Universidad de Oviedo
Universidá d'Uviéu
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Departamento de Química Orgánica e Inorgánica

Programa de Doctorado "Síntesis y Reactividad Química"

CATALYTIC FORMATION OF CARBON-CARBON AND CARBON-OXYGEN BONDS: SELECTIVE ACTIVATION OF C-SI AND O-SI BONDS

Belén Rubial Parrondo

Tesis doctoral

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Belén Rubial Parrondo

Memoria presentada para optar al grado de Doctor en Química con Mención de Doctor Internacional

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RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: Formación catalítica de enlaces carbono-carbono y carbono-oxígeno: Activación selectiva de enlaces C-Si y O-Si.	Inglés: Catalytic formation of carbon-carbon and carbon-oxygen bonds: Selective activation of C-Si and O-Si bonds.

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RESUMEN (en español)

En esta memoria se presentan los resultados obtenidos a partir del desarrollo de una nueva estrategia sintética de formación de enlaces C-C y C-O. Esta nueva metodología se basa en la activación de nucleófilos que contienen un resto sililo lábil frente a ácidos de Lewis o de Brønsted. Tras esta activación, se forma in situ un ácido de Lewis derivado de silicio, que se encuentra implicado en la promoción de las transformaciones que tienen lugar en el medio de reacción.

La activación de alquinilsilanos mediante complejos metálicos carbofílicos, como los de oro(I), es conocida. Cuando se activa un trimetil(alquinil)silano con un complejo de oro(I), se genera un ácido de Lewis derivado de silicio, y su electrofilia puede ser modulada a través del contranión que acompaña al catalizador metálico.

En la primera parte, se describe una nueva reacción de bisalquiniliación de aldehídos aromáticos empleando esta estrategia. Ésta proporciona acceso a 1,4-diinos, que son estructuras de relevancia sintética. Esta transformación muestra una buena tolerancia a otros grupos funcionales. Un estudio en mayor profundidad de su mecanismo de reacción reveló la participación de un intermedio de tipo sililéter bencílico y propargílico, que sufre un proceso de sustitución tipo S_N1 durante el segundo paso de alquinilación.

En la segunda parte, se presentan los estudios relacionados con varios procesos de sustitución que derivan del uso de esta metodología catalítica. En primer lugar, se describe una nueva reacción de alquinilación de éteres y acetatos bencílicos. Esta transformación también ha mostrado una buena compatibilidad con distintos grupos funcionales, y se ha aplicado a la síntesis de pequeñas moléculas funcionalizadas. También se ha expandido mediante el empleo de otros nucleófilos sililados, como alilsilanos y silil enol éteres. Por otro lado, el correspondiente trabajo experimental ha desvelado que el mecanismo de esta transformación es de tipo catiónico, lo que ha abierto una puerta hacia el desarrollo de un proceso enantioselectivo. En este sentido, se presentan algunos resultados preliminares.

Además, se ha estudiado el uso de siliéteres como nucleófilos sililados. Se ha explorado el uso de esta metodología en la síntesis de éteres bencílicos, dando lugar a una variedad de éteres en condiciones de reacción suaves.

RESUMEN (en Inglés)

This dissertation presents the results concerning the development of a new synthetic strategy for the formation of C-C and C-O bonds, based on the activation of nucleophiles containing a labile silyl moiety towards Lewis acids, such as gold(I) complexes, and Brønsted acids. A silicon based Lewis acid formed in situ is the responsible of the transformations taking place in the reaction media.

The activation of alkynylsilanes by carbophilic metal complexes, such as gold(I) species, is well known. When a trimethyl(alkynyl)silane is activated in this manner, a silicon based Lewis acid is formed in the media, and its electrophilicity can be modulated through the counteranion accompanying the gold(I) catalyst.

In Part I, a new bis-alkynylation reaction of aromatic aldehydes employing this strategy is reported. It gives access to 1,4-diynes, which are relevant synthetic scaffolds. This transformation shows a nice functional group tolerance. Further experimental work provided a better insight of its reaction mechanism, which involves a propargylic and benzylic silyl ether undergoing a S_N1 process for the second alkynylation step.

In Part II, the studies concerning several substitution processes involving this catalytic methodology are reported. In first place, a new alkynylation reaction of benzylic ethers and acetates is described. This transformation has also presented a nice functional group tolerance and it has been applied to the synthesis of highly functionalised small molecules. It has also been expanded to other silylated nucleophiles, such as allylsilanes and silyl enol ethers. On the other hand, the corresponding experimental work has unveiled a cationic mechanism for this process, which has opened the door to the development of an enantioselective transformation of this kind. Some preliminary results are also presented.

Besides, the use of silyl ethers as silylated nucleophiles has also been studied. The synthesis of benzylic ethers using this methodology has been explored, getting access to a variety of ethers under mild catalytic conditions.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN SÍNTESIS Y REACTIVIDAD QUÍMICA

A mi abuelo

To my grandfather

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When I look at this book, I hope it becomes a reflexion of these last almost five years of exponential growth, both professionally and personally. There have been wonderful and very hard times, but when it comes to look back, our brain wisely hides all the bad moments to our conscious mind, and presents us a collection of the great events that made this work worth the time and patience we spent on it.

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***

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Table of Contents

Abbreviations and Acronyms

A

Ac	acyl
Ad	adamantyl
approx.	approximately
Ar	aryl

B

BINAP	(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	benzyl

C

c	speed of light
ºC	Celsius degrees
cat.	catalytic
Cbz	carboxybenzyl
Cp	cyclopentadienyl
Cy	cyclohexyl

D

d	doublet
δ	NMR chemical shift
DCE	1,2-dichloroethane
dd	double doublet
DEPT	distortionless enhancement by polarization transfer
DIPA	diisopropylamine
DIPT	diisopropyl tartrate
DMF	dimethylformamide
DMI	dimethylimidazolidinone
d.r.	diastereomeric ratio
dt	double triplet

E

e	elementary charge
ε_0	vacuum permittivity

ee	enantiomeric excess
El	electrophile
equiv	equivalents
Et	ethyl

H

$\hbar$	reduced Planck constant or Dirac constant
h	hours
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HOMO	higher occupied molecular orbital
HRMS	high resolution mass spectroscopy

I

IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene

J

J	coupling constant
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine

L

LA	Lewis acid
LB	Lewis base
LDA	lithium diisopropylamide
LUMO	lower unoccupied molecular orbital

M

m	multiplet
m	mass
m-	*meta*
m_0	non-relativistic (rest) mass
Me	methyl
MO	molecular orbital
Ms	mesyl, methanesulfonyl
MW	microwave

N

*n*Bu	butyl
NCS	N-chlorosuccinimide
NHC	N-heterocyclic carbene
*n*Hex	hexyl
NMR	nuclear magnetic resonance
Np	naphthyl
Nu	nucleophile

O

o-	*ortho*

P

p-	*para*
Ph	phenyl
PMP	*p*-methoxyphenyl
PyBox	pyridine-bis(oxazolyne)

Q

q	quartet

R

rt	room temperature

S

s	singlet

T

t	triplet
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxyde
TBS, TBDMS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF	turnover frequency
Tol	tolyl
TON	turnover number
Ts	tosyl, toluenesulfonyl

V

v	speed, rate
vs.	versus

X

XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Z

Z	atomic number

Introduction

Introduction

This dissertation is focused on the development of new chemical methodology employing different catalytic species with different roles within the process, but whose behaviour can essentially be explained as Lewis acids. In particular, gold(I) and silicon species are used to perform new transformations presenting useful advantages when compared to other methodologies reported in the literature, or simply affording products that are not easily obtainable by other synthetic routes.

In order to put the results that will be explained in the following pages into context, it is necessary to point out a few general remarks, which will be discussed in further depth or extension later in this book.

The Importance of Lewis Acids in Organic Synthesis

In 1928, G. N. Lewis established his definition of an acid and a base using the following words:[1]

'It seems to me that with complete generality we may say that a basic substance is one which has a lone pair of electrons which may be used to complete the stable group of other atom and that an acid substance is one which can employ a lone pair from another molecule in completing the stable group of one of its own atoms. In other words, the basic substance furnishes a pair of electrons for a chemical bond; the acid substance accepts such a pair'.

In that same year, Brønsted and Lowry independently proposed their proton-based definitions, which had immediate acceptation, and it was not until the next decade when Lewis' definition demonstrated to be the most useful definition in terms of generality, thanks to the experimental evidences obtained from the observation of non protic substances behaving like acids or bases in classic titration processes with coloured indicators in aqueous solution, as well as the development of Quantum Mechanics and its influence on the Valence Bond and Molecular Orbital theories.

[1] For a review about the development and of LA and base definitions see W. B. Jensen, *Chem. Rev.* **1978**, *78*, 1–22.

A more practical definition of Lewis' base and acid concepts concerning the MO theory is the following one: [1]

'A base is a species which employs a doubly occupied orbital in initiating a reaction. An acid is a species which employs an empty orbital in initiating a reaction'.

Thus, these concepts cover not only the chemistry of acid-base reactions, but a wide range of chemical phenomena, such as ligand to metal coordination, nucleophilic and electrophilic substances or donor-acceptor reactions.

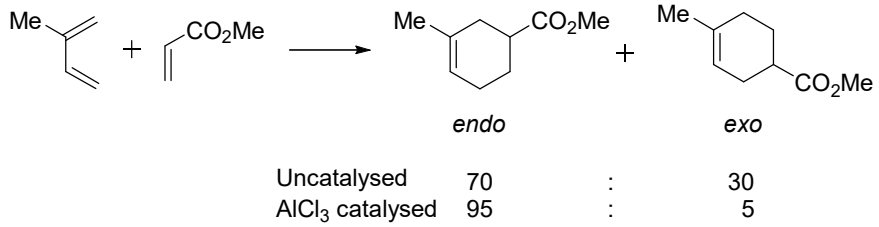
Catalytic methodologies are broadly used in chemical processes, because of their contribution to minimise the amount of starting materials, energy and time employed, and to improve the reaction selectivity.[2] Since the introduction of the Lewis acid (LA) concept, acid catalysed processes have developed especially fast, becoming a prominent field for some organometallic reagents, whose finally explained acid behaviour opened the door to many different applications.[3] Nowadays, LA-catalysed reactions have become a routine in the synthetic chemical world.

An example of the importance of this development is the Ziegler-Natta process, which allows the preparation of many polymeric materials of spread use in our daily lives, such us polyethylene or polyisoprene.[4a]

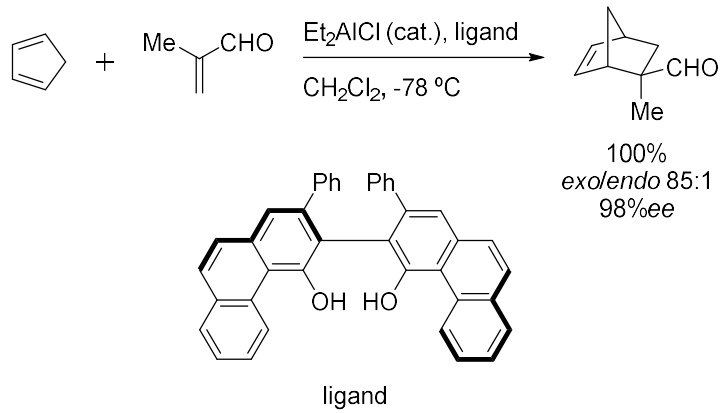
In the last decades, many classic reactions have been improved over and over applying new generations of LA catalysts. A clear example that can be used to illustrate these achievements is the enhancements in the Diels-Alder reaction (Scheme 1). This transformation can be promoted thermally with excellent yield but moderate selectivity between the *endo*- and *exo*-adducts, as usual for non-rigid dienophiles.[4b] LA catalysis allows the reaction to occur at room temperature, which decreases the energetic cost of the process, but also extremely improves the selectivity towards the *endo* adduct.[4c] Moreover,

[2] C. A. Busacca, D. R. Fandrick, J. J. Song, C. H. Senanayake, *Adv. Synth. Catal.* **2011**, *353*, 1825–1864.
[3] H. Yamamoto in *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH Verlag GmbH, **2000**, pp. 1–7.
[4] a) H. Sinn, W. Kaminsky, in *Advances in Organometallic Chemistry* (Ed.: F. G. A. Stone. and R. West), Academic Press, **1980**, pp. 99–149. b) K. N. Houk, L. J. Luskus, *J. Am. Chem. Soc.* **1971**, *93*, 4606–4607. c) T. Inukai, and T. Kojima *J. Org. Chem.* **1966**, *31*, 1121–1123. d) J. Bao, W. D. Wulff, A. L. Rheingold, *J. Am. Chem. Soc.* **1993**, *115*, 3814–3815.

providing the LA with an enantiopure chiral ligand affords very good stereoselectivity as well as regioselectivity (Scheme 2).[4d]



Scheme 1: Improved regioselectivity in a LA-catalysed Diels-Alder reaction.

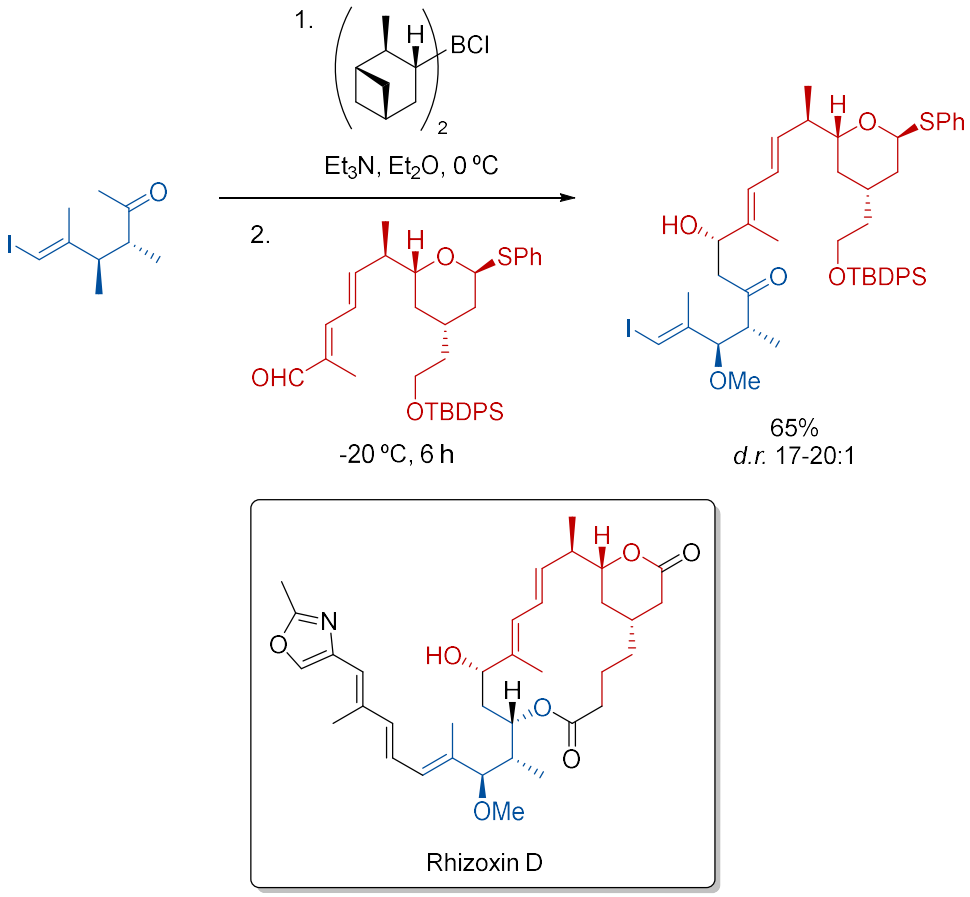


Scheme 2: Enantioselective LA-catalysed Diels-Alder reaction.

Besides the Diels-Alder and Hetero-Diels-Alder cycloadditions, a few other important mentions can be done. One case are aldol-type reactions, which can be catalysed by a great variety of metal and metalloid species, such as titanium, boron or lanthanum,[5] and are widely used in organic synthesis. Scheme 3 shows a key step in the total synthesis of Rhizoxin D, in which an aldol reaction, catalysed by a chiral organoboron compound, is used to couple two main fragments of the molecule with excellent diastereoselectivity.[6a]

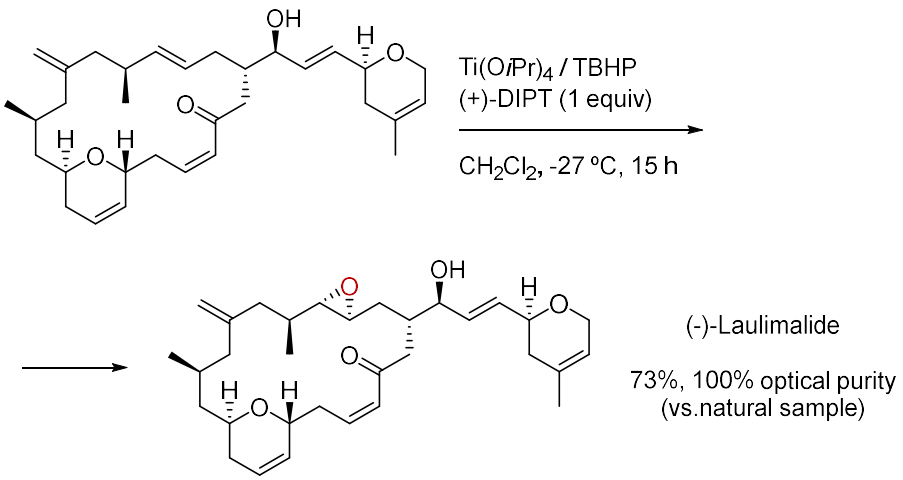
[5] L. Kürti, B. Czakó, in *Strategic Applications of Named Reactions in Organic Synthesis* (Ed. J. Hayhurst), Elsevier Academic Press, Burlington, MA, **2005**, pp. 8-9.

[6] a) J. De Brabander, W. Oppolzer, *Tetrahedron* **1997**, *53*, 9169–9202. b) I. Paterson, C. De Savi, M. Tudge, *Org. Lett.* **2001**, *3*, 3149–3152. c) G. H. Posner, M. H. Parker, J. Northrop, J. S. Elias, P. Ploypradith, S. Xie, T. A. Shapiro, *J. Med. Chem.* **1999**, *42*, 300–304.

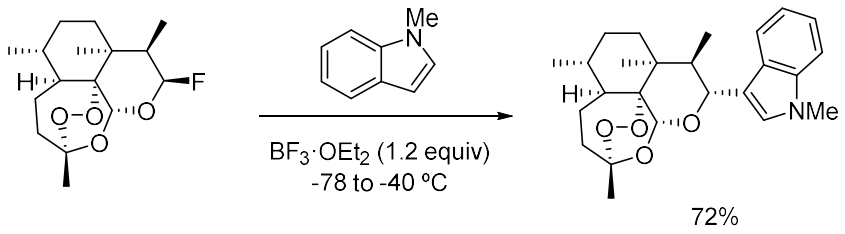


Scheme 3: Key aldol reaction step in the synthesis of Rhizoxin D. The final product is shown below the reaction.

Another important transformation is the Sharpless asymmetric epoxidation, which employs a titanium complex provided with a chiral ligand. Although it is limited to allylic alcohols, it is very reliable and also commonly used in total synthesis, even for final steps (see Scheme 4).[6b] The last example is the Friedel-Crafts alkylation, which is not just a useful transformation, but it also settled the bases for the broad and actively growing field of hydroarylations. Scheme 5 shows its application in the preparation of a semisynthetic antimalarial trioxane.[6c]



Scheme 4: Final step in the synthesis of (-)-Laulimalide. Sharpless asymmetric epoxidation provides the final product in good yield, and with excellent stereoselectivity and regioselectivity.



Scheme 5: Final step in the semisynthesis of an antimalarial trioxane. Friedel-Crafts reaction catalysed by a borane complex.

Always expanding towards more versatile, selective and powerful processes, chemists have explored the acidity of many elements and their corresponding ligand-based, additive-based or even co-catalyst-based alternatives. However, there is still unknown space to be explored, and this field is currently in growth. The noble metals (gold and platinum) were the last ones in gaining attention, well into the 20th century,[7] and even some well-known Lewis acids, like organosilicon compounds, have started to be applied quite recently.[8]

[7] a) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449. b) A. Stephen, K. Hashmi, *Gold Bull.* **2004**, *37*, 51–65. c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346. d) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072.

[8] M. Oishi, in *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH Verlag GmbH, **2000**, pp. 355–393.

Gold Species as Lewis Acids

Gold and platinum, as well as their close relatives in the Periodic Table, present unique LA properties. They are, like many metals, π-*acids*, but their behaviour differs from most of them.[7a]

A π-*acid* is defined as *any species that contains an empty orbital which can be stabilised by accepting part of the electronic density contained in any kind of carbon-carbon multiple bond, thus forming a coordination bond.*

In the particular case of gold, this bond is especially favourable, since it is a 'soft' transition metal, which prefers 'soft' bonding partners, such as carbon, instead of 'hard' partners, like oxygen. This makes gold rather more *carbophilic* than *oxophilic*, that is the opposite behaviour from most LA species. Oxophilicity in gold(III) species is slightly stronger than in gold(I) species, in the same way that oxophilicity in platinum(IV) is higher than in platinum(II) species.

However, oxidation from Pt^{II} to Pt^{IV} is fairly easier than oxidation from Au^{I} to Au^{III}. As a consequence, gold complexes are unlikely to undergo oxidative additions or reductive elimination.[9] They are also not too prone to α-hydride elimination. Instead, they undergo fast *proto-demetallation*.[7b]

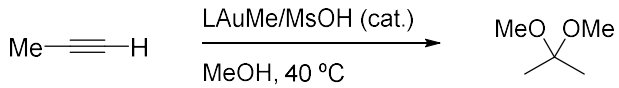
Since it was believed that gold(I) was unable to participate in reactions based on redox principles, its catalytic properties have been overlooked, when in fact, this makes it more selective and respectful with other functional groups, as well as easier to recover in its original state. Gold(I) complexes are also safe and offer a remarkable atom economy.[10]

[9] Very specific cases have been recently reported, but they rely on complex ligand designs or special activation conditions: a) M. Joost, A. Zeineddine, L. Estévez, S. Mallet−Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, *J. Am. Chem. Soc.* **2014**, *136*, 14654–14657. b) M. Joost, L. Estévez, K. Miqueu, A. Amgoune, D. Bourissou, *Angew. Chem. Int. Ed.* **2015**, *54*, 5236–5240. c) M. S. Winston, W. J. Wolf, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 7777–7782. d) C.-Y. Wu, T. Horibe, C. B. Jacobsen, F. D. Toste, *Nature* **2015**, *517*, 449–454. e) A. Tlahuext-Aca, M. N. Hopkinson, C. G. Daniliuc, F. Glorius, *Chem. Eur. J.* **2016**, *22*, 11587–11592. f) P. Gualco, S. Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, *Angew. Chem. Int. Ed.* **2011**, *50*, 8320–8324. g) R. Kumar, C. Nevado, *Angew. Chem. Int. Ed.* **2017**, *56*, 1994–2015.

[10] B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.

And, despite gold is considered expensive, its price is comparable to or even smaller than other precious and industrial metals, such as rhodium, iridium or palladium.[7a]

One of the first reports in which gold complexes were intentionally employed as LA catalysts is a study of the activity of several gold(I) species as catalysts for the addition of alcohols to alkynes, reported by Teles et al. in 1998 (Scheme 6).[11] In these experiments, it was found that gold complexes presented very high TON and TOF values, perfectly able to compete with other π-acids, and that they were easily tuned by changing the ligands attached to the metallic centre. This opened a door to a whole new catalytic world.



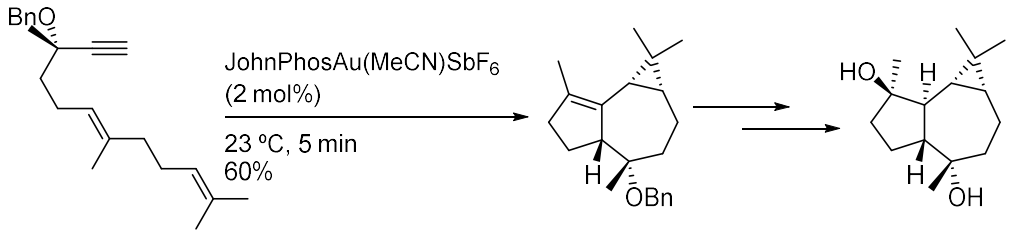
Scheme 6: Hydroalkoxylation of alkynes catalysed by gold(I) species.

During the past century and the beginning of the current one, the number of publications about gold catalysis has increased exponentially.[7b, 12] As Lewis acid, it is mainly employed for π-system activation, affording nucleophilic addition reactions, arylation reactions, cyclization reactions, and rearrangements. Due to its functional group tolerance, gold catalysts have found a place in total synthesis.[13] In the example below (Scheme 7), a gold complex performs an intramolecular cyclisation reaction of two π-systems from a terpene, providing a witty strategy to make this very particular scaffold accessible.[13c]

[11] a) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418. b) For a seminal work in gold(I) catalysis see: Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.

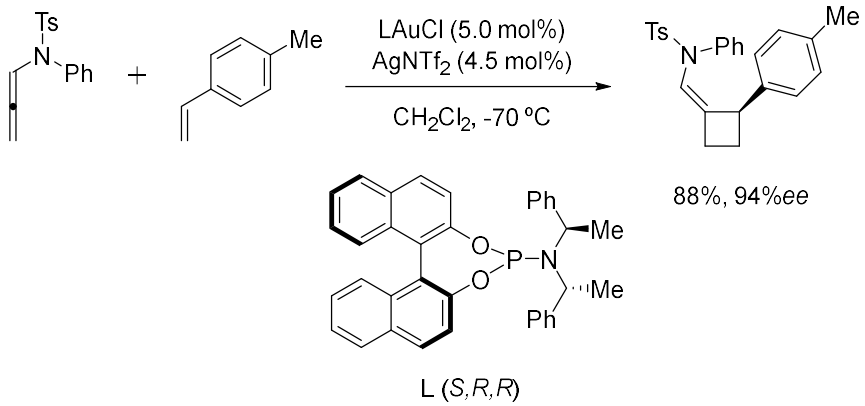
[12] For other selected reviews from the first decade of the 20th century see: a) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265. b) A. S. K. Hashmi, *Gold Bull.* **2003**, *36*, 3–9. c) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378.

[13] a) B. M. Trost, G. Dong, *Nature* **2008**, *456*, 485–488. b) M. S. Kirillova, M. E. Muratore, R. Dorel, A. M. Echavarren, *J. Am. Chem. Soc.* **2016**, *138*, 3671–3674. c) B. Ranieri, C. Obradors, M. Mato, A. M. Echavarren, *Org. Lett.* **2016**, *18*, 1614–1617. d) J. Carreras, M. Livendahl, P. R. McGonigal, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2014**, *53*, 4896–4899. e) K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2010**, *49*, 3517–3519.



Scheme 7: Step from the total synthesis of (-)-4b,7a-aromadendranediol.

Our research group has made their own contributions to the field of gold(I) catalytic methodology. Scheme 8 shows an example from a recent publication in which a gold(I) complex provided with a chiral ligand is used to promote the first intermolecular enantioselective [2+2] reaction between an allenamide and an olefin.[14]



Scheme 8: Enantioselective [2+2] addition catalysed by a gold(I) complex with an enantiopure chiral phosphoramidite as ligand.

[14] S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2012**, *51*, 11552–11555.

Silicon Species as Lewis Acids

Silicon is the most abundant element in the solid Earth, being most of it in the mantle, it is also cheap and has no general acute toxic effects.[15] Moreover, organosilicon compounds are not especially difficult to prepare, and they are soluble and stable in common organic solvents, whereas other frequently used LAs, such as metal halides, tend to aggregate and undergo disproportionation or ligand exchange.[8]

However, silicon-based Lewis acids have been one of the latest studied ones. They received attention firstly as protective groups, which created a useful variety of commercially available organosilicon compounds. And it was this fact what promoted the development of its use as LAs later in time.

Silicon: Elemental Properties and Differences from Carbon

Silicon is an element from group 14 in the Periodic Table, right below carbon. However, its properties differ in several things from its neighbour, starting by its electronegativity, 1.90 on the Pauling Scale (values for C and H on the same scale 2.55 and 2.20, respectively),[16] which is more similar to the values for some transition metals, like silver or copper.[17]

This low electronegativity value, as well as the presence of low energy available *d* orbitals, allows it to form hypervalent species, opening reaction pathways that are not possible for carbon. Another particular property of silicon derived from its *d* orbitals is the formation of strong bonds with oxygen. This is also partially explained by the electronegativity and size of oxygen, which is translated into a greater ionic component in this bond.[17,18]

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[15] A. v. Hirner, D. Flassbeck, R. Gruemping, in *Organometallic Compounds in the Environment* (Ed.: P.J. Craig), John Wiley & Sons, Ltd, **2003**, pp. 305-351.

[16] The Sanderson scale, which has never been widely accepted, but has explained successfully the peculiar properties of the electronegativities of post-transition metals, calculates an even lower value of 1.74 for Si, and similar values for C and H. J. E. Huheey, in *Inorganic Chemistry*, Harper&Row, New York, **1978**, p. 175-177.

[17] J. Y. Corey, in *Organic Silicon Compounds (1989)* (Eds.: S. Patai, Z. Rappoport), John Wiley & Sons, Ltd, **1989**, pp. 2-49.

[18] H. F. T. Klare, M. Oestreich, *Dalton Trans.* **2010**, *39*, 9176–9184.

Trivalent silyl cations are also different from carbocations. It is not possible to apply the knowledge we have about hyperconjugation effects in carbocations to related silylium ions and, since its electrophilicity is considerably higher, it is necessary to take into account the nucleophilicity of even the least coordinating solvents and anions.[19]

Silicon-Based Lewis Acids: Properties and General Preparation Methods

Organosilicon compounds are LAs due to the low electronegativity of silicon and its ability to expand its valence. They easily incorporate bases and nucleophiles present in the medium and, when forming hypervalent species, they become powerful nucleophiles for addition reactions.[17] This acidity depends on the electron-withdrawing properties of the substituents in the silicon atom. Thus, the species Me_3SiBr is a weaker acid than the species Me_3SiOTf.[18] Species like tetraalkylsilanes are extremely weak acids and do not serve for catalytic purposes. Instead, they are used as protecting groups. Even species such as the ones above mentioned are not too acidic and can be used for protection too.[8]

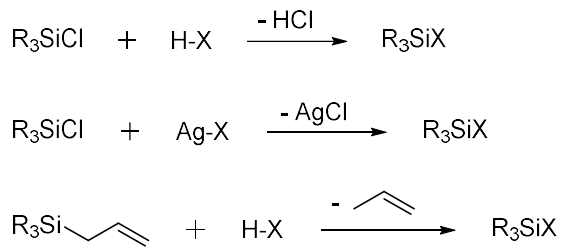
Although Me_3SiOTf is already a fairly acidic species and soon became a representative catalyst in this field,[8,20] there are reactions it is not able to promote. In order to create more acidic catalysts, it was necessary to synthesise silicon species whose nature is closer to a silylium ion, using less and less Lewis basic counteranions. They can be prepared from more simple organosilicon acids that are commercially available. Also, in some cases, such as Me_3SiOTf itself, these commercial reagents are sensitive to moisture or have traces of the conjugated protic acid, being more convenient to have them freshly prepared.[8]

A possible preparation method is the reaction of a silyl chloride with the silver salt or the conjugated acid of the desired counteranion. A cleaner method is the reaction of the conjugated acid of the desired counteranion with the allyl-substituted silane, generating propene gas as the only by-product, which is volatile (Scheme 9).[8]

---

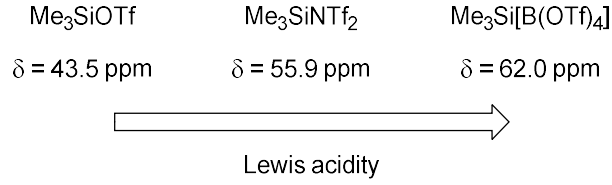
[19] a) J. B. Lambert, W. J. Schulz, J. A. McConnell, W. Schilf, *J. Am. Chem. Soc.* **1988**, *110*, 2201–2210. b) For more details about the difficult handling of silyl cations see: C. A. Reed, *Acc. Chem. Res.* **1998**, *31*, 325–332. c) K.-C. Kim, C. A. Reed, D. W. Elliott, L. J. Mueller, F. Tham, L. Lin, J. B. Lambert, *Science* **2002**, *297*, 825–827.

[20] R. Noyori, S. Murata, M. Suzuki, *Tetrahedron* **1981**, *37*, 3899–3910.



Scheme 9: Three methods to prepare organosilicon LAs of weakly coordinating counteranions.

Apart from triflate, bis(trifluoromethanesulfonyl)imidate (NTf_2^-), perchlorate or tetrakis(trifluoromethanesulfonyl)borate [$B(OTf)_4^-$] are among the most convenient and popular counteranions that are useful for this purpose.[7] The chemical shift of the silicon atom in the ^{29}Si-NMR spectra can be used to illustrate the acidity of each species (Scheme 10). The higher the chemical shift, the closer to a silylium ion the species will be, but it still will be a tetravalent species.[18,21]

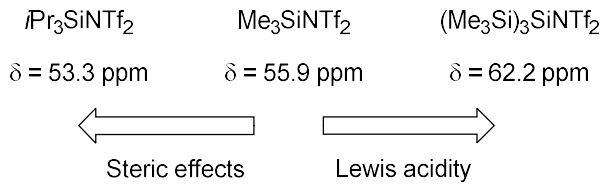


Scheme 10: ^{29}Si-NMR chemical shifts for different Si-based LAs.

The Lewis acidity can be also influenced by steric factors coming from the substituents in the silicon atom (Scheme 11).[18,22] Bulkier substituents will lead to less acidic species. However, although the group $(Me_3Si)_3Si$- is larger than the Me_3Si- group, the longer Si-Si bond, and the lower electronegativity of the Si atom compared to carbon, makes the species $(Me_3Si)_3SiNTf_2$ a more acidic LA.

[21] A. P. Davis, J. E. Muir, S. J. Plunkett, *Tetrahedron Lett.* **1996**, *37*, 9401–9402.

[22] a) B. Mathieu, L. de Fays, L. Ghosez, *Tetrahedron Lett.* **2000**, *41*, 9561–9564. b) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48–49.



Scheme 11: Effect of the Si substituents on the chemical shift of some Si-based LAs.

Reactions Catalysed by Silicon-Based Lewis Acids

Si-based LA catalysts have made an impact in C-C bond forming reactions, as well as in C-heteroatom bond forming reactions, rearrangements and even oxidation reactions.[8]

Being strong LAs, they create a strong electrophile when activating a substrate, allowing a great variety of nucleophiles to react with it. This strategy is the contrary to the one traditionally followed by other important C-C bond forming reactions, such as cross-coupling reactions or Grignard's reagent additions to carbonyl groups, which are based on a strong nucleophile that will react with a variety of electrophiles.[23]

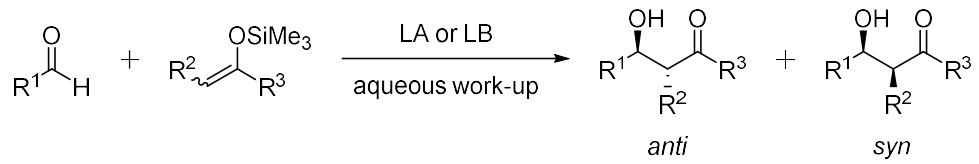
In order to discuss some examples of reactions catalysed by Si-based LAs, they will be presented sorted into groups according to the formal result of the reaction:

a) *Aldol-Type and Allylation Reactions*

One of the most successful LA-promoted reactions is the Mukaiyama aldol reaction between a silyl enol ether and a carbonyl compound (Scheme 12), first reported in 1974 and originally catalysed by $TiCl_4$, $SnCl_4$ or $BCl{\cdot}OEt_2$.[24]

[23] a) L. Kürti, B. Czakó, in *Strategic Applications of Named Reactions in Organic Synthesis* (Ed. J. Hayhurst), Elsevier Academic Press, Burlington, MA, **2005**, pp. 188-189. b) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824. c) J. Terao, N. Kambe, *Acc. Chem. Res.* **2008**, *41*, 1545–1554.

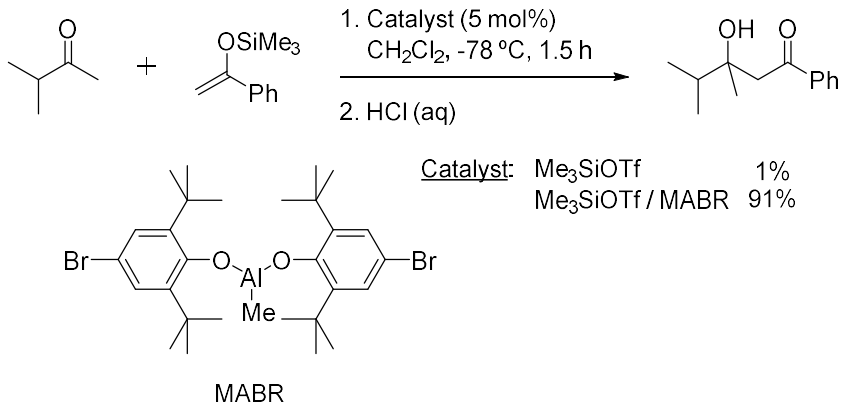
[24] a) L. Kürti, B. Czakó, in *Strategic Applications of Named Reactions in Organic Synthesis* (Ed. J. Hayhurst), Elsevier Academic Press, Burlington, MA, **2005**, pp. 298-299. b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.



Scheme 12: General scheme for the Mukaiyama reaction.

The first attempt to employ a Si-based LA was made by Noyori et al. using Me_3SiOTf, which turned out to be not acidic enough to activate aldehydes, but worked when using acetals as masked carbonyl compounds.[25]

The acidity problem has been solved by adding an extra LA to the medium to create in situ a more reactive catalyst, such as the $B(OTf)_3$ employed by Davis et al.[21,26a] or the bulky organoaluminum reagents employed by Yamamoto et al. (Scheme 13).[26b]



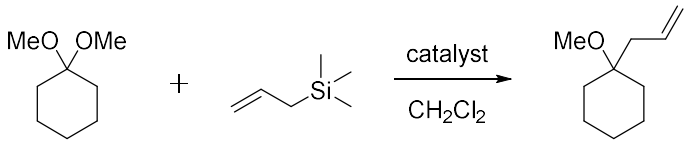
Scheme 13: Yamamoto's Al/Si-co-catalysed Mukaiyama reaction.

Reaction of allylic silanes with aldehydes, ketones and acetals are similar cases. Again, Me_3SiOTf is not acidic enough except for acetals, performing in long reaction times

[25] a) S. Murata, M. Suzuki, R. Noyori, *Tetrahedron Lett.* **1980**, *21*, 2527–2528. b) S. Murata, M. Suzuki, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249. c) S. Murata, M. Suzuki, R. Noyori, *Tetrahedron* **1988**, *44*, 4259–4275.

[26] a) A. P. Davis, S. J. Plunkett, *J. Chem. Soc., Chem. Commun.* **1995**, 2173–2174. b) M. Oishi, S. Aratake, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 8271–8272.

even for these last ones.[27a,b] Other LAs, like Davis' co-catalyst[27c] or Me_3SiNTf_2,[27d] can be employed. Scheme 14 shows an example in which Me_3SiNTf_2 is used as catalyst in the allylation of an acetal. As in the case of the Mukaiyama reaction, when using an acetal, only the mono-adduct is obtained.[27d]

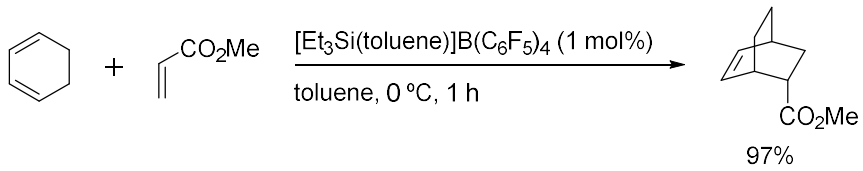


Catalyst: Me_3SiOTf (1 mol%) -60 to -45 °C, 18 h 81%
Me_3SiNTf_2 (5mol%) -78 °C,45 min 91%

Scheme 14: Allylation catalysed by different LAs.

b) Ring Construction: Diels-Alder and Ring Expansion Reactions

A few examples of reported Diels-Alder and Hetero-Diels-Alder reactions in which a Si-based LAs is used as catalyst show that they require a counteranion of very low basicity (Scheme 15).[8,28]



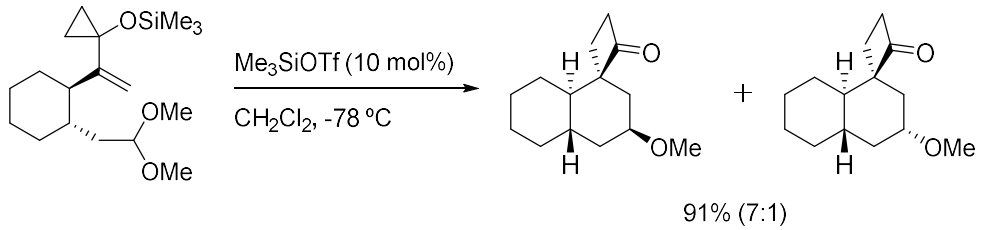
Scheme 15: Si-based LA-catalysed Diels-Alder reaction.[28a]

However, once again, Me_3SiOTf is acidic enough for acetals, being able to perform cyclizations reactions, like the one shown in Scheme 16, which includes a ring expansion

[27] a) A. Hosomi, *Acc. Chem. Res.* **1988**, *21*, 200–206. b) I. Fleming, J. Dunoguès, R. Smithers, in *Organic Reactions*, John Wiley & Sons, Inc., **2004**, pp. 57-575. c) A. P. Davis, M. Jaspars, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 470–471. d) A. Ishii, O. Kotera, T. Saeki, K. Mikami, *Synlett* **1997**, *1997*, 1145–1146.

[28] a) K. Hara, R. Akiyama, M. Sawamura, *Org. Lett.* **2005**, *7*, 5621–5623. b) B. Mathieu, L. Ghosez, *Tetrahedron* **2002**, *58*, 8219–8226. c) R. K. Schmidt, K. Müther, C. Mück-Lichtenfeld, S. Grimme, M. Oestreich, *J. Am. Chem. Soc.* **2012**, *134*, 4421–4428.

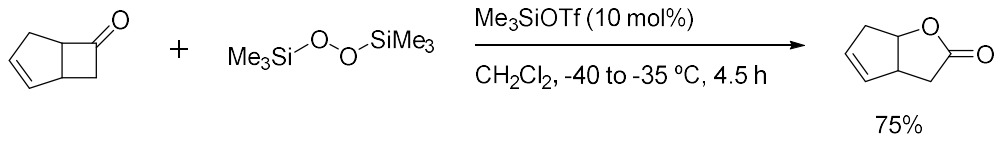
process. This strategy can also be used to build seven- and eight-membered ring spirocycles.[29]



Scheme 16: Ring expansion catalysed by Me_3SiOTf.

c) <u>Oxidations</u>

An example of very useful oxidation conditions provided by a Si-based LA catalyst are the ones shown in Scheme 17 for a Baeyer-Villiger oxidation of a ketone in the presence of a double bond that would be epoxidised in case of using peroxy acids.[30]



Scheme17: Baeyer-Villiger oxidation catalysed by a Si-based LA.

The world of Si-based LA catalysis has been explored in the last decades, but there is still room for improvements in terms of both catalyst development and new reactions to catalyse.

[29] B. M. Trost, D. C. Lee, *J. Am. Chem. Soc.* **1988**, *110*, 6556–6558.

[30] M. Suzuki, H. Takada, R. Noyori, *J. Org. Chem.* **1982**, *47*, 902–904.

Main Aims and Objectives

Main Aims and Objectives

Given the context provided in the general introduction and 'in-house' experience in the use of gold catalysis, it has been established as a main goal to explore the synthetic possibilities of generating Si-based Lewis acids in situ by activation of organosilicon reagents with gold(I) complexes.

For this purpose, the following general objectives will be taken into practise:

- To study the application of this strategy to the activation of oxygen containing functional compounds to create new C-C and C-heteroatom bonds.
- To compare this strategy with the use of Si-based Lewis acids instead of gold(I) complexes.
- To develop, optimise and generalise the transformations discovered during this work.
- To explain the observed results and come to a better understanding of the activation of oxygen containing functional groups by Si-based Lewis acids.

Part I

Bis-Alkynylation Reaction of Aldehydes with Alkynylsilanes: Synthesis of 1,4-Diynes

Section Index

Bis-Alkynylation Reaction of Aldehydes with Alkynylsilanes: Synthesis of 1,4-Diynes

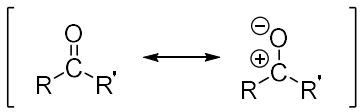
Introduction to Part I

1. Carbonyl Groups as Lewis Bases in C-C Bond Forming Processes: Addition Reactions to Carbonyl Groups Catalysed by Lewis Acids

The Basicity, Nucleophilicity and Electrophilicity of the Carbonyl Group

The oxygen atom in a carbonyl group is a basic centre according to Lewis' definition, since it has two electron pairs available for any LA to accept. Furthermore, the polarisation in the carbon-oxygen bond due to the higher electronegativity of oxygen versus carbon makes the oxygen nucleophilic, as well as the carbon electrophilic.

This is represented in the resonance hybrid for the carbonyl group, featuring one structure that contains a heteroatom-stabilised carbocation (Scheme I.1). The more alkyl or electron-donating substituents this carbocation has directly attached to it, the more stable it will be, and the less reactive too. That explains the higher reactivity of aldehydes versus ketones when it comes to addition reactions of nucleophiles to this electrophilic centre.[31]



Scheme I.1: Resonance structures of the carbonyl bond.

Lewis Acid-Catalysed Additions to Carbonyl Groups

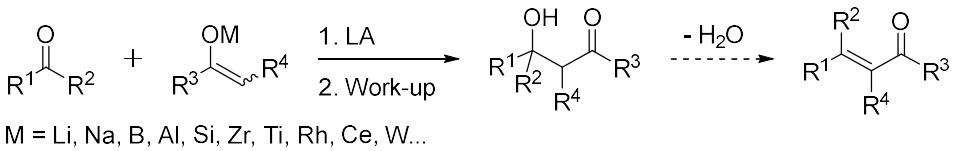
One of the most characteristic reactions of carbonyl groups is the nucleophilic addition, which is among the most popular and studied strategies for C-C bond forming

[31] K. P. C. Vollhardt and N. E. Shore in *Química Orgánica. Estructura y Función*, Ediciones Omega, **2000**, pp. 733-734.

reactions.[5,23,32] It has also been one of the main targets since the beginning of LA catalysis. Some examples of LA-catalysed nucleophilic addition reactions are discussed below.

a) Aldol-type reactions

One of the most widely studied examples of this kind is the aldol reaction, which have already been mentioned previously in this work (see Introduction, p. 40). An enolate, which can be generated in situ with a base or be preformed, is used as a nucleophile, obtaining a β-hydroxycarbonyl compound. This product can undergo dehydration under certain conditions to afford the corresponding α,β-unsaturated carbonyl compound (Scheme I.2).



Scheme I.2: General aldol-type reaction catalysed by a LA plus possible dehydration.

There are many LAs known to promote this transformation. B-, Al-, Si-, Ti-, Sc-, and La-based LAs are some of the most popular ones.[33] For many of them, diastereoselectivity can be tuned by employing chiral ligands or substituents, although the use of chiral auxiliaries, earlier developed, is still widely practiced.[5,23,33d]

Ti-, B-, and Al-based LAs were some of the first-developed catalysts, even at their chiral versions.[8,33a-c] In particular, titanium has always been a major player in this field, and not only for the aldol reaction. Perhaps being the most studied LA, it has proved to be very versatile.[34,35] Others, like in the case of Si-based LAs mentioned before (see p. 37), have

[32] For important examples of addition reactions to carbonyl groups see L. Kürti, B. Czakó, in *Strategic Applications of Named Reactions in Organic Synthesis* (Ed. J. Hayhurst), Elsevier Academic Press, Burlington, MA, **2005**, pp. a) 38-39, b) 48-49, c) 54-55, d) 162-163, e) 202-203, f) 232-233, g) 236-237, h) 298-299, i) 364-365, j) 374-375, k) 386-387, l) 392-393.

[33] K. Ishihara, W. D.Wulff, h. Urabe, F. Sato, S. Kobayashi, in *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH Verlag GmbH, **2000**, a) for B see pp. 111,112, 169-176, b) for Al see pp. 284-286, c) for Ti see pp. 817-825, d) for Sc see pp. 883-885.

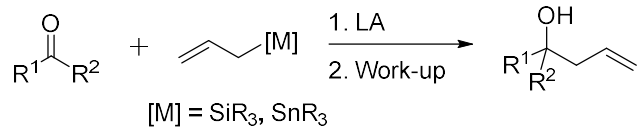
[34] R. O. Duthaler, A. Hafner, *Chem. Rev.* **1992**, *92*, 807–832.

[35] H. Urabe, F. Sato, K. Mikami, M. Terada, in *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH Verlag GmbH, **2000**, pp. 653-847.

recently started to be developed as a main synthetic tool. In particular, there are still very few chiral Si-based LAs.[36]

b) Allylation reactions

The allylation reaction is another important group of LA-catalysed addition reactions to carbonyl compounds. The usual nucleophiles used for this purpose are allyl stannanes or silanes, and the product is the corresponding homoallyl alcohol (Scheme I.3).[32g]



Scheme I.3: Lewis acid catalysed allylation reaction of a carbonyl compound.

The first reported allylation catalysed by a LA was the Sakurai-Hosomi allylation of aldehydes and ketones in 1976, in which an allylic trimethylsilane is used as a nucleophile.[37] The original catalyst, $TiCl_4$, is still the most generally used LA, but it can also be promoted by B,[38a] Ag,[38b] or Si species, although there is much less development done for this last one.[27] Later development of this transformation adapted it to the allylation of acetals,[39a,b] acyl chlorides,[39c] imines,[39d] alcohols,[39e] or Michael acceptors.[39f]

There is another important LA-catalysed allylation, known as Keck asymmetric allylation, which is based on a Ti^{IV} complex with (*R*)-BINOL as ligand and uses allylic

[36] Y. Sakaguchi, Y. Iwade, T. Sekikawa, T. Minami, Y. Hatanaka, *Chem. Commun.* **2013**, *49*, 11173–11175.

[37] A. Hosomi, H. Sakurai, *Tetrahedron Lett.* **1976**, *17*, 1295–1298.

[38] a) K. Ishihara, in *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH Verlag GmbH, **2000**, pp. 176-179. b) M. Wadamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 14556–14557.

[39] a) H. M. Zerth, N. M. Leonard, R. S. Mohan, *Org. Lett.* **2003**, *5*, 55–57. b) M. E. Jung, A. Maderna, *J. Org. Chem.* **2004**, *69*, 7755–7757. c) J. S. Yadav, B. V. S. Reddy, M. S. Reddy, G. Parimala, *Synthesis* **2003**, *2003*, 2390–2394. d) S. Yamasaki, K. Fujii, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2002**, *124*, 6536–6537. e) T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 8516–8522. f) P. H. Lee, D. Seomoon, S. Kim, K. Nagaiah, S. V. Damle, K. Lee, *Synthesis* **2003**, *2003*, 2189–2193.

tributylstannanes as nucleophiles. It was first reported in 1993 by Keck et al.,[40a] but it was soon improved in terms of ligand loading by Tagliavini.[40b] Its use is not as general as Sakurai's allylation, probably due to the toxicity of the organotin reagents employed.[41]

c) Prins reaction

The Prins reaction is an addition of an olefin to an aldehyde activated by an acid. The carbocation formed is then attacked by a nucleophile present in the reaction medium, either the solvent, the aldehyde itself, or the conjugated base of the employed acid. In the case of using water as solvent, the dehydration of the 1,3-diol formed will lead to the corresponding allylic alcohol (except for tetrasubstituted olefins). Otherwise, 3-substituted alcohols or 1,3-dioxanes will be obtained (Scheme I.4).[32i]

When the olefin is an homoallylic alcohol, the hydroxyl group acts as the first nucleophile to be added and the olefin reacts in second place, generating a cyclic product, and the reaction is known as Prins cyclisation. A third nucleophile is added to the carbocation formed after the addition of the olefin (Scheme I.4).[42a] Homopropargylic alcohols can also be used in an analogous fashion.[42b]

Brønsted acids are very popular catalysts for this transformation because they allow the use of water as solvent in many cases.[43] However, several LAs can promote it as well, such as B,[44a] Al,[44b] Sn,[44c] Au,[44d] or Si species.[42b]

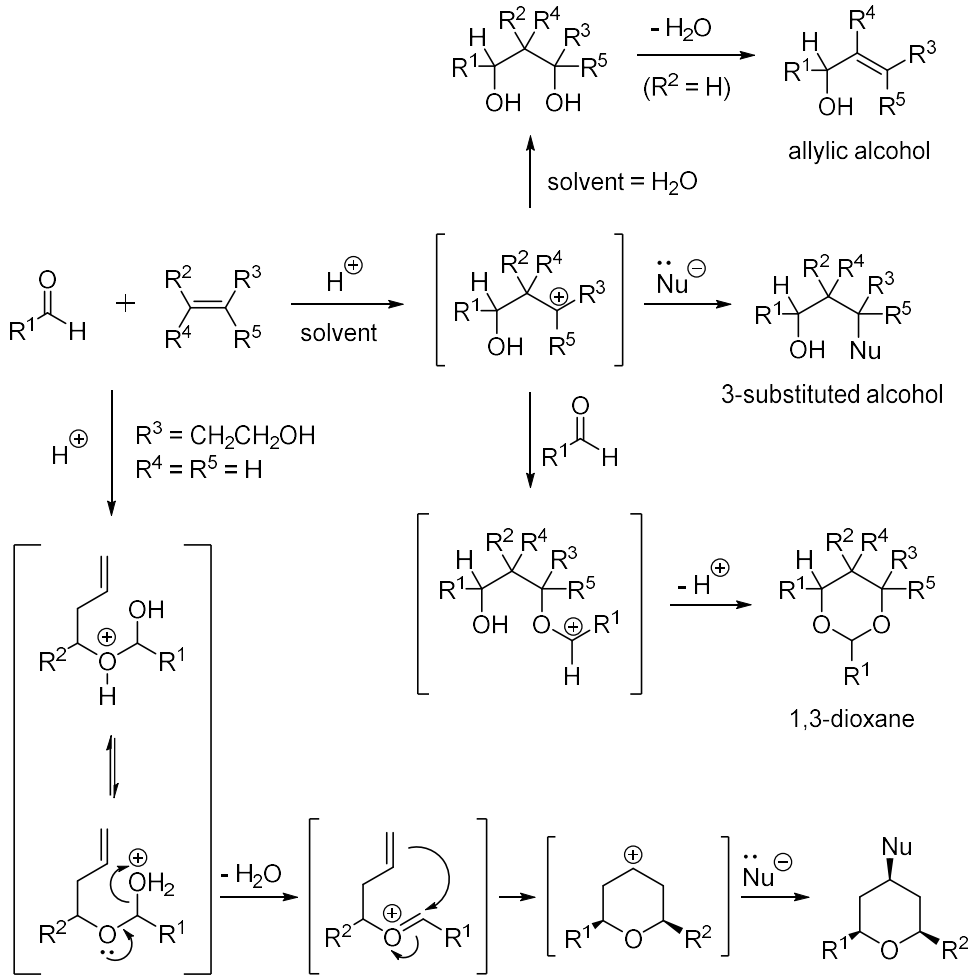
[40] a) G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468. b) A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Am. Chem. Soc.* **1993**, *115*, 7001–7002.

[41] According to the safety specifications for allyltributylstannane (97%) from Sigma-Aldrich®, the following H hazard statements are applied (among others): H301 (toxic if swallowed), H312 (harmful in contact with skin), H372 (causes damage to organs through prolonged or repeated exposure).

[42] a) F. K. Chio, J. Warne, D. Gough, M. Penny, S. Green (née Martinović), S. J. Coles, M. B. Hursthouse, P. Jones, L. Hassall, T. M. McGuire, et al., *Tetrahedron* **2011**, *67*, 5107–5124. b) S. N. Chavre, H. Choo, J. K. Lee, A. N. Pae, Y. Kim, Y. S. Cho, *J. Org. Chem.* **2008**, *73*, 7467–7471.

[43] a) J. S. Yadav, B. V. S. Reddy, G. G. K. S. N. Kumar, S. Aravind, *Synthesis* **2008**, *2008*, 395–400. b) V. Polshettiwar, R. S. Varma, *J. Org. Chem.* **2007**, *72*, 7420–7422.

[44] a) T. Bach, J. Löbel, *Synthesis* **2002**, *2002*, 2521–2526. b) J. S. Yadav, B. V. S. Reddy, M. S. Reddy, N. Niranjan, A. R. Prasad, *Eur. J. Org. Chem.* **2003**, *2003*, 1779–1783. c) S. Marumoto, J. J. Jaber, J. P. Vitale, S. D. Rychnovsky, *Org. Lett.* **2002**, *4*, 3919–3922. d) E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5452–5455.



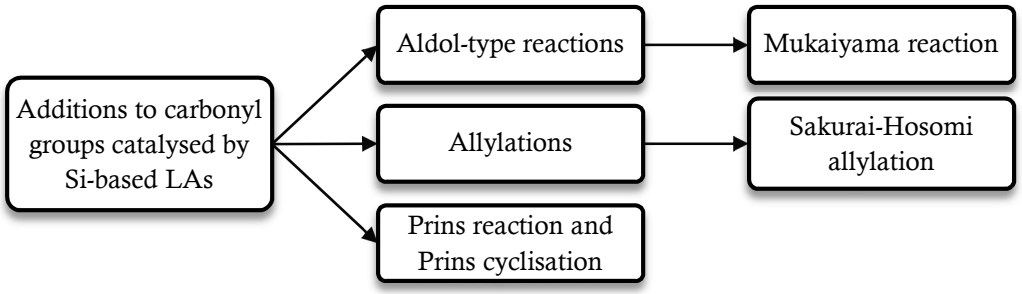
Scheme I.4: Possible products from a Prins reaction, catalysed by a Brønsted acid.

d) *Alkynylation reactions*

This is another important group of addition reactions to carbonyl groups and they will be discussed independently in section 2 of this introduction (p. 59).

