; Yang, X. *Org. Biomol. Chem.* **2015**, *13*, 4160. d) Luo, F.; Yang, J.; Li, Z. K.; Xiang, H. K.; Zhou, X. G. *Eur. J. Org. Chem.* **2015**, 2463.
265 a) Yin, Z.; Sun, P. *J. Org. Chem.* **2012**, *77*, 11339. b) Song, H.; Chen, D.; Pi, C.; Cui, X.; Wu, Y. *J. Org. Chem.* **2014**, *79*, 2955.
266 Han, S.; Sharma, S.; Park, J.; Kim, M.; Shin, Y.; Mishra, N. K.; Bae, J. J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2014**, *79*, 275.

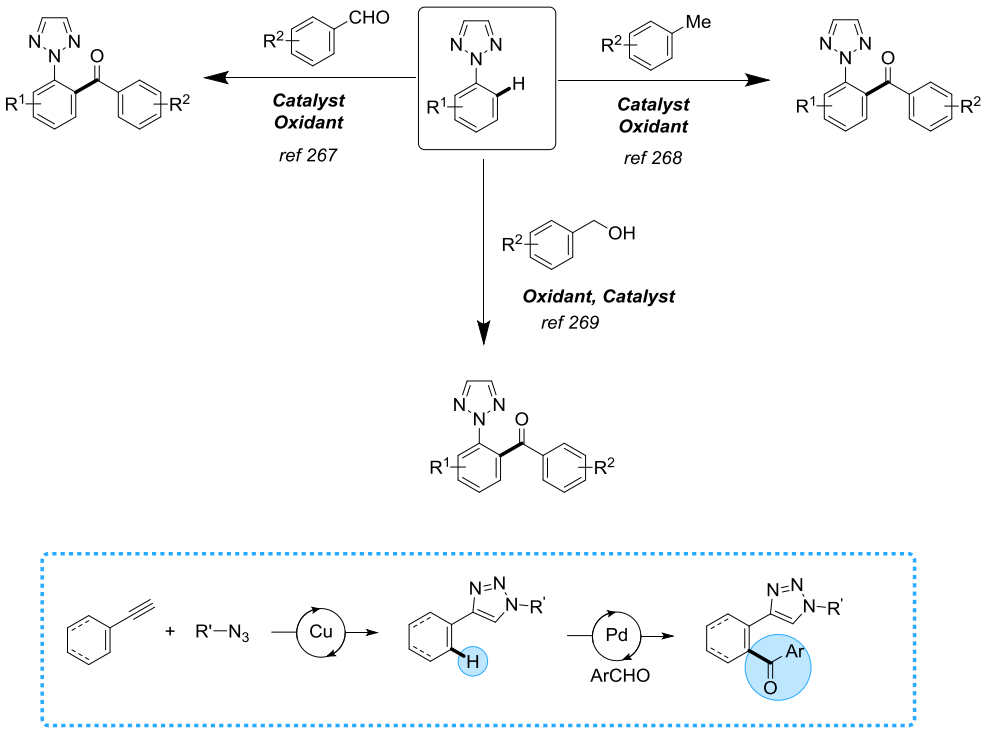
or a bimetallic Pd(III)-Pd(III) complex. Finally, reductive elimination upon **III** would result in the formation of the acylated product and regeneration of the active Pd(II) species to fullfil the catalytic cycle.



Scheme 4.28. Pd-catalyzed *ortho*-acylation of 2-phenylpyridine.

As mentioned before, 1,2,3-triazole-containing DGs have recently received a great deal of attention to accomplish C−H bond functionalizations. In particular, 2-phenyl-1,2,3-triazoles have been utilized as versatile compounds to perform metal-catalyzed C−H acylation processes with aldehydes,[267] toluene[268] and benzyl alcohols.[269] Given the practical bonus of easy-assembly of "click" triazoles *vs* 2-substituted 1,2,3-triazoles, we envisioned their alternative use in Pd-catalyzed C−H acylations with aldehydes. If successful, our protocol would complement existing methodologies to produce diaryl ketones featuring the unprecedent role of "click" triazoles as versatile DGs in C−H acylation events.

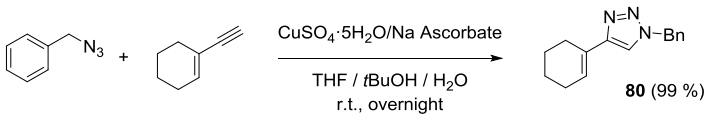
[267] Wang, Z.; Tian, Q.; Yu, X.; Kuang, C. *Adv. Synth. Catal.* **2014**, *356*, 961.
[268] He, P.; Tian, Q.; Kuang, C. *Synthesis* **2015**, *47*, 1309.
[269] Premi, C.; Patel, S. S.; Jain, N. *Eur. J. Org. Chem.* **2016**, 3788.



Scheme 4.29. Metal-catalyzed C−H acylation processes with 1,2,3-triazoles.

4.3.2 Results and discussion

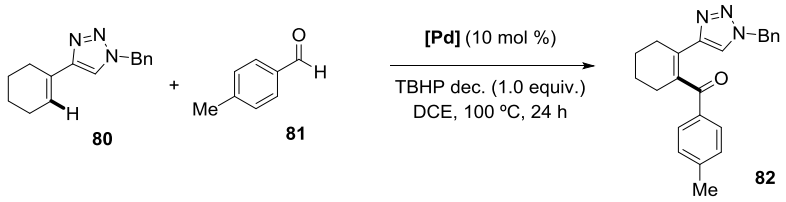
In order to test the feasibility of our approach, we first synthesized triazole derivative **80** in 99 % yield upon CuAAC (scheme 4.30).



Scheme 4.30. Synthesis of 1,2,3-triazole **80**.

Having selected triazole **80** as the model substrate, a variety of experimental variants such as metal, oxidant, solvent, ligand and temperature were systematically examined. Encouraged by our successful results on the development of a Pd-catalyzed C−H acetoxylation reaction, we first tested different Pd sources and used commercially available 4-methylbenzaldehyde **81** as acyl source and TBHP as oxidant in DCE at 100 ºC (Table 4.12).

Table 4.12. Screening of palladium sources.[a]



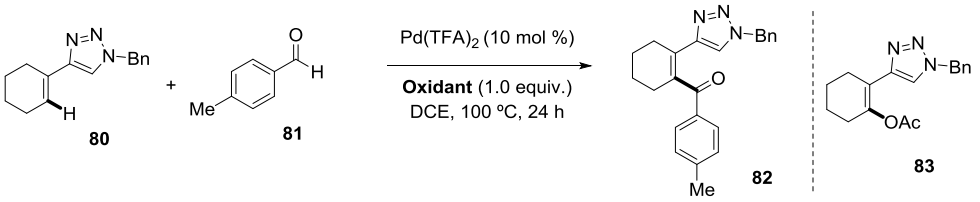
Entry	[Pd] catalyst	Yield (%)[b]	Entry	[Pd] catalyst	Yield (%)[b]
1	$Pd(OAc)_2$	29	6	$PdCl_2(PPh_3)_2$	0
2	$Pd(TFA)_2$	34	7	$PdCl_2(MeCN)_2$	0
3	$Pd(dba)_2$	24	8	PdI_2	0
4	$PdCl_2$	0	9	$PdCl_2(PhCN)_2$	0
5	$Pd(PPh_3)_4$	0			

[a]Reaction conditions: **80** (0.25 mmol), MePhCHO (2.0 equiv.), THBP (1.0 equiv.), DCE (1 mL) at 100 ºC for 24 h. [b]Isolated yield after purification by column chromatography.

As depicted in Table 4.12, a wide variety of palladium catalysts, including Pd(II) and Pd(0) salts were examined in the model reaction. The target acylation process occurred when using $Pd(OAc)_2$ (entry 1), $Pd(TFA)_2$ (entry 2) and $Pd(dba)_2$ (entry 3), albeit in low yields. Other Pd sources were found inactive under the standard conditions (entries 4-9). Accordingly, we further evaluated other reaction parameters utilizing $Pd(TFA)_2$ as the catalyst of choice, which provided product **82** in 34 % yield.

We next evaluated the influence of different oxidants in the reaction outcome. As depicted in Table 4.13, the only oxidant capable of promoting the target acylation was found to be TBHP, both in decane and aqueous solution (entry 1 and 2, respectively), which afforded acylated compound **82** in 34 % yield. Conversely, other peroxides (entries 4-8), metal salts (entries 9-12), and persulfates (entries 14-15) were entirely ineffective in the tested process.

Table 4.13. Screening of oxidants.[a]



Entry	Oxidant	Yield (%)[b]	Entry	Oxidant	Yield (%)[b]
1	TBHP dec.	34	10	Ag_2CO_3	0
2	TBHP aq.	34 (37)[c]	11	AgOAc	0
3	H_2O_2	0	12	$Cu(OAc)_2$	0
4	DTBP	n.d.	13	Oxone	0
5	CHP	n.d.	14	$K_2S_2O_8$	0
6	BPO	n.d.	15	$(NH_4)_2S_2O_8$	**0**
7	TBPB	n.d.	16	NBS	0
8	DCP	0	17	DDQ	**0**
9	Ag_2O	0	18	PIDA	**83** (43 %)

[a]Reaction conditions: **80** (0.25 mmol), MePhCHO (2.0 equiv), $Pd(TFA)_2$ (10 mol %), THBP (1.0 equiv.), DCE (1 mL) at 100 ºC for 24 h. [b]Isolated yield after purification by column chromatography. [c]Oxidant (4 equiv.)

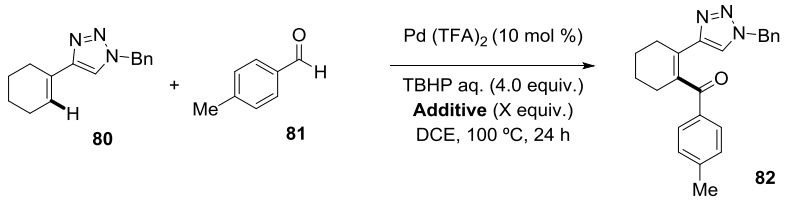
It is well-known that C−H functionalization reactions can be dramatically favored upon addition of certain additives. For instance, *N*-protected aminoacids have been extensively utilized in Pd-catalyzed C−H functionalization process,[270] and diamine-type ligands can be also beneficial additives in related processes.[271] Accordingly, we examined the influence of numerous additives in our model reaction. As depicted in Table 4.14, most of the additives entirely inhibited the process and starting material was recovered instead.

[270] a) Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. *J. Am. Chem. Soc.* **2014**, *136*, 894. b) Engle, K. M. *Pure Appl. Chem*. **2016**, *88*, 119. c) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 6169. d) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137. e) Baxter, R. D.; Sale, D.; Engle, K. M.; Yu, J.-Q.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 4600. f) Novak, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 12236.

[271] Gao, X.; Wu, B.; Huang, W.-X.; Chen, M.-W.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2015**, *54*, 11956.

However, certain carboxylic acids (entries 1-6) did not affect the reaction outcome and similar results to that obtained in their absence were achieved.

Table 4.14. Screening of additives.[a]

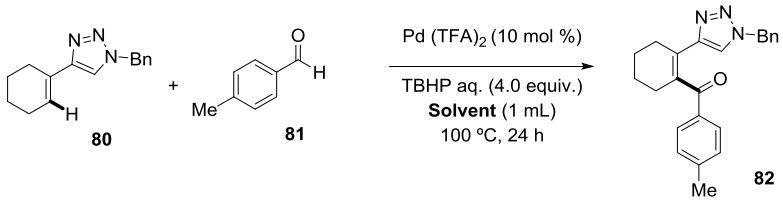


Entry	Additive	Yield (%)[b]	Entry	Additive	Yield (%)[b]
1[c]	2,4,6-trimethylbenzoic acid	32	14[c]	KI	n.d.
2[c]	2-(3,5-dimethylphenyl) acetic acid	33	15[c]	*N*-Acetylglycine	0
3[c]	PivOH	34	16[d]	Ac-Gly-OH	0
4[c]	Benzoic acid	33	17[d]	Boc-Phe-OH	0
5[c]	AcOH	30	18[d]	CBz-Phe-OH	0
6[c]	$AdCO_2H$	32	19[d]	Boc-Pro-OH	0
7[c]	2-Nitrobenzoic acid	0	20[d]	Boc-Gly-OH	0
8[c]	2-Picolinic acid	0	21[d]	Boc-Ala-OH	0
9[c]	TFA	0	22[d]	CBz-Leu-OH	0
10[c]	$TsOH·H_2O$	0	23[d]	Boc-Leu-OH	0
11[c]	TBAB	0.	24[e]	Bipy	0
12[c]	TBAI	n.d.	25[e]	Phen	0
13[c]	KBr	n.d.	26[e]	DMAP	0

[a]Reaction conditions: **80** (0.25 mmol), MePhCHO (2.0 equiv.), $Pd(TFA)_2$ (10 mol %), THBP (1.0 equiv.), additive (X equiv.), DCE (1 mL) at 100 ºC for 24 h. [b]Isolated yield after purification by column chromatography. [c]Additive (2 equiv.). [d]Additive (30 mol %.). [e]Additive (20 mol %.).

Finally, the target process was performed in different solvents and the particular use of a combination of DCE and MeCN (Table 4.15, entry 8) afforded slightly better results providing acylated triazole **82** in 42 % yield. Remarkably, the performance of the process at 70 ºC furnished similar results.

Table 4.15. Screening of solvents.[a]

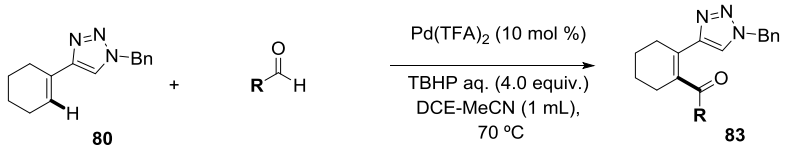


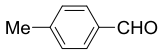
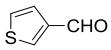
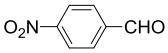
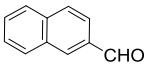
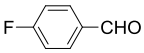
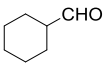
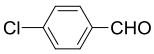
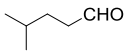
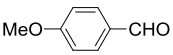
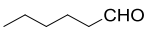
Entry	Solvent	Yield (%)[b]	Entry	Solvent	Yield (%)[b]
1	DCE	37	8	DCE-MeCN	42 (42)[c]
2	Toluene	n.d.	9	DCE-DMF	n.d.
3	MeCN	n.d.	10	DCE-NMP	n.d.
4	Dimethoxyethane	n.d.	11	DCE-DMA	n.d.
5	Chlorobenzene	n.d.	12	Bn_2O	n.d.
6	DMF	0	13	DCE-CCl_4	0
7	1,4-dioxane	n.d.	14	DCE-HFIP	0

[a]Reaction conditions: **80** (0.25 mmol), MePhCHO (2.0 equiv.), $Pd(TFA)_2$ (10 mol %), THBP (1.0 equiv.), solvent (1 mL) at 100 ºC for 24 h. [b]Isolated yield after purification by column chromatography. [c]Reaction at 70 ºC.

Although the catalyst system was far from being optimal, we decided to test the influence of using different aldehydes to evaluate if the use of more activated acyl sources could result in better yields. Interestingly, the particular use of 4-methoxybenzaldehyde provided the corresponding product in 46 % yield (Table 16, entry 5). However, other aromatic or aliphatic aldehydes were found less reactive.

Table 4.16. Screening of aldehydes for triazole **80**.[a]

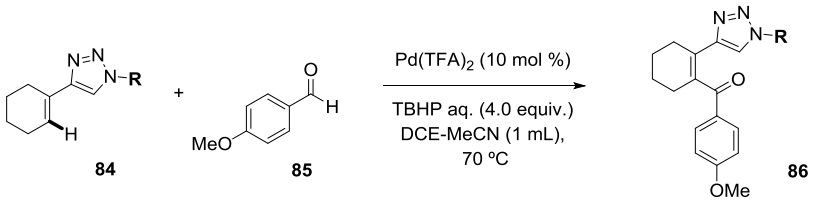


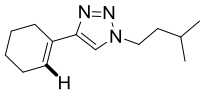
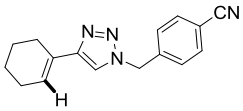
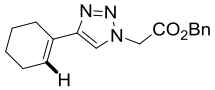
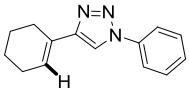
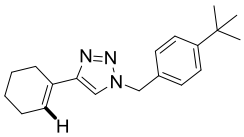
Entry	Aldehyde	Yield (%)[b]	Entry	Aldehyde	Yield (%)[b]
1		42	6		n.d.
2		0	7		32
3		38	8		n.d.
4		39	9		n.d.
5		46	10		n.d.

[a]Reaction conditions: **80** (0.25 mmol), RCHO (2.0 equiv.), $Pd(TFA)_2$ (10 mol %), TBHP aq. (4.0 equiv.), DCE-MeCN (1 mL) at 70 ºC for 24 h. [b]Isolated yield after purification by column chromatography.

In a final attempt to improve our system, we decided to test the influence of using different *N*1-substituted triazoles. In this respect, the electronic nature of the triazole unit acting as DG could be tuned and hence a superior reactivity could be expected for triazoles having a higher metal-binding ability. Importantly, the particular use of (4-cyano)benzyl substituent resulted in a remarkable 57 % yield of the corresponding coupling product. Unfortunately, other *N*1-substituted triazoles were found even less reactive than the model substrate.

Table 4.17. Screening of triazoles for aldehyde **85**.[a]

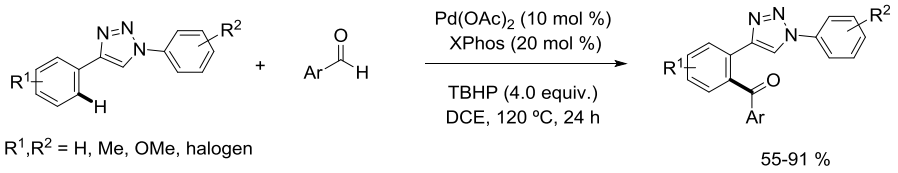


Entry	Triazole	Yield (%)[b]
1		29
2		57
3		n.d.
4		27
5		31

[a]Reaction conditions: Triazole (0.25 mmol), MeOPhCHO (2.0 equiv.), $Pd(TFA)_2$ (10 mol %), TBHP aq. (4.0 equiv.), DCE-MeCN (1 mL) at 70 ºC for 24 h. [b]Isolated yield after purification by column chromatography.

To our surprise, at the time we were performing our studies Jiang and coworkers reported a similar Pd-catalyzed acylation protocol assisted by "click" triazoles where the addition of XPhos as supporting ligand was crucial to obtain a good catalyst performance.[272]

[272] a) Zhao, F.; Chen, Z.; Liu, Y.; Xie, K.; Jiang, Y. *Eur. J. Org. Chem.* **2016**, 5971. b) Jiang, Y.; Ma, X.; Zhao, F.; Han, C. *Synlett* **2017**, *28*, 713.



Scheme 4.31. Palladium-catalyzed acylation process reported by Jiang.

4.3.3 Conclusions

The use of "click" triazoles as practical DGs in Pd-catalyzed C−H acylation events has been extensively studied. However, despite of our research efforts, an optimal system was not found and in all cases moderate yields were obtained. In any case, our hypothesis was found to be valid and the acylation of certain C(sp^2)–H bonds directed by simple "click" triazoles was successfully achieved, albeit in low to moderate yields. Further studies are currently under way in our group to explore new synthetic opportunities of 1,2,3-triazoles as versatile DGs in the realm of C−H functionalization.

Experimental

Experimental

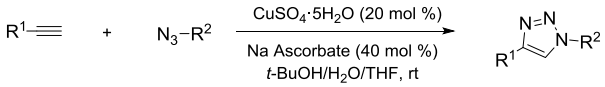
General Considerations

Reagents: Commercially available materials were used without further purification. Palladium(II) acetate recrystallized (97 % purity), (diacetoxy)iodobenzene (98 % purity), bis(*tert*-butylcarbonyloxy)iodobenzene (97 % purity), and 1,2-dichloroethane (spectrophotometric grade, ≥99 %) were purchased from Sigma-Aldrich. AcOH (acetic acid glacial, extra pure) was purchased from Scharlau and Ac_2O (acetic anhydride) was purchased from Panreac.

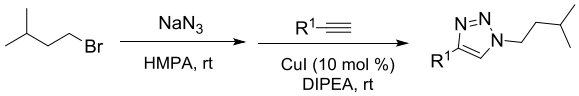
Analytical Methods: ^{1}H NMR and ^{13}C NMR spectra as well as IR, HRMS and melting points (where applicable) are included for all new compounds. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz and 500 MHz at 20 ºC. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.26 ppm), unless otherwise indicated. All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77 ppm), unless otherwise indicated, and were obtained with ^{1}H decoupling. Coupling constants, *J*, are reported in hertz. Melting points were measured using open glass capillaries in a Büchi SMP-20 apparatus. Mass spectra were performed by SGIker and were acquired on a time of flight (TOF) mass spectrometer (SYNAPT G2 HDMS from Waters, Milford, MA, USA) equipped with an electrospray source in positive mode (ESI^+). The chromatographic separation was performed using an ACQUITY UPLC system from Waters (Milford, MA, USA) equiped with an Acquity UPLC BEH C18 1.7 μm, 50 x 2.1 mm column at 30 °C. Mobile phases consisted of 0.1 % formic acid in water (A) and 0.1 % formic acid in methanol (B). Separation was carried out in 5 min: initial conditions were 5 % B, raised to 100 % B over 2.5 min, held at 100 % B until 4 min, decreased to 5 % B over 0.1 min and held at 5 % B until 5 min for re-equilibration of the system. Flow rate was 0.25 mL/min and injection volume was 5 μL. Infrared spectra were recorded on a Bruker Alpha P. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh).

4.1 Synthesis of the starting materials

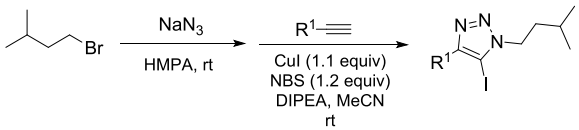
4.1.1 General procedure for the synthesis of 1,2,3-triazoles



General Procedure A: alkyne (1.0 equiv) and the corresponding azide (1.1 equiv) were dissolved in a mixture of deoxygenated *t*BuOH/H_2O (4:1, 1 mL/mmol). Then a deoxygenated aq. solution of $CuSO_4 \cdot 5H_2O$ (10 mol %, 1mL/mmol) followed by a deoxygenated aq. solution of sodium ascorbate (40 mol %, 1mL/mmol) was added. The resulting mixture was stirred under inert atmosphere at room temperature overnight. The solvent was partially evaporated under reduced pressure and the resulting solution was washed with aq. NH_4OH, extracted with AcOEt and washed with brine. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hex/AcOEt 7/3) unless otherwise noted.

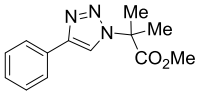


General Procedure B: 1-bromo-3-methylbutane (1.0 equiv) was drop wise added over a solution of NaN_3 (1.1 equiv) in HMPA (0.6 mL/mmol). The resulting solution was stirred under argon at room temperature for 4 hours. Then, CuI (10 mol %), alkyne (1.0 equiv) and DIPEA (5.0 mL/mmol) were subsequently added and the resulting solution was stirred at room temperature overnight. Next, it was washed with HCl 10 %, aq. NH_4OH, extracted with AcOEt and washed with brine. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hex/AcOEt 7/3) unless otherwise noted.

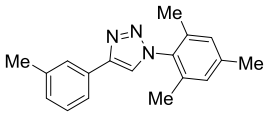


General Procedure C: 1-bromo-3-methylbutane (1.0 equiv) was dropwise added over a solution of NaN_3 (1.1 equiv) in HMPA (0.6 mL/mmol). The resulting solution was stirred

under argon at room temperature for 4 h. In a different flask CuI (1.0 equiv) was dissolved in MeCN (2.4 mL/mmol) under argon at room temperature. A solution of *N*-bromosuccinimide (1.2 equiv) in MeCN (2.4 mL/mmol) was added and stirred 5 min at room temperature. Later on, the previously prepared azide-containing solution along with alkyne (1.0 equiv) and DIPEA (1.1 equiv) were subsequently added and the resulting mixture was stirred at room temperature overnight. Next, the mixture was washed with HCl 10 %, aq. NH_4OH, extracted with AcOEt and washed with brine. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hex/AcOEt 7/3) unless otherwise noted.



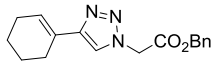
Methyl 2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl) propanoate (**68f**). Following the general procedure **A**, using *in situ* generated methyl 2-azido-2-methylpropanoate (7.4 mmol) and phenylacetylene (8.2 mmol, 0.9 mL) provided 216 mg (13 % yield) of **68f** as a white solid. Mp 101-103 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.84 (d, J = 7.0 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.33 (d, J = 7.4 Hz, 1H), 3.73 (s, 3H), 1.99 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 147.5, 130.7, 128.9, 128.2, 125.8, 118.5, 64.6, 53.4, 25.9. IR (neat, cm^{-1}): 3130, 1739, 1626, 1279, 1163, 1157, 1081, 767, 695. MS (ESI^+) m/z (%) 246 (M+H). HRMS calcd. for ($C_{13}H_{16}N_3O_2$): 246.1243, found 246.1240.



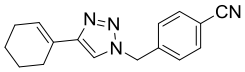
1-Mesityl-4-(*m*-tolyl)-1*H*-1,2,3-triazole (68m) Following the general procedure **A**, using 2-azido-1,3,5-trimethylbenzene[273] (3.90 mmol, 630 mg) and 3-ethynyltoluene (4.30 mmol, 0.54 mL) provided 1.05 g (97 % yield) of **68m** as a brown solid. Mp 91-92 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 12.4 Hz, 2H), 7.71 (d, J = 7.7 Hz, 1H), 7.34 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.00 (s, 2H), 2.42 (s, 3H), 2.39 (s, 3H), 2.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.7, 140.0, 138.6, 135.1, 133.5, 130.4, 129.1, 129.0, 128.8, 126.4, 122.9,

[273] Abram, S.-L.; Monte-Pérez, I.; Pfaff, F. F.; Farquhar, E. R.; Ray, K. *Chem. Commun.* **2014**, *50*, 9852.

121.5, 21.5, 21.2, 17.3. IR (neat, cm^{-1}): 2918, 1491, 1378, 1226, 1036, 784, 695. MS (ESI^+) m/z (%) 278 (M+H). HRMS calcd. for ($C_{18}H_{20}N_3$): 278.1657, found 278.1654.

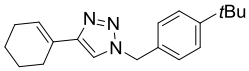


Benzyl 2-(4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazol-1-yl)acetate (68n). Following the general procedure **A**, using benzyl 2-azidoacetate[274] (9.00 mmol, 1.73 g) and 1-ethynylcyclohexene (10.00 mmol, 1.20 mL) provided 2.30 g (85 % yield) of **68n** as a white solid. Mp 95-98 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.36 (d, J = 7.3 Hz, 5H), 6.54 (s, 1H), 5.19 (d, J = 21.5 Hz, 4H), 2.38 (s, 2H), 2.20 (s, 2H), 1.72 (dd, J = 34.5, 5.9 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 150.1, 134.7, 128.9, 128.8, 128.6, 127.1, 125.5, 119.7, 68.0, 50.9, 26.5, 25.4, 22.5, 22.3. IR (neat, cm^{-1}): 2927, 2857, 2831, 1750, 1675, 1454, 1385, 1195, 942, 748, 698. MS (ESI^+) m/z (%) 298 (M+H). HRMS calcd. for ($C_{17}H_{20}N_3O_2$): 298.1556, found 298.1552.

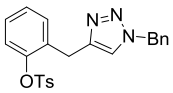


4-[(4-Cyclohex-1-en-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl]benzonitrile (68o). Following the general procedure **A**, using 4-(azidomethyl)benzonitrile[275] (8.60 mmol, 1.36 g) and 1-ethynylcyclohexene (9.50 mmol, 1.00 mL) provided 2.20 g (97 % yield) of **68o** as a white solid without requiring chromatographic purification. Mp 131-134 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.9 Hz, 2H), 7.36 (s, 1H), 7.30 (d, J = 7.9 Hz, 2H), 6.50 (s, 1H), 5.56 (s, 2H), 2.32 (s, 2H), 2.16 (s, 2H), 1.68 (dd, J = 32.6, 5.9 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.4, 140.3, 132.9, 128.3, 127.0, 125.7, 118.5, 118.3, 112.6, 53.3, 26.4, 25.3, 22.4, 22.2. IR (neat, cm^{-1}): 2934, 2860, 2831, 2232, 1446, 1314, 1197, 1036, 798, 768, 546. MS (ESI^+) m/z (%) 265 (M+H). HRMS calcd. for ($C_{16}H_{17}N_4$): 265.1453, found 265.1452.

[274] Pokorski, J. K.; Jenkins, L. M. M.; Feng, H.; Durell, S. R.; Bai, Y.; Appella, D. H. *Org. Lett.* **2007**, *9*, 2381.
[275] Liu, M.; Reiser, O. *Org. Lett.* **2011**, *13*, 1102.

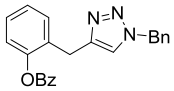


1-[4-(*Tert*-butyl)benzyl)]-4-(cyclohex-1-en-1-yl)-1H-1,2,3-triazole (68p). Following the general procedure **A**, using 1-ethynylcyclohex-1-ene (9.42 mmol, 1.10 mL) and 4-(*tert*-butyl)benzyl azide[276] (10.40 mmol, 1.96 g) provided 2.76 g (99 % yield) of **68p** as a white solid without requiring chromatographic purification. Mp 132-133 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.0 Hz, 2H), 7.33 (s, 1H), 7.22 (d, J = 7.9 Hz, 2H), 6.50 (t, J = 4.0 Hz, 1H), 5.48 (s, 2H), 2.37 (dq, J = 6.1, 3.3 Hz, 2H), 2.25-2.12 (m, 2H), 1.82- 1.56 (m, 4H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 149.8, 131.9, 127.7, 127.3, 125.9, 124.9, 118.1, 53.6, 34.5, 31.2, 26.3, 25.2, 22.4, 22.1. IR (neat, cm^{-1}): 1433, 1050, 710, 679. MS (ESI^{+}) m/z (%) 296 (M+H). HRMS calcd. for ($C_{19}H_{26}N_3$): 296.2127, found 296.2129.

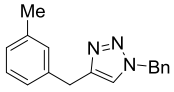


2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]phenyl 4-methylbenzenesulfonate (68q). Following the general procedure **A**, using 2-(prop-2-yn-1-yl)phenol[277] (7.20 mmol, 956 mg) and benzyl azide (7.20 mmol, 963 mg) provided 1.80 g (95 % yield) of 2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]phenol as a white solid. Then, such triazole (1.88 mmol, 500 mg) was dissolved in CH_2Cl_2 (5 mL) and tosyl chloride (2.26 mmol, 431 mg) was added. The mixture was cooled to 0 ºC, and triethylamine (2.26 mmol, 0.32 mL) was added. The resulting solution was warmed to room temperature and after complete consumption of the starting material, the reaction was acidified with HCl (10 %). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (anhydrous $MgSO_4$), filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography to provide 788 mg (99 %) of **68q** as a white solid. Mp 110-114ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.0 Hz, 2H), 7.41-6.99 (m, 12H), 5.48 (s, 2H), 3.93 (s, 2H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.7 146.3, 145.7, 134.9, 133.0, 132.7, 131.3, 130.0, 129.1, 128.7, 128.43, 128.0, 127.9, 127.4, 122.4, 122.0, 54.2, 26.4, 21.9. IR (neat, cm^{-1}): 1375, 1191, 1158, 1083, 868, 711, 550. MS (ESI^{+}) m/z (%) 420 (M+H). HRMS calcd. for ($C_{23}H_{22}N_3O_3S$): 420.1304, found 420.1305.

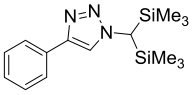
[276] Robinson, S. W.; Mustoe, C. L.; White, N. G.; Brown, A.; Thompson, A. L.; Kennepohl, P.; Beer, P. D. *J. Am. Chem. Soc.* **2015**, *137*, 499.
[277] Zhang, Q.; Takacs, J. M. *Org. Lett.* **2008**, *10*, 545.



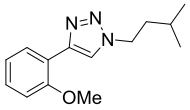
2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]phenyl benzoate (68r) To a solution 2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]phenol (1.88 mmol, 500 mg) in CH_2Cl_2 (5 mL) benzoyl chloride (2.20 mmol, 0.26 mL) was added. The mixture was cooled to 0 ºC, and triethylamine (2.26 mmol, 0.32 mL) was added. The resulting solution was warmed to room temperature and after complete consumption of the starting material, the reaction was acidified with HCl (10 %). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (anhydrous $MgSO_4$), filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography to provide 678 mg (98 % yield) of **68r** as a white solid. Mp 86-87ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 7.7 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.36-7.13 (m, 9H), 7.10 (s, 1H), 5.40 (s, 2H), 4.07 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.0, 149.1, 146.7, 134.9, 133.8, 131.2, 130.9, 130.2, 129.2, 129.1, 128.7, 128.6, 128.1, 128.0, 126.5, 122.7, 121.7, 54.1, 27.1. IR (neat, cm^{-1}): 1739, 1449, 1214, 1051, 701. MS (ESI$^+$) m/z (%) 370 (M+H). HRMS calcd. for ($C_{23}H_{20}N_3O_2$): 370.1477, found 370.1479.



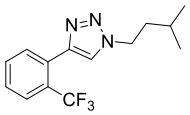
1-Benzyl-4-(3-methylbenzyl)-1*H*-1,2,3-triazole (68s). Following the general procedure **A**, using benzyl azide (4.23 mmol, 563 mg) and 3-(*m*-tolyl)-1-propyne (3.85 mmol, 500 mg) provided 778 mg (77 % yield) of **68s** as a white solid. Mp 77-78 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 5.9 Hz, 3H), 7.32-7.13 (m, 4H), 7.07 (dd, J = 12.0, 6.7 Hz, 3H), 5.48 (s, 2H), 4.06 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.0, 138.8, 138.0, 134.7, 129.3, 128.9, 128.4, 128.3, 127.8, 127.0, 125.5, 121.2, 53.8, 32.1, 21.2. IR (neat, cm^{-1}): 1607, 1124, 787, 709. MS (ESI$^+$) m/z (%) 264 (M+H). HRMS calcd. for ($C_{17}H_{18}N_3$): 264.1422, found 264.1422.



1-[Bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (68x) (Table 2). Following the general procedure **B**, using (chloromethylene)bis(trimethylsilane) (5.95 mmol, 1.30 mL) and phenylacetylene (5.95 mmol, 0.65 mL) provided 1.53 g (87 % yield) of **68x** as a white solid. Mp 81-86 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.79 (m, 2H), 7.54 (s, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.34-7.27 (m, 1H), 3.65 (s, 1H), 0.13 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.0, 131.2, 128.9, 128.0, 125.6, 120.2, 46.9, -0.9. IR (neat, cm^{-1}): 2882, 1249, 1045, 842, 760, 687. MS (ESI^{+}) m/z (%) 304 (M+H). HRMS calcd. for ($C_{15}H_{26}N_3Si_2$): 304.1665, found 304.1656.

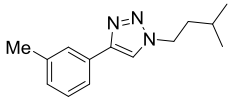


1-Isopentyl-4-(2-methoxyphenyl)-1*H*-1,2,3-triazole (68y). Following the general procedure **B**, using 1-ethynyl-2-methoxybenzene (3.78 mmol, 0.49 mL) provided 600 mg (69 % yield) of **68y** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 7.7 Hz, 1H), 7.97 (s, 1H), 7.18 (t, J = 7.9 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 4.26 (t, J = 7.6 Hz, 2H), 3.79 (s, 3H), 1.71 (q, J = 7.3 Hz, 2H), 1.50 (dt, J = 13.4, 6.7 Hz, 1H), 0.85 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.1, 142.4, 128.3, 126.9, 122.5, 120.3, 119.0, 110.3, 54.8, 48.0, 38.6, 25.0, 21.7. IR (neat, cm^{-1}): 1538, 1243, 1069, 752. MS (ESI^{+}) m/z (%) 246 (M+H). HRMS calcd. for ($C_{14}H_{20}N_3O$): 246.1606, found 246.1607.

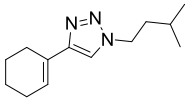


1-Isopentyl-4-[2-(trifluoromethyl)pheny])-1*H*-1,2,3-triazole (68z). Following the general procedure **B**, using 1-ethynyl-2-(trifluoromethyl)benzene (2.94 mmol, 0.41 mL) provided 413 mg (50 % yield) of **68z** as a white solid. Mp 40-41 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 7.8 Hz, 1H), 7.79-7.66 (m, 2H), 7.59 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 4.42 (t, J = 7.5 Hz, 2H), 1.83 (q, J = 7.3 Hz, 2H), 1.59 (dt, J = 13.5, 6.7 Hz, 1H), 0.95 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.0, 131.9, 131.5, 129.6, 128.1, 127.0 (d, J = 30 Hz), 125.9 (q, J = 10 Hz), 125.4, 122.6 (q, J = 10 Hz), 48.7, 38.9, 25.4, 22.1. IR

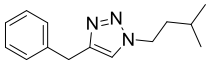
(neat, cm^{-1}): 1581, 1312, 1100, 767. MS (ESI^+) m/z (%) 284 (M+H). HRMS calcd. for ($C_{14}H_{27}N_3F_3$): 284.1375, found 284.1381.



1-Isopentyl-4-(m-tolyl)-1*H*-1,2,3-triazole (68za). Following the general procedure **B**, using 1-ethynyl-3-methylbenzene (8.61 mmol, 1.09 mL) provided 1.70 g (86 % yield) of **68za** as a white solid. Mp 51-52 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.70 (s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 4.39 (t, J = 7.5 Hz, 2H), 2.40 (s, 3H), 1.83 (q, J = 7.3 Hz, 2H), 1.61 (dt, J = 13.4, 6.7 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.6, 138.3, 130.5, 128.6, 128.5, 126.2, 122.6, 119.2, 48.5, 38.9, 25.3, 22.0, 21.3. IR (neat, cm^{-1}): 1433, 1079, 839, 716. MS (ESI^+) m/z (%) 230 (M+H). HRMS calcd. for ($C_{14}H_{20}N_3$): 230.1657, found 230.1661.

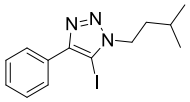


4-(Cyclohex-1-en-1-yl)-1-isopentyl-1*H*-1,2,3-triazole (68zb). Following the general procedure **B**, using 1-bromo-3-methylbutane (10.00 mmol, 1.20 mL) and 1-ethynylcyclohexene (10.00 mmol, 1.30 mL) provided 1.80 g (82 % yield) of **68zb** as a white solid. Mp 38-42 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (s, 1H), 6.46 (s, 1H), 4.30 (t, J = 7.5 Hz, 2H), 2.36 (s, 2H), 2.15 (s, 2H), 1.73 (p, J = 6.7, 6.0 Hz, 4H), 1.63 (p, J = 6.1 Hz, 2H), 1.54 (dt, J = 13.4, 6.6 Hz, 1H), 0.92 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.4, 127.4, 124.6, 118.1, 48.5, 39.1, 26.3, 25.4, 25.2, 22.5, 22.2, 22.1. IR (neat, cm^{-1}): 2951, 2929, 2868, 2837, 1459, 1434, 1216, 1052, 919, 832. MS (ESI^+) m/z (%) 220 (M+H). HRMS calcd. for ($C_{13}H_{22}N_3$): 220.1814, found 220.1804.

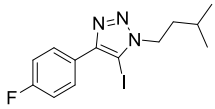


4-Benzyl-1-isopentyl-1*H*-1,2,3-triazole (68zc). Following the general procedure **B**, using 1-bromo-3-methylbutane (10.00 mmol, 1.20 mL) and 3-phenyl-1-propyne (10.00 mmol, 1.30 mL) provided 2.46 g (99 %) of **68zc** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (dq, J = 16.4, 8.0 Hz, 5H), 7.16 (s, 1H), 4.33 (t, J = 7.7 Hz, 2H), 4.11 (s, 2H), 1.78 (q, J = 7.3 Hz, 2H), 1.61 (dt, J = 13.4, 6.7 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$):

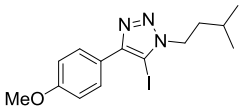
δ 146.4, 138.7, 128.0, 127.9, 125.7, 120.8, 47.7, 38.3, 31.5, 24.8, 21.5. IR (neat, cm^{-1}): 2956, 2870, 1495, 1455, 1216, 1048, 724, 697. MS (ESI^+) m/z (%) 230 (M+H). HRMS calcd. for ($C_{14}H_{20}N_3$): 230.1657, found 230.1674.



5-Iodo-1-isopentyl-4-phenyl-1*H*-1,2,3-triazole (68ze). Following the general procedure **C**, using phenylacetylene (4.89 mmol, 0.54 mL) provided 1.00 g (66 % yield) of **68ze** as a white solid. Mp 97-98 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 7.6 Hz, 2H), 7.52-7.33 (m, 3H), 4.46 (t, J = 7.8 Hz, 2H), 1.93-1.58 (m, 3H), 1.02 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.6, 130.3, 128.4, 127.4, 76.0, 49.4, 38.6, 25.6, 22.2. IR (neat, cm^{-1}): 1447, 1224, 1064, 985. MS (ESI^+) m/z (%) 342 (M+H). HRMS calcd. for ($C_{13}H_{17}N_3I$): 342.0467, found 342.0462.

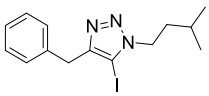


4-(4-Fluorophenyl)-5-iodo-1-isopentyl-1*H*-1,2,3-triazole (68zf). Following the general procedure **C**, using 4-fluorophenylacetylene (4.16 mmol, 0.48 mL) provided 790 mg (53 % yield) of **68zf** as a white solid. Mp 118-120 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00-7.75 (m, 2H), 7.13 (t, J = 8.7 Hz, 2H), 4.48-4.30 (m, 2H), 1.82 (ddd, J = 9.5, 7.8, 6.5 Hz, 2H), 1.68 (dt, J = 13.3, 6.7 Hz, 1H), 1.00 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3 (d, J = 247 Hz), 148.9, 129.3 (d, J = 9 Hz), 126.4 (d, J = 10 Hz), 115.4 (d, J = 21 Hz), 75.9, 49.4, 38.5, 25.6, 22.2. IR (neat, cm^{-1}): 1607, 1476, 1223, 838. MS (ESI^+) m/z (%) 360 (M+H). HRMS calcd. for ($C_{13}H_{16}N_3FI$): 360.0373, found 360.0373.

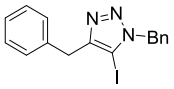


5-Iodo-1-isopentyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (68zg). Following the general procedure **C**, using 4-methoxyphenylacetylene (3.78 mmol, 500 mg) provided 600 mg (43 % yield) of **68zg** as a white solid. Mp 95-96 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 4.43 (t, J = 7.8 Hz, 2H), 3.84 (s, 3H), 1.95-1.60 (m, 3H),

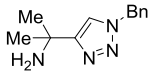
1.00 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7, 149.5, 128.7, 122.8, 113.9, 75.3, 55.2, 49.4, 38.6, 25.6, 22.2. IR (neat, cm^{-1}): 1614, 1339, 1117, 1066. MS (ESI^+) m/z (%) 372 (M+H). HRMS calcd. for ($C_{14}H_{19}N_3OI$): 372.0573, found 372.0565.



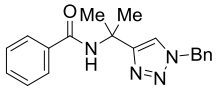
4-Benzyl-5-iodo-1-isopentyl-1*H*-1,2,3-triazole (68zh). Following the general procedure **C**, using 1-bromo-3-methylbutane (10.00 mmol, 1.20 mL) and 3-phenyl-1-propyne (10.00 mmol, 1.30 mL) provided 1.76 g (50 % yield) of **68zh** as a white solid. Mp 114-115 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23 (dd, J = 30.3, 7.2 Hz, 5H), 4.34 (t, J = 7.6 Hz, 2H), 3.95 (s, 2H), 1.67 (q, J = 7.2 Hz, 2H), 1.53 (dp, J = 13.3, 7.0 Hz, 1H), 0.91 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 149.6, 138.3, 128.1, 126.0, 82.9, 48.4, 37.9, 31.3, 24.7, 21.8. IR (neat, cm^{-1}): 2955, 2869, 1494, 1453, 1213, 1060, 723, 695. MS (ESI^+) m/z (%) 356 (M+H). HRMS calcd. for ($C_{14}H_{19}N_3I$): 356.0624, found 356.0620.



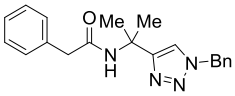
1,4-Dibenzyl-5-iodo-1*H*-1,2,3-triazole (68zi). Following the general procedure **C**, using benzyl azide (10.00 mmol, 1.30 g) and 3-phenyl-1-propyne (10.00 mmol, 1.30 mL) provided 1.10 g (30 % yield) of **68zi** as a yellowish solid. Mp 131-134 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.19 (m, 10H), 5.59 (s, 2H), 4.07 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.1, 138.3, 134.5, 129.0, 128.8, 128.6, 128.5, 127.9, 126.6, 78.9, 54.4, 32.5. IR (neat, cm^{-1}): 3026, 1493, 1454, 1211, 1082, 729, 693. MS (ESI^+) m/z (%) 376 (M+H). HRMS calcd. for ($C_{16}H_{15}N_3I$): 376.0311, found 376.0306.



2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (75).[213e] Following the general procedure **A**, using benzyl azide (17.7 mmol, 2.36 g) and 2-methylbut-3-yn-2-amine (19.5 mmol, 1.62 g) provided 3.10 g (81 % yield) of **75** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 3H), 7.31-7.29 (m, 3H), 5.51 (s, 2H), 1.51 (s, 6H).

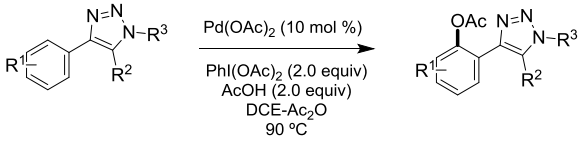


***N*-(2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)benzamide (76).**[123e] To a solution of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (14.20 mmol, 3.10 g) in CH_2Cl_2 (30 mL) triethylamine (43.00 mmol, 6 mL) was added and the mixture was cooled to 0 ºC. Benzoyl chloride (14.20 mmol, 1.65 mL) was added and the resulting solution was warmed to room temperature overnight. The reaction was quenched with $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with HCl (1M), dried (anhydrous $MgSO_4$), filtered and evaporated under reduced pressure to provide 4.30 g (94 % yield) of **76** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.3 Hz, 2H), 7.53-7.44 (m, 1H), 7.40 (dd, J = 13.8, 7.1 Hz, 5H), 7.34-7.22 (m, 2H), 7.01 (s, 1H), 5.52 (s, 2H), 1.86 (s, 6H).

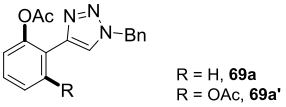


***N*-(2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)-2-phenylacetamide (79).**[213e] To a solution of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (18.00 mmol, 3.50 g) in CH_2Cl_2 (50 mL) triethylamine (54 mmol, 7.50 mL) was added and the mixture was cooled to 0 ºC. 2-Phenylacetyl chloride (18.00 mmol, 2.40 mL) was added and the resulting solution was warmed to room temperature overnight. The reaction was quenched with $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with HCl (1M), dried (anhydrous $MgSO_4$), filtered and evaporated under reduced pressure to provide 3.20 g (53 % yield) of **79** as a white solid. Mp 148-150 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.09 (m, 11H), 6.14 (s, 1H), 5.50 (s, 2H), 3.51 (s, 2H), 1.70 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 153.7, 135.2, 134.8, 129.4, 129.2, 129.0, 128.8, 128.2, 127.3, 120.5, 54.3, 51.6, 44.7, 28.0. IR (neat, cm^{-1}): 3251, 3128, 1665, 1557, 1333, 1056, 726, 690. MS (ESI^+) m/z (%) 335 (M+H). HRMS calcd. for ($C_{20}H_{23}N_4O$): 335.1872, found 335.1881.

4.2 Pd-catalyzed C(sp^2)-H acetoxylation.



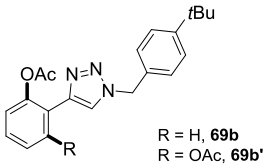
General Procedure: A reaction tube containing a stirring bar was charged with the corresponding triazole (if solid) (0.25 mmol, 1.00 equiv), $PhI(OAc)_2$ (0.50 mmol, 2.00 equiv) and $Pd(OAc)_2$ (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). The triazole (if liquid) (0.25 mmol, 1.00 equiv), AcOH (0.50 mmol, 2.00 equiv), 1,2-dichloroethane (0.50 mL) and Ac_2O (0.50 mL) were then added under argon atmosphere. The reaction tube was next warmed up to 90 ºC and stirred for 24 hours. The mixture was then allowed to warm to room temperature, filtered off through a pad of celite and washed with CH_2Cl_2. The resulting mixture was concentrated under reduced pressure and the corresponding product was purified by flash chromatography (hex/AcOEt 7/3). The yields reported in the thesis refer to isolated yields and represent an average of at least two independent runs.



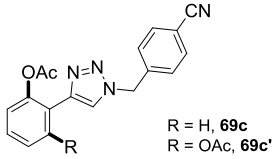
2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl acetate (69a). Following the general procedure, using 1-benzyl-4-phenyl-1*H*-1,2,3-triazole[278] (**68a**) (0.25 mmol, 59 mg) provided 33 mg (45 % yield) of **69a** as a white solid along with 23 mg (25 % yield) of **69a'** as a white solid. **69a**: Mp 162-163 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 7.4 Hz, 1H), 7.64 (s, 1H), 7.54-7.25 (m, 7H), 7.16 (d, J = 7.8 Hz, 1H), 5.59 (s, 2H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 147.0, 143.3, 134.4, 129.1, 129.0, 128.8, 128.6, 128.2, 126.3, 123.2, 123.0, 121.7, 54.2, 21.0. IR (neat, cm^{-1}): 1738, 1191, 852. MS (ESI$^+$) m/z (%) 294 (M+H). HRMS calcd. for ($C_{17}H_{16}N_3O_2$): 294.1243, found 294.1243. **69a'**: Mp 172-173 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.44-7.34 (m, 3H), 7.29 (dd, J = 7.3, 2.1 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 5.58 (s, 2H), 2.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 149.0, 139.3,

[278] Sharghi, H.; Khalifeh, R.; Doroodmand, M. M. *Adv. Synth. Catal.* **2009**, *351*, 207.

134.7, 129.1, 129.1, 128.8, 128.1, 123.2, 120.7, 54.1, 20.7. IR (neat, cm^{-1}): 1735, 1197, 883. MS (ESI^+) m/z (%) 352 (M+H). HRMS calcd. for ($C_{19}H_{18}N_3O_4$): 352.1297, found 352.1292.



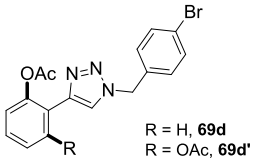
2-[1-(4-(*Tert*-butyl)benzyl)-1*H*-1,2,3-triazol-4-yl]phenyl acetate (69b). Following the general procedure, using 1-[4-*tert*-butyl)benzyl]-4-phenyl-1*H*-1,2,3-triazole[279] (**68b**) (0.25 mmol, 73 mg) provided 27.9 mg (32 % yield) of **69b** as a white solid along with 30.5 mg (30 % yield) of **69b'** as a white solid. **69b**: Mp 163-165 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 7.0 Hz, 1H), 7.62 (s, 1H), 7.45 (d, J = 7.9 Hz, 2H), 7.40-7.32 (m, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.1 Hz, 1H), 5.56 (s, 2H), 2.13 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 152.2, 147.2, 143.4, 131.6, 129.0, 128.7, 128.2, 126.5, 126.2, 123.5, 123.1, 121.7, 54.0, 34.8, 31.3, 21.2. IR (neat, cm^{-1}): 1750, 1202, 1178, 762. MS (ESI^+) m/z (%) 350 (M+H). HRMS calcd. for ($C_{21}H_{24}N_3O_2$): 350.1869, found 350.1869. **69b'**: Mp 189-196 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.45-7.33 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 5.53 (s, 2H), 2.02 (s, 6H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1, 152.3, 149.2, 139.5, 131.9, 129.3, 128.2, 126.3, 123.3, 121.0, 118.2, 54.0, 34.8, 31.4, 20.9. IR (neat, cm^{-1}): 1752, 1750, 1216, 1187, 1028. MS (ESI^+) m/z (%) 408 (M+H). HRMS calcd. for ($C_{23}H_{26}N_3O_4$): 408.1923, found 408.1927.



2-[1-(4-Cyanobenzyl)-1*H*-1,2,3-triazol-4-yl]phenyl acetate (69c). Following the general procedure, using 4-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]benzonitrile[280] (**68c**) (0.25 mmol, 65 mg) provided 35 mg (44 % yield) of **69c** as a yellow oil along with 25.1 mg (27 % yield) of **69c'** as a white solid. Mp 85-86 ºC **69c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, J = 7.5, 2.1 Hz, 1H), 7.79 (s, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.46-7.32 (m, 4H), 7.21 (dd, J = 7.7, 1.7

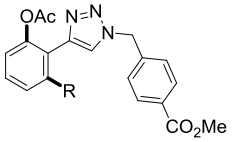
[279] Özçubukçu, S.; Ozkal, E.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2009**, *11*, 4680.
[280] Bidal, Y. D.; Lesieur, M.; Melaimi, M.; Cordes, D. B.; Slawin, A. M. Z.; Bertrand, G.; Cazin, C. S. *J. Chem. Commun.* **2015**, *51*, 4778.

Hz, 1H), 5.65 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 147.2, 144.0, 139.9, 132.9, 129.3, 128.7, 128.4, 126.5, 123.2, 123.1, 122.0, 118.2, 112.7, 53.3, 21.3. IR (neat, cm^{-1}): 1750, 1216, 1038, 765. MS (ESI$^+$) m/z (%) 319 (M+H). HRMS calcd. for ($C_{18}H_{15}N_4O_2$): 319.1195, found 319.1193. **69c'**: Mp 201-206 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.62 (s, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 5.65 (s, 2H), 2.09 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 149.3, 140.1, 133.1, 129.7, 128.4, 123.6, 121.0, 118.1, 117.9, 113.1, 53.5, 31.1, 21.0. IR (neat, cm^{-1}): 1747, 1197, 1026, 884. MS (ESI$^+$) m/z (%) 377 (M+H). HRMS calcd. for ($C_{20}H_{17}N_4O_4$): 377.1250, found 377.1240.



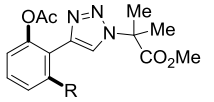
2-[1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl]phenyl acetate (69d). Following the general procedure, using 1-(4-bromobenzyl)-4-phenyl-1*H*-1,2,3-triazole[281] (**68d**) (0.25 mmol, 78 mg) provided 34.4 mg (37 % yield) of **69d** as a white solid along with 33.3 mg (31 % yield) of **69d'** as a yellowish solid. **69d**: Mp 135-139 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.36 (t, *J* = 10.0 Hz, 2H), 7.19 (d, *J* = 9.0 Hz, 3H), 5.54 (s, 2H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 147.3, 143.9, 133.7, 132.5, 129.8, 129.2, 128.8, 126.5, 123.3, 123.2, 123.1, 121.7, 53.6, 21.3. IR (neat, cm^{-1}): 1754, 1199, 1189, 1010, 760. MS (ESI$^+$) m/z (%) 372 (M+H). HRMS calcd. for ($C_{17}H_{15}N_3O_2Br$): 372.0348, found 372.0349. **69d'**: Mp 198-199 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.49 (m, 3H), 7.39 (t, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 5.52 (s, 2H), 2.07 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 149.2, 139.8, 133.9, 132.5, 129.8, 129.5, 123.4, 123.2, 121.0, 118.0, 53.6, 21.0. IR (neat, cm^{-1}): 1744, 1196, 1029, 883. MS (ESI$^+$) m/z (%) 430 (M+H). HRMS calcd. for ($C_{19}H_{17}N_3O_4Br$): 430.0402, found 430.0405.

[281] Bent, S. J.; Mahon, M. F.; Webster, R. L. *Dalton Trans* **2015**, *44*, 10253.



R = H, **69e**
R = OAc, **69e'**

Methyl 4-[(4-(2-acetoxyphenyl)-1*H*-1,2,3-triazol-1-yl)methyl]benzoate (69e). Following the general procedure, using methyl 4-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]benzoate[282] (**68e**) (0.25 mmol, 73 mg) provided 29 mg (33 % yield) of **69e** as a white solid along with 28 mg (28 % yield) of **69e'** as a white solid. **69e**: Mp 162-163 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (t, J = 7.9 Hz, 3H), 7.70 (s, 1H), 7.35 (q, J = 6.0 Hz, 4H), 7.16 (d, J = 7.9 Hz, 1H), 5.63 (s, 2H), 3.93 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 166.2, 147.1, 143.7, 139.4, 130.5, 130.3, 129.1, 128.6, 127.7, 126.3, 123.1, 121.7, 53.6, 52.2, 21.1. IR (neat, cm^{-1}): 1743, 1720, 1196, 726. MS (ESI^{+}) m/z (%) 352 (M+H). HRMS calcd. for ($C_{19}H_{18}N_3O_4$): 352.1297, found 352.1289. **69e'**: Mp 172-173 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.0 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 5.63 (s, 2H), 3.92 (s, 3H), 2.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 166.2, 149.1, 139.7, 139.6, 130.7, 130.4, 129.4, 127.7, 123.4, 120.8, 117.9, 53.6, 52.3, 20.8. IR (neat, cm^{-1}): 1741, 1716, 1194, 729. MS (ESI^{+}) m/z (%) 410 (M+H). HRMS calcd. for ($C_{21}H_{20}N_3O_6$): 410.1352, found 410.1342.

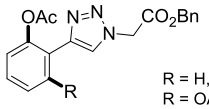


R = H, **69f**
R = OAc, **69f'**

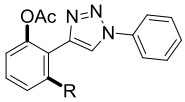
Methyl 2-[4-(2-acetoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-2-methylpropanoate (69f). Following the general procedure, using triazole (**68f)** (0.25 mmol, 61 mg) at 110 ºC provided 22.7 mg (30 % yield) of **69f** as a yellowish oil along with 46 mg (51 % yield) of **69f'** as a pale brown solid. **69f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, J = 7.6, 2.0 Hz, 1H), 7.93 (s, 1H), 7.41-7.30 (m, 2H), 7.18 (dd, J = 7.8, 1.6 Hz, 1H), 3.75 (s, 3H), 2.35 (s, 3H), 1.99 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 169.2, 147.4, 143.1, 129.2, 128.9, 126.6, 123.6, 123.2, 120.9, 64.6, 53.5, 26.1, 21.4. IR (neat, cm^{-1}): 1751, 1749, 1172, 1009, 831. MS (ESI^{+}) m/z (%) 304 (M+H). HRMS calcd. for ($C_{15}H_{18}N_3O_4$): 304.1297, found 304.1287. **69f'**: Mp 90-94 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.39 (t, J = 8.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 2H), 3.73 (s, 3H), 2.20 (s, 6H), 1.96 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8,

[282] Shin, J.-A.; Lim, Y.-G.; Lee, K.-H. *J. Org. Chem.* **2012**, *77*, 4117.

169.2, 149.2, 138.6, 129.3, 122.9, 120.9, 118.2, 64.6, 53.4, 25.8, 21.0. IR (neat, cm^{-1}): 1743, 1741, 1186, 1184, 1024. MS (ESI^+) m/z (%) 362 (M+H). HRMS calcd. for ($C_{17}H_{20}N_3O_6$): 362.1352, found 362.1347.



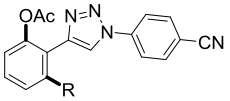
Benzyl 2-[4-(2-acetoxyphenyl)-1*H*-1,2,3-triazol-1-yl] acetate (69g). Following the general procedure, using benzyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate[283] (**68g**) (0.25 mmol, 73 mg) at 110 ºC provided 41.3 mg (47 % yield) of **69g** as a yellowish solid along with 24.6 mg (24 % yield) of **69g'** as a white solid. **69g**: Mp 81-87 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.6 Hz, 1H), 7.94 (s, 1H), 7.44-7.28 (m, 7H), 7.18 (d, *J* = 7.8 Hz, 1H), 5.24 (s, 4H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 169.2, 166.2, 147.4, 143.6, 134.6, 129.3, 129.0, 128.9, 128.8, 128.7, 126.5, 123.4, 123.2, 123.1, 68.2, 51.0, 21.3. IR (neat, cm^{-1}): 1749, 1261, 1175, 696. MS (ESI^+) m/z (%) 352 (M+H). HRMS calcd. for ($C_{19}H_{18}N_3O_4$): 352.1297, found 352.1292. **69g'**: Mp 181-187 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.47-7.31 (m, 6H), 7.10 (d, *J* = 8.2 Hz, 2H), 5.23 (s, 4H), 2.19 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 169.3, 166.2, 149.4, 139.4, 134.6, 129.6, 129.0, 128.9, 128.7, 125.2, 120.9, 118.1, 68.2, 51.0, 21.0. IR (neat, cm^{-1}): 1760, 1744, 1222, 1185, 1030. MS (ESI^+) m/z (%) 410 (M+H). HRMS calcd. for ($C_{21}H_{20}N_3O_6$): 410.1352, found 410.1353.



2-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)phenyl acetate (69h). Following the general procedure, using 1,4-diphenyl-1*H*-1,2,3-triazole[284] (**68h**) (0.25 mmol, 55 mg) provided 21 mg (30 % yield) of **69h** as a white solid along with 21.1 mg (25 % yield) of **69h'** as a yellowish solid. **69h**: Mp 117-119 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.25 (s, 1H), 8.16 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.7 Hz, 2H), 7.54-7.36 (m, 3H), 7.26 (dd, *J* = 7.6, 1.7 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): *δ* 169.2, 147.4, 144.0, 137.0, 129.9, 129.3, 128.9, 128.8, 126.5, 123.3, 123.1, 120.6, 119.8, 21.5. IR (neat, cm^{-1}): 1742, 1506,

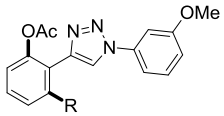
[283] Song, J. H.; Choi, P.; Lee, S. E.; Jeong, K. H.; Kim, T.; Kang, K. S.; Choi, Y. S.; Ham,. J. *Eur. J. Org. Chem.* **2013**, 6249.
[284] Deraedt, C.; Pinaud, N.; Astruc, D. *J. Am. Chem. Soc.* **2014**, *136*, 12092.

1214, 1189, 1036, 753. MS (ESI^+) m/z (%) 280 (M+H). HRMS calcd. for ($C_{16}H_{14}N_3O_2$): 280.1086, found 280.1083. **69h'**: Mp 130-140 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.79-7.73 (m, 2H), 7.55 (t, J = 7.8 Hz, 2H), 7.50-7.39 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 2.24 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 149.3, 139.8, 136.9, 130.0, 129.5, 129.1, 121.5, 121.1, 120.6, 117.8, 21.2. IR (neat, cm^{-1}): 1744, 1368, 1187, 1024, 762. MS (ESI^+) m/z (%) 338 (M+H). HRMS calcd. for ($C_{18}H_{16}N_3O_4$): 338.1141, found 338.1139.



R = H, **69i**
R = OAc, **69i'**

2-[1-(4-Cyanophenyl)-1*H*-1,2,3-triazol-4-yl]phenyl acetate (69i). Following the general procedure, using 4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile[285] (**68i**) (0.25 mmol, 62 mg) provided 29 mg (38 % yield) of **69i** as a white solid along with 24.4 mg (27 % yield) of **69i'** as a yellowish solid. **69i**: Mp 201-207 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.07 (dd, J = 7.6, 1.8 Hz, 1H), 7.90 (dd, J = 33.1, 8.4 Hz, 4H), 7.47-7.33 (m, 2H), 7.23 (d, J = 8.0 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 147.6, 144.9, 139.8, 134.2, 129.9, 129.0, 126.7, 123.5, 122.6, 120.7, 119.3, 117.8, 112.7, 21.6. IR (neat, cm^{-1}): 2223, 1748, 1519, 1215, 1185, 1025, 838. MS (ESI^+) m/z (%) 305 (M+H). HRMS calcd. for ($C_{17}H_{13}N_4O_2$): 305.1039, found 305.1037. **69i'**: Mp 142-158 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.95-7.80 (m, 4H), 7.43 (t, J = 8.2 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 2.22 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 149.2, 140.4, 139.6, 134.1, 129.9, 121.2, 121.1, 120.6, 117.8, 117.2, 112.5, 21.1. IR (neat, cm^{-1}): 2231, 1754, 1190, 1031, 836. MS (ESI^+) m/z (%) 363 (M+H). HRMS calcd. for ($C_{19}H_{15}N_4O_4$): 363.1093, found 363.1082.

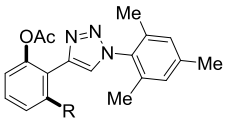


R = H, **69j**
R = OAc, **69j'**

2-[1-(3-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]phenyl acetate (69j). Following the general procedure, using 1-(3-methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole[286] (**68j**) (0.25 mmol, 63 mg) provided 30.2 mg (39 % yield) of **69j** as a white solid along with 21.1 mg (23 % yield) of **69j'** as a yellowish solid. **69j**: Mp 117-121 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.14 (dd, J = 7.6, 2.0 Hz, 1H), 7.49-7.35 (m, 4H), 7.27 (ddd, J = 24.7, 7.8, 1.2 Hz,

[285] Ramachary, D. B.; Shashank, A. B.; Karthik, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 10420.
[286] Chen, Z.; Yan, Q.; Liu, Z.; Xu, Y.; Zhang, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 13324.

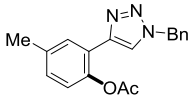
2H), 7.02 (dd, *J* = 8.3, 1.9 Hz, 1H), 3.92 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 160.7, 147.4, 143.9, 138.0, 130.7, 129.4, 129.0, 126.5, 123.3, 123.1, 119.9, 114.7, 112.4, 106.6, 55.7, 21.5. IR (neat, cm^{-1}): 1738, 1610, 1499, 1212, 1158, 1040, 754. MS (ESI^+) m/z (%) 310 (M+H). HRMS calcd. for ($C_{17}H_{16}N_3O_3$): 310.1192, found 310.1194. **69j'**: Mp 126-132 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.48 (t, *J* = 8.2 Hz, 2H), 7.43 (t, *J* = 2.3 Hz, 1H), 7.32 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.05 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.94 (s, 3H), 2.29 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.2, 160.8, 149.3, 139.7, 137.9, 130.8, 129.5, 121.5, 121.1, 117.8, 114.8, 112.4, 106.5, 55.8, 21.2. IR (neat, cm^{-1}): 1749, 1747, 1610, 1484, 1195, 1028. MS (ESI^+) m/z (%) 368 (M+H). HRMS calcd. for ($C_{19}H_{18}N_3O_5$): 368.1246, found 368.1245.



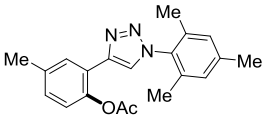
R = H, **69k**
R = OAc, **69k'**

2-(1-Mesityl-1*H*-1,2,3-triazol-4-yl)phenyl acetate (69k). Following the general procedure, using 1-mesityl-4-phenyl-1*H*-1,2,3-triazole[287] (**68k**) (0.25 mmol, 66 mg) at 110 ºC provided 19 mg (24 % yield) of **69k** as a white solid along with 61.2 mg (64 % yield) of **69k'** as white solid. **69k**: Mp 107-117 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, *J* = 6.8, 2.6 Hz, 1H), 7.84 (s, 1H), 7.44-7.33 (m, 2H), 7.19 (s, 1H), 7.02 (s, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 2.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 147.3, 143.0, 140.2, 135.2, 133.4, 129.2, 129.1, 128.8, 126.5, 123.7, 123.4, 123.1, 21.4, 21.2, 17.4. IR (neat, cm^{-1}): 1763, 1481, 1207, 1184, 1047, 758. MS (ESI^+) m/z (%) 322 (M+H). HRMS calcd. for ($C_{19}H_{20}N_3O_2$): 322.1556, found 322.1553. **69k'**: Mp 163-164 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.35 (t, *J* = 8.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.95 (s, 2H), 2.28 (s, 3H), 2.11 (s, 6H), 1.92 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.5, 149.1, 139.9, 138.5, 134.7, 133.0, 129.2, 128.9, 125.3, 120.5, 118.0, 20.9, 20.6, 16.9. IR (neat, cm^{-1}): 1745, 1496, 1457, 1185, 1024. MS (ESI^+) m/z (%) 380 (M+H). HRMS calcd. for ($C_{21}H_{22}N_3O_4$): 380.1610, found 380.1602.

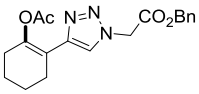
[287] Sau, S. C.; Roy, S. R.; Sen, T. K.; Mullangi, D.; Mandal, S. K. *Adv. Synth. Catal.* **2013**, *355*, 2982.



2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-3-methylphenyl acetate (69l). Following the general procedure, using 1-benzyl-4-(*m*-tolyl)-1*H*-1,2,3-triazole[288] (**68l**) (0.25 mmol, 62 mg) provided 38.4 mg (50 % yield) of **69l** as a yellowish solid. Mp 119-122 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.84 (m, 1H), 7.59 (s, 1H), 7.38 (dt, J = 4.7, 1.7 Hz, 3H), 7.30 (dd, J = 7.4, 2.2 Hz, 2H), 7.17-7.10 (m, 1H), 7.00 (d, J = 8.2 Hz, 1H), 5.56 (s, 2H), 2.37 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 145.0, 143.6, 136.2, 134.7, 129.8, 129.3, 129.1, 129.0, 128.3, 123.0, 122.8, 121.7, 54.3, 21.2, 21.0. IR (neat, cm^{-1}): 1755, 1496, 1371, 1182, 1069, 822, 715. MS (ESI^{+}) m/z (%) 308 (M+H). HRMS calcd. for ($C_{18}H_{18}N_3O_2$): 308.1399, found 308.1397.



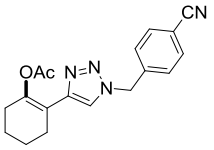
2-(1-Mesityl-1*H*-1,2,3-triazol-4-yl)-3-methylphenyl acetate (69m). Following the general procedure, using1-mesityl-4-(*m*-tolyl)-1*H*-1,2,3-triazole (**68m**) (0.25 mmol, 69 mg) provided 60.4 mg (72 % yield) of **69m** as a yellow solid. Mp 107-109 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 1.5 Hz, 1H), 7.82 (s, 1H), 7.19 (dd, J = 8.4, 2.1 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 7.01 (s, 2H), 2.42 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H), 2.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 145.0, 143.6, 136.2, 134.7, 129.8, 129.3, 129.1, 129.0, 128.3, 123.0, 122.8, 121.7, 54.3, 21.2, 21.0. IR (neat, cm^{-1}): 1760, 1494, 1367, 1183, 1039, 908, 730. MS (ESI^{+}) m/z (%) 336 (M+H). HRMS calcd. for ($C_{20}H_{22}N_3O_2$): 336.1712, found 336.1701.



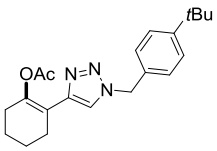
Benzyl 2-[4-(2-acetoxycyclohex-1-en-1-yl)-1*H*-1,2,3-triazol-1-yl]acetate (69n). Following the general procedure, using benzyl 2-(4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazol-1-yl)acetate (**68n**) (0.25 mmol, 74 mg) provided 65.7 mg (74 % yield) of **69n** as a yellow solid. Mp 59-66 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.37-7.23 (m, 5H), 5.13 (d, J = 8.0 Hz, 4H),

[288] Yamaguchi, K.; Oishi, T.; Katayama, T.; Mizuno, N. *Chem. Eur. J.* **2009**, *15*, 10464.

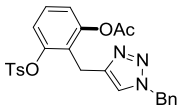
2.64-2.55 (m, 2H), 2.32-2.24 (m, 2H), 2.11 (s, 3H), 1.79-1.65 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 166.2, 145.5, 144.7, 134.5, 128.7, 128.6, 128.4, 122.8, 115.0, 67.7, 50.6, 27.8, 26.2, 22.4, 21.9, 21.1. IR (neat, cm^{-1}): 2937, 1751, 1457, 1188, 1104, 1056, 749, 698. MS (ESI$^+$) m/z (%) 356 (M+H). HRMS calcd. for ($C_{19}H_{22}N_3O_4$): 356.1610, found 356.1601.



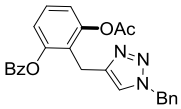
2-[1-(4-Cyanobenzyl)-1*H*-1,2,3-triazol-4-yl]cyclohex-1-en-1-yl acetate (69o). Following the general procedure, using 4-[(4-cyclohex-1-en-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl]benzonitrile (**68o**) (0.25 mmol, 66 mg) provided 58 mg (72 % yield) of **69o** as a white solid. Mp 111-117 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.2 Hz, 2H), 7.44 (s, 1H), 7.30 (d, J = 8.3 Hz, 2H), 5.57 (s, 2H), 2.64-2.56 (m, 2H), 2.32-2.24 (m, 2H), 2.12 (s, 3H), 1.81-1.69 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 145.9, 145.5, 140.2, 132.9, 128.3, 121.3, 118.2, 115.0, 53.3, 48.6, 28.0, 26.5, 22.6, 22.0, 21.4. IR (neat, cm^{-1}): 2941, 2226, 1738, 1374, 1220, 1097, 765. MS (ESI$^+$) m/z (%) 323 (M+H). HRMS calcd. for ($C_{18}H_{19}N_4O_2$): 323.1508, found 323.1502.



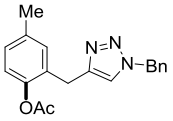
2-[1-(4-(*Tert*-butyl)benzyl)-1*H*-1,2,3-triazol-4-yl]cyclohex-1-en-1-yl acetate (69p). Following the general procedure, using 1-[4-(*tert*-butyl)benzyl)]-4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazole (**68p**) (0.25 mmol, 74 mg) provided 66 mg (75 % yield) of **69p** as a white solid. Mp 134-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 7.9 Hz, 2H), 7.32 (s, 1H), 7.20 (d, J = 7.9 Hz, 2H), 5.47 (s, 2H), 2.64 (dd, J = 5.9, 3.3 Hz, 2H), 2.28 (d, J = 6.0 Hz, 2H), 2.01 (s, 3H), 1.88-1.50 (m, 4H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 151.9, 145.2, 144.7, 131.6, 128.1, 128.0, 126.1, 126.0, 121.0, 115.3, 53.7, 34.6, 31.2, 27.8, 26.2, 22.5, 22.0, 21.1. IR (neat, cm^{-1}): 1750, 1213, 1191. MS (ESI$^+$) m/z (%) 354 (M+H). HRMS calcd. for ($C_{21}H_{28}N_3O_2$): 354.2182, found 354.2180.



2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-3-(tosyloxy)phenyl acetate (69q). Following the general procedure, using 2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]phenyl 4-methylbenzenesulfonate (**68q**) (0.25 mmol, 104.9 mg) provided 77 mg (65 % yield) of **69q** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.0 Hz, 2H), 7.36-7.26 (m, 5H), 7.24-7.15 (m, 3H), 7.12 (s, 1H), 7.00 (dd, J = 13.1, 8.2 Hz, 2H), 5.38 (s, 2H), 3.89 (s, 2H), 2.44 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.7, 150.1, 148.2, 145.8, 145.4, 134.8, 132.4, 129.9, 128.8, 128.4, 128.2, 127.7, 127.6, 125.5, 121.9, 121.8, 119.8, 53.8, 21.6, 21.5, 20.6. IR (neat, cm^{-1}): 1752, 1492, 1209, 1168, 727. MS (ESI^{+}) m/z (%) 478 (M+H). HRMS calcd. for ($C_{25}H_{26}N_3O_5S$): 478.1358, found 478.1359.

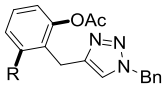


3-Acetoxy-2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]phenyl benzoate (69r). Following the general procedure, using 2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]phenyl benzoate (**68r**) (0.25 mmol, 92.3 mg) provided 66 mg (62 % yield) of **69r** as a yellowish solid. Mp 116-117ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.7 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.39-7.28 (m, 4H), 7.20-7.10 (m, 3H), 7.09 (s, 1H), 7.02 (d, J = 8.1 Hz, 1H), 5.37 (s, 2H), 4.04 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 165.0, 150.2, 150.1, 145.9, 135.0, 133.9, 130.2, 129.0, 128.9, 128.7, 128.5, 127.9, 124.6, 121.9, 120.8, 120.5, 54.1, 21.9, 20.8. IR (neat, cm^{-1}): 1765, 1731, 1462, 1264, 1173, 1061, 1025, 702. MS (ESI^{+}) m/z (%) 428 (M+H). HRMS calcd. for ($C_{25}H_{22}N_3O_4$): 428.1532, found 428.1533.



2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-4-methylphenyl acetate (69s). Following the general procedure, using 1-benzyl-4-(3-methylbenzyl)-1*H*-1,2,3-triazole (**68s**) (0.25 mmol, 66 mg) provided 52 mg (65 % yield) of **69s** as yellow solid. Mp 85-86 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 6.3 Hz, 3H), 7.22 (dd, J = 7.1, 2.2 Hz, 2H), 7.06 (t, J = 8.4 Hz,

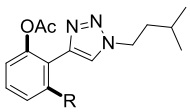
3H), 6.90 (d, *J* = 7.9 Hz, 1H), 5.43 (s, 2H), 3.95 (s, 2H), 2.28 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 146.8, 146.5, 135.9, 134.8, 131.2, 130.5, 128.9, 128.5, 128.4, 127.8, 122.3, 121.5, 54.0, 27.1, 20.8, 20.7. IR (neat, cm^{-1}): 1752, 1366, 1124, 1052, 635. MS (ESI^+) m/z (%) 322 (M+H). HRMS calcd. for ($C_{19}H_{20}N_3O_2$): 322.1477, found 322.1479.



(69t')

R = H, **69t**
R = OAc, **69t'**

2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]phenyl acetate (69t). Following the general procedure, using 1,4-dibenzyl-1*H*-1,2,3-triazole (**68t**) (0.25 mmol, 62 mg) provided 12.3 mg (16 % yield) of **69t** as a yellow oil along with 45.6 mg (50 % yield) of **69t'** as yellowish solid. **69t**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (h, *J* = 5.3 Hz, 3H), 7.32-7.22 (m, 4H), 7.19 (td, *J* = 5.7, 2.8 Hz, 1H), 7.11-7.04 (m, 2H), 5.46 (s, 2H), 4.03 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.5, 149.0, 147.0, 135.0, 131.1, 130.8, 129.2, 128.7, 128.1, 128.1, 126.4, 122.9, 121.7, 54.2, 27.4, 20.9. IR (neat, cm^{-1}): 1747, 1366, 1207, 1172, 1048, 750, 726. MS (ESI^+) m/z (%) 308 (M+H). HRMS calcd. for ($C_{18}H_{18}N_3O_2$): 308.1399, found 308.1388. **69t'**: Mp 107-109 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.33 (m, 2H), 7.32 (s, 1H), 7.29 (d, *J* = 3.4 Hz, 1H), 7.22 (dd, *J* = 7.5, 2.2 Hz, 2H), 7.07 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 5.42 (s, 2H), 4.00 (s, 2H), 2.19 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.3, 150.0, 146.0, 135.1, 129.1, 128.6, 128.0, 127.9, 124.5, 122.0, 120.6, 54.2, 21.9, 20.9. IR (neat, cm^{-1}): 1759, 1463, 1371, 1210, 1200, 1170, 1023, 722. MS (ESI^+) m/z (%) 366 (M+H). HRMS calcd. for ($C_{20}H_{20}N_3O_4$): 366.1454, found 366.1454.

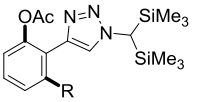


R = H, **69w**
R = OAc, **69w'**

2-(1-Isopentyl-1*H*-1,2,3-triazol-4-yl)phenyl acetate (69w). Following the general procedure, using 1-(isopentyl)-4-phenyl-1*H*-1,2,3-triazole[289] (**68w**) (0.25 mmol, 54 mg) at 110 ºC provided 28.7 mg (42 % yield) of **69w** as a white solid along with 36.4 mg (44 % yield) of **69w'** as a yellowish solid. **69w**: Mp 83-90 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 6.4 Hz, 1H), 7.72 (s, 1H), 7.32 (p, *J* = 7.2, 6.7 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 1H), 4.38 (t, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 1.80 (q, *J* = 7.3 Hz, 2H), 1.59 (dt, *J* = 13.5, 6.7 Hz, 1H),

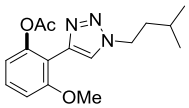
[289] Chen, Z.; Yan, Q.; Yi, H.; Liu, Z.; Lei, A.; Zhang, Y. *Chem. Eur. J.* **2014**, *20*, 13692.

0.95 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1, 147.2, 143.2, 129.0, 128.8, 126.4, 123.6, 123.1, 121.5, 48.7, 39.1, 25.5, 22.2, 21.4. IR (neat, cm^{-1}): 1758, 1371, 1189, 758. MS (ESI$^+$) m/z (%) 274 (M+H). HRMS calcd. for ($C_{15}H_{20}N_3O_2$): 274.1556, found 274.1553. **69w'**: Mp 136-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.39 (t, J = 8.2 Hz, 1H), 7.09 (d, J = 8.1 Hz, 2H), 4.41 (t, J = 7.4 Hz, 2H), 2.19 (s, 6H), 1.81 (q, J = 7.1 Hz, 2H), 1.57 (dt, J = 13.3, 6.8 Hz, 1H), 0.96 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1, 149.3, 138.9, 129.3, 123.3, 120.9, 118.3, 48.8, 39.2, 25.6, 22.3, 21.1. IR (neat, cm^{-1}): 1747, 1197, 1027, 883. MS (ESI$^+$) m/z (%) 332 (M+H). HRMS calcd. for ($C_{17}H_{22}N_3O_4$): 332.1610, found 332.1622.



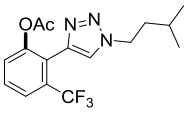
R = H, **69x**
R = OAc, **69x'**

2-[1-(Bis(trimethylsilyl)methyl)-1*H*-1,2,3-triazol-4-yl]phenyl acetate (69x). Following the general procedure, using 1-[bis(trimethylsilyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (**68x**) (0.25 mmol, 76 mg) at 110ºC provided 18.9 mg (21 % yield) of **69x** as a white solid along with 47.2 mg (45 % yield) of **69x'** as a white solid. **69x**: Mp 139-143 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-8.09 (m, 1H), 7.55 (s, 1H), 7.33 (dt, J = 6.0, 2.5 Hz, 2H), 7.19-7.14 (m, 1H), 3.68 (s, 1H), 2.32 (s, 3H), 0.12 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.9, 147.2, 142.3, 128.8, 126.5, 123.9, 123.0, 122.4, 46.7, 21.5, -1.0. IR (neat, cm^{-1}): 1749, 1249, 1197, 843, 765. MS (ESI$^+$) m/z (%) 362 (M+H). HRMS calcd. for ($C_{17}H_{28}N_3O_2Si$): 362.1720, found 362.1716. **69x'**: Mp 137-139 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.34 (m, 2H), 7.07 (d, J = 8.2 Hz, 2H), 3.66 (s, 1H), 2.13 (s, 6H), 0.10 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.9, 149.4, 138.0, 129.2, 124.0, 120.6, 119.0, 46.6, 21.0, -1.1. IR (neat, cm^{-1}): 1764, 1760, 1217, 1189, 1027, 843. MS (ESI$^+$) m/z (%) 420 (M+H). HRMS calcd. for ($C_{19}H_{30}N_3O_4Si$): 420.1775, found 420.1769.

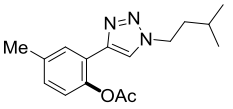


2-(1-Isopentyl-1*H*-1,2,3-triazol-4-yl)-3-methoxyphenyl acetate (69y). Following the general procedure, using 1-isopentyl-4-(2-methoxyphenyl)-1*H*-1,2,3-triazole (**68y**) (0.25 mmol, 61 mg) provided 71 mg (93 % yield) of **69y** as a white solid. Mp 99-100 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.32 (q, J = 7.4, 6.6 Hz, 1H), 6.86 (dd, J = 29.7, 8.3 Hz,

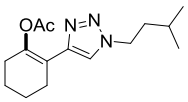
2H), 4.41 (t, *J* = 7.7 Hz, 2H), 3.88 (s, 3H), 2.31 (s, 3H), 1.85 (q, *J* = 7.3 Hz, 2H), 1.64 (dt, *J* = 13.4, 6.7 Hz, 1H), 0.99 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 157.3, 149.2, 139.3, 128.9, 124.2, 116.0, 113.4, 108.5, 55.9, 48.5, 38.9, 25.5, 22.1, 21.1. IR (neat, cm^{-1}): 1756, 1261, 1074, 737. MS (ESI^+) m/z (%) 304 (M+H). HRMS calcd. for ($C_{16}H_{22}N_3O_3$): 304.1661, found 304.1662.



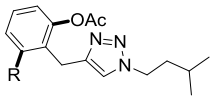
2-(1-Isopentyl-1*H*-1,2,3-triazol-4-yl)-3-(trifluoromethyl)phenyl acetate (69z). Following the general procedure, using 1-isopentyl-4-[2-(trifluoromethyl)pheny])-1*H*-1,2,3-triazole (**68z**) (0.25 mmol, 71 mg) provided 66 mg (77 % yield) of **69z** as a white solid. Mp 60-62 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 4.44 (t, *J* = 7.3 Hz, 2H), 2.03 (s, 3H), 1.82 (q, *J* = 7.2 Hz, 2H), 1.55 (dt, *J* = 13.4, 6.7 Hz, 1H), 0.95 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 150.4, 138.9, 131.0 (q, *J* = 30 Hz), 129.8, 126.7, 124.6, 123.7 (q, *J* = 6Hz), 121.9, 48.7, 38.9, 25.3, 22.1, 20.4. IR (neat, cm^{-1}): 1769, 1319, 1190, 1007, 807. MS (ESI^+) m/z (%) 342 (M+H). HRMS calcd. for ($C_{16}H_{19}N_3O_2F_3$): 342.1429, found 342.1433.



2-(1-Isopentyl-1*H*-1,2,3-triazol-4-yl)-4-methylphenyl acetate (69za). Following the general procedure, using 1-isopentyl-4-(*m*-tolyl)-1*H*-1,2,3-triazole (**68za**) (0.25 mmol, 57 mg) provided 59 mg (82 % yield) of **69za** as a white solid. Mp 67-69 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.71 (s, 1H), 7.09 (dd, *J* = 45.9, 8.3 Hz, 2H), 4.40 (t, *J* = 7.5 Hz, 2H), 2.38 (s, 3H), 2.31 (s, 3H), 1.82 (q, *J* = 7.3 Hz, 2H), 1.60 (dt, *J* = 13.3, 6.5 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 144.9, 143.1, 136.1, 129.5, 129.0, 122.9, 122.7, 121.3, 48.6, 39.0, 25.4, 22.1, 21.2, 20.8. IR (neat, cm^{-1}): 1769, 1430, 1214, 948. MS (ESI^+) m/z (%) 288 (M+H). HRMS calcd. for ($C_{16}H_{22}N_3O_2$): 288.1712, found 288.1711.

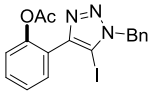


2-(1-Isopentyl-1*H*-1,2,3-triazol-4-yl)cyclohex-1-en-1-yl acetate (69zb). Following the general procedure, using 4-(cyclohex-1-en-1-yl)-1-isopentyl-1*H*-1,2,3-triazole (**68zb**) (0.25 mmol, 55 mg) at 110 ºC provided 51.9 mg (75 % yield) of **69zb** as a yellow solid. Mp 73-81 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 4.28 (t, J = 7.4 Hz, 2H), 2.64-2.53 (m, 2H), 2.26 (t, J = 6.0 Hz, 2H), 2.15 (s, 3H), 1.70 (q, J = 7.1 Hz, 6H), 1.49 (dt, J = 13.4, 6.7 Hz, 1H), 0.88 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 144.9, 144.2, 120.9, 115.1, 48.3, 38.9, 27.8, 26.2, 25.3, 22.4, 22.0, 21.9, 21.2. IR (neat, cm^{-1}): 2938, 2846, 1748, 1371, 1215, 1198, 1150, 1103, 1058. MS (ESI^{+}) m/z (%) 278 (M+H). HRMS calcd. for ($C_{15}H_{24}N_3O_2$): 278.1869, found 278.1860.

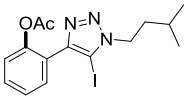


R = H, **69zc**
R = OAc, **69zc'**

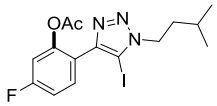
2-[(1-Isopentyl-1*H*-1,2,3-triazol-4-yl)methyl]phenyl acetate (**69zc**). Following the general procedure, using 4-benzyl-1-isopentyl-1*H*-1,2,3-triazole (**68zc**) (0.25 mmol, 57 mg) provided 12.2 mg (17 % yield) of **69zc** as a yellow oil along with 46.6 mg (54 % yield) of **69zc'** as white solid. **69zc**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, J = 7.0 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.09 (d, J = 10.7 Hz, 2H), 4.34-4.27 (m, 2H), 4.05 (s, 2H), 2.26 (s, 3H), 1.76 (q, J = 7.3 Hz, 2H), 1.58 (dt, J = 13.4, 6.7 Hz, 1H), 0.96 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 149.0, 146.5, 131.3, 130.9, 128.1, 126.4, 122.9, 121.5, 48.8, 39.1, 27.3, 25.7, 22.3, 21.0. IR (neat, cm^{-1}): 2957, 1764, 1367, 1202, 1169, 1047, 749. MS (ESI^{+}) m/z (%) 288 (M+H). HRMS calcd. for ($C_{16}H_{22}N_3O_2$): 288.1712, found 288.1713. **69zc'**: Mp 96-100 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.29 (m, 1H), 7.13-6.97 (m, 3H), 4.37-4.21 (m, 2H), 4.03 (s, 2H), 2.26 (q, J = 2.1, 1.6 Hz, 6H), 1.79-1.69 (m, 2H), 1.64-1.50 (m, 1H), 1.00-0.93 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.3, 150.0, 145.5, 127.8, 124.7, 121.7, 120.6, 48.7, 39.0, 25.6, 22.2, 21.8, 20.8. IR (neat, cm^{-1}): 1757, 1463, 1373, 1199, 1165, 1052, 1023, 869. MS (ESI^{+}) m/z (%) 346 (M+H). HRMS calcd. for ($C_{18}H_{24}N_3O_4$): 346.1767, found 346.1763.



2-(1-Benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)phenyl acetate (69zd). Following the general procedure, using 1-benzyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole[290] (**68zd**) (0.25 mmol, 90 mg) provided 71 mg (68 % yield) of **69zd** as a white solid. Mp 130-131 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 7.7 Hz, 1H), 7.53-7.15 (m, 8H), 5.68 (s, 2H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 148.5, 134.3, 131.0, 130.1, 128.9, 128.5, 127.7, 125.9, 123.3, 123.1, 79.7, 54.5, 21.0. IR (neat, cm^{-1}): 1737, 1195, 912, 761. MS (ESI^{+}) m/z (%) 420 (M+H). HRMS calcd. for ($C_{17}H_{15}N_3O_2I$): 420.0209, found 420.0215.