Additions to Carbonyl Groups Catalysed by Silicon-Based Lewis Acids

The main cases of additions to carbonyl groups catalysed by Si-based LAs has already been discussed in previous pages. In order to provide with a practical overview, they are briefly summarised in Scheme I.5.



Scheme I.5: Additions to carbonyl groups catalysed by Si-based LAs.

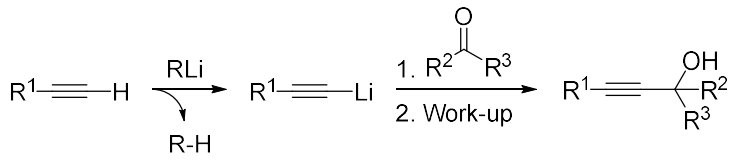
2. Mono- and Bis-Alkynylation of Carbonyl Groups

Among the different C-C bond forming reactions by addition of nucleophiles to carbonyl groups, alkynylation reactions are particularly interesting because they give access to propargylic alcohols, which can participate in numerous nucleophilic substitutions catalysed by transition metal complexes or Lewis acids.[45]

One particular nucleophilic substitution would be another alkynylation reaction, affording a 1,4-diyne, which are not easily accessible, but are interesting building blocks.[46]

Synthesis of Propargylic Alcohols by Alkynylation of Carbonyl Groups

The classic way of introducing an alkynyl moiety in a carbonyl group is by using the corresponding lithium acetylide (Scheme I.6), and it is broadly used, even in the industrial world. Lithium acetylides are very reactive; they react with aldehydes and ketones, as well as other functional groups with a double C-O bond.[47] However, due to their high reactivity and to their conventional preparation methods using organolithium reagents, this strategy is not compatible with many functional groups, and it requires special precautions.[48] Because of these handicaps, enantioselective versions are also scarce.[49]



Scheme I.6: Synthesis of propargyl alcohols by addition of a lithium acetylide.

[45] For a review on this kind of nucleophilic substitutions see: a) N. Ljungdahl, N. Kann, *Angew. Chem. Int. Ed.* **2009**, *48*, 642–644. b) R. J. Detz, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2009**, *2009*, 6263–6276. c) O. Debleds, E. Gayon, E. Vrancken, J.-M. Campagne, *Beilstein J. Org. Chem.* **2011**, *7*, 866–877. d) D.-Y. Zhang, X.-P. Hu, *Tetrahedron Lett.* **2015**, *56*, 283–295.

[46] C. Tedeschi, C. Saccavini, L. Maurette, M. Soleilhavoup, R. Chauvin, *J. Organomet. Chem.* **2003**, *670*, 151–169.

[47] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596–2616.

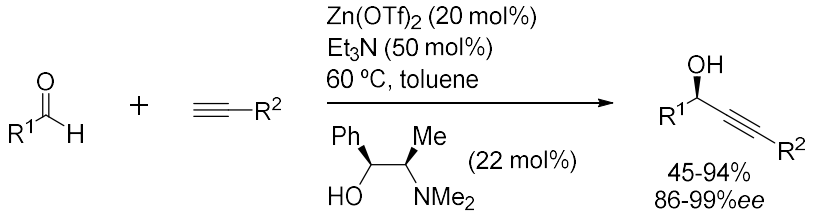
[48] J. A. Schwindeman, C. J. Woltermann, R. J. Letchford, *Chem. Health Saf.* **2002**, *9*, 6–11.

[49] S. Kotani, K. Kukita, K. Tanaka, T. Ichibakase, M. Nakajima, *J. Org. Chem.* **2014**, *79*, 4817–4825.

Other less reactive alkynylating reagents have been developed in order to achieve more versatile and enantioselective transformations, like alkynylboranes,[50a] zinc acetylides,[50b-d] indium acetylides,[50e] or silver acetylides.[50f] These methods still use stoichiometric amounts of metals, despite the fact that they are relatively recent. Moreover, they are frequently prepared from lithium or Grignard acetylides, which means the functional group tolerance of the methodology is still limited.

Furthermore, many of these methods have been developed for aldehydes only, since ketones are not reactive enough. However, a few ketone alkynylation methods have been developed using zinc acetylides and a chiral Brønsted or Lewis acid co-catalyst to activate the carbonyl group.[51]

The first alkynylation of aldehydes using catalytic amounts of both the metal species and the chiral ligand, was reported by Carreira et al. in 2001.[52] The zinc acetylide was formed in catalytic amounts in the presence of a zinc salt and substoichiometric amounts of a base. Also, the metal was provided with a chiral ligand to control the face selection along the addition step (Scheme I.7).



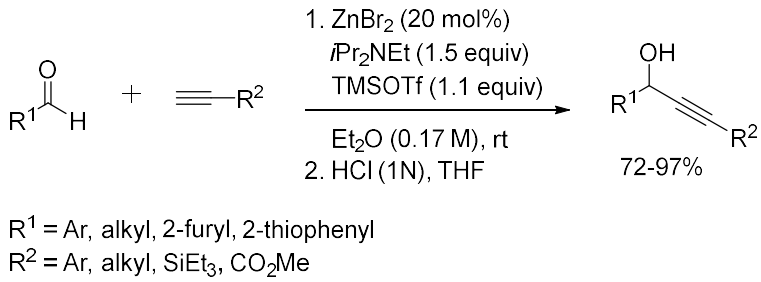
Scheme I.7: First catalytic enantioselective addition of zinc acetylides to aldehydes.

[50] a) E. J. Corey, K. A. Cimprich, *J. Am. Chem. Soc.* **1994**, *116*, 3151–3152. b) D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605–2606. c) C. Chen, L. Hong, Z.-Q. Xu, L. Liu, R. Wang, *Org. Lett.* **2006**, *8*, 2277–2280. d) G. Gao, D. Moore, R.-G. Xie, L. Pu, *Org. Lett.* **2002**, *4*, 4143–4146. e) N. Sakai, R. Kanada, M. Hirasawa, T. Konakahara, *Tetrahedron* **2005**, *61*, 9298–9304. f) S. P. Shahi, K. Koide, *Angew. Chem. Int. Ed.* **2004**, *43*, 2525–2527.

[51] a) P. G. Cozzi, *Angew. Chem. Int. Ed.* **2003**, *42*, 2895–2898. b) G. Lu, X. Li, X. Jia, W. L. Chan, A. S. C. Chan, *Angew. Chem. Int. Ed.* **2003**, *42*, 5057–5058.

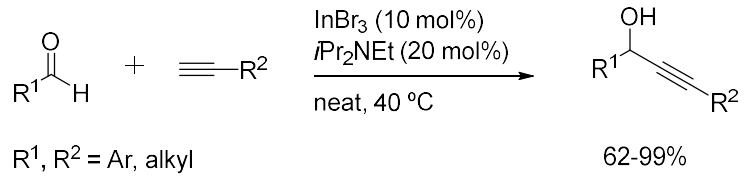
[52] N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.

Further progress was achieved by using other metallic acetylides, such as those derived from Cs,[53a] Ag,[53b] Cu,[53c] or Rh.[53d] These reactions usually require mild heating conditions. The introduction of another Lewis acid catalyst to activate the carbonyl group allows to lower the temperature. For example, in the reaction shown in Scheme I.8, a stoichiometric amount of a Si-based Lewis acid is used, obtaining the corresponding propargylic silyl ether. Subsequent hydrolysis would afford the propargylic alcohol.[54]



Scheme I.8: Si-based LA and $ZnBr_2$ catalysed alkynylation.

Sometimes the catalytic metal that forms the acetylide can also act as the LA that activates the aldehyde. This is the case for $InBr_3$, employed by Shibasaki et al. (Schemes I.9 and I.10). This transformation can also be applied to ketones by increasing the catalyst loading and using $In(OTf)_3$ as a stronger LA.[55a] Besides, it can also render an enantioselective transformation by using an enantioselective chiral ligand such as (*R*)-BINOL (Scheme I.11).[55b]

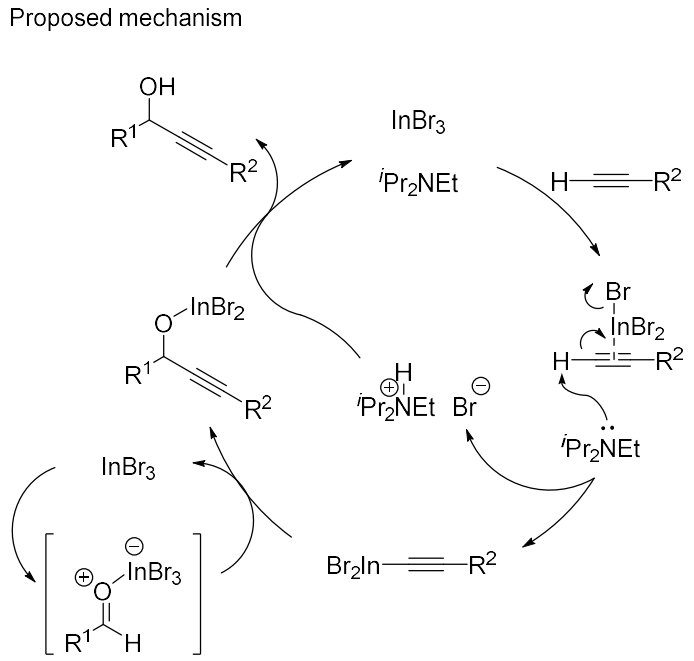


Scheme I.9: Aldehyde alkynylation catalysed by a LA and a LB.

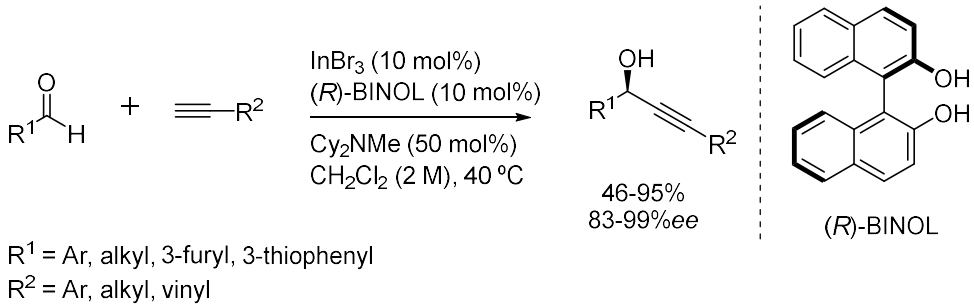
[53] a) D. Tzalis, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 1463–1465. b) X. Yao, C.-J. Li, *Org. Lett.* **2005**, *7*, 4395–4398. c) Y. Asano, H. Ito, K. Hara, M. Sawamura, *Organometallics* **2008**, *27*, 5984–5996. d) P. K. Dhondi, J. D. Chisholm, *Org. Lett.* **2006**, *8*, 67–69.

[54] C. W. Downey, B. D. Mahoney, V. R. Lipari, *J. Org. Chem.* **2009**, *74*, 2904–2906.

[55] a) R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, M. Shibasaki, *Org. Lett.* **2005**, *7*, 1363–1366. b) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760–13761.



Scheme I.10: Proposed mechanism for the LA-LB catalysis depicted in Scheme I.9.



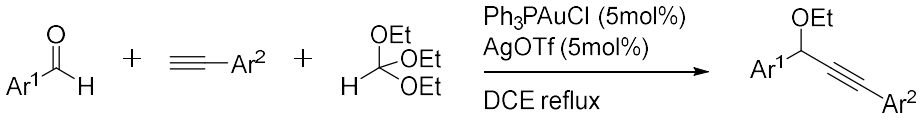
Scheme I.11: Enantioselective $InBr_3$-catalysed alkynylation of aldehydes.

Copper and gold acetylides are well known, but they are weak nucleophiles and there are not many examples of them being added to aldehydes. Instead, they can be added to iminium or oxocarbenium cations.[56,57] There is only one precedent in literature in which

[56] J. Liu, S. Dasgupta, M. P. Watson, *Beilstein J. Org. Chem.* **2015**, *11*, 2696–2706.

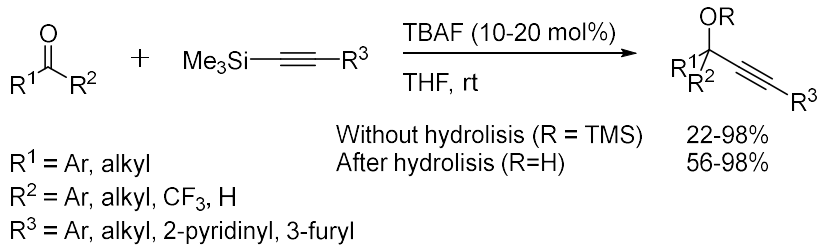
[57] a) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585. b) V. K.-Y. Lo, Y. Liu, M.-K. Wong, C.-M. Che, *Org. Lett.* **2006**, *8*, 1529–1532. c) B. Huang, X. Yao, C.-J. Li, *Adv. Synth. Catal.* **2006**, *348*,

a gold(I) acetylide is formally added to a carbonyl group (Scheme I.12), however, the mechanism of this transformation is not clear, an there is no strong evidence about the degree of involvement of each catalytic species.[57e,58]



Scheme I.12: Proposed gold(I) acetylide addition to a carbonyl group in the presence of an orthoester to afford the corresponding propargylic ether.

Finally, there are not many alternatives to metal acetylides when it comes to catalytic approaches, but alkynylsilanes can be used in the presence of catalytic amounts of fluorides. When the fluoride becomes attached to the silicon atom, it increases the nucleophilicity of the species, so it can attack the carbonyl group (Scheme I.13).[59,60]



Scheme I.13: Alkynylation of carbonyl groups with alkynylsilanes.

1528–1532. d) F. Xiao, Y. Chen, Y. Liu, J. Wang, *Tetrahedron* **2008**, *64*, 2755–2761. e) C. Li, F. Mo, W. Li, J. Wang, *Tetrahedron Lett.* **2009**, *50*, 6053–6056.

[58] a) B. Schlummer, J. F. Hartwig, *Org. Lett.* **2002**, *4*, 1471–1474. b) D. C. Rosenfeld, S. Shekhar, A. Takemiya, M. Utsunomiya, J. F. Hartwig, *Org. Lett.* **2006**, *8*, 4179–4182. c) Z. Li, J. Zhang, C. Brouwer, C.-G. Yang, N. W. Reich, C. He, *Org. Lett.* **2006**, *8*, 4175–4178.

[59] V. R. Chintareddy, K. Wadhwa, J. G. Verkade, *J. Org. Chem.* **2011**, *76*, 4482–4488.

[60] E. W. Colvin, in *Silicon in Organic Synthesis*, Butterworth-Heinemann, **1981**, pp. 134–140.

Synthesis of 1,4-Diynes

Among the uses of propargylic alcohols in nucleophilic substitutions, C-C forming reactions are especially relevant, since they give access to more complex building blocks in one step.[61]

One particularly interesting kind of products that can be obtained from propargylic substitution are 1,4-diynes, also called *skipped diynes*. The 1,4-diyne fragment can be considered the linear C_5-brick occurring in some natural products in the same way the isoprene unit is the branched C_5-brick occurring in terpenes.[46,62] Their allenyne tautomeric structure has also been recognised in some natural products, such as antibiotic mycomycin.[63] On the other hand, they also have interesting synthetic utilities.[64]

However, neither methods to directly obtain 1,4-diynes are broadly developed, nor the use of propargylic alcohols for this purpose is common. The main strategies reported so far can be sorted out into 4 groups:

[61] a) G. W. Kabalka, M.-L. Yao, S. Borella, *J. Am. Chem. Soc.* **2006**, *128*, 11320–11321. b) G. W. Kabalka, M.-L. Yao, S. Borella, *Org. Lett.* **2006**, *8*, 879–881.c) Z. Zhan, J. Yu, H. Liu, Y. Cui, R. Yang, W. Yang, J. Li, *J. Org. Chem.* **2006**, *71*, 8298–8301. d) M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2012**, *134*, 8770–8773. e) X. Wang, A. Guram, E. Bunel, G.-Q. Cao, J. R. Allen, M. M. Faul, *J. Org. Chem.* **2008**, *73*, 1643–1645.

[62] a) J. S. Kim, Y. J. Lim, K. S. Im, J. H. Jung, C. J. Shim, C. O. Lee, J. Hong, H. Lee, *J. Nat. Prod.* **1999**, *62*, 554–559. b) Y. J. Lim, C.-O. Lee, J. Hong, D. Kim, K. S. Im, J. H. Jung, *J. Nat. Prod.* **2001**, *64*, 1565–1567. c) L. Chill, A. Miroz, Y. Kashman, *J. Nat. Prod.* **2000**, *63*, 523–526. d) Y. J. Lim, J. S. Kim, K. S. Im, J. H. Jung, C.-O. Lee, J. Hong, D. Kim, *J. Nat. Prod.* **1999**, *62*, 1215–1217.

[63] a) W. D. Celmer, I. A. Solomons, *J. Am. Chem. Soc.* **1952**, *74*, 1870–1871. b) R. E. Bew, J. R. Chapman, E. R. H. Jones, B. E. Lowe, G. Lowe, *J. Chem. Soc. C* **1966**, 129–135.

[64] a) D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *Chem. Eur. J.* **2011**, *17*, 9571–9575. b) D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *Chem. Eur. J.* **2009**, *15*, 838–842. c) B. Ramanathan, A. J. Keith, D. Armstrong, A. L. Odom, *Org. Lett.* **2004**, *6*, 2957–2960. d) V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2008**, *47*, 5224–5228. e) K. Tanaka, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 10296–10297.

a) Substitution on propargylic halides and sulfonates

Although catalytic methods for C(*sp*)-C(sp^2)[65] or C(*sp*)-C(*sp*) couplings[66] are widely studied, this is not the case for C(*sp*)-C(sp^3) bond forming reactions. Some advances have been accomplished during the last decades,[67] like the adaptation of the Sonogashira reaction to the coupling of C(*sp*)-C(sp^3) bonds by Fu et al.[67f] However, classical ionic routes are still mostly used, involving stoichiometric amounts of metals.

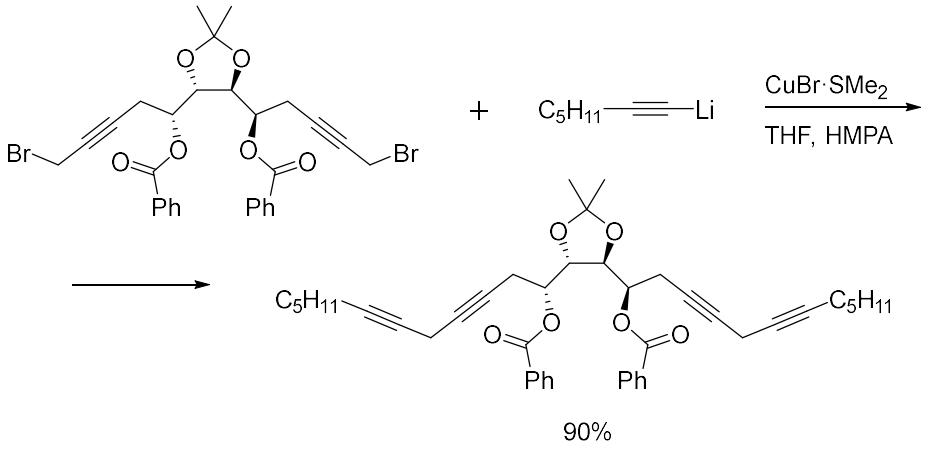
In the particular case of 1,4-diynes, the most commonly employed strategy is the nucleophilic attack of a lithium, magnesium or copper acetylide to a propargylic halide or sulfonate.[46,68] It involves the use of stoichiometric amounts of metals, strong bases and low temperatures, as well as previous protection steps in order to use further functionalised fragments. It also generates a large amount of salts as undesirable by-products. A coupling of this kind employing a lithium acetylide, stoichiometric amounts of a copper salt and a base is shown in Scheme I.14. The halide fragment presents several protected groups and the lithium acetylide has no other functional groups.[46]

[65] a) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46–49. b) R. Chinchilla, C. Nájera, *Chem. Soc. Rev.* **2011**, *40*, 5084–5121. c) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470. d) M. Carril, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 4940–4943. e) M. Schilz, H. Plenio, *J. Org. Chem.* **2012**, *77*, 2798–2807. f) M. Suginome, M. Shirakura, A. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 14438–14439. g) I. M. Lyapkalo, M. A. K. Vogel, *Angew. Chem. Int. Ed.* **2006**, *45*, 4019–4023. h) L. Cornelissen, M. Lefrancq, O. Riant, *Org. Lett.* **2014**, *16*, 3024–3027. i) W.-H. Guo, Z.-J. Luo, W. Zeng, X. Zhang, *ACS Catal.* **2017**, *7*, 896–901.

[66] a) A.-C. Bédard, S. K. Collins, *J. Am. Chem. Soc.* **2011**, *133*, 19976–19981. b) T. Gibtner, F. Hampel, J.-P. Gisselbrecht, A. Hirsch, *Chem. Eur. J.* **2002**, *8*, 408–432. c) S. Wang, L. Yu, P. Li, L. Meng, L. Wang, *Synthesis* **2011**, *2011*, 1541–1546. d) K. Balaraman, V. Kesavan, *Synthesis* **2010**, *2010*, 3461–3466.

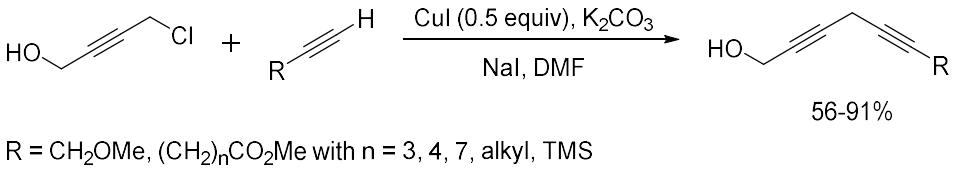
[67] a) Y. Zhu, T. Xiong, W. Han, Y. Shi, *Org. Lett.* **2014**, *16*, 6144–6147. b) F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 5742–5745. c) L.-M. Yang, L.-F. Huang, T.-Y. Luh, *Org. Lett.* **2004**, *6*, 1461–1463. d) C. W. Cheung, P. Ren, X. Hu, *Org. Lett.* **2014**, *16*, 2566–2569. e) M. Chen, X. Zheng, W. Li, J. He, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 4101–4103. f) M. Eckhardt, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643. g) H. Huang, G. Zhang, L. Gong, S. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283.

[68] a) T. Jeffery, S. Gueugnot, G. Linstrumelle, *Tetrahedron Lett.* **1992**, *33*, 5757–5760. b) S. Durand, J.-L. Parrain, M. Santelli, *Synthesis* **1998**, *1998*, 1015–1018. c) F. Montel, R. Beaudegnies, J. Kessabi, B. Martin, E. Muller, S. Wendeborn, P. M. J. Jung, *Org. Lett.* **2006**, *8*, 1905–1908. d) J. Kessabi, R. Beaudegnies, P. M. J. Jung, B. Martin, F. Montel, S. Wendeborn, *Org. Lett.* **2006**, *8*, 5629–5632.



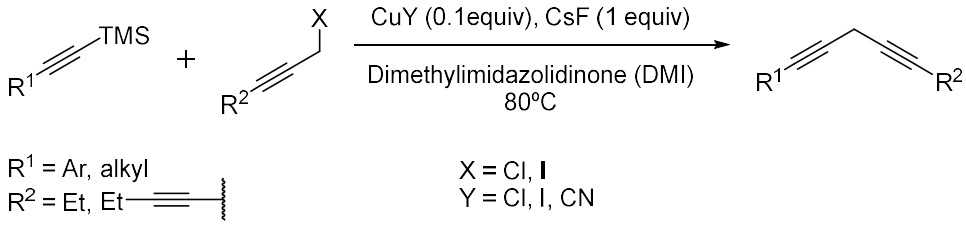
Scheme I.14: Propargylic substitution employing a lithium acetylide, stoichiometric amounts of a copper salt and a base.

The use of bases to form the copper acetylide allows the presence of some other functional groups in the alkyne. Also, substoichiometric amounts of copper can be used by adding sodium iodide (Scheme I.15).[68b]



Scheme I.15: Parrain-Santelli conditions using substoichiometric amounts of copper iodide and a base.

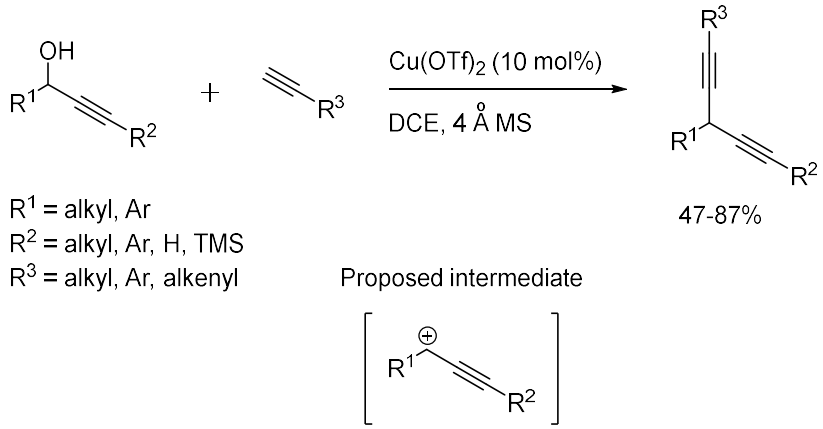
Another alternative that allows the use of catalytic amounts of the copper salt is the use of an alkynylsilane to generate the copper acetylide in situ. A fluoride source is necessary in this case (Scheme I.16).[68c]



Scheme I.16: Substitution by a copper acetylide formed from an alkynylsilane in the presence of a fluoride source.

b) Substitutions on propargylic alcohols and derivatives

Activation of hydroxyl groups with LAs to convert them into good leaving groups is a common substitution strategy. Several Lewis and Brønsted acids have been reported to activate propargylic alcohols in order to perform an alkynylation.[69] Recently, Zhan et al. reported a copper(II) triflate catalysed alkynylation of propargylic alcohols (Scheme I.17). Aryl-substituted alcohols were more suitable for this transformation than the alkyl-substituted ones. This is attributed to the instability of the cationic intermediate postulated to be involved in the mechanism.[69a]



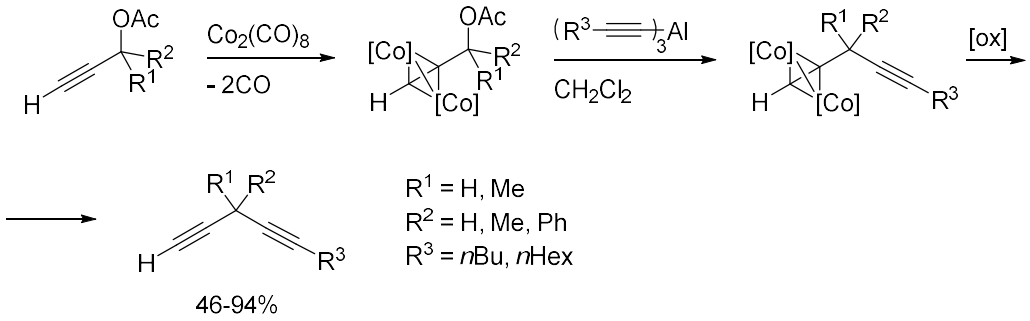
Scheme I.17: LA-catalysed alkynylation of propargylic alcohols.

This carbocation has been proposed in other cases of LA-activation of propargylic alcohols. When an alkynylsilane has been used as a nucleophile, it has been suggested that this species attacks the cationic intermediate and the species Me_3SiOH is released as a by-product.[69c]

[69] a) T. Wang, X. Chen, L. Chen, Z. Zhan, *Org. Lett.* **2011**, *13*, 3324–3327. b) J. S. Yadav, B. V. S. Reddy, N. Thrimurtulu, N. M. Reddy, A. R. Prasad, *Tetrahedron Lett.* **2008**, *49*, 2031–2033. c) T. Wang, R. Ma, L. Liu, Z. Zhan, *Green Chem.* **2010**, *12*, 1576–1579.

There are other examples of transition metals promoting these substitution reactions through an alternative mechanism that involves the in situ formation of a reactive allenylidene complex after activation of the hydroxyl group.[70]

On the other hand, the triple bond of an alkyne can also be used to activate the propargylic position by creating a cobalt complex (Nicholas reaction). When a η^2-$Co_2(CO)_6$ alkyne complex is formed, the development of positive charge in the propargylic position is feasible, and the triple bond is protected. Neutral nucleophiles such as allylsilanes or enol ethers must be used, since metal acetylides would also react with the cobalt centre. Unfortunately, alkynylsilanes do not react with this kind of intermediates. Aluminium acetylides, which are more difficult to handle, can be used instead (Scheme I.18).[71]



Scheme I.18: Propargylic substitution using a Nicholas reaction.

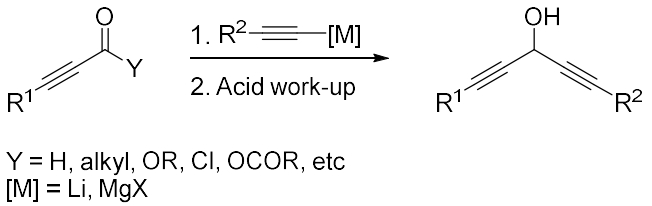
c) Additions to carbonyl groups

The reaction of lithium and Grignard acetylides with propargylic carbonyl compounds in a selective manner (1,2-addition) is well known (Scheme I.19). In this way, a hydroxyl-substituted 1,4-diyne is obtained.[72]

[70] a) V. Cadierno, M. P. Gamasa, J. Gimeno and Elena Lastra, *J. Organomet. Chem.* **1994**, *474*, C27–C29. b) M. P. Gamasa, J. Gimeno, C. González-Bernardo, J. Borge, S. García-Granda, *Organometallics* **1997**, *16*, 2483–2485.

[71] S. Padmanabhan, K. M. Nicholas, *Tetrahedron Lett.* **1983**, *24*, 2239–2242.

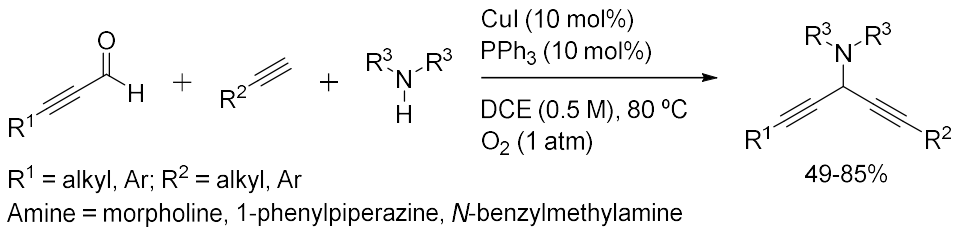
[72] a) G. Casy, M. Furber, K. A. Richardson, G. R. Stephenson, R. J. K. Taylor, *Tetrahedron* **1986**, *42*, 5849–5856. b) A. H. Alberts, H. Wynberg, *J. Chem. Soc., Chem. Commun.* **1988**, 748–749. c) M. G. Barlow, S. Tajammal, A. E. Tipping, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2485–2494. d) C. K. Tseng, K. G. Migliorese, S. I. Miller, *Tetrahedron* **1974**, *30*, 377–383. e) Y.-Z. An, Y. Rubin, C.



Scheme I.19: Addition of lithium and magnesium acetylides to propargylic carbonyl compounds.

Other metallic acetylides have been used, such as Al and Ce acetylides,[46] or the enantioselective addition of zinc acetylides reported by Carreira et al.[52]

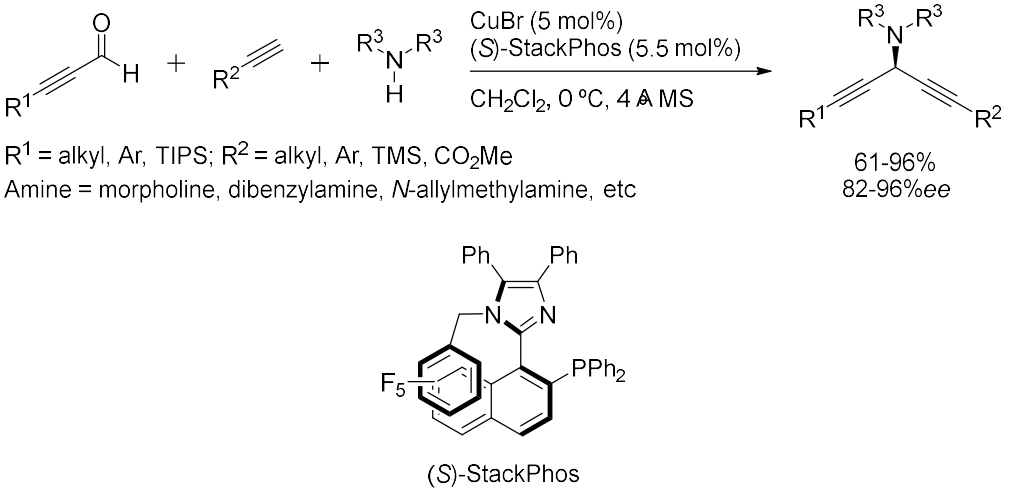
Recently, a few multicomponent reactions, in which an aldehyde reacts with a secondary amine to afford an iminium salt that subsequently suffers the addition of the metallic acetylide, have been reported (Scheme I.20).[73] According to the proposed mechanism, a copper complex under oxidative conditions catalyses both the formation of the iminium salt and that of the key copper acetylide.[73a] The use of a chiral phosphine as a ligand for the copper complex that acts as a LA affords the products in an enantioselective manner (Scheme I.21).[73b]



Scheme I.20: Multicomponent reaction yielding 3-amino-1,4-diynes.

Schaller, S. W. McElvany, *J. Org. Chem.* **1994**, *59*, 2927–2929. f) S. Kammermeier, P. Siemsen, P. Seiler, F. Diederich, R. R. Tykwinski, *Chem. Commun.* **1998**, 1285–1286. g) Y. Kuwatani, N. Watanabe, I. Ueda, *Tetrahedron Lett.* **1995**, *36*, 119–122. h) R. Suzuki, H. Tsukuda, N. Watanabe, Y. Kuwatani, I. Ueda, *Tetrahedron* **1998**, *54*, 2477–2496.

[73] a) Y.-J. Choi, H.-Y. Jang, *Eur. J. Org. Chem.* **2016**, *2016*, 3047–3050. b) P. H. S. Paioti, K. A. Abboud, A. Aponick, *J. Am. Chem. Soc.* **2016**, *138*, 2150–2153.



Scheme I.21: Structure of the chiral ligand used in multicomponent reactions (Scheme 20).

d) Bis-alkynylation of carbonyl groups

A very practical way to obtain a 1,4-diyne is the bis-alkynylation of a carbonyl group, that is, the introduction of two alkynyl moieties in the same carbonyl group and in a cascade reaction. Lithium and Grignard acetylides can perform these double addition reactions to acyl chlorides.[74]

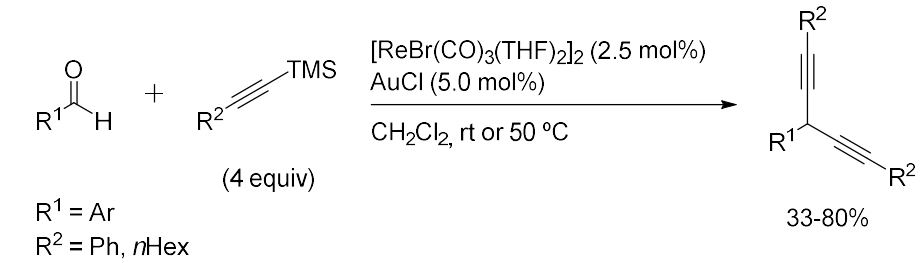
In the case of aldehydes and ketones, two steps would formally take place: first, an addition to the carbonyl group, and second, a propargylic substitution. Despite the apparently simple principles of this idea, only two precedent 1,4-diyne synthesis of this kind can be found in the literature.

The first one is a work from 2007 by Takai et al., consisting on a bis-alkynylation reaction of aromatic aldehydes using alkynylsilanes and catalysed by two metal species: a rhenium(I) complex and gold(I) chloride (Scheme I.22).[75a] The mechanistic proposal below shows a carbocation intermediate for the second substitution step. It also shows that both

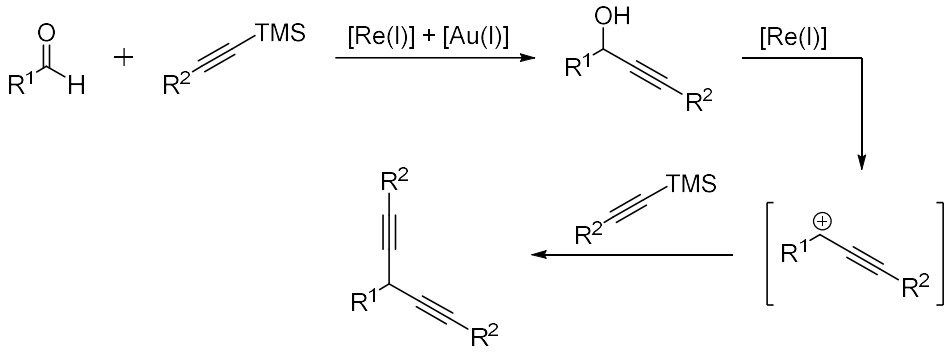
[74] a) D.-J. Chen, P.-C. Ting, Y.-C. Lin, G.-H. Lee, Y. Wang, *J. Chem. Soc., Dalton Trans.* **1995**, 3561–3562. b) I. Y. Wu, M. C. Cheng, Y. C. Lin, Y. Wang, *Organometallics* **1993**, *12*, 1686–1693.

[75] a) Y. Kuninobu, E. Ishii, K. Takai, *Angew. Chem. Int. Ed.* **2007**, *46*, 3296–3299. b) C. A. Campos, J. B. Gianino, D. M. Pinkerton, B. L. Ashfeld, *Org. Lett.* **2011**, *13*, 5680–5683.

catalytic species are involved in the first addition step, however, only the rhenium(I) complex is able to promote the substitution step.

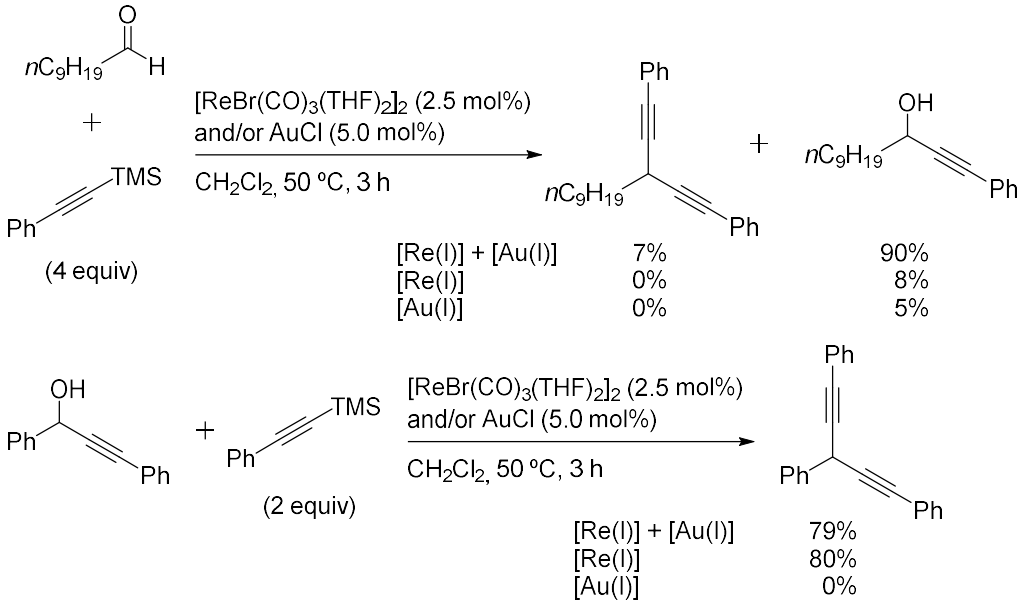


Mechanistic proposal



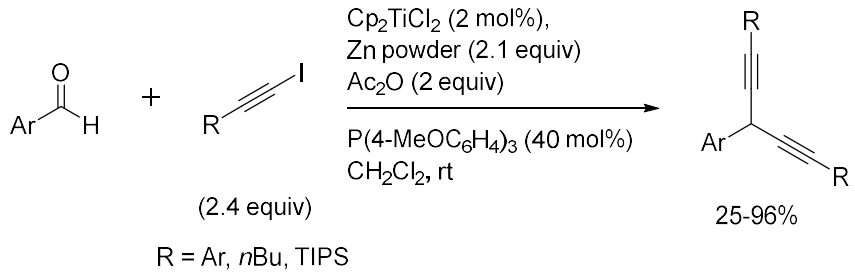
Scheme I.22: Bis-alkynylation of aromatic aldehydes by Takai et al.

The proposed mechanism is solidly based on experimental work (Scheme I.23).[75a] Aliphatic aldehydes only undergo the first addition step under these conditions. When using only one of the catalytic species in the reaction between decanal and trimethyl(phenylethynyl)silane very low amounts of product were observed. On the other hand, when using the 1,3-diphenyl-2-propyn-1-ol as substrate for the substitution step with trimethyl(phenylethynyl)silane, unlike gold(I) chloride, the rhenium complex proved to be able to promote the reaction.

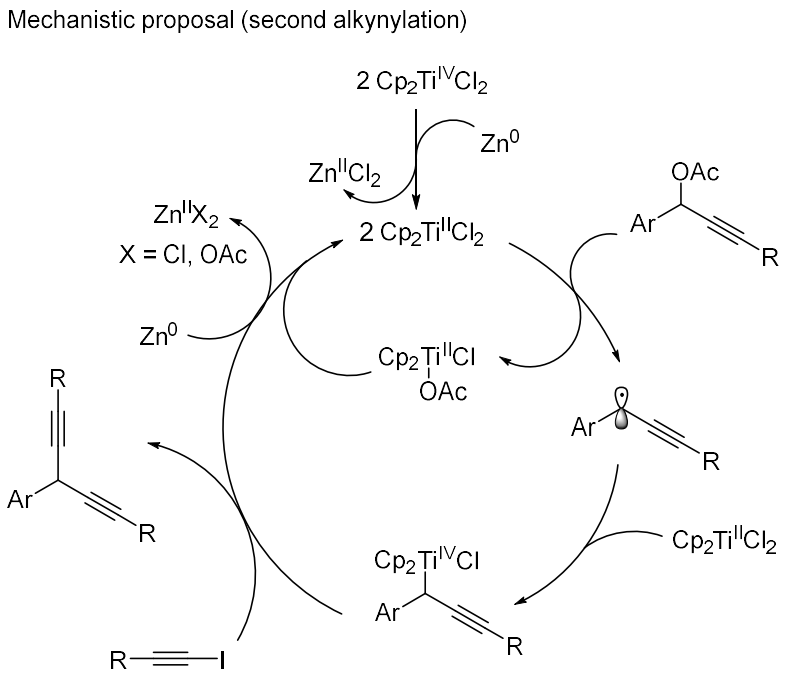


Scheme I.23: Experimental base for Takai's mechanistic proposal (yields determined by ^{1}H-NMR analysis).

The second precedent example in the literature is a bis-alkynylation reaction of aromatic aldehydes using iodoalkynes and catalysed by a titanium(IV) complex.[75b] Besides, stoichiometric amounts of zinc powder and acetic anhydride, and substoichiometric amounts of a phosphine are necessary (Scheme I.24). The role of the phosphine, as well as the nature of the metal acetylide in the first addition step, are unknown. However, other LAs fail in promoting any of the steps, suggesting that the titanium complex is not working merely as a LA. According to experimental observations, the zinc and the titanium complex work synergistically to afford the propargylic acetate proposed as an intermediate. Regarding the second step, a radical mechanism is proposed (Scheme I.25).



Scheme I.24: Ti-catalysed bis-alkynylation of aromatic aldehydes by Campos et al.



Scheme I.24: Mechanistic proposal for the Ti-catalysed bis-alkynylation of aromatic aldehydes (Scheme I.24).

3. Organosilicon Reagents as Nucleophiles

Apart from the use of organolithium compounds, Grignard reagents and other highly reactive organometallic derivatives, organosilicon compounds have gained attention in the last decades and are being increasingly used for devising new approaches to C-C bond formation purposes.[76]

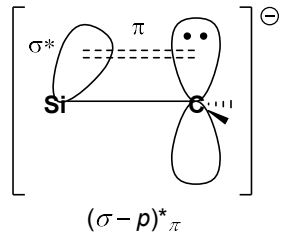
Organosilicon reagents are those compounds that present C-Si bonds. This bond is slightly weaker than a C-C bond (318 kcal/mol vs. 334 kcal/mol, respectively). It is strong enough towards homolytic fission. However, it can be quite easily cleaved by reaction with ionic reagents. On the other hand, the difference in electronegativity between C and Si creates a polarisation of the C-Si bond with a partial positive charge located at the Si atom and a negative one at the C atom. Thus, nucleophiles will target the Si atom. It is also well known that the presence of a Si atom stabilises anions and C-metal bonds in α-position (Si-C^-) and cations in β-position (Si-C-C^+).[77a] These two facts are termed as the *α-effect* and the *β-effect*.

The α-effect

The reactivity of organosilanes is attributed to the likely involvement of the bonding *p*-orbitals and the empty *d*-orbitals present in the silicon atom. Hence, for the case of an α-silyl substituted anion, the empty *d*-orbitals in the Si atom, forming part of the σ^* orbital of the C-Si bond, accept electronic density from a carbanion present in α-position, thus stabilising it (Scheme I.25).[77c]

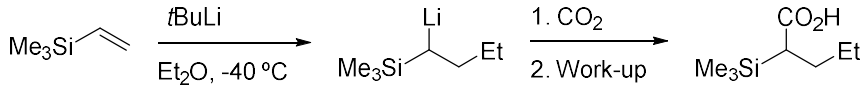
[76] a) G. G. Furin, O. A. Vyazankina, B. A. Gostevsky, N. S. Vyazankin, *Tetrahedron* **1988**, *44*, 2675–2749. b) J. W. J. Kennedy, D. G. Hall, *Angew. Chem. Int. Ed.* **2003**, *42*, 4732–4739.

[77] E. W. Colvin, in *Silicon in Organic Synthesis*, Butterworth-Heinemann, **1981**, a) pp. 4–14, b) pp. 15-20, c) pp.21-29, d) pp. 44-82, e) pp. 97-124, f) pp. 125-133, g) pp. 165-170.



Scheme I.25: Hyperconjugation between the σ^* orbital in the C-Si bond and the filled *p*-orbital in the carbanion.

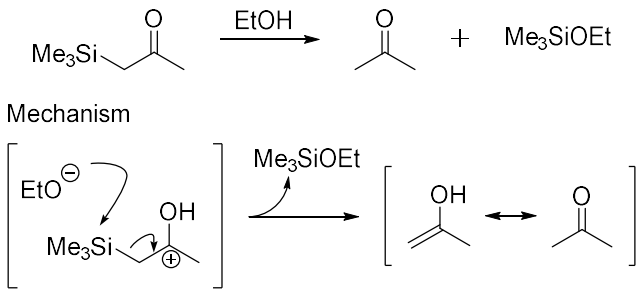
This explains the higher acidity of the protons in α-position, or why an organolithium reagent will add to the double bond of a vinylsilane at the β-position (Scheme I.26).[78]



Scheme I.26: Regioselective addition of *tert*-butyllithium to a vinylsilane.

The β-effect

Silanes with functional groups in β-position often present a higher reactivity than expected. For example, in Scheme I.27 a case of an abnormally labile trimethylsilyl moiety in the presence of a protic solvent is depicted. The mechanism below shows the carbocation formed by protonation of the carbonyl group is stabilised by the Si atom, which is also a good electrophilic centre for the conjugated base of the acid to attack.[77b]

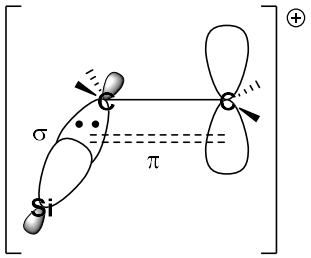


Scheme I.27: Labile Me_3Si-C bond as a consequence of the β-effect.

[78] J. E. Mulvaney, Z. G. Gardlund, *J. Org. Chem.* **1965**, *30*, 917–920.

Also vinyl-, allyl-, benzyl- and alkynylsilanes are stronger nucleophiles than expected, and they react in a regioselective way, so the electron deficiency is generated in the β-position to the Si atom.[77d-f]

The hyperconjugation of the empty *p*-orbital with the filled orbitals in the C-Si σ–bond stabilises the carbocations at the β-position, and this is the main cause for this selective behaviour (Scheme I.28).[77b]



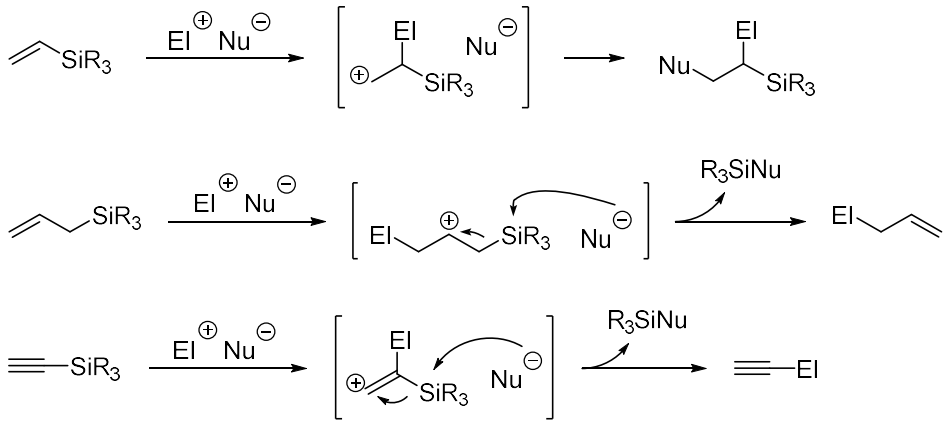
$(\sigma - p)_{\pi}$

Scheme I.28: Electronic basis for the β-effect in silicon chemistry.

General Reactivity of Vinylsilanes, Allylsilanes and Alkynylsilanes versus Electrophiles

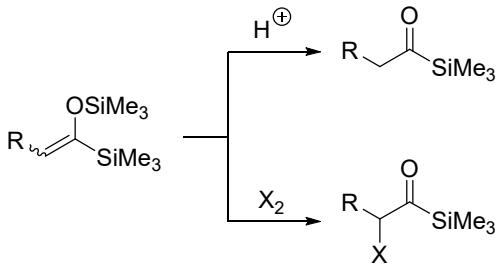
The nucleophilic attack of vinyl-, allyl- and alkynylsilanes to electrophiles is controlled by the β-effect in all of them, and usually with total regioselectivity, which converts them into very reliable synthetic building blocks. They also usually react in this manner under mild conditions, and, unlike analogous compounds based on most of the main group metals, they are typically stable and easy to handle.[77d,e,g]

A general scheme of the regioselectivity of these compounds when undergoing a nucleophilic attack is provided in Scheme I.29.



Scheme I.29: Reactivity patterns for vinyl-allyl-and alkynylsilanes towards electrophiles.

Some exceptions noticed in the regioselectivity for common vinylsilanes have been observed when other stabilising groups are present in the molecule. For example, the presence of an oxygen atom at the same carbon can invert the usual selectivity (Scheme I.30).[77d]



Scheme I.30: Directing effect in double bonds bearing a trimethylsilyloxy group.

Vinylsilanes are less reactive than allylsilanes. In other words, the activation energy for the formation of the carbocation is lower in the case of the allylsilane. This is due to the easier overlapping of the σ-orbitals in the Si-C bond over the π-system. In vinylsilanes, the maximum overlapping requires a 90º-rotation of the C-Si bond, which increases the total activation energy of the process.[77e]

On the other hand, allylsilanes and alkynylsilanes usually undergo fast desilylation before they can be attacked by another nucleophile. In the case of allylsilanes, the double bond shifts its position.[77e,g]

4. Reaction of Alkynylsilanes with Gold(I) Complexes

It has been shown that alkynylsilanes and allylsilanes can react with electrophiles, undergoing an exchange of the trimethylsilyl moiety by the electrophile. One possible kind of electrophiles that can be used are π-Lewis acids. Such is the case of gold(I) species, whose chemistry has gained a momentum in the last decade due to its interesting properties (see p. 34).

Properties of Gold(I) Complexes as π-Lewis Acids

Current studies in cationic gold(I) catalysis have repeatedly evidenced its particularly strong Lewis acidity, as well as its ability to stabilise cationic intermediates. These features are unexpected from the point of view of the conventional considerations regarding transition metals, and can only be fully explained by taking into account the relativistic effects.[79]

Relativistic effects in chemistry are derived from the high speed of the electrons moving around the atom nucleus. One basic consequence of the Theory of Relativity is the increase in the mass of a body when its speed approaches the speed of light (Scheme I.31). Therefore, it is necessary to apply a correction to the calculated mass of those electrons whose speed is close enough to *c* (universally constant speed of light). This should be generally done for nucleus with atomic number Z>70.[79a,e]

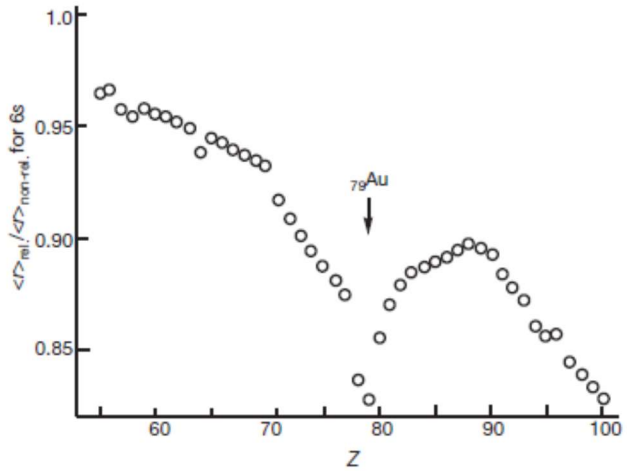
$$\text{Relative mass: } m = m_0/\sqrt{[1-(v/c)^2]}$$

$$\text{Bohr radius: } a_0 = 4\pi\varepsilon_0\hbar^2/m_e e^2$$

Scheme I.31: Relative mass of a body as a function of the ratio between the body speed v and light speed c, and Bohr radius a_0 as a function of the mass of the electron m_e (m_0 = non-realtivistic (rest) mass, $\hbar$ = reduced Planck constant or Dirac constant, ε_0 = vacuum permittivity, e = elementary charge).

[79] For some reviews about this topic see: a) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403. b) P. Pyykkö, *Angew. Chem. Int. Ed.* **2004**, *43*, 4412–4456. c) P. Pyykkö, *Inorg. Chim. Acta* **2005**, *358*, 4113–4130. d) P. Pyykkö, *Chem. Soc. Rev.* **2008**, *37*, 1967–1997. e) A. Leyva-Pérez, A. Corma, *Angew. Chem. Int. Ed.* **2012**, *51*, 614–635.

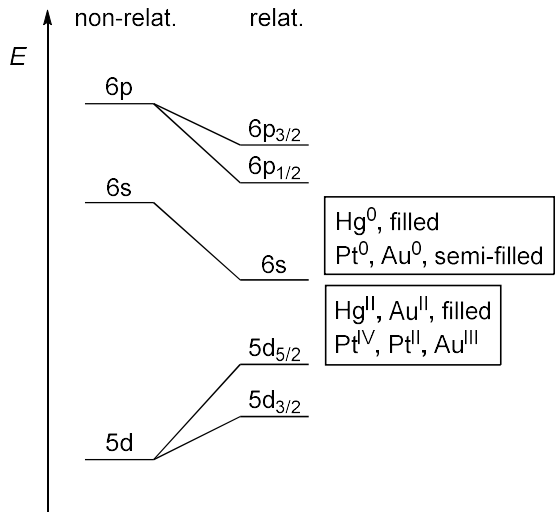
Since the Bohr radius of an atom is inversely proportional to the mass of the electron (Scheme I.31), an increment in this mass results in a decrease in this radius. This contraction has a direct effect on the *s* and *p* orbitals of the atom, which are more energetically stable. The corresponding electrons in these orbitals feel a stronger attraction by the nucleus and have higher ionization energies. It also increases the electronegativity of the element concerned. This effect is especially strong in the case of gold, as can be seen in Scheme I.32. On the other hand, electrons in *d* and *f* orbitals are better shielded and perceive a weaker nuclear attraction, experimenting an expansion and destabilisation.[79a] The comparison between the energies of the different orbitals whether the relativistic effects are considered or not is shown in Scheme I.33.[79e]



Scheme I.32: Calculated relativistic contraction of the *6s* orbital for different Z values.

The contraction of the *6s* and *6p* orbitals in the gold atom is the reason why gold(I) species are such good Lewis acids, since the LUMO is more accessible for a LB to donate electronic density. This contraction is significantly greater than in other π-acid metals, such as silver, in which relativistic effects do not play such an important role. A sample of this difference can be seen when comparing ionization potentials (9.23 for Au vs. 7.58 for Ag)[80] and electronegativities (2.4 for Au vs. 1.9 for Ag).[80a]

[80] a) C. M. Brown, M. L. Ginter, *J. Opt. Soc. Am., JOSA* **1978**, *68*, 243–246. b) H.-P. Loock, L. M. Beaty, B. Simard, *Phys. Rev. A* **1999**, *59*, 873–875.



Scheme I.33: Schematic view of the molecular orbital energies for hypothetic Pt, Au, and Hg compounds before and after relativistic considerations.