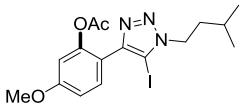
2-(5-Iodo-1-isopentyl-1*H*-1,2,3-triazol-4-yl)phenyl acetate (69ze). Following the general procedure, using 5-Iodo-1-isopentyl-4-phenyl-1*H*-1,2,3-triazole (**68ze**) (0.25 mmol, 85 mg) provided 98 mg (98 % yield) of **69ze** as a white solid. Mp 94-95 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.7 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 4.60-4.36 (m, 2H), 2.20 (s, 3H), 1.88 (q, J = 7.3 Hz, 2H), 1.70 (dq, J = 13.7, 6.3 Hz, 1H), 1.04 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1, 148.5, 147.7, 131.1, 130.0, 125.8, 123.4, 123.2, 79.1, 49.6, 38.6, 25.7, 22.3, 21.1. IR (neat, cm^{-1}): 1753, 1197, 907, 768. MS (ESI^{+}) m/z (%) 400 (M+H). HRMS calcd. for ($C_{15}H_{19}N_3O_2I$): 400.0522, found 400.0522.



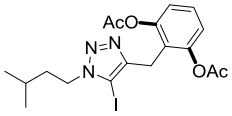
5-Fluoro-2-(5-iodo-1-isopentyl-1*H*-1,2,3-triazol-4-yl)phenyl acetate (69zf). Following the general procedure, using 4-(4-fluorophenyl)-5-iodo-1-isopentyl-1*H*-1,2,3-triazole (**68zf**) (0.25 mmol, 90 mg) provided 73 mg (71 % yield) of **69zf** as a brown solid. Mp 62-63 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, J = 8.6, 6.1 Hz, 1H), 7.14-6.89 (m, 2H), 4.45 (t, J = 7.7 Hz, 2H), 2.17 (s, 3H), 1.84 (q, J = 7.4 Hz, 2H), 1.67 (dt, J = 13.5, 7.2 Hz, 1H), 1.01 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 162.8 (d, J = 249 Hz), 149.4 (d, J = 11

[290] Zhou, Y.; Lecourt, T.; Micouin, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 2607.

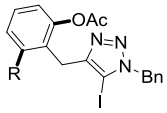
Hz), 147.1, 132.1 (d, J = 10 Hz), 119.6 (d, J = 3 Hz), 113.1 (d, J = 21 Hz), 111.1 (d, J = 25 Hz), 79.2, 49.6, 38.5, 25.6, 22.2, 21.0. IR (neat, cm^{-1}): 1763, 1459, 1200, 833. MS (ESI^+) m/z (%) 418 (M+H). HRMS calcd. for ($C_{15}H_{18}N_3O_2FI$): 418.0428, found 418.0441.



2-(5-Iodo-1-isopentyl-1*H*-1,2,3-triazol-4-yl)-5-methoxyphenyl acetate (69zg). Following the general procedure, using 5-iodo-1-isopentyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (**68zg**) (0.25 mmol, 93 mg) provided 77 mg (72 % yield) of **69zg** as a white solid. Mp 86-87 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.6 Hz, 1H), 6.87 (dd, J = 8.7, 2.6 Hz, 1H), 6.77 (d, J = 2.6 Hz, 1H), 4.43 (t, J = 7.8 Hz, 2H), 3.83 (s, 3H), 2.15 (s, 3H), 1.83 (q, J = 7.3 Hz, 2H), 1.66 (dt, J = 13.4, 6.7 Hz, 1H), 1.00 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 160.8, 149.5, 147.6, 131.6, 115.7, 111.8, 108.8, 78.9, 55.5, 49.5, 38.5, 25.6, 22.2, 21.0. IR (neat, cm^{-1}): 1764, 1622, 1187, 1090, 840. MS (ESI^+) m/z (%) 430 (M+H). HRMS calcd. for ($C_{16}H_{21}N_3O_3I$): 430.0628, found 430.0632.

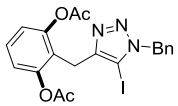


2-[(5-Iodo-1-isopentyl-1*H*-1,2,3-triazol-4-yl)methyl]-1,3-phenylene diacetate (69zh'). Following the general procedure, using 4-benzyl-5-iodo-1-isopentyl-1*H*-1,2,3-triazole (**68zh**) (0.25 mmol, 89 mg) provided 84.8 mg (72 % yield) of **69zh'** as yellowish solid. Mp 122-126 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 8.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 2H), 4.36-4.26 (m, 2H), 3.96 (s, 2H), 2.28 (s, 6H), 1.73 (q, J = 6.9 Hz, 2H), 1.61 (dp, J = 13.4, 6.7 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 150.0, 148.4, 127.6, 122.8, 120.2, 77.5, 49.1, 38.5, 25.5, 22.2, 22.1, 21.2. IR (neat, cm^{-1}): 1764, 1466, 1366, 1203, 1171, 1031, 860, 773, 726. MS (ESI^+) m/z (%) 472 (M+H). HRMS calcd. for ($C_{18}H_{23}N_3O_4I$): 472.0733, found 472.0742.

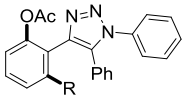


R = H, **69zi**
R = OAc, **69zi'**

2-[(1-Benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)methyl]phenyl acetate (**69zi**). Following the general procedure, using 1,4-dibenzyl-5-iodo-1*H*-1,2,3-triazole (**68zi**) (0.25 mmol, 94 mg) and $PhI(OAc)_2$ (0.25 mmol, 83 mg) provided 28 mg (23 % yield) of **69zi'** along with 44.7 mg (41 % yield) of **69zi** as a yellowish solid. Mp 133-138ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, J = 7.0 Hz, 3H), 7.32-7.24 (m, 4H), 7.19 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 5.58 (s, 2H), 4.01 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.3, 149.8, 149.1, 134.5, 131.1, 129.9, 129.0, 128.5, 128.0, 127.8, 126.1, 122.7, 78.9, 54.3, 27.5, 21.2. IR (neat, cm^{-1}): 1752, 1492, 1209, 1168, 1098, 727. MS (ESI$^+$) m/z (%) 434 (M+H). HRMS calcd. for ($C_{18}H_{17}IN_3O_2$): 434.0287, found 434.0288.



2-[(1-Benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)methyl]-1,3-phenylene diacetate (**69zi'**) Following the general procedure, using 1,4-dibenzyl-5-iodo-1*H*-1,2,3-triazole (**68zi**) (0.25 mmol, 94 mg) provided 108.1 mg (88 % yield) of **69zi'** as yellow solid. Mp 139-153 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, J = 7.1 Hz, 3H), 7.28 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 6.2 Hz, 2H), 7.02 (d, J = 8.2 Hz, 2H), 5.52 (s, 2H), 3.97 (s, 2H), 2.25 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 149.9, 149.1, 134.4, 128.8, 128.3, 127.6, 122.7, 120.1, 78.1, 54.0, 22.1, 21.1. IR (neat, cm^{-1}): 1761, 1462, 1369, 1203, 1174, 1029, 741. MS (ESI$^+$) m/z (%) 492 (M+H). HRMS calcd. for ($C_{20}H_{19}N_3O_4I$): 492.0420, found 492.0410.

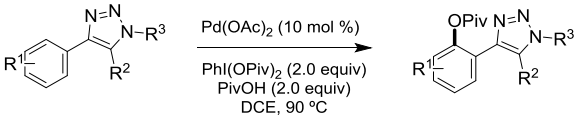


R = H, **69zj**
R = OAc, **69zj'**

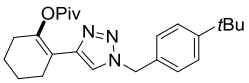
2-(1,5-Diphenyl-1*H*-1,2,3-triazol-4-yl)phenyl acetate (69zj). Following the general procedure, using 1,4,5-triphenyl-1*H*-1,2,3-triazole[71] (**68zj**) (0.25 mmol, 74 mg) provided 40 mg (45 % yield) of **69zj** as a white solid along with 36.2 mg (35 % yield) of **69zj'** as white solid. **69zj**: Mp 137-153 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.10 (m, 14H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 148.6, 141.7, 136.4, 134.8, 131.1, 129.6, 129.3, 129.1, 129.0, 128.8, 126.9, 125.8, 125.1, 123.7, 123.1, 20.9. IR (neat, cm^{-1}): 1761,

1495, 1365, 1198, 1173, 995, 915, 772, 761, 691. MS (ESI^+) m/z (%) 356 (M+H). HRMS calcd. for ($C_{22}H_{18}N_3O_2$): 356.1399, found 356.1400. **69zj'**: Mp 61-78 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.49-7.09 (m, 13H), 1.97 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.5, 150.0, 137.3, 136.8, 136.1, 129.8, 129.5, 129.5, 129.3, 129.1, 129.0, 127.0, 125.4, 120.4, 117.9, 20.9. IR (neat, cm^{-1}): 1759, 1365, 1179, 1026, 996, 755, 696. MS (ESI^+) m/z (%) 414 (M+H). HRMS calcd. for ($C_{24}H_{20}N_3O_4$): 414.1454, found 414.1449.

4.3 Pd-catalyzed C(sp^2)-H pivaloxylation.

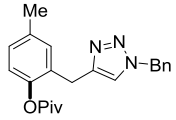


General Procedure: A reaction tube containing a stirring bar was charged with the correspoding triazole (0.25 mmol, 1.00 equiv), $PhI(OPiv)_2$ (0.50 mmol, 2.00 equiv), PivOH (0.50 mmol, 2.00 equiv) and $Pd(OAc)_2$ (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then 1,2-dichloroethane (1.00 mL) was added under argon atmosphere. The reaction tube was next warmed up to 90 ºC and stirred for 24 hours. The mixture was then allowed to warm to room temperature, filtered off through a pad of celite and washed with CH_2Cl_2. The resulting mixture was concentrated under reduced pressure and the corresponding product was purified by flash chromatography (hex/EtOAc 7/3). The yields reported in the thesis refer to isolated yields and represent an average of at least two independent runs.

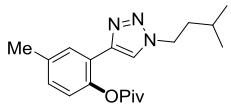


2-(5-Iodo-1-isopentyl-1*H*-1,2,3-triazol-4-yl)phenyl pivalate (73p). Following the general procedure, using 1-[4-(*tert*-butyl)benzyl)]-4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazole (**68p**) (0.25 mmol, 74 mg) provided 76 mg (77 % yield) of **73p** as a white solid. Mp 88-89 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 8.0 Hz, 2H), 7.33 (s, 1H), 7.19 (d, J = 8.0 Hz, 2H), 5.43 (s, 2H), 2.67 (d, J = 5.2 Hz, 2H), 2.19 (t, J = 5.6 Hz, 2H), 1.74 (dt, J = 8.1, 5.3 Hz, 4H), 1.29 (s, 9H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.9, 151.8, 145.2, 144.3, 131.2, 128.2, 126.0, 121.2, 115.4, 53.8, 38.6, 34.5, 31.2, 27.3, 26.9, 26.7, 26.4, 22.5, 22.0. IR (neat,

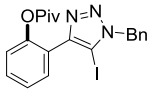
cm^{-1}): 1739, 1115, 715. MS (ESI$^+$) m/z (%) 396 (M+H). HRMS calcd. for ($C_{24}H_{34}N_3O_2$): 396.2651, found 396.2666.



2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-4-methylphenyl pivalate (73s). Following the general procedure, using 1-benzyl-4-(3-methylbenzyl)-1*H*-1,2,3-triazole (**68s**) (0.25 mmol, 66 mg) provided 55 mg (60 % yield) of **73s** as a yellow solid. Mp 99-100 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 6.3 Hz, 3H), 7.31-7.21 (m, 2H), 7.13-7.01 (m, 3H), 6.90 (d, J = 7.9 Hz, 1H), 5.46 (s, 2H), 3.97 (s, 2H), 2.31 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 147.0, 146.9, 135.7, 134.9, 131.3, 130.4, 129.0, 128.5, 128.4, 127.9, 122.1, 121.7, 54.0, 39.1, 27.2, 20.8. IR (neat, cm^{-1}): 1744, 1199, 736. MS (ESI$^+$) m/z (%) 396 (M+H). HRMS calcd. for ($C_{22}H_{26}N_3O_2$): 364.1947, found 364.1948.



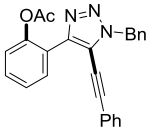
2-(5-Iodo-1-isopentyl-1*H*-1,2,3-triazol-4-yl)phenyl pivalate (73za). Following the general procedure, using1-isopentyl-4-(*m*-tolyl)-1*H*-1,2,3-triazole (**68za**) (0.25 mmol, 57 mg) provided 58 mg (70 % yield) of **73za** as a white solid. Mp 78-80 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.68 (s, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 4.40 (t, J = 7.5 Hz, 2H), 2.39 (s, 3H), 1.81 (q, J = 7.3 Hz, 2H), 1.60 (d, J = 5.3 Hz, 1H), 1.36 (s, 9H), 0.97 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.9, 145.7, 143.2, 135.8, 129.7, 129.6, 123.3, 122.4, 121.6, 48.6, 39.1, 27.3, 25.4, 22.2, 20.8. IR (neat, cm^{-1}): 1742, 1498, 1110, 790. MS (ESI$^+$) m/z (%) 330 (M+H). HRMS calcd. for ($C_{19}H_{28}N_3O_2$): 330.2182, found 330.2193.



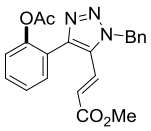
2-(5-Iodo-1-isopentyl-1*H*-1,2,3-triazol-4-yl)phenyl pivalate (73zd). Following the general procedure, using 1-benzyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole (**68zd**) (0.25 mmol, 90 mg) provided 78 mg (68 % yield) of **73zd** as a white solid. Mp 105-107 ºC. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.55-7.43 (m, 3H), 7.42-7.26 (m, 5H), 7.19 (d, J = 8.1 Hz, 1H), 5.67 (s, 2H), 1.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3, 149.1, 148.5, 134.2, 131.3, 130.1, 128.8, 128.4, 127.9, 125.6, 123.6, 122.9, 80.1, 54.4, 38.8, 26.9. IR (neat, cm^{-1}): 1747, 1730, 1093, 731. MS (ESI^+) m/z (%) 462 (M+H). HRMS calcd. for ($C_{20}H_{21}N_3O_2I$): 462.0678, found 462.0688.

4.4 Further transformations (Scheme 4.17-4.18)

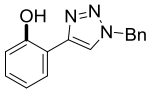


2-(1-Benzyl-5-(phenylethynyl)-1*H*-1,2,3-triazol-4-yl)phenyl acetate (70). A reaction tube containing a stirring bar was charged with 2-(1-benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)phenyl acetate (**69zd**) (0.12 mmol, 50 mg), $PdCl_2(PPh_3)_2$ (0.012 mmol, 8.20 mg), and K_2CO_3 (0.18 mmol, 25 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Phenylacetylene (0.18 mmol, 20 μL), and THF (1.0 mL) were then added under argon atmosphere. The reaction tube was next warmed up to 80 ºC and stirred 12 hours. The resulting mixture was concentrated under reduced pressure and the corresponding product was purified by flash chromatography (hex/EtOAc 8/2) to provide 39 mg (83 % yield) of **70** as an orange oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 7.7 Hz, 1H), 7.57-7.34 (m, 11H), 7.34-7.23 (m, 2H), 5.75 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 148.0, 145.34, 134.6, 131.5, 130.0, 130.1, 129.7, 128.9, 128.6, 128.5, 128.0, 125.9, 123.4, 123.0, 121.2, 119.1, 102.2, 75.0, 53.1, 21.2. IR (neat, cm^{-1}): 1763, 1190, 729, 689. MS (ESI^+) m/z (%) 394 (M+H). HRMS calcd. for ($C_{25}H_{20}N_3O_2$): 394.1556, found 394.1566.



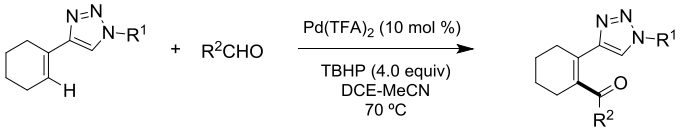
Methyl (*E*)-3-(4-(2-acetoxyphenyl)-1-benzyl-1*H*-1,2,3-triazol-5-yl)acrylate (71). A reaction tube containing a stirring bar was charged with 2-(1-benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)phenyl acetate (**69zd**) (0.17 mmol, 70 mg), $Pd(OAc)_2$ (0.017 mmol, 1.90 mg), TBAB (0.013 mmol, 4.20 mg) and $NaHCO_3$ (0.42 mmol, 35 mg). The reaction tube was then

evacuated and back-filled with dry argon (this sequence was repeated up to three times). Methyl acrylate (0.42 mmol, 38 μL), and DMF (2.0 mL) were then added under argon atmosphere. The reaction tube was next warmed up to 80 ºC and stirred 12 hours. The resulting mixture was concentrated under reduced pressure and the corresponding product was purified by flash chromatography (hex/EtOAc 7/3) to provide 44 mg (69 % yield) of **71** as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.51 (m, 3H), 7.47-7.39 (m, 4H), 7.37-7.22 (m, 3H), 6.14 (d, J = 16.1 Hz, 1H), 5.77 (s, 2H), 3.78 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 166.1, 148.4, 143.9, 134.4, 131.1, 130.4, 129.5, 129.2, 128.6, 126.9, 126.8, 126.3, 123.6, 123.4, 123.2, 52.8, 52.0, 20.7. IR (neat, cm^{-1}): 1715, 1644, 1176, 908, 726. MS (ESI^+) m/z (%) 378 (M+H). HRMS calcd. for ($C_{21}H_{20}N_3O_4$): 378.1454, found 378.1467.

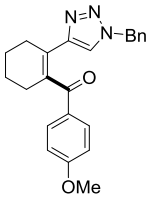


2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenol (72). A reaction tube containing a stirring bar was charged with 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)phenyl acetate **69a** (0.17 mmol, 50 mg) and dissolved in MeOH (4 mL) at 0 ºC. Then Cs_2CO_3 (0.17 mmol, 55 mg) was added and the resulting solution was stirred at room temperature for 5 hours under argon atmosphere. The solvent was partially evaporated under reduce pressure and the resulting solution was washed with aq. NH_4Cl, extracted with CH_2Cl_2 and washed with brine. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hex/EtOAc 9/1) to provide 40 mg (94 % yield) of **72** as a white solid. Mp 142-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.46-7.27 (m, 6H), 7.21 (t, J = 8 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.85 (t, J = 8.0 Hz, 1H), 5.58 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.8, 148.0, 134.0, 129.7, 129.2, 129.0, 128.10, 125.8, 119.4, 118.8, 117.6, 113.8, 54.5. IR (neat, cm^{-1}): 3200, 1210, 690. MS (ESI^+) m/z (%) 252 (M+H). HRMS calcd. for ($C_{15}H_{14}N_3O$): 252.1137, found 252.1149.

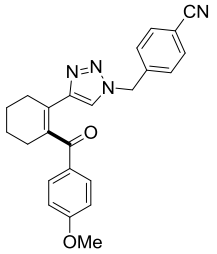
4.5 Pd-catalyzed C(sp^2)-H acylation.



General Procedure: A reaction tube containing a stirring bar was charged with the corresponding triazole (0.25 mmol, 1.00 equiv) and $Pd(TFA)_2$ (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, 1,2-dichloroethane (1.00 mL), acetonitrile (1.00 mL), aldehyde (0.50 mmol, 2.00 equiv) and TBHP (70 wt.% in H_2O, 0.50 mmol, 2.00 equiv.) were then added under argon atmosphere. The reaction tube was next warmed up to 70 ºC and stirred for 24 hours. The mixture was then allowed to warm to room temperature, filtered off through a pad of celite and washed with CH_2Cl_2. The resulting mixture was concentrated under reduced pressure and the corresponding product was purified by flash chromatography (hex/EtOAc 7/3). The yields reported in the thesis refer to isolated yields and represent an average of at least two independent runs.



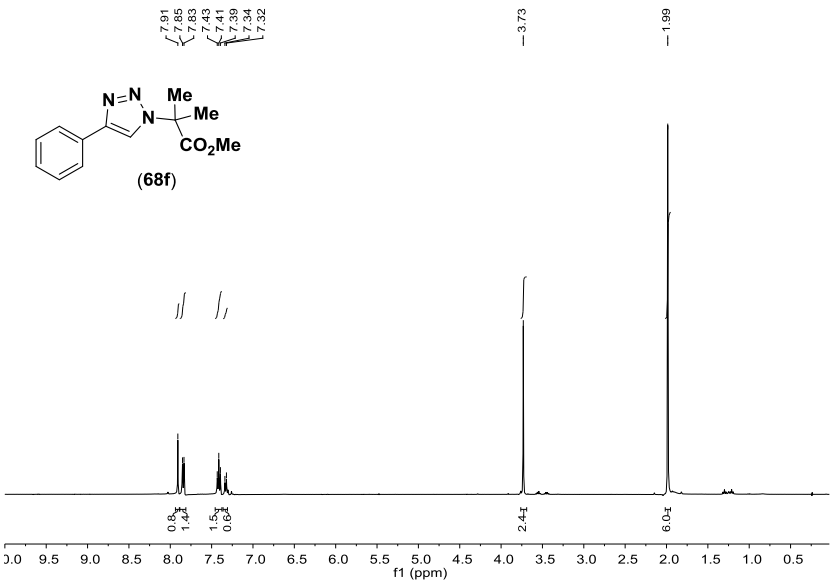
2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)cyclohex-1-en-1-yl)(4-methoxyphenyl)methanone (82). Following the general procedure, using 1-benzyl-4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazole (**80**) (0.25 mmol, 60 mg) and 4-methoxybenzaldehyde (0.5 mmol, 68 mg), provided 43 mg (46 % yield) of **82** as a yellowish solid. Mp 146-149 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.8 Hz, 2H), 7.22 (dt, J = 14.3, 7.0 Hz, 3H), 7.14 (s, 1H), 6.88 (d, J = 7.2 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 5.29 (s, 2H), 3.80 (s, 3H), 2.70 (s, 2H), 2.37 (s, 2H), 1.93-1.73 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 163.6, 146.8, 136.5, 134.7, 131.6, 128.8, 128.3, 127.4, 126.6, 122.1, 113.8, 55.4, 53.6, 28.2, 27.5, 22.2, 21.9. IR (neat, cm^{-1}): 3128, 2939, 2834, 1660, 1596, 1575, 1240, 1165, 1028, 844, 711. MS (ESI$^+$) m/z (%) 374 (M+H). HRMS calcd. for ($C_{23}H_{24}N_3O_2$): 374.1869, found 374.1881.



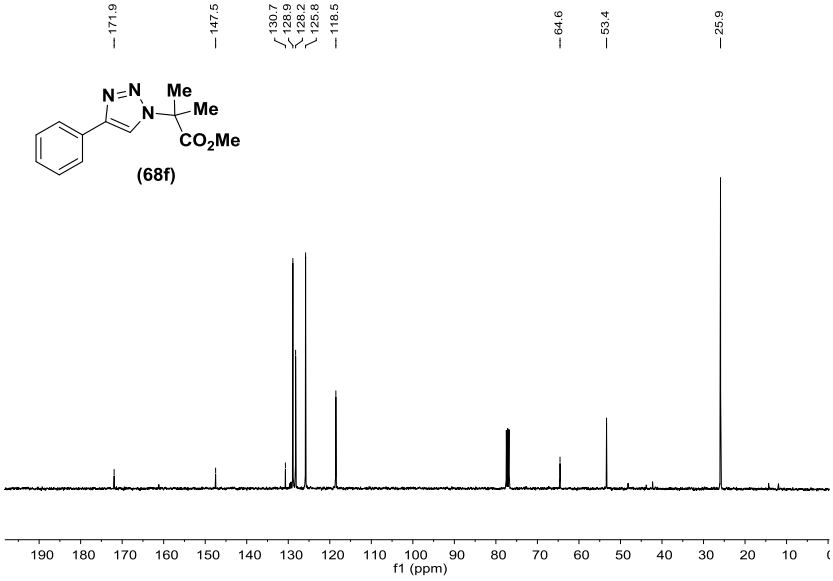
4- [(4-(2-(4- Methoxybenzoyl) cyclohex-1-en-1-yl) -1*H*-1,2,3-triazol-1-yl) methyl] benzonitrile (86b). Following the general procedure, using 4-[(4-(cyclohex-1-en-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl]benzonitrile (0.25 mmol, 66 mg) and 4-methoxybenzaldehyde (0.50 mmol, 68 mg), provided 57 mg (57 % yield) of **86b** as a yellowish solid. Mp 149-151 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.17 (s, 1H), 6.89 (d, J = 8.1 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 5.36 (s, 2H), 3.82 (s, 3H), 2.71 (s, 2H), 2.35 (s, 2H), 1.82 (dq, J = 23.9, 5.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 163.6, 147.3, 140.1, 137.1, 132.7, 131.8, 128.2, 127.7, 126.4, 122.4, 118.3, 113.9, 112.3, 55.6, 53.0, 28.2, 27.5, 22.3, 21.9. IR (neat, cm^{-1}): 2943, 2233, 1747, 1594, 1417, 1171, 1153, 1018, 835, 758. MS (ESI^{+}) m/z (%) 374 (M+H). HRMS calcd. for ($C_{24}H_{23}N_4O_2$): 299.1821, found 399.1819.

Appendix

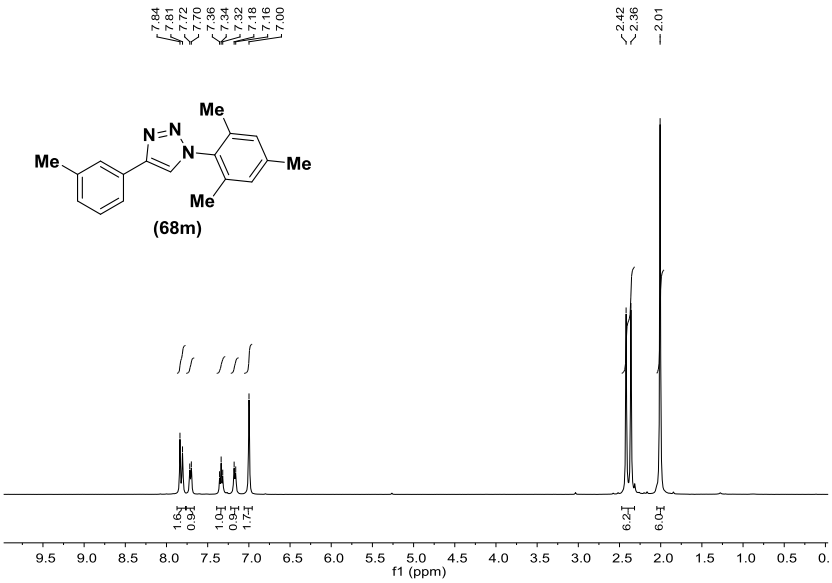
APPENDIX : ^{1}H NMR and ^{13}C NMR Spectra



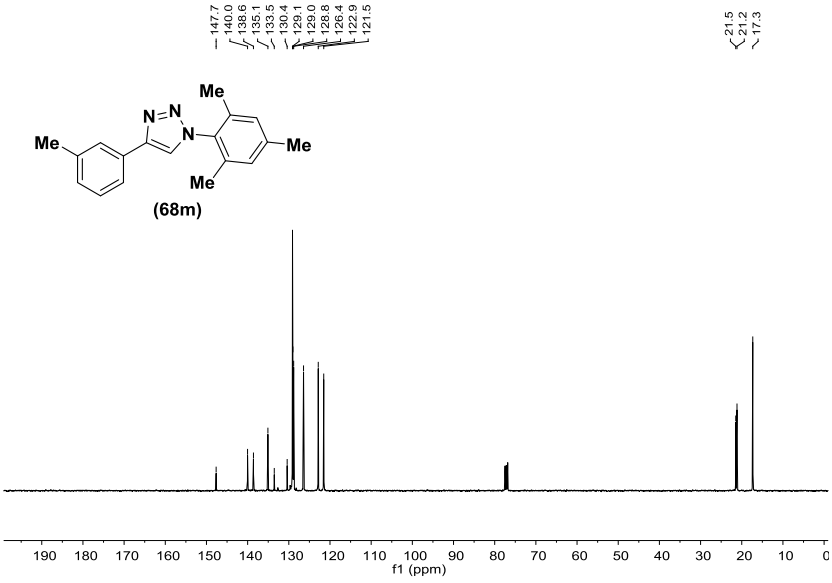
Spectrum 4.1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68f**.



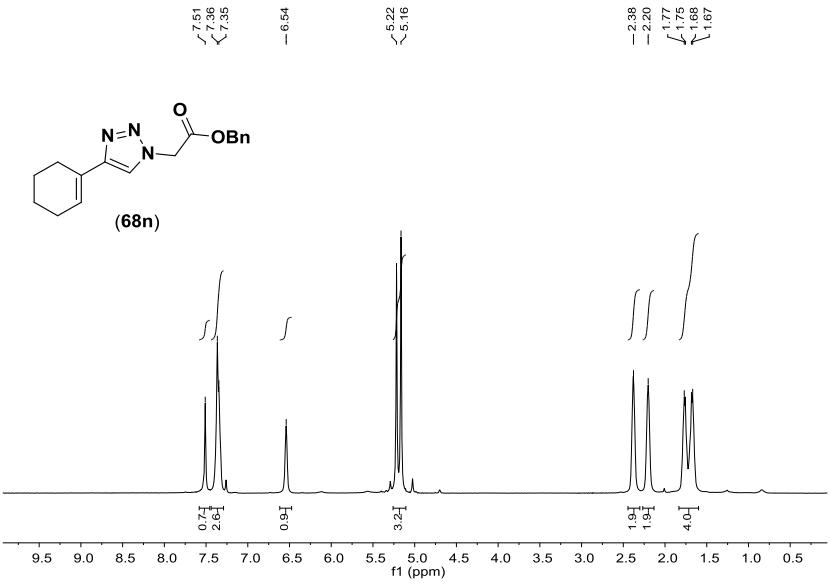
Spectrum 4.2. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68f**.



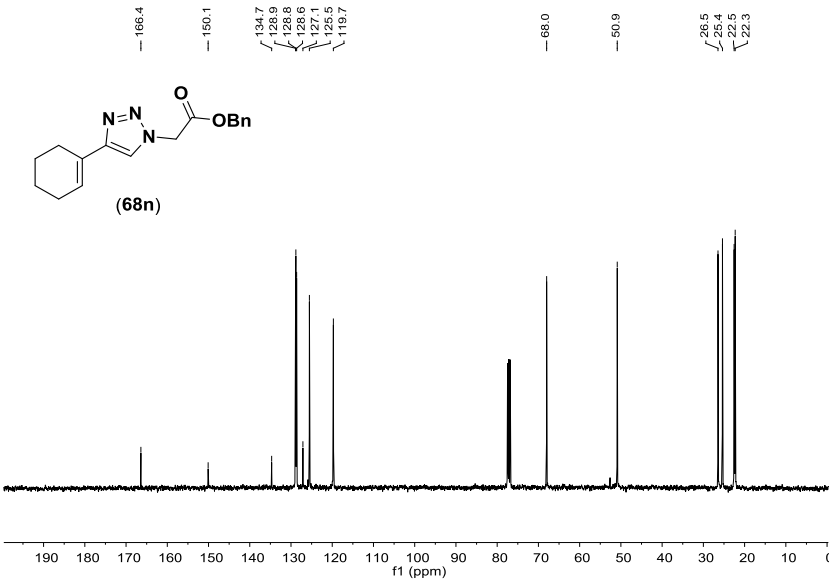
Spectrum 4.3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68m**.



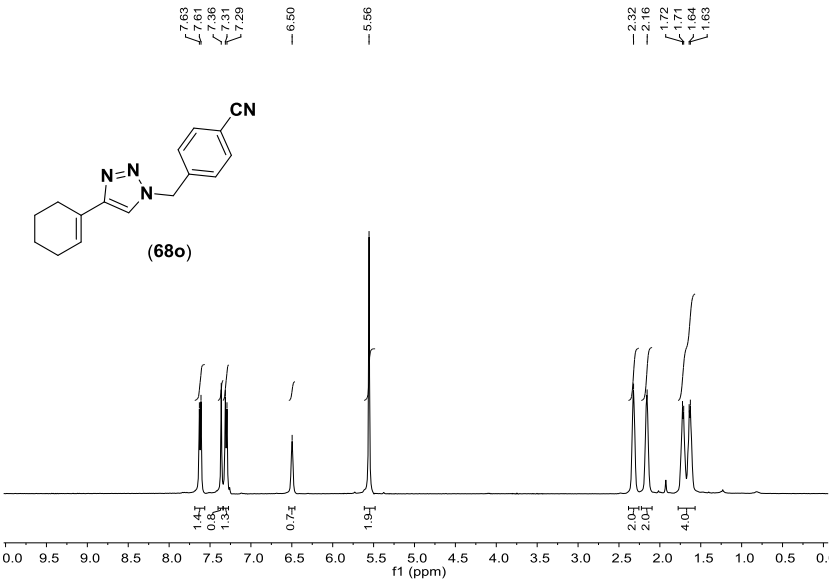
Spectrum 4.4. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68m**.



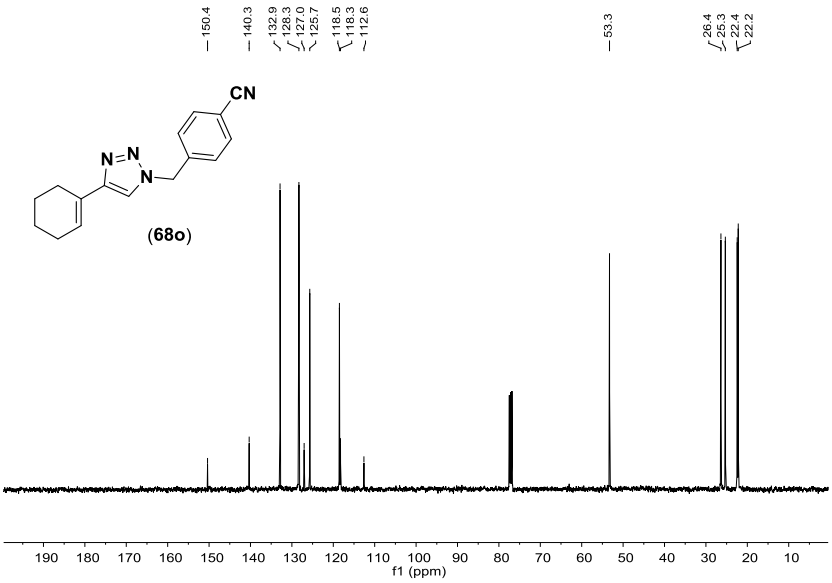
Spectrum 4.5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68n**.



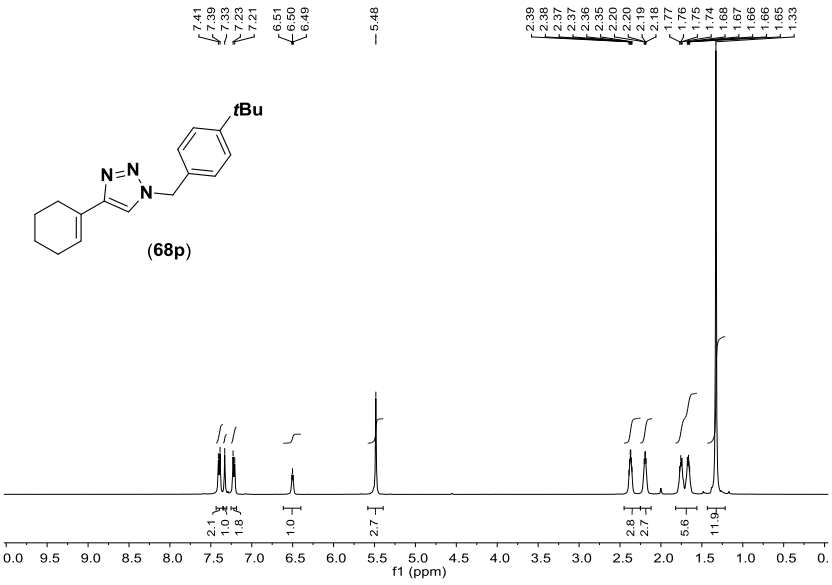
Spectrum 4.6. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68n**.



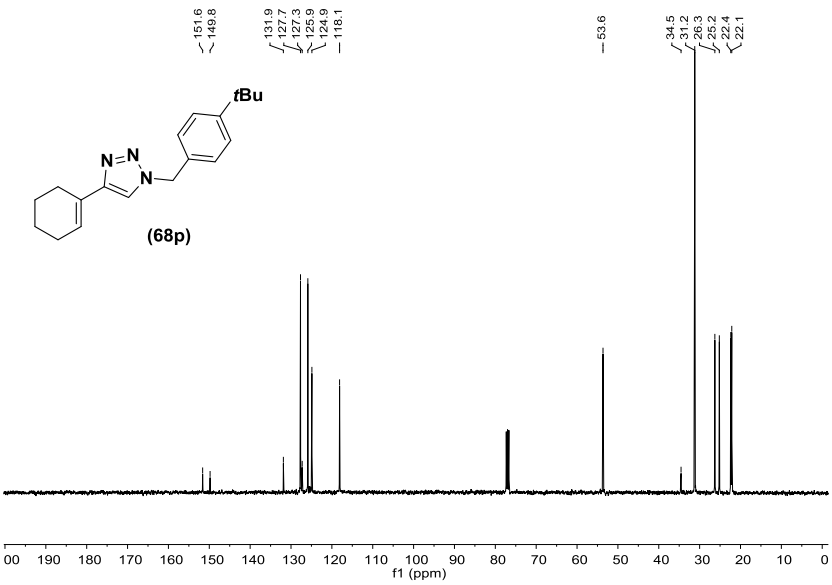
Spectrum 4.7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68o**.



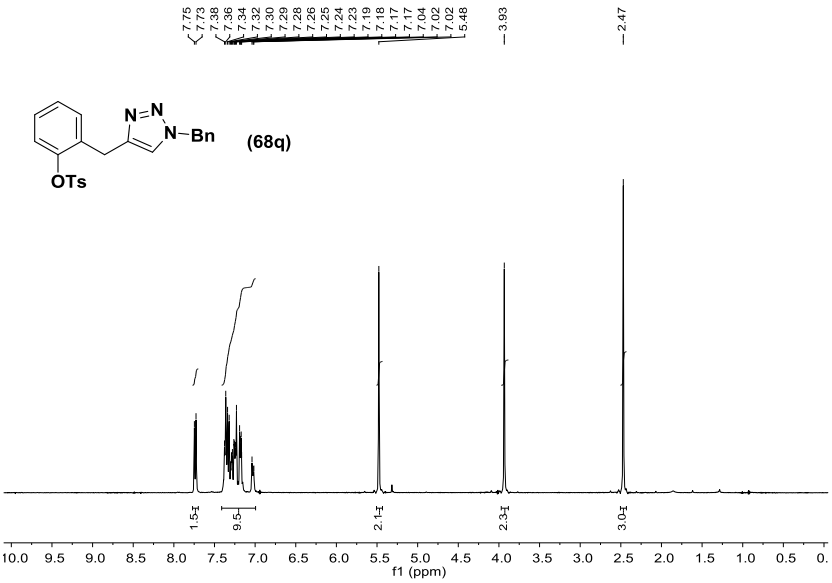
Spectrum 4.8. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68o**.



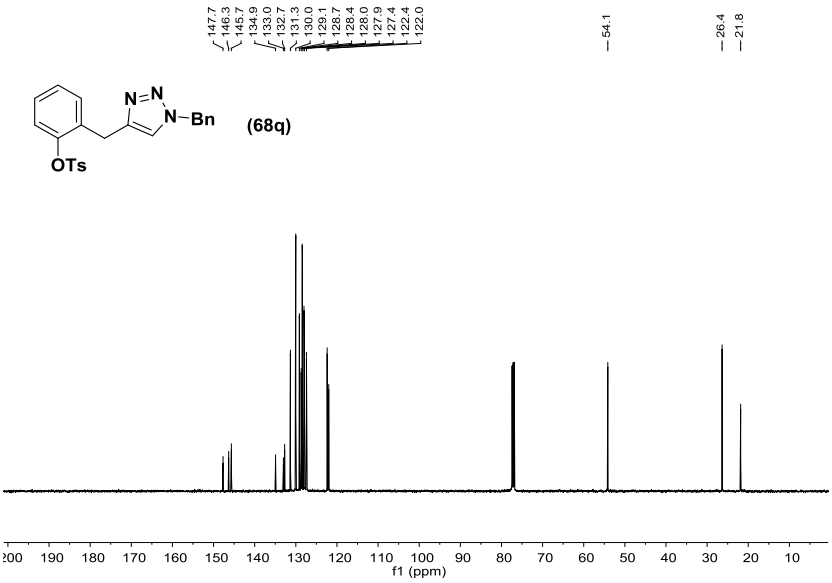
Spectrum 4.9. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68p**.



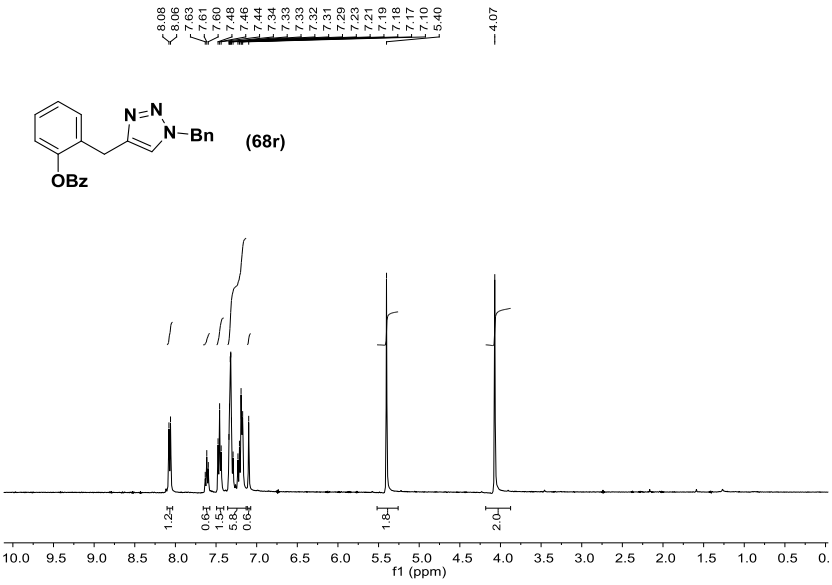
Spectrum 4.10. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68p**.



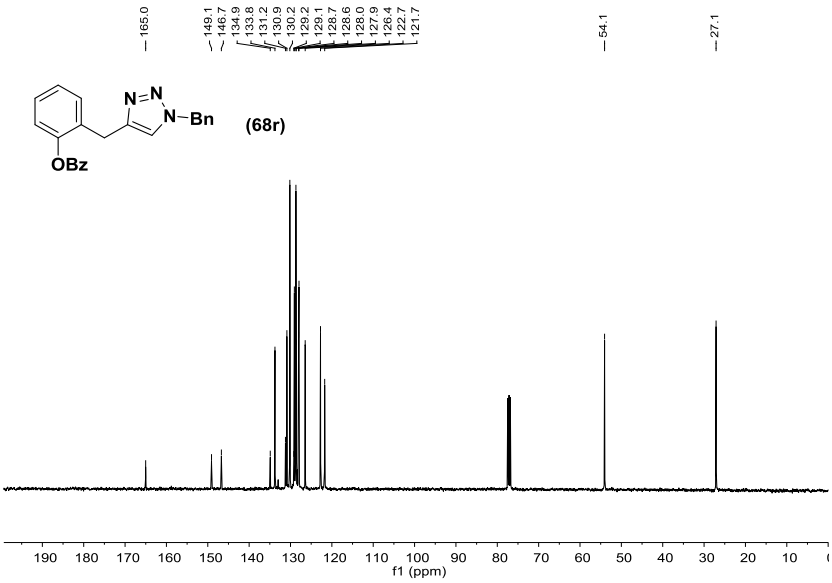
Spectrum 4.11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68q**.



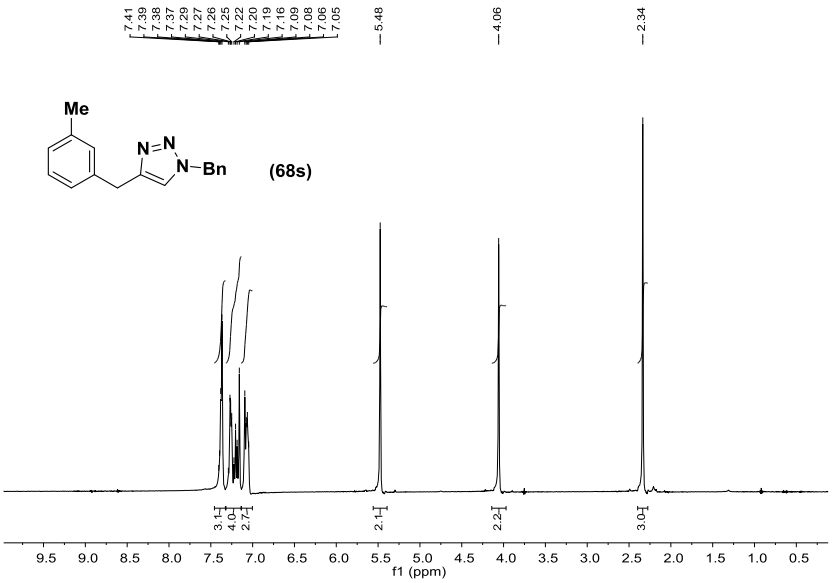
Spectrum 4.12. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68q**.