The contraction of the empty *6s* orbital also has an effect on the bonds between a gold atom and a ligand, making the bonding energies greater than those corresponding to the bond to a silver atom. For example, calculations for the cationic species $AuPH_3^+$ and $AgPH_3^+$ show that the occupancy of the *6s* orbital is much higher in the case of gold (0.438 vs. 0.156 electrons), which translates into a greater covalent like bond. When a second ligand is considered (species $Au(PH_3)_2^+$ and $Ag(PH_3)_2^+$), there is a raise in the occupancy of the *6s* orbital that was again higher for gold (0.796 for Au vs. 0.449 for Ag), whereas the occupancy in the *6p* orbitals remains very low in the case of gold (0.011electrons). This might be used as a rough explanation for the higher acidity of gold(I) species, although deeper considerations would be needed in order to fully understand its behaviour.[81]

On the other hand, gold(I) is a large cation with diffuse orbitals around it, so its acidic behaviour is expected to be more influenced by orbital interactions rather than charge interactions, which means it can be classified as a *soft* Lewis acid.[82] It will prefer to interact with *soft* Lewis bases, such as π-systems.

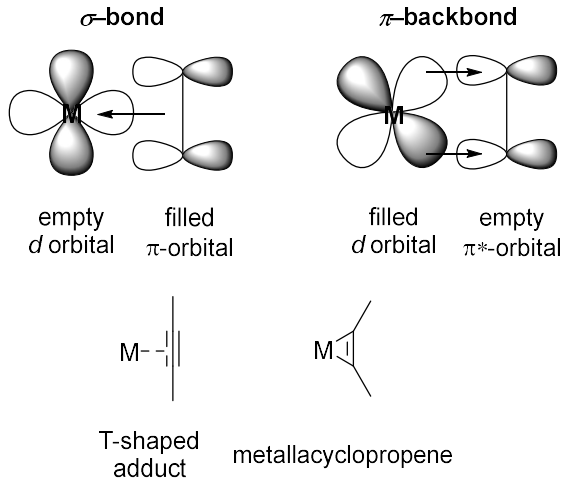
Regarding the different π -systems, gold does not selectively coordinate to one type of multiple bond, but it exhibits a superior reactivity towards a nucleophilic attack when

[81] P. Schwerdtfeger, H. L. Hermann, and H. Schmidbaur, *Inorg. Chem.* **2003**, *42*, 1334-1342.
[82] R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539.

activating an alkyne versus an alkene. Since alkynes have a lower LUMO than alkenes, the corresponding π-complex should also have a lower LUMO, being more accessible for nucleophiles, which could explain this difference in reactivity.

The Dewar-Chatt-Duncanson model explains the bond between a metal centre and a π-system as a combination of a σ-donation of electronic density from a filled π orbital in the alkyne to an empty *d* orbital in the metal and a π-back-donation of electronic density from a filled *d* orbital in the metal to a π*orbital in the alkyne. The bigger the π-backbonding is, the greater the reduction in the bonding order in the alkyne. Thus, metals for which backbonding is low form a coordination species that is closer to a simple metal-alkyne adduct. For those metals in which backbonding is high, the species formed would be more accurately described as a metallacyclopropene (Scheme I.34).[83]

In the case of Au^{I}-alkyne complexes, this backbonding is especially low, being the T-shaped adduct structure the most accurate one.[79a] This is also another explanation for the high activation ability of gold(I) species to alkynes, since Au^{I}-alkene complexes present higher backbonding, and their structure is more similar to the metallacycle case.[84]



Scheme I.34: Dewar-Chatt-Duncanson model for alkyne coordination and limit structures proposed for π-complexes.

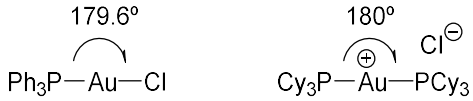
[83] a) J. Chatt, L. A. Duncanson, *J. Chem. Soc.* **1953**, 2939–2947. b) J. Chatt, L. A. Duncanson, L. M. Venanzi, *J. Chem. Soc.* **1955**, 4456–4460.

[84] a) R. H. Hertwig, W. Koch, D. Schröder, H. Schwarz, J. Hrušák, P. Schwerdtfeger, *J. Phys. Chem.* **1996**, *100*, 12253–12260. b) M. S. Nechaev, V. M. Rayón, G. Frenking, *J. Phys. Chem. A* **2004**, *108*, 3134–3142.

Gold(I) Complexes in Homogeneous Catalysis: Coordination Geometry and Ligand Tuning

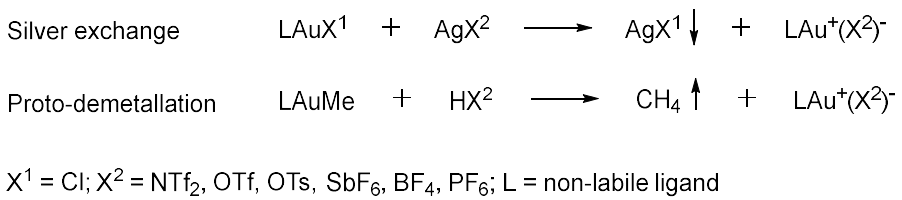
Since the study by Teles et al. in 1998 about the activity of different gold(I) catalysts for the addition of alcohols to alkynes,[11a] a great variety of gold(I) complexes has been developed. The advantage of gold(I) complexes versus species such as gold(I) chloride is its higher stability,[85] and the possibility to modulate their reactivity through the ligand employed.

A very important characteristic of gold(I) complexes is its strong preference for coordinating only two ligands, usually in an essentially linear geometry. It is the element in group 11 with the least disposition to increase this coordination number.[7a] For example, Ph_3PAuCl has a bonding angle of 179.6º (Scheme I.35), and in the case of the complex $[Au(PCy_3)_2]^+ Cl^-$, the angle is exactly 180º.



Scheme I.35: Bonding angle in two linear gold(I) complexes.

This tendency means that the abstraction of one of the ligands is necessary to generate a sufficiently reactive catalytic species. There are two usual strategies to generate the cationic gold(I) complex: the abstraction of a chloride ligand with a silver salt of a weakly coordinating counteranion, or the proto-demetallation on a methyl-gold compound with the conjugated acid of the desired counteranion (Scheme I.36). Both chloride and methyl pre-catalysts are air and moisture stable compounds.



Scheme I.36: Main strategies for the generation of a cationic gold(I) complex.

[85] a) C. H. Gammons, Y. Yu, A. E. Williams-Jones, *Geochim. et Cosmochim. Acta* **1997**, *61*, 1971–1983. b) H. Schmidbaur, *Gold Bull.* **2000**, *33*, 3–10. c) H. Schmidbaur, A. Schier, *Organometallics* **2010**, *29*, 2–23.

Both strategies are usually carried out in situ, since the gold(I) species with these counteranions are not usually stable enough to be isolated. This is not an ideal way to generate the catalyst because the corresponding silver salts are very hygroscopic and difficult to weight accurately,[86a] and the corresponding conjugated acids may also come from commercial sources with water traces.[8] Besides, the silver chloride suspended in the reaction medium might not be totally innocent.[87]

In 2005, Gagosz et al. reported the use of air and moisture stable gold(I) complexes containing a bistriflimidate counteranion. It is a fairly weakly coordinating counteranion and these species exhibit a good reactivity. Furthermore, they can be synthesised and isolated in a crystalline form.[88,89]

Another alternative is adding a second labile ligand, such as acetonitrile, pyridine, benzotriazole or a tertiary amine, that will easily dissociate in solution, to generate a species that is air and moisture stable, and perfectly isolable, while having a very weakly coordinating counteranion, such as the fluorinated ones, thus obtaining very active catalysts.[90]

Regarding the non-labile ligand, phosphines, phosphites and, more recently, N-heterocyclic carbenes (NHCs) are the most used ones to modify both the electronic and steric properties of the catalyst.[91] In general terms, phosphines are more or less electron-

[86] a) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136. b) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615.

[87] a) D. Weber, M. R. Gagné, *Org. Lett.* **2009**, *11*, 4962–4965. b) S. R. Patrick, I. I. F. Boogaerts, S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Beilstein J. Org. Chem.* **2011**, *7*, 892–896. c) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019. d) A. Zhdanko, M. E. Maier, *ACS Catal.* **2015**, *5*, 5994–6004. e) B. Ranieri, I. Escofet, A. M. Echavarren, *Org. Biomol. Chem.* **2015**, *13*, 7103–7118.

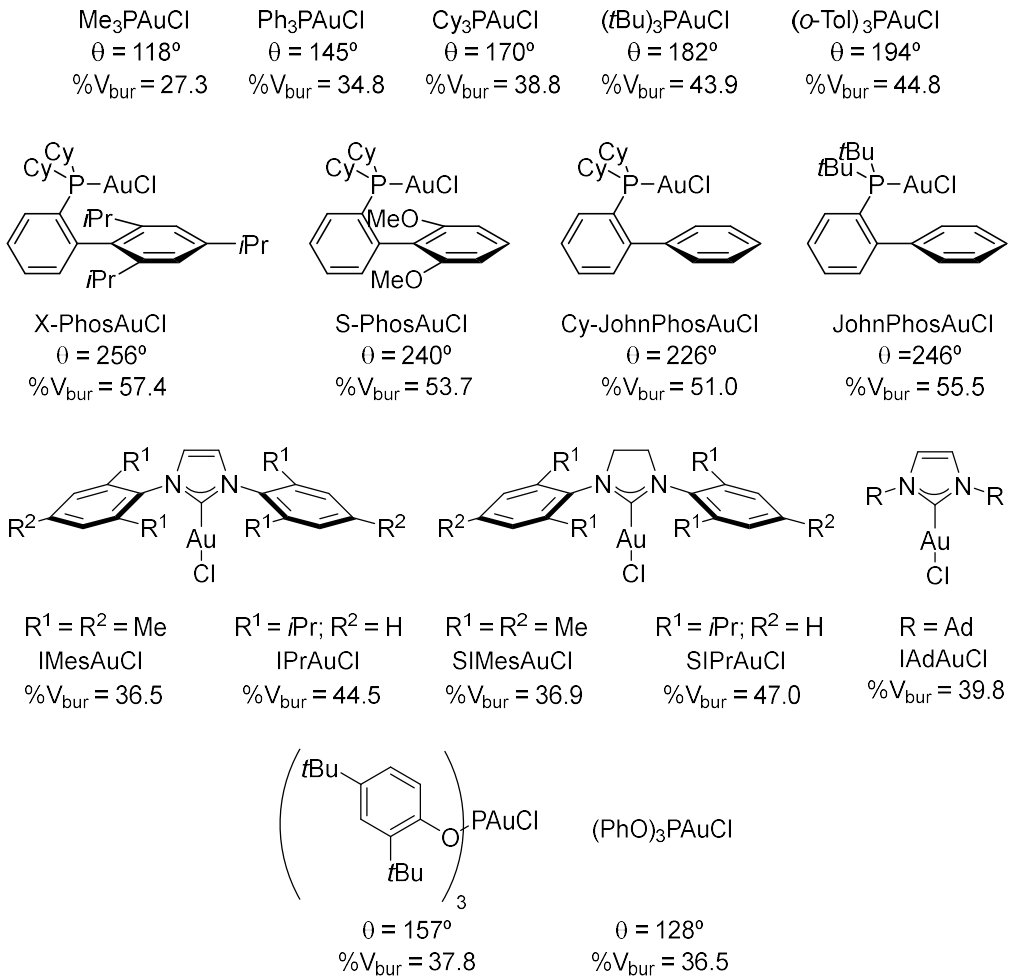
[88] a) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136. b) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615.

[89] Similar results are achieved with tosylate as a counteranion: a) P. Roembke, H. Schmidbaur, S. Cronje, H. Raubenheimer, *J. Mol. Catal. A* **2004**, *212*, 35–42. b) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, et al., *Chem. Eur. J.* **2010**, *16*, 956–963.

[90] a) C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148. b) P. Nun, S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 9113–9115. c) H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov, X. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 12100–12102.

[91] a) H. Clavier, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 841–861. b) S. P. Nolan, *Acc. Chem. Res.* **2011**, *44*, 91–100. c) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378.

donating ligands depending on their substituents, but they are usually more electron-donating than phosphites, which have a higher capacity to accept electronic density via π-backbond, and less electron-donating than NHCs, which have a greater σ–donating character.[91b,92] The steric volume of the ligand can also modify the reactivity and stability of the gold complex.[85] It can be measured using the Tolman angle (θ) for phosphines, phosphites, and conic ligands in general, or the percent buried volume ($\%V_{bur}$) for NHCs.[91a,92] Scheme I.37 shows the steric properties of some usual ligands in gold catalysis.[91a]



Scheme I.37: Tolman angles and percent buried volume of some usual ligands in gold homogeneous catalysis.

[92] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313–348.

Gold(I) Acetylides

Gold(I) acetylides have received a lot of attention recently. Their photochemical properties are known since decades ago, and are interesting for probe design.[93] They have also been studied in supramolecular chemistry to achieve a better understanding of metal-metal interactions and other related concepts, like *aurophilicity*.[94] But more recently, interesting applications in homogeneous catalysis have been found.[95]

Gold acetylides can be easily prepared by reaction of the corresponding alkyne with a base and substitution of a chloride ligand, among other methods.[96] Obtaining catalytic amounts of a gold acetylide requires using a gold acetylide complex as a catalyst in some cases,[93] or having some molecule in the medium reacting as a base,[97] but in others, an active enough gold catalyst does not need a base.[93] Other very efficient way of obtaining a gold acetylide is the reaction of a cationic gold(I) complex with an alkynylsilane.[93a,98]

The efficiency of this strategy to form a gold acetylide relies on the silicon β-effect previously described. Scheme I.38 shows a plausible mechanism for the silicon-gold

[93] a) D. Li, X. Hong, C.-M. Che, W.-C. Lo, S.-M. Peng, *J. Chem. Soc., Dalton Trans.* **1993**, 2929–2932. b) Y.-P. Zhou, E.-B. Liu, J. Wang, H.-Y. Chao, *Inorg. Chem.* **2013**, *52*, 8629–8637. c) Y.-P. Zhou, M. Zhang, Y.-H. Li, Q.-R. Guan, F. Wang, Z.-J. Lin, C.-K. Lam, X.-L. Feng, H.-Y. Chao, *Inorg. Chem.* **2012**, *51*, 5099–5109. d) F. K.-W. Hau, X. He, W. H. Lam, V. W.-W. Yam, *Chem. Commun.* **2011**, *47*, 8778–8780. e) X. He, N. Zhu, V. W.-W. Yam, *Dalton Trans.* **2011**, *40*, 9703–9710.

[94] S.-Y. Yu, Q.-F. Sun, T. K.-M. Lee, E. C.-C. Cheng, Y.-Z. Li, V. W.-W. Yam, *Angew. Chem. Int. Ed.* **2008**, *47*, 4551–4554.

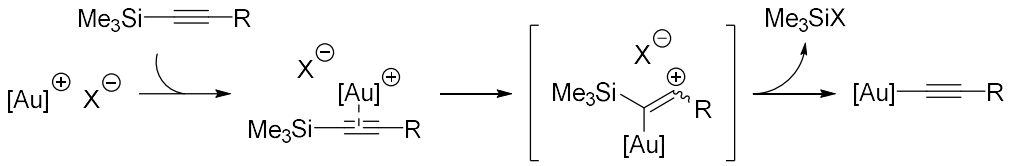
[95] a) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072. b) A. S. K. Hashmi, *Acc. Chem. Res.* **2014**, *47*, 864–876. c) I. Braun, A. M. Asiri, A. S. K. Hashmi, *ACS Catal.* **2013**, *3*, 1902–1907. d) A. Grirrane, H. Garcia, A. Corma, E. Álvarez, *Chem. Eur. J.* **2013**, *19*, 12239–12244. e) Y. Tokimizu, M. Wieteck, M. Rudolph, S. Oishi, N. Fujii, A. S. K. Hashmi, H. Ohno, *Org. Lett.* **2015**, *17*, 604–607. f) J. Bucher, T. Wurm, K. S. Nalivela, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2014**, *53*, 3854–3858. g) A. Grirrane, H. Garcia, A. Corma, E. Álvarez, *ACS Catal.* **2011**, *1*, 1647–1653. h) A. Leyva-Pérez, A. Doménech, S. I. Al-Resayes, A. Corma, *ACS Catal.* **2012**, *2*, 121–126.

[96] a) A. S. K. Hashmi, I. Braun, M. Rudolph, F. Rominger, *Organometallics* **2012**, *31*, 644–661. b) G. F. Manbeck, M. C. Kohler, M. R. Porter, R. A. S. Jr, *Dalton Trans.* **2011**, *40*, 12595–12606. c) A. S. K. Hashmi, T. Lauterbach, P. Nösel, M. H. Vilhelmsen, M. Rudolph, F. Rominger, *Chem. Eur. J.* **2013**, *19*, 1058–1065. Supp. Inf. General Procedure 1. d) G. C. Fortman, A. Poater, J. W. Levell, S. Gaillard, A. M. Z. Slawin, I. D. W. Samuel, L. Cavallo, S. P. Nolan, *Dalton Trans.* **2010**, *39*, 10382–10390. e) G. Ferguson, J. F. Gallagher, A.-M. Kelleher, T. R. Spalding, F. T. Deeney, *J. Organomet. Chem.* **2005**, *690*, 2888–2894.

[97] G. Abbiati, E. Rossi, *Beilstein J. Org. Chem.* **2014**, *10*, 481–513.

[98] P. Starkov, F. Rota, J. M. D'Oyley, T. D. Sheppard, *Adv. Synth. Catal.* **2012**, *354*, 3217–3224.

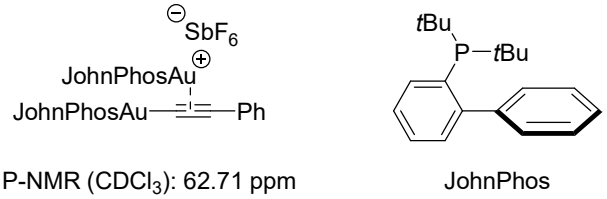
exchange that takes place.[98] First, the gold(I) complex acts as a π-acid, activating the alkyne. The donation of electronic density from the alkyne to the gold centre is favoured by the presence of the silicon atom, which stabilises the carbocation formed in beta position. Any other basic molecule in the medium can react with the trimethylsilyl group, and the carbocation undergoes an elimination to afford the gold(I) acetylide.



Scheme I.38: Mechanism for the formation of a gold(I) acetylide from an alkynylsilane and a gold(I) complex.

In recent catalytic applications in which gold(I) acetylides have been found to be an intermediate in the process, also σ,π-digold acetylene species have been observed, and even isolated and characterised.[95g, 99] They are formed from the gold acetylide by coordination of another equivalent of the catalyst, and can be determinant for the outcome of the reaction in some cases.

One important characteristic of these species is that they are *fluxional*, that is, both gold centres can exchange positions in solution. This exchange is very fast, and it can be observed by ^{31}P-NMR spectroscopy, since they present only one ^{31}P signal. For example, the complex shown in Scheme I.39 presents a single ^{31}P signal at 62.71 ppm.[95g]



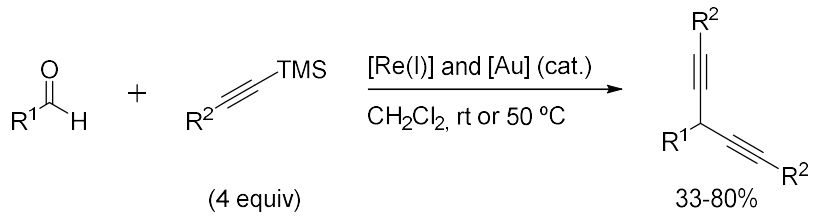
^{31}P-NMR ($CDCl_3$): 62.71 ppm JohnPhos

Scheme I.39: Fluxional σ,π-digold complex with only one ^{31}P signal in ^{31}P-NMR spectroscopy.

[99] a) T. J. Brown, R. A. Widenhoefer, *Organometallics* **2011**, *30*, 6003–6009. b) R. E. M. Brooner, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2013**, *52*, 11714–11724. c) A. Gómez-Suárez, S. P. Nolan, *Angew. Chem. Int. Ed.* **2012**, *51*, 8156–8159. d) A. S. K. Hashmi, T. Lauterbach, P. Nösel, M. H. Vilhelmsen, M. Rudolph, F. Rominger, *Chem. Eur. J.* **2013**, *19*, 1058–1065. e) L. Jašíková, J. Roithová, *Organometallics* **2013**, *32*, 7025–7033.

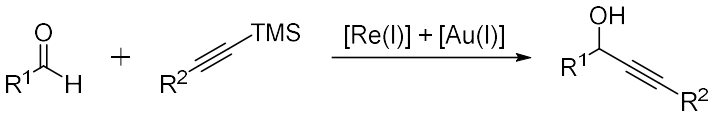
Aims in Part I

A bis-alkynylation reaction of aromatic aldehydes to afford 1,4-diynes, reported by Takai et al., has been described and analysed in Section 2 of the introduction to this Part I (p. 70).[75a] Being this process solidly studied, it has been proved that gold(I) chloride cannot catalyse by itself any of the alkynylation steps (a summary is shown in Scheme I.40).

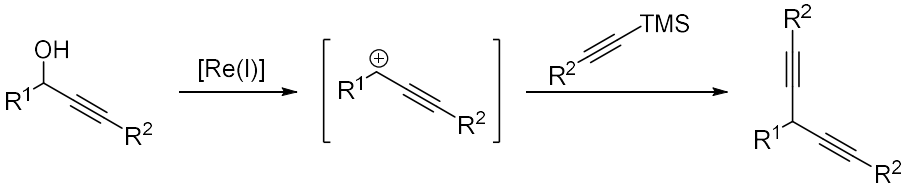


Two-steps proposed mechanism by Takay et al.:

1) Both catalysts have been demostrated to be involved in the first alkynylation step.



2) Gold(I) has not been found to play any role in the second alkynylation step



Scheme I.40: Summary of the work by Takai et al. and their mechanistic proposal.

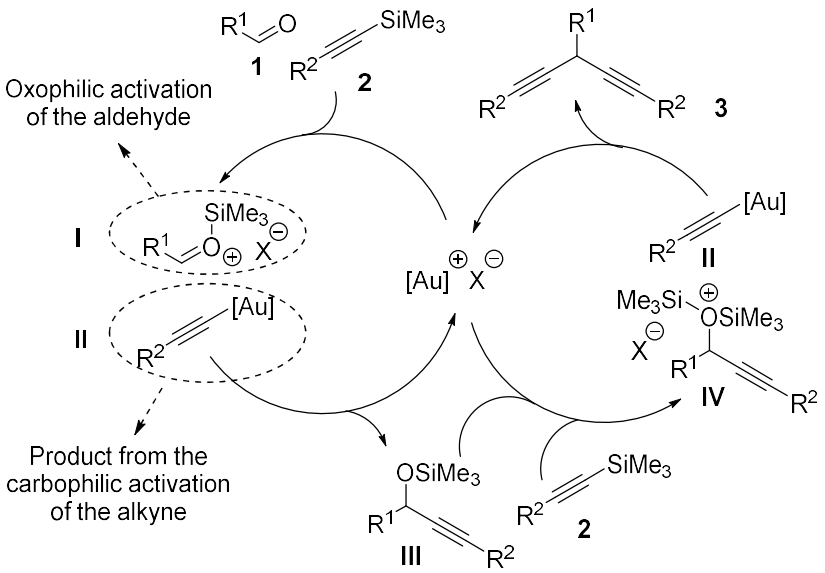
Based on the previous experience working in gold(I) catalysis of our research group,[14,100] and on the established knowledge that both the stability and the reactivity of

[100] a) S. Suárez-Pantiga, C. Hernández-Díaz, M. Piedrafita, E. Rubio, J. M. González, *Adv. Synth. Catal.* **2012**, *354*, 1651–1657. b) S. Suárez-Pantiga, E. Rubio, C. Alvarez-Rúa, J. M. González, *Org. Lett.* **2009**, *11*, 13–16. c) J. González, J. Santamaría, A. Ballesteros, *Angew. Chem. Int. Ed.* **2015**, *54*, 13678–13681. d) P. Morán-Poladura, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2015**, *54*, 3052–3055.

the gold(I) complex can be conveniently modulated through the use of different ligands,[84] it was decided to explore the challenging possibility that a single gold(I) complex with a suitable ligand could, in its own right, promote a similar transformation without the need of any other catalyst in the reaction medium.

The mechanistic hypothesis that would support this idea is shown in Scheme I.41. The gold(I) complex would activate the alkynylsilane to form the corresponding gold(I) acetylide, whose nucleophilicity would depend on the ligand used, and liberating in the medium a silicon species, Me_3SiX, whose electrophilicity would depend on the counteranion employed. If this silicon species is acidic enough, it would react with the carbonyl group in the aldehyde, increasing the electrophilicity of its carbonylic carbon, and hence, the nucleophilic attack of the gold acetylide would be possible. In this manner, both a carbophilic and an oxophilic activation are taking place, whereas gold(I) complexes usually only achieve carbophilic activations.

After the first addition of one alkynyl moiety, the $-OSiMe_3$ group formed can be activated by another Me_3SiX molecule in an analogous way, promoting the substitution by a second equivalent of a gold acetylide.



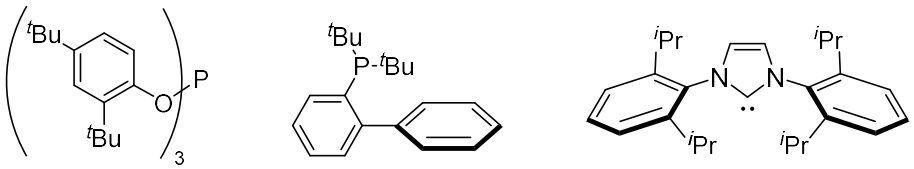
Scheme I.41: Mechanistic hypothesis.

The following pages describe the results obtained in the accomplishment of this aim, which was carried out starting by the optimisation of the reaction conditions, and followed by the study of the scope of this new process. Finally, some experimental evidences were assembled and discussed to analyse the accuracy of the mechanistic hypothesis made.

Results and Discussion

Initial Results

The validation of the hypothesis that has been previously postulated started by testing different auxiliary ligands for the gold(I) complex, including a phosphite (**L1**), two phosphines with different steric demand [PPh_3 (**L2**) and (2-biphenyl)di-*tert*-butylphosphine JohnPhos (**L3**)], and the more σ-donating N-heterocyclic carbene (NHC) [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene IPr (**L4**)]. Their structures are shown in Scheme I.42. Bistriflimidate was chosen as a counteranion, on a routine basis, to avoid the use of hygroscopic and unstable silver salts.



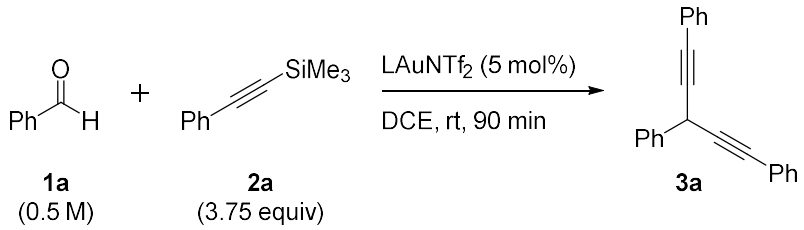
L1 **L3** **L4**

Scheme I.42: Structures for ligands **L1**, **L3** and **L4**.

Initially, the reactions were carried out in 1,2-dichloroethane (DCE), at room temperature. Commercially available benzaldehyde (**1a**) and trimethyl(phenylethynyl)silane (**2a**) were used as model substrates. At the onset, an excess of **2a** was used to assure the rapid regeneration of the catalytic Si-based species.[101] Conversions and yields referring the results of the different catalysts employed were collected after 90 minutes for comparison purposes, and are presented in Table I.1.

[101] 3.75 equiv, corresponding to 300 μL, which was considered a handy amount to measure.

Table I.1: Ligand screening for the gold(I)-catalysed aldehyde bis-alkynylation.



Entry	Ligand (L)	Conversion (% /Yield (%)
1	**L1** $P(OAr)_3$	100/64
2	**L2** PPh_3	88/58
3	**L3** JohnPhos	100/86
4	**L4** IPr	92/55

All the ligands tested under these conditions proved to be valid for this transformation, being JohnPhos (**L3**, entry 3) the one that gave the best results in terms of both conversion and yield.[102] Besides, when the reaction using **L3** was conducted in CH_2Cl_2 as solvent, instead of DCE, the formation of compound **3a** took place in 72% yield.

At the same time, the possible effect of using other counteranions was also tested. Both complexes JohnPhosAu(MeCN)SbF_6 and JohnPhosAuSbF_6, this last one generated in situ by addition of the corresponding silver salt to the gold(I) chloride species, were essayed. None of them succeeded in promoting this transformation at any extent. Furthermore, the same lack of reactivity was noticed when triflate, tetrafluoroborate or tosylate counteranions were used.

In the same sense, the role of the spectator substituents onto silicon was also explored. Interestingly, no reaction was observed when employing other alkynylsilanes with less labile silicon moieties, such as *tert*-butyldimethyl(phenylethynyl)silane.

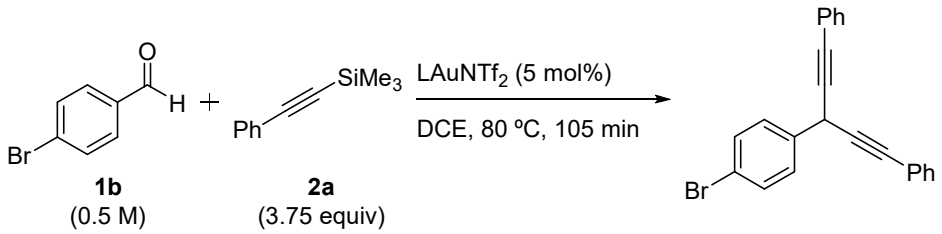
[102] The use of biarylphosphines in gold(I) catalysis was initially developed by Echavarren et al. and it has been observed to improve yields and reaction times in certain occasions in comparison with other phosphines: a) C. Ferrer, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109. b) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358–1373.

Optimisation of the Reaction Conditions

The reaction conditions previously described were tested using a benzaldehyde derivative with an electron withdrawing group as substrate, such is the case of 4-bromobenzaldehyde (**1b**). Under those conditions, **1b** was found unreactive. Given this, it was considered that an increase in the reaction temperature could be used to promote the reaction, while offering a convenient and simple tool to provide access to a wider variety of products.

The reaction using as gold(I) catalysts those derived from ligands **L1**, **L3** and **L4** were tested in DCE at 80 ºC for the reaction of **1b** with **2a**. Again, JohnPhos (**L3**) proved to be a superior ligand, affording a higher yield, as well as a cleaner crude reaction mixture (Table I.2). In this case, the reaction time was established as a function of the total consumption of the limiting reactant, which was observed for all the cases at 105 minutes.

Table I.2: Ligand screening under thermal conditions.



1b (0.5 M) **2a** (3.75 equiv)

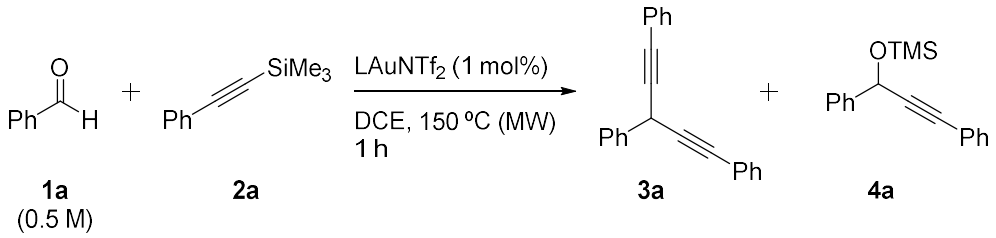
Entry	Ligand (L)	Conversion (%)/Yield (%)
1	**L1** $P(OAr)_3$	100/60
2	**L3** JohnPhos	100/75
3	**L4** IPr	100/65

At this point, it was challenging to explore the possibility of lowering the catalyst loading if higher temperature was used. Microwave heating is an attractive tool for setting reactions at temperatures over the boiling point of the solvent, since sealed tubes are

required. At the same time, it could provide with a more efficient heating process that would not result into yield loss through side reactions.[103]

Once again, catalysts based on ligands **L1** to **L4** were tested using as low as 1 mol% catalyst loading in the reaction of **1a** with **2a**, in 1,2-dichloroethane at 150 ºC, using microwave heating. In this case, a mixture of the mono-alkynylated (**4a**) and bis-alkynylated (**3a**) products was observed in most cases, being **L3** the only ligand that furnished complete conversion to **4a** after 1 hour (Table I.3).

Table I.3: Ligand screening at 150 ºC with only 1 mol% catalyst loading.



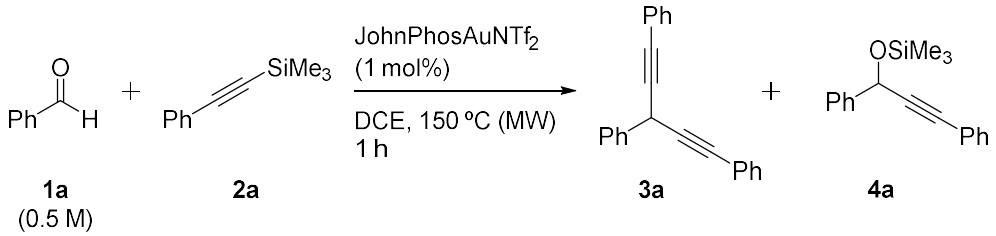
Entry	Ligand (L)	**3a** / **4a**[a]
1	**L1** $P(OAr)_3$	0.53/0.47
2	**L2** PPh_3	0.87/0.13
3	**L3** JohnPhos	1.00/0.00
4	**L4** IPr	0.77/0.23

[a]Ratios determined from the crude mixture by ^{1}H-NMR integration, and referred to the total integration of **3a** plus **4a**.

Under these conditions, the efficiency of the catalyst containing ligand **L3** was tested conducting the reaction in other solvents. Less polar solvents than DCE were used, like toluene or 1,4-dioxane. This last one is less polar than DCE but exhibits a higher coordination capacity. More polar solvents, like tetrahydrofuran (THF) or acetonitrile, which would be the most coordinating one among the rest mentioned, were also employed (Table I.4).

[103] L. Perreux, A. Loupy, in *Microwaves in Organic Synthesis* (Ed.: A. Loupy), Wiley-VCH Verlag GmbH, **2006**, pp. 134–218.

Table I.4: Solvent screening at 150 ºC with 1 mol% catalyst loading.



1a (0.5 M) **2a** **3a** **4a**

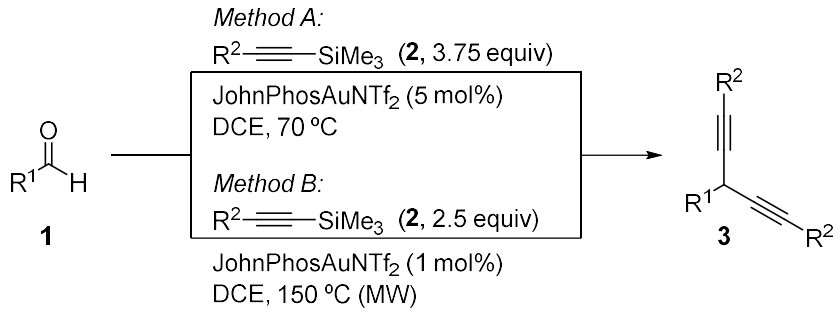
Entry	Solvent	**3a** / **4a**[a]
1	DCE	1.00/0.00
2	Toluene	0.34/0.66
3	1,4-dioxane	0.17/0.83
4	THF	0.00/1.00
5	MeCN	0.00/1.00

[a] Ratios determined from the crude mixture by ^{1}H-NMR integration, and referred to the total integration of **3a** plus **4a**. Total conversion was observed.

DCE was the only solvent that afforded full conversion to **3a** in comparable reaction time (Table I.4, entry 1). Very slow conversion of **4a** into **3a** was observed in toluene and 1,4-dioxane (entries 2 and 3). Interestingly, the second alkynylation step was not observed when using THF or acetonitrile, obtaining only product **4a** (entries 4 and 5).

Considering these results, two sets of experimental conditions can be considered as appropriate for the preparation of bis-alkynylation products **3**. Thus, depending on whether we search for a fast process using low catalyst loading, or softer conditions, lower costs in terms of energy spent, but higher catalyst loading, both methods outlined in Scheme I.43 as methods A and B represent valuable options for this purpose.

Further optimisation of the amount of equivalents of alkynylsilane also allowed to lower its number to 2.5 equivalents in the case of method B. On the other hand, the temperature for conventional heating (method A) was found to be dependent on the substrate when studying the scope of the reaction (see Table I.5). However, a value of 70 ºC resulted into a cleaner crude reaction mixture for most of them.



Scheme I.43: Methods A and B for the bis-alkynylation of aldehydes.

Study of the Reaction Scope

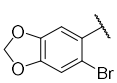
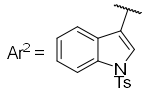
Several aldehydes and alkynylsilanes were tested using methods A and B, in order to have an accurate view of the possibilities that both reaction conditions offered. Table I.5 (p. 97) contains the specific conditions used and the yields obtained for several aromatic aldehydes, and aromatic and aliphatic alkynylsilanes. For a better visual inspection of the products obtained, their structures are depicted in Scheme I.44 (p. 98).

As it is mentioned in Table I.5, the reaction time was found to be a parameter that had to be carefully monitored, otherwise the yield would drop considerably. This is especially important for very short reaction times, like in the case of products **3e**, **3h**, **3n**, **3r** or **3s** (entries 6, 9, 15, 19 and 20, method B). The yield at lower conversions was found, in all cases, to be smaller than the one obtained when full conversion of the starting material was noticed, nicely accommodating a gradual evolution of the process.

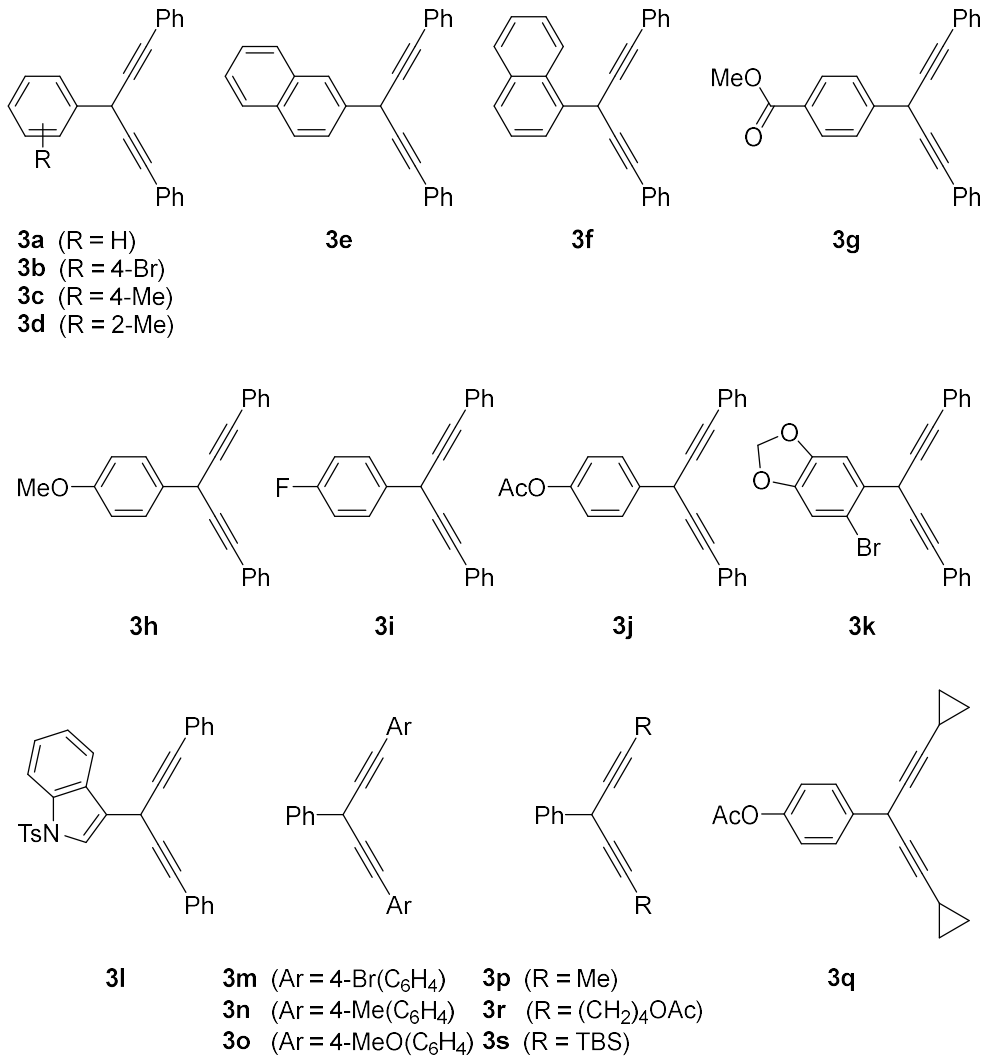
Despite this fact, the inspection of the crude reaction mixture by ^{1}H-NMR analysis never revealed any signal indicating the presence of other by-products or evidences of significant decomposition processes taking place. Only the signals that belonged to the product would appear in the spectrum, and just the signals in the aromatic region would occasionally present a wider shape, suggesting the formation of some polymeric materials.

Table I.5: Study of the reaction scope for methods A and B.

		Method A			Method B	
Entry	**3** (R^1, R^2)	T (ºC)	t (min)[a]	Yield[b]	t (min)[a]	Yield[b]
1	**3a** (Ph, Ph)	rt	90	86%	35	70%
2	**3b** (4-BrC_6H_4, Ph)	70	180	72%	105	42%
3	**3b** (4-BrC_6H_4, Ph)	80	105	75%		
4	**3c** (4-MeC_6H_4, Ph)	70	30	65%	15	73%
5	**3d** (2-MeC_6H_4, Ph)	70	30	77%	15	74%
6	**3e** (2-NpC_6H_4, Ph)	70	15	60%	5	50%
7	**3f** (1-NpC_6H_4, Ph)	70	30	58%		
8	**3g** [4-(MeCO_2)C_6H_4, Ph]	80	120	53%[c]		
9	**3h** (4-MeOC_6H_4, Ph)	70	30	66%	3	67%
10	**3i** (4-FC_6H_4, Ph)	70	30	77%		
11	**3j** (4-AcOC_6H_4, Ph)	70	20	77%		
12	**3k** (Ar^1, Ph)	70	15	73%		
13	**3l** (Ar^2, Ph)	rt	120	45%		
14	**3m** (Ph, 4-BrC_6H_4)	70	240	65%	100	37%
15	**3n** (Ph, 4-MeC_6H_4)	70	240	57%	5	40%
16	**3o** (Ph, 4-MeOC_6H_4)				20	50%
17	**3p** (Ph, Me)				15[d]	30%
18	**3q** (4-AcOC_6H_4, cyclopropyl)				90[d]	31%
19	**3r** (Ph, $(CH_2)_4$OAc)				5[d]	25%
20	**3s** [Ph, Si(*t*Bu)Me_2]				1	39%
21	**3u** (Ph, 1-cyclohexenyl)	70	480	35%		

Ar^1 =  Ar^2 = 

[a] Reaction time monitored by TLC for method A and by doing a time screening for each substrate for method B. [b] Isolated yield unless otherwise stated. [c] Yield recorded from the crude reaction by ^{1}H-NMR inspection, using acetanilide as internal standard. Mono-alkynylated **4g** was also present in 12% yield. [d] At 120 ºC with 5 mol% catalyst loading.



Scheme I.44: Structures for compounds **3a-s**.

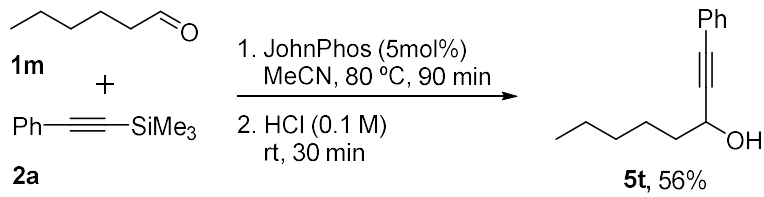
Several 4-substituted benzaldehyde derivatives with both electron-donating (products **3h**, **3j**, **3k**, or **3q**, entries 9, 11, 12 and 18) and electron-withdrawing groups (products **3b**, **3g**, or **3i**, entries 2, 3, 8 and 10) proved to be suitable for this transformation. Besides, the outcome was virtually the same when comparing two *para-* and *ortho-*substituted isomers (products **3c** and **3d**, entries 4 and 5). Functional groups such as esters (**3g**, **3j**, and **3q**, entries 8, 11, and 18) and bromine atoms (**3b** and **3k**, entries 2, 3 and) were also tolerated, which would not be possible using other alkynylation methods, such as organolithium reagents or Sonogashira conditions.

Other aromatic patterns of the starting aromatic aldehyde could also be employed, such as a labile indolyl moiety (**3l**, entry 13) or a naphthyl moiety (**3e** and **3f**, entries 6 and 7), although moderate yields were obtained. Similar results were obtained for substrates 1-naphthaldehyde and 2-naphthaldehyde, which have different steric demand.

Regarding the starting alkynylsilane **2**, several aromatic substituents bearing electron-donating and electron-withdrawing groups were tested (products **3m-o**, entries 14-16), affording moderate to good yields. An enyne scaffold could also be employed, although it afforded a lower yield than the aromatic ones (**3u**, entry 21).

It was observed that method B offered a slight improvement for some substrates, such as the case of **3c** (entry 4), but it was not a systematic tendency. Remarkably, it allowed to use aliphatic alkynylsilanes, which did not react under the conditions for method A. However, it was necessary to raise the catalyst loading to 5 mol% in most cases (**3p**, **3q**, **3r**, entries 17-19), and the yields obtained varied from low to moderated. A very interesting product that could be prepared using this approach was **3s** (entry 20), whose TBS groups could be subsequently cleaved and substituted for other functionalization using standard protocols.

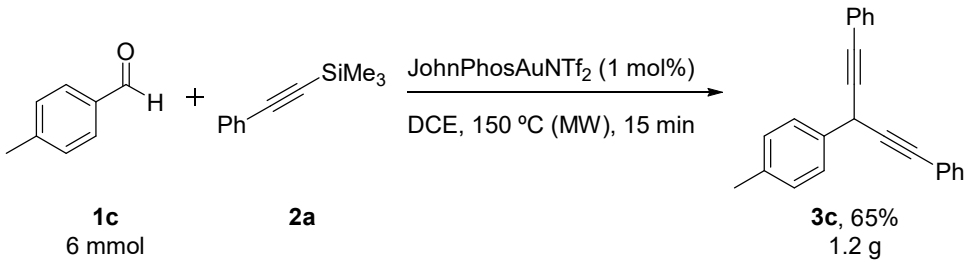
Hexanal, an aliphatic aldehyde, failed to react under conditions from both methods A and B. Interestingly, a change in the solvent to acetonitrile afforded the mono-alkynylated product **5t** in moderate yield (Scheme I.45), opening a new way for the catalytic alkynylation of aldehydes.



Scheme I.45: Mono-alkynylation of hexanal adapting method A to acetonitrile as solvent.

On the other hand, ketones such as acetophenone, benzophenone or trifluoroacetophenone were tested using both methods A and B, and they were found to be unreactive.

The robustness of method B was tested by increasing the scale from the routinely use 0.4 mmol of aldehyde to 6 mmol, obtaining 1.2 g of product **3c** (Scheme I.46).

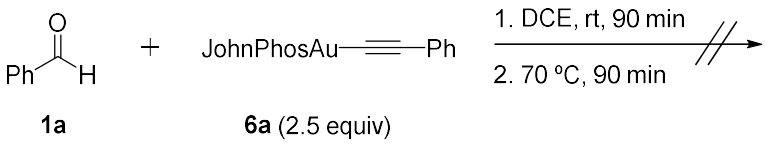


Scheme I.46: Gram-scale preparation of **3c**.

Mechanistic Studies

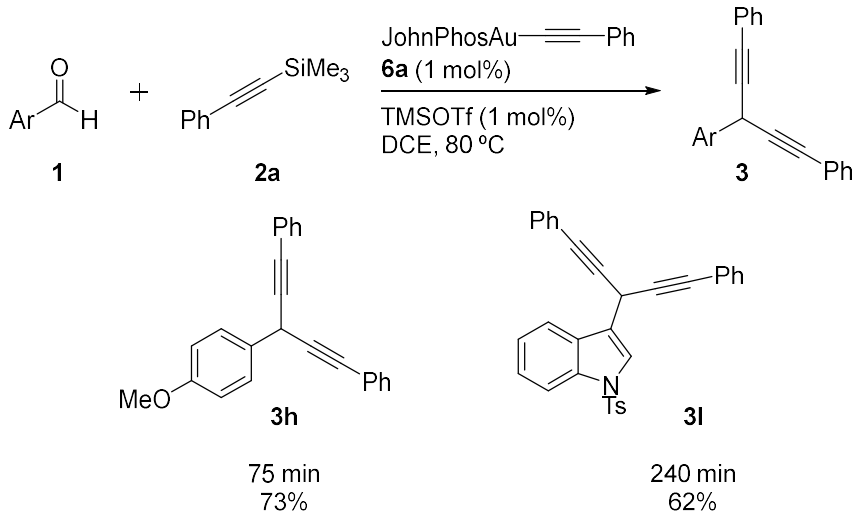
The results obtained support the idea of a single gold(I) complex being able to catalyse this bis-alkynylation reaction of aldehydes, and they are coherent with the mechanistic hypothesis depicted in Scheme I.41 (p. 88). However, some additional experimental work that could give a more solid base to this mechanistic proposal, revealing deeper insights on it, was further pursued.

In order to support the authenticity of the key hypothetic roles attributed to both the gold(I) and the silicon catalytic species, two further experiments were run. First, considering the possibility of the gold(I) acetylide being added to the aldehyde without this last one needing any activation, aldehyde **1a** and gold acetylide **6a** were stirred at room temperature for one hour and a half. TLC analysis did not reveal any change in the composition of the reaction mixture. Then, the reaction was heated at 70 ºC for the same period of time. NMR analysis of the crude reaction mixture didn't reveal any product from any kind of C-C bond-forming process (Scheme I.47).



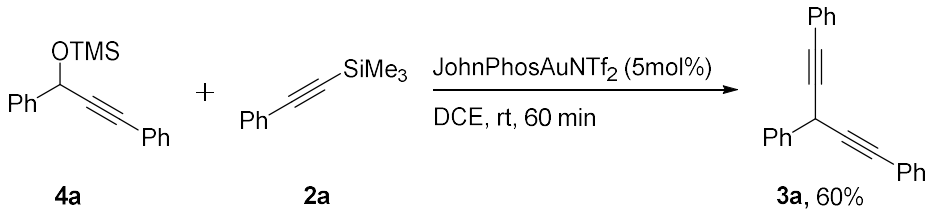
Scheme I.47: Gold(I) acetylide **6a** failed in the addition to aldehyde **1a** in the absence of the silicon species Me_3SiNTf_2.

The use of catalytic amounts of **6a** along with catalytic amounts of freshly distilled Me_3SiOTf succeeded in promoting the transformation employing only a 1 mol% catalyst loading of both species, at 80 ºC. These two experiments suggest that the hypothetical role of the silicon species activating the aldehyde is correct. Furthermore, these alternative conditions were used to improve the yield obtained for product **3h** and for the labile indole derivative **3l**, offering a convenient synthetic approach to these kind of compounds (Scheme I.48).



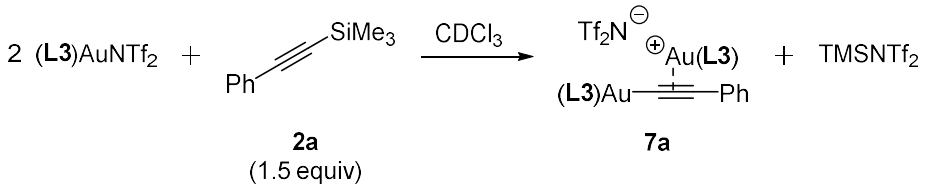
Scheme I.48: Activation of aldehydes **1** with TMSOTf.

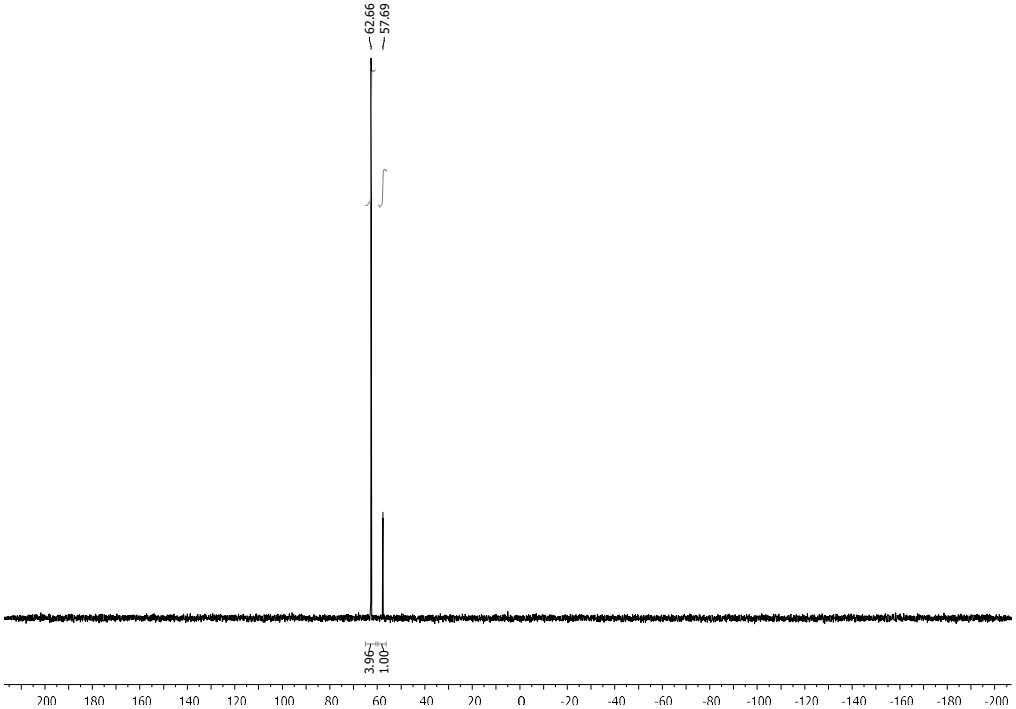
On the other hand, the proposed intermediate **III** contained in the mechanistic hypothesis was synthesised for the particular case of **1a** and **2a** as starting materials, that is, compound **4a**. When pure **4a** was allowed to react with **2a** in the presence of the gold catalyst JohnPhosAuNTf$_2$, at room temperature, product **3a** was obtained in 60% isolated yield. This result proves the ability of this gold(I) species to catalyse the second alkynylation step, as well as confirms the role of proposed intermediate **III** (Scheme I.49).



Scheme I.49: Alkynylation of propargyl silyl ether **4a**.

In order to prove the formation of a gold(I) acetylide, alkynylsilane **2a** was added to a solution of JohnPhosAuNTf$_2$ in dry CDCl$_3$. The mixture was monitored by means of ^{31}P-NMR spectroscopy, observing almost immediately the formation of the σ,π-digold phenylacetylene adduct **7a** (signal at 62.7 ppm), and remaining some JohnPhosAuNTf$_2$ in the medium (signal at 57.7 ppm). No gold(I) acetylide **6a** was observed (signal at 64.44)[96b] (Scheme I.50). Formation of **7a** was also observed when using an excess of **2a** (20 equiv), but no remaining JohnPhosAuNTf$_2$ complex was observed in this case.

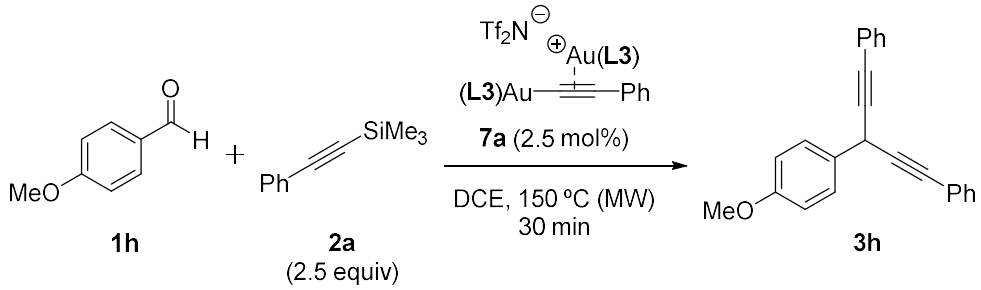




Scheme I.50: Gold(I) species formed after reaction of **2a** with JohnphosAuNTf$_2$.

Species **7a** was also synthesised by addition of JohnPhosAuNTf$_2$ to a solution of the gold(I) acetylide **6a**. Subsequent solvent elimination and recrystallization afforded pure **7a** (see Experimental Section, p. 189), which was used as catalyst (2.5 mol%) in the

reaction of **1h** with **2a**. The target alkynylation reaction did not take place neither at room temperature nor at 70 ºC, but the desired product **3h** was obtained when heating at 150 ºC (method B) (Scheme I.51).

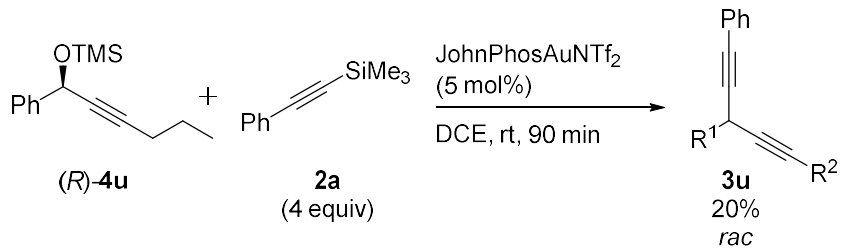


Scheme I.51: σ,π-digold phenylacetylene adduct **7a** as catalytic species for the aldehyde bis-alkynylation reaction.

Additional Results

Since it is possible to perform the second alkynylation step on the corresponding propargylic silyl ether, as it was shown for compound **4a** (see Scheme I.49), the development of an enantioselective version of this transformation represented a very interesting but demanding option to continue expanding the potential of this strategy. According to the proposed working hypothesis, it should involve the formation of a propargylic carbocation after activation of the trimethylsililoxy group.