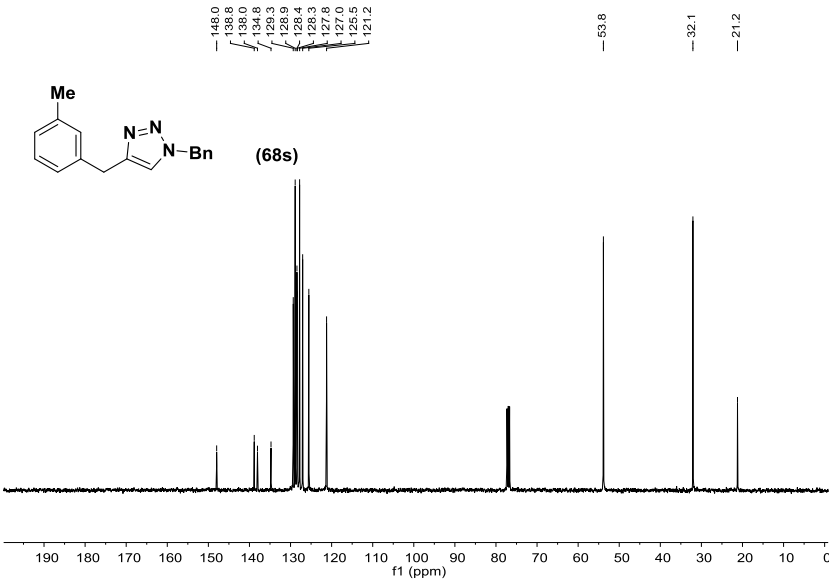
Spectrum 4.13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68r**.



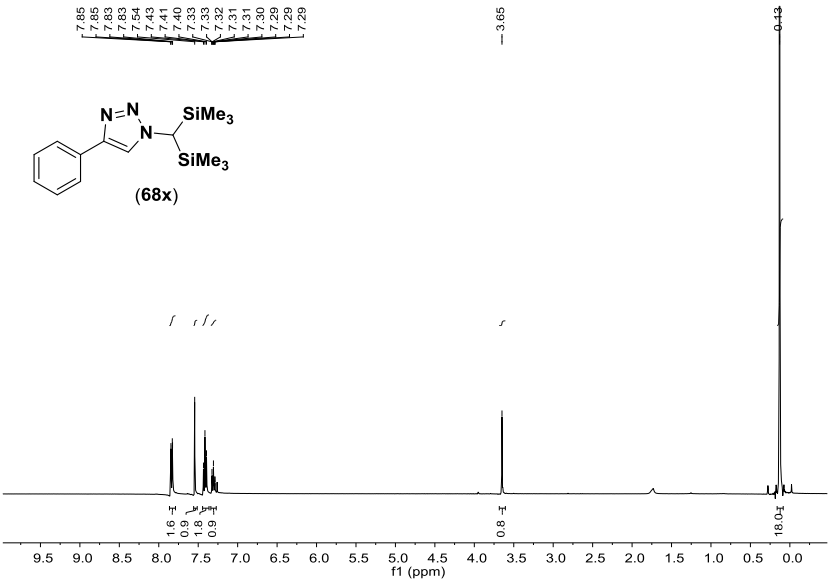
Spectrum 4.14. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68r**.



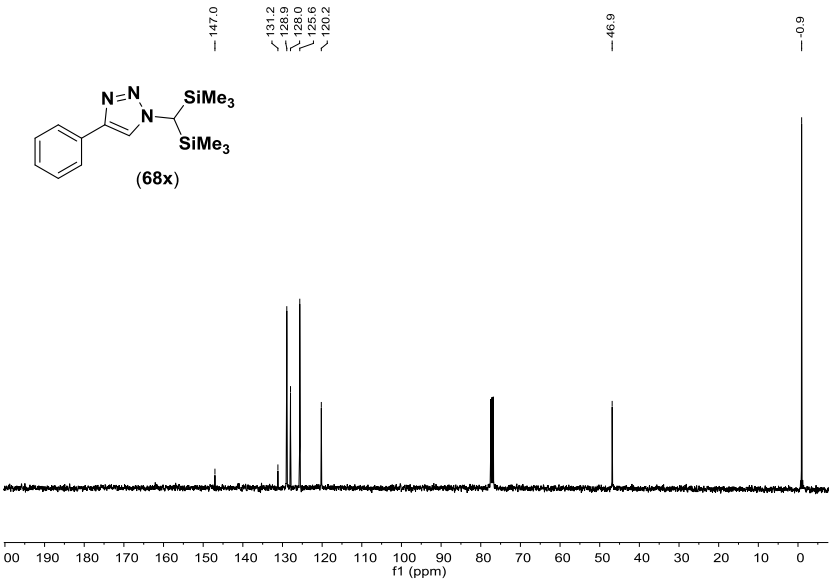
Spectrum 4.15. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68s**.



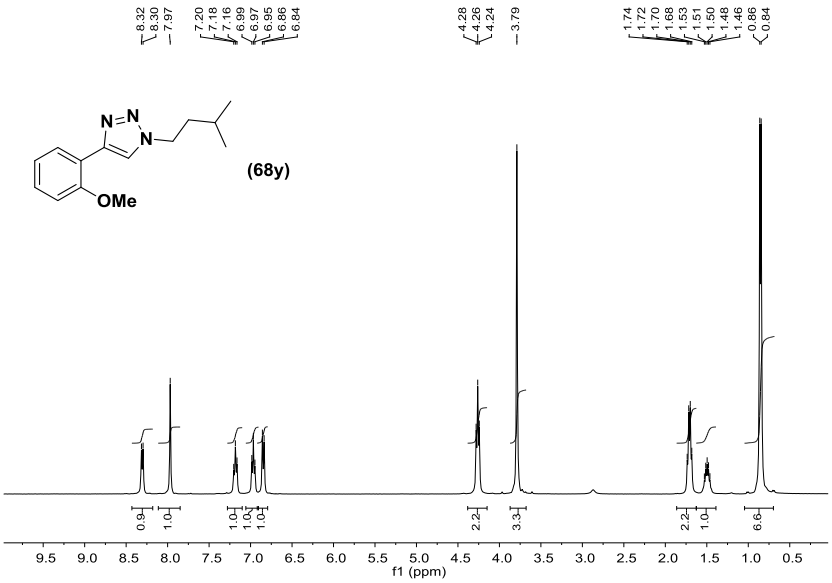
Spectrum 4.16. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68s**.



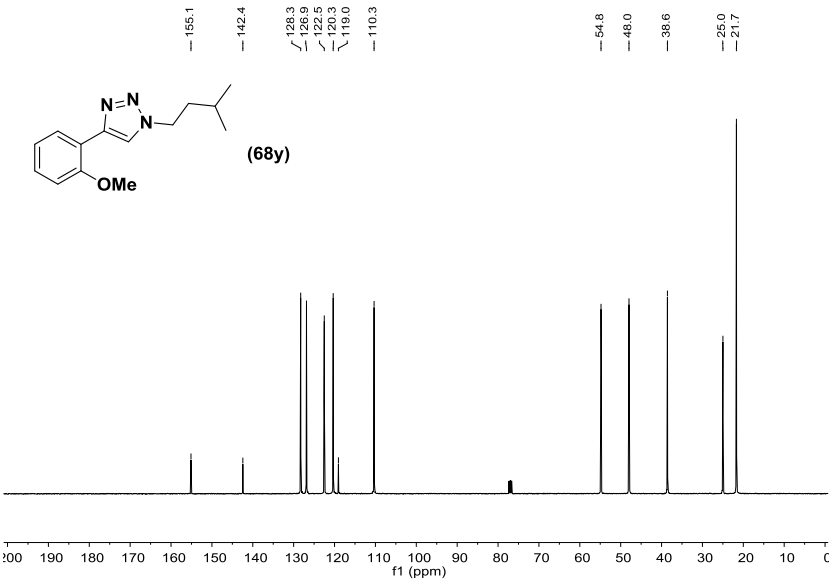
Spectrum 4.17. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68x**.



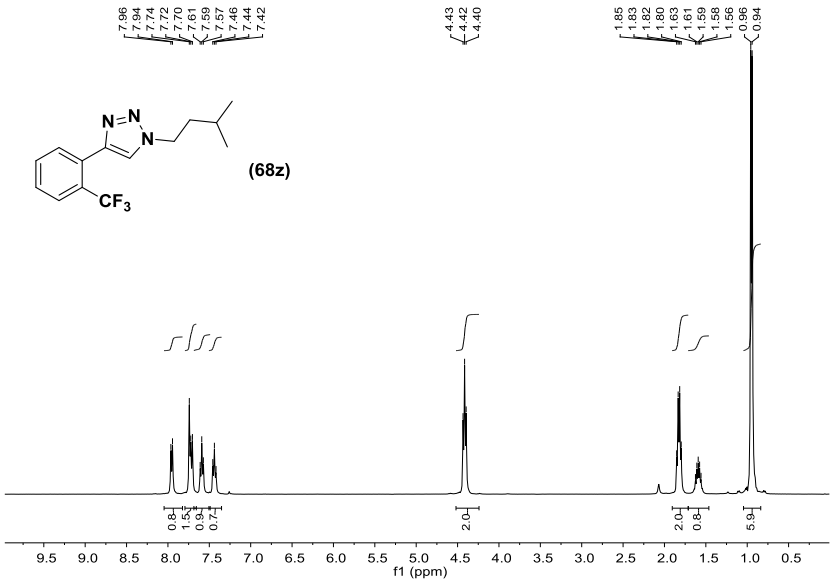
Spectrum 4.18. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68x**.



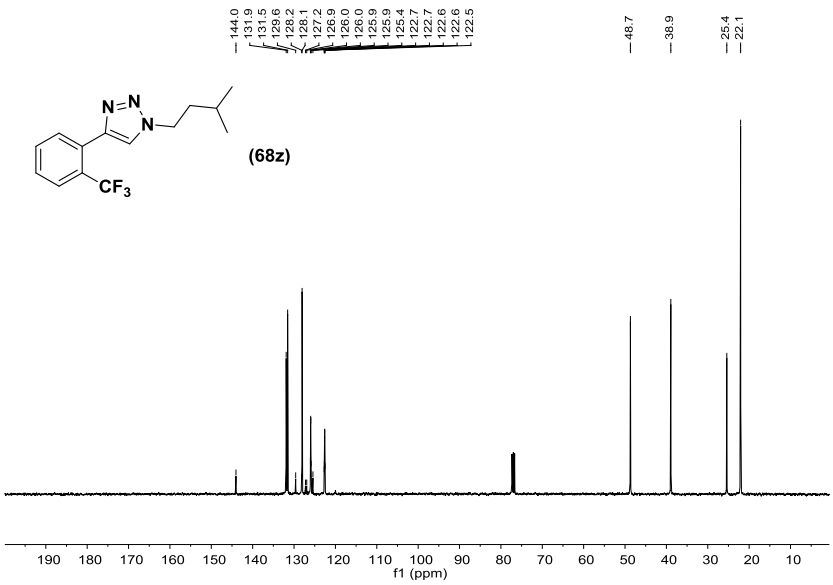
Spectrum 4.19. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68y**.



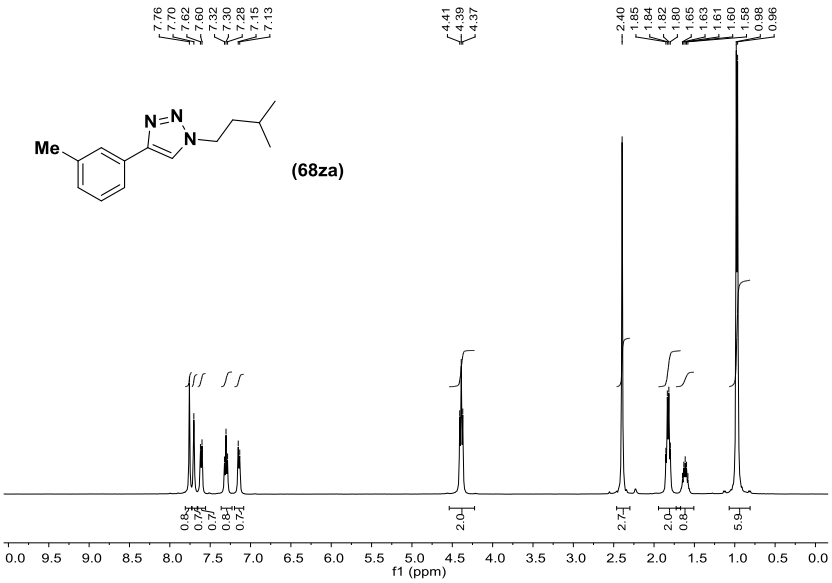
Spectrum 4.20. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68y**.



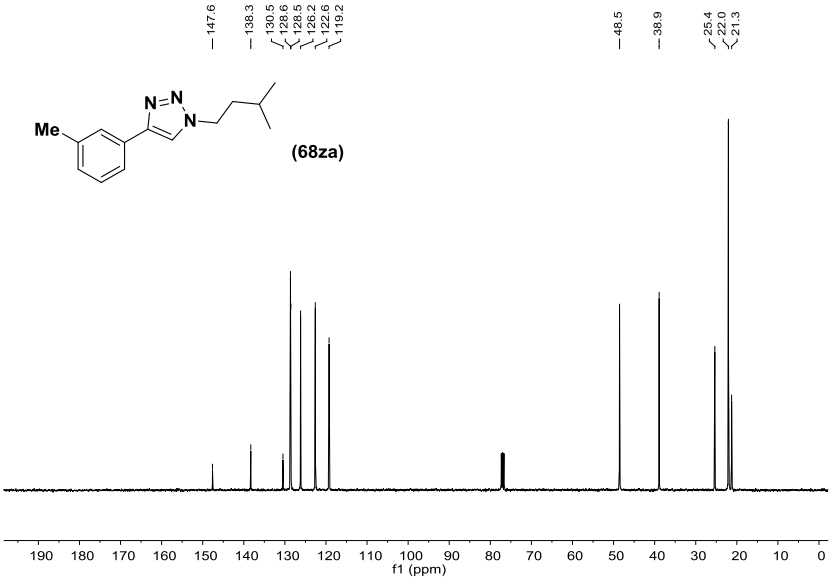
Spectrum 4.21. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68z**.



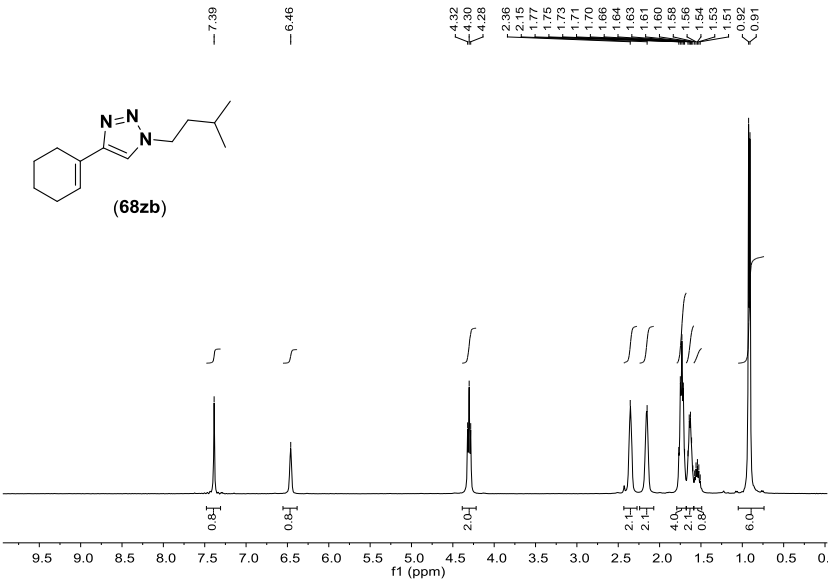
Spectrum 4.22. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68z**.



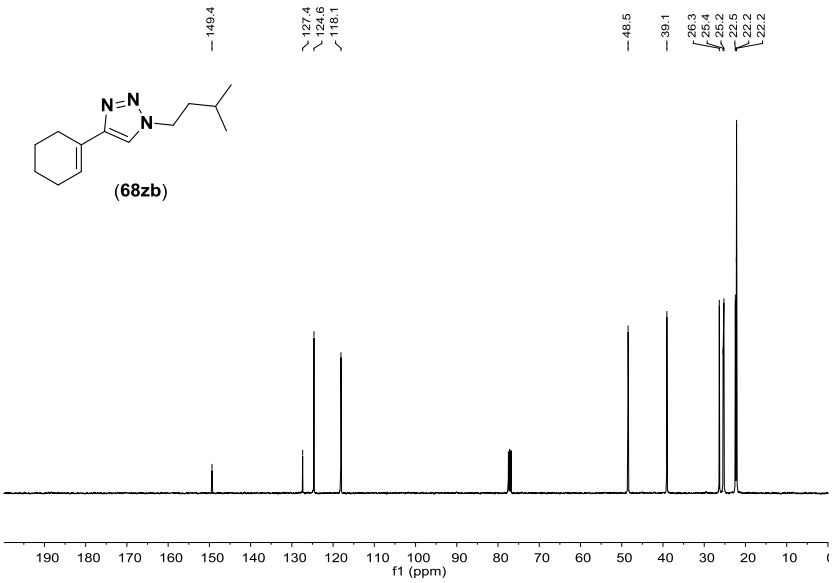
Spectrum 4.23. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68za**.



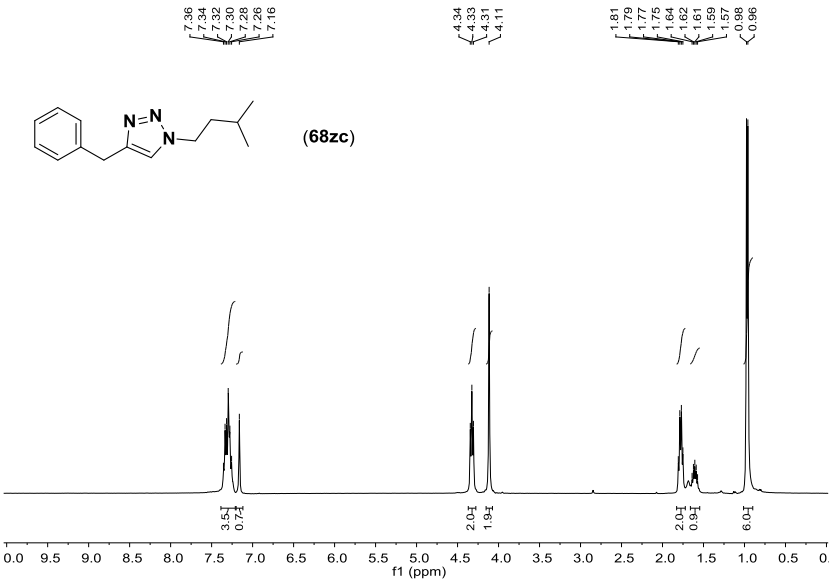
Spectrum 4.24. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68za**.



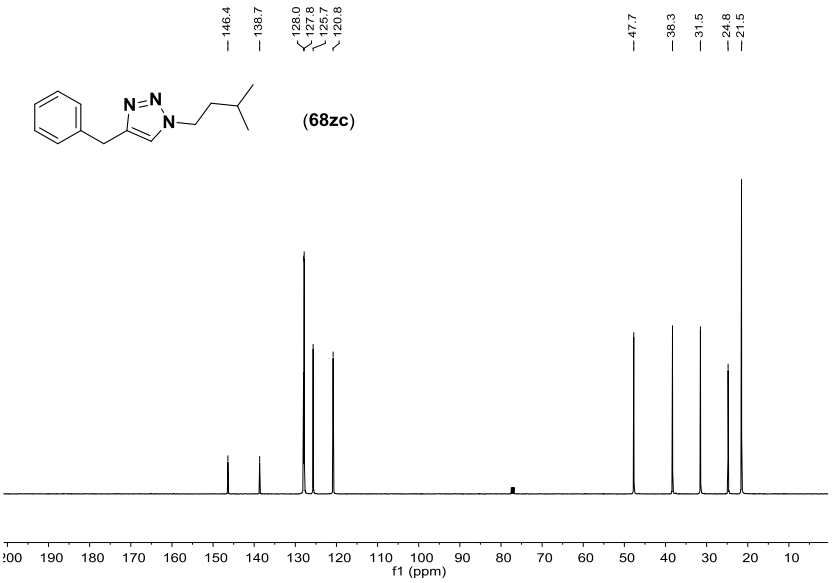
Spectrum 4.25. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68zb**.



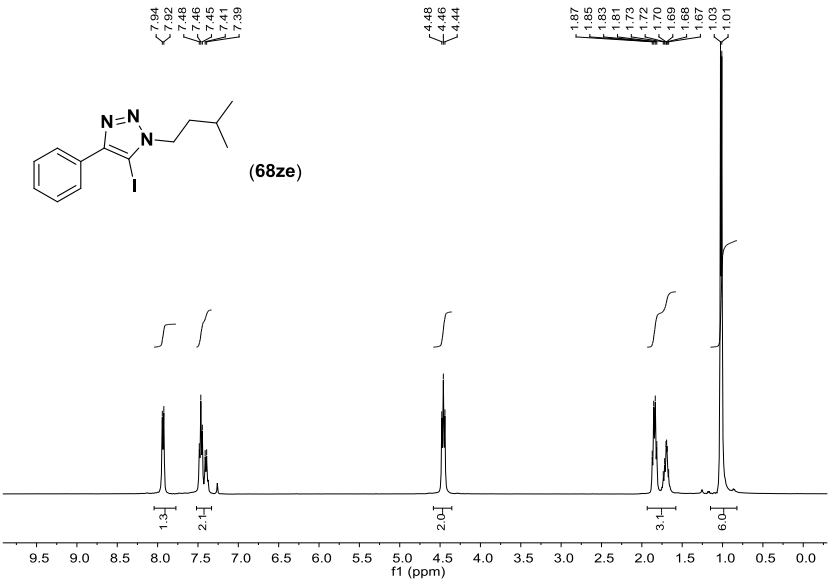
Spectrum 4.26. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68zb**.



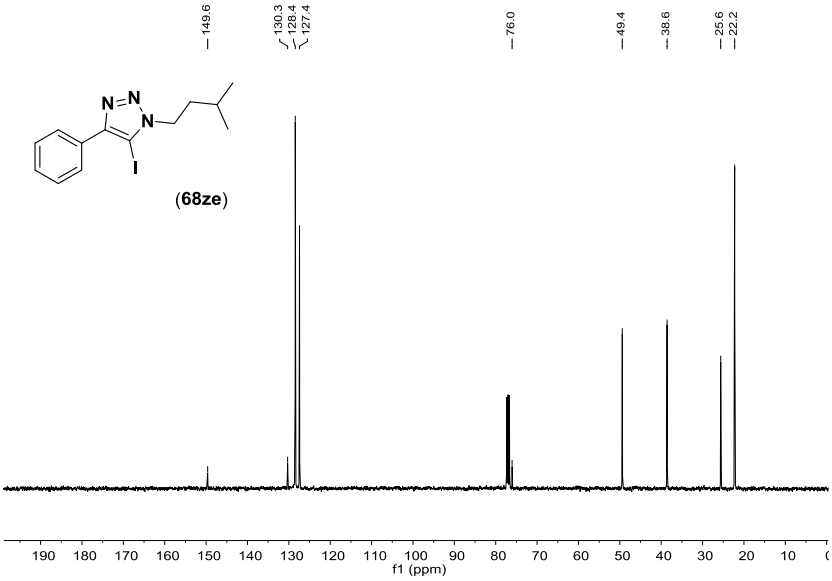
Spectrum 4.27. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68zc**.



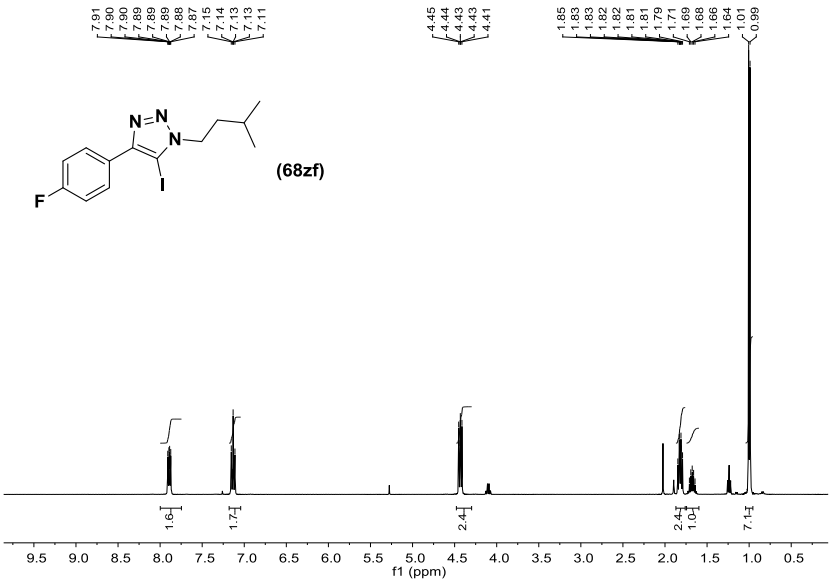
Spectrum 4.28. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68zc**.



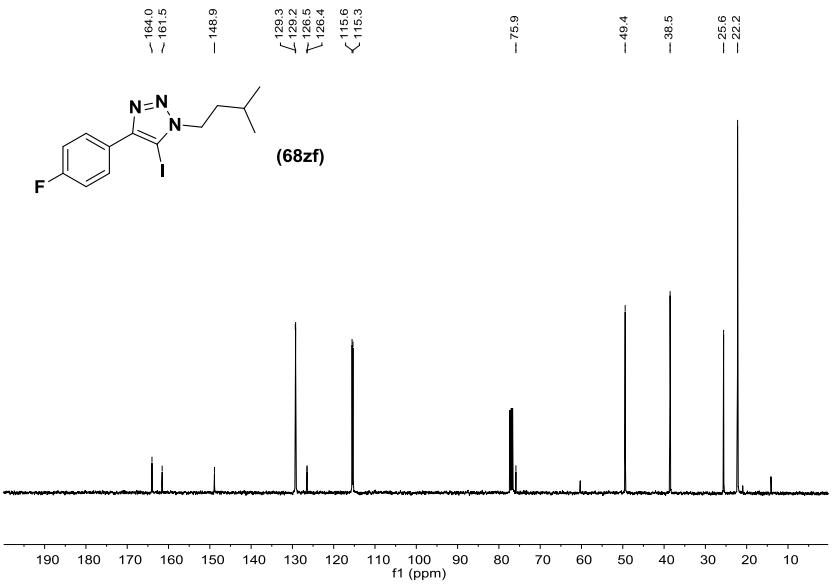
Spectrum 4.29. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68ze**.



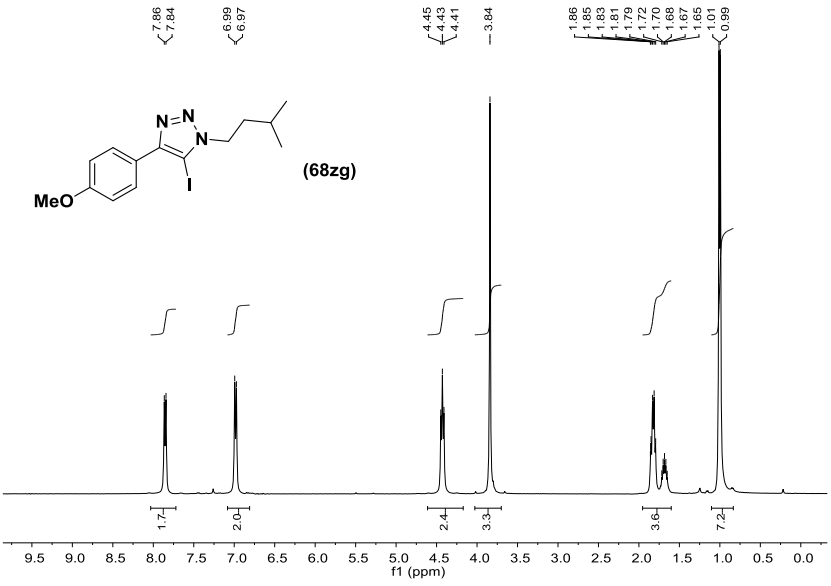
Spectrum 4.30. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68ze**.



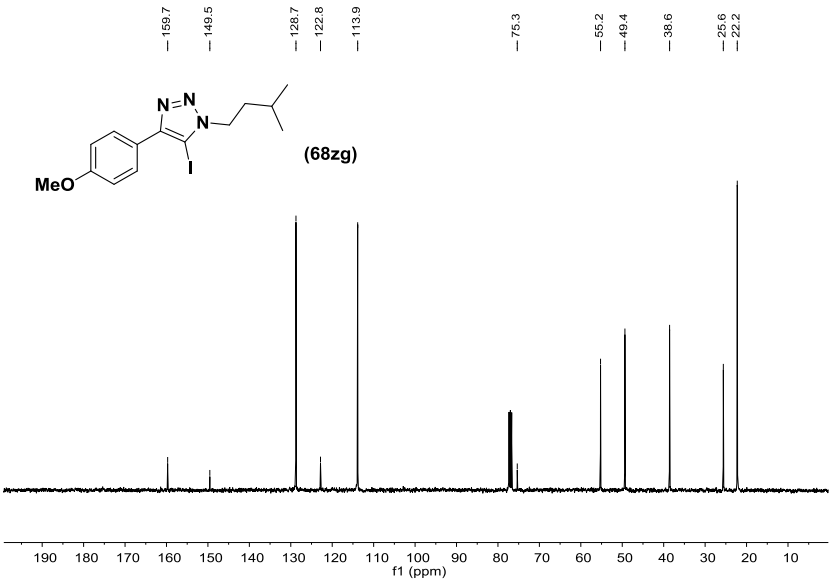
Spectrum 4.31. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68zf**.



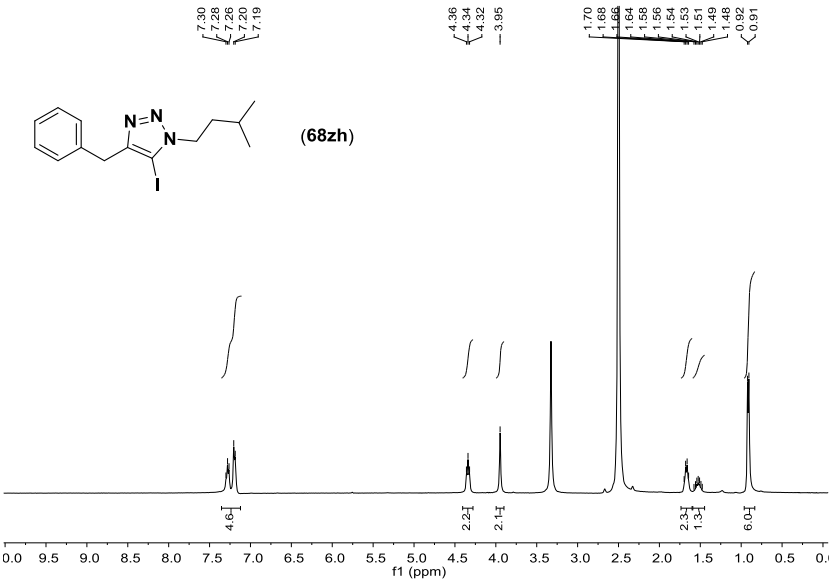
Spectrum 4.32. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68zf**.



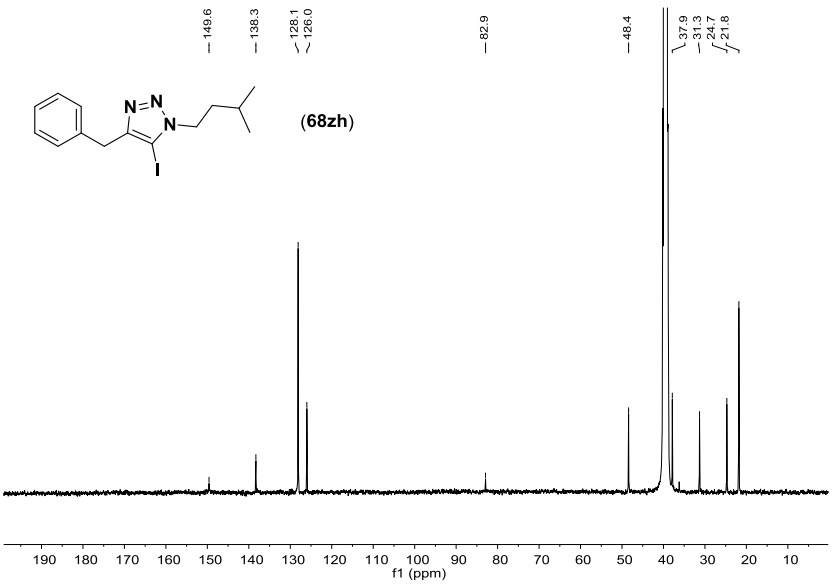
Spectrum 4.33. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68zg**.



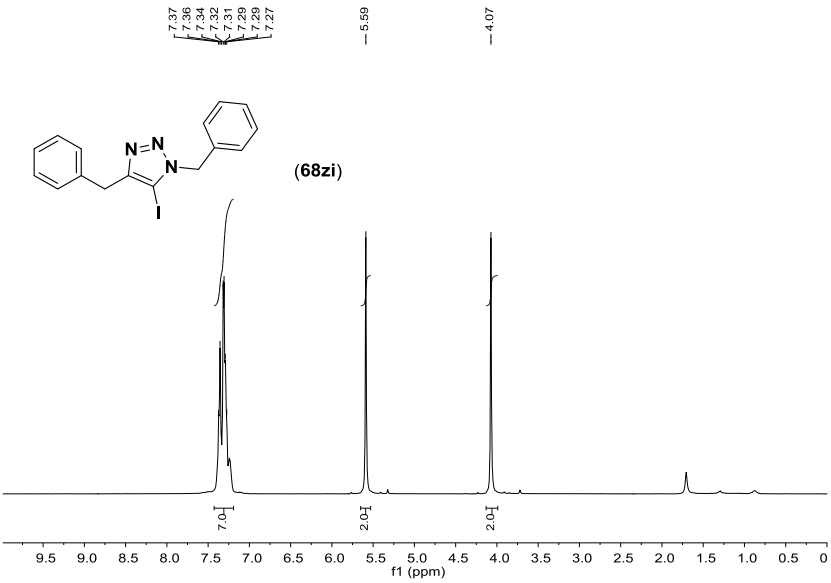
Spectrum 4.34. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68zg**.



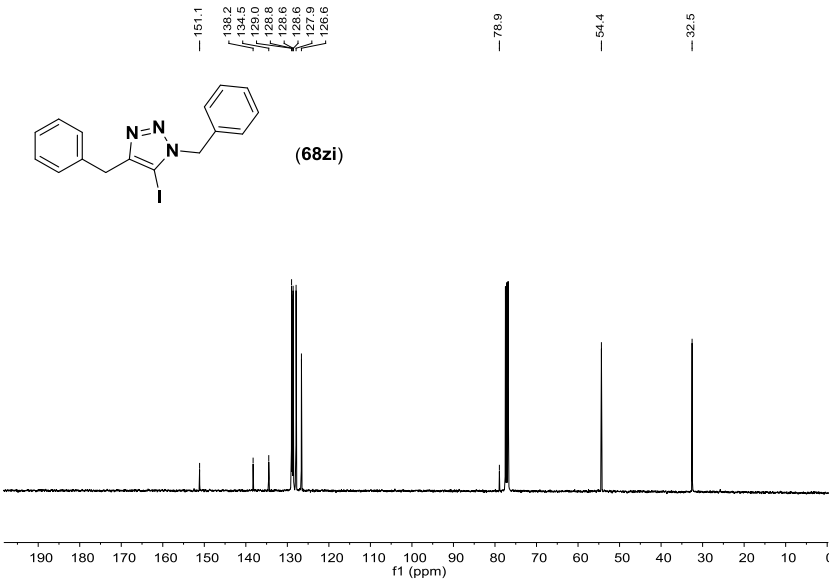
Spectrum 4.35. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **68zh**.



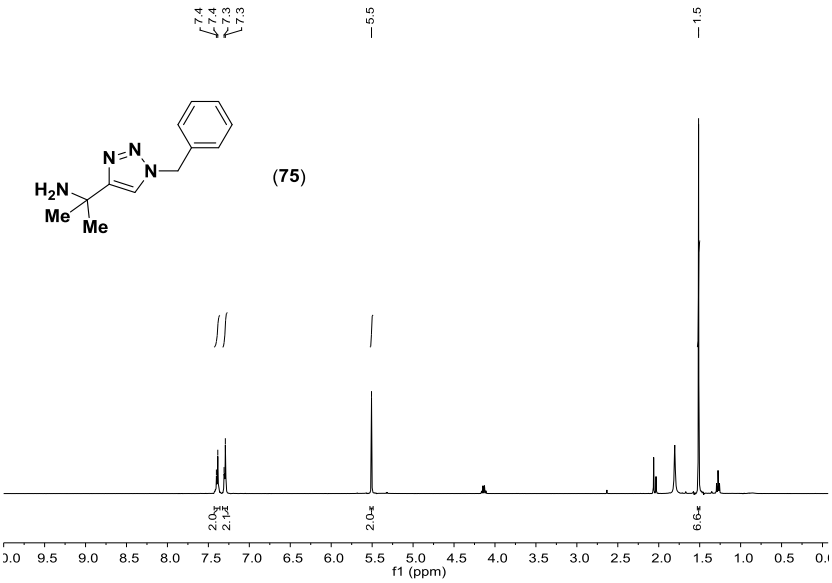
Spectrum 4.36. ^{13}C NMR (101 MHz, DMSO-d_6) spectrum of compound **68zh**.



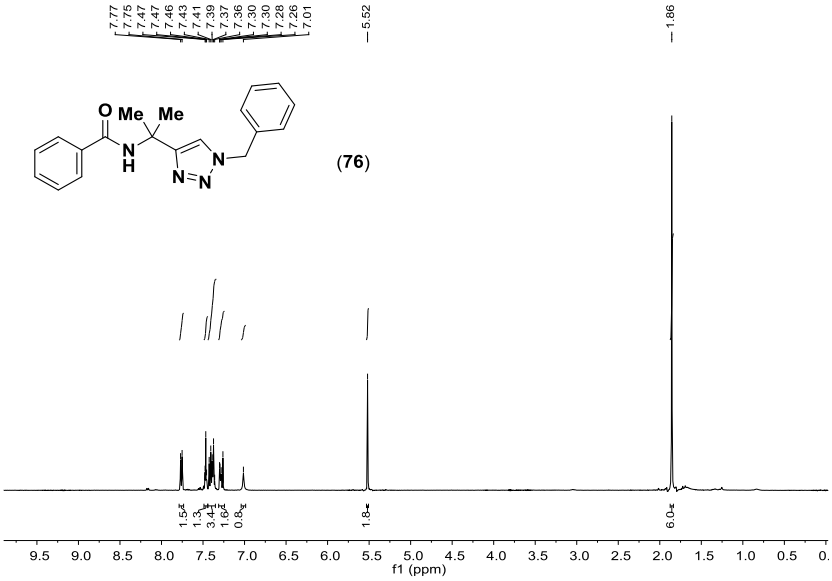
Spectrum 4.37. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68zi**.



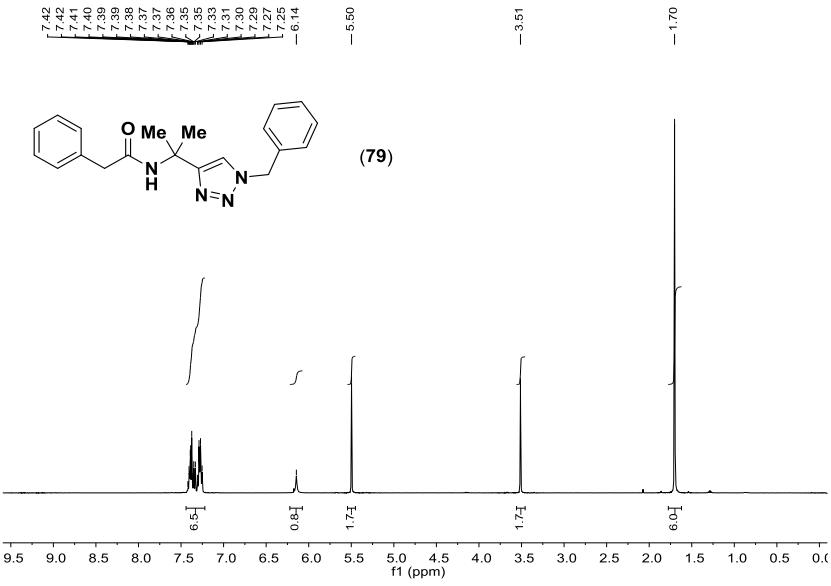
Spectrum 4.38. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **68zi**.



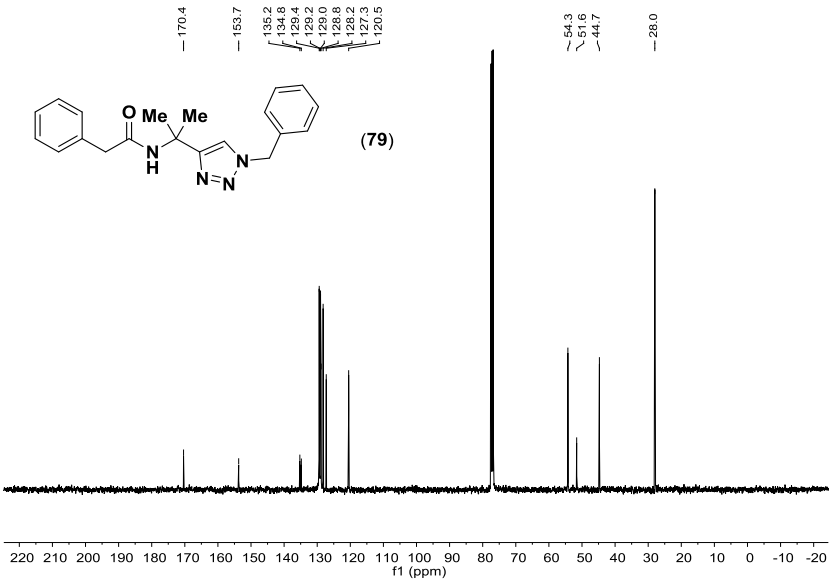
Spectrum 4.39. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **75**.



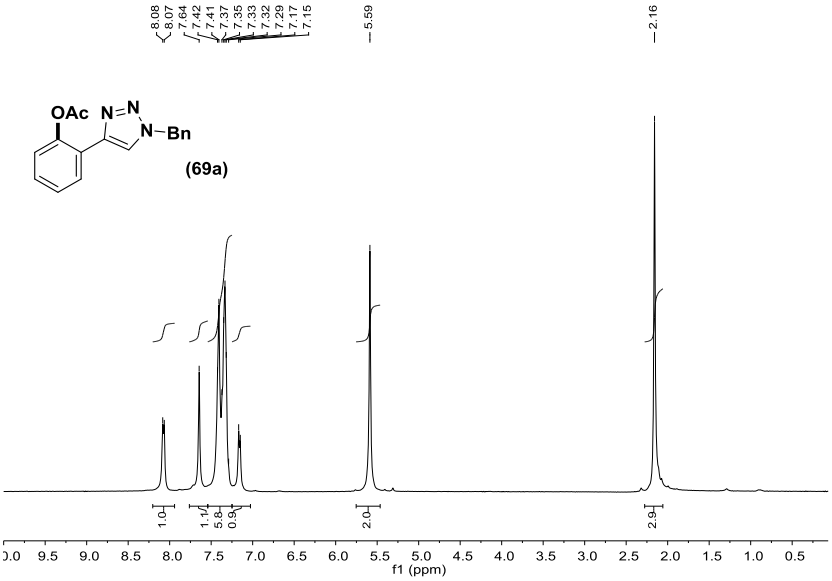
Spectrum 4.40. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **76**.



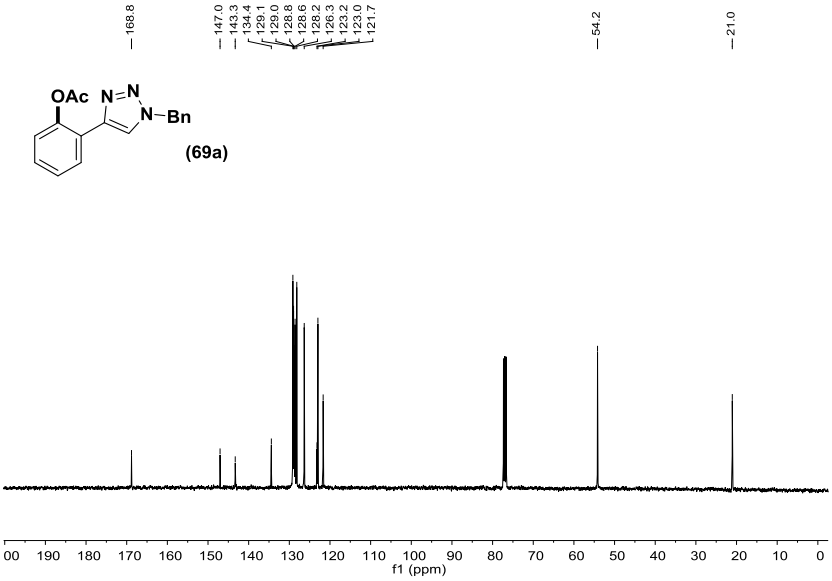
Spectrum 4.41. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **79**.



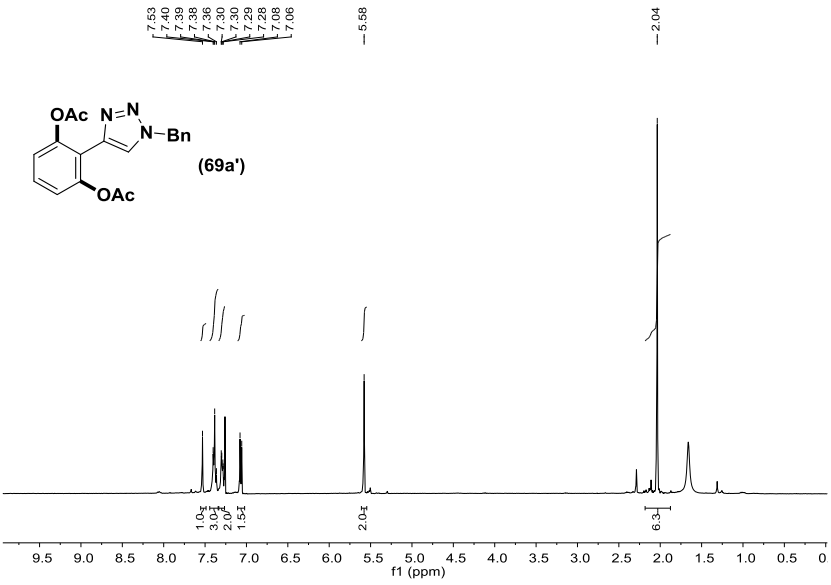
Spectrum 4.42. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **79**.



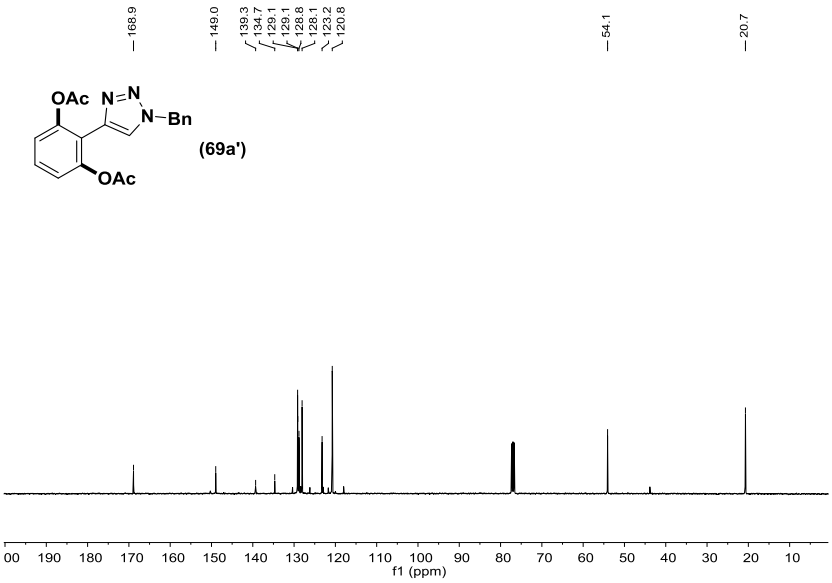
Spectrum 4.43. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69a**.



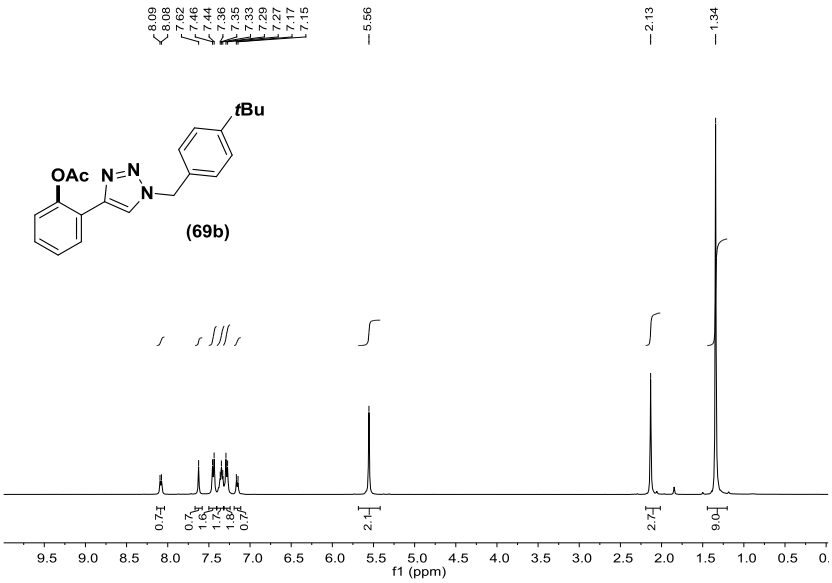
Spectrum 4.44. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69a**.



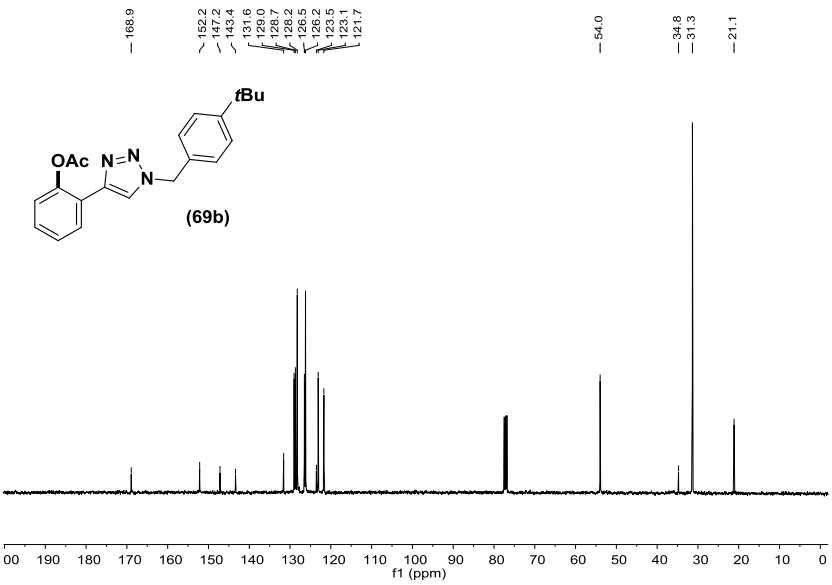
Spectrum 4.45. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69a'**.



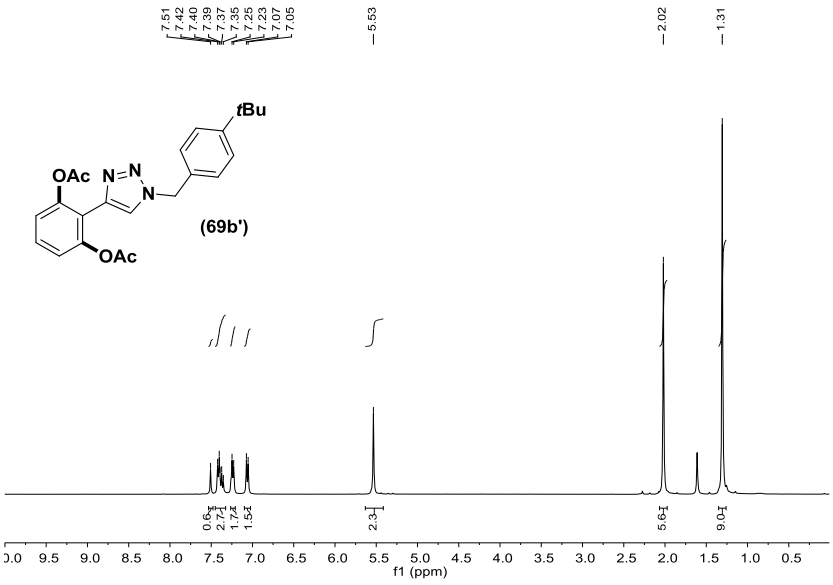
Spectrum 4.46. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69a'**.



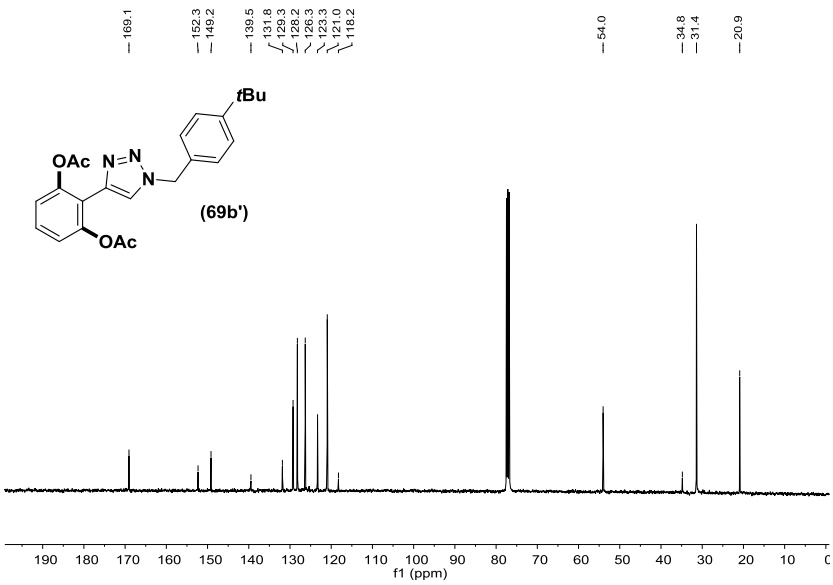
Spectrum 4.47. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69b**.



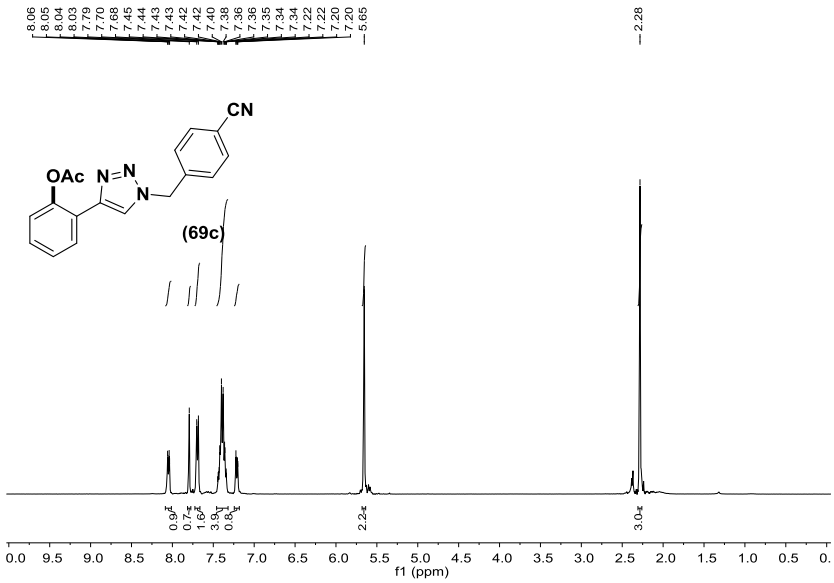
Spectrum 4.48. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69b**.



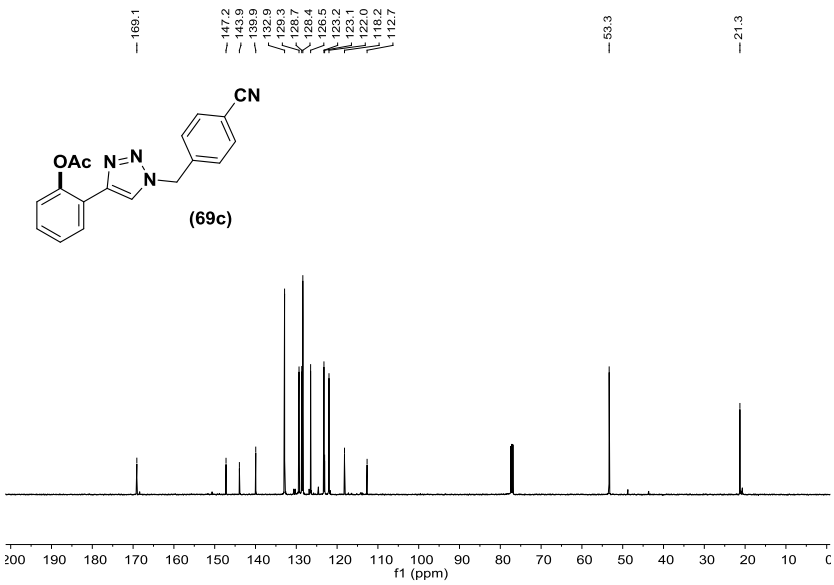
Spectrum 4.49. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69b'**.



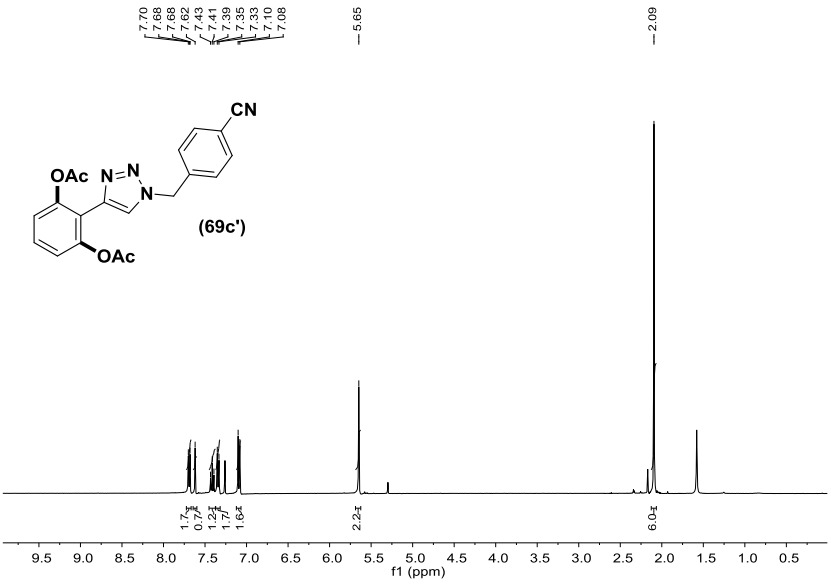
Spectrum 4.50. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69b'**.



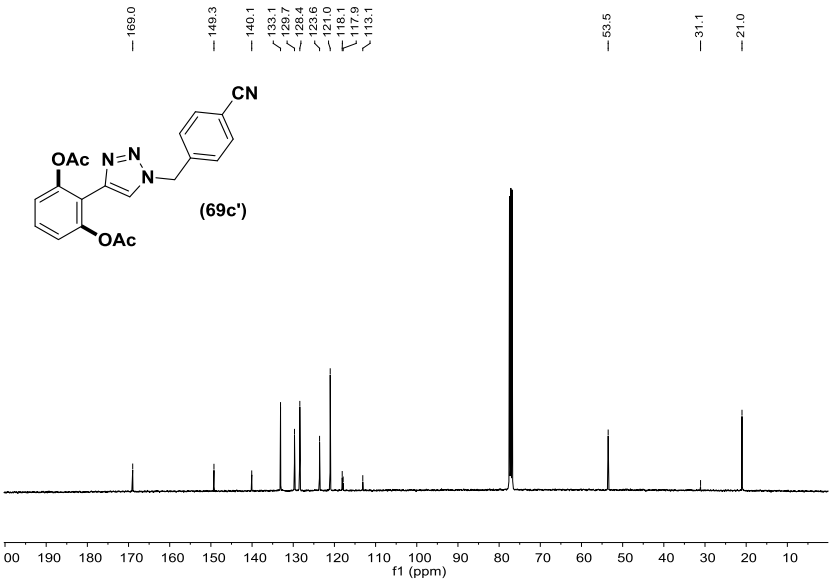
Spectrum 4.51. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69c**.



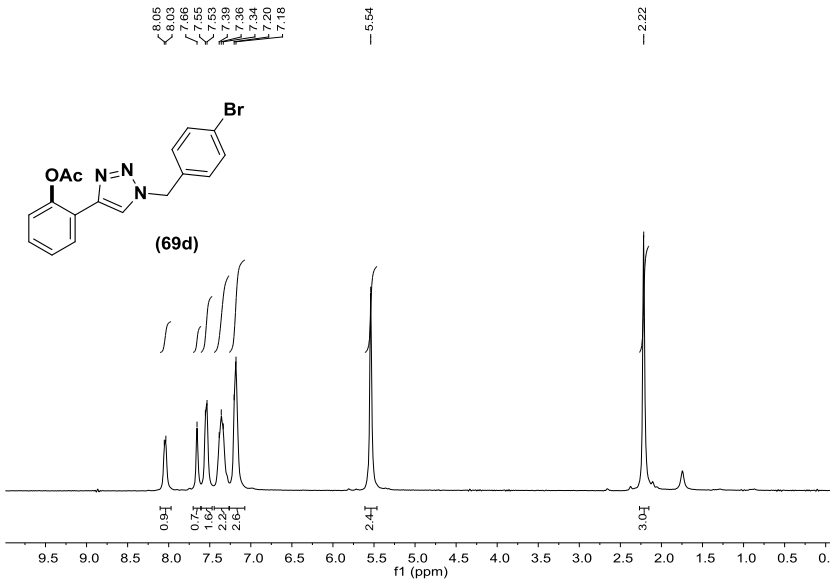
Spectrum 4.52. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69c**.



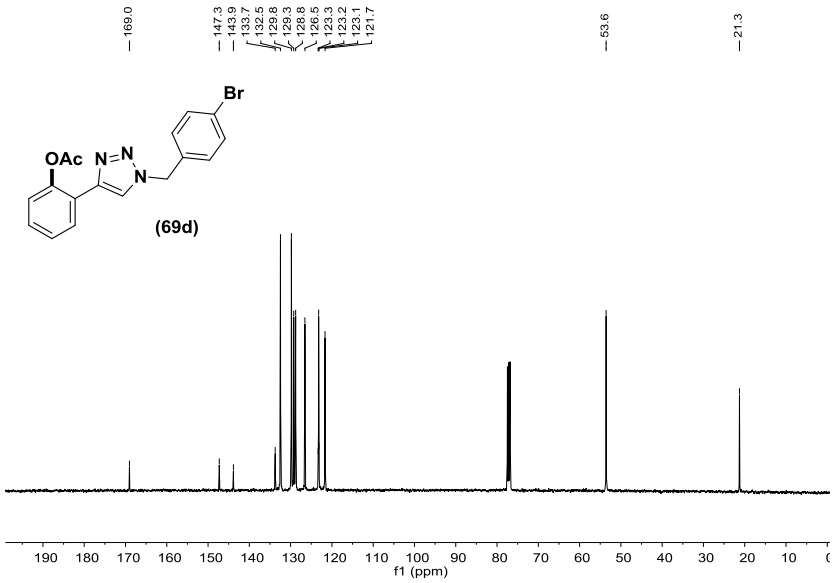
Spectrum 4.53. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69c'**.



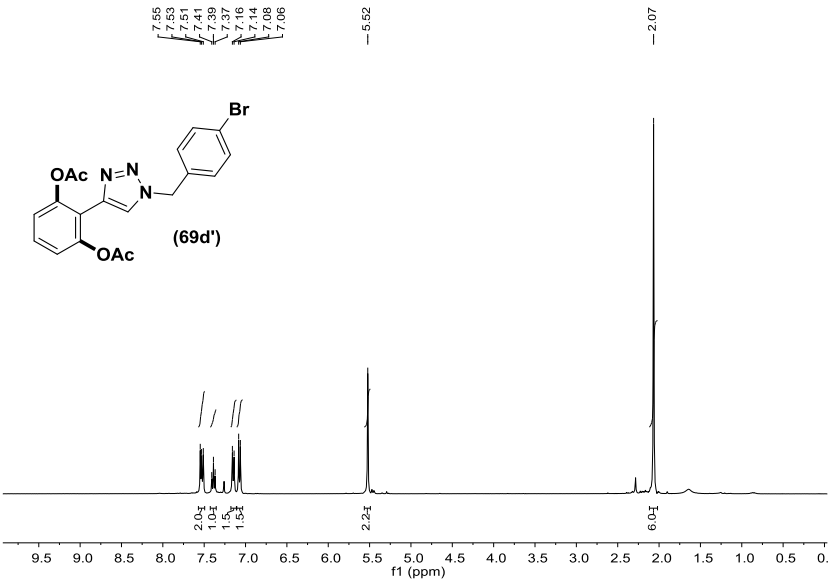
Spectrum 4.54. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69c'**.



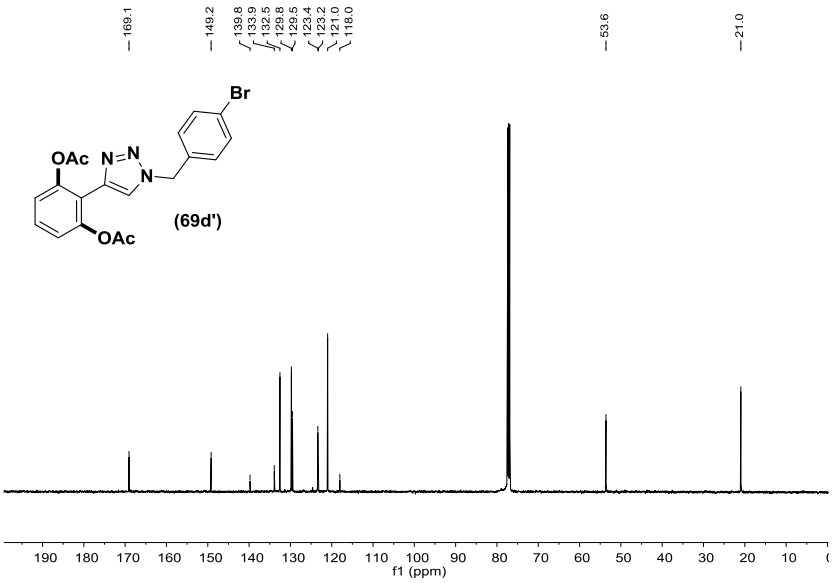
Spectrum 4.55. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69d**.



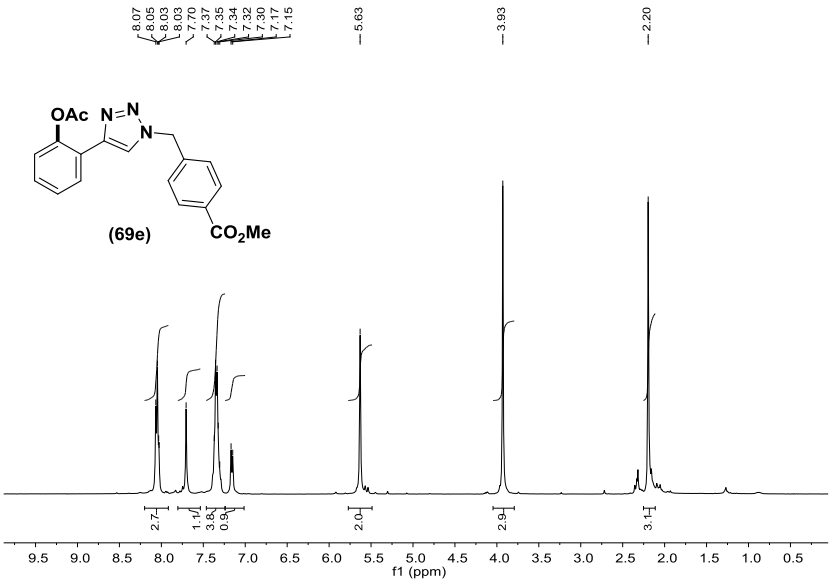
Spectrum 4.56. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69d**.



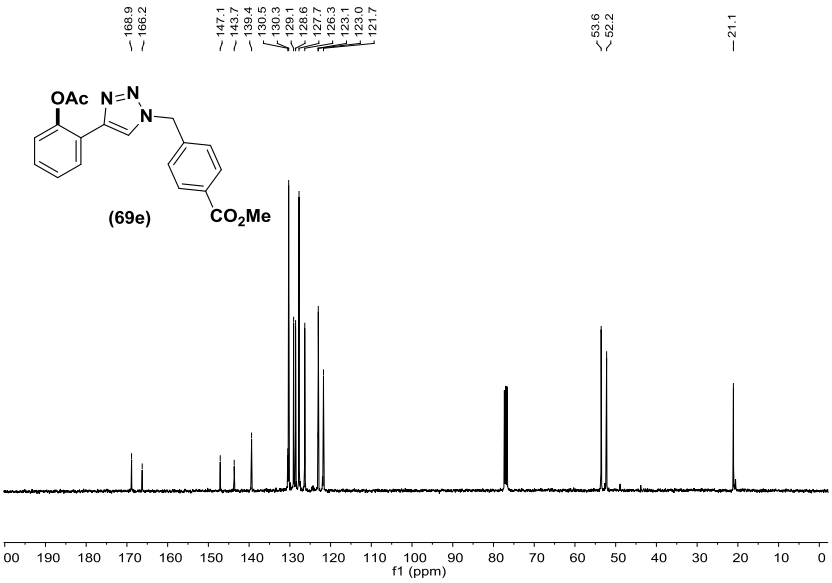
Spectrum 4.57. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69d'**.



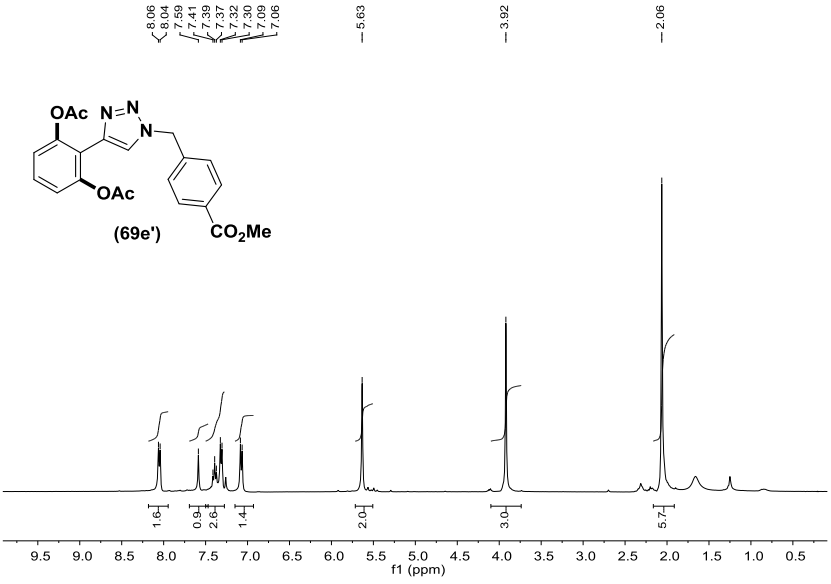
Spectrum 4.58. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69d'**.



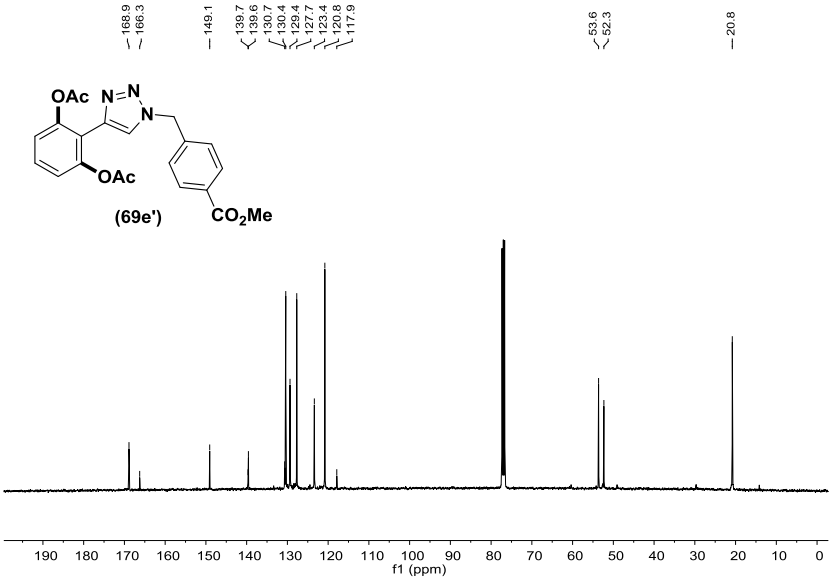
Spectrum 4.59. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69e**.



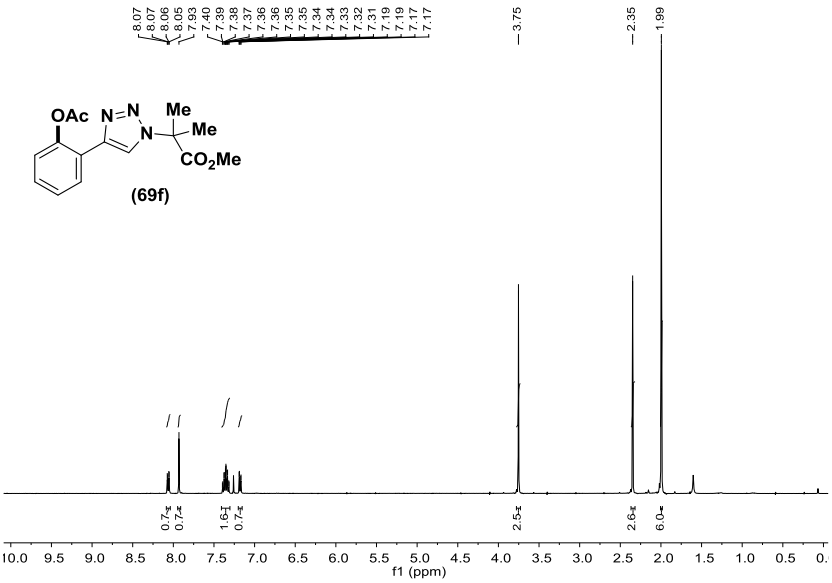
Spectrum 4.60. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69e**.



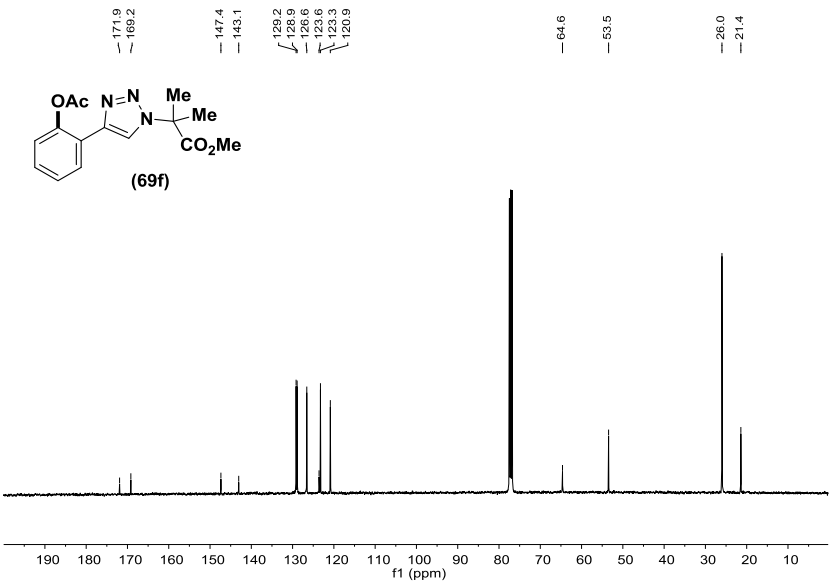
Spectrum 4.61. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69e'**.



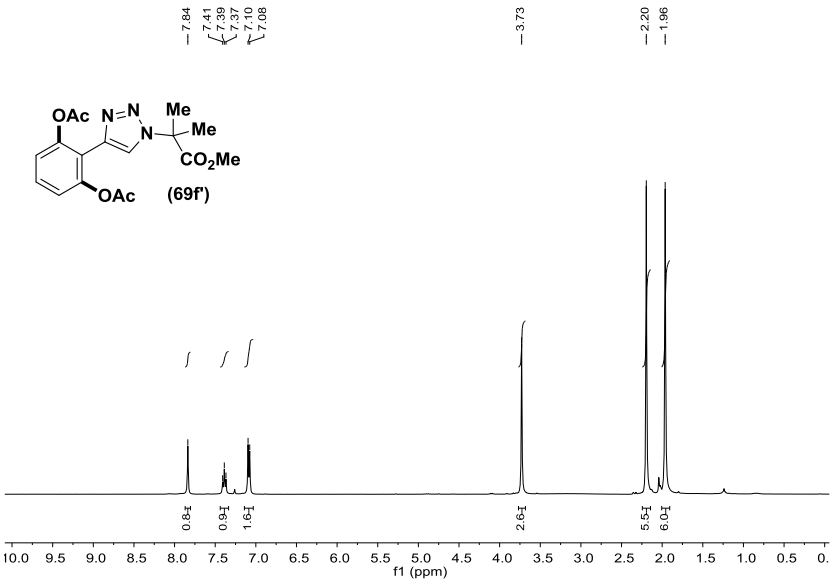
Spectrum 4.62. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69e'**.



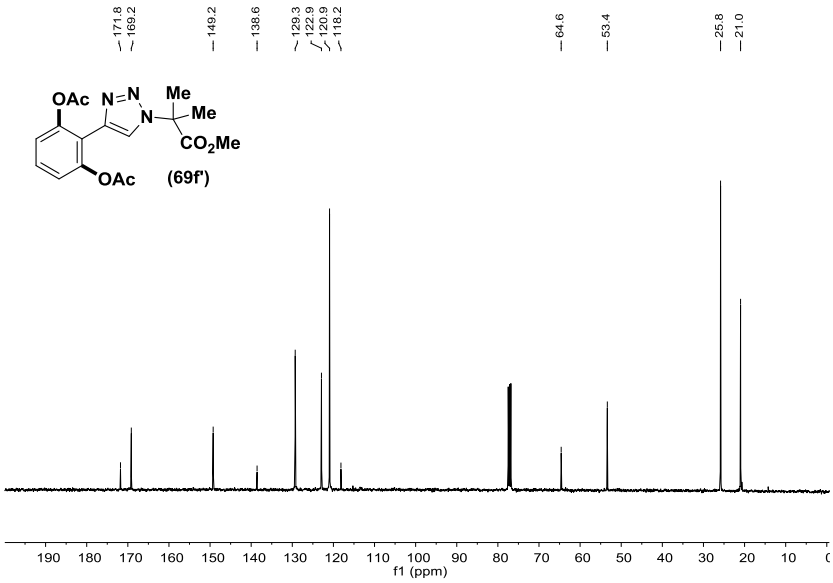
Spectrum 4.63. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69f**.



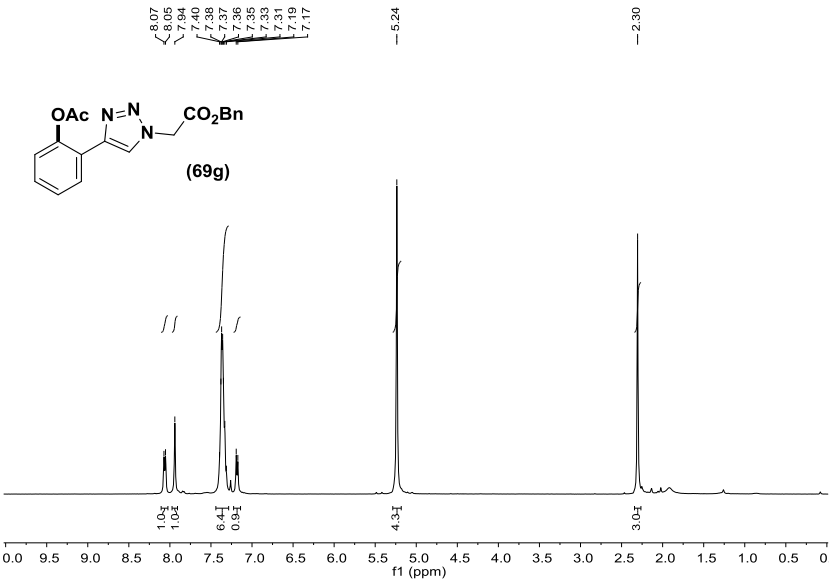
Spectrum 4.64. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69f**.



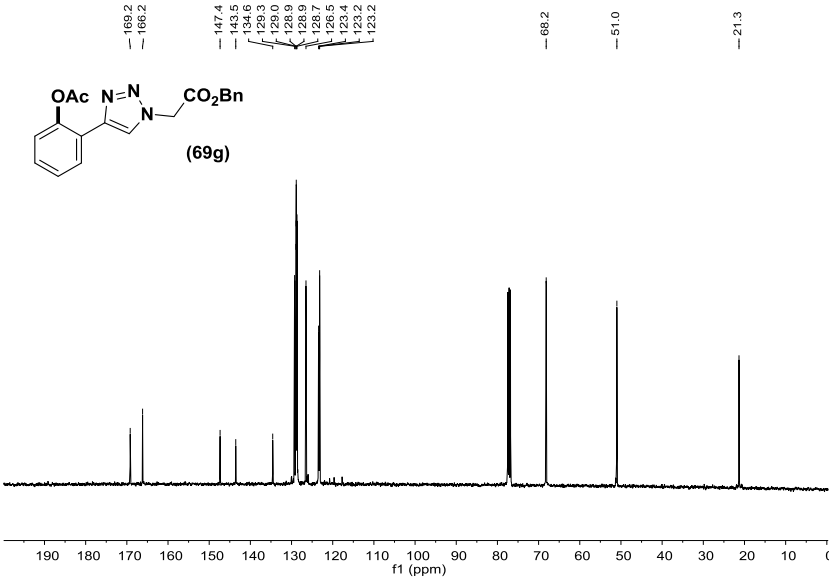
Spectrum 4.65. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69f'**.



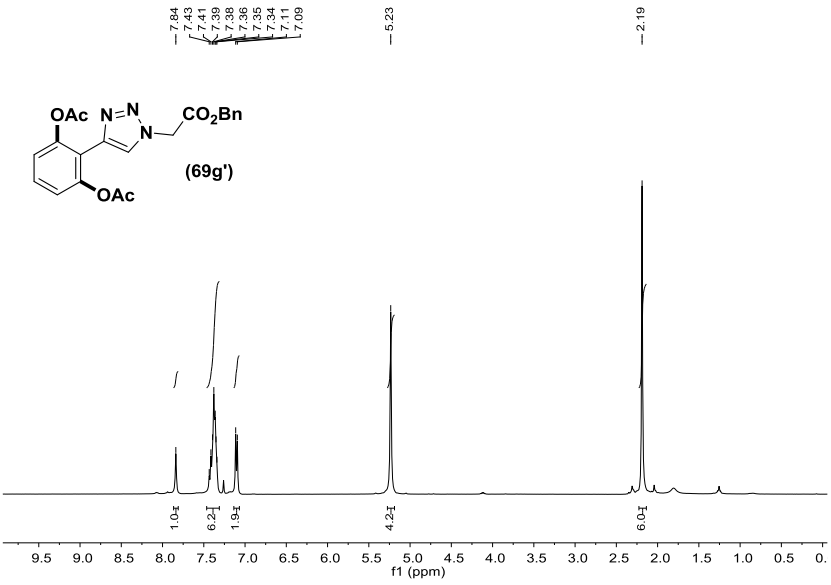
Spectrum 4.66. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69f'**.



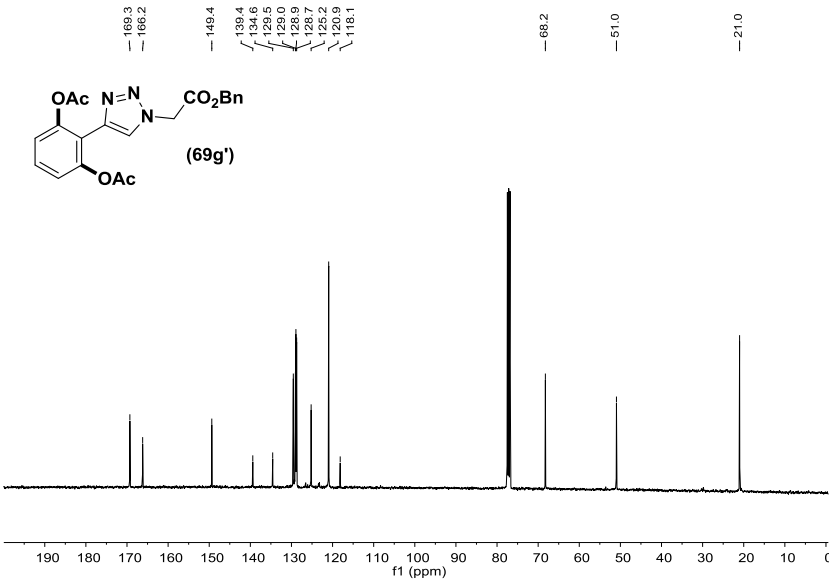
Spectrum 4.67. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69g**.



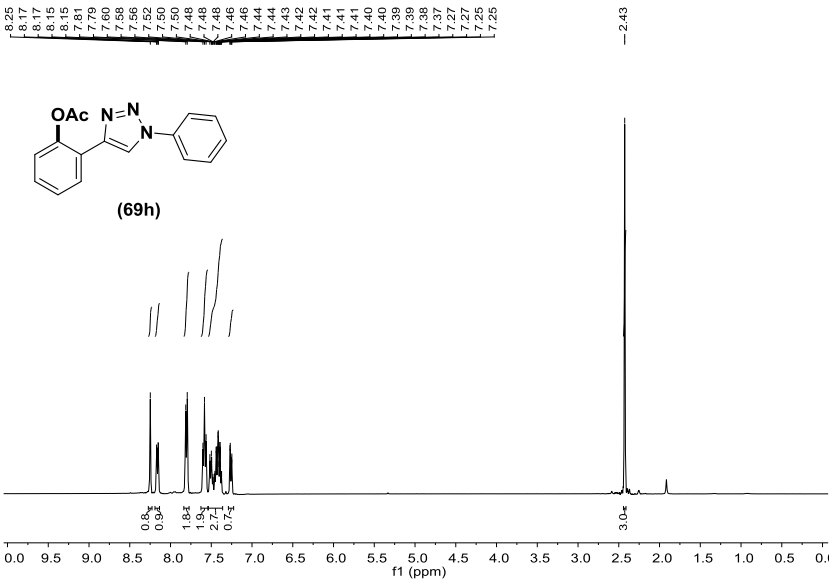
Spectrum 4.68. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69g**.



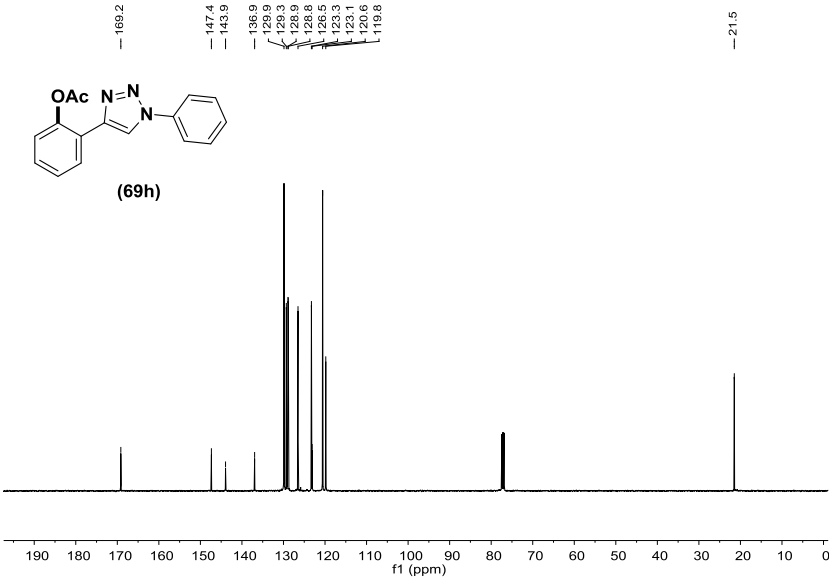
Spectrum 69. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69g'**.



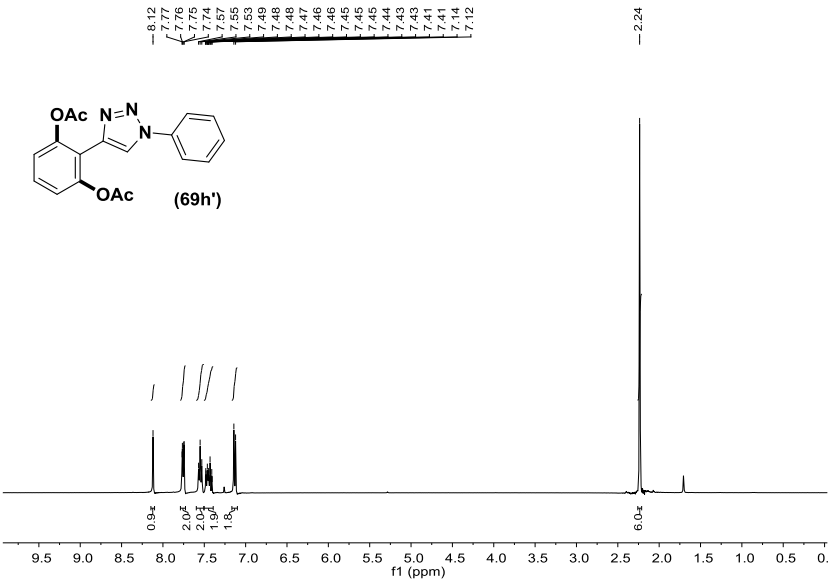
Spectrum 4.70. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69g'**.



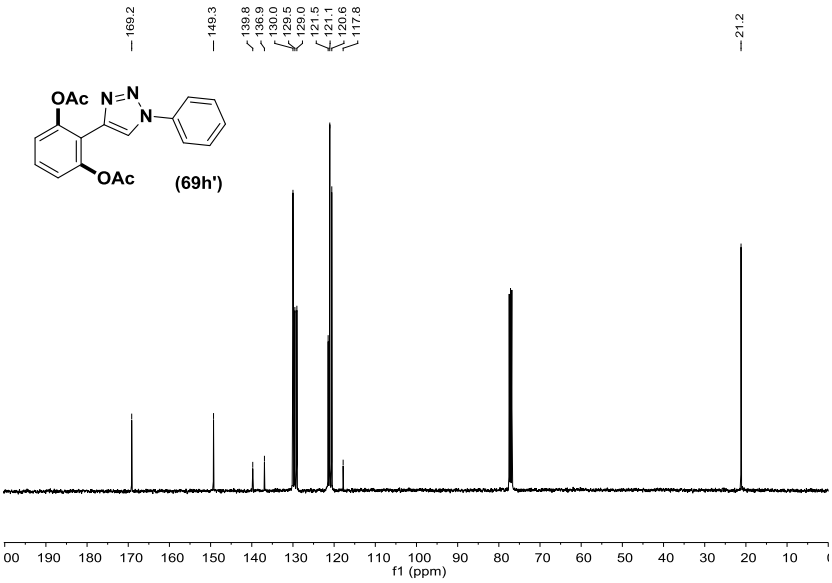
Spectrum 4.71. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69h**.