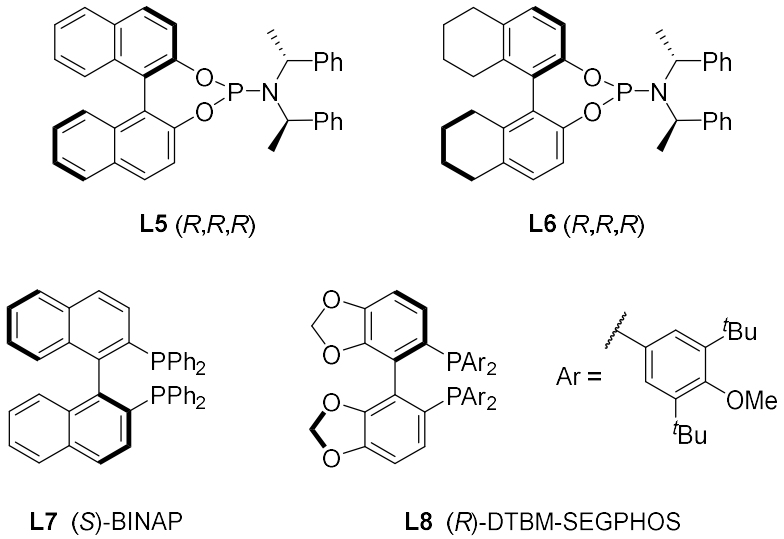
In order to acquire evidences of the existence of that carbocation, enantioenriched compound (*R*)-**4u** (98%*ee*) was synthesised, following Shibasaki's conditions.[55b] When (*R*)-**4u** was used as a substrate under conditions depicted in Scheme I.52, compound **3u** was obtained as a racemic mixture.



Scheme I.52: Catalytic alkynylation of benzylic propargylic silyl ether (*R*)-**4u** with loss of stereochemical information.

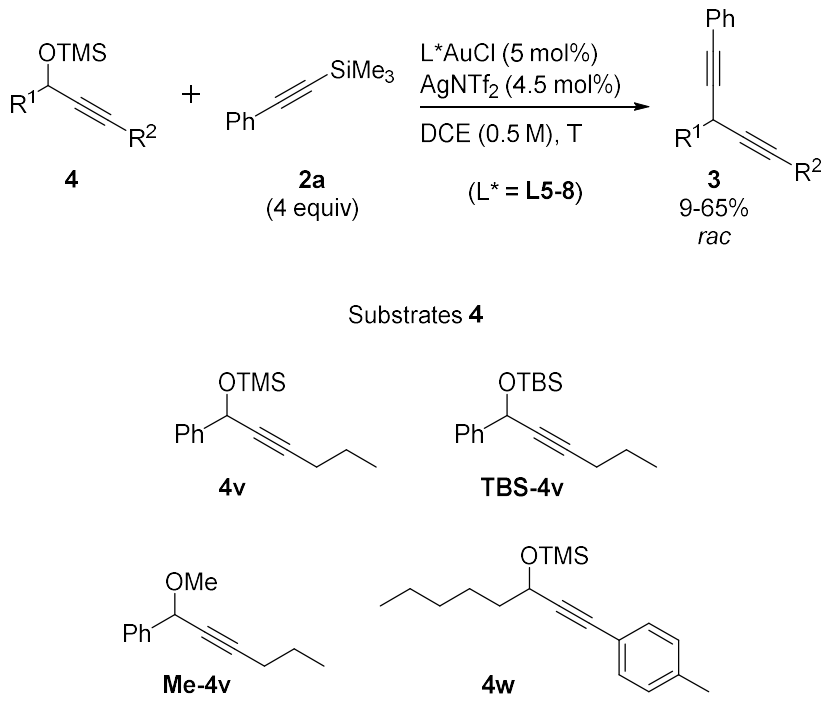
The total loss of chiral purity noticed nicely supports the participation of the invoked cationic intermediate. Besides, this fact opens up the possibility of enantioselectively accessing to chiral 1,4-diynes through carbon-carbon bond formation, using different alternatives.

First, the use of a chiral ligand in the gold(I) complex as a form of inducing chirality in the product was tested, using several chiral phosphines and phosphoramidites. Their structures are depicted in Scheme I.53.



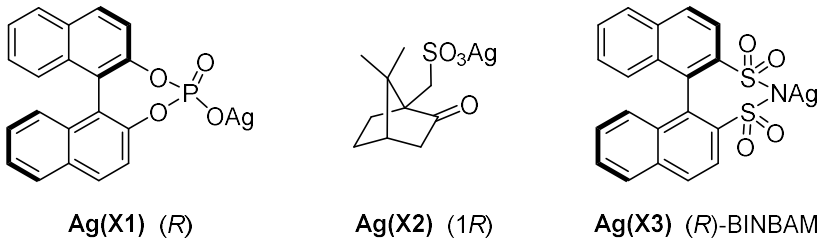
Scheme I.53: Essayed chiral ligands for the gold(I) catalyst.

Different substrates **4** were employed and reacted with **2a** (4 equiv), in DCE as solvent (0.5 M), and in the presence of a gold(I) complex provided with a chiral ligand (Scheme I.54). Different temperatures were used, including room temperature, 0, -20 and -60 ºC. Low to moderate yields of the corresponding product **3** were obtained, but racemic diynes were formed in all cases and no enantiomeric excess was accomplished.

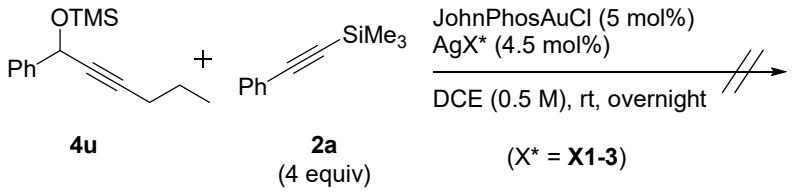


Scheme I.54: Chiral ligand preliminary tests.

Alternatively, the use of a chiral counteranion was tested employing silver salts derived from chiral organic acids, such as the ones shown in Scheme I.55. Unfortunately, in these cases, no reaction at all was observed (Scheme I.56).



Scheme I.55: Silver salts of chiral counteranions **X1-3**.



Scheme I.56: Chiral counteranion preliminary tests.

Final Remarks

Gold(I) complexes have been proved to be efficient catalysts promoting aldehyde bis-alkynylation reactions with alkynylsilanes. Besides, the selection of the auxiliary ligand in the gold complex has been shown to affect the efficiency of the resulting synthetic process when provided with the proper ligand.

After a process of optimisation of the reaction conditions, two convenient methods have been reported in order to achieve a useful scope for this transformation. A broad variety of 1,4-diynes have been generated in moderate to very good yields, and with reasonable functional group tolerance.

The mechanistic insight of this process has also been further studied, discovering the participation of gold(I) acetylides and σ,π-digold acetylene adduct species, as well as a silicon-based LA formed in situ. The combined use of the carbophilic activation of an alkynylsilane by a gold(I) complex with the oxophilic activation of the carbonyl reaction partner by a Si-based LA generated in situ has not been previously reported in the literature.

On the other hand, the possibility of an enantioselective second alkynylation step has been investigated, with very unpromising, although still preliminary, results. Further knowledge about the phenomena taking place in the reaction medium might provide with a better basis for continuing these tests.

Considering the knowledge acquired from the mechanistic studies of the reported bis-alkynylation, this brand new developed strategy has been envisioned to be much more versatile than its initial use may show. In particular, the activation and subsequent alkynylation of other oxygenated groups has been immediately targeted as an interesting application. The concerning results will be presented in the following pages of this dissertation.

Part II

Coupling Reactions of Benzyl Methyl Ethers and Benzyl Acetates with Nucleophiles Containing a Silyl Moiety

Section Index

Coupling Reactions of Benzyl Methyl Ethers and Benzyl Acetates with Nucleophiles Containing a Silyl Moiety

Introduction to Part II

1. Catalytic Cross-Coupling Reactions in Organic Synthesis

The pursuit of a synthetic chemist is to obtain the target molecule as directly as possible, in high yield, with the highest possible selectivity, through a safe and economical process that generates the minimal possible waste. In this sense, catalytic methods to form C-C bonds, but also to form C-heteroatom bonds (O, N, S…), are always desirable and constantly evolving, in an attempt to cover every single problem a chemist can come across.

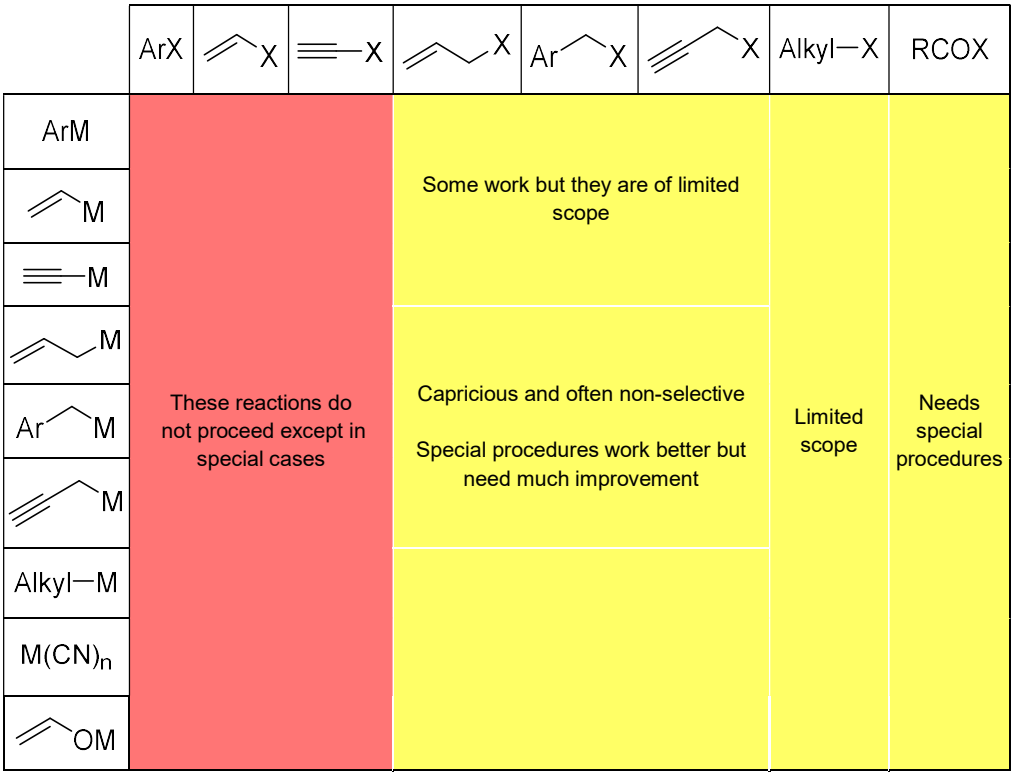
Transition metal catalysed cross coupling reactions are one of the pillars of organic synthesis, as it has been recently recognised by the Nobel Foundation. This type of processes has reached a wide variety of applications since they started to develop, especially for the case of C-C bond forming reactions.

Only about half a century ago, there were only a few limited methods of non-catalysed C-C coupling reactions using Grignard reagents. Table II.1 summarises these cases and their limitations.[104] Red colour refers to transformations that do not proceed except in special cases. Yellow colour refers to transformations which are known and useful but are not very general or present other kinds of limitations.

Nowadays, C-C coupling reactions, especially those catalysed by palladium complexes, have covered many of the deficiencies observed in Table II.1, as it can be seen in Table II.2. Red and yellow colours refer to the same kinds of transformations than in Table II.1, and green colour refers to generally well-known and not very limited reactions, although some of them are still in strong development.[104]

[104] E. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738–6764.

Table II.1: Non-catalysed C-C coupling reactions with Grignard reagents, extracted from Ref. 104.



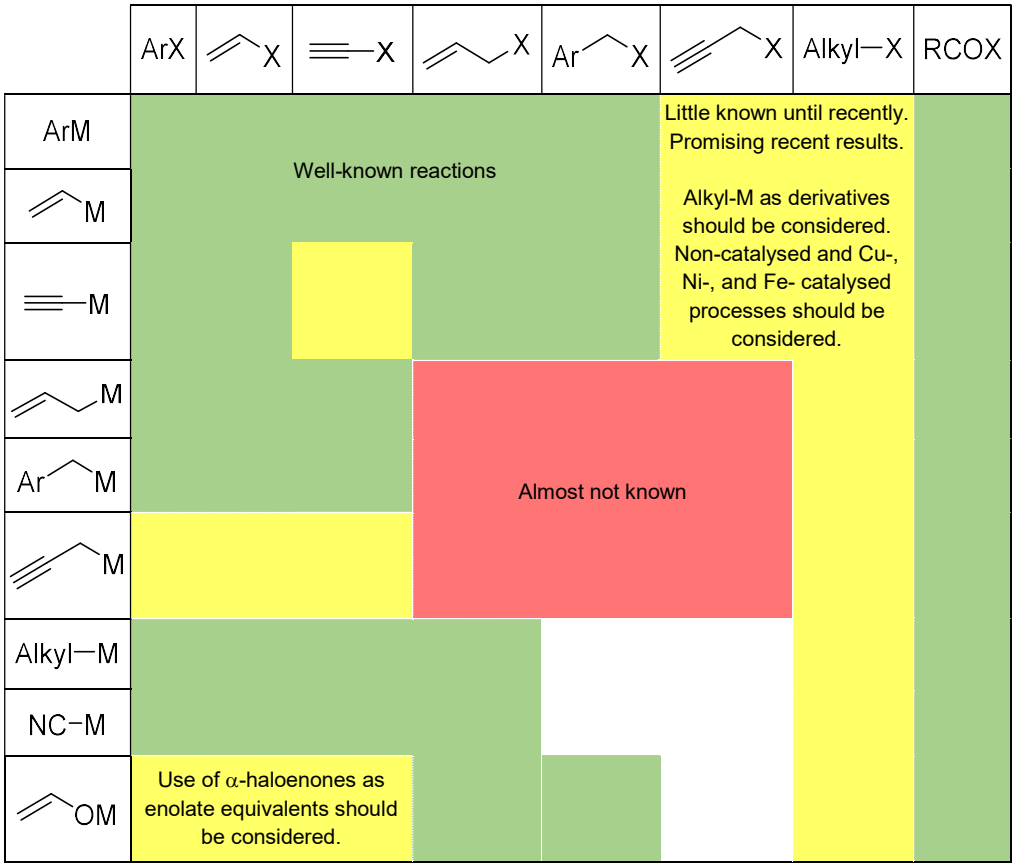
Nickel, copper and iron catalysed couplings have also developed recently, coming very handy to assist palladium couplings in some of their limitations. However, there is still room for improvements and expansion in the world of coupling reactions.[105,106,107]

[105] For a review on Ni-catalysed coupling reactions see: a) E. J. Tollefson, L. E. Hanna, E. R. Jarvo, *Acc. Chem. Res.* **2015**, *48*, 2344–2353. b) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299–309. c) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.

[106] For a review on Cu-catalysed coupling reactions see: a) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971. b) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131. c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364.

[107] For a review on Fe-catalysed coupling reactions see: a) W. M. Czaplik, M. Mayer, J. Cvengroš, A. J. von Wangelin, *ChemSusChem* **2009**, *2*, 396–417. b) A. A. O. Sarhan, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 2730–2744. c) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863.

Table II.2: Pd-catalysed C-C coupling reactions and its limitations, extracted from Ref. 104.



The fact that several limitations have been identified associated with these known coupling reactions is interesting for process design, as it opens a field for developing new strategies regarding certain coupling partners. This is the case of some constrains noticed for the coupling of alkynyl nucleophiles with C(sp^3)-electrophiles. A deeper approach to this kind of alkynylation strategies will be done in the following pages.

2. Alkyne Cross-Coupling Reactions

The introduction of an alkynyl moiety in a molecule is particularly interesting because it is present in many functional materials, enhancing rigidity or favouring order, and it is also a functional group that allows further modification when building complex molecules.

Historical Overview

Since the last decades of the 19th century until the beginning of the second half of the 20th century, several homo- and hetero-coupling reactions of two alkynes were reported (Glaser coupling, Eglinton reaction and Cadiot-Chodkiewicz coupling).[108] Later, in 1963, Castro and Stephens reported the first *sp*-*sp*^{2} coupling reaction.[109]

But the real breakthrough in *sp*-*sp*^{2} coupling was made in 1975 by Sonogashira and Hagihara,[110] when they discovered that the addition of a copper(I) salt as a co-catalyst in the alkyne version of the Heck reaction[111] allowed it to occur at room temperature. Right away, other palladium-catalysed couplings also proved to be suitable for alkynes, like the Negishi reaction[112] using alkynylzinc reagents, the Suzuki-Miyaura reaction[113] using alkynylboron derivatives or the Stille reaction[114] with alkynyl stannanes (Scheme II.1). Pd-catalysed couplings with other metal and metalloid alkynyl derivatives are known, but their scope is very limited, even nowadays.[115]

[108] a) C. Glaser, *Justus Liebigs Ann. Chem.* **1870**, *154*, 137–171. b) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424. c) G. Eglinton, A. R. Galbraith, *J. Chem. Soc.* **1959**, 889–896. d) Chodkiewicz, W. Ann. Chim. Paris **1957**, 2, 819–69.

[109] R. D. Stephens, C. E. Castro, *J. Org. Chem.* **1963**, *28*, 3313–3315.

[110] K. Snogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

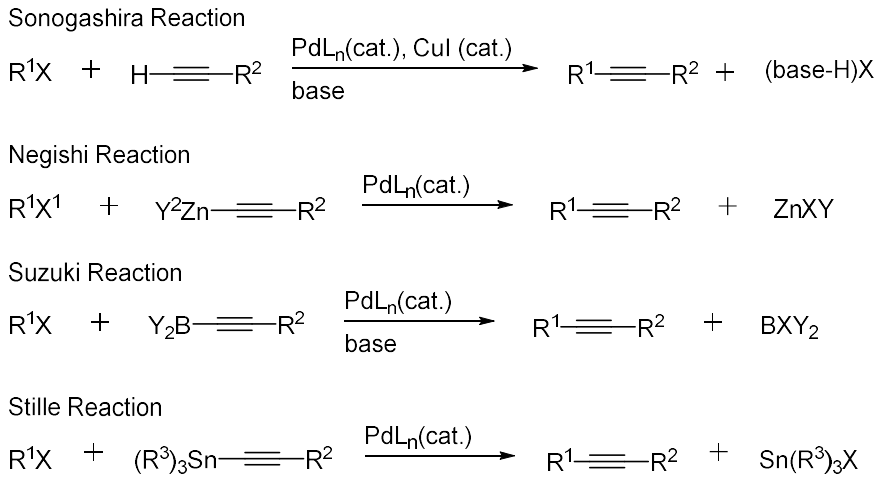
[111] H. A. Dieck, F. R. Heck, *J. Organomet. Chem.* **1975**, *93*, 259–263.

[112] a) A. O. King, N. Okukado, E. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683–684. b) E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, B. I. Spiegel, *J. Am. Chem. Soc.* **1978**, *100*, 2254–2256.

[113] N.Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437–3440.

[114] J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524.

[115] For a review on Pd-catalysed alkynylation reactions see E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2018.



Scheme II.1: General Sonogashira, Negishi, Suzuki and Stille Reactions.

These Sonogashira, Negishi, Suzuki and Stille Pd-catalysed alkynylations have evolved in the last decades, broadening their scope. Currently, they offer a diverse tool to build many different products, but they still have some limitations.

Palladium-Catalysed Alkynylation Reactions in the Early 21st Century: Scope Overview and Other Alternatives Regarding Organic Electrophiles

The limitations in the use of organic electrophiles in Pd-catalysed cross couplings are mainly derived from the effectiveness of the first step in the general mechanism for this kind of couplings, consisting on an oxidative addition[115,116] of this electrophile to the palladium complex. In this regard, a classification of the different electrophiles in terms of the leaving group employed, and the hybridisation of the carbon attached to it, is useful to illustrate the areas in which further investigation could be required.

Table II.3 shows a summary of the general scope of Pd-catalysed alkynylation reactions known until the beginning of the 21st century.[115] Leaving groups (X) such as halides, especially bromide and iodide, as well as triflate,[116] are some of the most

[116] A. M. Echavarren, D. J. Cárdenas, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH Verlag GmbH, **2004**, pp. 1–40.

commonly used, since they have proved to perform very successfully in the oxidative addition process.

Table II.3: General scope of Pd-catalysed alkynylation reactions, until early this century, regarding the hybridisation of the electrophile employed (information extracted from ref. 115).

RX	R	Pd-Catalysed Alkynylation	Uncatalysed and Cu-Catalysed Alkynylation (no Pd)
C(sp^2)-X	Aryl	Widely applicable and satisfactory	Generally inferior or inapplicable
	Alkenyl	Widely applicable and satisfactory	Generally inferior or inapplicable
	Acyl	Widely applicable and satisfactory	Alkynylcopper reactions may be competitive
C(sp)-X	Alkynyl	Not widely investigated. Homo-coupling is a potential problem. There are indirect alternatives.	The Cadiot-Chodkiewicz reaction is the most commonly used
C(sp^3)-X	Allyl	Little is known	Cu-catalysed reaction with alkynylmagnesium is generally satisfactory.
	Benzyl	Alkylindium reagents are promising	Cu-catalysed reaction with alkynylmagnesium is generally satisfactory.
	Propargyl	Widely applicable, but produces allenynes selectively.	Cu-catalysed reaction with alkynylmagnesium is generally satisfactory.
	Alkyl	Not applicable due to slow oxidative addition	Alkynyllithium reagents (and other electropositive metals) can be used with primary and some secondary alkyl halides. Alkynylalanes can be used for some tertiary halides.

Regarding the alkynylation of electrophiles with sp^3 hybridisation, at the beginning of this century, only the use of allyl, benzyl and propargyl derivatives in Pd-catalysed reactions was known. However, propargyl derivatives produced allenynes instead of 1,4-diynes, and only a few promising results had been achieved in the case of benzyl derivatives. Alkyl derivatives had been found not reactive in some cases, due to the slow rate of the oxidative addition step. In other occasions, the alkylmetal intermediate underwent unproductive intramolecular β-hydride elimination faster than intermolecular

transmetalation. A third problem that one can come across is the oxidative dimerization of the alkynylmetal species.[115,117]

Alternatively, Cu-catalysed coupling reactions using alkynylmagnesium reagents can be successful when employing electrophiles with sp^3 hybridisation (see Table II.3). However, these methods are severely limited by the well-known functional group incompatibility associated to Grignard reagents. Because of these handicaps, alkynylation using non-catalytic strategies was still considered as a solid and feasible method for aliphatic substrates.

On the other hand, it has to be taken into account that, since these sp^3-hybridised electrophiles were usually halides or triflates, no other groups of this kind can be present in the molecule without being equally targeted by the catalyst.

Recent Advances in sp^3-Hybridised Electrophile Alkynylation Reactions

The three main handicaps previously mentioned for the alkynylation of aliphatic electrophiles, that is, the slow oxidative addition undergone by alkyl halides, the fast β-elimination processes experimented by the alkylmetal intermediate, and the possible oxidative dimerization of the alkynylmetal species, have been recently overcome. The employment of new ligands and metals in some recent works has provided several improvements in the alkynylation of sp^3-hybridised electrophiles.

Alkynylation of non-activated primary halides via a Sonogashira type reaction was firstly reported by Fu et al. in 2003.[117b] But also Hu et al. have recently contributed with a Ni-catalysed coupling of alkynylmagnesium reagents[117a] and a Ni-catalysed Sonogashira reaction. [118] Non-activated secondary halides were addressed in 2006 by Glorius et al. with very limited scope concerning the alkyne, [119 a] but a few recent

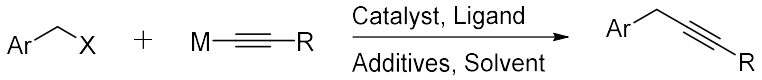
[117] a) O. Vechorkin, A. Godinat, R. Scopelliti, X. Hu, *Angew. Chem. Int. Ed.* **2011**, *50*, 11777–11781. b) M. Eckhardt, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643. c) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal.* **2004**, *346*, 1525–1532.

[118] P. M. Pérez García, P. Ren, R. Scopelliti, X. Hu, *ACS Catal.* **2015**, *5*, 1164–1171.

[119] a) G. Altenhoff, S. Würtz, F. Glorius, *Tetrahedron Lett.* **2006**, *47*, 2925–2928. b) Z. Qureshi, C. Toker, M. Lautens, *Synthesis* **2017**, *49*, 1–16. c) C. W. Cheung, P. Ren, X. Hu, *Org. Lett.* **2014**, *16*, 2566–2569. d) J. Yi, X. Lu, Y.-Y. Sun, B. Xiao, L. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12409–12413. e) T. Thaler, L.-N. Guo, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 2174–2177. f) G. Cahiez, O. Gager, J. Buendia, *Angew. Chem. Int. Ed.* **2010**, *49*, 1278–1281.

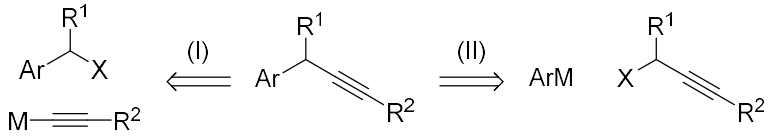
Sonogashira, Negishi and Stille type reactions have been reported,[119b-e] as well as other metal catalysed couplings.[119f] Other light-promoted[120] and radical mediated[121] couplings have also been recently discovered.

When it comes to primary benzyl halides (Scheme II.2), whose oxidative addition to several metal complexes has been known for decades,[122] it is surprising that the first successful attempt to develop a catalytic alkynylation cross coupling is from 2001, by Sarandeses et al., using organoindium reagents.[123a] After a deeper search for ligands and coupling partners, several Pd-catalysed coupling reactions were next reported,[123b-c] and more recently, a Ni-catalysed coupling using alkynylaluminium derivatives was described.[123d]



Scheme II.2: General reaction scheme for an alkynylation of a primary benzyl halide.

In the case of secondary benzyl halides (Scheme II.3), there are only two precedent examples in literature, along with other alternative coupling pathway, which is the use of a propargyl halide and an aryl organometallic compound.[124]



Scheme II.3: Possible pathways to obtain tertiary propargylic-benzylic systems.

[120] a) W. Liu, L. Li, C.-J. Li, *Nat. Commun.* **2015**, *6*, 6526. b) F. Le Vaillant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204. c) Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 11196–11199. d) H. Huang, G. Zhang, L. Gong, S. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283.

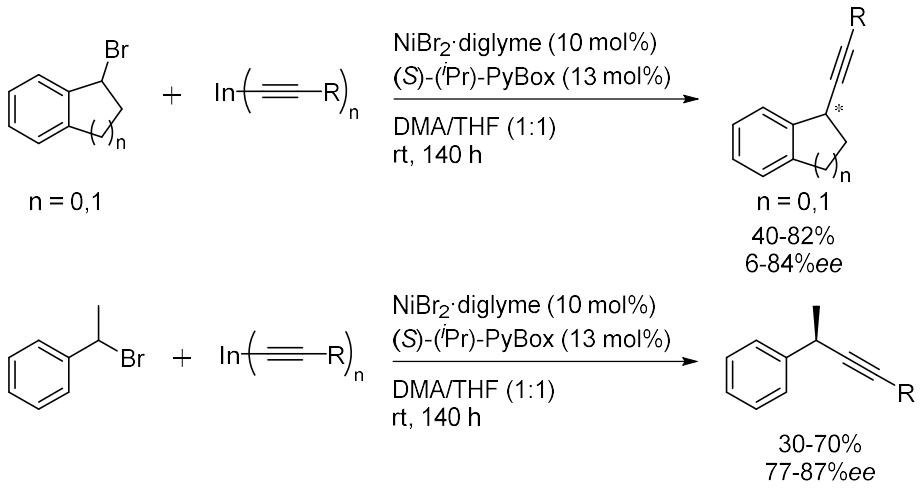
[121] A.-P. Schaffner, V. Darmency, P. Renaud, *Angew. Chem. Int. Ed.* **2006**, *45*, 5847–5849.

[122] J. K. Stille, K. S. Y. Lau, *Acc. Chem. Res.* **1977**, *10*, 434–442.

[123] a) I. Pérez, J. P. Sestelo, L. A. Sarandeses, *J. Am. Chem. Soc.* **2001**, *123*, 4155–4160. b) M. Qian, E. Negishi, *Tetrahedron Lett.* **2005**, *46*, 2927–2930. c) C. H. Larsen, K. W. Anderson, R. E. Tundel, S. L. Buchwald, *Synlett* **2006**, *2006*, 2941–2946. d) D. B. Biradar, H.-M. Gau, *Chem. Commun.* **2011**, *47*, 10467–10469.

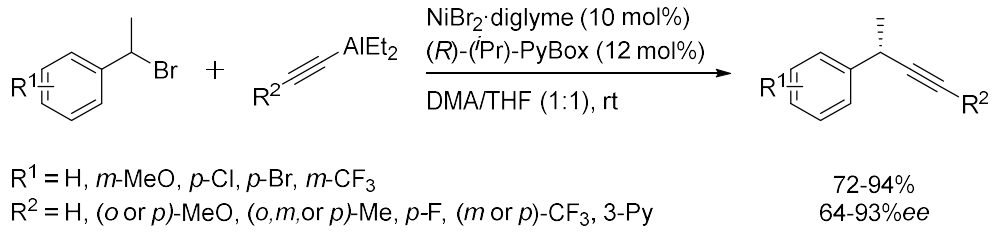
[124] a) S. W. Smith, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 12645–12647. b) N. D. Schley, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 16588–16593.

The first precedent example is a similar methodology to the one developed by Sarandeses et al., using organoindium compounds as nucleophiles and secondary substrates as electrophiles. This work was published seven years after the primary ones (Scheme II.4). Despite the long reaction times and the fact that the scope of the reaction presents some limitations, the PyBox-type ligand they used led to some good enantiomeric excesses.[125a]



Scheme II.4: Sarandeses' coupling of secondary benzyl halides.

Very recently, this same strategy has been applied to alkynylaluminium reagents by Zhou et al. with similar results (Scheme II.5).[125b]



Scheme II.5: Zhou's coupling of secondary benzyl halides.

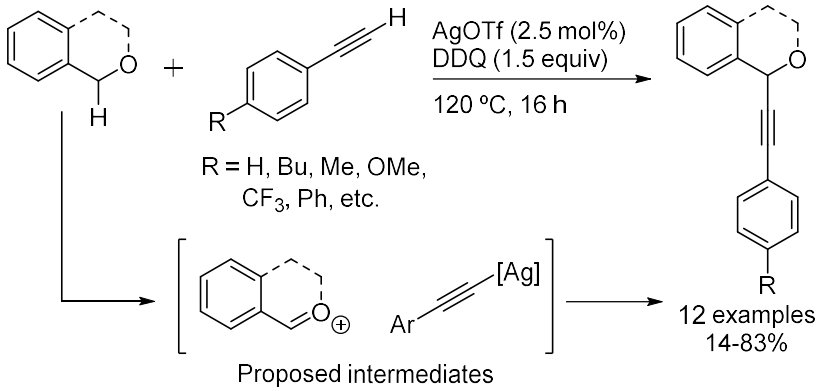
[125] a) J. Caeiro, J. Pérez Sestelo, L. A. Sarandeses, *Chem. Eur. J.* **2008**, *14*, 741–746. b) H. Fang, Z. Yang, L. Zhang, W. Wang, Y. Li, X. Xu, S. Zhou, *Org. Lett.* **2016**, *18*, 6022–6025.

Other Strategies to Obtain Propargylic-Benzylic Products

There are a few other options to obtain propargylic-benzylic scaffolds which are different from the typical metal-catalysed cross coupling reaction.

a) *Cross-dehydrogenative coupling (CDC)*

Metal-catalysed alkynylation reactions at secondary benzylic positions activated by the presence of a heteroatom (O, N) in the adjacent position, or involving alternatively a bisbenzylic position, have been accomplished by this method.[126a-c] Primary benzylic positions have also been activated in a process co-catalysed by three metal species.[126d] An example of a silver-catalysed alkynylation of a secondary benzylic substrate with and adjacent oxygen is shown in Scheme II.6.[126a]



Scheme II.6: Silver-catalysed dehydrogenative coupling targeting a secondary benzylic position activated by the presence of an adjacent oxygen.

b) *Decarboxylative reactions*

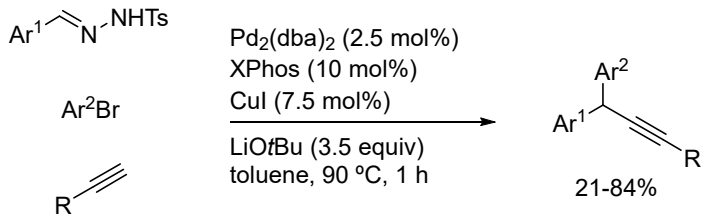
Decarboxylation of propargylic esters, usually catalysed by palladium complexes at high temperatures, with extrusion of CO_2, have afforded the alkynylation of primary benzylic or secondary bisbenzylic scaffolds.[127]

[126] a) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100. b) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811. c) C. A. Correia, C.-J. Li, *Adv. Synth. Catal.* **2010**, *352*, 1446–1450. d) S. Tang, P. Wang, H. Li, A. Lei, *Nat. Commun.* **2016**, *7*, 11676.

[127] a) S. N. Mendis, J. A. Tunge, *Org. Lett.* **2015**, *17*, 5164–5167. b) R. R. P. Torregrosa, Y. Ariyarathna, K. Chattopadhyay, J. A. Tunge, *J. Am. Chem. Soc.* **2010**, *132*, 9280–9282.

c) Three-component reactions

A palladium, copper and base catalysed process in which a tosylhydrazone derived from an aromatic aldehyde, an aryl bromide and a terminal alkyne couple into a bisbenzylic propargylic scaffold. The reaction does not work for related tosylhydrazones derived from aliphatic aldehydes. The Sonogashira coupling product between the alkyne and the aryl bromide is obtained as a by-product that can be minimised with the employment of the right solvent (Scheme II.7).[128]



Ar^1 = Ph, *p*-tolyl, 3,4-dimethoxyphenyl, 3,4-dichlorophenyl, 2-hexynylphenyl
Ar^2 = Ph, *m*-tolyl, *p*-anisyl, *p*-fluorophenyl, (o-phenyl)phenyl, 2-naphthyl, etc
R = Ar, TMS, CO_2Et, CH_2OTHP, 3-thienyl

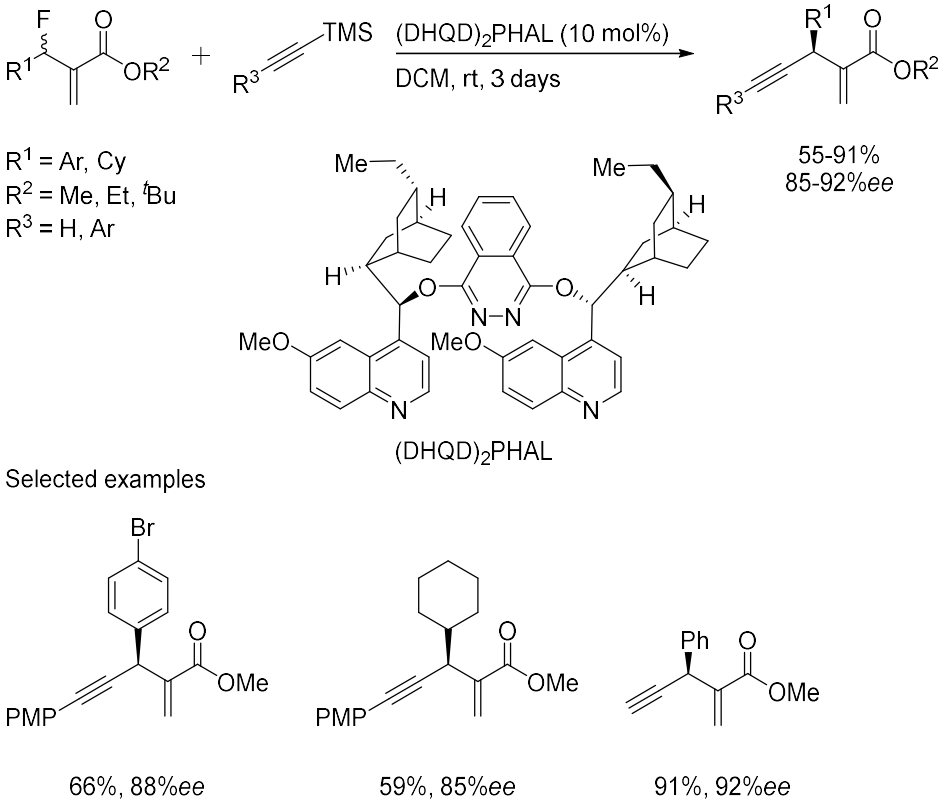
Scheme II.7: Three-component reaction to afford a bisbenzylic propargylic scaffold.

d) Catalytic nucleophilic substitution reactions

Carbocation chemistry sometimes offers a synthetically useful alternative to cross-coupling reactions. This topic will be reviewed in the following pages.

Recently, a substitution reaction in fluorinated Baylis-Hillman products to afford skipped enynes has been reported (Scheme II.8). It is catalysed by a chiral base, affording good enantiomeric excesses at long reaction times. A concerted mechanism is proposed for this transformation.[129]

[128] L. Zhou, F. Ye, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 13590–13591.
[129] T. Nishimine, H. Taira, E. Tokunaga, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* **2016**, *55*, 359–363.



Scheme II.8: Fluoride substitution catalysed by a chiral base.

3. Carbocations in Alkyne Coupling Reactions

Since the discovery of the existence of carbocations in organic chemistry by Norris, Kehrman and Wentzel in 1901[130] and their thorough study during the middle of the 20th century, these reaction intermediates have become a very useful tool to develop new transformations. Their importance was recognised with a Nobel prize to Olah in 1994 for his search on stable carbocations that were observable and his contribution to the knowledge of non-classic carbocations.[131]

In the academic world, carbocations started as a curiosity and soon became a powerful synthetic tool to manipulate functional group, to form bond to C(sp^3) atoms and to launch interesting skeletal rearrangement reactions. Some of the discoveries derived from their studies are now of common industrial application, such as the hydrocarbon chemistry in the petroleum industry, the Friedel-Crafts alkylation of the methanol-to-gasoline (MTG) or methanol-to-olefins (MTO) processes.[132]

Carbocations have also led to the development of many classic well-known reactions, such as cationic cascades, cyclization and rearrangement reactions (e.g. Wagner-Meerwein, pinacol and Prins-pinacol rearrangements, Nazarov reaction), S_N1 and S_N1' reactions, and other named reactions such as the Ritter reaction or the Schmidt reaction.[133]

The facial control on addition reactions to a planar carbocation have also allowed the development of enantioselective C-C bond formation strategies which are still in constant evolution.[133]

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[130] F. Kehrmann, F. Wentzel, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3815–3819.

[131] a) G. A. Olah, E. B. Baker, J. C. Evans, W. S. Tolgyesi, J. S. McIntyre, I. J. Bastien, *J. Am. Chem. Soc.* **1964**, *86*, 1360–1373. b) G. A. Olah, G. Klopman, R. H. Schlosberg, *J. Am. Chem. Soc.* **1969**, *91*, 3261–3268. c) G. A. Olah, G. D. Mateescu, L. A. Wilson, M. H. Gross, *J. Am. Chem. Soc.* **1970**, *92*, 7231–7232. d) G. A. Olah, G. D. Mateescu, J. L. Riemenschneider, *J. Am. Chem. Soc.* **1972**, *94*, 2529–2530. e) G. A. Olah, G. Asensio, H. Mayr, *J. Org. Chem.* **1978**, *43*, 1518–1520. f) G. A. Olah, G. K. S. Prakash, M. Arvanaghi, F. A. L. Anet, *J. Am. Chem. Soc.* **1982**, *104*, 7105–7108.

[132] a) D. M. McCann, D. Lesthaeghe, P. W. Kletnieks, D. R. Guenther, M. J. Hayman, V. Van Speybroeck, M. Waroquier, J. F. Haw, *Angew. Chem. Int. Ed.* **2008**, *47*, 5179–5182. b) J. Li, Y. Wei, J. Chen, P. Tian, X. Su, S. Xu, Y. Qi, Q. Wang, Y. Zhou, Y. He, et al., *J. Am. Chem. Soc.* **2012**, *134*, 836–839.

[133] For a review on carbocation chemistry in organic synthesis see: R. R. Naredla, D. A. Klumpp, *Chem. Rev.* **2013**, *113*, 6905–6948.

Carbocation Reactivity and Related Considerations

When developing a transformation based on the generation of a carbocation in a controlled manner, one has to take into account the reactivity of these species.

The stability of a carbocation is based on the ability of the substituents to donate electronic density to the positive centre and the steric effects of these substituents. Also, the polarity and nucleophilicity of the solvent in which it is generated is important, since it may promote the formation of the carbocation, but also may react with it. The same can be applied to other species formed in the medium during the process.[134]

In this sense, Mayr et al. have contributed to this field by ranking a large variety of carbocations according to a parameter related to its electrophilicity (E), as well as a series of nucleophiles according to a parameter representing its nucleophilicity (N). The equation shown in Scheme II.9 predicts the success of the reaction between a particular nucleophile and a particular carbocation chosen from Mayr's scale.

$$\log k_{(20\,^{o}C)} = s(N + E)$$

Scheme II.9: Equation developed by Mayr et al. to measure the stability of different carbocations. The parameter *s* corresponds to the sensitivity (specific for each electrophile) of the rate constants to variations in the nucleophile.

These parameters are very useful in S_N1 reactions in order to choose the right electrophile-nucleophile pair. According to these scales, benzylic, propargylic and allylic carbocations can react with a good variety of nucleophiles in a controlled manner, and this makes them very suitable for S_N1 reactions.

[134] a) H. Mayr, M. Patz, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938–957. b) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, et al., *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512. c) C. Schindele, K. N. Houk, H. Mayr, *J. Am. Chem. Soc.* **2002**, *124*, 11208–11214. d) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77. e) S. Minegishi, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2004**, *126*, 5174–5181.

Alcohols and Other Derived Leaving Groups as Tools to Generate Benzylic, Propargylic and Allylic Carbocations

Strategies to generate a carbocation can be very diverse, from an internal or external redox process to a reaction with an electrophile promoting an internal shift or rearrangement, or a substitution process. The reaction of catalytic amounts of an acid with a functional group in the molecule that will act as a leaving group is one of the most used strategies, and many interesting leaving groups have been developed to this aim.[133]

The substitution of activated alcohol groups by other nucleophiles is considered an important step towards the introduction of greener processes in industrial synthesis, since the only by-product they generate is water.[135] Despite the fact that a hydroxyl group is a poor leaving group, it is possible to activate it by using Brønsted or Lewis acids. S_N1 reactions promoted in this way have found applications in total synthesis and are a growing field.[133,136,137]

As an example, Scheme II.10 shows a Friedel-Crafts alkylation of secondary and tertiary propargylic, allylic and benzylic alcohols catalysed by a calcium(II) salt.[136a] In the same way, Scheme II.11 shows an indium(III)-, gallium(III)- or iron(III)-catalysed α-alkylation of carbonyl compounds using enol esters and activated alcohols.[136b]

However, in some cases, a hydroxyl group may not be suitable for the controlled generation of a carbocation, and the use of a derived functional group results into an activation process that is easier to handle. Sulfonyl esters are one of the most common alternatives for this purpose, but also carboxyl esters and even ethers can be used.[138]

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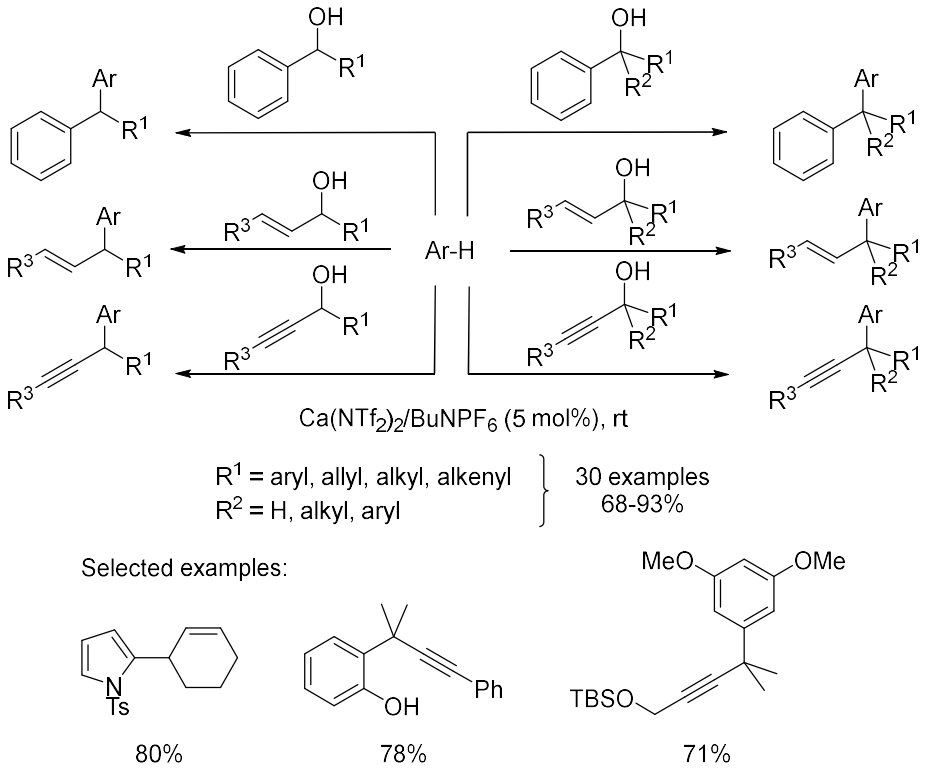
[135] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. Johnnie L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, et al., *Green Chem.* **2007**, *9*, 411–420.

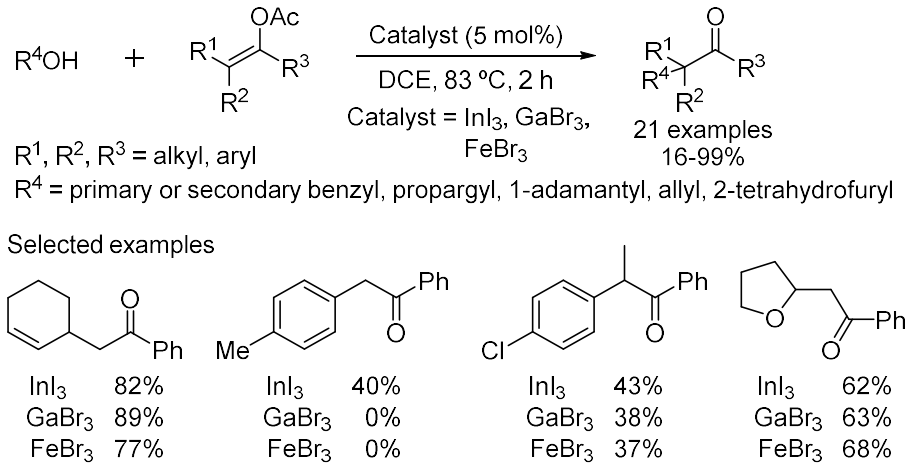
[136] For a recent review see: a) E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzziello, F. De Vincentiis, P. G. Cozzi, *Eur. J. Org. Chem.* **2011**, *2011*, 647–666. b) M. Dryzhakov, E. Richmond, J. Moran, *Synthesis* **2016**, *48*, 935–959. c) J.-M. Begouin, M. Niggemann, *Chem. Eur. J.* **2013**, *19*, 8030–8041. d) M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, *6*, 6.

[137] Other recent works: a) M. Niggemann, M. J. Meel, *Angew. Chem. Int. Ed.* **2010**, *49*, 3684–3687. b) Y. Nishimoto, Y. Onishi, M. Yasuda, A. Baba, *Angew. Chem. Int. Ed.* **2009**, *48*, 9131–9134.

[138] a) D. Nitsch, S. M. Huber, A. Pöthig, A. Narayanan, G. A. Olah, G. K. S. Prakash, T. Bach, *J. Am. Chem. Soc.* **2014**, *136*, 2851–2857. b) Y. Sawama, Y. Shishido, T. Kawajiri, R. Goto, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2014**, *20*, 510–516. c) P. Rubenbauer, E. Herdtweck, T. Strassner, T. Bach, *Angew. Chem. Int. Ed.* **2008**, *47*, 10106–10109. d) K. Mertins, I. Iovel, J. Kischel, A. Zapf,



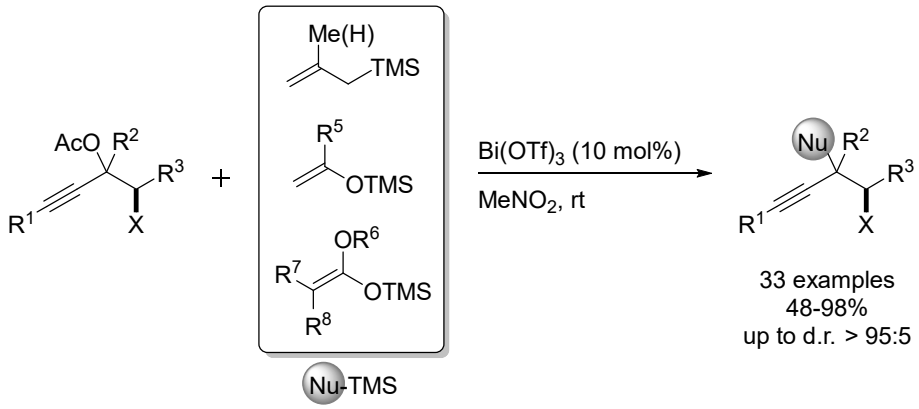
Scheme II.10: Ca(II)-catalysed Friedel-Crafts alkylation of activated alcohols.



Scheme II.11: Metal-catalysed α-alkylation of carbonyl compounds with activated alcohols.

M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 238–242. e) O. Mendoza, G. Rossey, L. Ghosez, *Tetrahedron Lett.* **2010**, *51*, 2571–2575.

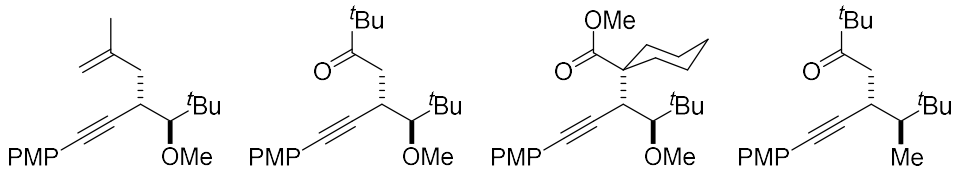
Scheme II.12 shows a Bi-catalysed nucleophilic substitution involving an acetate as leaving group, which is proposed to occur through the formation of a propargylic carbocation.[138a] When it comes to propargylic carbocations, alcohols are generally not good enough as leaving groups. It is known that the activation of the alkyne with $Co_2(CO)_8$ allows the substitution in some cases, but the metal complex has to be used in stoichiometric amounts (Nicholas reaction).[71,136a]



R^1 = PMP, PhS, cyclopropyl
R^2 = H, Me
R^3 = ^{t}Bu, ^{i}Pr, Et
X = Me, OMe, OBn

R^5 = ^{t}Bu, Ph
R^6 = Me, Ph
R^7, R^8 = H, alkyl

Selected examples:



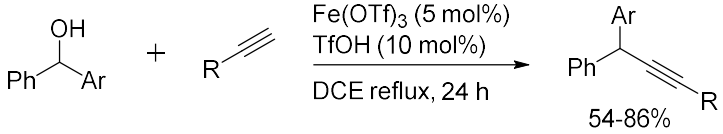
Scheme II.12: Bi-catalysed S_N1 on propargylic acetates.

Acid Catalysed Alkynylation S_N1 Reactions on Alcohols and Related Derivatives

S_N1 reactions on activated alcohols and their derived leaving groups also provide access to alkynylated compounds.

Terminal alkynes[139] and alkynylsilanes[140] are the most common alkyne sources in alcohol alkynylation reactions. In the second case, most examples that can be found in the literature arise from an extended application of an allylation strategy reported for allylsilanes, taking advantage from the fact that both nucleophiles tend to behave similarly under the same reaction conditions.[140]

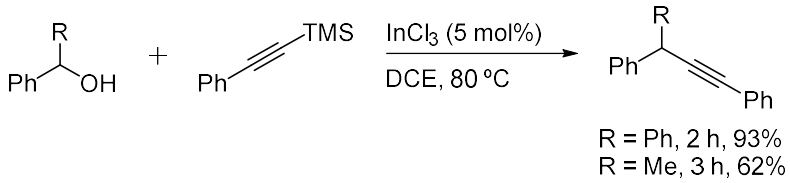
As an example of the utilisation of terminal alkynes previously mentioned, the combined use of an iron(III) salt and its conjugated Brønsted acid to promote the attack of a terminal alkyne on a bisbenzylic alcohol is depicted in Scheme II.13.[139a] In general, hydroxyl groups can only be activated in this manner when they give rise to a fairly stabilised carbocation, such as a bisbenzylic one.



Ar = Ph, *p*-Cl(C_6H_4), *p*-MeO(C_6H_4), *p*-^{t}Bu(C_6H_4), (*o,m,p*)-Me(C_6H_4)
R = Ph, (*o,m,p*)-Me(C_6H_4), *p*-F(C_6H_4), *p*-MeO(C_6H_4), *p*-Br(C_6H_4), *p*-Ph(C_6H_4)

Scheme II.13: Fe(III) and TfOH catalysed alkynylation of bis-benzylic alcohols.

Alkynylsilanes and other silylated nucleophiles have been reported to be able to attack a hydroxyl group activated by an indium(III) species, even on non-bisbenzylic substrates, although affording only moderate yields in this case (Scheme II.14).[140d]

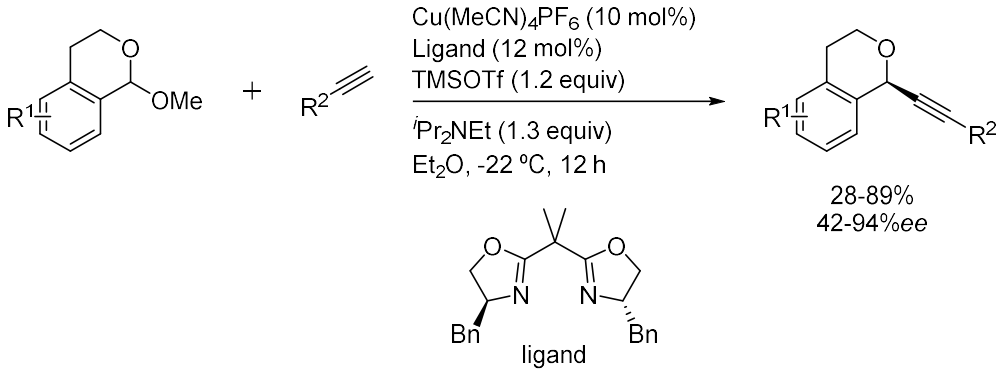


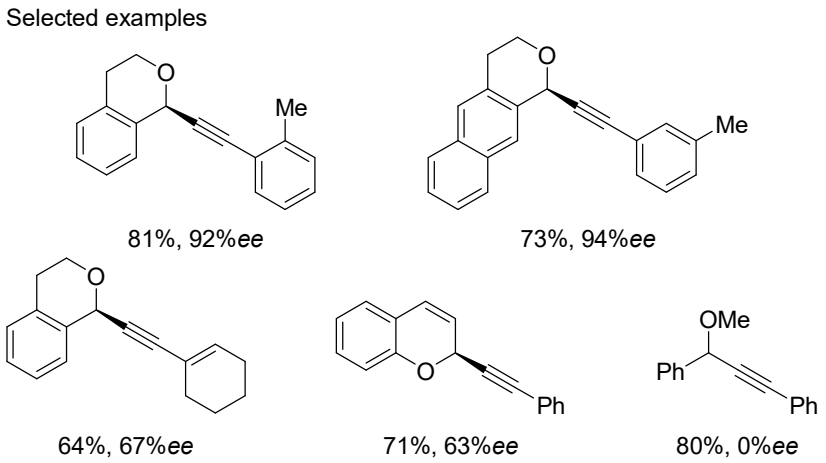
Scheme II.14: In(III)-catalysed alkynylation of benzylic alcohols.

[139] a) S.-K. Xiang, L.-H. Zhang, N. Jiao, *Chem. Commun.* **2009**, 6487–6489. b) K. Ren, P. Li, L. Wang, X. Zhang, *Tetrahedron* **2011**, *67*, 2753–2759.

[140] a) M. Saito, N. Tsuji, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2015**, *17*, 3000–3003. b) Y. Sawama, R. Goto, S. Nagata, Y. Shishido, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2014**, *20*, 2631–2636. c) S. K. De, R. A. Gibbs, *Tetrahedron Lett.* **2005**, *46*, 8345–8350. d) M. Yasuda, T. Saito, M. Ueba, A. Baba, *Angew. Chem. Int. Ed.* **2004**, *43*, 1414–1416.