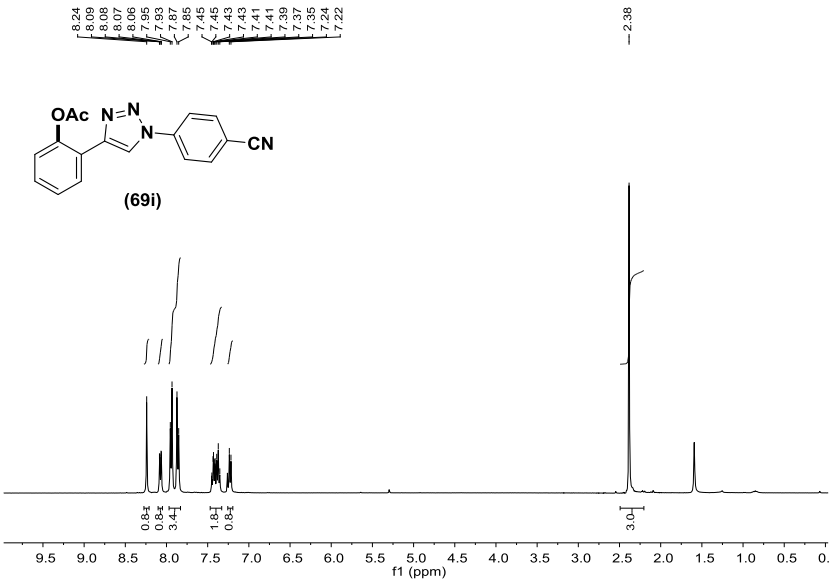
Spectrum 4.72. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69h**.



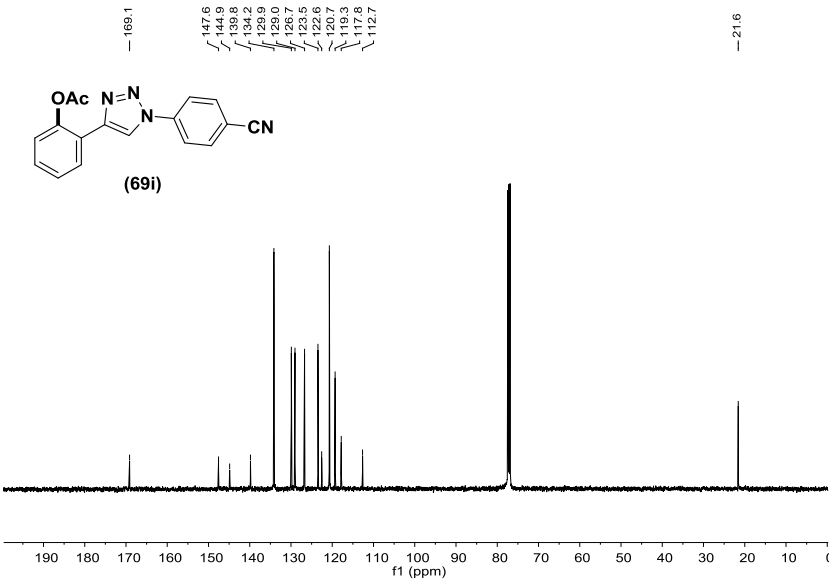
Spectrum 4.73. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69h'**.



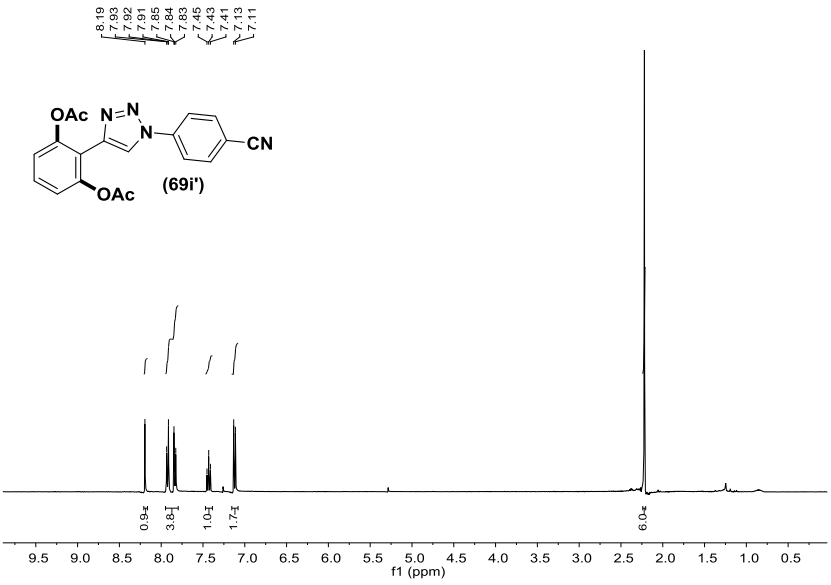
Spectrum 4.74. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69h'**.



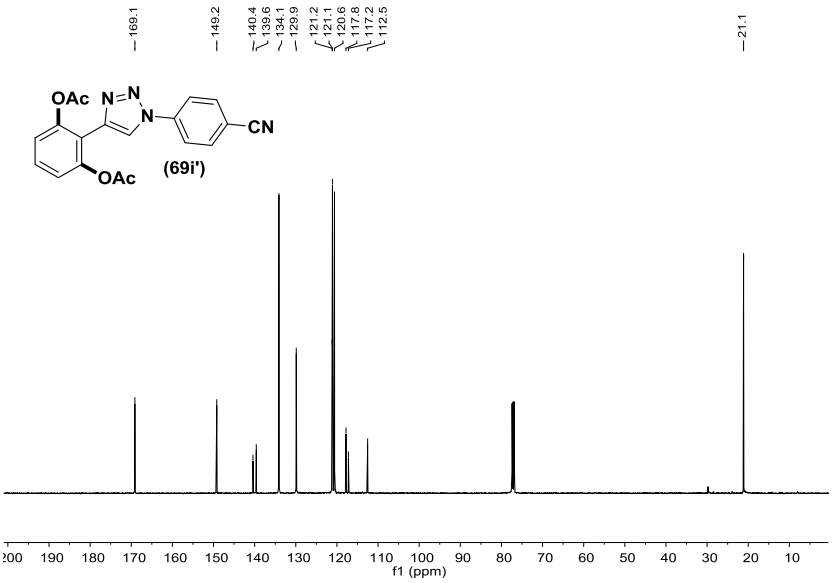
Spectrum 4.75. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69i**.



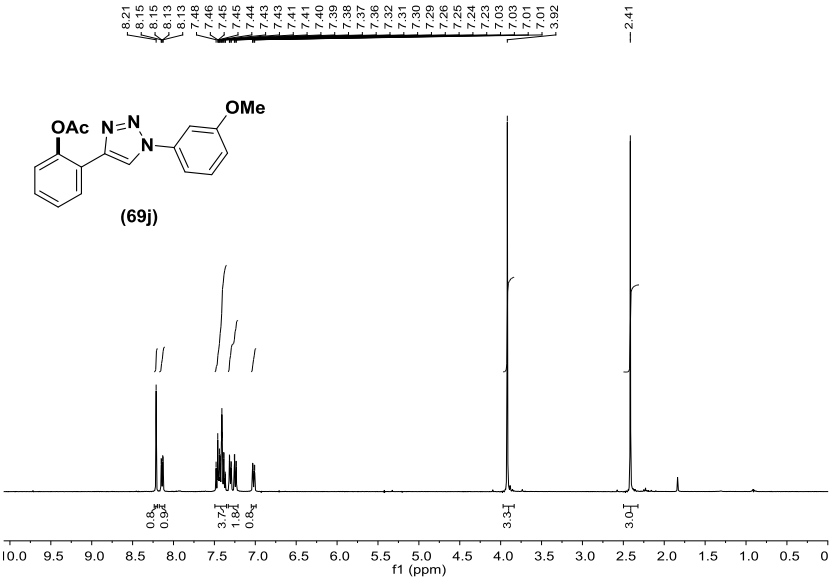
Spectrum 4.76. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69i**.



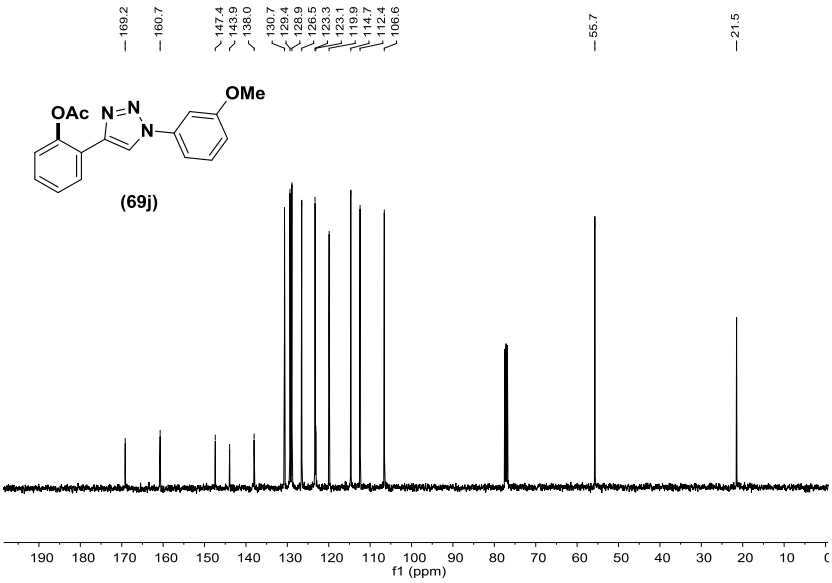
Spectrum 4.77. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69i'**.



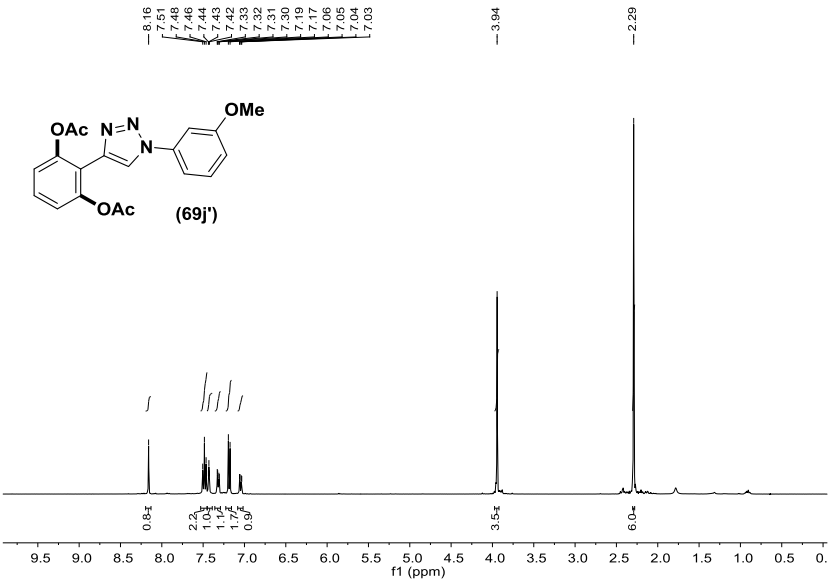
Spectrum 4.78. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69i'**.



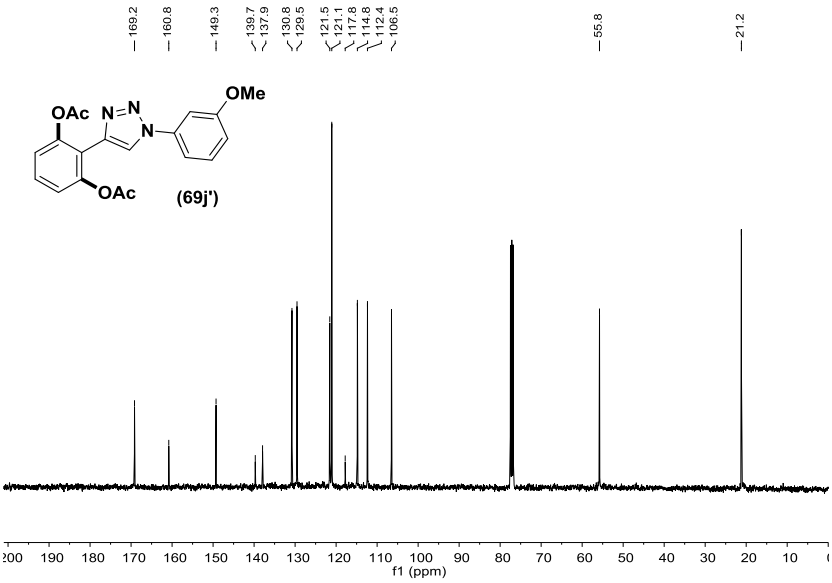
Spectrum 4.79. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69j**.



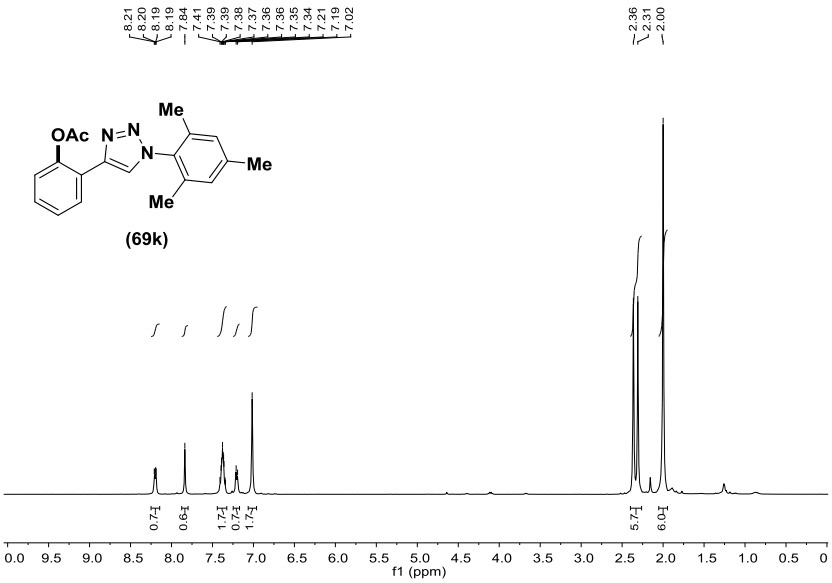
Spectrum 4.80. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69j**.



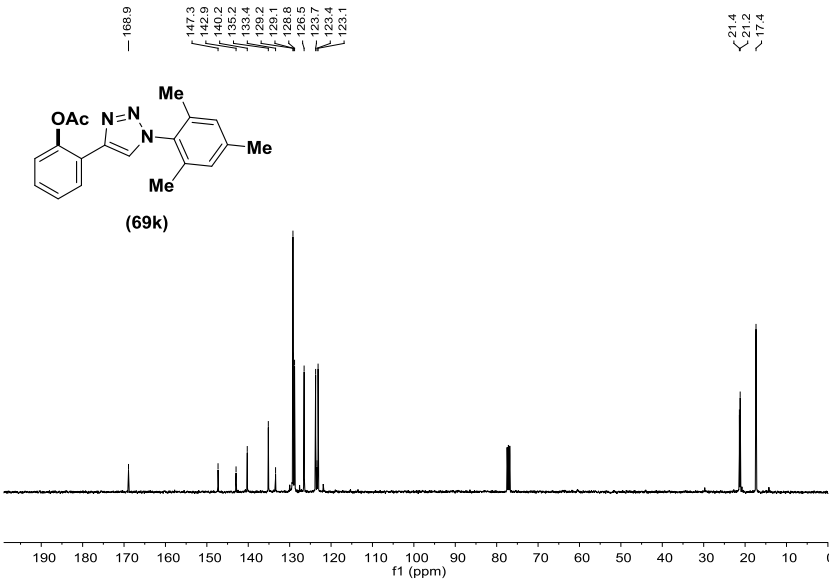
Spectrum 4.81. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69j'**.



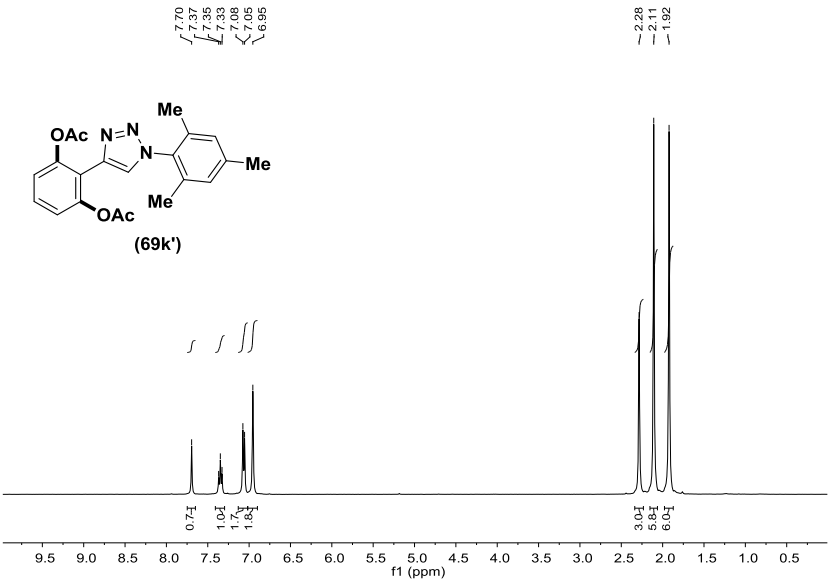
Spectrum 4.82. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69j'**.



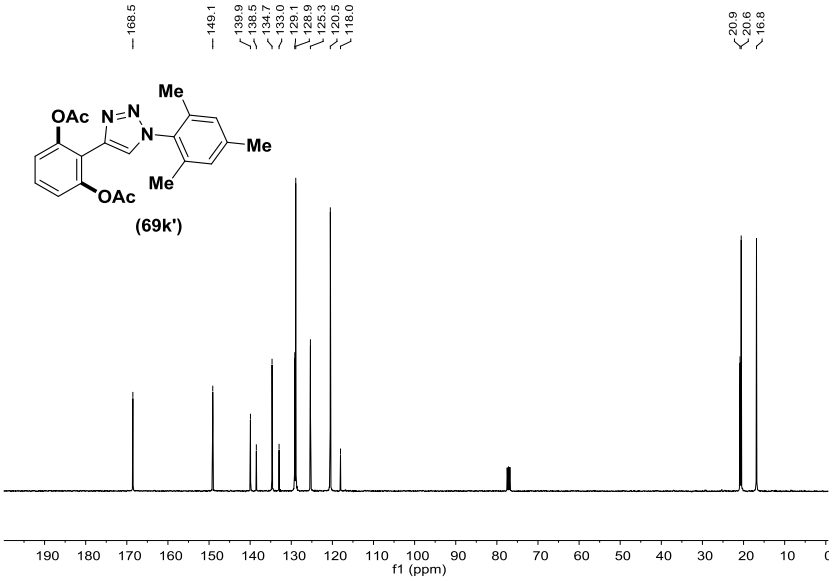
Spectrum 4.83. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69k**.



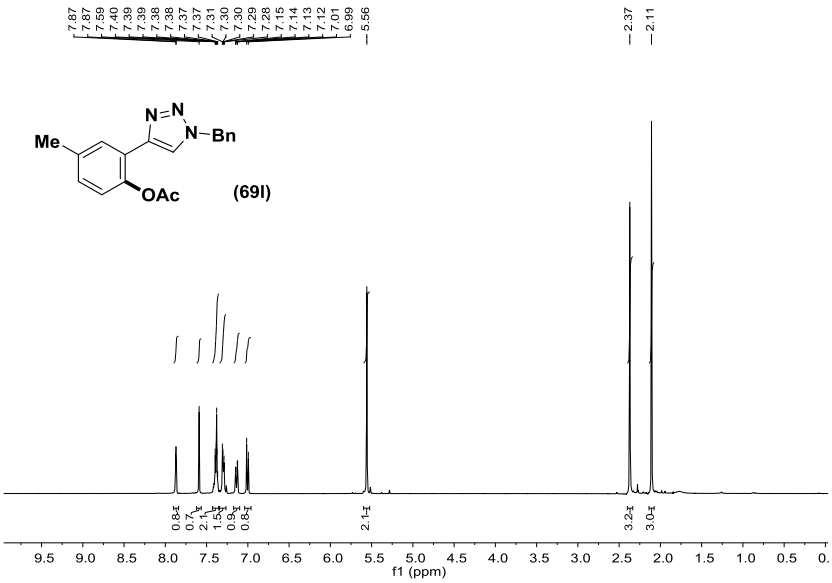
Spectrum 4.84. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69k**.



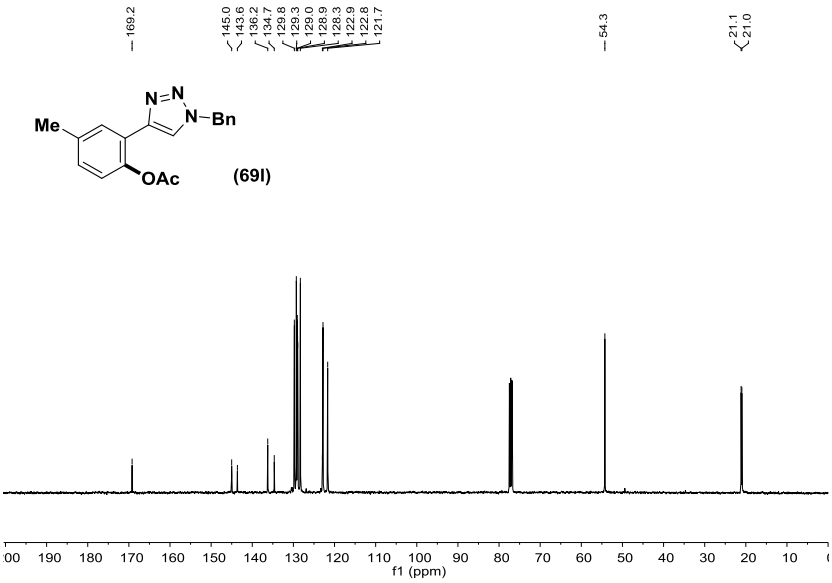
Spectrum 4.85. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69k'**.



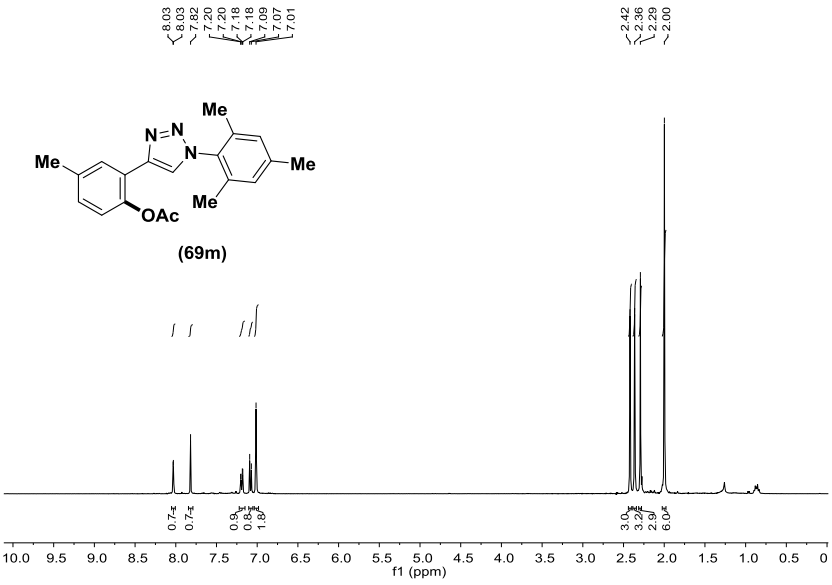
Spectrum 4.86. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69k'**.



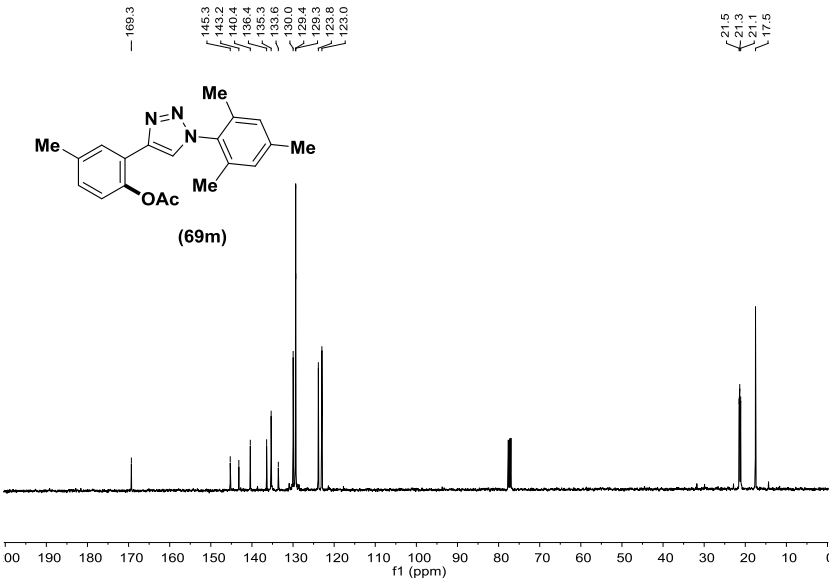
Spectrum 4.87. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69l**.



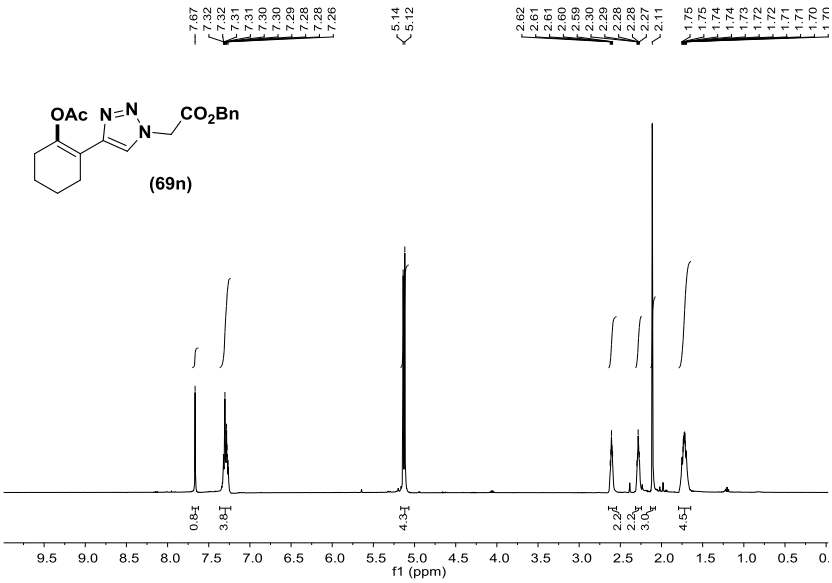
Spectrum 4.88. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69l**.



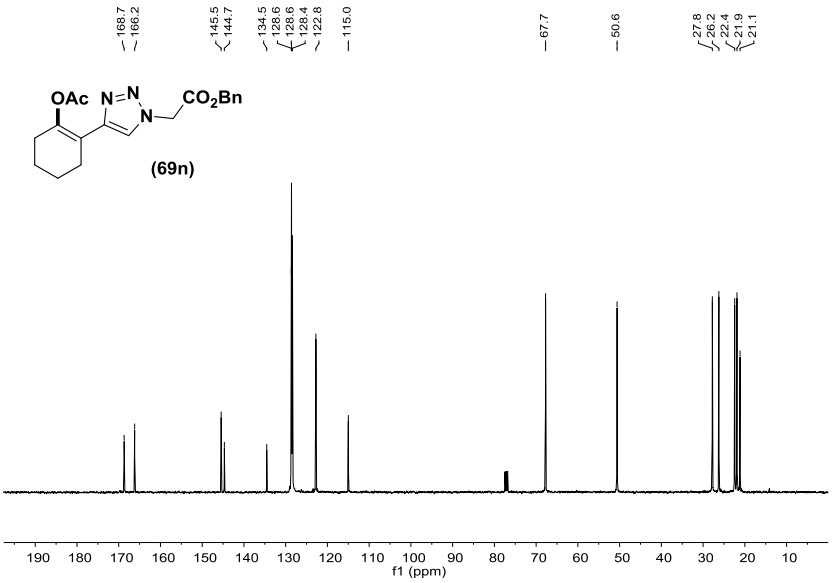
Spectrum 4.89. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69m**.



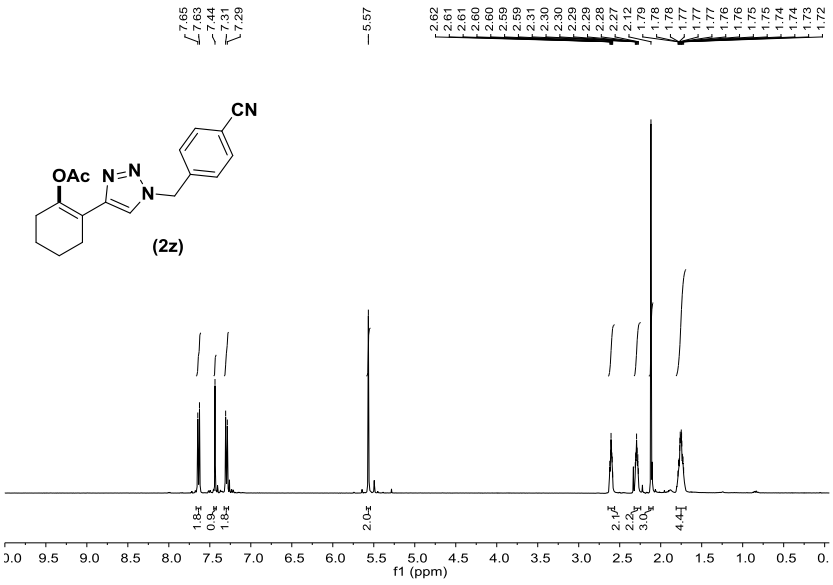
Spectrum 4.90. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69m**.



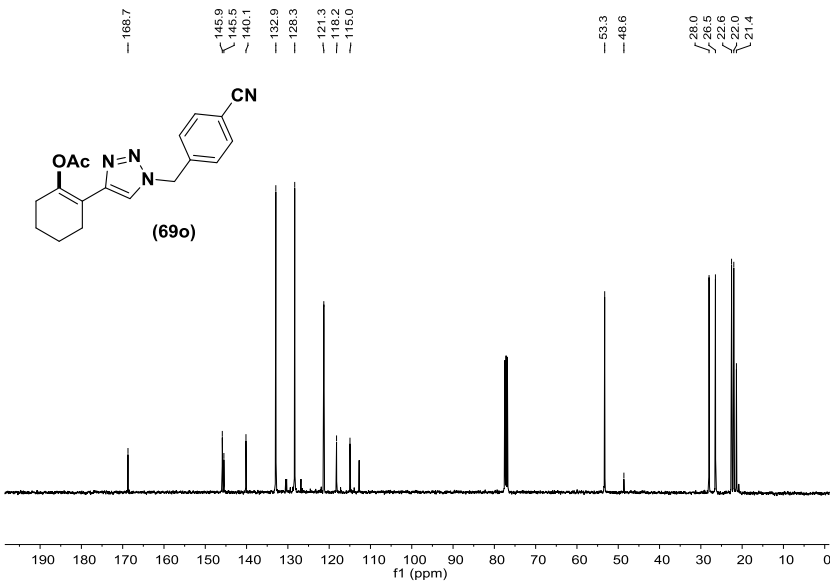
Spectrum 4.91. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69n**.



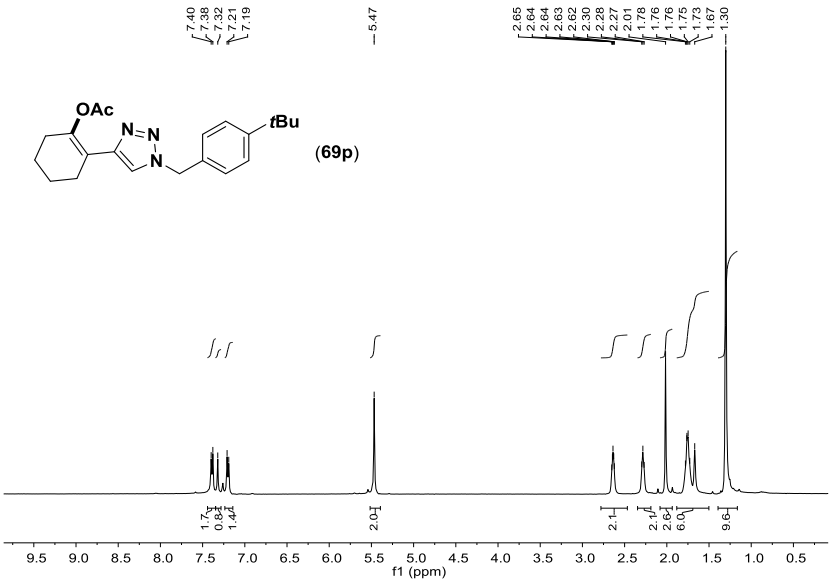
Spectrum 4.92. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69n**.



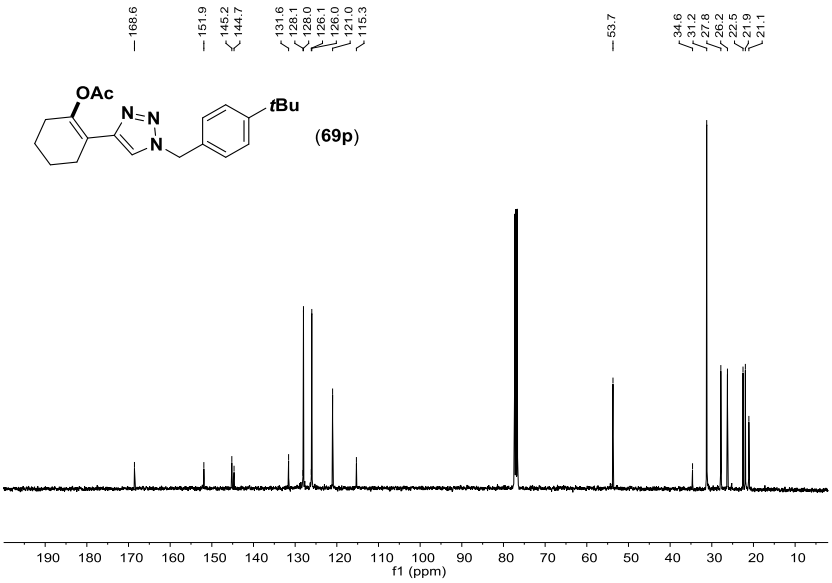
Spectrum 4.93. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69o**.



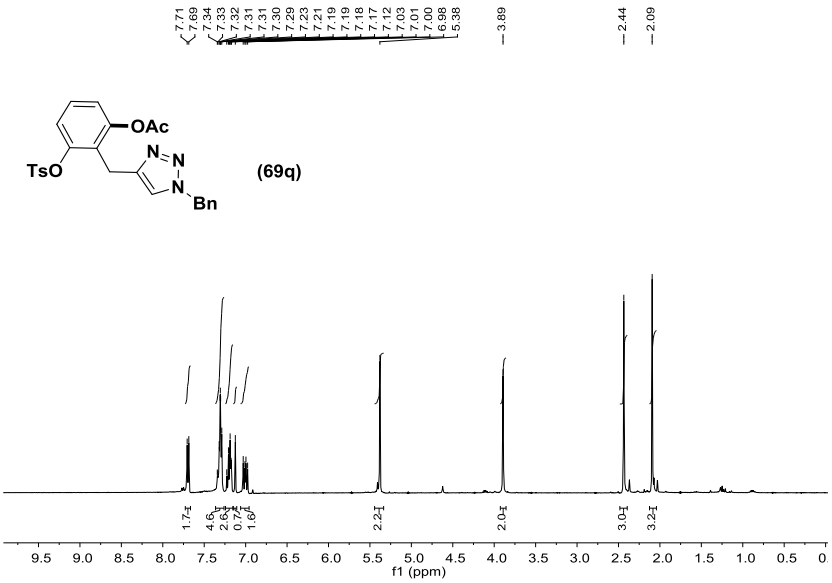
Spectrum 4.94. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69o**.



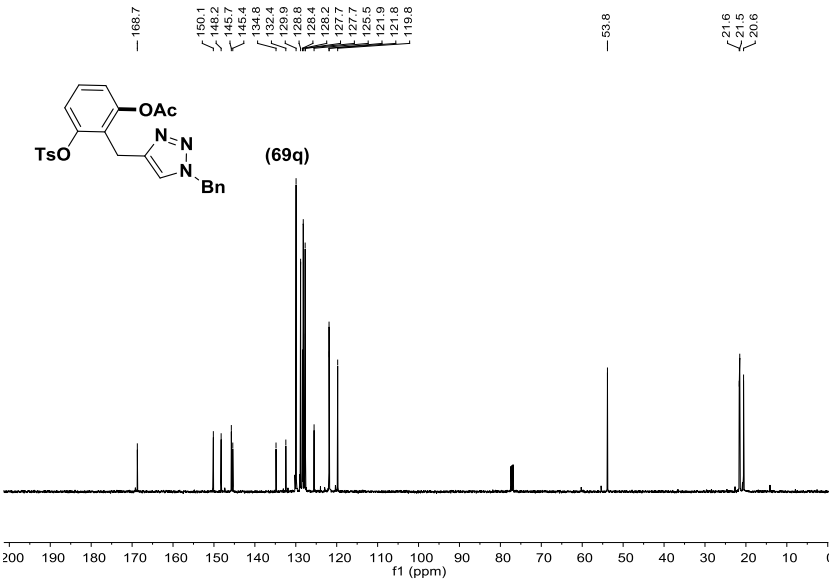
Spectrum 4.95. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69p**.



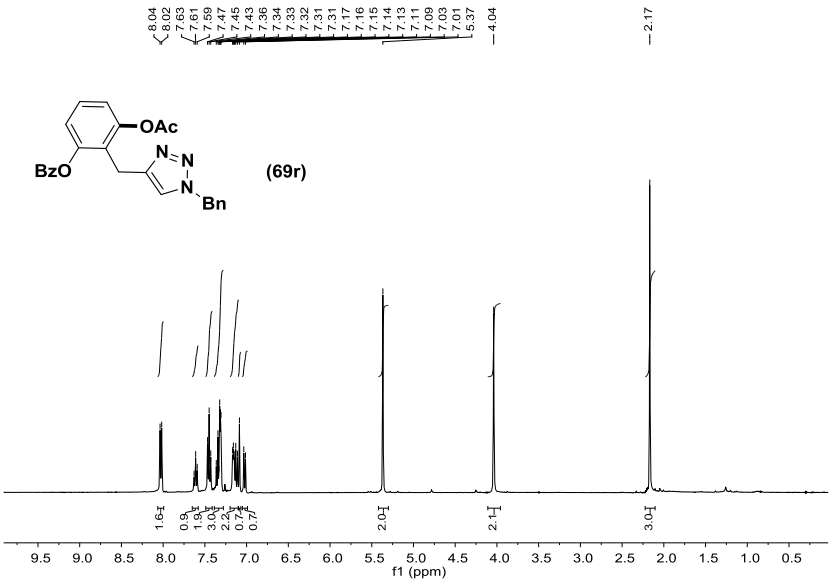
Spectrum 4.96. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69p**.



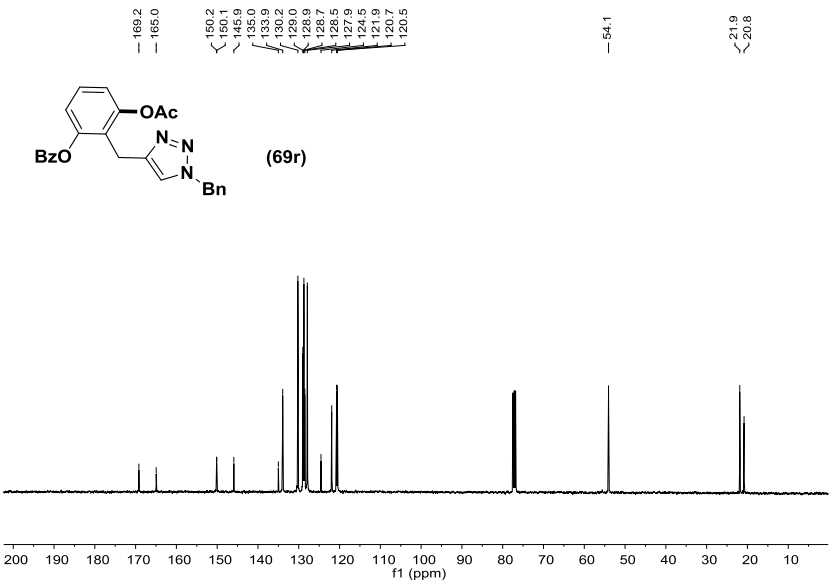
Spectrum 4.97. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69q**.



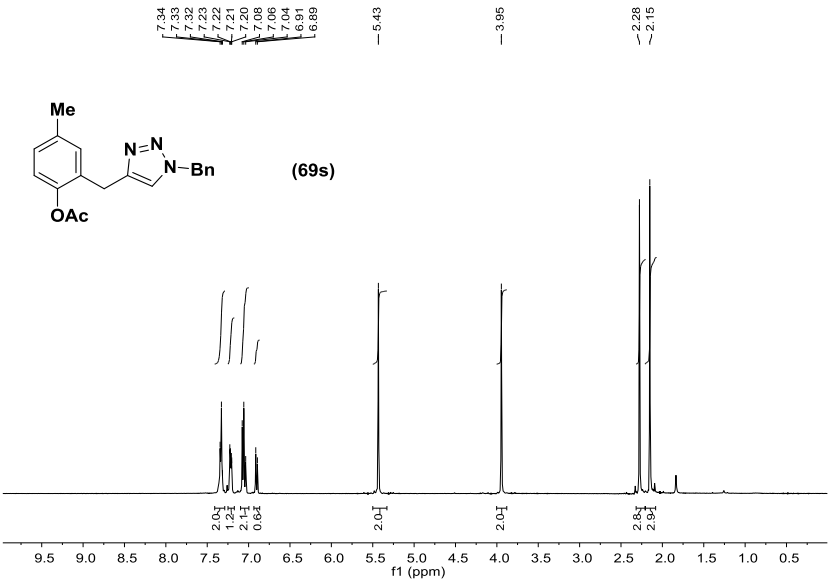
Spectrum 4.98. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69q**.



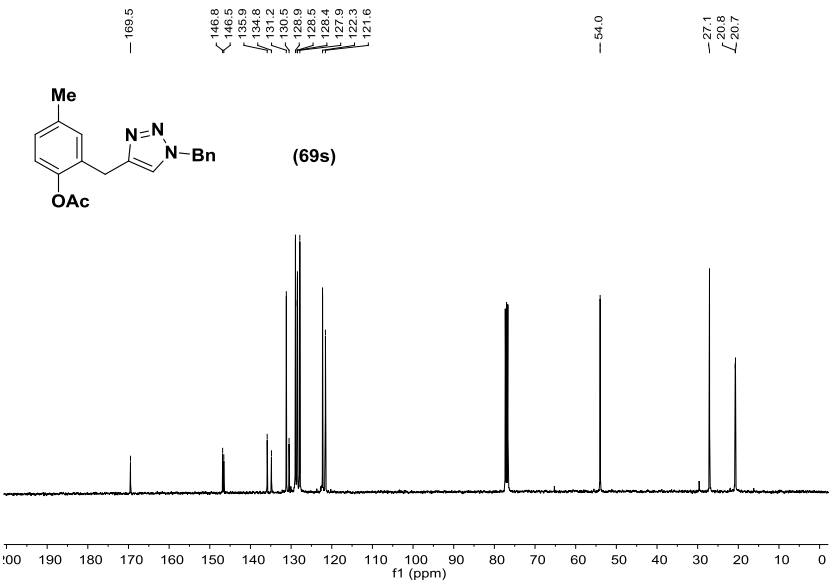
Spectrum 4.99. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69r**.



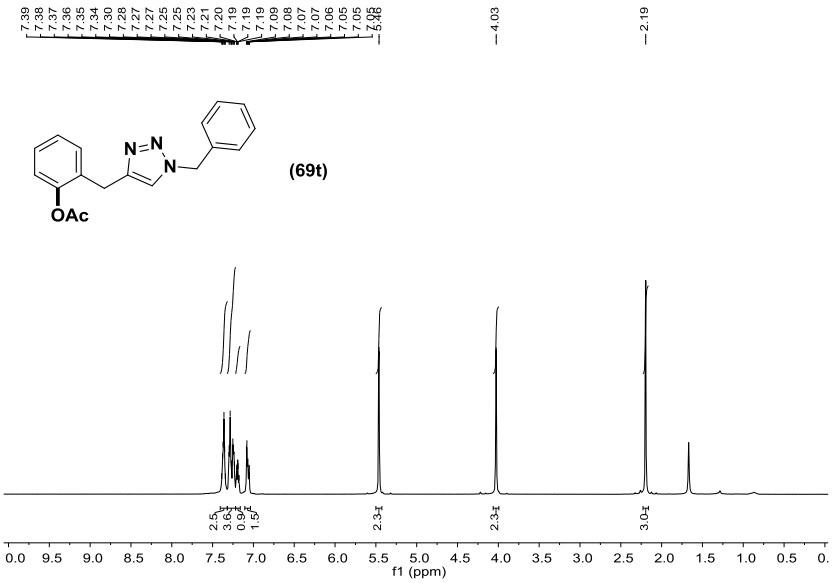
Spectrum 4.100. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69r**.