Regarding other leaving groups, several alkynylation reactions on isochroman acetals have been reported.[141] In these substrates, a methoxy group can be easily activated, since the adjacent oxygen atom will form a stable oxocarbenium ion. The cation formed can subsequently react with metal acetylides. In the example shown in Scheme II.15, a copper complex is employed to form the corresponding copper acetylide. A chiral ligand attached to the copper centre affords the product in an enantioselective manner.[141a]



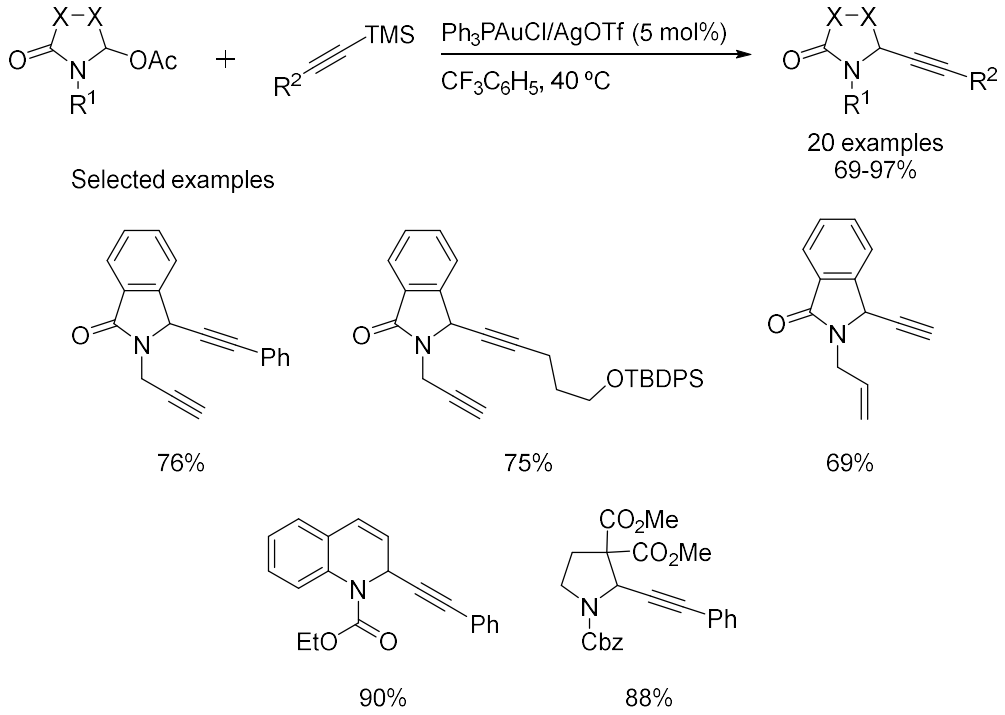


Scheme II.15: Cu(I)-catalysed alkynylation of isochroman acetals.

[141] a) P. Maity, H. D. Srinivas, M. P. Watson, *J. Am. Chem. Soc.* **2011**, *133*, 17142–17145. b) J. M. Gil-Negrete, J. Pérez Sestelo, L. A. Sarandeses, *Org. Lett.* **2016**, *18*, 4316–4319.

Activated acetates have also been used as leaving groups.[142] Recently, a similar approach to our strategy for the double alkynylation of aldehydes, described in Part I (p. 91 and following), has been published. It has been used in the alkynylation of acetates activated by the presence of an adjacent nitrogen atom (Scheme II.16).[142a]

Non-benzylic substrates also proved to be suitable for this transformation as long as no hydrogen atoms were present at the β-position, being susceptible of suffering an elimination process.



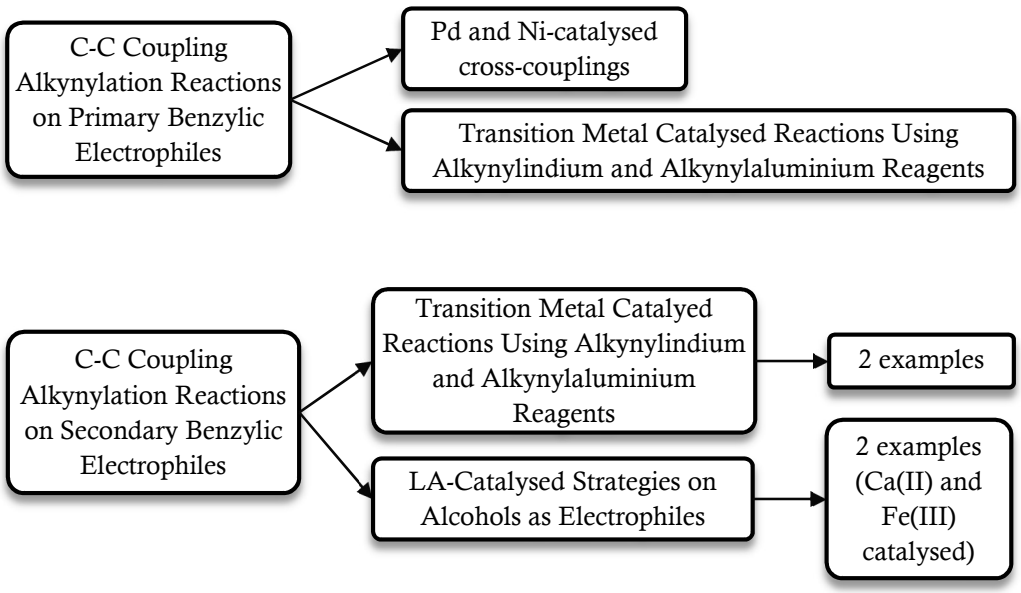
Scheme II.16: Gold(I)-catalysed N,O-Acetal alkynylation.

[142] a) M. Michalska, O. Songis, C. Taillier, S. P. Bew, V. Dalla, *Adv. Synth. Catal.* **2014**, *356*, 2040–2050. b) J. S. Yadav, B. V. Subba Reddy, N. N. Yadav, A. P. Singh, M. Choudhary, A. C. Kunwar, *Tetrahedron Lett.* **2008**, *49*, 6090–6094.

C-C Coupling Strategies using Benzylic Electrophiles and Regarding Alkynyl and Enol Derivatives as Nucleophiles

a) Coupling alkynylation strategies on benzylic electrophiles

In the last pages, the possibilities and limitations of different coupling reactions regarding the alkynylation of benzylic substrates have been reviewed. Considering only those cases in which a simple primary or secondary benzylic substrate (but not a bisbenzylic substrate, benzylic and propargylic substrate, or benzylic substrate with an adjacent heteroatom) is used as an electrophile, only a few examples can be found in the literature. A practical summary of these entries is presented in Scheme II.17.



Scheme II.17: Coupling alkynylation strategies on benzylic substrates.

a) Cationic coupling strategies on benzylic electrophiles using enol derivatives as nucleophiles

Regarding cationic strategies affording C-C coupling transformations, very few examples of enol derivatives being used as nucleophiles can be found, and also the use of benzylic electrophiles is scarce. A few cases of this type have been shown in p. 127.

4. Carbon-Oxygen Coupling Reactions: Synthesis of Ethers.

Carbon-oxygen bond formation reactions, and those in particular that allow the synthesis of ethers, are important in organic synthesis. On one hand, the presence of the ether functionality is prevalent in some natural products, such as sugar derivatives, polycyclic ether compounds and macrolides.[143] They are also used to modify the reactivity of natural products, finding other useful modified biological properties. For example, the introduction of trideuteriomethoxy groups is applied with this purpose.[144]

Since the Williamson reaction, which is still widely used but requires stoichiometric amounts of a base,[145] other strategies have been developed. Some of them include reductive etherifications,[146] decarboxylations,[147] or even electrolytically triggered reactions.[148]

Direct intermolecular coupling reactions have also been reported, including transition metal catalysed cross-coupling reactions, and substitution or addition reactions catalysed by acids. Some examples of these three types of reactions will be reviewed in the following pages.

Transition Metal Catalysed C-O Cross-Coupling Reactions

One type of transition metal species that are widely used as catalysts in C-O cross-coupling reactions are copper salts. Such is the case of the Cham-Lam coupling, which

[143] a) R. M. Moslin, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 15106–15107.b) D. J. Wardrop, J. Fritz, *Org. Lett.* **2006**, *8*, 3659–3662. c) N. G. Bandur, D. Brückner, R. W. Hoffmann, U. Koert, *Org. Lett.* **2006**, *8*, 3829–3831. d) C. S. Barry, J. D. Elsworth, P. T. Seden, N. Bushby, J. R. Harding, R. W. Alder, C. L. Willis, *Org. Lett.* **2006**, *8*, 3319–3322. e) A. B. Smith, V. Simov, *Org. Lett.* **2006**, *8*, 3315–3318.

[144] a) C. W. Cheung, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 3998–4001. b) P. Dash, M. Janni, S. Peruncheralathan, *Eur. J. Org. Chem.* **2012**, *2012*, 4914–4917.

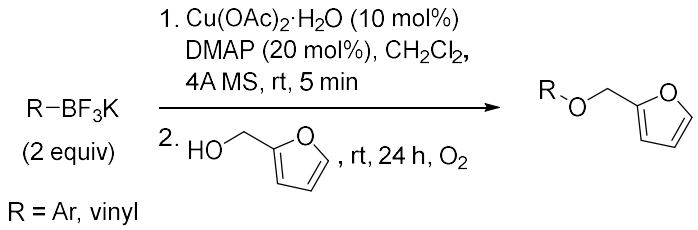
[145] a) K. P. C. Vollhardt and N. E. Shore in *Química Orgánica. Estructura y Función*, Ediciones Omega, **2000**, pp. 349-352. b) S. Czernecki, C. Georgoulis, C. Provelenghiou, *Tetrahedron Lett.* **1976**, *17*, 3535–3536.

[146] a) K. Iwanami, H. Seo, Y. Tobita, T. Oriyama, *Synthesis* **2005**, *2005*, 183–186. b) L. J. Gooßen, C. Linder, *Synlett* **2006**, *2006*, 3489–3491. c) N. Kalutharage, C. S. Yi, *Org. Lett.* **2015**, *17*, 1778–1781. d) R. Savela, R. Leino, *Synthesis* **2015**, *47*, 1749–1760.

[147] a) R. Kuwano, H. Kusano, *Org. Lett.* **2008**, *10*, 1979–1982. b) D. Kim, S. Reddy, O. V. Singh, J. S. Lee, S. B. Kong, H. Han, *Org. Lett.* **2013**, *15*, 512–515.

[148] T. Tajima, H. Kurihara, T. Fuchigami, *J. Am. Chem. Soc.* **2007**, *129*, 6680–6681.

employs organoboron compounds as coupling agents.[149] A synthesis of ethers with benzylic structure from the coupling of 2-furylmethanol with several organoboronate salts is shown in Scheme II.18 as an example of this transformation.[149a]



Scheme II.18: Copper(II)-catalysed synthesis of 2-furylmethyl ethers.

Another important input in C-O cross coupling is the work done by Buchwald et al..[144a,150] However, in general, metal-catalysed cross couplings have been more focused on the development of C(sp^2)-O bonds, and very few examples involving benzylic electrophiles can be found.[150c, 151] This particular type of C(sp^3)-electrophile is interesting because benzylic ethers are used as protecting groups.[152] The use of benzylic alcohols as nucleophiles is also scarce.[153] An example of the use of benzylic carbonates is shown in Scheme II.19. It consists on a Pd-catalysed decarboxylative coupling using phenols as nucleophiles.[151]

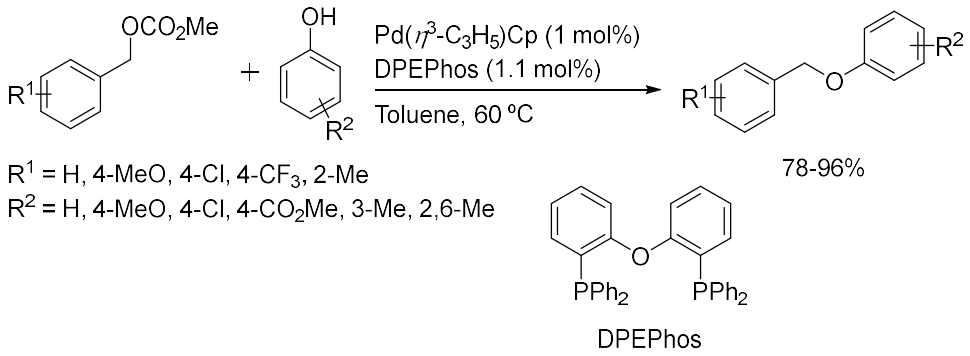
[149] a) T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 1381–1384. b) R. E. Shade, A. M. Hyde, J.-C. Olsen, C. A. Merlic, *J. Am. Chem. Soc.* **2010**, *132*, 1202–1203.

[150] a) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 4321–4326. b) G. Nordmann, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 4978–4979. c) M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 973–976.

[151] R. Kuwano, H. Kusano, *Org. Lett.* **2008**, *10*, 1979–1982.

[152] P. G. M. Wuts, T. W. Greene, in *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., **2006**, pp. 16–366.

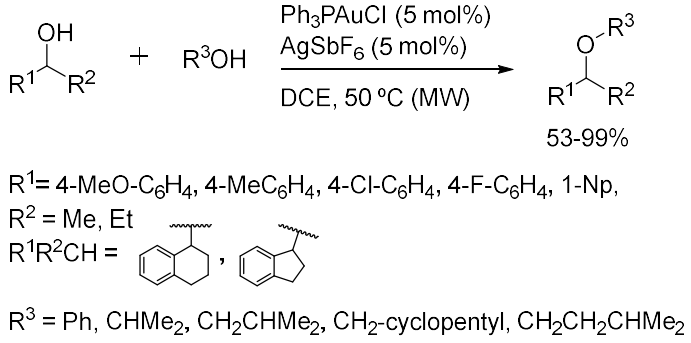
[153] Aliphatic alcohols, including one benzylic alcohol, were used as nucleophiles in S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 11592–11598.



Scheme II.19: Pd-catalysed decarboxylative coupling involving benzylic carbonates.

Substitution Reactions

Acid catalysed S_N1 reactions provide a powerful tool for synthesising ethers from activated electrophiles. Lewis and Brønsted acids are the usual catalysts for this kind of transformations.[154] In 2015, a gold(I) catalysed substitution of aliphatic alcohols and phenols on secondary benzylic alcohols was reported (Scheme II.20).[154b]

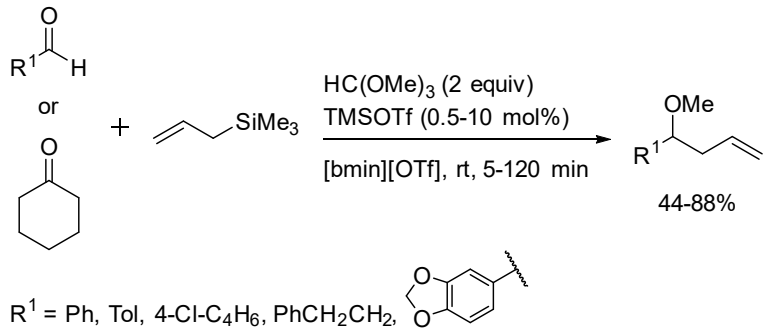


Scheme II.20: S_N1 reaction on secondary benzylic alcohols.

[154] a) A. Chatupheeraphat, H.-H. Liao, S. Mader, M. Sako, H. Sasai, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 4803–4807. b) A. R. S. Vinson, V. K. Davis, A. Arunasalam, K. A. Jesse, R. E. Hamilton, M. A. Shattuck, A. C. Hu, R. G. Iafe, A. G. Wenzel, *Synlett* **2015**, *26*, 765–770. c) R. Sanz, A. Martínez, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Eur. J. Org. Chem.* **2006**, *2006*, 1383–1386. d) D. Lee, C. L. Williamson, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2012**, *134*, 8260–8267.

Addition Reactions to Carbonyl Compounds

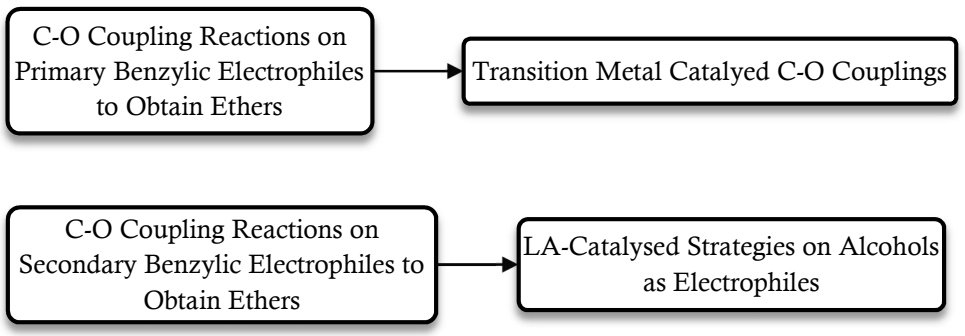
1,2- and 1,4-nucleophilic addition reactions to carbonyl compounds, followed by an alkylation reaction, are another way to synthesise ethers.[155] For example, an TMSOTf catalysed addition of allyltrimethylsilane to an aldehyde in the presence of an orthoester affords the corresponding allylic methyl ether (Scheme II.21). An ionic liquid is used as solvent.



Scheme II.21: Synthesis of allylic methylethers by 1,2-addition to carbonyl compounds.

C-O Coupling Strategies Using Benzylic Electrophiles

In summary, a collection of the previously mentioned strategies to obtain benzylic ethers using C-O coupling strategies on benzylic electrophiles is presented in Scheme II.22.



Scheme II.22: Coupling alkynylation strategies on benzylic substrates.

[155] a) E. M. Phillips, M. Riedrich, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 13179–13181. b) P. W. Anzalone, R. S. Mohan, *Synthesis* **2005**, *2005*, 2661–2663.

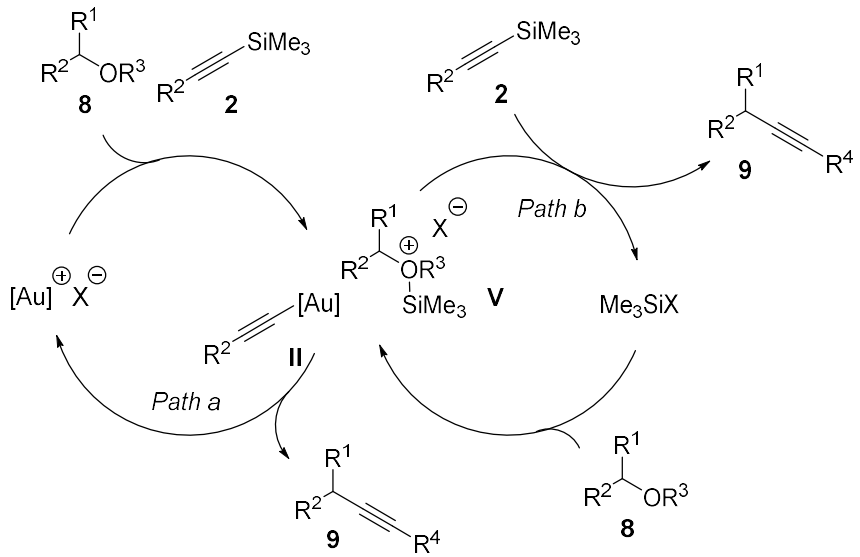
Regarding only those cases in which simple benzylic electrophiles were used (not bisbenzylic or benzylic and propargylic electrophiles), few examples of cationic strategies can be found in the literature for secondary benzylic substrates.

Aims in Part II

Given the facts learnt about the mechanism proposed for the bis-alkynylation of aldehydes, this approach that combines the initial carbophilic activation of an alkynylsilane, releasing a strong Si-based Lewis acid, with a subsequent oxophilic activation of a carbonyl group could be implemented to activate other oxygen-containing functionalities. Eventually, uncommon bond forming events could be foreseen.

The previous reported facts that have been detailed in the introduction section to this Part II suggest that the development of new strategies to form a C(*sp*)-C(sp^3) bond involving primary, secondary or tertiary benzylic sp^3-carbons would be a nice addition to the existing synthetic repertory.

Considering the Lewis acid nature of the silicon species generated in the reaction medium, a hypothetic substitution pathway was envisioned for this purpose (Scheme II.23). At the onset, a formally related mechanistic hypothesis to the one proposed for the second alkynylation step in aldehydes was considered (path a). However, the lack of chirality induction when using chiral phosphines as ligands for the gold(I) complex (additional results in Part I, p. 103) strongly suggested that the alkynylsilane could participate as the nucleophile, competing satisfactorily with the gold(I) acetylide. Thus, this mechanistic possibility was also covered in the initial plan, as illustrated in path b.



Scheme II.23: Mechanistic hypothesis.

On this second basis, a study to evaluate the possibility of an analogous reactivity in the presence of other silylated nucleophiles, such as allylsilanes and silyl enol ethers, and the development of an enantioselective version for this alkynylation reaction were also intriguing proposals.

Besides, silyl ethers were another unexplored kind of nucleophiles in this strategy, and the lack of precedent similar transformations made them a clear target for this work.

The results obtained in the development and optimisation of the reaction conditions, and the study of the scope of this new process, as well as the experimental tests to evaluate the accuracy of the mechanistic hypothesis made, are described in the following pages. Furthermore, some exploratory studies directed to the development of an enantioselective substitution reaction will be discussed. Finally, the first results of another ongoing exploratory study concerning silyl ethers as nucleophiles will be presented.

Results and Discussion

1. Alkynylation of Benzylic Methyl Ethers and Acetates

Exploratory Study of Different Methyl Ethers and Acetates

Different experiments were conducted for the purpose of validating the proposed working hypothesis. First, in order to find appropriate coupling partners for alkynylsilanes, an exploratory study using different benzyl methyl ethers was carried out. The most significant results are collected in Table II.4. For a better visual inspection of the products obtained, their structures are depicted in Scheme II.24.

Benzyl methyl ether (**8a**, entry 1) failed to react with **2a**, even using high temperature conditions (microwave heating in sealed tubes was employed for performing reactions at 120ºC in DCE).[156] However, a more activated benzylic substrate like **8b** reacted completely under the same conditions, affording **9b** in moderate yield, from a complex mixture in which no other by product could be identified. Lower temperature led to similar results, but required a 30 times longer reaction period (entries 2 and 3). Similarly, 2-naphthyl methyl ether (**8c**) afforded the corresponding product **9c** in slightly lower isolated yield (entry 4).

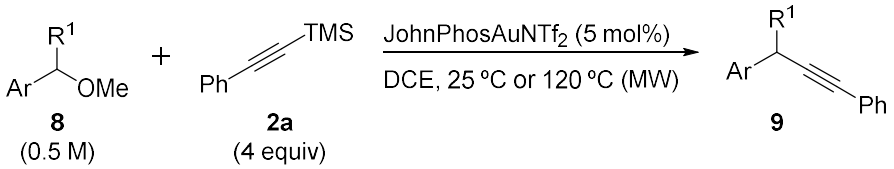
Secondary benzylic substrate **8d** also furnished moderate yield for product **9d**. However, a competitive elimination process was observed (entry 5). Thus, in this case, not only the desired alkynylation compound **9d** was found, but also product (E)-1-phenylpent-1-ene.

On the other hand, the double benzylic substrate **8e** presented a wonderful reactivity and product **9e** was obtained in virtually quantitative isolated yield, upon reaction for 1 hour at room temperature (entry 6). This is a remarkable result when compared to previous recent synthesis of the same or very similar compounds following a similar strategy. For example, iron(III) catalysis affords 1,3,3-triphenylprop-1-yne only in moderate yield, and using an even higher catalyst loading. Other coupling reactions furnish

[156] Other solvents were also tested (toluene, acetonitrile, THF and 1,4-dioxane) but lack of reactivity or very little conversion was observed in all cases.

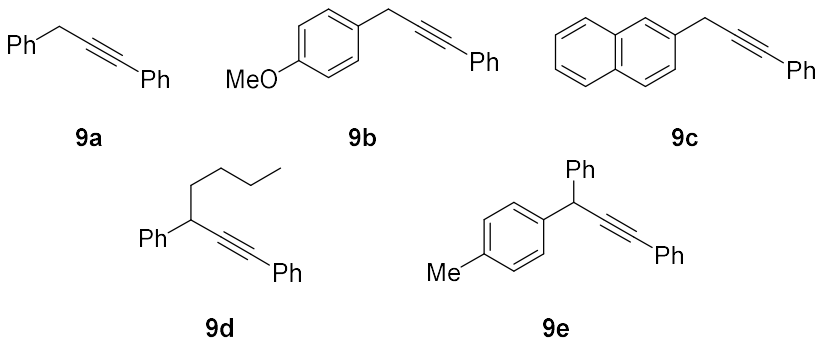
this same product in good yield, but lower than the one observed for **8e** (Scheme II.25).[140b,127c,128]

Table II.4: Reaction of **2a** with different benzyl methyl ethers.

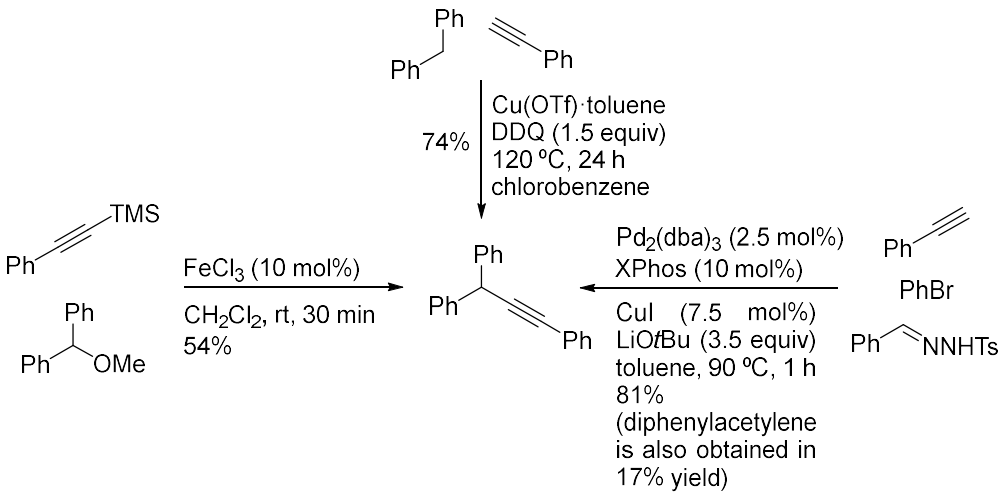


Entry	**8** (Ar; R^1)	T/t	**9** (Yield)[a]
1	**8a** (Ph; H)	120 ºC/45 min	**9a** (-)
2	**8b** (*p*-anisyl; H)	rt/30 min	**9b** (41%)
3	**8b** (*p*-anisyl; H)	120 ºC/1 min	**9b** (40%)
4	**8c** (2-Np; H)	120 ºC/15 min	**9c** (33%)
5	**8d** (Ph, Bu)	rt/3 h	**9d** (49%)[b]
6	**8e** (*p*-Tol; Ph)	rt/1 h	**9e** (98%)

[a] Isolated yield unless otherwise stated. [b] Yield determined by ^{1}H-NMR monitoring of the reaction crude, using 1,3,5-trimethoxybenzene as internal standard. 20% of the competitive elimination product, (*E*)-1-phenylpent-1-ene, was also obtained.



Scheme II.24: Coupling products from reactions of **8a-e** with **2a** (Table II.4).



Scheme II.25: Other coupling strategies to obtain 1,3,3-triphenylprop-1-yne.

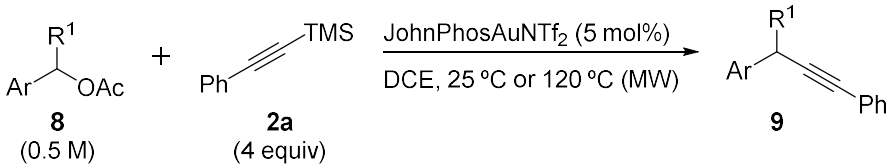
When compound **9e** was synthesised using the cross-dehydrogenative coupling and the three-component cross-coupling reaction depicted in Scheme II.25,[127c,128] it was obtained in 83% and 73% yield, respectively.

Then, benzylic substrates featuring a better leaving group, such as an acetate, were tested. The results obtained are summarised in Table II.5.

Contrary to benzyl methyl ether **8a**, primary benzylic acetate **8f** reacted under high temperature conditions to afford **9a** in relatively good yield (entry 1). Although this improvement was not so evident for substrate **8c** in terms of yield, shorter reaction times were needed (entry 2).

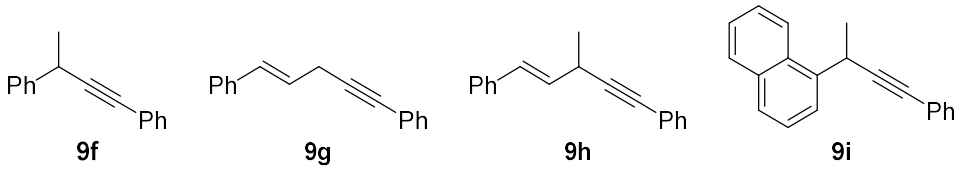
Product **9d** was also obtained in better yield (entry 5). Besides, secondary benzylic substrates **8h** and **8l** showed an excellent selectivity for the substitution process versus the elimination one under high temperature conditions (entries 3, 4 and 8). Acetates also allowed to obtain double unsaturated allylic-propargylic products **9g** and **9h** in moderate yield, and with total selectivity towards the alkynylation in position 3 of the allylic scaffold, observing the shift of the double bond.

Table II.5: Reaction of **2a** with different secondary benzylic acetates



.Entry	**8** (Ar; R^1)	T/t	**9** (Yield)[a]
1	**8f** (Ph; H)	120 ºC/15 min	**9a** (63%)
2	**8g** (2-Np; H)	120 ºC/5 min	**9c** (43%)
3	**8h** (Ph; Me)	rt/4 h	**9f** (54%)
4	**8h** (Ph; Me)	120 ºC/5 min	**9f** (74%)
5	**8i** (Ph, Bu)	rt/2 h	**9d** (57%)[b]
6	**8j** (Ph, vinyl)	rt/45 min	**9g** (35%)
7	**8k** (Ph, (*E*)-CH=CHMe)	rt/45 min	**9h** (55%)
8	**8l** (1-Np, Me)	120 ºC/5 min	**9i** (67%)

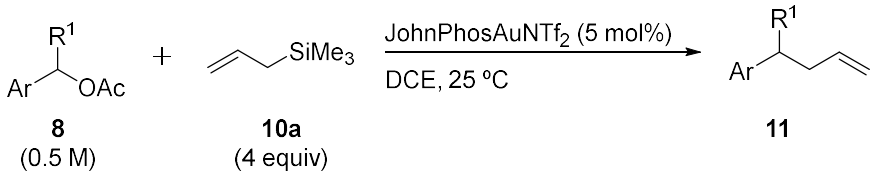
[a] Isolated yield. [b] 18% of the competitive elimination product, (*E*)-1-phenylpent-1-ene, was also obtained.



Scheme II.26: Coupling products from reactions of **8f-k** with **2a** (Table II.5).

The compatibility of other silylated nucleophiles with these reaction conditions was also tested. Thus, allyltrimethylsilane (**10a**) reacted with acetates **8i** and **8m** at room temperature, furnishing allylated products as the result of the desired C-C coupling reaction (Table II.6).

Table II.6: Reaction of **8i** and **8l** with **10a**.



8 (0.5 M) + **10a** (4 equiv) → **11**

Entry	**8** (Ar; R^1)	T/t	**11** (Yield)[a]
1	**8i** (Ph; Bu)	rt/2 h	**11a** (51%)
2	**8i** (Ph; Bu)	rt/24 h	**11a** (82%)[b,c]
3	**8m** [Ph, (*E*)-CH=CHPh]	rt/1 h	**11b** (84%)
4	**8m** [Ph, (*E*)-CH=CHPh]	rt/1 h	**11b** (93%)[b]

[a] Isolated yield unless otherwise stated. [b] Toluene was used as solvent. [c] From an inseparable mixture of **11a** and elimination product 1-phenyl-1-pentene (14% yield). Yields estimated from the crude mixture by ^{1}H-NMR.

11a **11b**

Scheme II.27: Products from reactions of **8i** and **8l** with **10a**.

Acetate **8i** afforded the corresponding product **11a** in moderate yield, whereas the use of toluene instead of 1,2-dichloroethane considerably improved this result (entries 1 and 2). However, in this case, it was obtained in an inseparable mixture of **11a** and the competitive elimination product 1-phenyl-1-pentene.[157] More activated substrate **8m** was found to perform very well in both DCE and toluene, but better outcome was achieved using this last solvent, affording product **11b** in excellent yield (entries 3 and 4).

Alkynylation of Methyl β-Haloethers

With these results in hand, and considering that under the conditions employed for alkynylation reactions based on cross coupling strategies any other carbon-halogen

[157] This mixture was also described as inseparable by Kabalka et al. (ref. 61a).

atom would be susceptible of been targeted by the catalyst, another valuable application was envisioned for this transformation: a chemoselective process in which an alcohol derived leaving group suffered an alkynylation reaction, while a carbon-halogen bond, also present in the molecule, remained unaltered. The opposite selectivity of a transition metal cross-coupling reaction would be achieved, providing a complementary alkynylation method to the existing repertory. Moreover, this halogen atom could be useful for further modification.[158]

Readily accessible β-haloethers **12**, which can be easily obtained from the corresponding styrenes in just one step,[159] were chosen as bi-functional substrates. It was anticipated that the neighbouring halogen atom could provide with anchimeric assistance to the cleavage of the alkoxy moiety upon its selective activation under the reaction conditions.[160]

Conditions previously described for obtaining compounds **9** and **11** were applied to a variety of β-haloethers **12** in their reaction with **2a**, and the outcome is shown in Table II.7. The structures of compounds **13** are depicted in Scheme II.28.

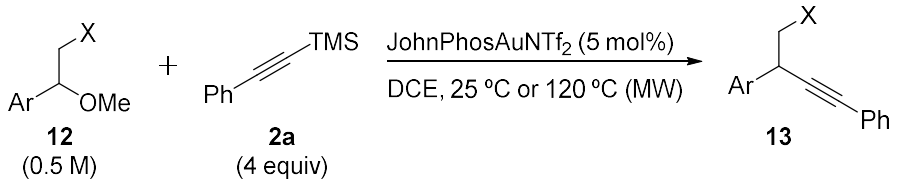
Firstly, the nature of the halogen atom was tested (entries 1-4). The bromide **12b** proved to afford better yields than chloride **12a** or iodide **12c**. Surprisingly, the iodine derivative was stable enough under high temperature conditions to produce **13c** in moderate yield. Upon finding better results choosing bromine as the halogen, a series of β-bromoethers were tested afterwards.

[158] Bromo-organic compounds are important in organic synthesis. For a review see: I. Saikia, A. J. Borah, P. Phukan, *Chem. Rev.* **2016**, *116*, 6837–7042.

[159] a) B. Das, K. Venkateswarlu, K. Damodar, K. Suneel, *J. Molec. Catal. A* **2007**, *269*, 17–21. b) J. Rodriguez, J.-P. Dulcère, *Synthesis* **1993**, *1993*, 1177–1205.

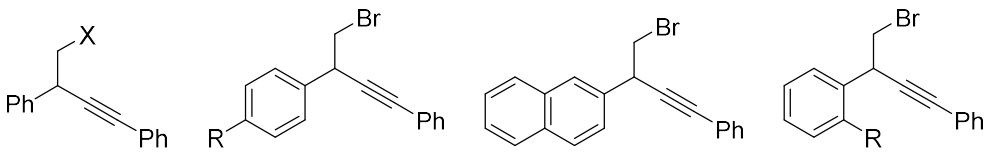
[160] a) R. C. Fahey, D. J. Lee, *J. Am. Chem. Soc.* **1966**, *88*, 5555–5560. b) M. L. Poutsma, J. L. Kartch, *J. Am. Chem. Soc.* **1967**, *89*, 6595–6604. c) R. C. Fahey, H. J. Schneider, *J. Am. Chem. Soc.* **1968**, *90*, 4429–4434. d) A. Hassner, F. Boerwinkle, A. B. Lavy, *J. Am. Chem. Soc.* **1970**, *92*, 4879–4883. d) T. Ohwada, N. Tani, Y. Sakamaki, Y. Kabasawa, Y. Otani, M. Kawahata, K. Yamaguchi, *PNAS* **2013**, *110*, 4206–4211.

Table II.7: Reaction of **2a** with different β-haloethers **12**.



Entry	**12** (Ar; X)	T/t	**13** (Yield)[a]
1	**12a** (Ph; Cl)	120 ºC/30 min	**13a** (40%)
2	**12b** (Ph; Br)	120 ºC/15 min	**13b** (73%)
3	**12b** (Ph; Br)	rt/17 h	**13b** (36%)[b]
4	**12c** (Ph; I)	120 ºC/15 min	**13c** (52%)
5	**12d** (*p*-$MeOC_6H_4$; Br)	120 ºC/1 min	**13d** (73%)
6	**12d** (*p*-$MeOC_6H_4$; Br)	rt/30 min	**13d** (73%)
7	**12e** (*p*-MeC_6H_4; Br)	120 ºC/5 min	**13e** (76%)
8	**12f** (*p*-BrC_6H_4; Br)	120 ºC/3 h	**13f** (74%)
9	**12g** [*p*-$(MeCO_2)C_6H_4$; Br]	120 ºC/6 h	**13g** (24%)[c]
10	**12h** (*p*-FC_6H_4; Br)	120 ºC/1 h	**13h** (81%)
11	**12i** (2-Np; Br)	120 ºC/5 min	**13i** (64%)
12	**12i** (2-Np; Br)	rt/1 h 10 min	**13i** (59%)
13	**12j** (*o*-$MeOC_6H_4$; Br)	120 ºC/1 min	**13j** (45%)
14	**12k** (*o*-MeC_6H_4; Br)	120 ºC/10 min	**13k** (85%)

[a] Isolated yield unless otherwise stated. [b] 49% conversion observed. [c] Yield determined by ^{1}H-NMR monitoring of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. 48% conversion observed.



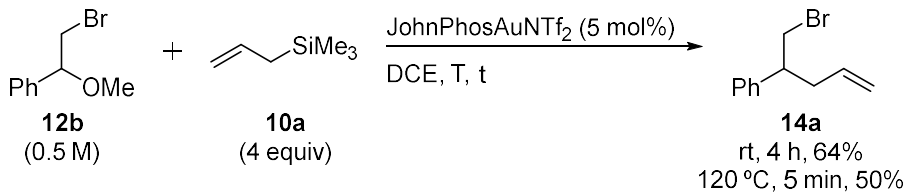
Scheme II.28: Products from reactions of **12a-k** with **2a** (Table II.7).

Thermal conditions using microwave heating led to equal or better results in shorter times for obtaining compounds **9** than room temperature conditions, as it can be seen in Table II.4. Also, in the case of substrates **12**, much longer reaction times and catalyst deactivation were observed in many cases, so yields for compounds **13** were lower because not total conversion were obtained. For example, compound **13b** was obtained in much lower yield and conversion at room temperature than at 120 ºC (entries 2 and 3).

A remarkable difference in the required reaction time for the conversion of the different substrates **12** was encountered. Thus, those having properly located electron donating groups (**12d**, **12e**, **12j** and **12k**, entries 5, 7, 13 and 14, respectively) reacted faster than those with electron withdrawing groups (**12f-h**, entries 8-10). Some of those activated compounds were able to perform with complete conversion at room temperature, but no significant change in the yield was observed (entries 5 vs. 6, and 11 vs. 12).

In general, moderate to very good yields were obtained with all substrates employed containing electron donating and electron withdrawing groups. Only ester **12g**, with a more potent electron withdrawing group, failed to afford complete conversion and resulted in a relatively low yield (entry 9). Reactions with very activating substituents were usually smooth and easy to control by accommodating the time variable.

The viability of using allylsilanes as proper nucleophiles in this C-C bond forming event showing unprecedented chemoselectivity was also tested. Gratifyingly, allyltrimethylsilane was found a useful reaction partner at room temperature, affording catalytically the target product **14a** in fair yield, as depicted in Scheme II.29. In the case of nucleophile **10a**, thermal conditions gave a faster reaction but resulted into a lower isolated yield for product **14a**.



12b (0.5 M) + **10a** (4 equiv) → **14a** rt, 4 h, 64% / 120 ºC, 5 min, 50%

Scheme II.29: Reaction of **12b** with **10a** at room temperature.

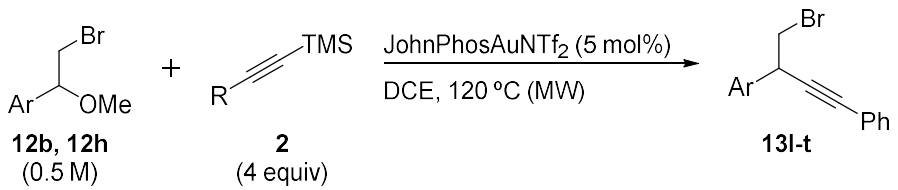
Next, the scope for the alkyne was studied, paying special attention to explore both the nature of the alkyne and the functional group tolerance, in search for otherwise

difficult to elaborate combinations of functional groups in a straight forward manner (Table II.8). The structures of the compounds **13** obtained are depicted in Scheme II.30 (p. 148).

Electron donating groups, like a methoxy group in alkyne **2d**, and electron withdrawing groups, such as a bromide in alkyne **2c**, were tolerated in the aromatic ring of the alkyne (entries 1 and 2). Enyne **2i** could also be employed and afforded product **13o** in reasonably good yield (entry 4). Interesting aliphatic alkynylsilanes, like the long chain featuring **2j** and the functionalised one presented in **2g**, produced a moderate yield of the corresponding coupling products **13n** and **13p** (entries 3 and 5).

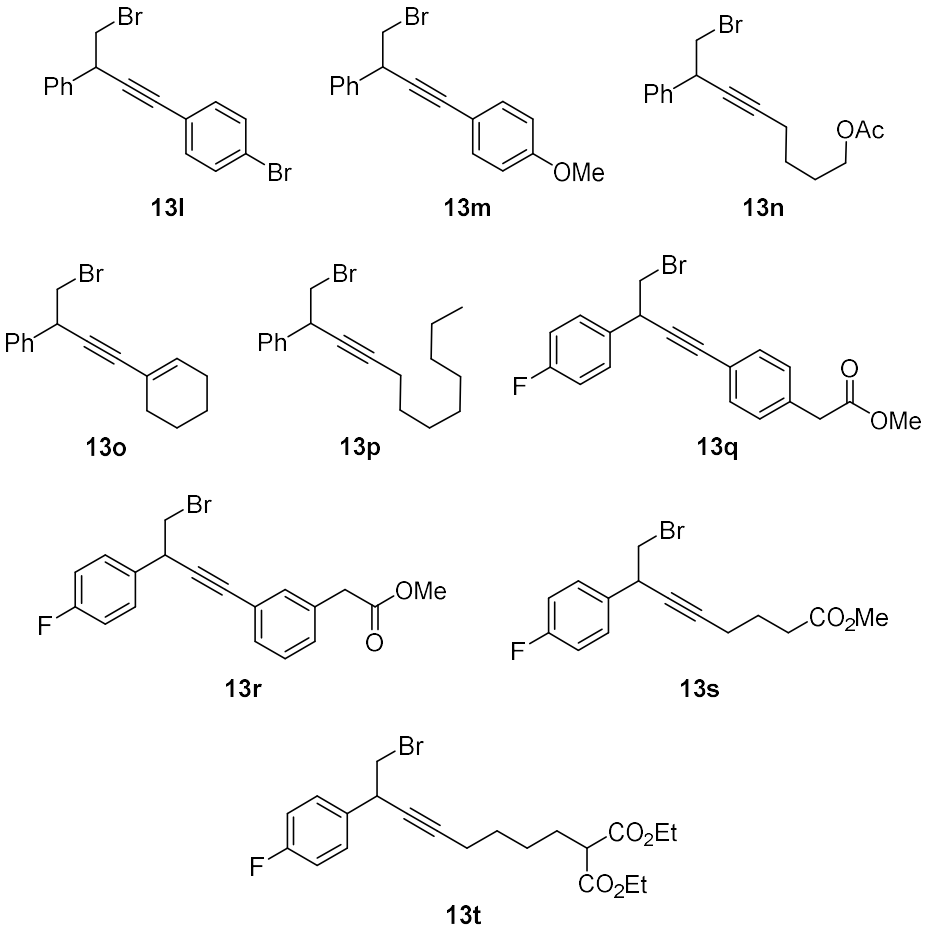
Looking for products with diverse structure and interesting functionalised positions, a set of esters (**13q-t**) were synthesised using these experimental conditions, in moderate to generally good yields.

Table II.8: Study of the scope of different alkynylsilanes **2** and allylsilane **10a**.



Entry	**12** (Ar)	**2**/**10a** (R)	T/t	**13**/**14** (Yield)[a]
1	**12b** (Ph)	**2c** (*p*-BrC_6H_4)	120 ºC/15 min	**13l** (62%)
2	**12b** (Ph)	**2d** (*p*-$MeOC_6H_4$)	120 ºC/5 min	**13m** (65%)
3	**12b** (Ph)	**2g** [$(CH_2)_4OAc$]	120 ºC/5 min	**13n** (46%)
4	**12b** (Ph)	**2i** (1-cyclohexenyl)	120 ºC/3 min	**13o** (60%)
5	**12b** (Ph)	**2j** (octyl)	120 ºC/5 min	**13p** (51%)
6	**12h** (*p*-FC_6H_4)	**2k** [*p*-$(CH_2CO_2Me)C_6H_4$]	120 ºC/1 h	**13q** (71%)
7	**12h** (*p*-FC_6H_4)	**2l** [*m*-$(CH_2CO_2Me)C_6H_4$]	120 ºC/1 h	**13r** (61%)
8	**12h** (*p*-FC_6H_4)	**2m** [$(CH_2)_3CO_2Me$]	120 ºC/1 h	**13s** (37%)
9	**12h** (*p*-FC_6H_4)	**2n** [$(CH_2)_4CH(CO_2Et)_2$]	120 ºC/1 h	**13t** (71%)

[a] Isolated yield.



Scheme II.30: Products **13** from the scope of different nucleophiles **2**.

No significant difference in the reaction time was observed among the use of alkynes in entries 1-5. The same was observed in the case of entries 6-9. This suggests that the reaction time is mainly influenced by the reactivity of the β-bromoether.

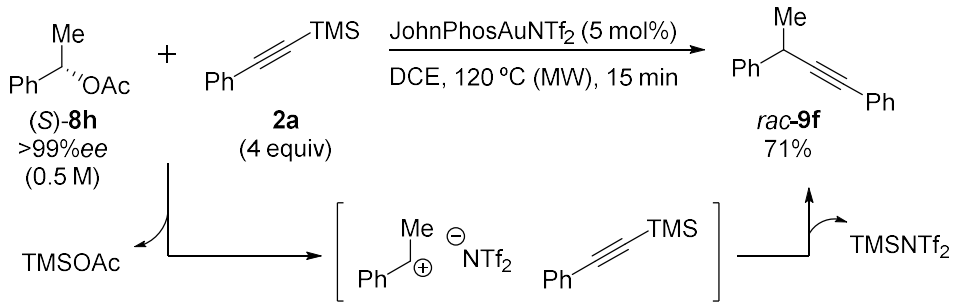
On the other hand, these simple but densely functionalised scaffolds obtained in products **13q-t** illustrate the usefulness of this transformation, since only two key steps are required, namely: a bromoalkoxylation of the corresponding commercial vinylarene, and the gold(I)-catalysed coupling with the alkynylsilane.

Mechanistic Insights: Experimental Approaches.

a) *Study of the possible cationic nature of the mechanism*

The precedent works found in literature for the activation of alcohols and their derivatives activation with Lewis acids strongly suggest that a cationic intermediate will be likely involved in a transformation with the characteristics of the one described in these previous pages.

In order to unveil the truth of this hypothesis, enantioenriched compound (*S*)-**8h**, which is easily accessible from the commercially available enantioenriched alcohol (see Experimental Section, p. 208), was tested in its reaction with **2a**. Racemic compound **9f** was obtained, as would be expected from the behaviour of a cationic intermediate in this kind of transformation (Scheme II.31).

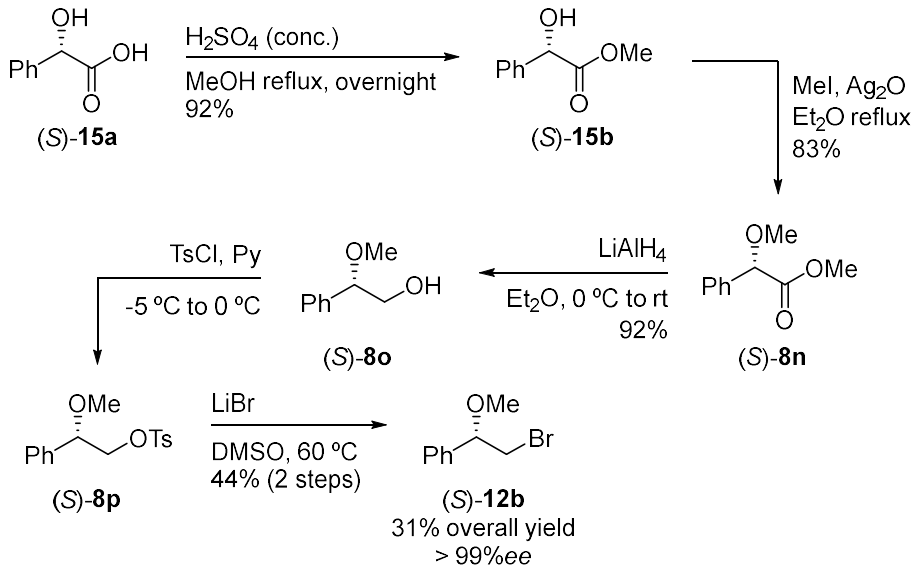


Scheme II.31: Reaction of enantioenriched compound (*S*)-**8h** with **2a**.

With the same purpose, enantioenriched compound (*S*)-**12b** was prepared following the synthetic pathway illustrated in Scheme II.32.[161] Parting from commercially available L-(+)-mandelic acid, compound (*S*)-**15a**, the methyl ester was easily obtained through a conventional esterification reaction under acid conditions, affording compound (*S*)-**15b** in excellent yield. Smooth methylation conditions using silver oxide and methyl iodide were selected for the transformation of (*S*)-**15b** in (*S*)-**8n** without risking the loss of the chiral purity in the desired product. Reduction of the ester group to the corresponding alcohol using lithium aluminium hydride furnished compound (*S*)-**8o** in very good yield. The hydroxyl group in (*S*)-**8o** was transformed into tosylate following conventional

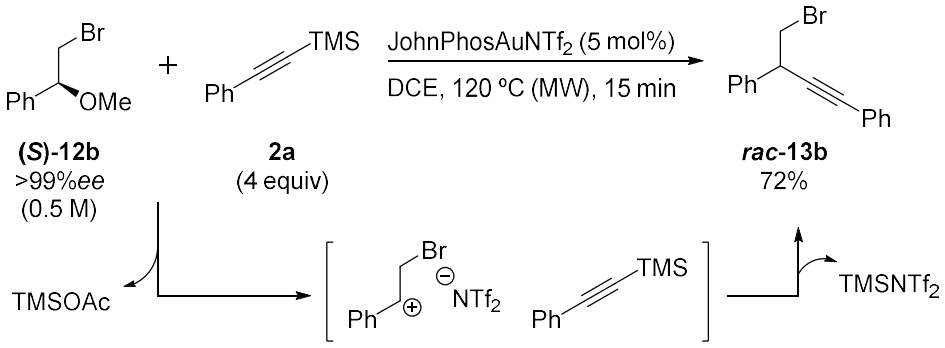
[161] Detailed procedures and bibliographical references in Experimental Section, p. 211.

procedures, and substituted by a bromine atom using a classical S_N2 procedure. Product (*S*)-**12b** was obtained in a satisfying 31% overall yield with no chiral purity loss (see Experimental Section p. 211).



Scheme II.32: Preparation of compound (*S*)-**12b**.

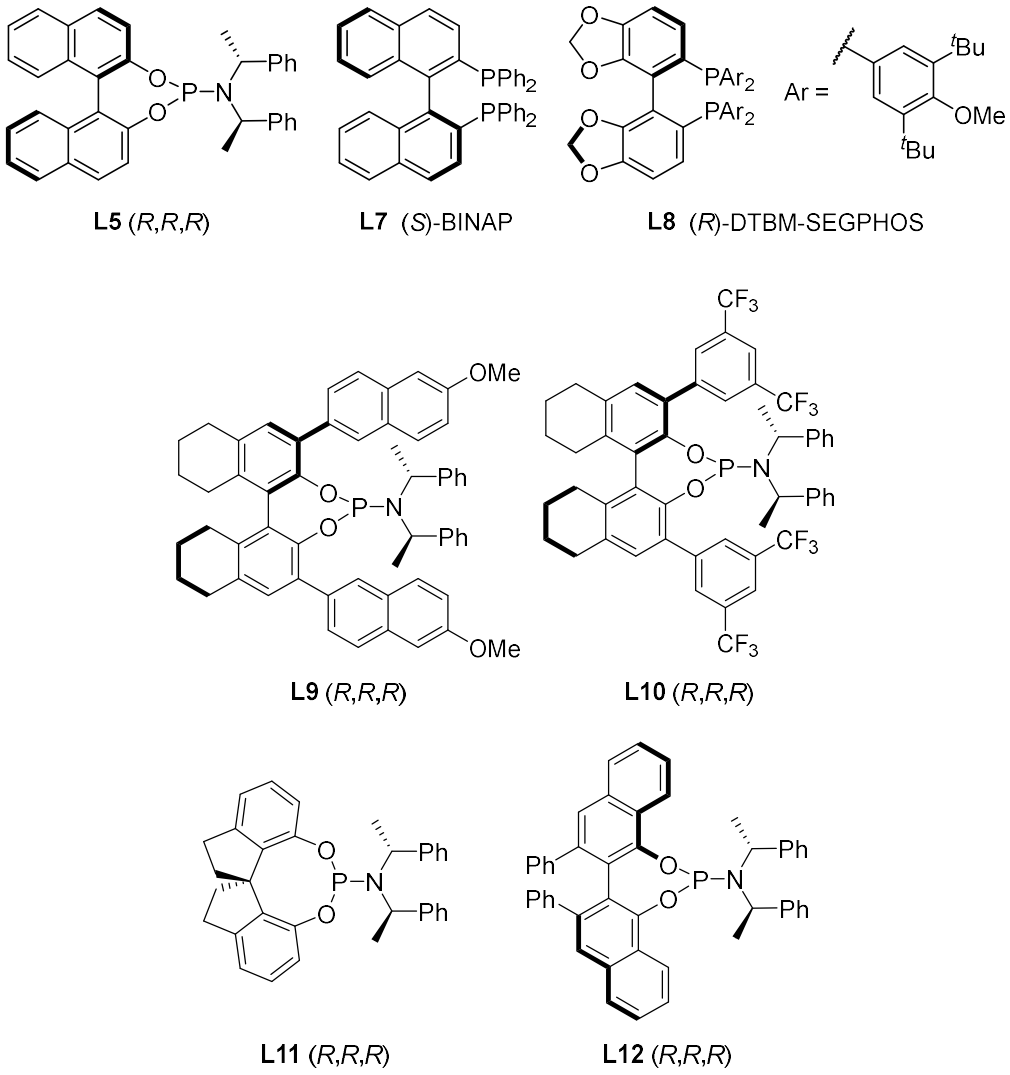
The same stereochemical probe was designed for compound (*S*)-**12b** in its reaction with **2a**. Again, the corresponding racemic products **13b** was obtained, which supports this cationic intermediate proposed for the case of β-bromoethers too (Scheme II.33).



Scheme II.33: Reaction of enantioenriched compound **(*S*)-12b** with **2a**.

b) Study of the role of the gold(I) complex and the Si-based Lewis acid in the catalytic process

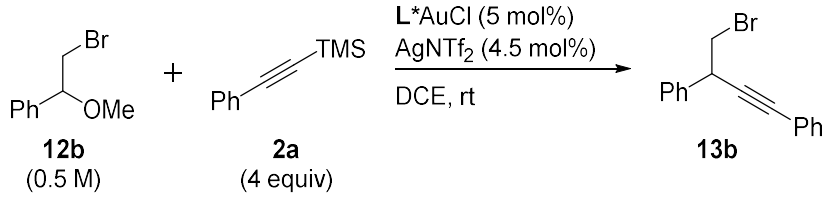
A previous lack of chiral induction had been noticed for the gold(I) catalysed alkynylation of propargyl silyl ethers **4** (p. 103). Now, gold(I) complexes derived from several chiral enantioselective ligands (for their structures see Schemes II.34) were again tested in this unusual coupling reaction of an ether in presence of an alkylbromide substituent.



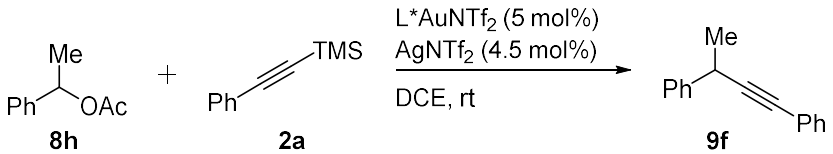
Scheme II.34: Structures of chiral ligands **L5** and **L7-12** used in Table II.9.

When using these chiral ligands in the alkynylation reactions of compounds **12b** and **9f**, similar results were obtained: low conversions and yields were observed, and racemic products were formed as racemic mixtures (Table II.9).

Table II.9: Chiral ligands in the gold(I) catalysed alkynylation of compounds **12b** and **8h** with **2a**.



12b (0.5 M) + **2a** (4 equiv) → **13b**



8h (0.5 M) + **2a** (4 equiv) → **9f**

Entry	Substrate	L*	**Product** (Yield, %*ee*)[a]
1	**12b**	**L5**	**13b** (29%, *rac*)
2	**12b**	**L7**	**13b** (25%, *rac*)
3	**12b**	**L8**	**13b** (24%, *rac*)
4	**12b**	**L9**	**13b** (14%, *rac*)
5	**12b**	**L11**	**13b** (18%, *rac*)
6	**12b**	**L12**	No reaction
7	**8h**	**L5**	**9h** (22%, *rac*)
8	**8h**	**L10**	**9h** (29%, *rac*)

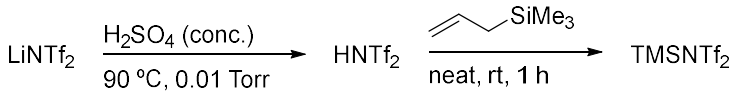
[a] Isolated yields.

This outcome may suggest that the gold(I) acetylide is not nucleophilic enough to enter the process in a more satisfactorily manner than the alkynylsilane. This last one could be reacting instead with the cationic intermediate, which is expected to be highly reactive according to Mayr's scales.[134] If this was the case, a single Si-based Lewis acid would be

able to account for the formation of the observed products, acting as an efficient scavenger for the leaving group.

In order to prove this affirmation, commercially available TMSOTf was firstly tested as Si-based Lewis acid, but no reaction was observed in the case of substrates **12b** and **8h** with **2a** at room temperature. This fact, summed to the equal observation made when using chiral phosphates and sulfonates as counteranions for the alkynylation of compounds **4**, suggested that the nucleophilicity of the counteranion was also a feature of this transformation that should be finely tuned.