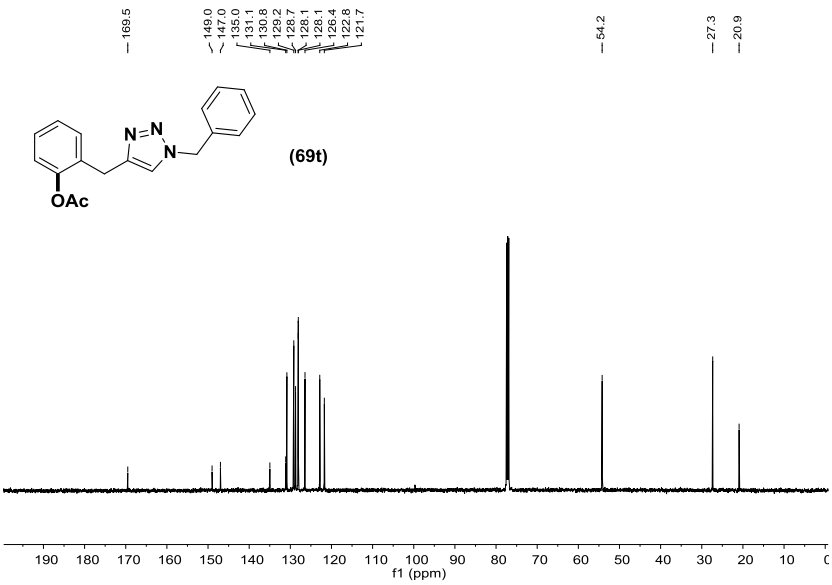
Spectrum 4.101. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69s**.



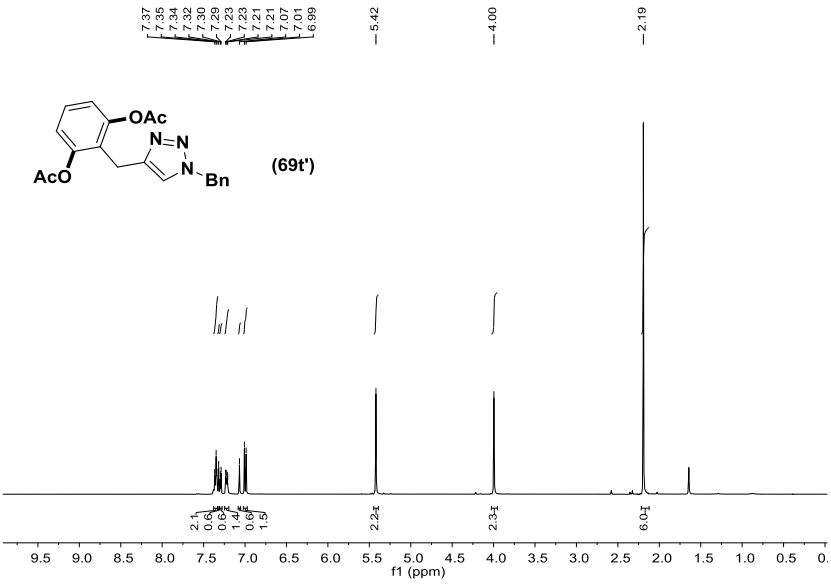
Spectrum 4.102. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69s**.



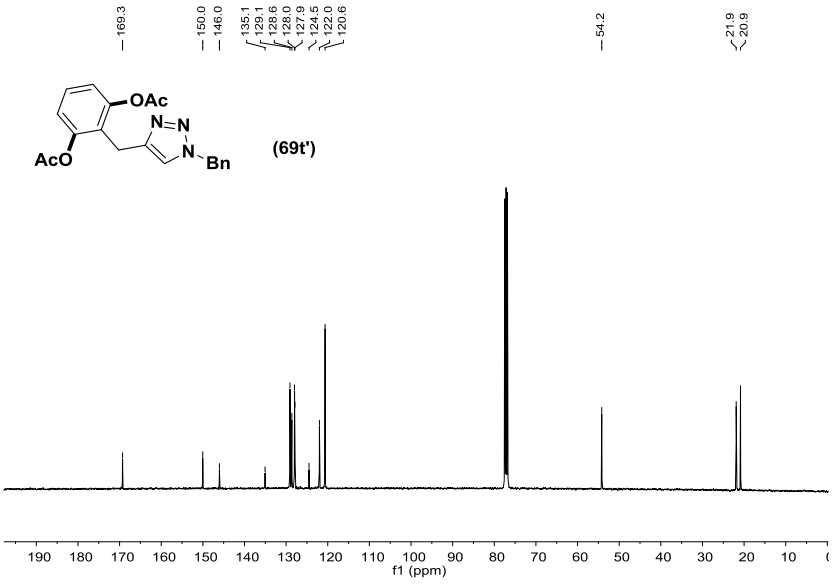
Spectrum 4.103. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **69t**.



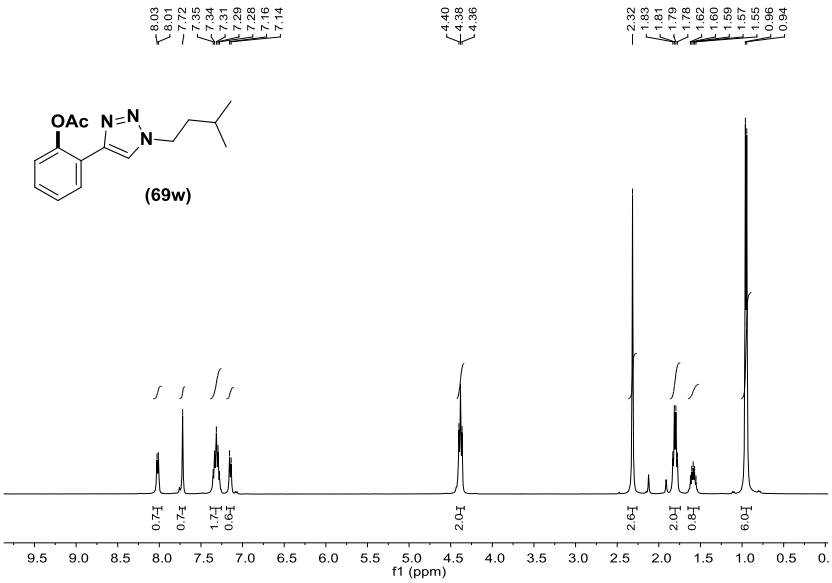
Spectrum 4.104. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69t**.



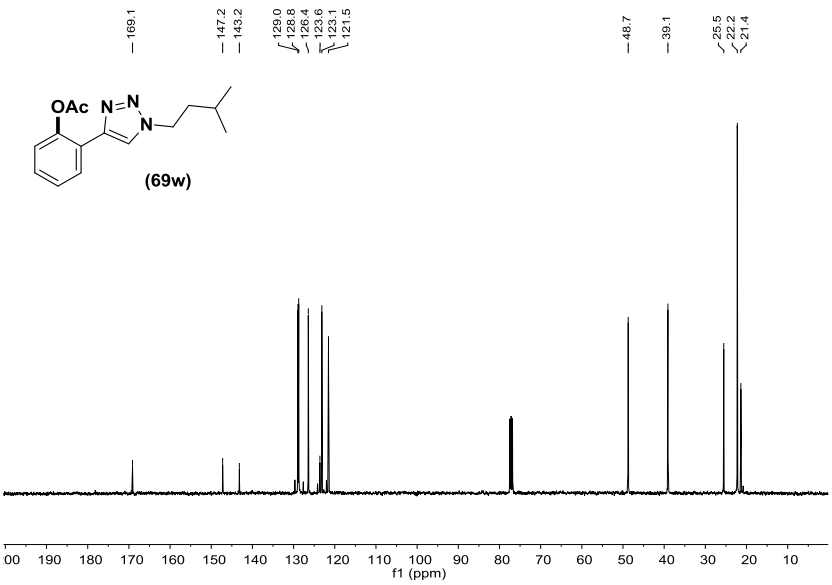
Spectrum 4.105. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69t'**.



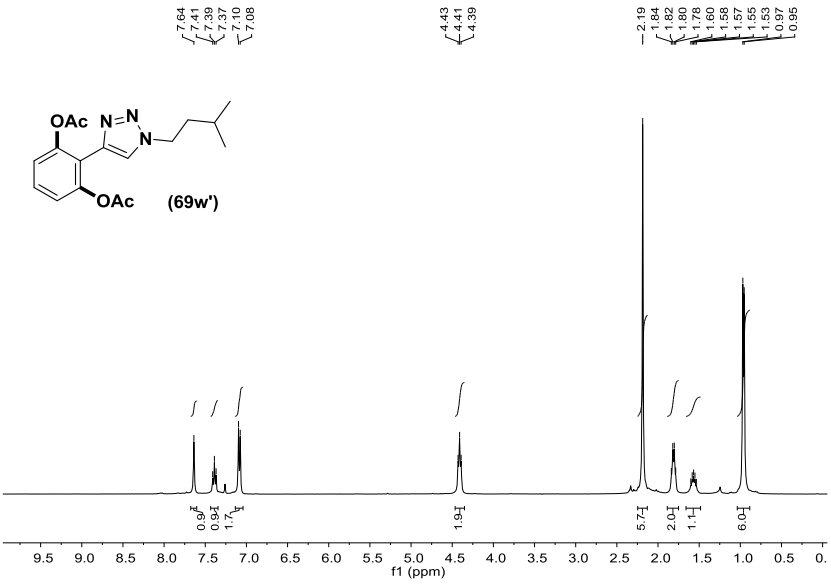
Spectrum 4.106. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69t'**.



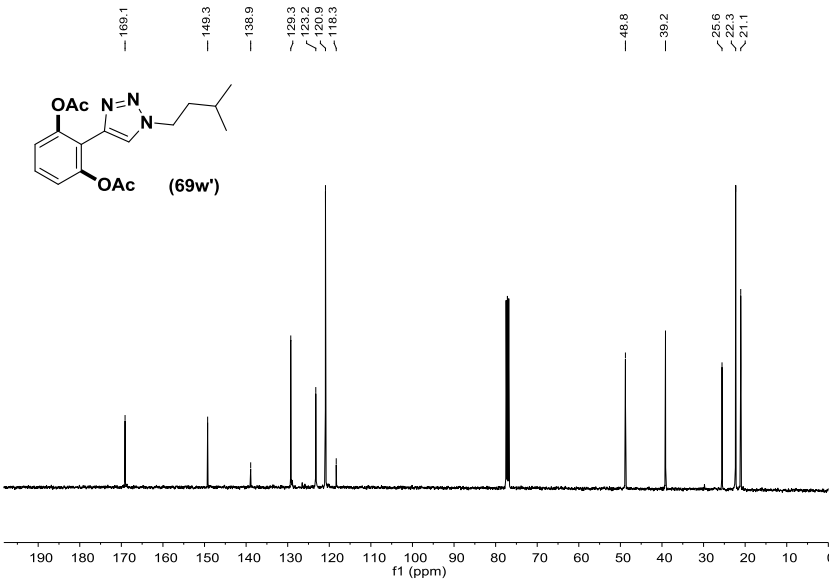
Spectrum 4.107. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69w**.



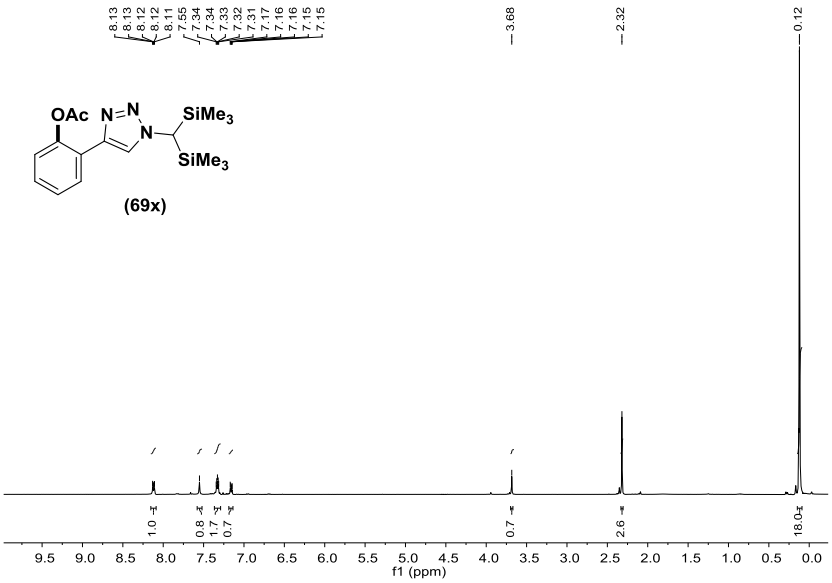
Spectrum 4.108 . ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69w**.



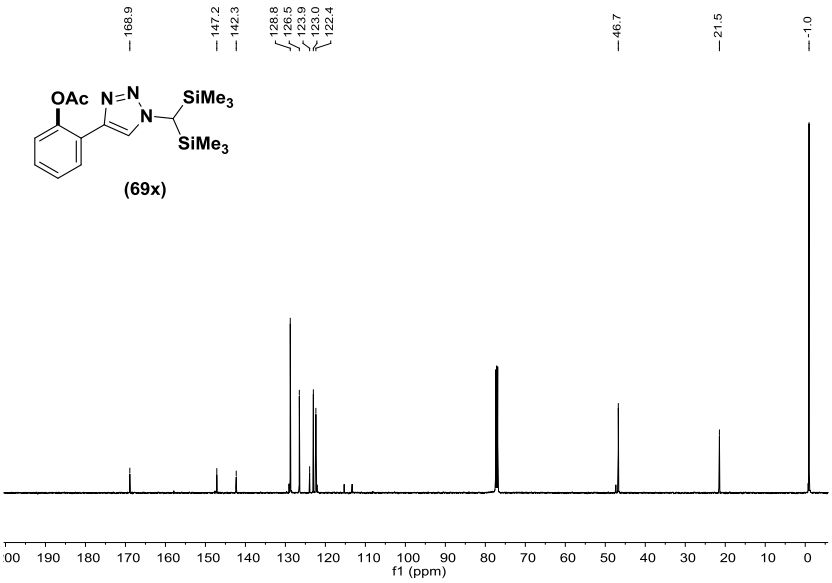
Spectrum 4.109. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69w'**.



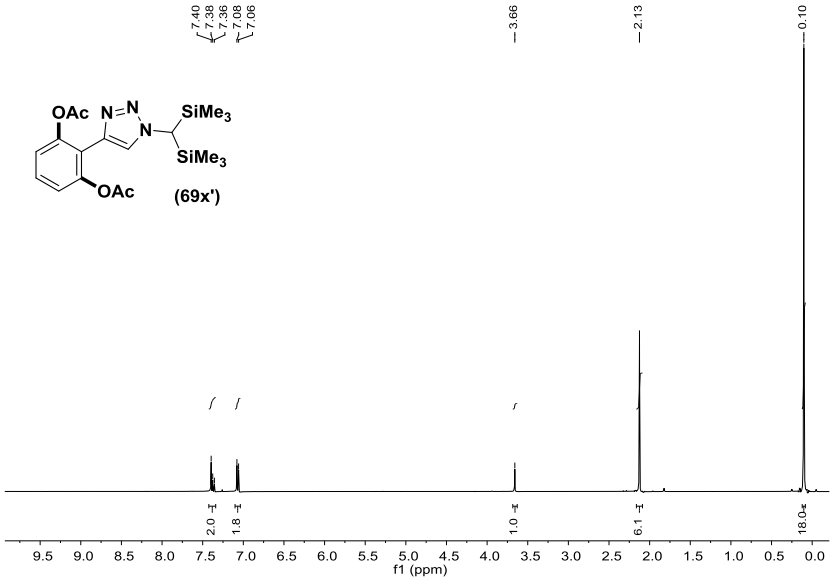
Spectrum 4.110. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69w'**.



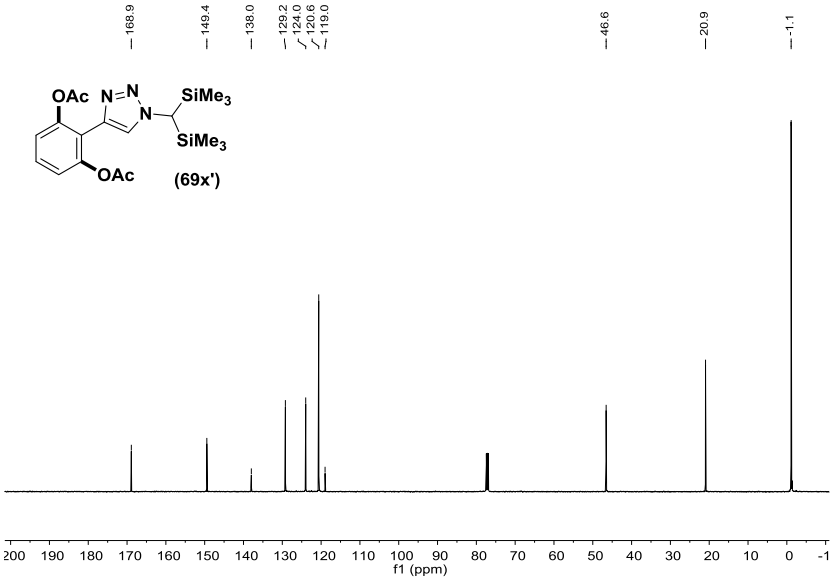
Spectrum 4.111. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69x**.



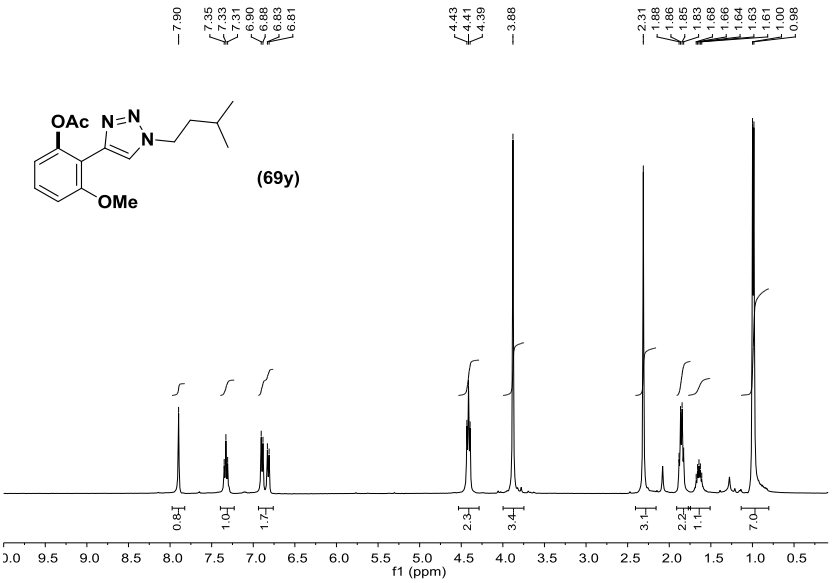
Spectrum 4.112. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69x**.



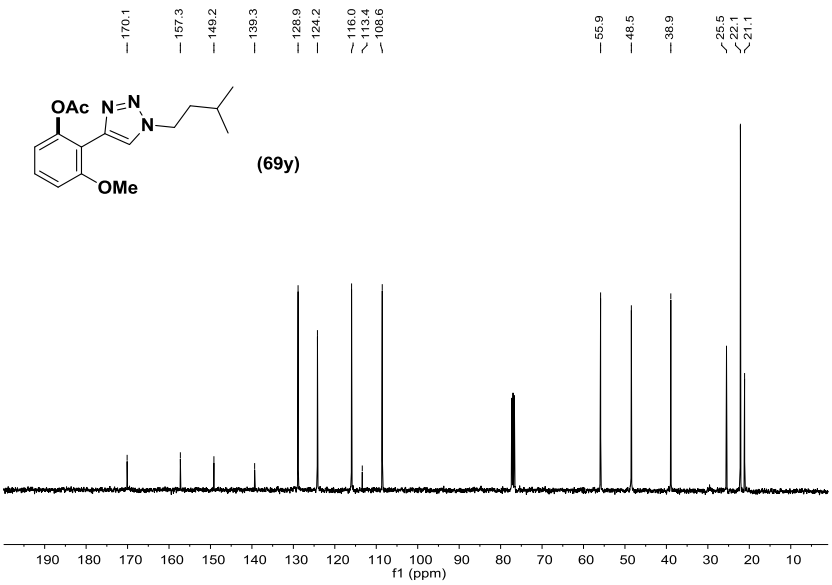
Spectrum 4.113. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69x'**.



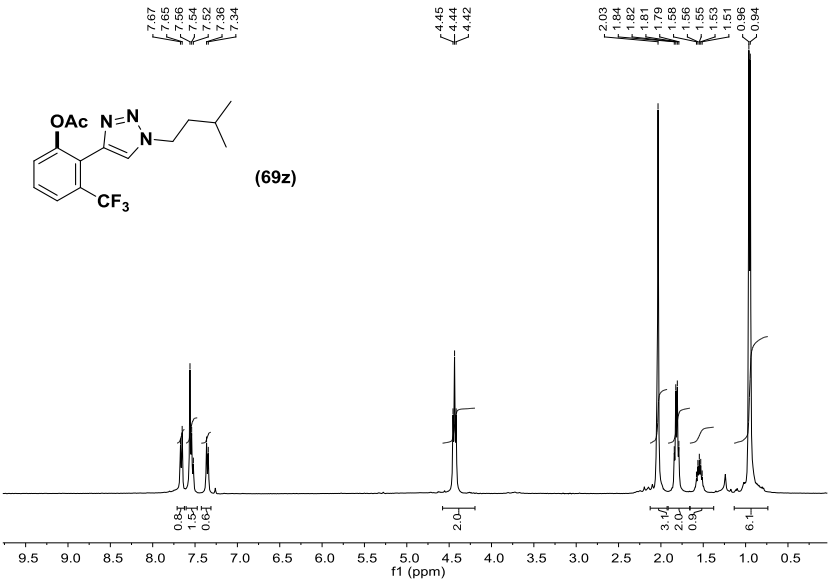
Spectrum 4.114. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69x'**.



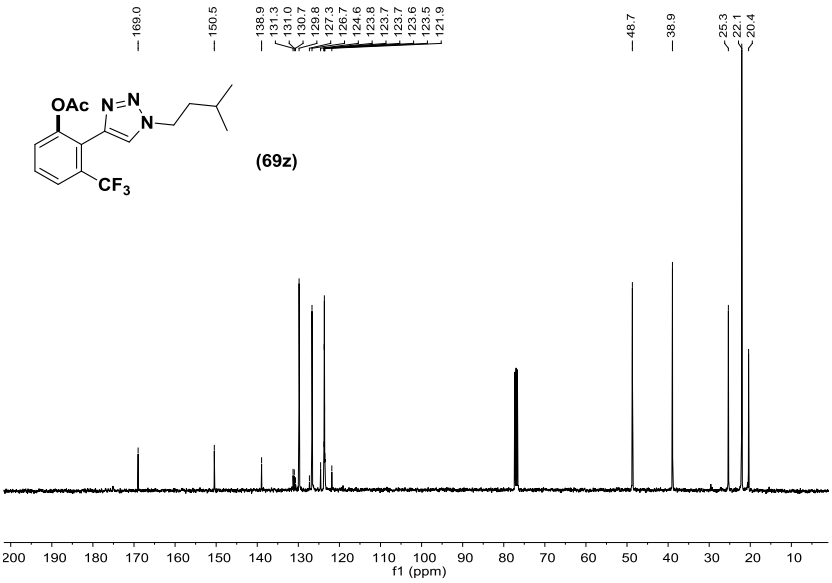
Spectrum 4.115. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69y**.



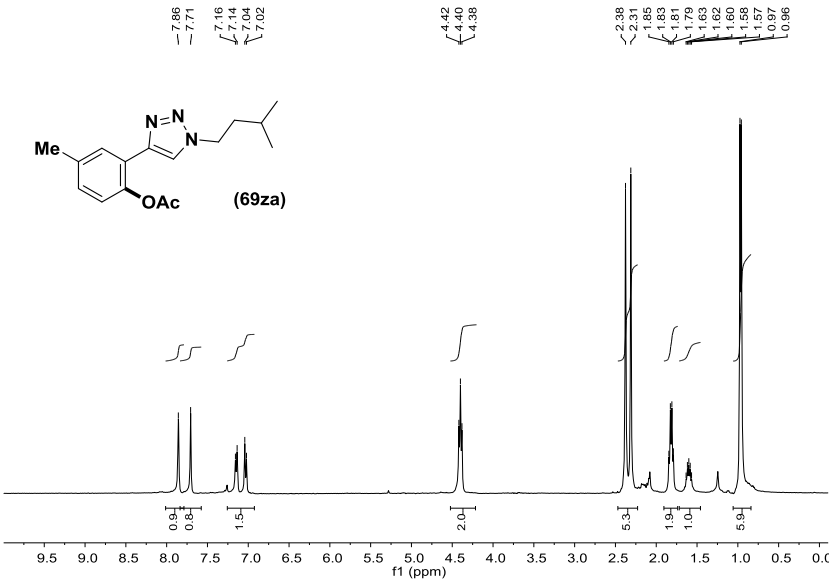
Spectrum 4.116. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69y**.



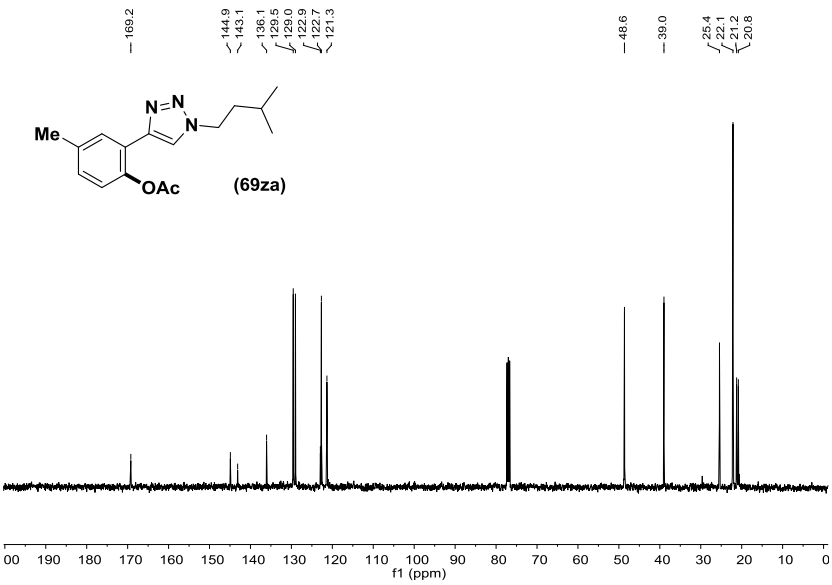
Spectrum 4.117. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69z**.



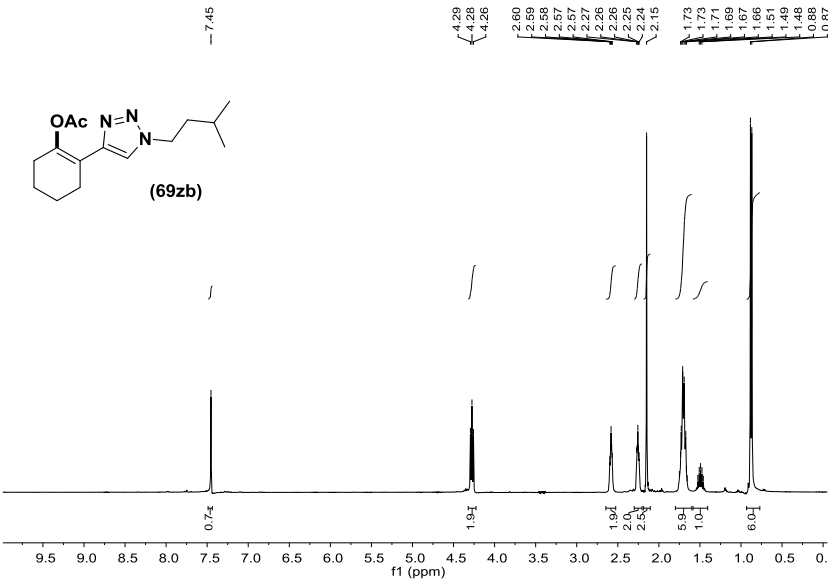
Spectrum 4.118. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69z**.



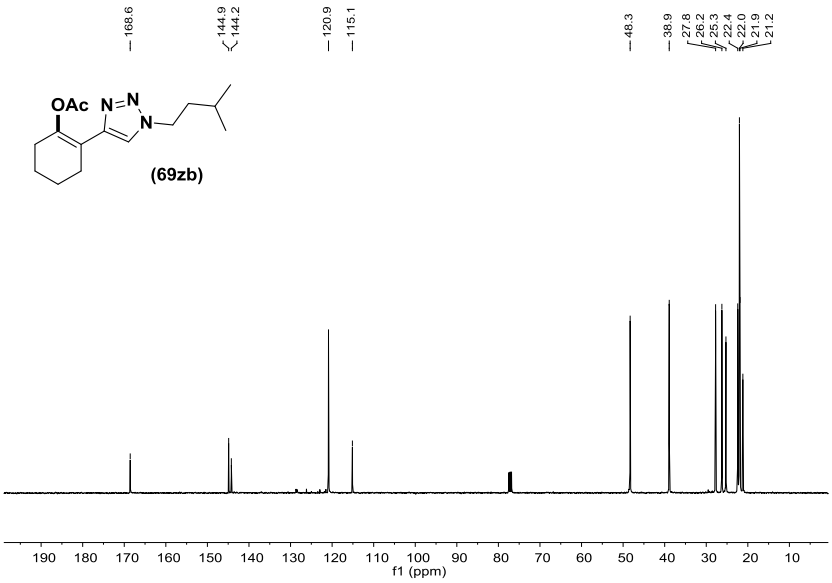
Spectrum 4.119. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69za**.



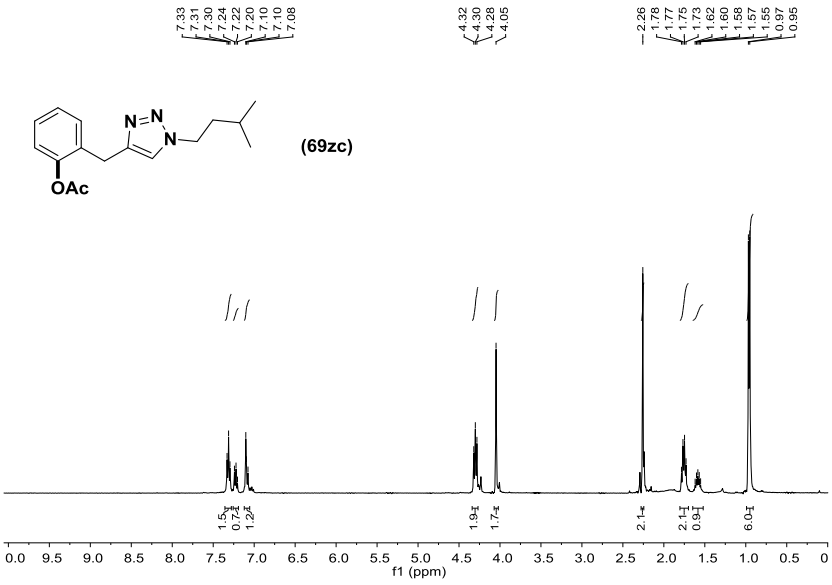
Spectrum 4.120 . ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69za**.



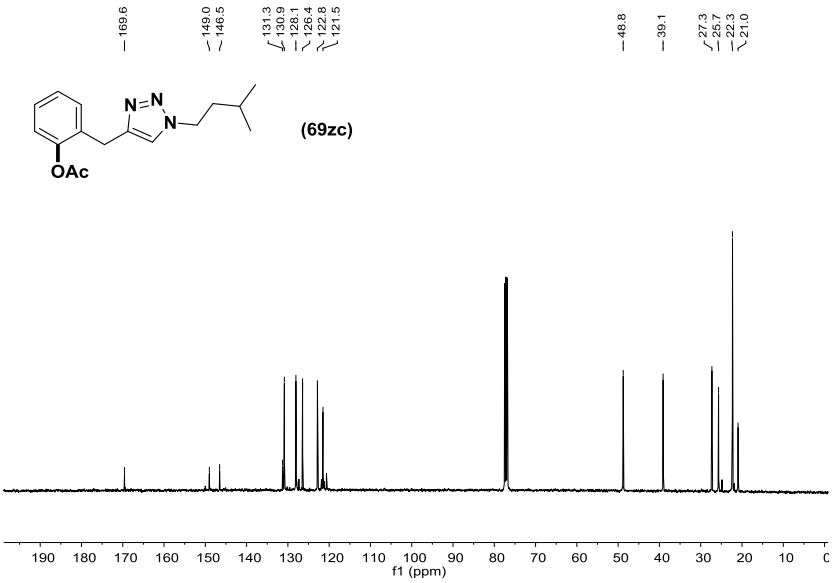
Spectrum 4.121. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zb**.



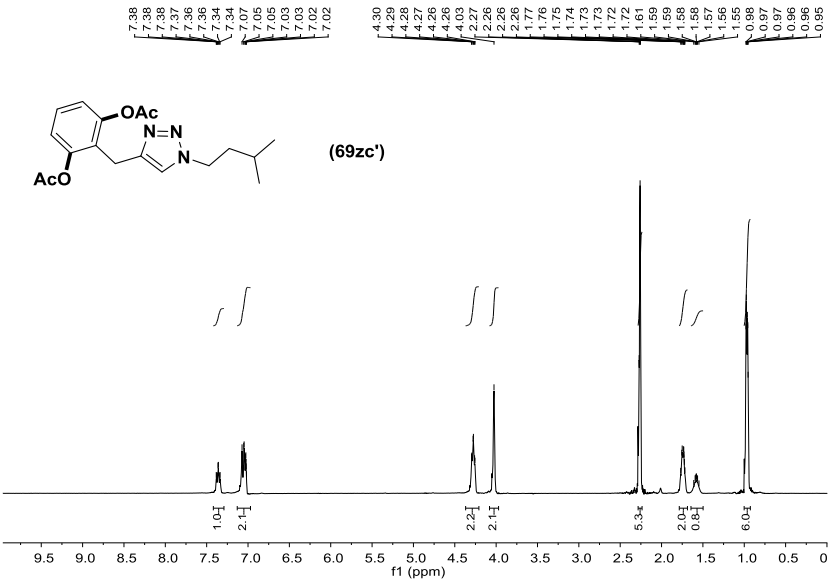
Spectrum 4.122. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69zb**.



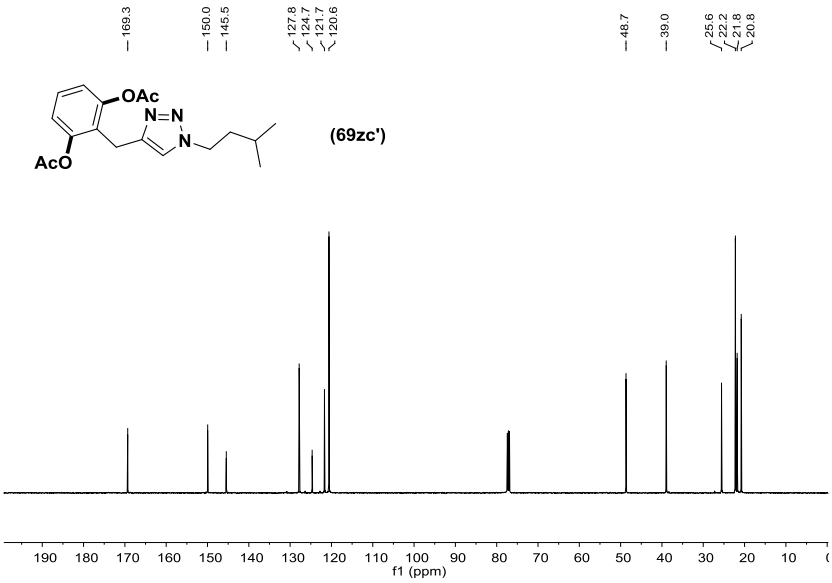
Spectrum 4.123. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zc**.



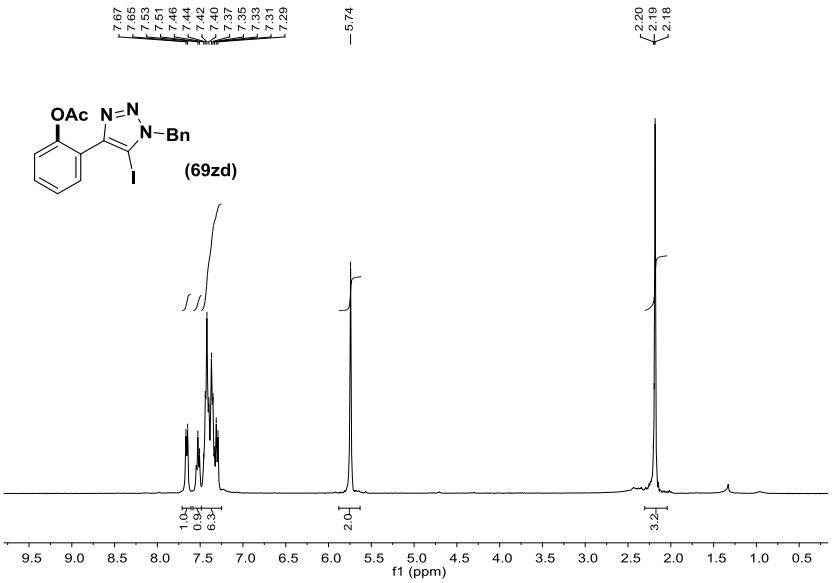
Spectrum 4.124. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69zc**.



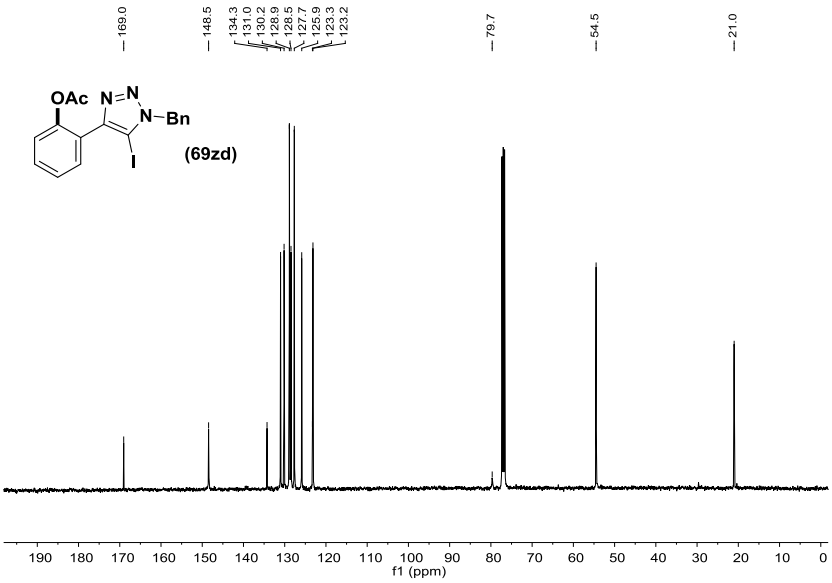
Spectrum 4.125. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zc'**.



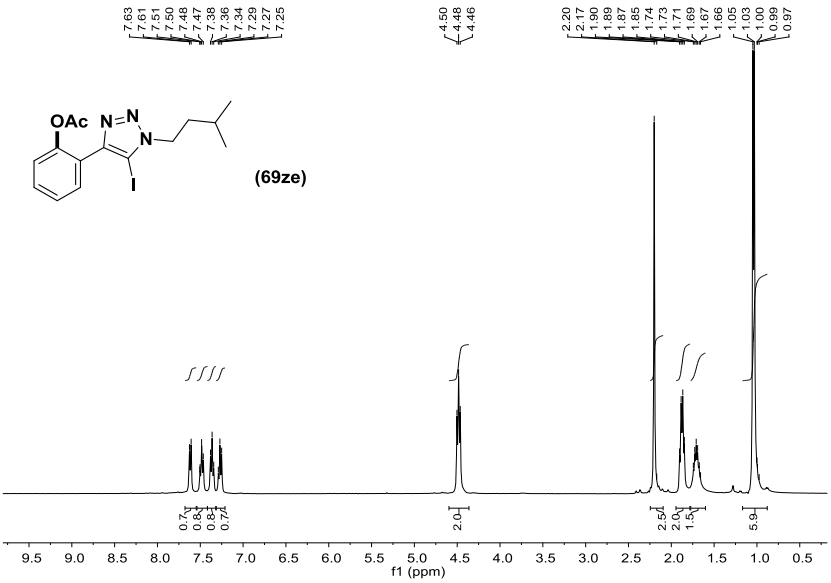
Spectrum 4.126. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69zc**.



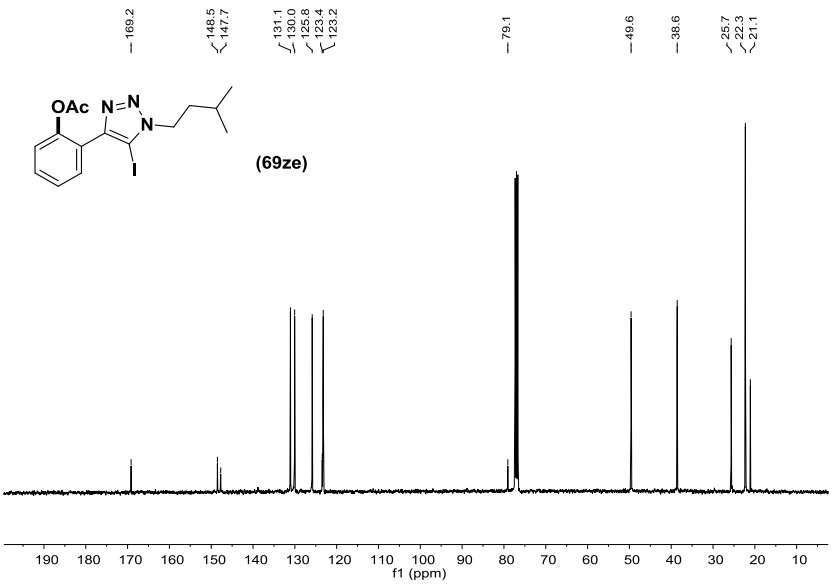
Spectrum 4.127. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zd**.



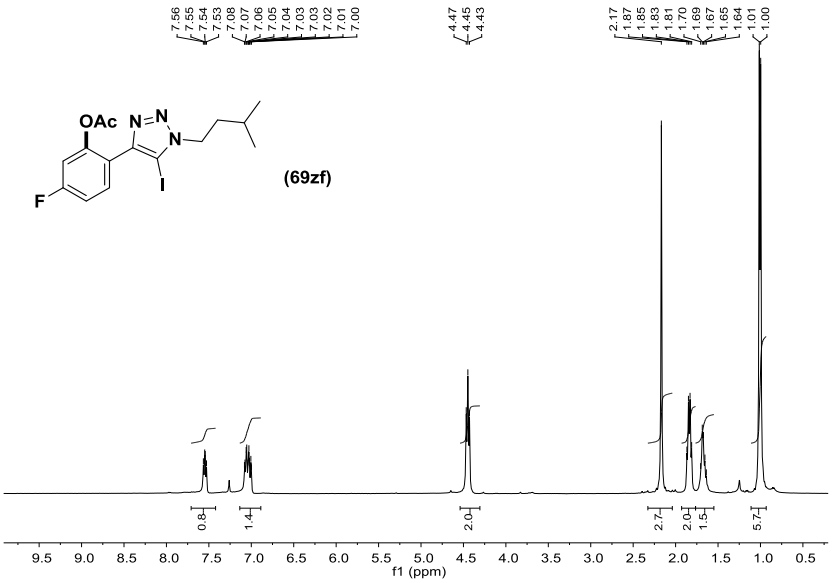
Spectrum 4.128. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69zd**.



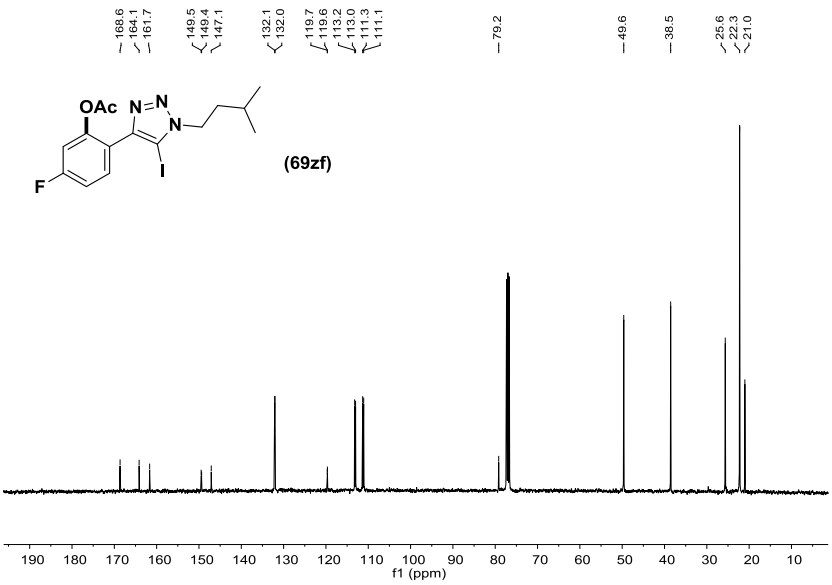
Spectrum 4.129. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69ze**.



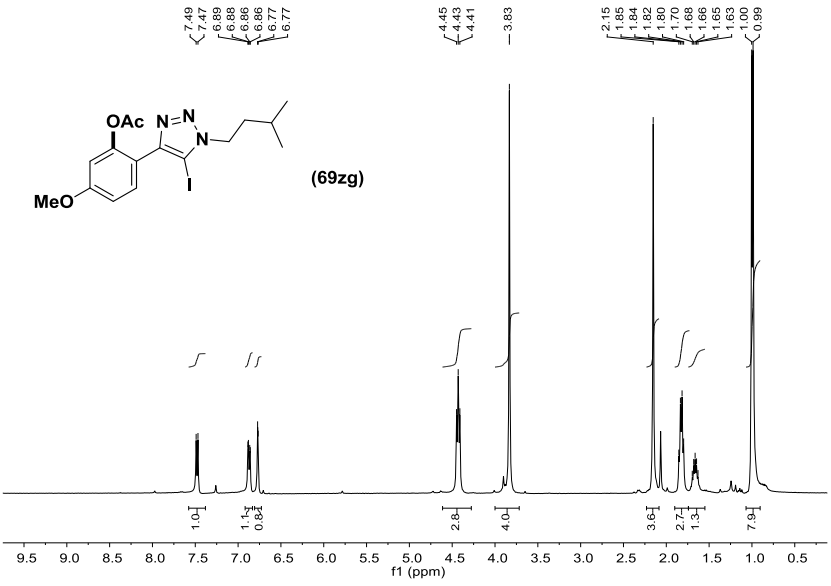
Spectrum 4.130. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69ze**.