Then, the species $TMSNTf_2$ was freshly synthesised, following the synthetic pathway that is shown in Scheme II.35.[162] The species $HNTf_2$ sublimates when heated at 90 ºC under vacuum, which allows to easily isolate it and keep under an inert atmosphere. The reaction of $HNTf_2$ with allyltrimethylsilane in absence of solvent affords $TMSNTf_2$ in virtually quantitative yield. Conveniently, propene is the only by-product, and both this compound and the excess of allyltrimethylsilane are volatile and can be removed under vacuum.



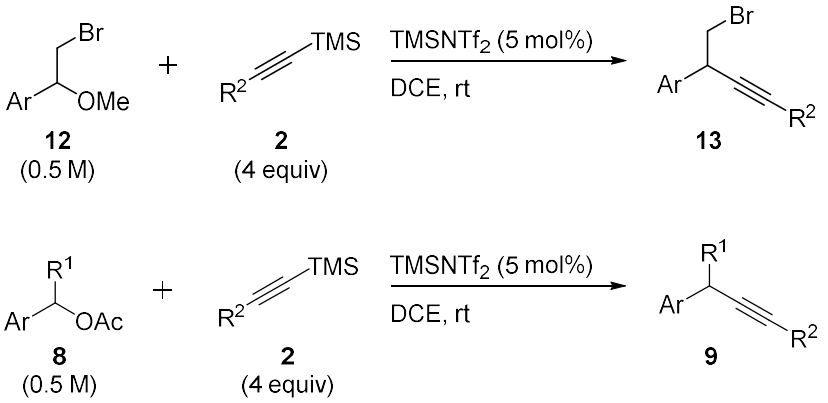
Scheme II.35: General preparation of $TMSNTf_2$.

$TMSNTf_2$ was used as catalyst for the alkynylation of several substrates **9** and **12** (Table II.10).

Although the corresponding alkynylation product was obtained in all cases, the yields were generally lower than the ones obtained using gold(I) catalysis to eventually promote a smooth releasing of the Si-based Lewis acid into the solution. There were two exceptions: substrate **12i**, for which the yield considerably improved (entry 3), and substrate **8h**, for which the yield was essentially the same as the one obtained using a gold(I) catalyst.

[162] Detailed procedure and bibliographical references in Experimental Section, p. 233.

Table II.10: $TMSNTf_2$ as catalyst in the reaction of **2a** with several acetates and β-bromoethers.



Entry	Substrate (Ar; R^1)	**2** (R^2)	Product (Yield)[a]
1	**12b** (Ph)	**2i** (1-cyclohexenyl)	**13o** (48%)
2	**12f** (*p*-BrC_6H_4)	**2a** (Ph)	**13f** (48%)[a]
3	**12i** (2-Np)	**2a** (Ph)	**13i** (87%)
4	**8c** (2-Np; H)	**2a** (Ph)	**9c** (24%)
5	**8h** (Ph; Me)	**2a** (Ph)	**9f** (72%)
6	**8k** (Ph; (*E*)-CH=CHMe)	**2a** (Ph)	**9h** (54%)

[a] Isolated yield unless otherwise stated. [b] Yield determined by ^{1}H-NMR inspection of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.

These results suggested that the generation rate in the reaction medium for $TMSNTf_2$ is also something that must be carefully controlled. In general, the use of a gold(I) catalyst allows the releasing of this species in a manner that better suits the reactivity of the rest of the compounds involved in the process.

Another reason why gold(I) catalysis offers more robust conditions for this transformation is the instability of the species $TMSNTf_2$, which is highly hygroscopic. Even when handled under an argon atmosphere at every moment and transferred in solution to the reaction medium, it is difficult to assure its purity.

One more important fact learnt from these experiments is that the chiral species that would be more likely to enantioselectively promote this transformation could be a

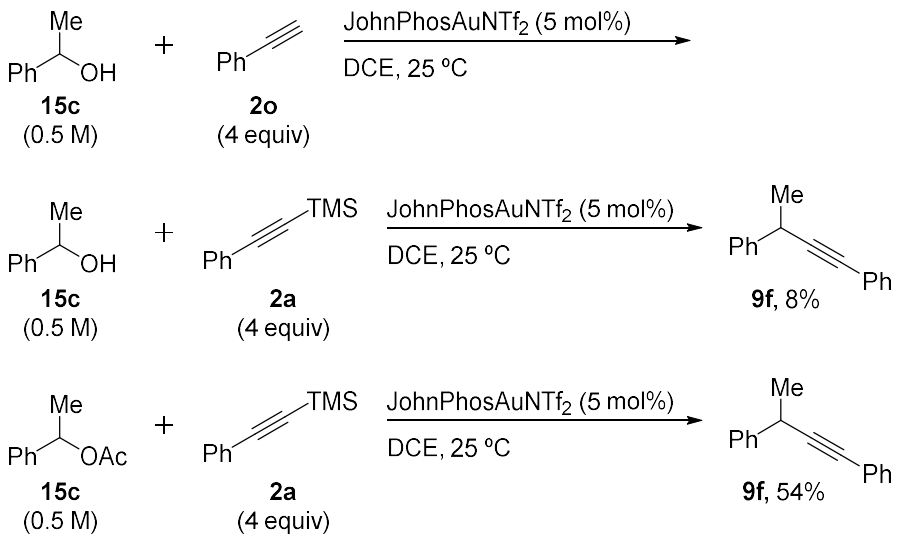
chiral Si-based organocatalyst. It would be a species with the structure TMSX*, where X* should be a chiral enantiopure organic fragment with a coordination capacity that should match that of the bistriflimidate counteranion.

a) Control experiments

Several control experiments were carried out in order to acquire further detailed knowledge about the requirements for this coupling to occur.

First, an alcohol that was structurally analogous acetate **8h**, substrate **15c**, was tested under standard room temperature reaction conditions, using both alkynylsilane **2a** and phenylacetylene (**2o**) as nucleophiles (Scheme II.36). The outcome in the case of using acetate **8h** is also included for comparison purposes.

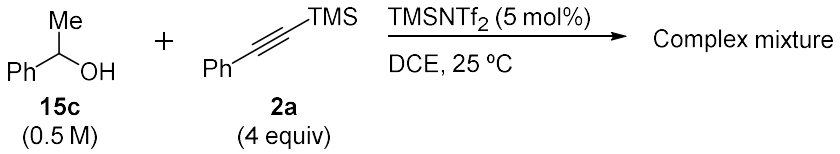
As expected, no reaction was observed when a terminal alkyne was used as a nucleophile. On the other hand, using alkynylsilane **2a**, a complex crude mixture was obtained, from which the product could hardly be isolated in an 8% yield.



Scheme II.36: Au(I)-catalysed reaction of alcohol **15c** with alkynylsilane **2a** or terminal alkyne **2q**.

Given these results, it can be stated that a hydroxyl group is not a suitable leaving group for this S_N1 coupling. Furthermore, the outcome concerning alkynylsilane **2a** reinforces the hypothetic role adjudicated to the Si-based Lewis acid.

In second place, the species $TMSNTf_2$ was tested as a catalyst in the reaction of alcohol **15c** with alkynylsilane **2a**, under room temperature conditions. A complex crude mixture was obtained in this case and no product could be isolated (Scheme II.37).



Scheme II.37: $TMSNTf_2$ catalysed reaction of alcohol **15c** with alkynylsilane **2a**.

This is also in concordance with the observed reactivity in the analogous gold(I)-catalysed reaction shown in Scheme II.36. The fact that a little amount of the product could be isolated in that case could be attributed to the smooth releasing of the Si-based Lewis acid species the gold(I) complex is able to perform.

Additional Results

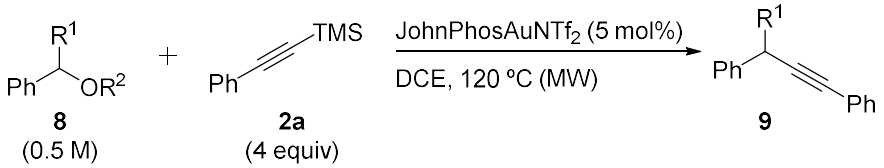
a) *Study of the influence of the leaving group*

The results obtained for substrates **8a** and **8f** using high temperature reaction conditions indicates there is a strong influence of the leaving group used for the formation of the corresponding carbocation in this particular substrate.

In order to obtain further insight into this subject, substrates **8q** and **8r**, with other ester leaving groups, were tested. In the same way, substrates **8s-v** were also used to see what effect the leaving group had in the case of secondary benzylic compounds (Table II.11, results for substrates **8a**, **8f** and **8h** are included for comparison purposes).

Substrates **8q** and **8r** failed to react, and substrates **8s-v** afforded the corresponding products in lower yields than the corresponding acetate **8h**. As expected, it can be observed that esters are better leaving groups than ethers (entries 1 vs. 2 and 5 vs. 9). On the other hand, less basic esters lead to worse yields (entries 5 vs. 6 and 7), but also esters which are similar in basicity but are more hindered have that effect (entries 5 vs. 8).

Table II.11: Reactions of substrates **8** featuring different leaving groups.



Entry	Substrate (R^1; R^2)	Product (Yield)[a]
1	**8a** (H, Me)	**9a** (-)
2	**8f** (H, Ac)	**9a** (63%)
3	**8q** (H, $COCF_3$)	**9a** (-)
4	**8r** (H, COPh)	**9a** (-)
5	**8h** (Me, Ac)	**9f** (72%)
6	**8s** (Me, $COCF_3$)	**9f** (61%)[b]
7	**8t** (Me, $COCH_2Cl$)	**9f** (49%)[b]
8	**8u** (Me, COPh)	**9f** (47%)[b,c]
9	**8v** (Me, Ph)	**9f** (22%)[b]

[a] Isolated yield unless otherwise stated. [b] Yield determined by ^{1}H-NMR inspection of the crude reaction using 1,3,5-trimethoxybenzene as internal standard. [c] 72% conversion observed.

These results seem to be coherent considering the needs of a trimethylsilyl species to coordinate to the leaving group. The more basic the leaving group is, the more efficient the activation will be. Besides, the trimethylsilyl moiety possesses a volume that is certainly bigger than a proton and it will be harder to accommodate next to the leaving group.

Final Remarks

A new alkynylation of benzylic alcohol derivatives has been developed. Part of the interest of this transformation relies on the lack of methodology for the alkynylation of simple benzylic alcohols or derivatives.

On the other hand, this strategy has proved to be efficient not only for the alkynylation of several methyl ethers and esters, but also methyl ethers with a bromide in alpha position to the ether. This scaffold is particularly interesting because it allows further functionalisation, but also because it unveils this transformation as a complementary one to cross coupling reactions.

The synthetic utility of this reaction has been demonstrated by the synthesis of several interesting and functionalised small molecules, such as compounds **13n**, **13o** or **13q-t**.

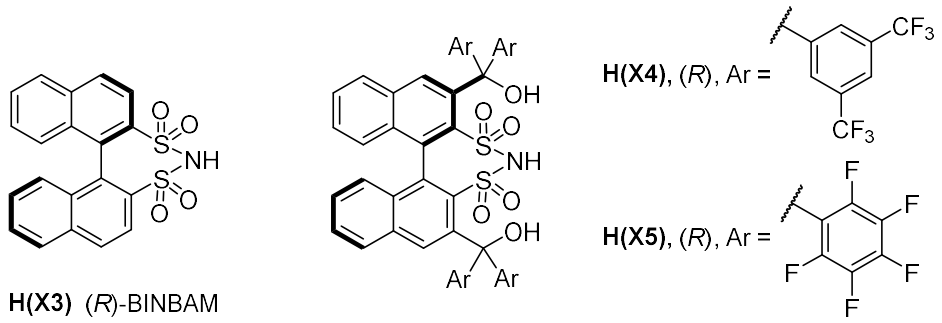
Furthermore, the cationic nature of the mechanism predicted for this process, as well as the role proposed for the silicon species formed in the reaction medium, has been supported with experimental evidences and studied in depth. The knowledge derived from this experimental work has been used to explore the possibility of an enantioselective version. Although disappointing results have been found by the time being, this is still a 'just born' methodology, and later efforts must be done in order to take full advantage of its possibilities.

2. Exploratory Studies for the Development of an Enantioselective S_N1 Coupling Reaction of Benzylic Acetates with Silylated Nucleophiles

Exploratory Studies Towards an Enantioselective Alkynylation on Benzylic Acetates

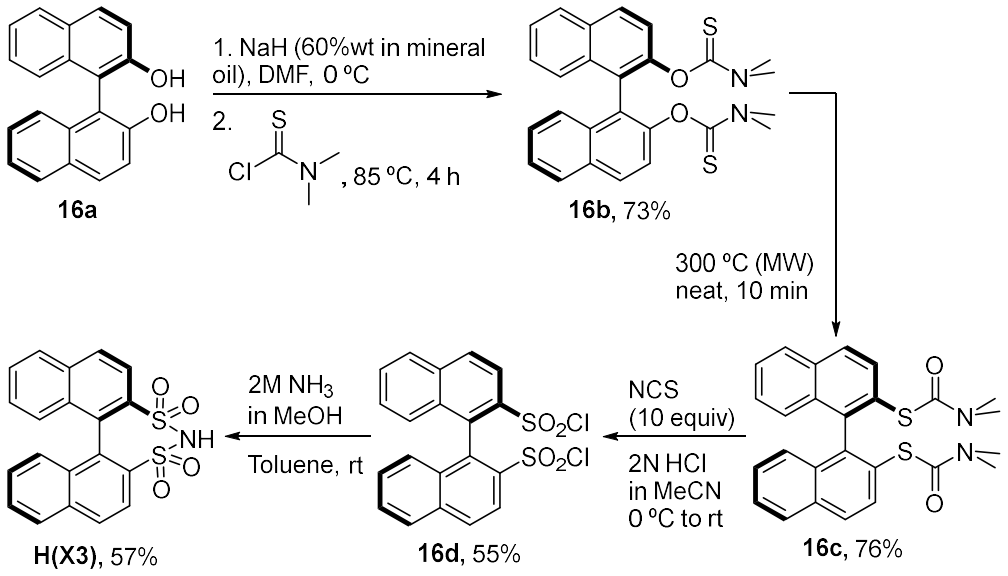
With the results previously described in hand, an exploratory study on the challenging chiral counteranion based approached for developing an enantioselective alkynylation strategy was considered, and a preliminary experimental work was conducted. Initially, a methodology based on an analogous species to $TMSNTf_2$, but with a chiral counteranion, was envisioned.

Since a very weakly coordinating counteranion seemed to be needed, those counteranions whose structure was similar to or derived from the structure of the bistriflimidate counteranion were thought to be the most suitable option to start this study. Thus, chiral enantioselective counteranions **X3-5**, whose conjugated acid structures are depicted in Scheme II.38, were selected.

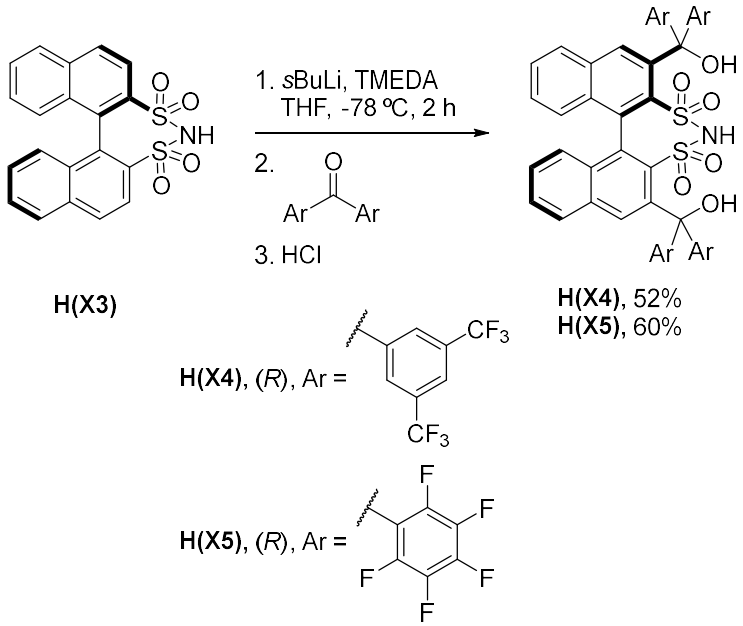


Scheme II.38: Conjugated acids of the chiral counteranions **X3-5** considered for this study.

Species **H(X3)-H(X5)** were prepared following an established procedure existing in the literature, and its experimental details can be found in the Experimental Section of this book (p. 235). The followed synthetic pathway is depicted in Schemes II.39 and II.40.



Scheme II.39: Preparation of compound **H(X3)**.



Scheme II.40: Preparation of compounds **H(X4)** and **H(X5)**.

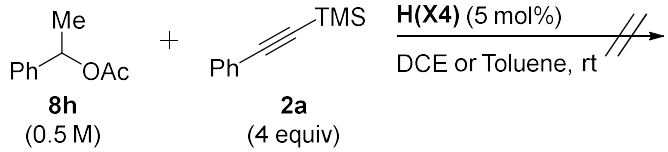
Reaction of (*R*)-BINOL (**16a**) with dimethylthiocarbamoyl chloride and subsequent thermal rearrangement of the product afforded compound **16c**, which contains a sulfur atom in the position that was previously occupied by an oxygen atom. Good yields

were observed for these two first steps. However, the rearrangement process is experimentally very demanding, since it requires unusually high reaction temperatures. Oxidation of **16c** with N-chlorosuccinimide afforded compound **16d** in reasonably good yield. Inconveniently, the last step, consisting on an addition of ammonia to compound **16d**, afforded **H(X3)** only in moderate yield (Scheme II.40).

Compounds **H(X4)** and **H(X5)** were obtained in only one more synthetic step, consisting on a deprotonation with *sec*-butyl lithium directed by the bis-sulfonimide group and the subsequent addition to the corresponding bisaromatic ketone (Scheme II.41).

In a first attempt to pre-form the species **TMS(X3)**, the same method as for the synthesis of $TMSNTf_2$ was essayed (see p. 233). However, it was found to be inefficient, since no reaction occurred and the starting material **H(X3)** was recovered. When trying to apply this same method for species **H(X4)** and **H(X5)**, a decomposition of the starting material was observed. This fact is in concordance with the observations made by professor List et al., who first implemented the use of these acids as organocatalysts.[163]

Then, acid **H(X4)** was tested as catalyst for the reaction of substrate **8h** with **2a**, in an attempt to achieve the deprotection of the alkynylsilane, and hence, generate catalytic amounts of **TMS(X4)** in situ. Both 1,2-dichloroethane and toluene were essayed as solvents (Scheme II.41). However, no reaction was observed.



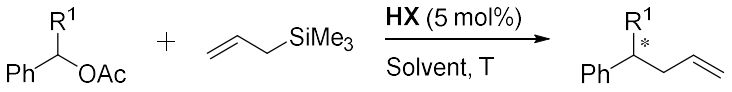
Scheme II.41: H(X4) failed to promote the alkynylation of **8h** with **2a**.

[163] a) L. Ratjen, M. van Gemmeren, F. Pesciaioli, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 8765–8769. b) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518–533. c) P. García-García, F. Lay, P. García-García, C. Rabalakos, B. List, *Angew. Chem. Int. Ed.* **2009**, *48*, 4363–4366.

Exploratory Studies Towards an Enantioselective Allylation on Benzylic Acetates

Since the results for the alkynylation reactions seemed discouraging, other more labile silylated nucleophiles, such as allylsilane **10a** were tested (Table II.12).

Table II.12: Allylations of substrates **8** with 10a using chiral counteranions **X4** and **X5**.



8 (0.5 M) + **10a** (2 equiv) → **11**

Entry	**8** (R^1)	Solvent	**X**	T/t	**11** (Yield/%*ee*)[a]
1	**8h** (Me)	Toluene	**X4**	rt/17 h	**11c** (-/-)[c]
2	**8m** [(*E*)-CH=CHPh]	Mes/Pent (1:1)[b]	**X5**	rt/17 h	**11b** (32%/23%*ee*)
3	**8m** [(*E*)-CH=CHPh]	Mes/Pent (1:1)[b]	**X5**	-60 ºC/24 h	**11b** (-/-)
4	**8m** [(*E*)-CH=CHPh]	Mes/Pent (1:1)[b]	**X5**	-20 ºC/24 h	**11b** (-/-)

[a] Isolated yield. [b] Mes = mesitylene; Pent = pentane. [c] Formation of the elimination product was found instead.

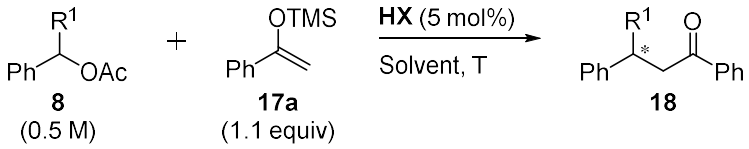
In this case, the nucleophile was labile enough to generate the desired catalytic amount of the **TMSX** species. However, the reactivity was not the desired one in the case of substrate **8h**. Substrate **8m** was then tested, since it would give rise more easily to a carbocation. Even this allylic acetate showed low reactivity, indicating that maybe the amount of **TMSX** formed is really small, and not enough to promote this transformation.

Anyway, at room temperature, a 32% yield of the target compound was produced. At the same time, a modest enantiomeric excess for the elaborated stereocentre was noticed (entry 2). Further attempts to improve the enantioselectivity lowering the reaction temperature failed, since, under these conditions, no reactivity was found (entries 3 and 4).

Exploratory Studies Towards an Enantioselective Substitution on Benzylic Acetates with Silyl Enol Ethers

Looking for an even more labile silylated nucleophile, we turned our attention to silyl enol ethers. The outcome of the catalytic reactivity of silyl enol ether **17a** with different acetates is listed in Tables II.13.

Table II.13: Screening of reaction conditions for substrates **8h**, **8m** and **17a**.



Entry	**8** (R^1)	Solvent	**X**	T/t	**18** (Yield/%*ee*)[a]
1	**8h** (Me)	DCE	**X4**	rt/17 h	**18a** (12%/4%*ee*)[d,b]
2	**8h** (Me)	Toluene	**X4**	rt/17 h	**18a** (10%/12%*ee*)[d,b]
3	**8m** (CH=CHPh)[c]	DCE	**X4**	rt/1 h	**18b** (86%/*rac*)
4	**8m** (CH=CHPh)[c]	Toluene	**X4**	rt/1 h	**18b** (98%/15%*ee*)
5	**8m** (CH=CHPh)[c]	MeCN	**X4**	rt/1 h	**18b** (82%/*rac*)
6	**8m** (CH=CHPh)[c]	Toluene	**X4**	-60 ºC/1 h	**18b** (96%/17%*ee*)
7	**8m** (CH=CHPh)[c]	Toluene	**X4**	-60 ºC/1 h	**18b** (99%/17%*ee*)[b]
8	**8m** (CH=CHPh)[c]	Toluene	**X4**	-60 ºC/1 h	**18b** (96%/17%*ee*)[e]
9	**8m** (CH=CHPh)[c]	Pentane	**X4**	-60 ºC/1 h	**18b** (-/-)
10	**8m** (CH=CHPh)[c]	Tol/Pent (1:1)[f]	**X4**	-60 ºC/1 h	**18b** (67%/21%*ee*)[e]
11	**8m** (CH=CHPh)[c]	Mes/Pent (1:1)[f]	**X4**	-60 ºC/1 h	**18b** (99%/23%*ee*)[e]
12	**8m** (CH=CHPh)[c]	Mes/Pent (1:1)[f]	**X4**	-60 ºC/1 h	**18b** (99%/22%*ee*)[e,g]
13	**8m** (CH=CHPh)[c]	Mes/Pent (1:1)[f]	**X4**[h]	-60 ºC/1 h	**18b** (99%/22%*ee*)[e]
14	**8m** (CH=CHPh)[c]	Mes/Pent (1:1)[f]	**X4**	-90 ºC/22 h	**18b** (93%/24%*ee*)[e]
15	**8m** (CH=CHPh)[c]	Mes/Pent (1:1)[f]	**X5**	-60 ºC/17 h	**18b** (87%/34%*ee*)[d,e]
16	**8m** (CH=CHPh)[c]	Mes/PhCl (1:1)[f]	**X5**	-60 ºC/19 h	**18b** (78%/11%*ee*)[d,e]

[a] Isolated yield. [b] 0.25 M concentration of substrate **8** was used. [c] The (*E*)-isomer was used. [d] Opposite enantiomer. [e] 0.05 M concentration of substrate **8** was used. [f] Tol = Toluene, Pent = Pentane, Mes = Mesitylene. [g] Slow addition of **8** over 1 h was used. [h] 1 mol% of **X4** was used.

Apart from the results shown in Table II.13, acid **H(X3)** was also tested as catalyst for this reaction, using several solvents (1,2-dichloroethane, toluene and diethyl ether), at room temperature and 80 ºC, and it failed to promote it in all cases.

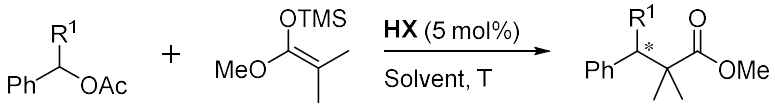
As it can be seen in Table II.13, when using **H(X4)** or **H(X5)**, a very reactive substrate **8** is necessary to obtain good yields in its coupling with a silyl enol ether. Only substrate **8m** afforded satisfactory results in this sense (entries 1 and 2 vs. 5 and 6).

On the other hand, only low enantiomeric excesses were obtained using polar or slightly polar solvents (entries 1-3 and 5). The use of toluene very slightly improved this enantiomeric excess obtained (entries 4 and 6-8). However, pentane failed as solvent for this transformation (entry 9), which suggested that some π-stacking interactions may be involved and allow the substitution process to take place. Considering the different effects of the non-polar solvents employed, mixtures of pentane with non-polar aromatic solvents were essayed (entries 10-15). They also provided a very little improvement in the enantiomeric excess. Finally, a polar aromatic solvent, such as chlorobenzene, was tested to see the combined effect of polarity and π-stacking interactions (entry 16), and it led to poorer results.

Other methods to slow the reactivity and improve the selectivity, like lowering the temperature (entries 10-20), or the catalyst loading (entry 13), or the slow addition of substrate **8** failed to improve the enantioselectivity of the transformation. Catalyst **HX5** provided slightly worse yields and slightly better enantiomeric excesses, but no significant improvement was achieved.

Similar results were accounted when using [(1-methoxy-2-methylprop-1-en-1-yl)oxy]trimethylsilane, **17b**, as nucleophile. While good chemical yields were obtained using both **H(X4)** and **H(X5)** as catalysts, no significant enantiomeric excess was found (Table II.14).

Table II.14: Screening of reaction conditions for substrates **8m** and **17b**.



8 (0.5 M) + **17b** (1.1 equiv) → **19**

Entry	**8** (R^1)	Solvent	**X**	T/t	**19** (Yield/%*ee*)[a]
1	**8m** (CH=CHPh)[b]	Toluene	**X4**	-60 ºC/1 h	**19a** (73%/2%*ee*)
2	**8m** (CH=CHPh)[b]	Mes/Pent (1:1)[c]	**X5**	-60 ºC/19 h	**19a** (94%/6%*ee*)[d]

[a] Isolated yield. [b] The (*E*)-isomer was used. [c] Pent = Pentane, Mes = Mesitylene. [d] 0.05 M concentration of substrate **8** was used.

Final Remarks

This outcome suggests that a possible improvement could require the modification of the catalyst structure, in order to obtain a better facial selection in the attack of the carbocation or a tighter ionic pair. However, counteranions like **X4** and **X5** are limited in structure by the presence of the tertiary alcohol groups, which make them instable towards its own acidity if the aryl groups do not have relatively strong electron withdrawing groups.[163a]

Further design on the scaffold of this kind of species developed by List et al. might provide with the qualities mentioned above.

As it has been mentioned in the introduction to this dissertation, the activity of Si-based Lewis acids is strongly dependent on the solvent basicity. The generation of a strong Lewis acid in solution might be a key issue for the development of an efficient catalytic process that gives access to the modification of less active substrates, like **8h**. Thus, modifications in the structure of the counteranion would also mean further improvements in this sense.

3. Synthesis of Benzylic Ethers by Nucleophilic Substitution on Acetates Using Silyl Ethers as Nucleophiles.

Considering that acetates are significantly better leaving groups than ethers, as also observed in previous pages, we thought about the possibility of using trimethylsilyl ethers as nucleophiles.

The compound $TMSNTf_2$ was observed to be unstable and difficult to handle, since a yellow colour would appear and progressively increase in intensity in the solution containing this species after a few hours of its mixing with the solvent. Besides, for some acetates, the results of the alkynylation using $TMSNTf_2$ as catalyst presented a lack of reproducibility if the catalyst solution was not used immediately after its preparation.

For this reason, and since $HNTf_2$ does not present this instability problems, it was selected as a catalyst to in situ promote the initial desilylation of the silyl ether reagent, releasing catalytic amounts of the key $TMSNTf_2$ in the reaction medium.

Optimisation of the Reaction Conditions

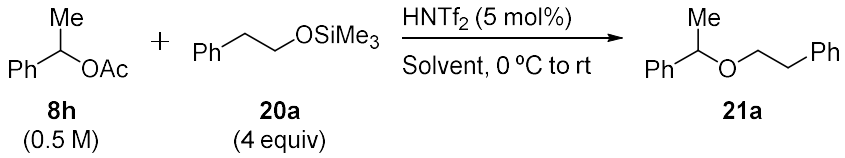
In search for an efficient C-O bond formation process, the activation of silyl ether **20a** in the presence of substrate **8h** was tested under a variety of conditions (Table II.15).

Solvents of different polarities and coordinating capacities were tested in first place (entries 1-5). Neither very polar and coordinating solvents, such as acetonitrile (entry 4), nor low polarity solvents, such as toluene (entry 3), proved to be suitable for this transformation, since they produced **21a** in moderate or low yield. Curiously, the use of dichloromethane resulted into a slightly but significantly lower yield than the use of 1,2-dichloroethane. Two solvents provided **21a** in good yield: DCE and 1,4-dioxane (entries 2 and 5). The first one was selected for continuing the screening of other reaction variables, since the reaction time needed in this case for the total conversion of the starting material was considerably shorter.

A lower number of equivalents of **20a** led to a moderate yield of **21a**, for which 4 equivalents were required to achieve the best possible yield for the conditions described in DCE (entry 6).

The catalyst $HNTf_2$ was synthesised following the procedure previously indicated in p. 153 and added in a 0.1 M solution, in the corresponding solvent used for each case. The addition of the catalyst was made at 0 ºC and the reaction mixture was then allowed to warm up to room temperature, thus achieving cleaner crude reaction mixtures. In an attempt to soften even more the reaction conditions employed, the concentration of substrate **8h** was lower to 0.2 M (entry 7), with negative effects in the product yield when comparing to the 0.5 M concentration that was being used in the rest of the cases.

Table II.15: Screening of different reaction variables for the reaction of substrate **8h** with **20a**.



8h (0.5 M) + **20a** (4 equiv) → **21a**

Entry	Solvent	t	Conversion	**21a** (Yield)[a]
1	CH_2Cl_2	50 min	100%	66%
2	DCE	1 h	100%	73%
3	Toluene	50 min	100%	55%
4	MeCN	5 h	26%	26%
5	1,4-Dioxane	5 h	100%	71%
6	DCE	1 h	100%	50%[b]
7	DCE	1 h	100%	54%[c]

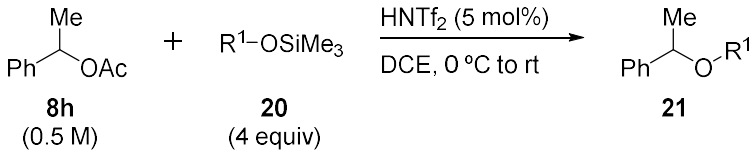
[a] Yields determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b] 3 equiv of **20a** were used. [c] 0.2 M concentration of **8h** was used

Considering products **21** are formally able to behave also as substrates and be equally activated by $TMSNTf_2$, some of the results shown in this table were surprising as well as encouraging. Total conversions were observed in all cases, and very promising yields were also obtained, especially in the cases of entries 2 and 5. In general, quite short reaction times were also found.

Study of the Reaction Scope

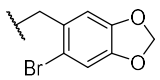
Conditions described in Table II.15, entry 2, were selected for the study of the reaction scope, considering the yield obtained, but also the reaction time. Using therein reported conditions, the scope of the reaction using **8h** as model electrophile and different silyl ethers **20** as nucleophiles was studied (Table II.16). For a better inspection of the reaction products, their structures are depicted in Scheme II.42.

Table II.16: Reaction of different silyl ethers **20** with acetate **8h**.

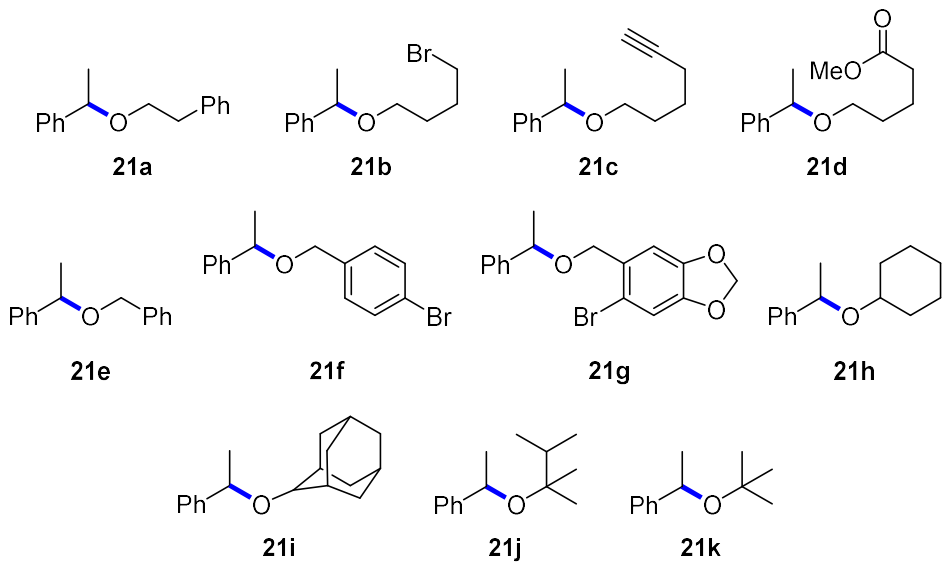


Entry	**20** (R^1)	t	**21**(Yield)[a]
1	**20a** (CH_2CH_2Ph)	1 h	**21a** (67%)
2	**20b** ($(CH_2)_4Br$)	1 h	**21b** (79%)
3	**20c** ($(CH_2)_4C{\equiv}CH$)	2 h	**21c** (54%)
4	**20d** ($(CH_2)_4CO_2Me$)	2 h	**21d** (-)[c]
5	**20e** (CH_2Ph)	1 h	**21e** (75%)
6	**20f** ($CH_2(p\text{-}BrC_6H_4)$)	1 h	**21f** (74%)
7	**20g** (CH_2Ar)[b]	2 h	**21g** (-)[d]
8	**20h** (Cy)	4 h	**21h** (43%)
9	**20i** (2-Ad)	2 h	**21i** (51%)
10	**20j** (2,3-dimethylbutane)	2 h	**21j** (-)[c]
11	**20k** (^{t}Bu)	2 h	**21k** (-)[c]
12	**20l** (cyclohex-2-en-1-yl)	30 min	**21l** (-)[d]

[a] Isolated yield.

[b] Ar = 

[c] Starting materials were recovered (80%, 80% and 66% of **8h** was recovered, respectively). [d] A complex mixture was obtained.



Scheme II.42: Structures of compounds **21a-k** (the new formed bond is marked in blue).

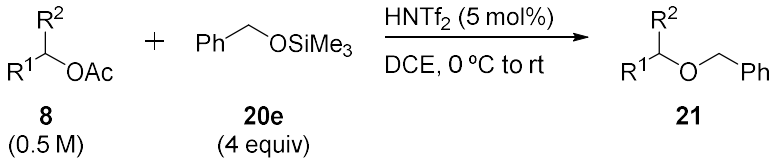
An interesting variety of silyl ethers **20** proved to be reactive under these conditions. Generally, primary non-activated ethers (entries 1-3) provided moderate to very good yields. Unexpectedly, substrate **20d** (entry 4) was found totally unreactive. Satisfyingly, substrates **20b** and **20c**, which are usefully functionalised, performed well under these reaction conditions and total functional group tolerance was observed.

Primary benzylic silyl ethers **20e** and **20f** also provided good yields (entries 5 and 6), but a more activated and labile substrate of this kind (**20g**) failed to perform in a controlled manner (entry 7).

Secondary silyl ethers were also tested (entries 8 and 9), affording moderate yields of the corresponding products **21h** and **21i**. However, tertiary silyl ethers **20j** and **20k** were not reactive under these conditions (entries 10 and 11). Allylic substrate **20l** showed an uncontrolled reactivity under these reaction conditions, and a complex mixture was obtained.

On the other hand, an exploratory study of the scope for the corresponding acetate partner was also undertaken, and the preliminary results are summarised in Table II.17.

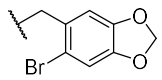
Table II.17: Reaction of different acetates **8** with silyl ether **20e**.



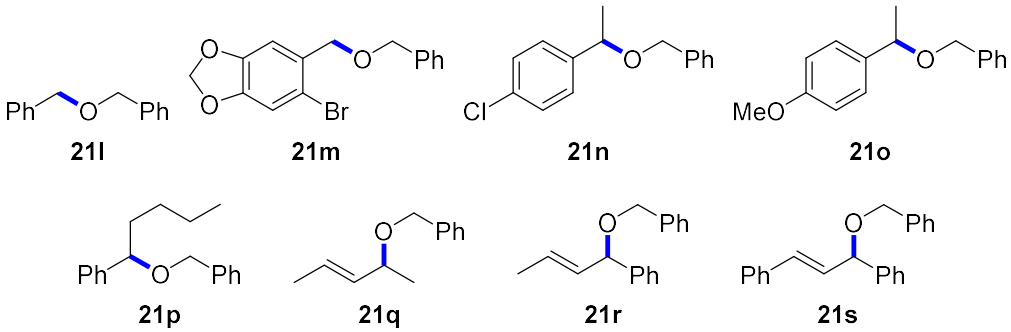
8 (0.5 M) + **20e** (4 equiv) → **21**

Entry	**8** (R^1; R^2)	t	**21** (Yield)[a]
1	**8f** (Ph, H)	2 h	**21l** (-)[c]
2	**8w** (Ar[b], H)	1 h	**21m** (66%)
3	**8x** (*p*-ClC_6H_4, Me)	1 h 40 min	**21n** (83%)
4	**8y** (*p*-$MeOC_6H_4$, Me)	30 min	**21o** (-)[d]
5	**8i** (Ph, Bu)	3 h	**21p** (60%)
6	**8z** (Me, CH=CHMe)	30 min	**21q** (-)[d]
7	**8k** (Ph, CH=Me)	30 min	**21r** (-)[d]
8	**8m** [Ph, (*E*)-CH=CHPh]	30 min	**21s** (-)[d]

[a] Isolated yield.

[b] Ar = 

[c] Silyl ether **20a** was used instead of **20e**. Starting materials were recovered. [d] A complex mixture was obtained.



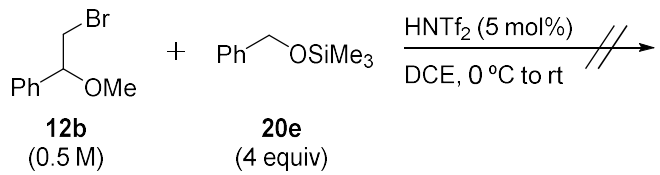
Scheme II.43: Structures of compounds **21l-s** (the new formed bond is marked in blue).

Primary benzylic acetate **8f** failed to react under these conditions. However, a more activated primary benzylic substrate, such as **8w**, was able to afford a good yield of the corresponding ether **21m** (entries 1 and 2).

Benzylic secondary acetate **8x**, despite having a modestly deactivating chlorine atom attached to the *para* position, provided a very good yield of product **21n**. Unfortunately, substrate **8y**, decorated with an electron-donating dioxolane cycle, as well as a bromine atom in *ortho* position, was found too active for these reaction conditions and only a complex mixture of decomposition products was observed. Substrate **8i**, provided with a longer aliphatic chain, performed showing a good reactivity. However, allylic acetates **8z**, **8k**, and **8m** proved to be too reactive for these reaction conditions.

Regarding those cases in which substrates **8** were not able to perform in a controlled manner, it seems clear that a set of milder reaction conditions should be developed in order to apply this strategy to substrates enjoying greater reactivity.

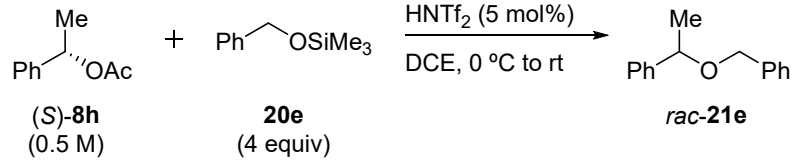
Finally, β-bromoether **12b** was also tested and it proved to be unreactive under these initial standard conditions developed (Scheme II.44).



Scheme II.44: β-Bromoether **12b** failed to form a new C-O bond under these reaction conditions.

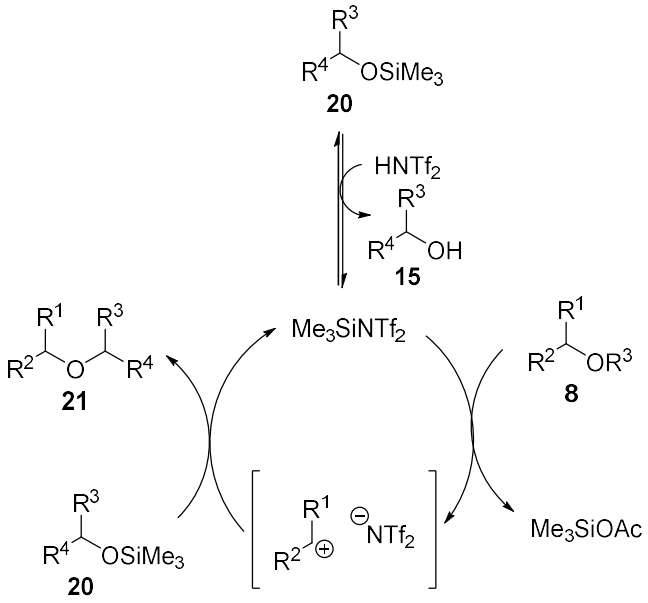
Stereochemical Outcome of the C-O Coupling Developed

Research about the possible cationic nature of the intermediates involved in this transformation was also conducted. Thus, when substrate (*S*)-**8h** reacted with silyl ether **20e**, the corresponding product **21e** was obtained in a racemic form (Scheme II.45).



Scheme II.45: Reaction of **(*S*)-8h** with **20e** to afford racemic product **21e**.

This result supports the possibility of a cationic intermediate being involved in the mechanism of this transformation, which is sketched as tentatively in Scheme II.46. Besides, it suggests the possible development of an enantioselective version in the future.

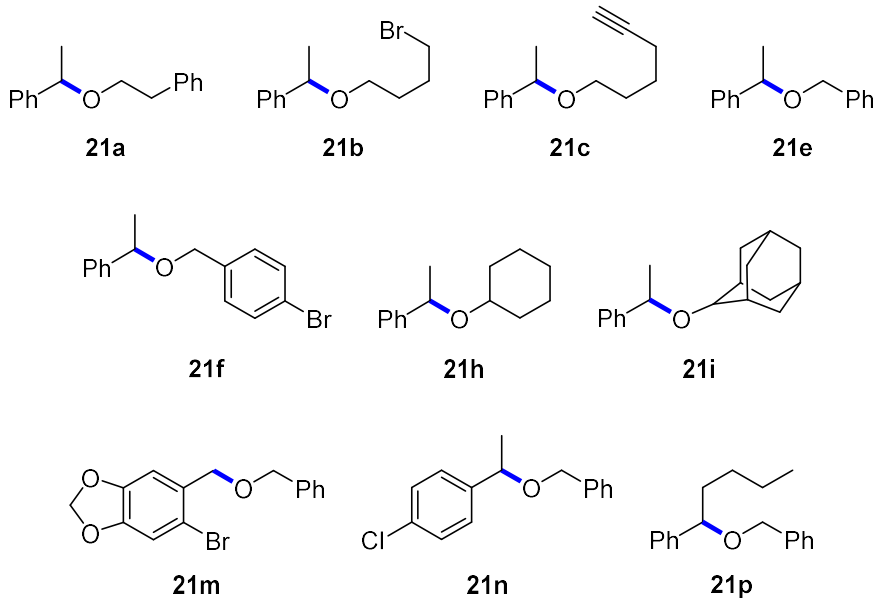


Scheme II.46: Mechanistic hypothesis.

Final Remarks

A first generation of experimental conditions were developed to enable the synthesis of a wide variety of ethers by a catalytic formation of a C-O bond. Benzylic acetates and trimethylsilyl ethers could be coupled in a process catalysed by a Si-based Lewis acid. Simple addition of an acid to trigger the silyl ether affords the generation of the catalytic species in solution, conducting the reaction under very mild conditions. The molecules obtained and the yields accessed are depicted in Scheme II.47.

Further studies are currently in progress, aiming to expand the scope of the process and to eventually access the target molecules in an enantioselective manner.



Scheme II.47: Structures of obtained C-O coupling products **21** (the new formed bond is marked in blue).

Conclusions/Conclusiones

Conclusions

- ✓ In this dissertation, a new synthetic methodology is disclosed. The process is based on the activation of compounds containing a labile silyl moiety towards acid catalysts. As a consequence, this activation process releases another silicon based Lewis acid in the reaction medium, which have been used to promote C-C and C-O bond forming events.

- ✓ Gold(I) complexes and Brønsted acids, such as bistriflimide, have proved to be suitable initiators of this catalytic process, affording a smooth and controlled generation of the silicon based Lewis acid in solution. The direct use of this silicon species has been observed to provide more aggressive conditions and a less predictable outcome in terms of product yield.

- ✓ This strategy has proved to be effective for the activation of alkynylsilanes, allylsilanes, silyl enol ethers and silylethers, which have been used as nucleophiles towards different oxygen containing electrophiles, such as aldehydes, ethers and acetates.

- ✓ This methodology has proved to be suitable for obtaining molecules such as 1,4-diynes, for which only a scarce number of approaches are known, as well as for the development of uncommon coupling reactions, such as the alkynylation of secondary benzylic substrates.

- ✓ A first attempt to achieve an enantioselective coupling reaction through this strategy shows encouraging preliminary results.

- ✓ Furthermore, an unprecedented chemoselectivity has been identified using this synthetic strategy for the alkynylation of benzylic methyl ethers containing a halogen atom at the β-position. The methoxy group acts as a leaving group when activated by the silicon based Lewis acid, and affords the incorporation of an alkynyl moiety to this position, whereas the carbon-halogen bond remains unaltered.

- ✓ Silyl ethers have also succeeded in their role as nucleophiles for this transformation, undergoing a C-O coupling process under mild reaction conditions to obtain benzylic ethers.

Conclusiones

- ✓ En esta memoria se presenta una nueva metodología sintética, basada en la activación de compuestos con restos sililo lábiles frente a catalizadores ácidos. Como consecuencia de este proceso de activación libera en el medio de reacción otro ácido de Lewis derivado de silicio, que ha sido utilizado para iniciar reacciones de formación de enlaces C-C y C-O.

- ✓ Los complejos de oro (I) y los ácidos de Brønsted, como la bistriflimida, han demostrado ser apropiados para iniciar este proceso catalítico, generando en disolución el catalizador ácido de silicio de manera controlada. El uso de esta especie de silicio directamente como catalizador ha llevado a condiciones de reacción más agresivas y resultados menos predecibles en términos de rendimiento del producto.

- ✓ Se ha demostrado que esta estrategia es adecuada para la activación de alquinilsilanos, alilsilanos, silil enol éteres y sililéteres, que han sido utilizados como nucleófilos frente a diferentes electrófilos con grupos oxigenados, como aldehídos, éteres y acetatos.

- ✓ El proceso es adecuado para obtener moléculas como 1,4-diinos, para cuya preparación la metodología existente es escasa, y para el desarrollo de reacciones de acoplamiento poco habituales, como la alquinilación de sustratos bencílicos secundarios.

- ✓ Se ha realizado una primera aproximación al diseño de una reacción de acoplamiento enantioselectiva, con resultados preliminares alentadores.

- ✓ Además, se ha observado una quimioselectividad sin precedentes en la alquinilación de metil bencil éteres con un átomo halógeno en posición β. La activación por el ácido de Lewis de silicio convierte al grupo metoxilo en un buen grupo saliente, y permite la incorporación de un resto alquinilo en esa posición, mientras que el enlace carbono-halógeno permanece inalterado.

- ✓ También se han empleado satisfactoriamente sililéteres como nucleófilos en esta transformación, experimentando un acoplamiento C-O en condiciones de reacción suaves para dar éteres bencílicos como productos.

Part III

Experimental Section

Section Index

Experimental Section

This section collects the experimental details and procedures related to the reactions contained in this work. It includes some general aspects about the working conditions and the analytical techniques employed, as well as the experimental procedures for obtaining some of the starting materials and the final products. Also, a collection of the characterisation data for final compounds is provided. The NMR spectra corresponding to their spectroscopic data are annexed at the end of this book.

General Remarks

Reactions, Solvents and Chromatography

All reactions discussed as results of this work were carried out using oven dried glassware under an atmosphere of nitrogen (99.99%) or argon (99.999%). 1,2-Dichloroethane, pentane and 1,4-dioxane were distilled from CaH_2 and sodium, respectively, prior their use. Acetonitrile, toluene, or THF were purified through an Innovative Technology System, provided with two one metre length columns, filled with activated alumina.

Reactions at room temperature, or with conventional heating were performed in a RR9803012 place Carousel Reaction Station™ from Radleys Discovery Technologies, equipped with gastight threaded caps with a valve, cooling reflux head system, and digital temperature controller. Microwave assisted reactions were carried out in a Biotage Initiator Microwave System apparatus and microwave vials were sealed using reseal septa.

Commercial reagents were purchased with the best quality affordable and used without further purification unless otherwise stated.

TLC was performed on aluminium-backed plates coated with silica gel 60, with F245 indicator, and developed with phosphomolybdic acid, *p*-anisaldehyde or potassium permanganate stains. Column chromatography was carried out on silica gel (230-400 mesh). Solvents used in column chromatography were obtained from commercial suppliers and used without further purification unless otherwise noted.

Data Collection

^{1}H-NMR (300, 400 MHz) and ^{13}C-NMR (75, 100MHz) spectra were measured in $CDCl_3$, at room temperature, on a Bruker DPX-300 MHz, Bruker AV-300 MHz, and Bruker AV-400 MHz apparatus, with $CDCl_3$ (^{1}H-NMR δ = 7.26, ^{13}C-NMR δ = 77.2) as internal standard. Data are reported as follows: chemical shift, multiplicity (s: singlet, brs: broad singlet, d: doublet, t: triplet, q: quartet, dd: double doublet, dt: double triplet, m: multiplet), coupling constants (*J* in Hz) and integration. ^{13}C multiplicities were assigned by DEPT experiments.

High resolution mass spectra (HRMS) were determined by the University of Burgos with a VG AutoSpec M mass spectrometer, the University of Vigo (CACTI) with a Bruker Microflex spectrometer, and the University of Oviedo with a Bruker Impact II spectrometer.

Melting points (m.p.) of solid compounds were measured on a Gallenkamp apparatus and are uncorrected.

Enantiomeric excess data were calculated from data provided by HPLC analysis (Waters 2695 with Photodiode Array V-UV 2996 or 996) and comparison with the corresponding racemic products. Chiracel OD-H and Chiracel ADH columns with chiral filling (250 x 4.6 mm) were employed.

Experimental Remarks for Bis-Alkynylation Reactions of Aromatic Aldehydes

1. Starting Materials

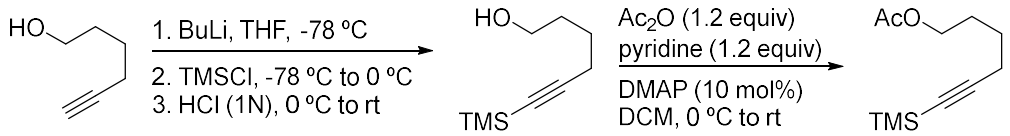
Aldehydes 1

Aldehydes **1** were obtained from commercial suppliers and purified as follows: 20mmol of the aldehyde **1** was solved in 50 mL of diethyl ether and this mixture was washed three times with 20 mL portions of aqueous saturated sodium hydrogen carbonate solution, the organic and aqueous layers were separated, the organic layer was dried over sodium sulfate, and diethyl ether was evaporated under reduced pressure. Liquid aldehydes were also subsequently distilled.

Aldehyde **1m** was obtained by tosylation of indole-3-carboxaldehyde following procedures described in the literature.[164]

Alkynylsilanes 2

Alkynylsilanes **2a** and **2b** were obtained from commercial suppliers and distilled prior their use. Alkynylsilanes **2c** and **2d** were prepared by a Sonogashira coupling of the corresponding aryl iodide and trimethylsilylacetylene.[165] **2g** were obtained from the corresponding terminal alkyne **2p** containing a hydroxyl group, by protection with trimethylsilyl chloride in both the alkyne and the alcohol moieties, cleavage of the O-Si bond formed, and subsequent acetylation of the alcohol (Scheme III.1).[166]

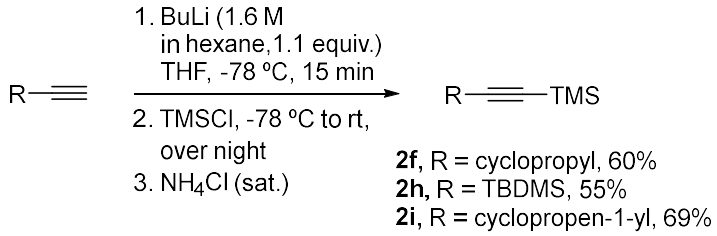


Scheme III.1: Synthetic pathway for the preparation of alkynylsilane **2g**.

[164] M. Carmen de la Fuente, D. Domínguez, *Tetrahedron* **2011**, *67*, 3997–4001.
[165] Sakai, N.; Komatsu, R.; Uchida, N.; Ikeda, R.; Konakahara, T. *Org. Lett.* **2010**, *12*, 1300-1303.
[166] Srihari, P.; Sridhar, Y. *Eur. J. Org. Chem.* **2011**, *2011*, 6690-6697.

Alkynylsilanes **2f**, **2h** and **2i** were prepared according to the following procedure (Scheme III.2):

General procedure for the synthesis of alkynylsilanes **2f**, **2h** *and* **2i**

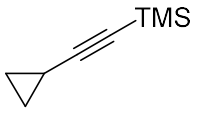


Scheme III.2: Procedure for the preparation of alkynylsilanes **2f**, **2h** and **2i**.

30 mmol (1 equiv) of the corresponding terminal acetylene were solved in 10 mL of THF. The solution was cooled to -78 ºC, and 19.1 mL (30.6 mmol, 1.02 equiv) of 1.6 M BuLi solution in hexanes were added. After stirring at -78 ºC for 15 minutes, 3.9 mL of chlorotrimethylsilane (30.6 mmol, 1.02 equiv) were added. The reaction mixture was allowed to slowly warm from -78 ºC to room temperature and kept stirring overnight. The crude reaction mixture was quenched with 10 mL of NH_4Cl aqueous saturated solution and diluted with 10 mL of hexane. Both aqueous and organic layers were separated. The aqueous layer was extracted with hexane (2 x 5 mL), the organic phases were combined, washed with water (4 x 10 mL) and brine (2 x 10 mL) and dried over anhydrous sodium sulphate. The isolated product was purified by column chromatography (silica gel, hexanes) and obtained as a colourless liquid. Yields are indicated in Scheme III.2.

Spectroscopic data of compounds **2f** *and* **2h**[167]

2f: (cyclopropylethynyl)trimethylsilane



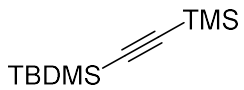
Appearance: Colourless liquid

Yield: 60%

[167] For spectroscopic data of compound **2i** see R. J. Rahaim, J. T. Shaw, *J. Org. Chem.* **2008**, *73*, 2912–2915.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 1.30-1.21 (m, 1H), 0.79-0.67 (m, 4H), 0.12 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 110.3 (C), 79.6 (C), 8.7 (CH_2), 0.4 (CH), 0.2 (CH_3).

2h: *tert*-butyldimethyl((trimethylsilyl)ethynyl)silane



Appearance: Colourless liquid

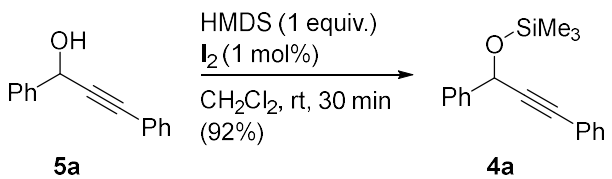
Yield: 55% (colourless liquid)

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 1.30-1.21 (m, 1H), 0.79-0.67 (m, 4H), 0.12 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 110.3 (C), 79.6 (C), 8.7 (CH_2), 0.4 (CH), 0.2 (CH_3).

Propargylic Silyl Ethers 4

Compound **4** were synthesised in a two-step pathway. First, alkynylation of the corresponding aldehyde **1**, and second, silylation of the resulting propargylic alcohol **5**.[168] The synthetic procedure of **4a** is shown as a representative example, and the rest of the ethers were prepared in an analogous fashion.

General procedure for the preparation of compound **4a**

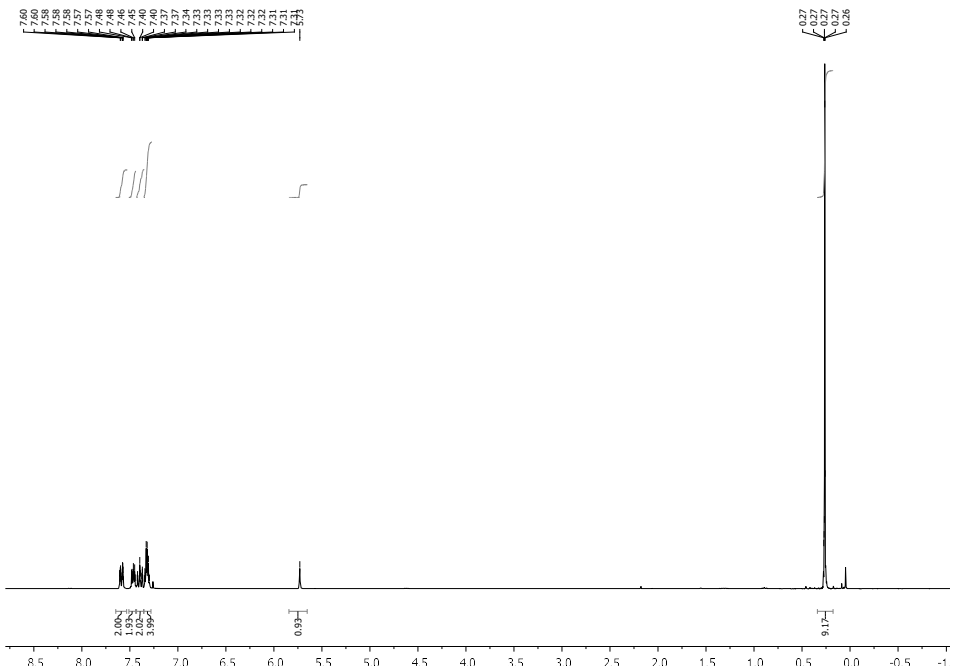


5a **4a**

Scheme III.3: Silylation of compound **4a**.

[168] **5a** was prepared according to a) W. Yan, Q. Wang, Y. Chen, J. L. Petersen, X. Shi, *Org. Lett.* **2010**, *12*, 3308–3311. For spectroscopy data see b) H. A. Stefani, R. Cella, F. A. Dörr, C. M. P. de Pereira, F. P. Gomes, G. Zeni, *Tetrahedron Lett.* **2005**, *46*, 2001–2003.

Under a nitrogen atmosphere, 4.165 g of 1,3-diphenyl-2-propyn-1-ol (**5a**) (20 mmol, 1 equiv) and 50.7 mg of iodine (0.2 mmol, 0.01 equiv) were solved in 80 mL of CH_2Cl_2, and the mixture was cooled to 0 ºC. A solution of 4.2 mL of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (20 mmol, 1 equiv) in 20 mL of CH_2Cl_2 was added dropwise during 5 minutes, and the mixture was allowed to slowly warm up to room temperature. After stirring for 30 minutes at room temperature, 0.248 g of sodium thiosulfate (1.0 mmol, 0.05 equiv) were added. The reaction mixture was filtered through a path of Celite®, then washed with water and dried over anhydrous sodium sulphate. Dichloromethane was eliminated at reduced pressure, and 5.160 g of **4a** (18.4 mmol, 92%) were obtained as a pale yellow oil, and it was used without further purification (see Scheme III.4).[169] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ (ppm) = 7.63-7.54 (m, 2H), 7.51-7.43 (m, 2H), 7.43-7.36 (m, 2H) 7.35-7.27 (m, 4H), 5.73 (s, 1H), 0.27 (s, 9H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ (ppm) = 141.4 (C), 131.6 (CH), 128.45 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 126.5 (CH), 122.8 (C), 89.7 (C), 86.0 (C), 65.2 (CH), 0.4 (CH_3).



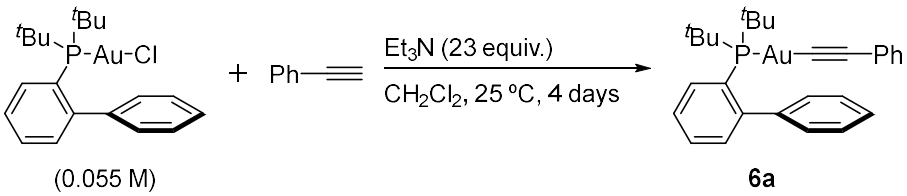
Scheme III.4: ^{1}H-NMR spectrum of crude product **4a**.

[169] The ^{1}H-NMR spectrum of the crude product seemed clean and it was observed that distillation under reduced pressure led to partial decomposition of compound **4a** being the decomposition products also separated along with the desired product, thus contaminating it.

Gold(I) Complexes

Gold complexes 1,3-bis(2,6-di-isopropylphenyl)imidazol-2-ylidenegold(I) chloride (IPrAuCl), [170] $IPrAuNTf_2$, [171] $Ph_3PAuNTf_2$, [172] di-*tert*-butyl-(*o*-biphenyl)-phosphinegold(I) bis(trifluoromethanesulfonimidate) ((JohnPhos)$AuNTf_2$),[173] and (2,4-di-*tert*-butylphenyl)phosphite gold(I) bis(trifluoromethanesulfonimidate)[100a] were prepared according to well-known procedures previously described in the literature.

Synthesis of gold acetylide **6a**

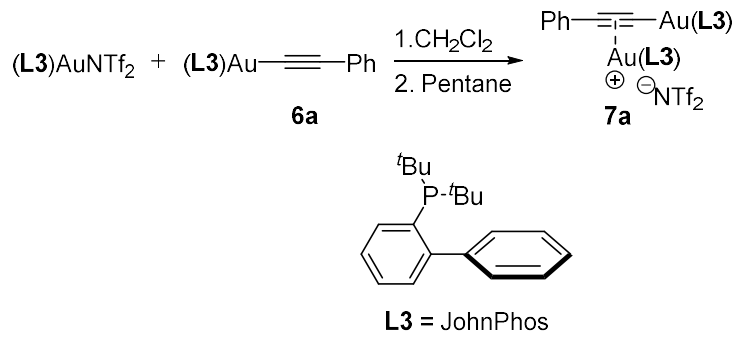


Scheme III.5: Preparation of gold acetylide **6a**.

The followed procedure was adapted from the one described by S. Hashmi and co-workers.[174] Under a nitrogen atmosphere, (2-biphenyl)di-*tert*-butylphosphine gold(I) chloride (0.531 g, 1.0 mmol, 1 equiv) was added to a solution of phenyl acetylene (220 µL, 2 mmol, 2 equiv) in a mixture of CH_2Cl_2 (18 mL) and triethylamine (3.2 mL). After stirring for 4 days at 25 °C, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (neutral alumina, hexanes/ethyl acetate/ Et_3N = 5:1:0.1). The white solid obtained was recrystallized from a saturated solution in CH_2Cl_2 by the addition of hexane. 0.425 g (0.71 mmol, 71%) of the gold(I)-acetylide **6a** were obtained as colourless crystals.

[170] P. de Frémont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 2411–2418.
[171] L. Ricard, F. Gagosz, *Organometallics* **2007**, *26*, 4704–4707.
[172] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136.
[173] C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179
[174] For the original procedure see ref. 96a. For spectral data see ref. 96b.

Synthesis of σ,π-digold phenylacetylene adduct **7a**

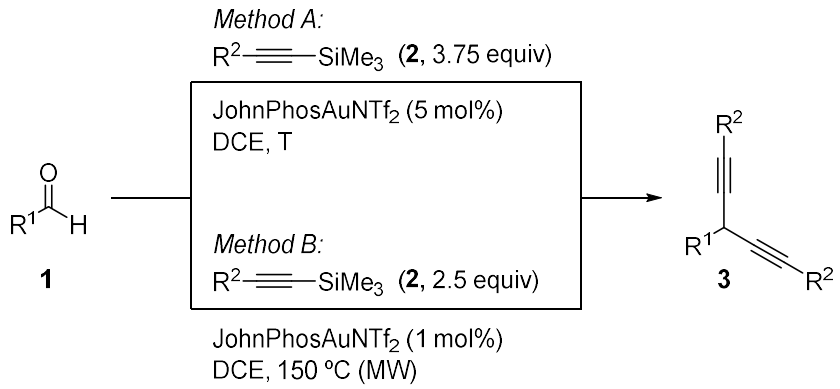


Scheme III.6: Preparation of complex **7a**.

An equimolar mixture (0.1 mmol) of JohnPhosAuNTf$_2$ and **6a** was solved in 1 mL of dichloromethane and stirred for 15 minutes. Then, 3 mL of pentane were added to afford 0.128 g of **7a** (0.093 mmol, 93%) as colourless crystals.

2. 1,4-Diynes 3

General Procedures for the Bis-Alkynylation of Aromatic Aldehydes



Scheme III.7: General conditions for methods A and B.

Method A: Conventional heating reactions

Under an argon atmosphere, 15.5 mg of JohnPhosAuNTf$_2$ (0.02 mmol, 0.05 equiv) were solved in 0.8 mL of 1,2-dichloroethane at room temperature. Then, 1.5 mmol of the corresponding alkynylsilane **2** (3.75 equiv) and 0.4 mmol (1 equiv) of the corresponding aldehyde **1** were added. The mixture was heated at the temperature and during the time indicated in Table I.5 (p. 97). The reaction mixture was cooled to room temperature and 0.4 mL of toluene were added. 1,2-Dichloroethane was eliminated at reduced pressure, and the product contained in the remaining toluene solution was purified by flash chromathography (hexanes) using a short path of silica gel, recovering firstly the excess of alkynylsilane, and secondly the desired product **3** in the yields indicated in Table I.5.

Method B: Microwave assisted reactions

Under an argon atmosphere, 3.1 mg of JohnPhosAuNTf$_2$ (0.004 mmol, 0.01 equiv) were place in a microwave vial and solved in 0.8 mL of 1,2-dichloroethane at room temperature. Then, 1 mmol of the corresponding alkynylsilane **2** (2.5 equiv) and 0.4 mmol of the corresponding aldehyde **1** were added. The mixture was heated at the temperature and during the time indicated in Table I.5 (p. 97). Afterwards, the reaction mixture was cooled to room temperature and 0.4 mL of toluene were added. 1,2-Dichloroethane was eliminated at reduced pressure, and the product contained in the remaining toluene solution was purified by flash chromatography (hexanes) using a short path of silica gel, recovering firstly the excess of alkynylsilane, and secondly the desired product **3** in the yields indicated in Table I.5.

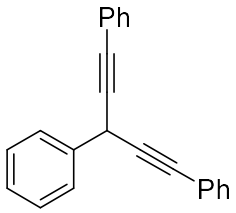
Gram-scale preparation of **3c**

Under an argon atmosphere, 46.5 mg of JohnPhosAuNTf$_2$ (0.06 mmol, 0.01 equiv) were place in a microwave vial and solved in 12 mL of 1,2-dichloroethane at room temperature. Then, 3 mL of alkynylsilane **2a** (15 mmol, 2.5 equiv) and 0.7 mL of aldehyde **1c** (6 mmol, 1 equiv) were added. The mixture was heated at 150 ºC for 15 minutes. Afterwards, the reaction mixture was cooled to room temperature and 5 mL of toluene were added. 1,2-Dichloroethane was eliminated at reduced pressure, and the product contained in the remaining toluene solution was purified by column chromatography

(silica gel, hexanes/dichloromethane 20:1) recovering firstly the excess of alkynylsilane, and secondly 1.20 g of the desired product **3c** (65%).

1,4-Diyne **3** *Characterisation Data*

3a: penta-1,4-diyne-1,3,5-triyltribenzene



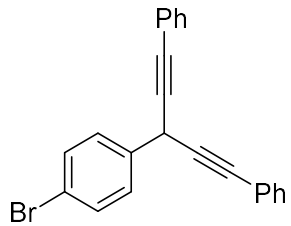
Appearance: Yellow oil

Yield: 86% (method A), 70% (method B).

HRMS calcd. for $C_{23}H_{16}$: 292.1252
HRMS (EI) found: 292.1255

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.76 -7.69 (m, 2H), 7.56-7.49 (m, 4H), 7.48-7.40 (m, 2H), 7.39-7.30 (m, 7H), 5.25 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 138.0 (C), 131.9 (CH), 128.8 (CH), 128.35 (CH), 128.3 (CH), 127,6 (CH), 127.4 (CH), 123.0 (C), 86.7 (C), 82.9 (C), 30.2 (CH).

3b: (3-(4-bromophenyl)penta-1,4-diyne-1,5-diyl)dibenzene



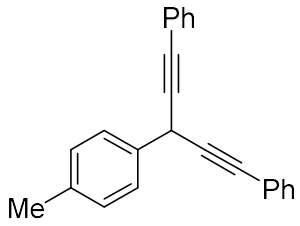
Appearance: Yellow oil

Yield: 72% (method A), 42% (method B).

HRMS calcd. for $C_{23}H_{15}{}^{79}Br$: 370.0357
HRMS (EI) found: 370.0356

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.61-7.46 (m, 8H), 7.36-7.29 (m, 6H), 5.18 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 137.1 (C), 131.8 (CH), 129.1 (CH), 128.5 (CH), 128.3 (CH), 122.7 (C), 121.6 (C), 86.0 (C), 83.2 (C), 29.7 (CH).

3c: (3-(p-tolyl)penta-1,4-diyne-1,5-diyl)dibenzene



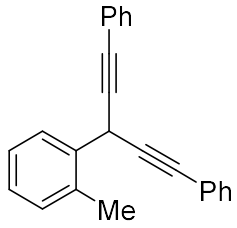
Appearance: Pale yellow solid
m.p. = 85-87 ºC (decomp.)

Yield: 65% (method A), 73% (method B).

HRMS calcd. for $C_{24}H_{18}$: 306.1409
HRMS (EI) found: 306.1407

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.58 (d, *J* = 8.0 Hz, 2H), 7.51-7.45 (m, 4H), 7.35-7.28 (m, 6H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.19 (s, 1H), 2.38 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 137.2 (C), 135.1 (C), 131.8 (CH), 129.4 (CH), 128.2 (CH), 127.2 (CH), 123.1 (C), 86.9 (C), 82.6 (C), 29.8 (CH), 21.1 (CH_3).

3d: (3-(o-tolyl)penta-1,4-diyne-1,5-diyl)dibenzene



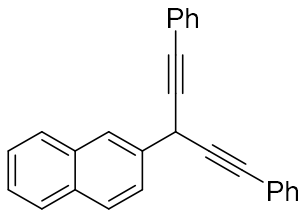
Appearance: Pale yellow solid
m.p. = 86-87 ºC (decomp.)

Yield: 77% (method A), 74% (method B).

HRMS calcd. for $C_{24}H_{18}$: 306.1409
HRMS (EI) found: 306.1415

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.82-7.72 (m, 1H), 7.52-7.42 (m, 4H), 7.39-7.12 (m, 9H), 5.23 (s, 1H), 2,57 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 136.2 (C), 135.9 (C), 131.8 (CH), 130.9 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 126.6 (CH), 123.1 (C), 86.4 (C), 82.5 (C), 28.3 (CH), 19.4 (CH_3).

3e: 2-(1,5-diphenylpenta-1,4-diyn-3-yl)naphthalene



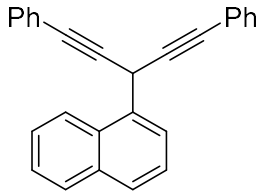
Appearance: Pale yellow solid
m.p. = 97-99 ºC (decomp.)

Yield: 60% (method A), 50% (method B).

HRMS calcd. for $C_{27}H_{18}$: 342.1409
HRMS (EI) found: 342.1406

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 8.21 (s, 1H), 8.02-7.83 (m, 4H), 7.65-7.51 (m, 6H), 7.44-7.34 (m, 6H), 5.46 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 135.8 (C), 133.9 (C), 133.3 (C), 132.3 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 126.8 (CH), 126.6 (CH), 126.3 (CH), 126.1 (CH), 123.4 (C), 87.1 (C), 83.6 (C), 30.8 (CH).

3f: 1-(1,5-diphenylpenta-1,4-diyn-3-yl)naphthalene



Appearance: Pale yellow solid
m.p. = 107-109 ºC (decomp.)

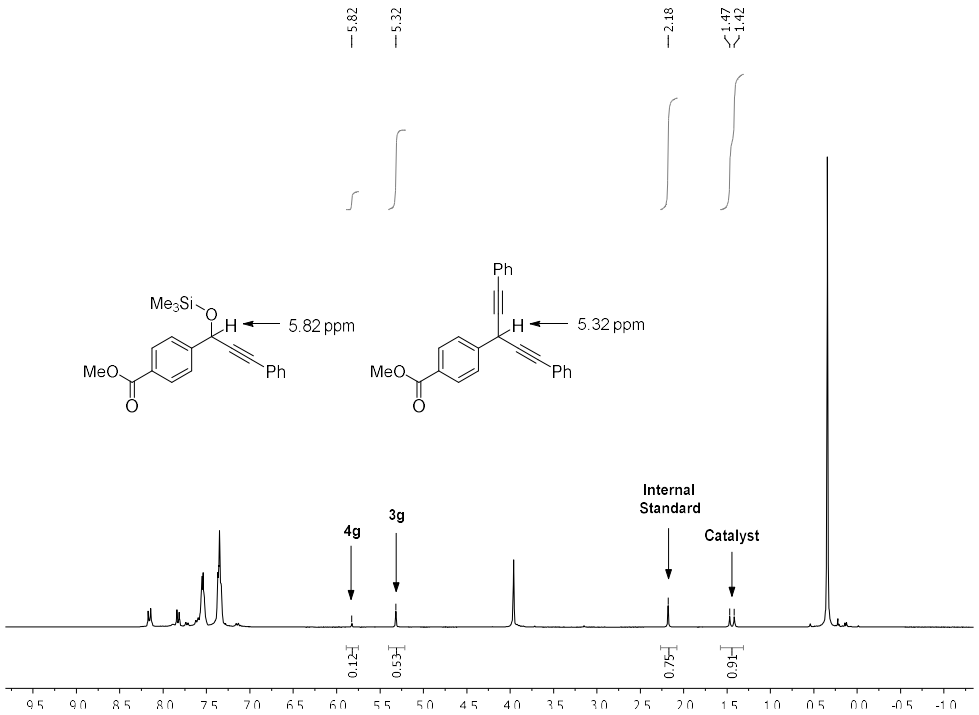
Yield: 58% (method A)

HRMS calcd. for $C_{27}H_{18}$: 342.1409
HRMS (EI) found: 342.1403

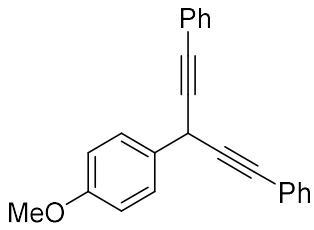
^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 8.47 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.61-7.47 (m, 6H), 7.39-7.28 (m, 6H), 5.82 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 134.2 (C), 133.5 (C), 131.9 (CH), 130.7 (C), 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 126.4 (CH), 125.9 (CH), 125.6 (CH), 125.4 (CH), 124.0 (CH), 123.0 (C), 86.6 (C), 83.4 (C), 28.3 (CH).

3g: methyl 4-(1,5-diphenylpenta-1,4-diyn-3-yl)benzoate

Conversion > 95%. Estimated yield with internal standard (acetanilide, 13.5 mg, 0.1 mmol, 0.25 equiv): 53% **3g**, 12% **4g**. The ^{1}H-NMR spectrum shows representative signals of both **4g** and **3g** products in the crude reaction, along with the internal standard, whose methyl group signal was used as reference (2.18 ppm). It is also possible to see the *tert*-butyl group signals of the catalyst at 1.47 and 1.42 ppm.



3h: (3-(4-methoxyphenyl)penta-1,4-diyne-1,5-diyl)dibenzene



Appearance: Pale yellow solid

m.p. = 84– 86 ºC (decomp.)

Yield: 66% (method A), 67% (method B).

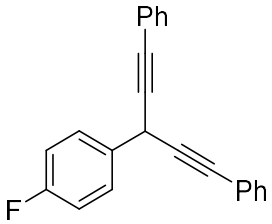
HRMS calcd. for $C_{24}H_{18}O$: 322.1358

HRMS (EI) found: 322.1358

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.59 (d, *J* = 8.5 Hz, 2H), 7.53-7.43 (m, 4H), 7.37-7.27 (m, 6H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.17 (s, 1H), 3.83 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 159.0 (C), 131.8 (CH), 130.1 (C), 128.4 (CH), 128.2 (CH), 123.0 (C), 114.1 (CH), 86.9 (C), 82.6 (C), 55.4 (CH_3), 29.3 (CH).

3i: (3-(4-fluorophenyl)penta-1,4-diyne-1,5-diyl)dibenzene



Appearance: Yellow oil

Yield: 77% (method A)

HRMS calcd. for $C_{23}H_{15}F$: 310.1158

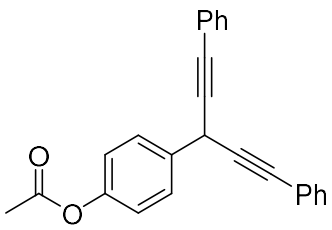
HRMS (EI) found: 310.1157

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.75-7.64 (m, 2H), 7.60-7.47 (m, 4H), 7.43-7.29 (m, 6H), 7.21-7.07 (m, 2H), 5.24 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 162.6 (d, $J_{1, C\text{-}F}$ = 245.7 Hz, C), 134.2 (d, $J_{4, C\text{-}F}$ = 2.8 Hz, C), 132.2 (CH), 129.4 (d, $J_{3, C\text{-}F}$ = 8.1 Hz, CH), 128.8 (CH), 128.7 (CH), 123.2 (C), 116.0 (d, $J_{2, C\text{-}F}$ = 21.6 Hz, CH), 86.8 (C), 83.5 (C), 29.9 (CH).

^{19}F-NMR (282 MHz, $CDCl_3$, 25 ºC) δ (ppm) -115.0.

3j: 4-(1,5-diphenylpenta-1,4-diyn-3-yl)phenyl acetate



Appearance: Pale yellow solid

m.p. = 93-95 ºC (decomp.)

Yield: 77% (method A)

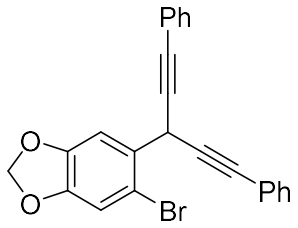
HRMS calcd. for $C_{25}H_{18}O_2$: 350.1307

HRMS (EI) found: 350.1303

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.69 (d, J = 8.5 Hz, 2H), 7.55-7.43 (m, 4H), 7.38-7.28 (m, 6H), 7.12 (d, J = 8.6 Hz, 2H), 5.20 (s, 1H), 2.31 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 169.9 (C), 150.4 (C), 135.9(C), 132.3 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 123.2 (C), 122.3 (CH), 86.7 (C), 83.4 (C), 30.0 (CH), 21.6 (CH_3).

3k: 5-bromo-6-(1,5-diphenylpenta-1,4-diyn-3-yl)benzo[d][1,3]dioxole



Appearance: Pale yellow solid

m.p. = 132-134 ºC (decomp.)

Yield: 73% (method A)

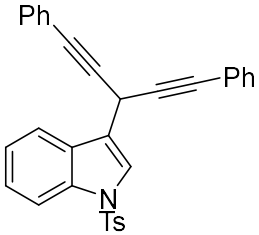
HRMS calcd. for $C_{24}H_{15}O_2{}^{79}Br$: 414.0255

HRMS (EI) found: 414.0259

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.54-7.46 (m, 4H), 7.45 (s, 1H), 7.36-7.28 (m, 6H), 7.05 (s, 1H), 6.00 (s, 2H), 5.48 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 148.0 (C), 147.8 (C), 131.9 (CH), 130.9 (C), 128.4 (CH), 128.2 (CH), 122.8 (C), 113.6 (C), 112.8 (CH), 109.3 (CH), 102.0 (CH_2), 87.0 (C), 82.6 (C), 30.6 (CH).

3l: 3-(1,5-diphenylpenta-1,4-diyn-3-yl)-1-tosyl-1H-indole



Appearance: Orange oil

Yield: 45% (method A)

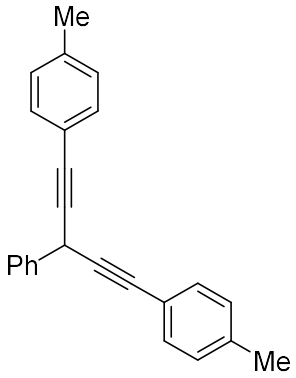
HRMS calcd. for $C_{32}H_{23}NO_2S$: 485.1450

HRMS (EI) found: 485.1438

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 8.02 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.85-7.76 (m, 3H), 7.54-7.43 (m, 4H), 7.42-7.17 (m, 10H), 5.33 (s, 1H), 2.34 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 145.0 (C), 135.6 (C), 135.3 (C), 131.9 (CH), 130.0 (CH), 128.8 (C), 128.5 (CH), 128.3 (CH), 127.0 (CH), 125.0 (CH), 123.8 (CH), 123.3 (CH), 122.7 (C), 120.2 (CH), 119.4 (C), 113.8 (CH), 84.9 (C), 82.4 (C), 22.3 (CH), 21.6 (CH_3).

3m: 4,4'-(3-phenylpenta-1,4-diyne-1,5-diyl)bis(methylbenzene)



Appearance: Yellow oil

Yield: 57% (method A), 40% (method B).

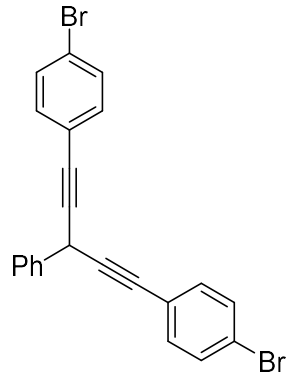
HRMS calcd. for $C_{25}H_{20}$: 320.1565

HRMS (EI) found: 320.1565

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.76-7.67 (m, 2H), 7.48-7.38 (m, 6H), 7.38-7.30 (m, 1H), 7.18 (d, 4H), 5.23 (s, 1H), 2.37 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 138.3 (C), 131.7 (CH), 129.0 (CH), 128.7 (CH), 127.4 (CH), 127.3 (CH), 120.0 (C), 86.0 (C), 82.9 (C), 30.1 (CH), 21.5 (CH_3).

3n: 4,4'-(3-phenylpenta-1,4-diyne-1,5-diyl)bis(bromobenzene)



Appearance: Yellow oil

Yield: 65% (method A), 37% (method B).

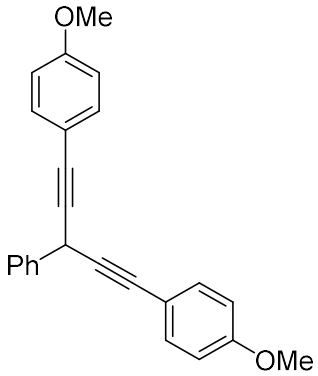
HRMS calcd. for $C_{23}H_{14}{}^{79}Br_2$: 447.9462

HRMS (EI) found: 447.9455

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.69-7.62 (m, 2H), 7.49-7.39 (m, 6H), 7.38-7.30 (m, 5H), 5.19 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 137.5 (C), 133.3 (CH), 131.5 (CH), 128.9 (CH), 127.8 (CH), 127.3 (CH), 122.6 (C), 121.8 (C), 87.5 (C), 82.0 (C), 30.2 (CH).

3o: 4,4'-(3-phenylpenta-1,4-diyne-1,5-diyl)bis(methoxybenzene)



Appearance: Yellow oil

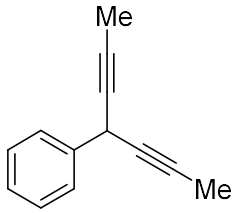
Yield: 50% (method B)

HRMS calcd. for $C_{25}H_{20}O_2$: 352.1463
HRMS (EI) found: 352.1480

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.70 (d, *J* = 7.9 Hz, 2H), 7.49-7.37 (m, 6H), 7.37-7.29 (m, 1H), 6.90-6.80 (m, 4H), 5.21 (s, 1H), 3.81 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 160.0 (C), 138.8 (C), 133.6 (CH), 129.1 (CH), 127.8 (CH), 127.7 (CH), 115.6 (C), 114.3 (CH), 85.8 (C), 83.0 (C), 55.7 (CH_3), 30.5 (CH).

3p: hepta-2,5-diyn-4-ylbenzene



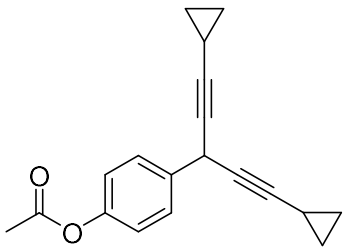
Appearance: Yellow oil

Yield: 30% (method B)

HRMS calcd. for $C_{13}H_{12}$: 168.0939
HRMS (EI) found: 168.0937

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.60-7.51 (m, 2H), 7.44-7.33 (m, 2H), 7.33-7.25 (m, 1H), 4.74-4.65 (m, 1H), 1.89 (d, *J* = 2.6 Hz, 6H)
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 139.1 (C), 128.5 (CH), 127.2 (CH), 127.1 (CH), 78.2 (C), 77.0 (C), 28.9 (CH), 3.7 (CH_3).

3q: 4-(1,5-dicyclopropylpenta-1,4-diyn-3-yl)phenyl acetate



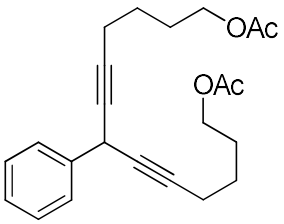
Appearance: Yellow oil

Yield: 31% (method B)

HRMS calcd. for $C_{19}H_{18}O_2$: 278.1307
HRMS (EI) found: 278.1311

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.49 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 4.63 (s, 1H), 2.29 (s, 3H), 1.34-1.19 (m, 2H), 0.80-0.59 (m, 8H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 169.5 (C), 149.6 (C), 136.6 (C), 128.2 (CH), 121.4 (CH), 85.8 (C), 72.8 (C), 28.4 (CH), 21.1 (CH_3), 8.1 (CH_2), -0.4 (CH).

3r: 7-phenyltrideca-5,8-diyne-1,13-diyl diacetate



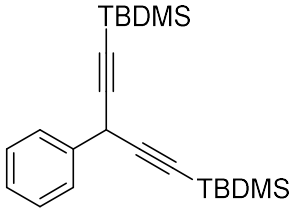
Appearance: Pale yellow oil

Yield: 25% (method B)

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.51 (d, *J* = 6 Hz, 2H), 7.43-7.20 (m, 3H), 4.70 (s, 1H), 4.07 (t, *J* = 6.4 Hz, 4H), 2.36-2.21 (m, 4H), 2.04 (s, 6H), 1.83-1.51 (m, 8H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 171.5 (C), 139.4 (C), 128.9 (CH), 127.6 (CH), 127.5 (CH), 82.4 (C), 78.8 (C), 64.4 (CH_2), 29.3 (CH), 28.2 (CH_2), 25.6 (CH_2), 21.4 (CH_3), 18.9 (CH_2).

3s: (3-phenylpenta-1,4-diyne-1,5-diyl)bis(tert-butyldimethylsilane)



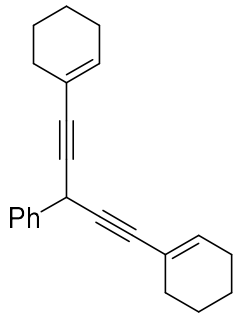
Appearance: Yellow oil

Yield: 39% (method B)

HRMS calcd. for $C_{23}H_{36}Si_2$: 368.2356
HRMS (EI) found: 368.2353

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.59 (d, *J* = 7.2 Hz, 2H), 7.45-7.25 (m, 3H), 4.84 (s, 1H), 0.99 (s, 18H), 0.16 (s, 12H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 137.4 (C), 128.5 (CH), 127.3 (CH), 127.2 (CH), 103.2 (C), 85.5 (C), 30.8 (CH), 26.1 (CH_3), 16.8 (C), 4.7 (CH_3).

3t: 1,1'-(3-phenylpenta-1,4-diyne-1,5-diyl)dicyclohex-1-ene



Appearance: Yellow oil

Yield: 35% (method A)

HRMS calcd. for $C_{23}H_{24}$: 300.1875

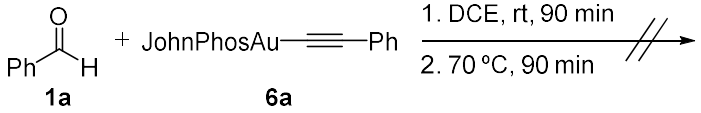
HRMS (EI) found: 300.1878

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.58 (d, *J* = 7.5 Hz, 1H), 7.43-7.23 (m, 3H), 6.14 (s, 2H), 4.99 (s, 1H), 2.31-1.96 (m, 8H), 1.79-1.46 (m, 8H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 38.89 (C), 134.94 (CH), 128.69 (CH), 127.35 (CH), 120.64 (C), 84.43 (C), 84.32 (C), 29.98 (CH), 29.39 (CH_2), 25.78 (CH_2), 22.49 (CH_2), 21.71 (CH_2).

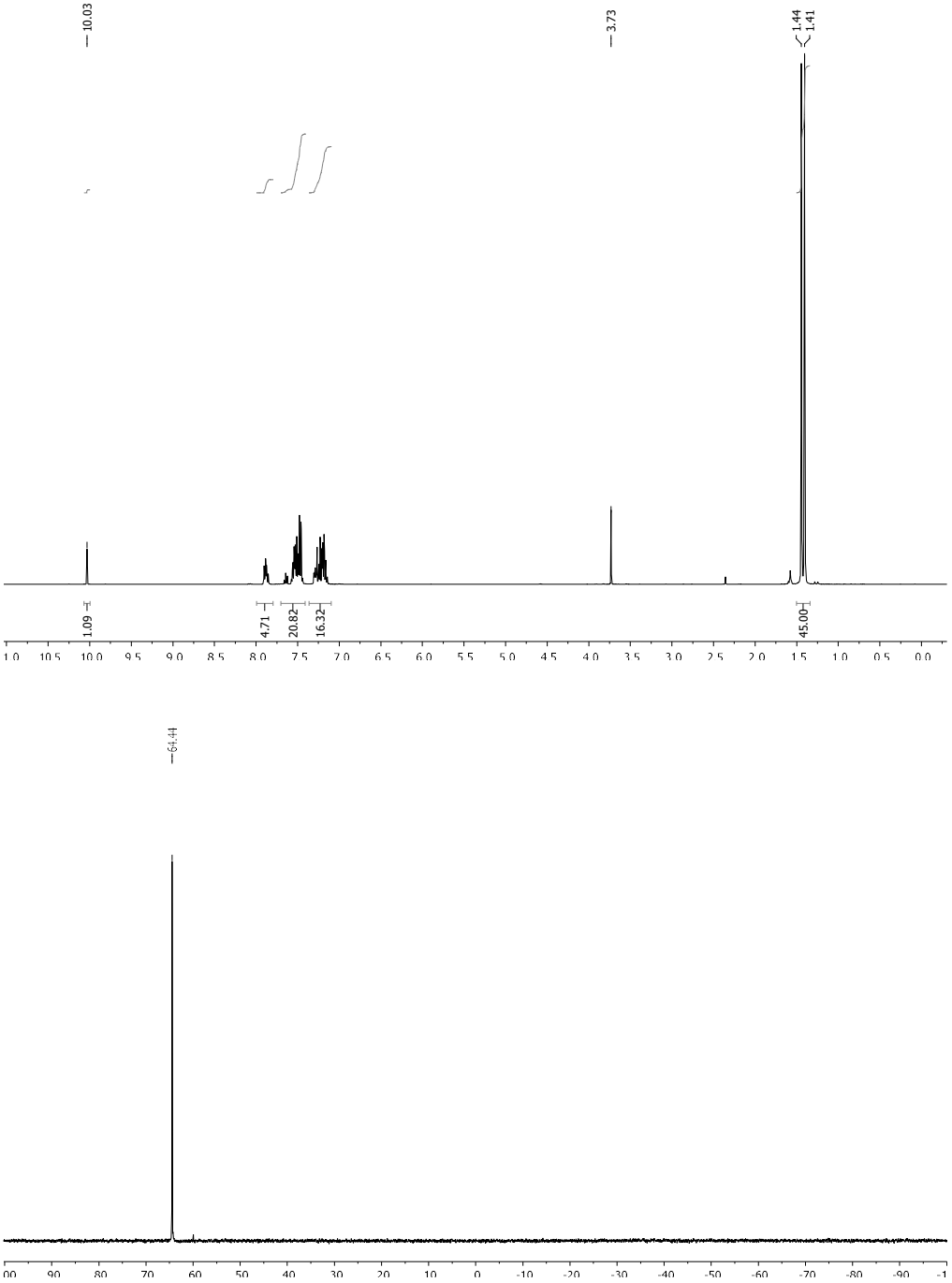
3. Mechanistic Studies

Procedure for the Reaction of Gold(I) Acetylide* 6a *with Aldehyde* 1a *in Absence of Me_3SiNTf_2



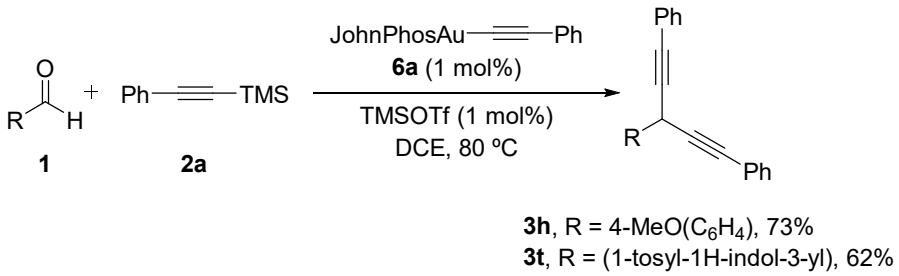
Scheme III.8: Conditions for the reaction between **1a** and **6a**.

A mixture of **1a** (2 μL, 0.018 mmol, 1 equiv) and **6a** (26.9 mg, 0.045 mmol, 2.5 equiv) in 1,2-dichloroethane (0.4 mL) was stirred for 90 minutes. The reaction was followed by TLC analysis and no change was observed. Subsequently, it was heated at 70 ºC for 90 minutes with the same result. ^{1}H-NMR and ^{31}P-NMR spectra of the crude reaction are shown below.



Scheme III.9: ^{1}H-NMR and ^{31}P-NMR spectra of the crude reaction of **1a** with **6a**, respectively.

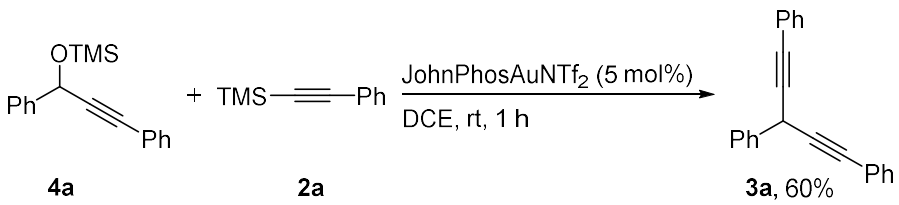
Reaction of Aromatic Aldehydes with* 2a *Using Gold(I)-Acetylide* 6a *and TMSOTf as Catalysts.



Scheme III.10: Reaction of aldehydes **1** with **2a** using **6a** and TMSOTf as catalysts.

Under an argon atmosphere, 2.4 mg of **6a** (0.004 mmol, 0.01 equiv) were solved in 0.7 mL of 1,2-dichloroethane at room temperature. Subsequently, 198 μL of **2a** (1 mmol, 2.5 equiv), 0.4 mmol of the corresponding aldehyde **1** (1 equiv) and 0.1 mL of a 0.04 M 1,2-dichloroethane solution of TMSOTf (0.01 equiv) were added in this order. The mixture was heated at 80 ºC during the time indicated in Scheme I.46 (p. 100). Afterwards, the reaction mixture was cooled to room temperature and 0.4 mL of toluene were added. 1,2-Dichloroethane was eliminated at reduced pressure, and the product contained in the remaining toluene solution was purified by flash chromatography (hexane) using a short path of silica gel, recovering firstly the excess of alkynylsilane, and secondly the desired product **3**. Product **3h** was obtained in 73% yield (66% by method A, see Table I.5) and product **3t** in 62% yield (45% by method A).

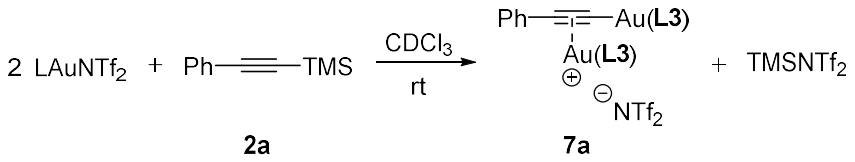
Alkynylation of Propargylic Silyl Ether* 4a *(see Scheme I.47, p. 101).



Scheme III.11: Alkynylation of propargyl silyl ether **4a**.

Under an argon atmosphere, 15.5 mg of JohnPhosAuNTf$_2$ were solved in 0.8 mL of 1,2-dichloroethane. Then 300 μL of **2a** (1.5 mmol, 3.75 equiv) and 11.2 mg of **4a** (0.4 mmol, 1 equiv) were added. After stirring at room temperature for 1 hour, 0.4 mL of toluene were added. 1,2-Dichloroethane was eliminated at reduced pressure, and the product contained in the remaining toluene solution was purified by flash chromatography (hexane) using a short path of silica gel, recovering firstly the excess of alkynylsilane, and secondly the desired product **3a** in 60% yield.

***Activation of Alkynylsilane* 2a *by JohnPhosAuNTf$_2$ with Formation of σ,π-digold Phenylacetylene Adduct* 7a.**

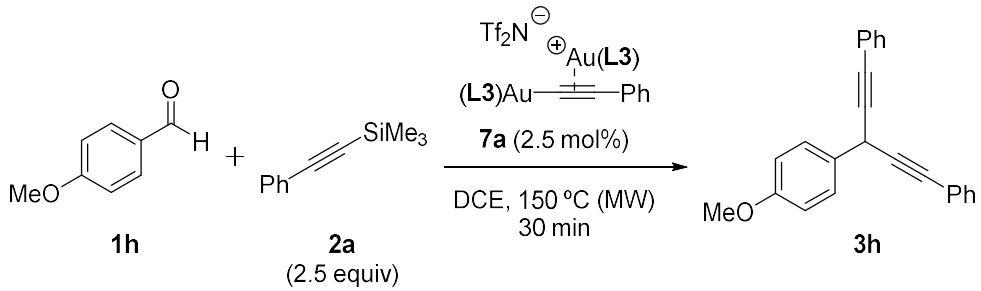


Scheme III.12: Study of the activation of **2a** with JohnPhosAuNTf$_2$.

Under an argon atmosphere, 6 μL of **2a** (0.03 mmol, 1.5 equiv) were added to a solution of 15.5 mg of JohnPhosAuNTf$_2$ (0.02 mmol, 1 equiv) in 0.8 mL of dry $CDCl_3$ at room temperature,[175] and the mixture was monitored by ^{1}H-NMR and ^{31}P-NMR. It was immediately observed by ^{31}P-NMR a signal at 62.7 ppm, along with the JohnPhosAuNTf$_2$ signal at 57.7 ppm (see spectrum in p. 102).

[175] $CDCl_3$ was dried by refluxing over P_2O_5 for 2 hours and distilling under an argon atmosphere.

Procedure for the Bis-Alkynylation of **1h** *Using σ,π-Digold Complex* **7a** *as Catalyst*



Scheme III.13: Bis-alkynylation of **1h** using **7a** as catalyst.

Complex **7a** (13.7 mg, 0.01 mmol, 0.025 equiv) was solved in 0.8 mL of 1,2-dichloroethane. Then, **1h** (48 μL, 0.4 mmol, 1 equiv) and **2a** (198 μL, 1 mmol, 2.5 equiv) were added. The reaction mixture was heated at 150 ºC (microwave assisted) for 30 minutes. After cooling at room temperature, 0.4 mL of toluene were added. 1,2-Dichloroethane was eliminated at reduced pressure, and the product contained in the remaining toluene solution was purified by flash chromatography (hexane) using a short path of silica gel, recovering firstly the excess of alkynylsilane, and secondly the desired product **3h** in 72% yield.

Experimental Remarks for Benzylic Methyl Ether and Acetate Alkynylation Reactions

1. Starting Materials

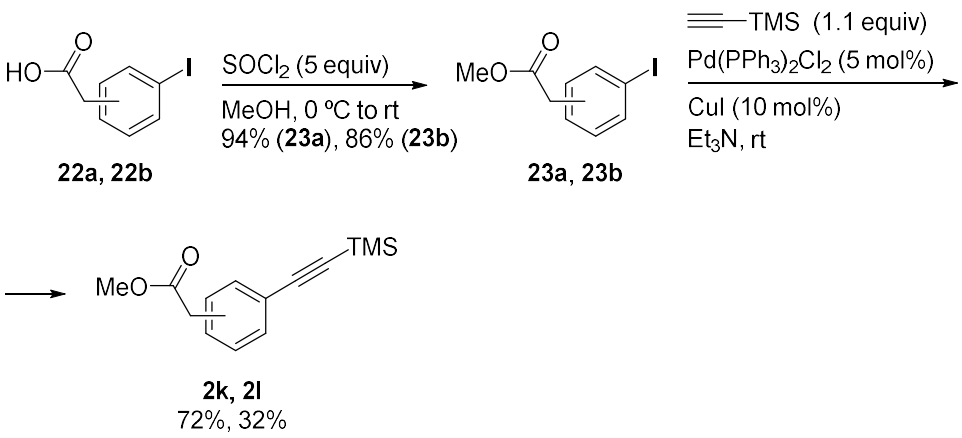
Gold(I) Complexes

Gold(I) complexes were prepared as indicated for the complexes used in the bis-alkynylation reactions (see p. 189).

Alkynylsilanes **2**

Alkynylsilanes **2a-i** were obtained as indicated in p. 185. Alkynylsilane **2j** was prepared using the same procedure as indicated for alkynylsilanes **2f**, **2h** and **2i** (p. 185).[176]

Preparation of **2k** *and* **2l**

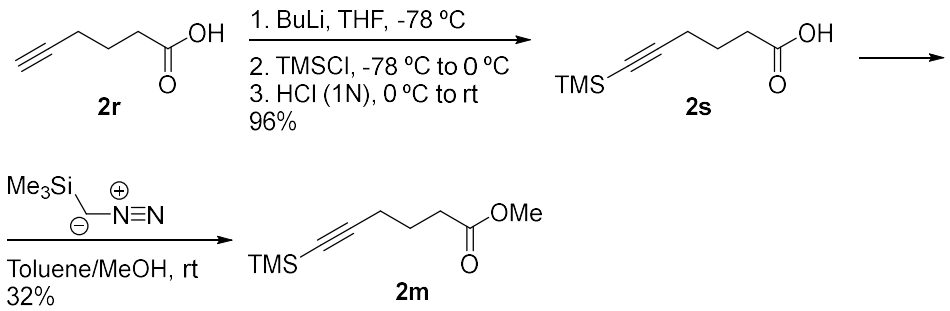


Scheme III.14: Preparation of compounds **2k** and **2l**.

[176] For spectroscopic data of compound **2j** see O. Vechorkin, D. Barmaz, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 12078–12079.

Methylation of the acid group in compounds **22a** and **22b** was carried out according to a reported procedure. [177] Later Sonogashira coupling procedure was performed following described conditions for iodoarenes.[165]

Preparation of **2m**



Scheme III.15: General route for the preparation of **2m**.

Compound **2o** was transformed into compound **2p** by deprotonation with *n*BuLi, reaction with trimethylsilyl chloride and subsequent hydrolysis of the silyl ester formed.[178] Methylation of **2p** with a diazo compound was performed according to a reported procedure in which toluene was used instead of benzene.[179]

Preparation of **2n**

Compound **2q** (see p. 185) was transformed into the iodide derivative **2t** using a variation of the Apple reaction.[180] Nucleophilic substitution reaction with diethyl malonate in the presence of sodium hydride afforded compound **2n** (Scheme III.16).[181]

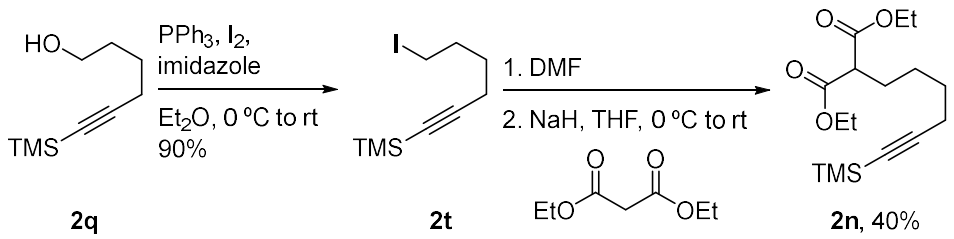
[177] I. G. Boutselis, X. Yu, Z.-Y. Zhang, R. F. Borch, *J. Med. Chem.* **2007**, *50*, 856–864.

[178] S. Bräse, H. Wertal (nee Nüske), D. Frank, D. Vidović, A. de Meijere, *Eur. J. Org. Chem.* **2005**, *2005*, 4167–4178.

[179] E. C. McLaughlin, M. P. Doyle, *J. Org. Chem.* **2008**, *73*, 4317–4319.

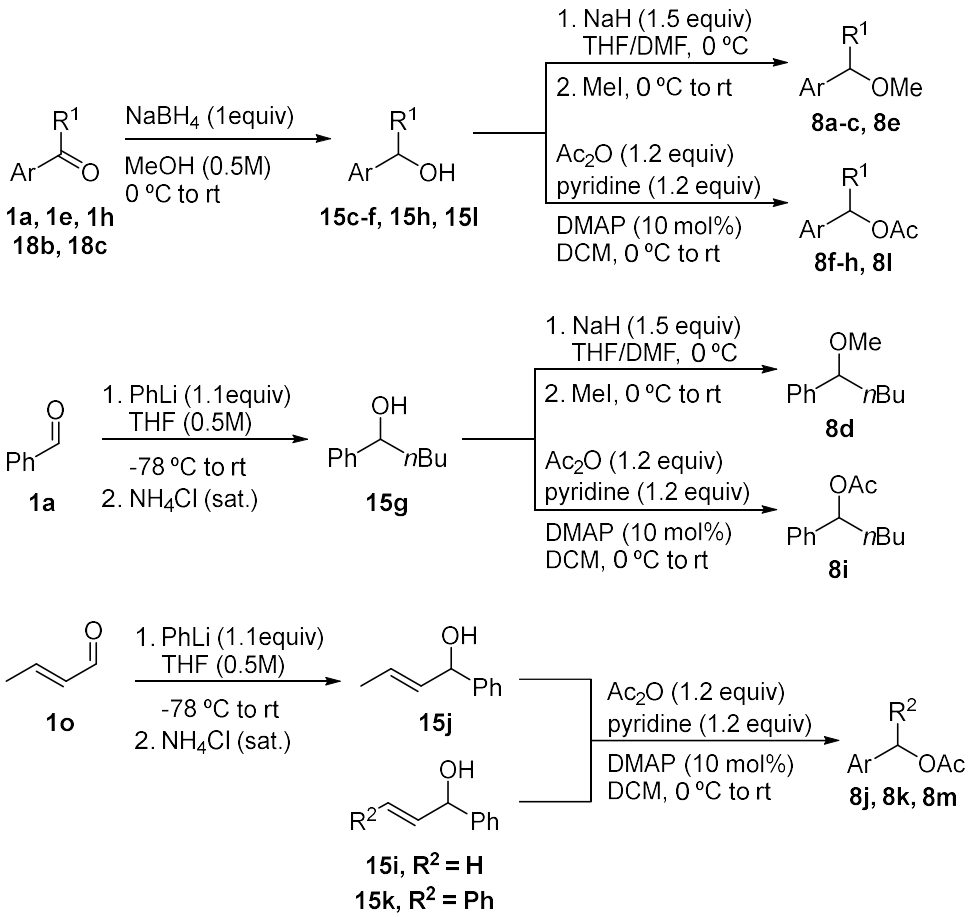
[180] a) S. Bräse, H. Wertal (nee Nüske), D. Frank, D. Vidović, A. de Meijere, *Eur. J. Org. Chem.* **2005**, *2005*, 4167–4178. b) R. Appel, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–811.

[181] K. M. Brummond, M. M. Davis, C. Huang, *J. Org. Chem.* **2009**, *74*, 8314–8320.



Scheme III.16: General route for the preparation of **2n**.

Acetates and Methyl Ethers 8



Scheme III.17: General synthetic pathways for the preparation of compounds **8** (for a better inspection of the structures of compounds **1**, **8**, **15** and **18**, see Index of Structures, p. 253).

Benzylic alcohols **15c-f**, **15h** and **15l** were prepared by reduction of the corresponding aldehyde or ketone with sodium borohydride (1 equiv). Slow addition of the reducing agent to a 0.5 M solution of the carbonyl compound in MeOH, at 0 ºC, and stirring at room temperature for 10 min afforded the corresponding alcohol in almost quantitative yield in most cases (Scheme III.17).

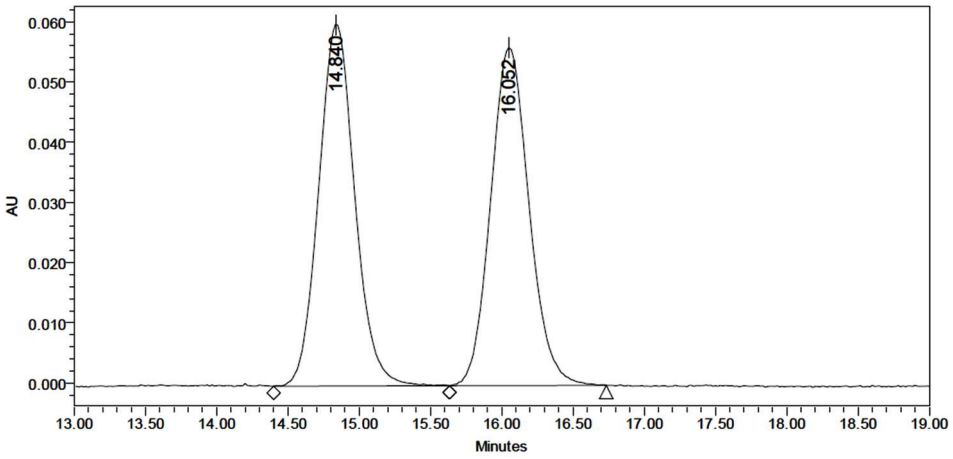
Alcohol **15g** was obtained by addition of *n*BuLi to benzaldehyde (**1a**): 3 mL of benzaldehyde (30 mmol, 1 equiv) were solved in THF (60 mL), and the mixture was cooled to -78 ºC. Then, 20 mL of a 1.6 M solution of *n*BuLi in hexanes were added. The reaction was allowed to slowly warm up to room temperature, overnight. After quenching with a saturated aqueous solution of NH_4Cl (10 mL), 30 mL of ethyl acetate were added. The organic and the aqueous layer were separated. The aqueous layer was extracted twice with 10 mL of ethyl acetate. The organic layers were combined, washed with brine and dried over sodium sulfate. Solvents were eliminated under reduced pressure and the product was purified by column chromatography (silica, hexanes/ethyl acetate 4:1), affording an 82% yield.

Alcohol **15j** was obtained by addition of PhLi to trans-crotonaldehyde (**1o**),[182] whereas **15i** and **15k** were obtained from commercial suppliers. Compounds **8a-e** and **8f-m** were obtained by methylation[183] or acylation,[184] respectively, of the corresponding compound **15** using reaction conditions previously described in the literature.

Compound (*S*)-**8h** was prepared by acylation of commercially available alcohol (*S*)-**15d** (Scheme III.18).[184] The enantiomeric excess was analysed by HPLC techniques (Chiracel® OD-H, hexane/isopropanol 99:1, 0.5 mL/min) and racemic **8h** was used as reference. HPLC chromatograms are shown below.

[182] F. Nowrouzi, J. Janetzko, R. A. Batey, *Org. Lett.* **2010**, *12*, 5490–5493.
[183] S. H. Lee, I. S. Kim, Q. R. Li, G. R. Dong, L. S. Jeong, Y. H. Jung, *J. Org. Chem.* **2011**, *76*, 10011–10019.
[184] M. I. Monterde, R. Brieva, V. M. Sánchez, M. Bayod, V. Gotor, *Tetrahedron: Asymmetry* **2002**, *13*, 1091–1096.

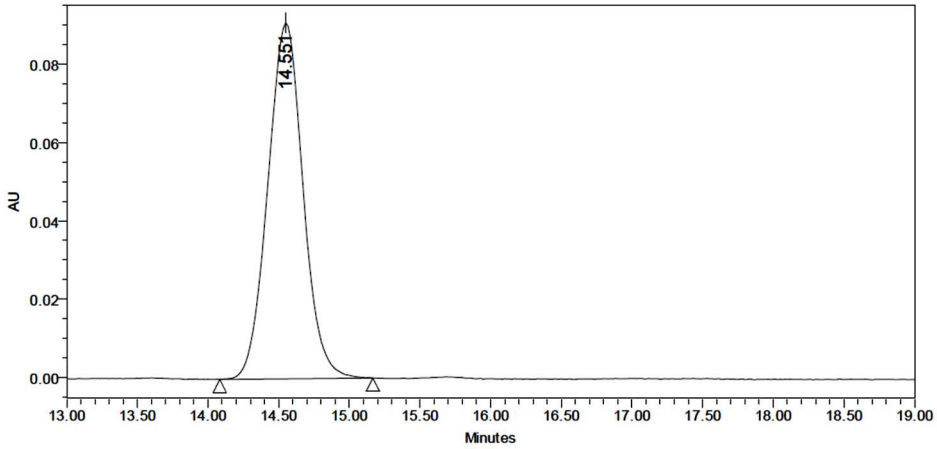
*Compound rac-***8h**



Peak Results

	Name	RT	% Area	Area	Height	Amount	Units
1		14.840	50.17	1057474	60167		
2		16.052	49.83	1050452	56131		

Compound **(*S*)-8h**



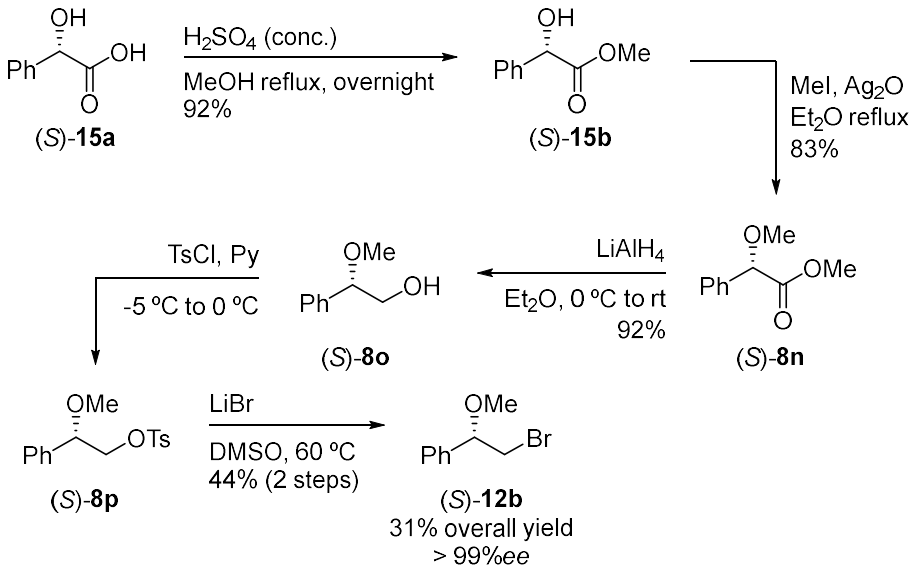
Peak Results

	Name	RT	% Area	Area	Height	Amount	Units
1		14.551	100.00	1574253	90892		

β-Haloethers 12

Compounds **12** were obtained from the corresponding vinylarene using the procedure reported by Das et al..[185]

Preparation of (*S*)-**12b**



Scheme III.18: Preparation of compound (*S*)-**12b**.