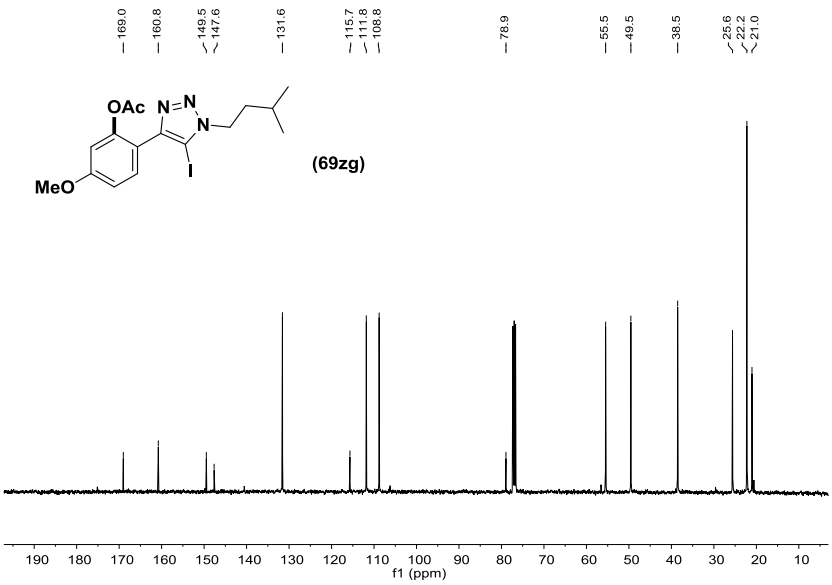
Spectrum 4.131. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zf**.



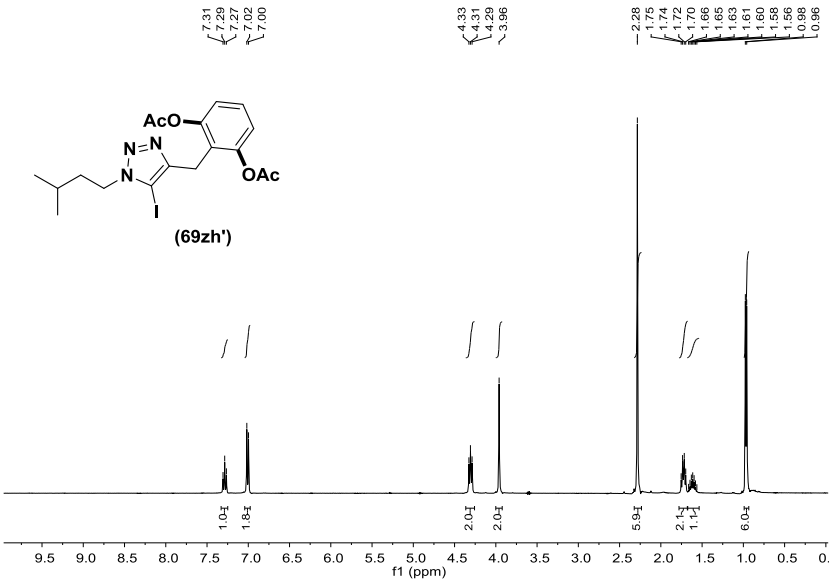
Spectrum 4.132. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69zf**.



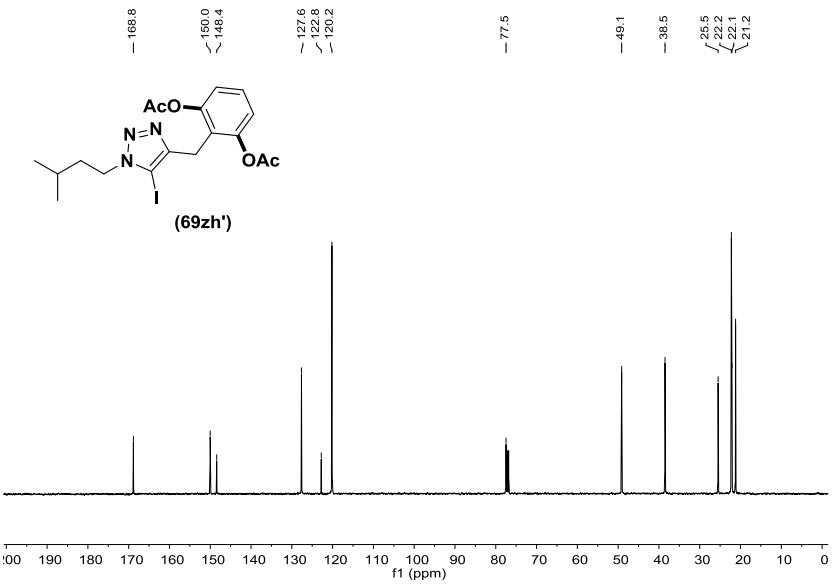
Spectrum 4.133. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zg**.



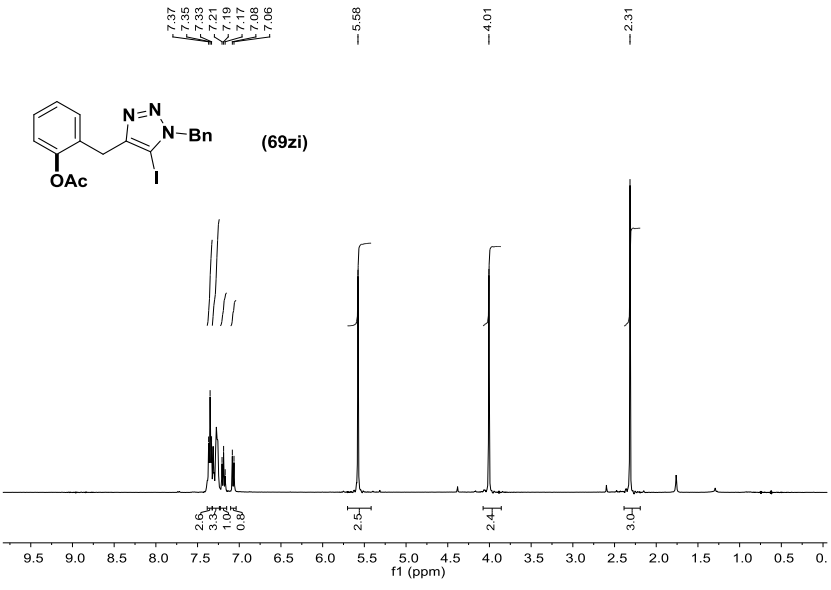
Spectrum 4.134. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69zg**.



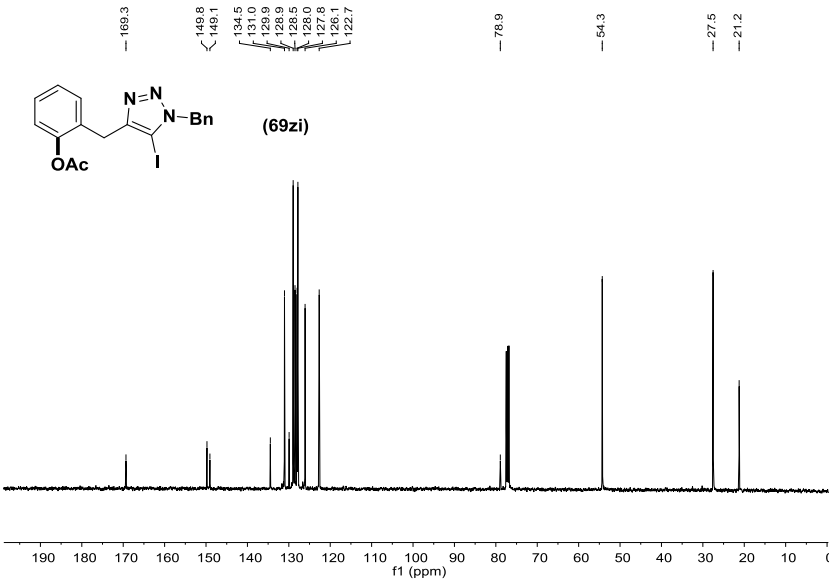
Spectrum 4.135. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zh'**.



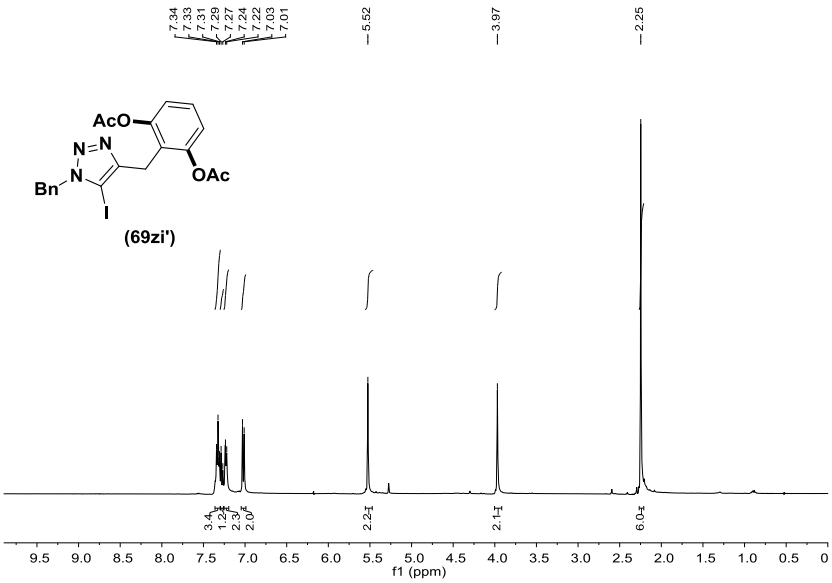
Spectrum 4.136. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69zh'**.



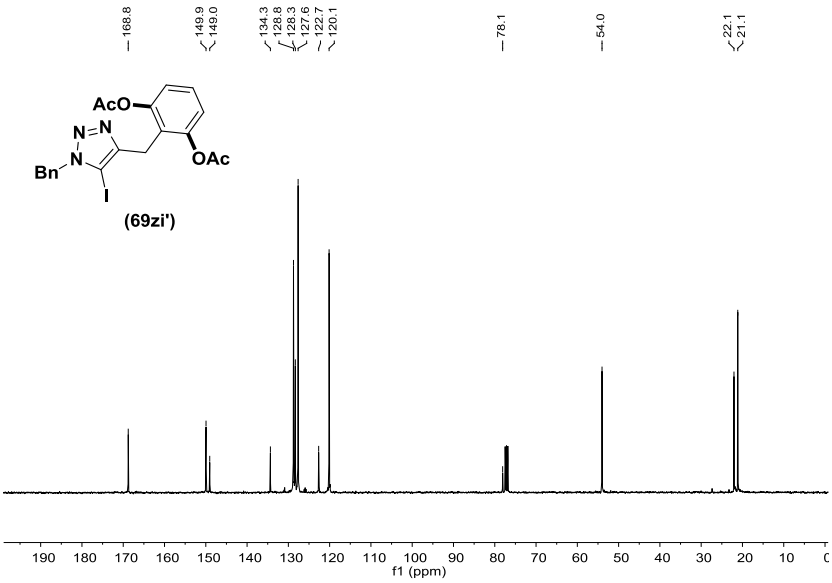
Spectrum 4.137. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zi**.



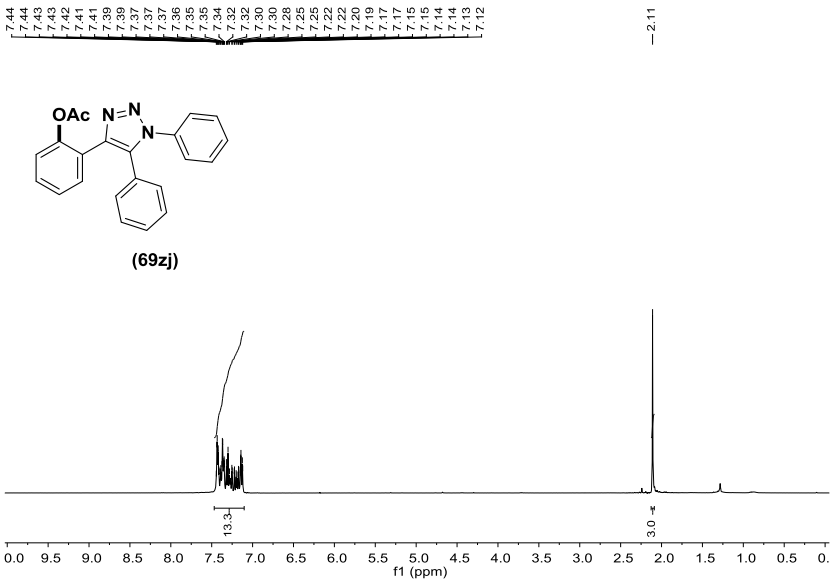
Spectrum 4.138. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69zi**.



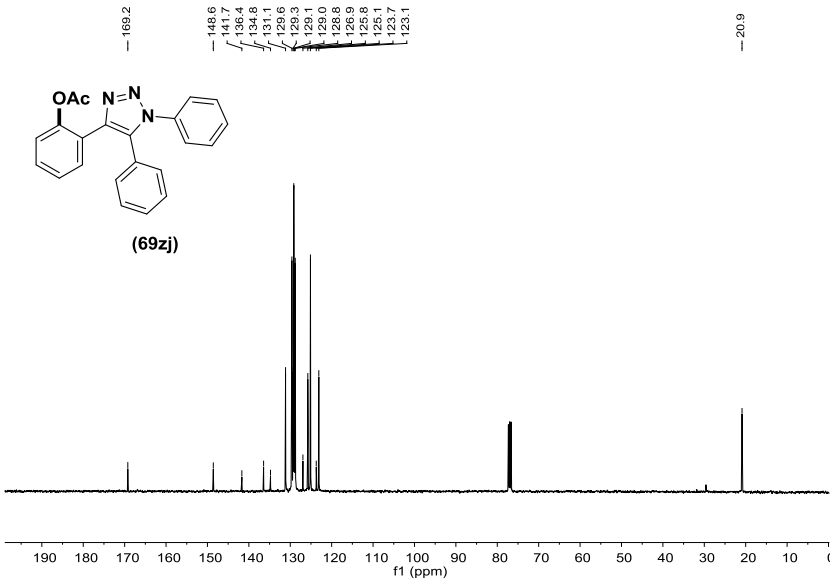
Spectrum 4.139. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zi'**.



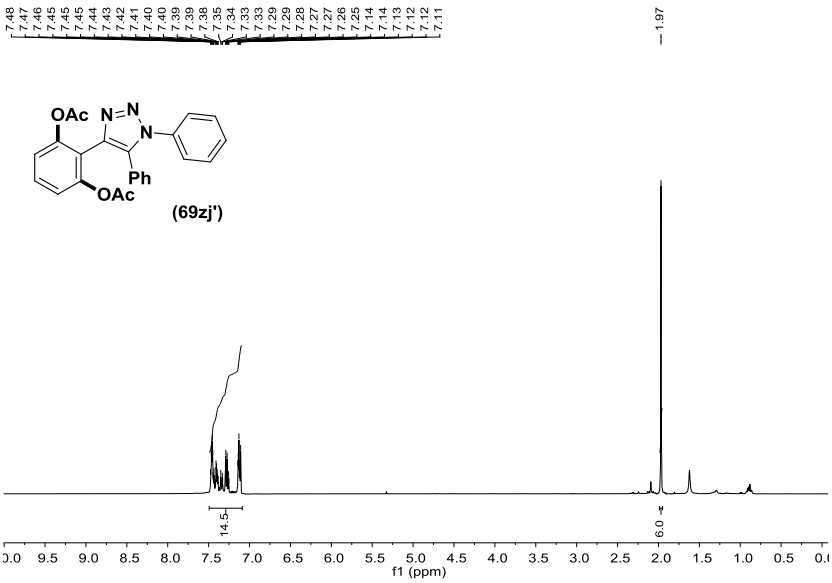
Spectrum 4.140. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69zi'**.



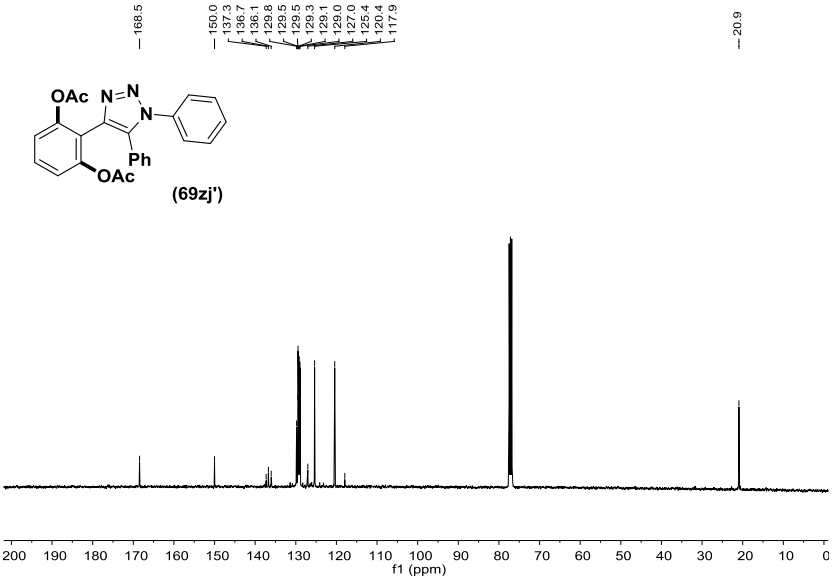
Spectrum 4.141. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zj**.



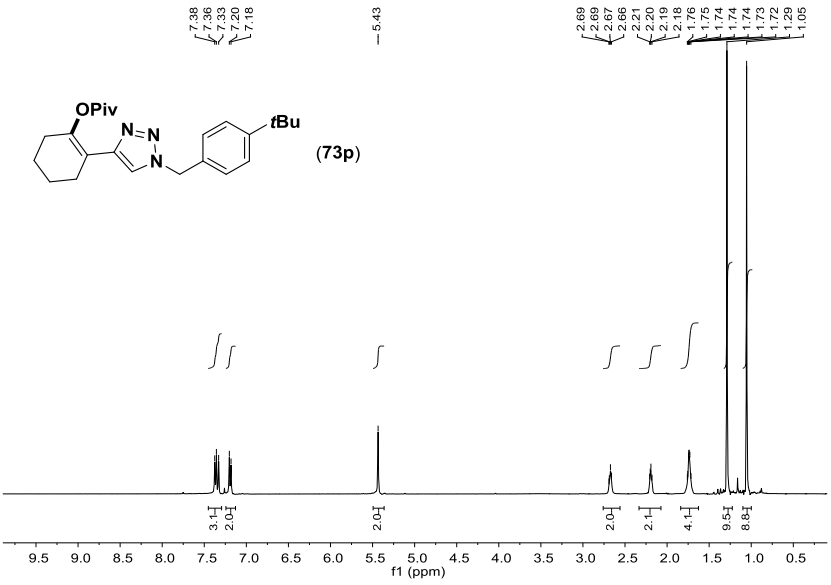
Spectrum 4.142. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **69zj**.



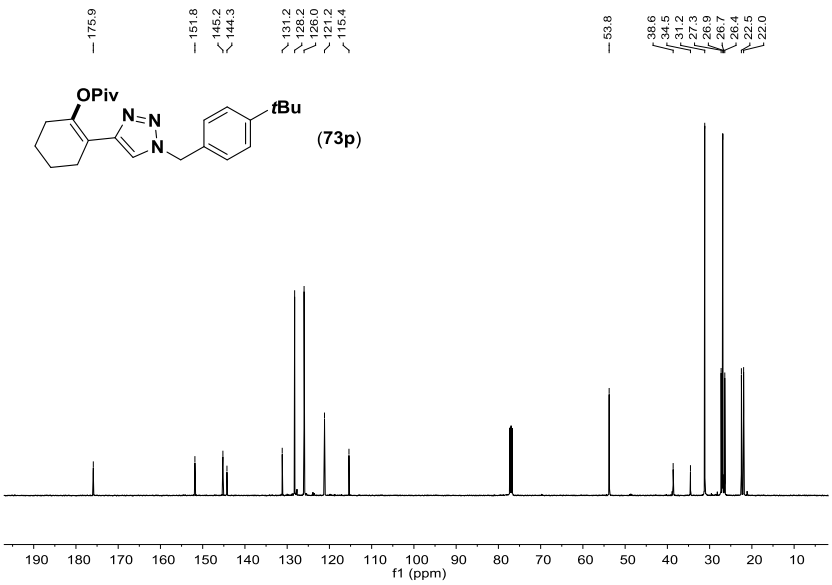
Spectrum 4.143. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69zj'**.



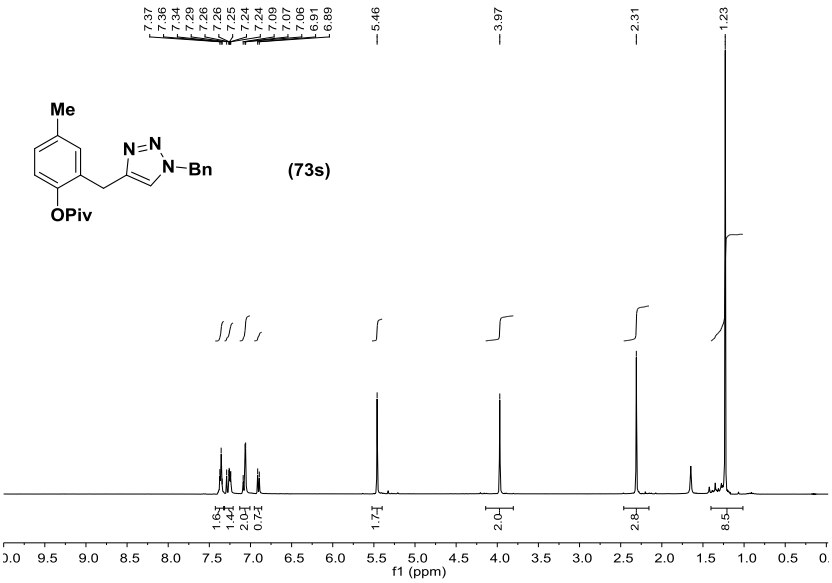
Spectrum 4.144. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **69zj'**.



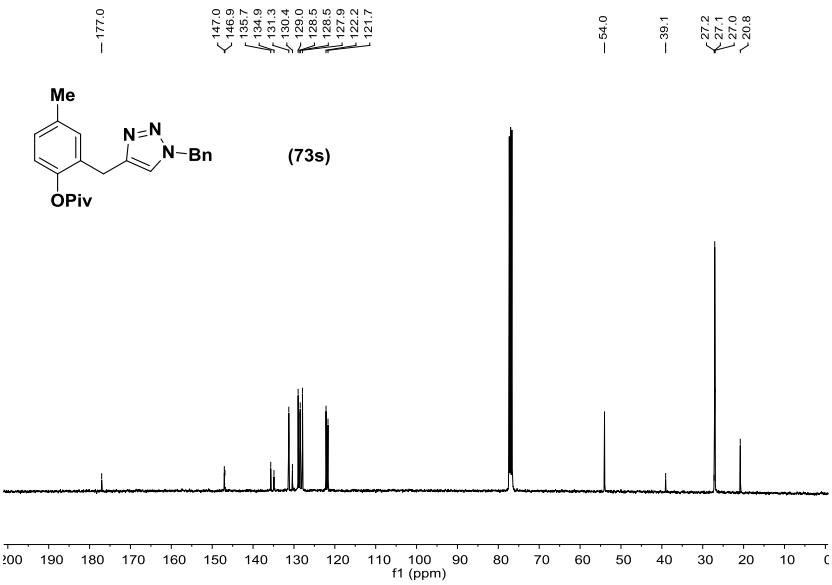
Spectrum 4.145. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **73p**.



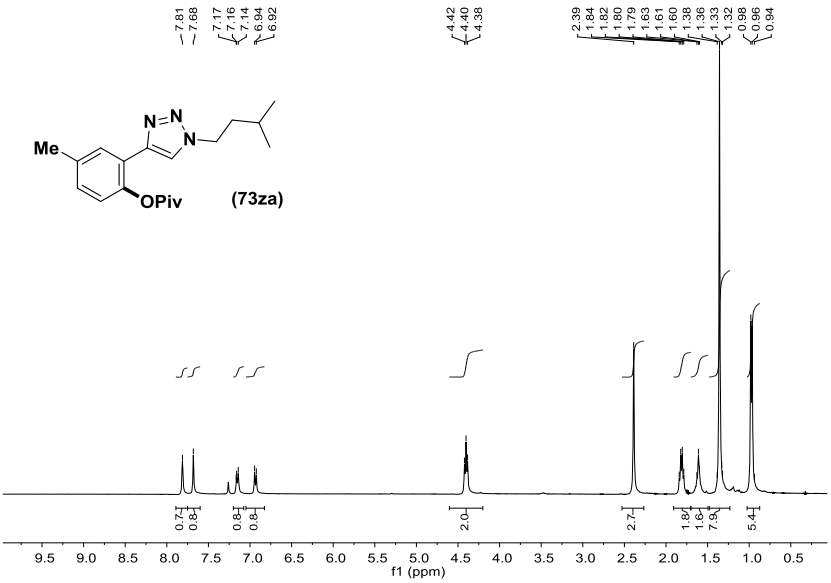
Spectrum 4.146. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **73p**.



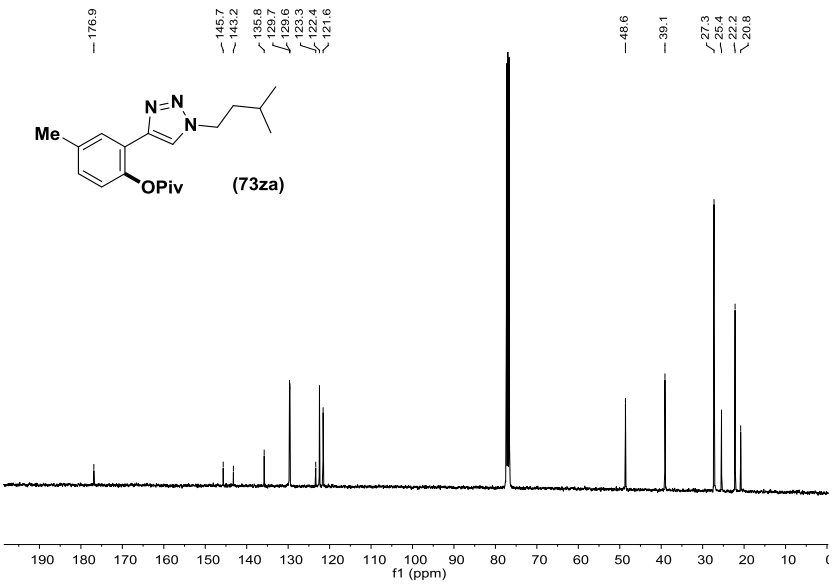
Spectrum 4.147. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **73s**.



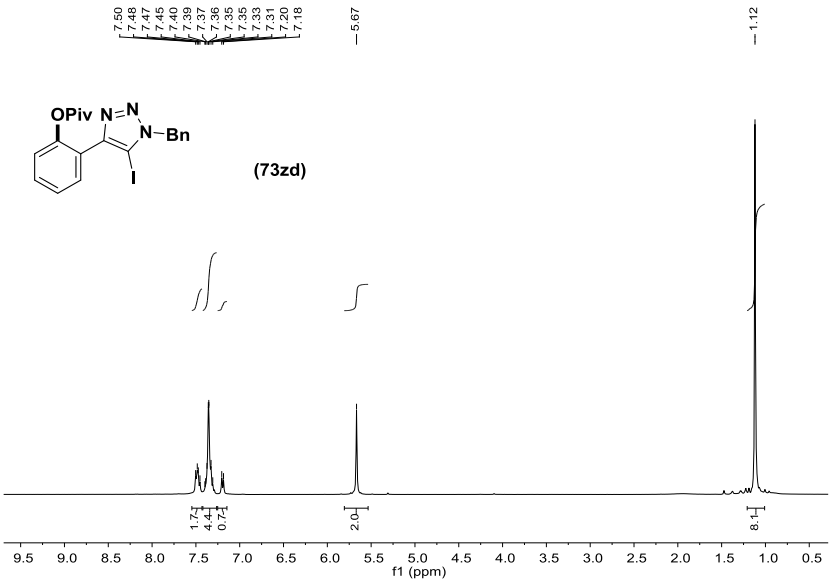
Spectrum 4.148. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **73s**.



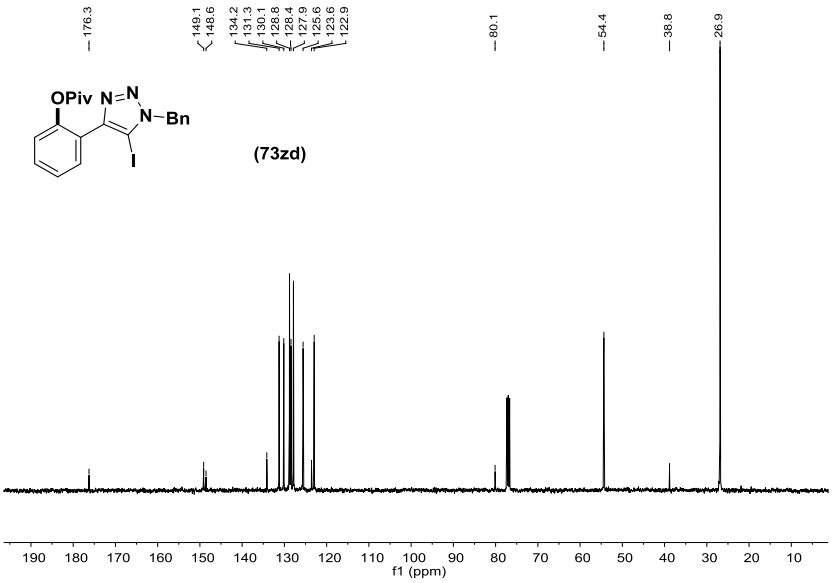
Spectrum 4.149. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **73za**.



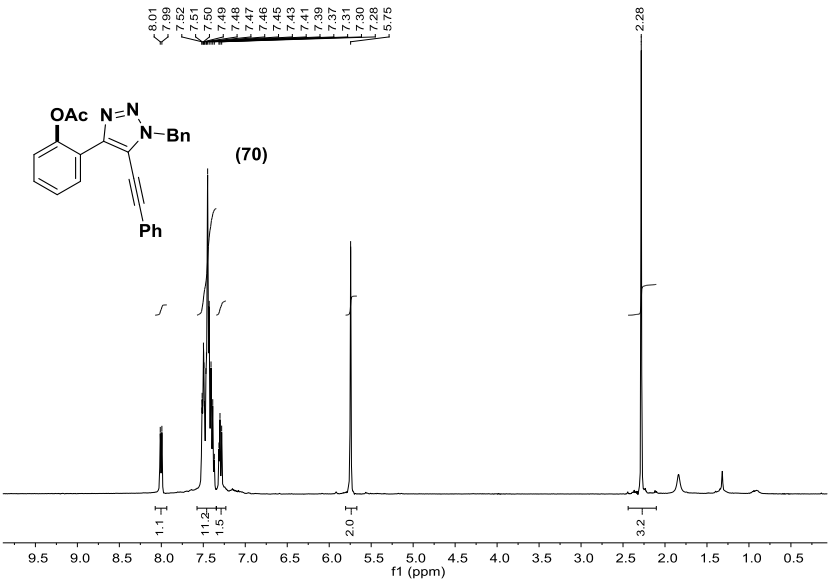
Spectrum 4.150. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **73za**.



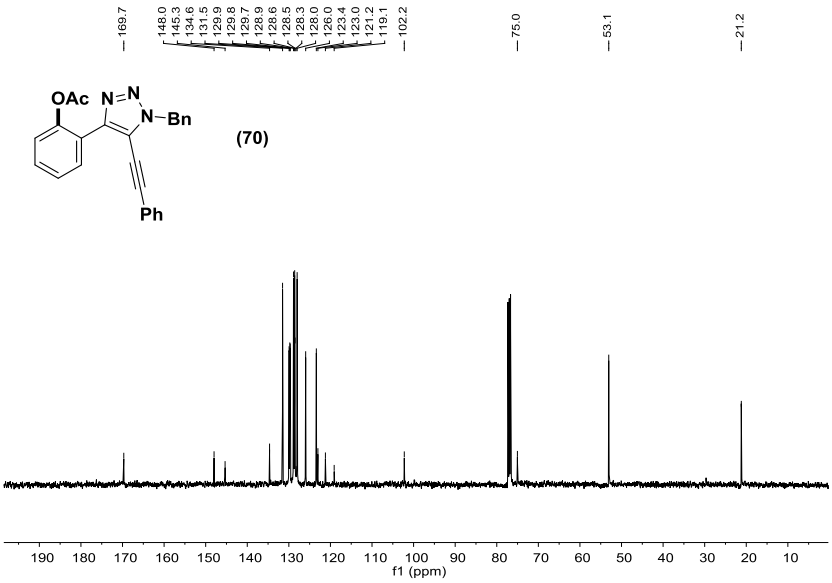
Spectrum 4.151. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **73zd**.



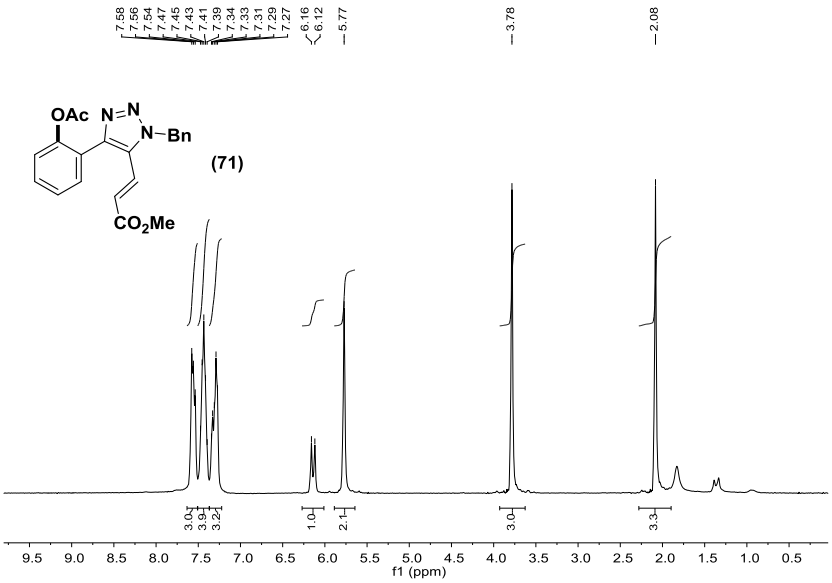
Spectrum 4.152. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **73zd**.



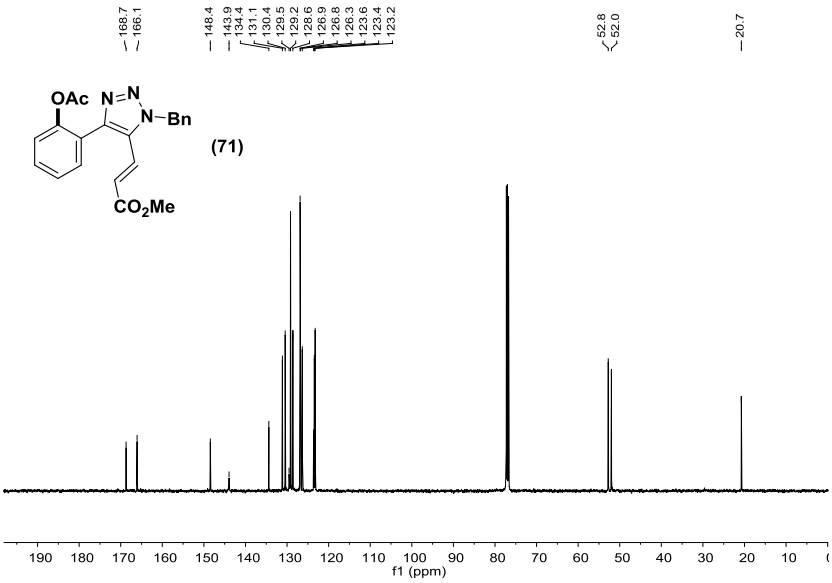
Spectrum 4.153. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **70**.



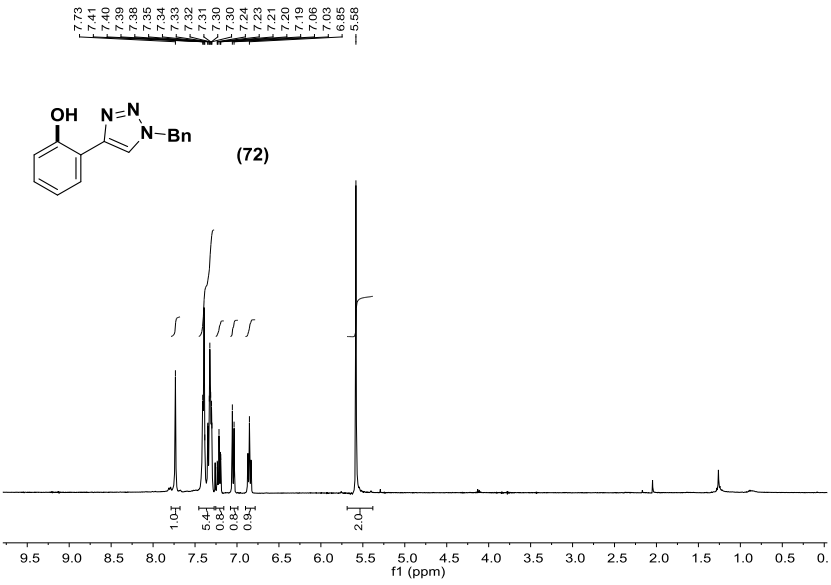
Spectrum 4.154. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **70**.



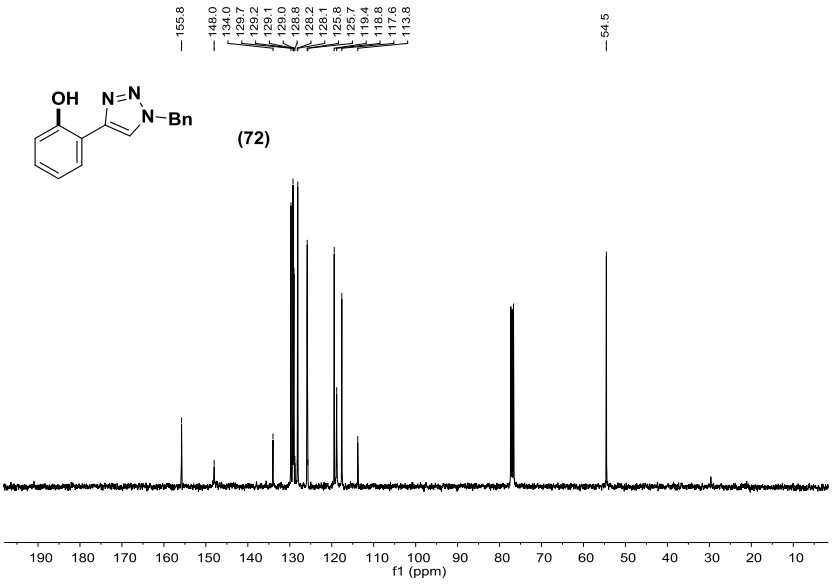
Spectrum 4.155. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **71**.



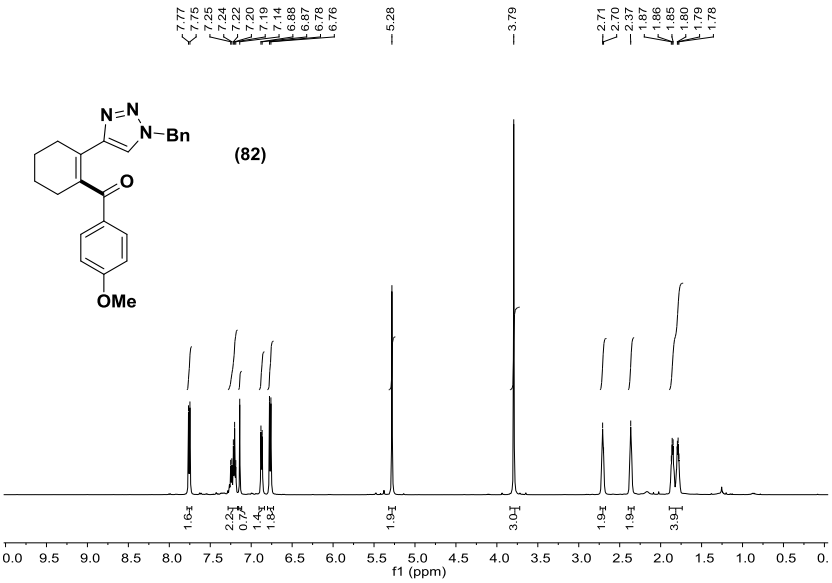
Spectrum 4.156. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **71**.



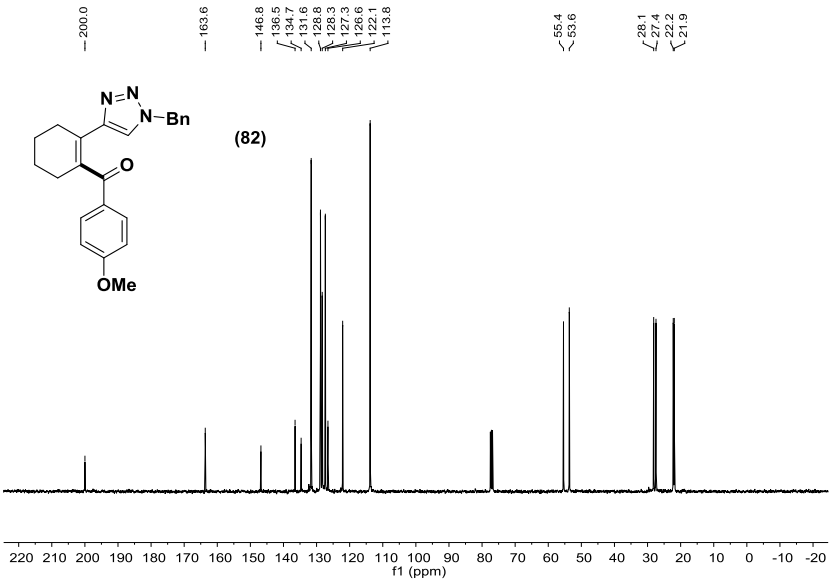
Spectrum 4.157. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **72**.



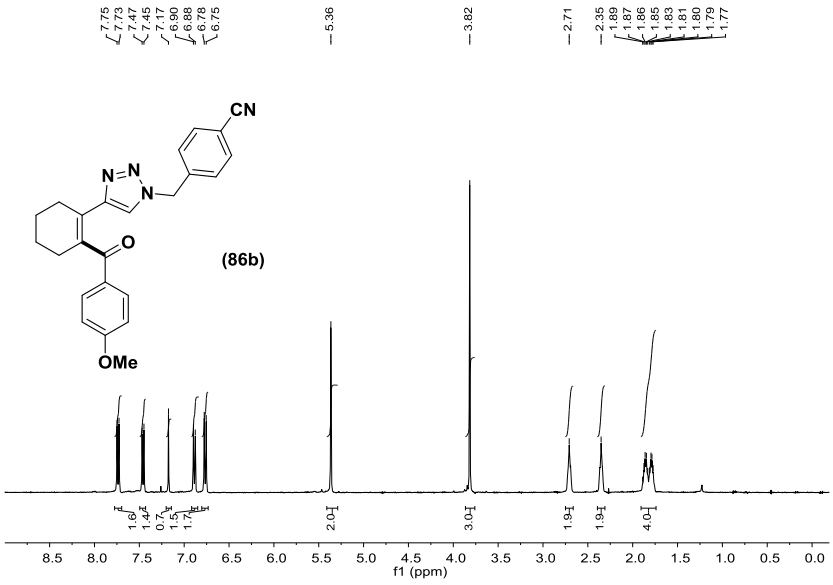
Spectrum 4.158. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **72**.



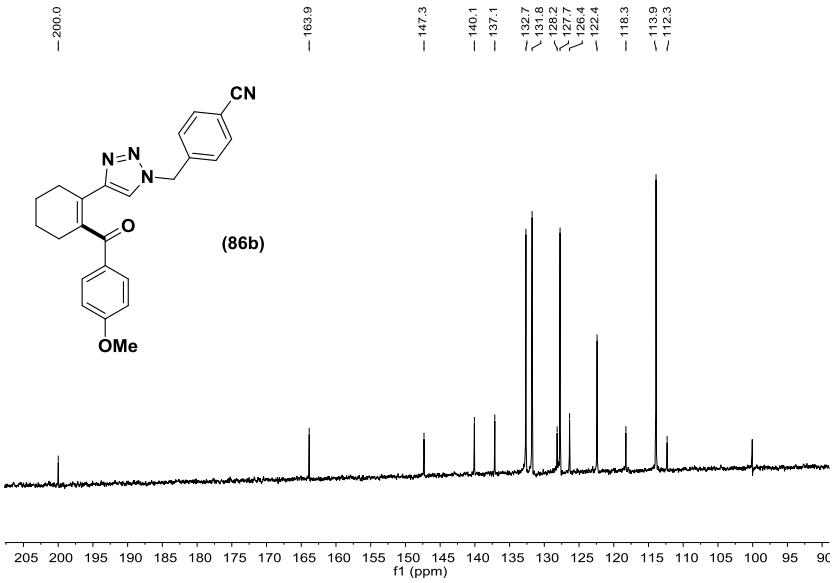
Spectrum 4.159. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **82**.



Spectrum 4.160. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **82**.



Spectrum 4.161. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **86b**.



Spectrum 4.162. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **86b**.