Compound (*S*)-**15a** was obtained from commercial suppliers and ester (*S*)-**15b** was synthesised as follows: 30 mmol of (*S*)-**15a** were solved in methanol, 1 mL of concentrated sulfuric acid was added and the mixture was heated at reflux temperature overnight. Methanol was evaporated at reduced pressure and diethyl ether and water was added. Both layers were separated. The aqueous layer was extracted with diethyl ether twice. The organic layer was dried over sodium sulfate, and the solvent was eliminated at reduced pressure. The crude product was used without further purification for the next step.

[185] B. Das, K. Venkateswarlu, K. Damodar, K. Suneel, *J. Molec. Catal. A* **2007**, *269*, 17–21.

Compound (*S*)-**8n** was obtained by methylation of (*S*)-**15a** according to a procedure described in literature.[186] A known procedure was also used to reduce (*S*)-**8n** to (*S*)-**8o**.[187]

Preparation of (*S*)-**8p**

8 mmol of (*S*)-**8o** were solved in dry pyridine (12 mL)[188] and the mixture was cooled to -5 ºC. Tosyl chloride (2 equiv) was added and the mixture was stirred until it was completely solved. The mixture was stirred at 0 ºC for 12 hours. After quenching with water, dichloromethane and water were added and the aqueous layer was extracted twice with the organic solvent. The organic layer was washed with HCl (1N) and brine and dried over sodium sulfate. Solvents were eliminated at reduced pressure and the crude product was used for the next step without further purification.

Preparation of (*S*)-**12b**

LiBr (3 equiv) was solved in DMSO (20 mL) and 8 mmol of (*S*)-**8p** were added. The mixture was heated at 60 ºC overnight. After cooling at room temperature, water and diethyl ether were added. Both layers were separated and the aqueous layer was extracted with diethyl ether. The organic layer was washed with water and brine and dried over sodium sulfate. Solvents were eliminated at reduced pressure. The crude mixture was purified by column chromatography (silica gel, hexane/ethyl acetate 80:1). Product (*S*)-**12b** was obtained in 31% overall yield.[189]

The enantiomeric excess was analysed by HPLC techniques (Chiracel® OD-H, hexane/isopropanol 99:1, 0.5 mL/min) and racemic **12b** was used as reference. HPLC chromatograms are shown below.

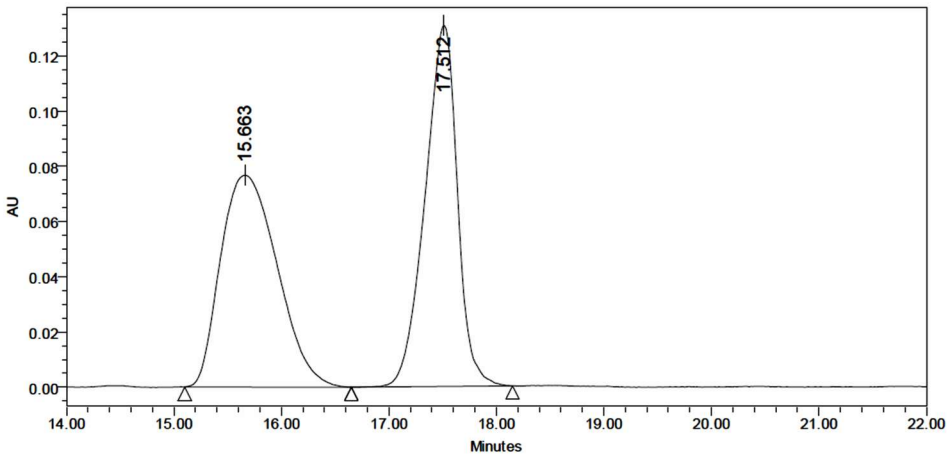
[186] A. F. Cunningham, E. P. Kuendig, *J. Org. Chem.* **1988**, *53*, 1823–1825.

[187] P. C. Bulman Page, Y. Chan, H. Heaney, M. J. McGrath, E. Moreno, *Eur. J. Org. Chem.* **2011**, *2011*, 5347–5354.

[188] Distilled over NaOH and under an argon atmosphere.

[189] For spectroscopic data see P. Phukan, P. Chakraborty, D. Kataki, *J. Org. Chem.* **2006**, *71*, 7533–7537.

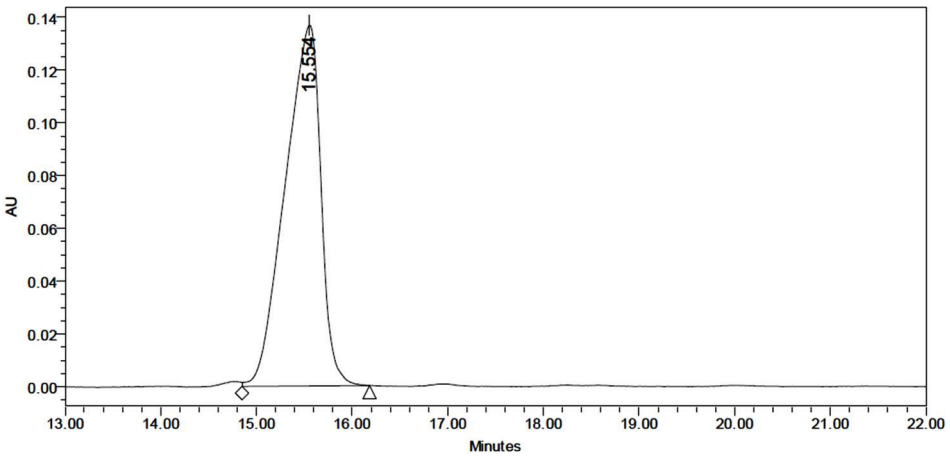
Compound ***rac*-12b**



Peak Results

	Name	RT	% Area	Area	Height	Amount	Units
1		15.663	50.73	2813614	76792		
2		17.512	49.27	2732290	130931		

Compound ***(S)*-12b**

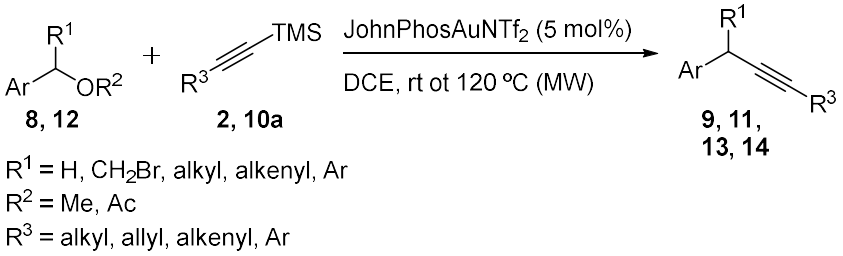


Peak Results

	Name	RT	% Area	Area	Height	Amount	Units
1		15.554	100.00	3537951	136831		

2. Alkynylation Products 9, 11, 13 and 14.

General Procedures for the Alkynylation of Benzylic Ethers and Acetates



Scheme III.19: General scheme for the alkynylation of ethers and acetates.

Method A: Reactions at room temperature

7.8 mg of JohnPhosAuNTf$_2$ (0.01 mmol, 0.05 equiv) were solved in 0.4 mL of 1,2-dichloroethane at room temperature. Subsequently, 0.2 mmol (1 equiv) of the corresponding compound **8** or **12** and 0.8 mmol (4 equiv) of the corresponding alkynylsilane **2** or allylsilane **10a** were added. The mixture was stirred at room temperature during the time indicated in Tables II.4-7. Afterwards, 0.2 mL of toluene were added to the crude mixture, 1,2-dichloroethane was eliminated under reduced pressure, and the product contained in the remaining toluene solution was purified by column chromatography (the excess of **2** was separated before with hexanes and then the product was separated with hexanes/ethyl acetate mixtures) in silica gel, to afford products **9**, **11**, **13** or **14** in the yields indicated in Tables II.4-7.

Method B: Microwave assisted reactions

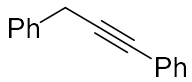
7.8 mg of JohnPhosAuNTf$_2$ (0.01 mmol, 0.05 equiv) were placed in a sealed microwave vial and solved in 0.4 mL of 1,2-dichloroethane at room temperature. Subsequently, 0.2 mmol (1 equiv) of the corresponding compound **8** or **12** and 0.8 mmol (4 equiv) of the corresponding alkynylsilane **2** or allylsilane **10a** were added. The mixture was stirred at the temperature and during the time indicated in Tables II.4-5 and II.7-8. Afterwards, the mixture was cooled to room temperature, 0.2 mL of toluene were added to the crude mixture, 1,2-dichloroethane was eliminated under reduced pressure, and the

product contained in the remaining toluene solution was purified by column chromatography (the excess of **2** was separated before with hexanes and then the product was separated with hexanes/ethyl acetate mixtures) in silica gel, to afford products **9**, **11**, or **13** in the yields indicated in Tables II.4-5 and II.7-8.

Characterisation Data of Products 9, 11, 13, and 14

Products **9**

9a: 1,3-diphenylprop-1-yne



Appearance: Slightly yellowish oil

Yield: 63% (B)

Eluent: Hexanes

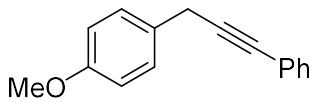
HRMS calcd. for $C_{15}H_{12}$: 192.0939

HRMS (EI) found: 192.0942

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.55-7.25 (m, 10H), 3.88 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 136.9 (C), 131.8 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 126.8 (CH), 123.8 (C), 87.7 (C), 82.8 (C), 25.9 (CH_2).

9b: 3-(4-methoxyphenyl)-1-phenylprop-1-yne



Appearance: Slightly yellowish oil

Yield: 41% (A), 40% (B)

Eluent: Hexanes/AcOEt 80:1

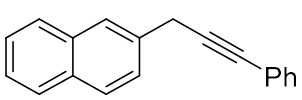
HRMS calcd. for $C_{16}H_{14}O$: 222.1045

HRMS (EI) found: 222.1042

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.51-7.40 (m, 2H), 7.38-7.24 (m, 5H), 6.94-6.83 (m, 2H), 3.81 (s, 3H), 3.78 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 158.6 (C), 131.8 (CH), 129.1 (CH), 129.0 (C), 128.4 (CH), 127.9 (CH), 123.9 (C), 114.1 (CH), 88.2 (C), 82.6 (C), 55.5 (CH_3), 25.1 (CH_2).

9c: 2-naphthyl-1-phenylprop-1-yne



Appearance: Slightly yellowish oil

Yield: 33% (B, from **8c**), 43% (B, from **8g**),

Eluent: Hexanes

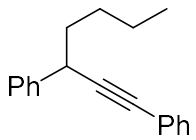
HRMS calcd. for $C_{19}H_{14}$: 242.1096

HRMS (EI) found: 242.1095

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.94-7.75 (m, 4H), 7.58-7.41 (m, 5H), 7.38-7.28 (m, 3H), 4.00 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 134.4 (C), 133.7 (C), 132.6 (C), 131.9 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.7 (CH), 126.4 (CH), 126.3 (CH), 125.8 (CH), 123.9 (C), 87.6 (C), 83.1 (C), 26.2 (CH_2).

9d: 1,3-diphenylhept-1-yne



Appearance: Colourless liquid

Yield: 49% (A, from **8d**), 57% (A, from **8i**).

Eluent: Hexanes

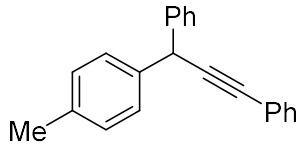
HRMS calcd. for $C_{19}H_{21}$ (M+1): 249.1638

HRMS (ESI) found: 249.1636

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.55-7.20 (m, 10H), 3.86 (t, J = 7.2 Hz, 1H), 1.95-1.75 (m, 2H), 1.68-1.25 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 142.6 (C), 131.8 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 126.8 (CH), 124.1 (C), 92.0 (C), 83.4 (C), 38.6 (CH, CH_2), 29.8 (CH_2), 22.6 (CH_2), 14.2 (CH_2).

9e: 3-(4-methylphenyl)-1,3-diphenylprop-1-yne



Appearance: Slightly yellowish oil

Yield: 98% (A)

Eluent: Hexanes

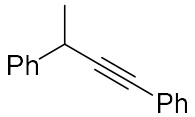
HRMS calcd. for $C_{22}H_{19}$ (M+1): 283.1481

HRMS (ESI) found: 283.1472

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.57-7.45 (m, 4H), 7.42-7.23 (m, 8H), 7.18 (d, *J* = 7.8 Hz, 2H), 5.23 (s, 1H), 2.37 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 142.1 (C), 139.0 (C), 136.7 (C), 131.9 (CH), 129.5 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.0 (CH), 123.8 (C), 90.6 (C), 84.9 (C), 43.6 (CH), 21.2 (CH_3).

9f: 1,3-diphenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 54% (A), 74% (B)

Eluent: Hexanes

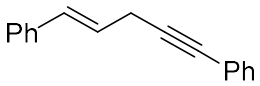
HRMS calcd. for $C_{16}H_{14}$: 206.1096

HRMS (EI) found: 206.1101

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.55-7.44 (m, 4H), 7.43-7.23 (m, 6H), 4.02 (q, *J* = 7.2 Hz, 1H), 1.62 (d, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 143.5 (C), 131.8 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.1 (CH), 126.8 (CH), 123.9 (C), 92.8 (C), 82.6 (C), 32.7 (CH), 24.7 (CH_3).

9g: (*E*)-1,5-diphenylpent-1-en-4-yne



Appearance: Slightly yellowish oil

Yield: 35% (A)

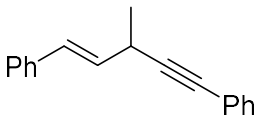
Eluent: Hexanes

HRMS calcd. for $C_{17}H_{14}$: 218.1096

HRMS (EI) found: 218.1092

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.55-7.20 (m, 10H), 6.75 (d, *J* =15.7 Hz, 1H), 6.28 (dt, *J* = 15.7, 5.7 Hz, 1H), 3.40 (dd, *J* = 5.7, 1.8 Hz, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 137.3 (C), 131.8 (CH), 131.6 (CH), 128.7 (CH), 128.4 (CH), 128.0 (CH), 127.5 (CH), 126.5 (CH), 124.4 (CH), 123.8 (C), 86.9 (C), 83.0 (C), 23.2 (CH_2).

9h: (*E*)-1,5-diphenyl-3-methylpent-1-en-4-yne



Appearance: Slightly yellowish oil

Yield: 55% (A)

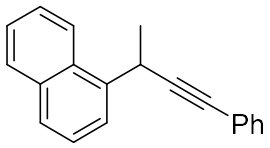
Eluent: Hexanes

HRMS calcd. for $C_{18}H_{16}$: 232.1252

HRMS (EI) found: 232.1251

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.60-7.20 (m, 10H), 6.72 (dd, *J* = 15.7, 1.5 Hz, 1H), 6.28 (dd, *J* = 15.7, 6.1 Hz, 1H), 3.67-3.45 (m, 1H), 1.48 (d, *J* = 7.04 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 137.3 (C), 131.8 (CH), 131.3 (CH), 129.7 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 126.5 (CH), 123.9 (C), 91.8 (C), 82.9 (C), 29.8 (CH), 22.0 (CH_3).

9i: 3-(1-naphthyl)-1-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 67% (A)

Eluent: Hexanes

HRMS calcd. for $C_{20}H_{17}$ (M+1): 257.1325

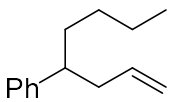
HRMS (ESI) found: 257.1325

^{1}**H-NMR** (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 8.20 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J*= 8.3 Hz,1H), 7.85 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.63-7.41(m, 5H), 7.38-7.27(m, 3H), 4.76 (q, *J* = 7.1 Hz, 1H), 1.76 (d, *J* = 7.1 Hz, 3H).

^{13}**C-NMR** (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 139.0 (C), 134.2 (C), 131.8 (CH), 130.7 (C), 129.2 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 126.2 (CH), 125.9 (CH), 125.7 (CH), 124.5 (CH), 123.9 (C), 123.4 (CH), 93.0 (C), 82.9 (C), 29.3 (CH), 23.6 (CH_3).

Products **11**

11a: 4-phenyloct-1-ene



Appearance: Slightly yellowish oil

Yield: 51% (A)

Eluent: Hexanes

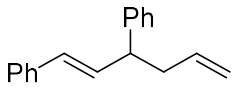
HRMS calcd. for $C_{14}H_{21}$ (M+1): 189.1638

HRMS found: 189.1642

^{1}**H-NMR** (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.36-7.10 (m, 5H), 5.80-5.60 (m, 1H), 5.06-4.85 (m, 2H), 2.70-2.52 (m, 1H), 2.44-2.30 (m, 2H), 1.81-1.47 (m, 2H), 1.42-1.05 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 3H).

^{13}**C-NMR** (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 145.7 (C), 137.5 (CH), 128.4 (CH), 127.9 (CH), 126.1 (CH), 115.8 (CH_2), 46.1 (CH), 41.6 (CH_2), 36.9 (CH_2), 29.9 (CH_2),22.9 (CH_2) 14.2 (CH_3).

11b: (*E*)-1,3-diphenylhexa-1,5-diene



Appearance: Colourless oil

Yield: 93% (A)

Eluent: Hexanes

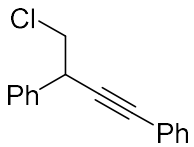
HRMS calcd. for $C_{18}H_{19}$ (M+1): 235.1481

HRMS (ESI) found: 235.1479

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.55-7.15 (m, 10H), 6.56-6.34 (m, 2H), 6.00-5.75 (m, 1H), 5.22-5.00 (m, 2H), 3.70-3.50 (m, 1H), 2.75-2.55 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 144.0 (C), 137.6 (C), 136.7 (CH), 133.6 (CH), 129.9 (CH), 128.7 (CH), 128.6 (CH), 127.9 (CH), 127.3 (CH), 126.5 (CH), 126.3 (CH), 116.5 (CH_2), 49.1 (CH), 40.4 (CH_2).

Products **13**

13a: 4-chloro-1,3-diphenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 40% (B)

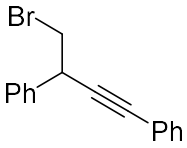
Eluent: Hexanes/AcOEt 80:1

HRMS calcd. for $C_{16}H_{14}{}^{35}Cl$ (M+1): 241.0779

HRMS found: 241.0776

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.63-7.07 (m, 9H), 4.20 (t, J = 7.0 Hz, 1H), 3.81 (qd, J = 10.6, 7.0 Hz, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 138.4 (C), 132.0 (CH), 128.9 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 123.2 (C), 88.1 (C), 84.9 (C), 49.1 (CH_2), 41.7 (CH).

13b: 4-bromo-1,3-diphenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 36% (A), 73% (B)

Eluent: Hexanes/AcOEt 80:1

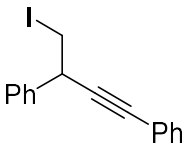
HRMS calcd. for $C_{16}H_{13}{}^{79}Br$: 284.0201

HRMS (EI) found: 284.0208

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.60-7.30 (m, 10H), 4.26 (t, *J* = 7.0 Hz, 1H), 3.78-3.60 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 139.0 (C), 131.9 (CH), 128.9 (CH), 128.43 (CH), 128.41 (CH), 128.03 (CH), 128.01 (CH), 123.2 (C), 88.6 (C), 84.9 (C), 41.5 (CH), 37.3 (CH_2).

13c: 4-iodo-1,3-diphenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 52% (B)

Eluent: Hexanes/AcOEt 80:1

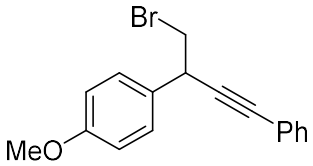
HRMS calcd. for $C_{16}H_{14}{}^{127}I$ (M+1): 333.0135

HRMS found: 333.0127

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.56-7.28 (m, 10H), 4.19 (t, *J* = 7.0 Hz, 1H), 3.53 (d, *J* = 7.0 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 140.0 (C), 131.9 (CH), 128.9 (CH), 128.44 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 123.2 (C), 89.6 (C), 84.9 (C), 41.7 (CH), 11.9 (CH_2).

13d: 4-bromo-3-(4-methoxyphenyl)-1-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 73% (A), 73% (B)

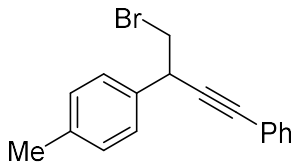
Eluent: Hexanes/AcOEt 40:1

HRMS calcd. for $C_{17}H_{15}{}^{79}BrO$: 314.0306

HRMS (EI) found: 314.0308

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.54-7.44 (m, 2H), 7.43-7.36 (m, 2H), 7.35-7.27(m, 3H), 6.96-6.85 (m, 2H), 4.20 (t, *J* =7.2 Hz, 1H), 3.82 (s, 3H), 3.72-3.56 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 159.3 (C), 131.9 (CH), 131.0 (C), 129.1 (CH), 128.4 (CH), 128.35 (CH), 123.1 (C), 114.2 (CH), 88.9 (C), 84.7 (C), 55.5 (CH_3), 40.7 (CH), 37.7 (CH_2).

13e: 4-bromo-3-(4-methylphenyl)-1-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 76% (B)

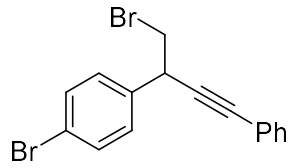
Eluent: Hexanes/AcOEt 80:1

HRMS calcd. for $C_{17}H_{15}{}^{79}Br$: 298.0357

HRMS (EI) found: 298.0369

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.52-7.44 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.33-7.29 (m, 3H), 7.20 (d, *J* = 7.7 Hz, 2H), 4.21 (t, *J* = 7.2 Hz, 1H), 3.69 (ddd, *J* = 9.8, 7.7 Hz, 1H), 3.64 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.37 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 137.7 (C), 136.1 (C), 131.9 (CH), 129.6 (CH), 128.4 (CH), 128.35 (CH), 127.9 (CH), 123.3 (C), 88.9 (C), 84.8 (C), 41.2 (CH), 37.5 (CH_2), 21.3 (CH_3).

13f: 4-bromo-3-(4-bromophenyl)-1-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 74% (B)

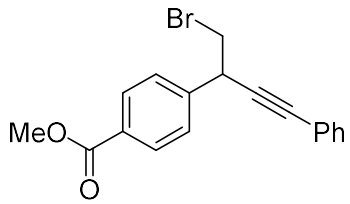
Eluent: Hexanes/AcOEt 80:1

HRMS calcd. for $C_{16}H_{12}{}^{79}Br_2$: 361.9303

HRMS (EI) found: 361.9608

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.57-7.43 (m, 1H), 7.39-7.28 (m, 5H), 4.21 (t, *J* = 6.9 Hz, 1H), 3.70 (dd, *J* = 9.9, 7.1 Hz, 1H), 3.62 (dd, *J* = 9.9, 6.7 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 138.0 (C), 132.0 (CH), 131.9 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 122.9 (C), 122.0 (C), 87.9 (C), 85.3 (C), 40.8 (CH), 36.9 (CH_2).

13g: methyl 4-(1-bromo-4-phenylbut-3-yn-2-yl)benzoate



Appearance: Slightly yellowish oil

Yield: 24% (B, 48% conv.)

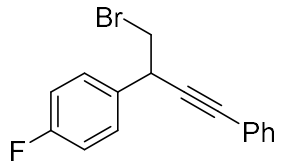
Eluent: Hexanes/AcOEt 40:1

HRMS calcd. for $C_{18}H_{16}{}^{79}BrO_2$ (M+1): 343.0328

HRMS (ESI) found: 343.0328

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 8.05 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.51-7.42 (m, 2H), 7.37-7.28 (m, 3H), 4.30 (t, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.78-3.60 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 166.9 (C), 144.0 (C), 132.0 (CH), 130.2 (CH), 129.9 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 122.9 (C), 87.8 (C), 85.4 (C), 52.4 (CH_3), 41.3 (CH), 36.7 (CH_2).

13h: 4-bromo-3-(4-fluorophenyl)-1-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 81% (B)

Eluent: Hexanes/AcOEt 80:1

HRMS calcd. for $C_{16}H_{12}{}^{79}BrF$: 302.0106

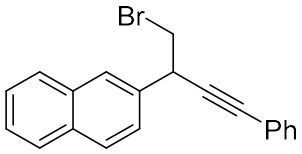
HRMS (EI) found: 302.0101

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.52-7.39 (m, 4H), 7.37-7.28 (m, 3H), 7.13-7.02 (m, 2H), 4.23 (t, *J* = 6.9, 1H), 3.69 (dd, *J* = 9.9, 7.3 Hz, 1H), 3.62 (dd, *J* = 9.9, 6.6 Hz, 1H).

^{19}F-NMR (282 MHz, $CDCl_3$, 25 ºC) δ (ppm) -114.46.

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 162.5 (d, *J* = 246.4 Hz, C), 134.7 (d, *J* = 3.1 Hz, C), 131.9 (CH), 129.65 (d, *J* = 8.2 Hz, CH), 128.55 (CH), 128.5 (CH), 123.0 (C), 115.8 (d, *J* = 21.6 Hz, CH), 88.3 (C), 85.1 (C), 40.7 (CH), 37.3 (CH_2).

13i: 4-bromo-3-(naphtha-2-yl)-1-phenylbut-1-yne



Appearance: White solid

m.p. 71.5-73.7 ºC (decomp.)

Yield: 59% (A), 64% (B)

Eluent: Hexanes/AcOEt 80:1

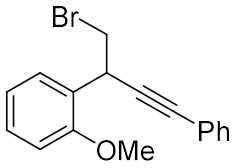
HRMS calcd. for $C_{20}H_{15}{}^{79}Br$: 334.0357

HRMS (EI) found: 334.0356

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.92 (brs, 1H), 7.91-7.82 (m, 3H), 7.57 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.55-7.46 (m, 4H), 7.37-7.30 (m, 3H), 4.42 (t, *J* = 7.0 Hz, 1H), 3.79 (dd, *J* = 9.9, 7.6 Hz, 1H), 3.75 (dd, *J* = 9.9, 6.6 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 136.3 (C), 133.5 (C), 133.1 (C), 132.0 (CH), 128.8 (CH), 128.5 (CH, CH), 128.1 (CH), 127.9 (CH), 127.2 (CH), 126.5 (CH), 126.3 (CH), 125.7 (CH), 123.2 (C), 88.6 (C), 85.2 (C), 41.7 (CH), 37.1 (CH_2).

13j: 4-bromo-3-(2-methoxyphenyl)-1-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 45% (B)

Eluent: Hexanes/AcOEt 80:1

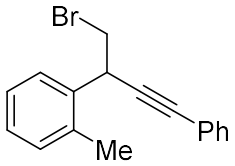
HRMS calcd. for $C_{17}H_{15}{}^{79}BrO$: 314.0306

HRMS (EI) found: 314.0299

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.66 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.56-7.46 (m, 2H), 7.36-7.27 (m, 4H), 7.01 (td, *J* = 7.6, 1.1 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 4.73 (dd, *J* = 8.3, 4.6 Hz, 1H), 3.88 (s, 3H), 3.76 (dd, *J* = 9.4, 4.6 Hz, 1H), 3.58 (dd, *J* = 9.4, 8.4 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 156.4 (C), 132.0 (CH), 129.4 (CH), 129.2 (CH), 128.4 (CH), 128.2 (CH), 126.8 (C), 123.4 (C), 120.9 (CH), 110.6 (CH), 89.1 (C), 84.3 (C), 55.6 (CH_3), 36.5 (CH_2), 35.4 (CH).

13k: 4-bromo-3-(2-methylphenyl)-1-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 85% (B)

Eluent: Hexanes/AcOEt 80:1

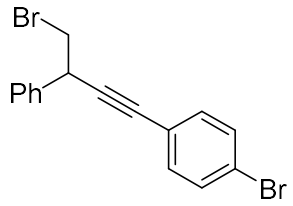
HRMS calcd. for $C_{17}H_{15}{}^{79}Br$: 298.0357

HRMS (EI) found: 298.0347

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.68-7.60 (m, 1H), 7.57-7.47 (m, 2H), 7.40-7.18 (m, 6H), 4.50 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.77-3.60 (m, 2H), 2.47 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 137.3 (C), 135.5 (C), 131.9 (CH), 130.9 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 126.8 (CH), 123.3 (C), 89.1 (C), 84.2 (C), 38.2 (CH), 35.9 (CH_2), 19.5 (CH_3).

13l: 4-bromo-1-(4-bromophenyl)-3-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 62% (B)

Eluent: Hexanes/AcOEt 80:1

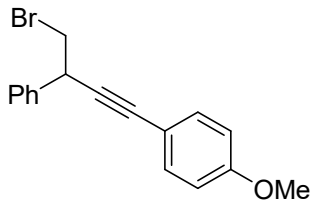
HRMS calcd. for $C_{16}H_{12}{}^{79}Br_2$: 361.9306

HRMS (EI) found: 361.9315

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.56-7.27 (m, 9H), 4.24 (t, *J* = 7.0 Hz, 1H), 3.75-3.58 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 138.8 (C), 133.4 (CH), 131.7 (CH), 129.0 (CH), 128.1 (CH), 128.0 (CH), 122.6 (C), 122.1 (C), 89.9 (C), 83.9 (C), 41.6 (CH), 37.1 (CH_2).

13m: 4-bromo-1-(4-methoxyphenyl)-3-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 65% (B)

Eluent: Hexanes/AcOEt 40:1

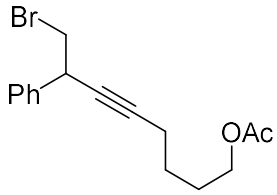
HRMS calcd. for $C_{17}H_{15}{}^{79}BrO$: 314.0306

HRMS (EI) found: 314.0292

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.52-7.27 (m, 7H), 6.85 (dt, *J* = 8.7, 2.5 Hz, 2H), 4.23 (t, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 3.75-3.59 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 159.7 (C), 139.3 (C), 133.3 (CH), 128.9 (CH), 128.1 (CH), 128.0 (CH), 115.3 (C), 114.1 (CH), 87.1 (C), 84.8 (C), 55.5 (CH_3), 41.6 (CH), 37.5 (CH_2).

13n: 8-bromo-7-phenyloct-5-yn-1-yl acetate



Appearance: Slightly yellowish oil

Yield: 46% (B)

Eluent: Hexanes/AcOEt 40:1

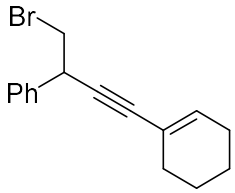
HRMS calcd. for $C_{16}H_{20}{}^{79}BrO_2$ (M+1): 323.0641

HRMS (ESI) found: 323.0638

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.42-7.26 (m, 5H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.99 (tt, *J* = 7.0, 2.2 Hz, 1H), 3.61-3.50 (m, 2H), 2.31 (td, *J* = 6.9, 2.2 Hz, 2H), 2.05 (s, 3H), 1.85-1.71 (m, 2H), 1.69-1.56 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 171.3 (C), 139.5 (C), 128.8 (CH), 127.9 (CH), 127.8 (CH), 84.5 (C), 79.8 (C), 64.2 (CH_2), 41.1 (CH), 37.9 (CH_2), 28.0 (CH_2), 25.4 (CH_2), 21.2 (CH_3), 18.7 (CH_2).

13o: 4-bromo-1-(cyclohex-1-en-1-yl)-3-phenylbut-1-yne



Appearance: Slightly yellowish oil

Yield: 60% (B)

Eluent: Hexanes/AcOEt 80:1

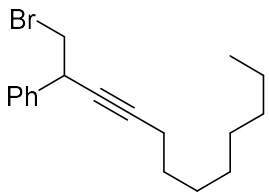
HRMS calcd. for $C_{16}H_{17}{}^{79}Br$: 288.0514

HRMS (EI) found: 288.0515

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.47-7.14 (m, 5H), 6.19-6.06 (m, 1H), 4.11 (t, *J* = 6.8 Hz, 1H), 3.69-3.44 (m, 2H), 2.31-1.95 (m, 4H), 1.73-1.44 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 139.4 (C), 135.1 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 120.6 (C), 86.7 (C), 85.7 (C), 41.4 (CH), 37.7 (CH_2), 29.5 (CH_2), 25.8 (CH_2), 22.5 (CH_2), 21.7 (CH_2).

13p: 1-bromo-2-phenyloct-3-yne



Appearance: Slightly yellowish oil

Yield: 51% (B)

Eluent: Hexanes/AcOEt 80:1

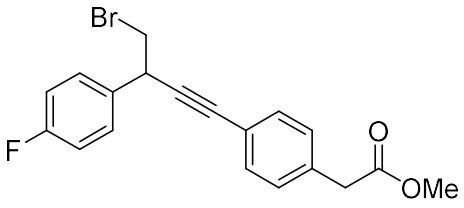
HRMS calcd. for $C_{18}H_{25}{}^{79}Br$: 320.1140

HRMS (EI) found: 320.1131

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.45-7.24 (m, 5H), 3.99 (tt, *J* = 6.9, 2.4 Hz, 1H), 3.63-3.49 (m, 2H), 2.25 (td, *J* = 6.9, 2.2 Hz, 2H), 1.63-1.15 (m, 12H), 0.96-0.80 (t, *J* = 6.0 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 139.7 (C), 128.8 (CH), 128.0 (CH), 127.8 (CH), 85.4 (C), 79.1 (C), 41.1 (CH), 38.1 (CH_2), 32.0 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.05 (CH_2), 29.0 (CH_2), 22.9 (CH_2), 19.0 (CH_2), 14.3 (CH_3).

13q: methyl 2-(4-(4-bromo-3-(4-fluorophenyl)but-1-yn-1-yl)phenyl)acetate



Appearance: Slightly yellowish oil

Yield: 71% (B)

Eluent: Hexanes/AcOEt 40:1

HRMS calcd. for $C_{19}H_{16}{}^{79}BrFNaO_2$ (M+23): 397.0210

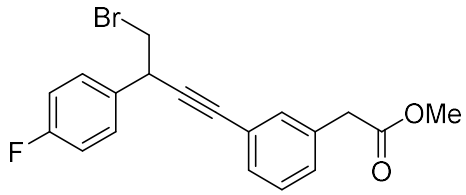
HRMS (ESI) found: 397.0207

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.50-7.40 (m, 4H), 7.32-7.21 (m, 2H), 7.15-7.00 (m, 2H), 4.24 (t, *J* = 6.9 Hz, 1H), 3.76-3.57 (m, 4H), 3.73 (s, 3H).

^{19}F-NMR (282 MHz, $CDCl_3$, 25 ºC) δ (ppm) -114.43.

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 171.7 (C), 162.4 (d, *J* = 246.5 Hz, C), 134.7 (d, *J* = 3.1 Hz, C), 134.4 (C), 132.1 (CH), 129.6 (d, *J* = 8.2 Hz, CH), 129.5 (CH), 121.8 (C), 115.7 (d, *J* = 21.6 Hz, CH), 88.5 (C), 84.8 (C), 52.3 (CH_3), 41.2 (CH_2), 40.6 (CH), 37.3 (d, *J* = 1.6 Hz, CH_2).

13r: methyl 2-(3-(4-bromo-3-(4-fluorophenyl)but-1-yn-1-yl)phenyl)acetate



Appearance: Slightly yellowish oil

Yield: 61% (B)

Eluent: Hexanes/AcOEt 40:1

HRMS calcd. for $C_{19}H_{16}{}^{79}BrFNaO_2$ (M+23): 397.0210

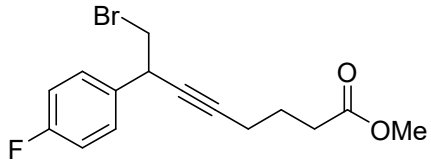
HRMS (ESI) found: 397.0209

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.52-7.37 (m, 4H), 7.36-7.22 (m, 2H), 7.16-7.03 (m, 2H), 4.25 (t, *J* = 6.9 Hz, 1H), 3.80-3.57 (m, 4H), 3.73 (s, 3H).

^{19}F-NMR (282 MHz, $CDCl_3$, 25 ºC) δ (ppm) -114.42.

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 171.8 (C), 162.5 (d, *J* = 246.6 Hz, C), 134.7 (d, *J* = 3.4 Hz, C), 134.3 (C), 132.7 (CH), 130.7 (CH), 129.7 (d, *J* = 8.4 Hz, CH), 129.6 (CH), 128.8 (CH), 123.3 (C), 115.8 (d, *J* = 21.6 Hz, CH), 88.5 (C), 84.8 (C), 52.3 (CH_3), 41.0 (CH_2), 40.7 (CH), 37.3 (d, J = 1.6 Hz, CH_2).

7s: methyl 8-bromo-7-(4-fluorophenyl)oct-5-ynoate



Appearance: Slightly yellowish oil

Yield: 37% (B)

Eluent: Hexanes/AcOEt 40:1

HRMS calcd. for $C_{15}H_{16}{}^{79}BrFNaO_2$ (M+23): 349.0210

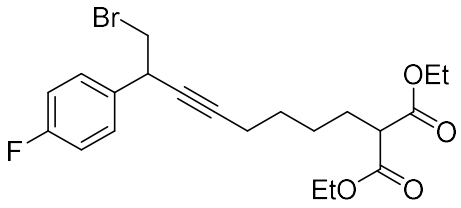
HRMS (ESI) found: 349.0205

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.40-7.29 (m, 2H), 7.10-6.97 (m, 2H), 4.02-3.91 (m, 1H), 3.68 (s, 3H), 3.60-3.44 (m, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.33 (td, *J* = 6.9, 2.2 Hz, 2H), 1.86 (p, *J* =7.2 Hz, 2H).

^{19}F-NMR (282 MHz, $CDCl_3$, 25 ºC) δ (ppm) -114.78.

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 173.8 (C), 162.4 (d, *J* = 246.3 Hz, C), 135.2 (d, *J* = 3.2 Hz, C), 129.5 (d, *J* = 8.1 Hz, CH), 115.6 (d, *J* = 21.6 Hz, CH), 84.2 (C), 80.0 (C), 51.8 (CH_3), 40.2 (CH), 37.8 (d, *J* = 1.4 Hz, CH_2), 33.0 (CH_2), 24.1 (CH_2), 18.4 (CH_2).

7t: dimethyl 2-(8-bromo-7-(4-fluorophenyl)oct-5-yn-1-yl)malonate



Appearance: Slightly yellowish oil

Yield: 71% (B)

Eluent: Hexanes/AcOEt 40:1

HRMS calcd. for $C_{21}H_{26}{}^{79}BrFNaO_4$ (M+23): 463.0891

HRMS (ESI) found: 463.0886

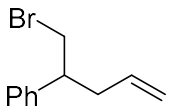
^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.40-7.28 (m, 2H), 7.11-6.90 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 4H), 4.01-3.90 (m, 1H), 3.60-3.43 (m, 2H), 3.31 (t, *J* = 7.5 Hz, 1H), 2.26 (td, *J* = 6.8, 2.2 Hz, 2H), 1.92 (q, *J* = 7.7 Hz, 2H), 1.65-1.37 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 6H).

^{19}F-NMR (282 MHz, $CDCl_3$, 25 ºC) δ (ppm) -114.90.

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 169.6 (C), 162.4 (d, *J* = 246.1Hz, C), 135.3 (d, *J* = 3.1 Hz, C), 129.6 (d, *J* = 8.2 Hz, CH), 115.6 (d, *J* = 21.5 Hz, CH), 85.0 (C), 79.4 (C), 61.5 (CH_2), 52.1 (CH), 40.2 (CH), 37.9 (d, *J* = 1.7 Hz, CH_2), 28.5 (CH_2), 28.4 (CH_2), 26.7 (CH_2), 18.7 (CH_2), 14.3 (CH_3).

Products **14**

14a: 5-bromo-4-phenylpent-1-ene



Appearance: Slightly yellowish oil

Yield: 64% (A), 50% (B)

Eluent: Hexanes/AcOEt 80:1

HRMS calcd. for $C_{11}H_{14}{}^{79}Br$: 225.0273

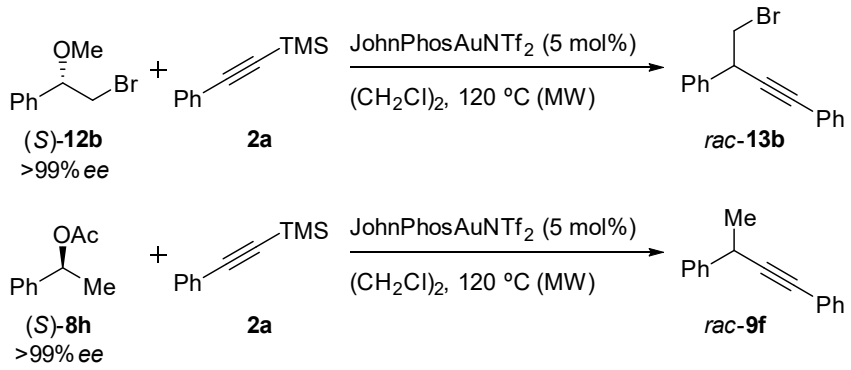
HRMS (EI) found: 225.0279

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.44-7.11 (m, 5H), 5.76-5.54 (m, 1H), 5.13-4.92 (m, 2H), 3.68-3.50 (m, 2H), 3.13-2.97 (m, 1H), 2.74-2.55 (m, 1H), 2.55-2.35 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 142.0 (C), 135.6 (CH), 128.7 (CH), 127.9 (CH), 127.3 (CH), 117.4 (CH_2), 47.7 (CH), 38.6 (CH_2), 38.2 (CH_2).

3. Mechanistic Studies

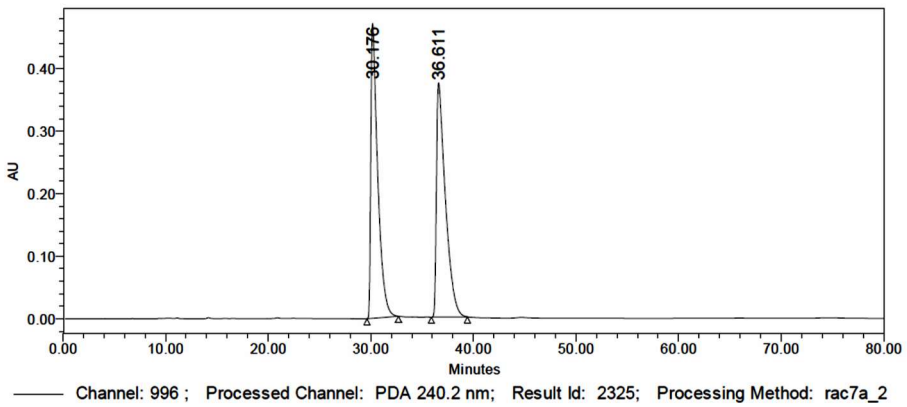
Tests for Validation of the Cationic Mechanistic Hypothesis



Scheme III.20: Reactions of (*S*)-**12b** and (*S*)-**8h** with **2a** to give the corresponding racemic products.

Following procedure B, compounds (*S*)-**12b** and (*S*)-**8h** afforded the racemic compounds **13b** and **9f**, respectively. The enantiomeric excess of both compounds was analysed by HPLC techniques (Chiracel® OD-H, hexane, 0.8 mL/min, in both cases) using racemic compounds **13b** and **9f** as reference. HPLC chromatograms are shown below.

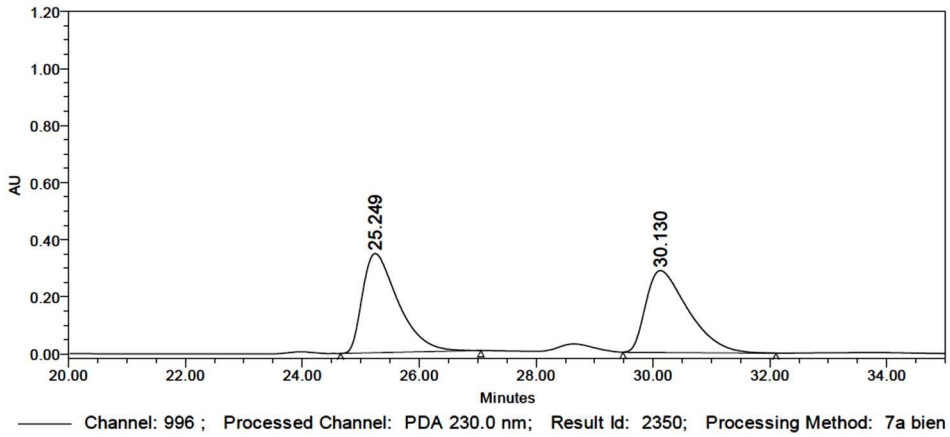
Compound rac-**13b**



Processed Channel Descr.: PDA 240.2 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.2 nm	30.176	21947458	49.26	471861
2	PDA 240.2 nm	36.611	22608195	50.74	374776

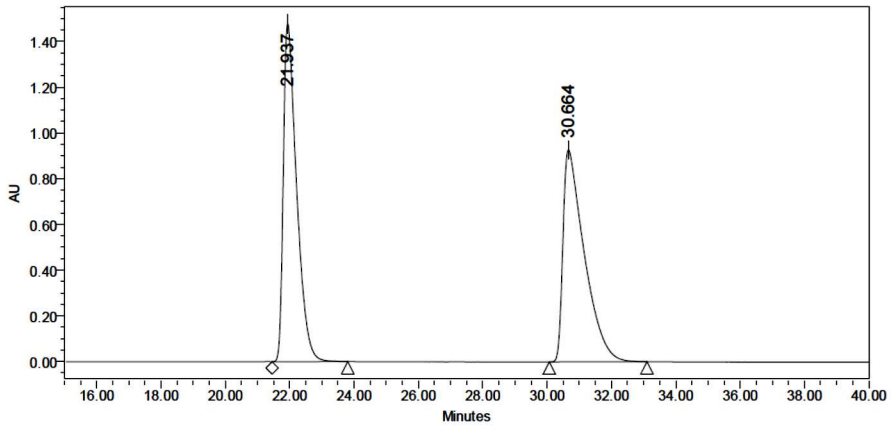
*Compound rac-***13b** *obtained from (S)-***12b**



Processed Channel Descr.: PDA 230.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 230.0 nm	25.249	14776958	50.58	347796
2	PDA 230.0 nm	30.130	14437587	49.42	286921

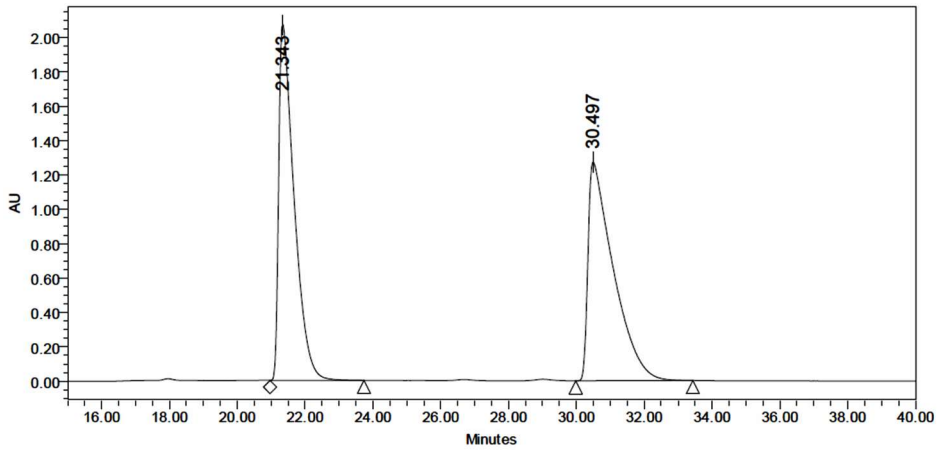
*Compound rac-***9f**



Peak Results

	Name	RT	% Area	Area	Height	Amount	Units
1		21.937	49.82	42318742	1479858		
2		30.664	50.18	42618402	927054		

*Compound rac-***9f** *obtained from (S)-***8h**

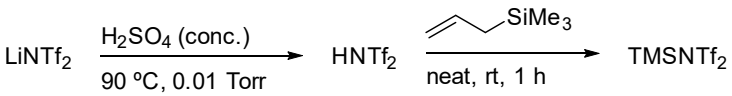


Peak Results

	Name	RT	% Area	Area	Height	Amount	Units
1		21.343	49.68	65149704	2071792		
2		30.497	50.32	65991389	1272992		

Synthesis and Use of the TMSNTf$_2$

Preparation of TMSNTf$_2$



Scheme III.21: General preparation of TMSNTf$_2$.

0.5 mmol commercially available LiNTf$_2$ are placed in a round bottom flask provided with a stirring bar and 1 mL of concentrated sulfuric acid is added. A distillation system provided with a two-necked collector flask (also with a stirring bar inside) is attached and the mixture is heated at 90 ºC under reduced pressure (approx. 0.01 mmHg). Solid HNTf$_2$ sublimates under these conditions and is collected in the two-necked flask, which is cooled with an ice bath. This collector flask with the stirring bar are previously emptied under vacuum, filled with argon, and weighted after releasing the overpressure. The difference in weight after the sublimation process provides the amount of HNTf$_2$ obtained. This procedure affords a 50-60% yield of the product for this amount of starting material. Yields are not reproducible for less than 0.5 mmol.

300 μL of allyltrimethylsilane **10a** are added to the flask and the mixture is stirred at room temperature for 1 hour. The excess of **10a** is eliminated under reduced pressure and $TMSNTf_2$ is obtained as a colourless liquid in quantitative yield. Subsequently, and always keeping the argon atmosphere, a 0.1 M solution of the $TMSNTf_2$ in the reaction solvent is made.

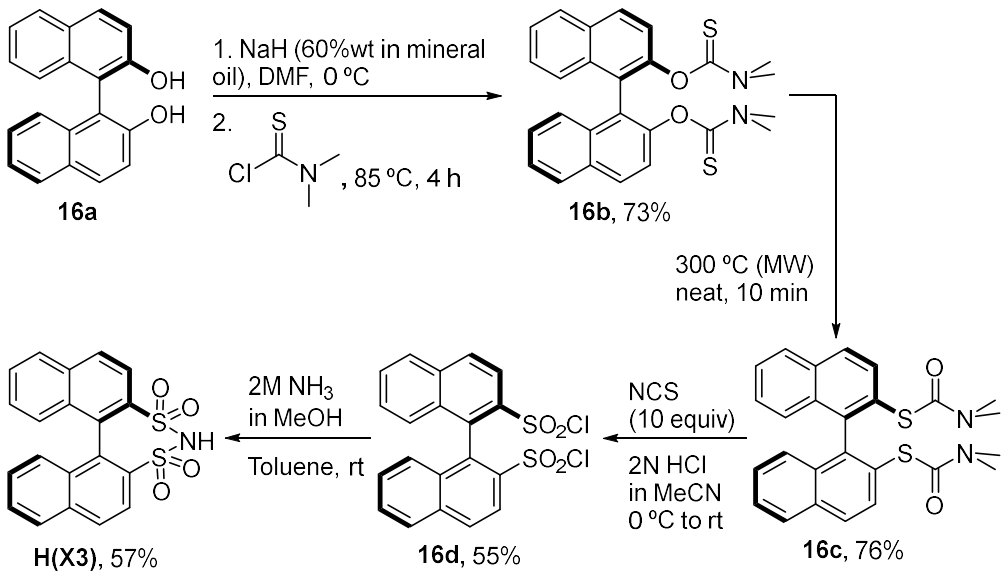
Procedure for reactions using $TMSNTf_2$ as catalyst

Alkynylation method A is used with a modification: 0.1 mL of the $TMSNTf_2$ 0.1 M solution (0.01 mmol, 0.05 equiv) are added in last place to the reaction mixture.

Experimental Remarks for the Exploratory Studies Towards an Enantioselective S_N1 Reaction

1. Starting Materials

Preparation of Chiral Acids H(X3-5)



Scheme III.22: Synthetic pathway for the preparation of compound **H(X3)**.

Compound **H(X3)** was prepared in a five-step synthetic sequence (Scheme III.22), parting from commercial (*R*)-BINOL.

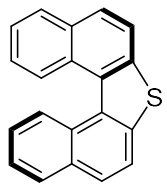
Preparation of **16b**

5.73 g of (*R*)-BINOL (20 mmol, 1 equiv) were solved in DMF (40 mL), the mixture was cooled to 0 °C and 2.40 g of NaH (60%wt in mineral oil, 60 mmol, 3 equiv) were added slowly. Then, 7.42 g of dimethylcarbamoyl chloride were added in one portion. The mixture was allowed to warm to room temperature and afterwards heated at 85 °C for 4 hours. Once it cooled again to room temperature, the reaction product was precipitated by addition of this mixture over a 1% aqueous solution of KOH (200 mL), with vigorous stirring. The solid precipitated was separated by filtration and washed with water. The slightly yellowish solid obtained was solved in dichloromethane, and this organic phase

was dried over sodium sulfate. Solvents were eliminated under vacuum. The dried solid was recrystallized in ethanol. After evaporating the solvent in the remaining solution and repeating the recrystallization once more, a total of 6.65 g of product were obtained (73% yield).[190]

Preparation of **16c**

2 g of **16b** was placed in two sealed 10 mL microwave vials (1 g per vial) and heated in a sand bath at 300 ºC for 10 min. After cooling at room temperature, a vitreous solid was obtained. The content of both vials was solved in dichloromethane, embed in 2 g of silica gel and purified by column chromatography (silica gel, first dichloromethane/hexanes 3:1 to separate by-product **16e** (Scheme III.23),[191] then diethyl ether). The remaining starting material was recovered from the column before the product and reused. 1.45 g of product (76% yield) were obtained as a white solid.[190]



16e

Scheme III.16: Product **16e**.

Preparation of **16d**

3.00 g of compound **23c** (6.5 mmol, 1 equiv) were suspended in 33 mL of MeCN and 6.5 mL of 2N HCl were added. The mixture was cooled to 0 ºC and 8.68 g (65 mmol, 10 equiv) of N-chlorosuccinimide[192] were added in small portions. The mixture was stirred at room temperature for 1 hour. Diethyl ether and water were added and both layers were separated. The aqueous layer was extracted twice with diethyl ether. The organic layer was dried over sodium sulfate and solvents were eliminated under reduced pressure. The solid

[190] For spectroscopic data see: M. Treskow, J. Neudörfl, R. Giernoth, *Eur. J. Org. Chem.* **2009**, *2009*, 3693–3697.

[191] D. Fabbri, G. Delogu, O. De Lucchi, *J. Org. Chem.* **1993**, *58*, 1748–1750.

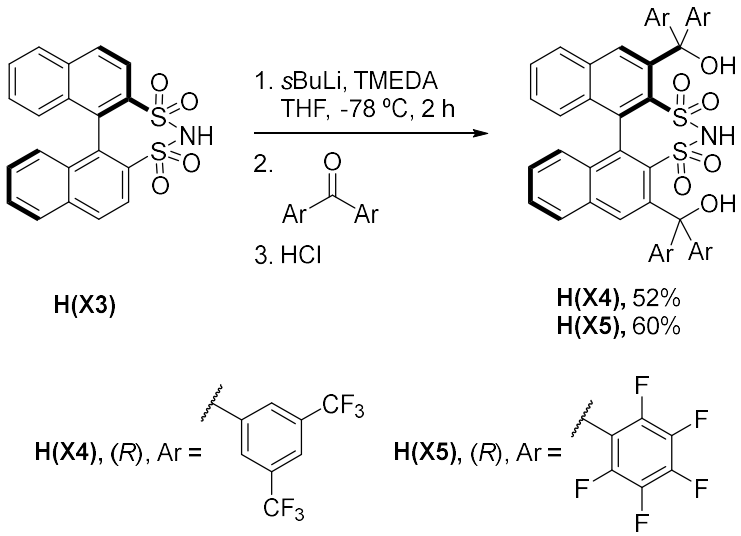
[192] Purified as in D. D. Perrin, W. L. F. Armarengo, D. R. Perrin in *Purification of Laboratory Chemicals* (Ed. D. D. Perrin), Pergamon Press, Oxford, **1980**, p. 172.

obtained was purified by column chromatography (silica gel, dichloromethane/hexanes 1:1). 1.61 g of the pure product were obtained as a white solid (55% yield).[190]

Preparation of **H(X3)**

3.62 g of compound **23d** (8.0 mmol, 1 equiv) were suspended in 80 mL of toluene. 25 mL of a 2M ammonia solution in methanol (48.1 mmol, 6 equiv) were added at room temperature, dropwise and very slowly (approx. 1 drop per minute). Once the addition was finished, solvents were evaporated at reduced pressure, and the solid obtained was purified by column chromatography (silica gel, ethyl acetate/methanol 10:1). A mixture of salts **M(X3)** (**M** = metal) was obtained. This mixture was solved in chloroform and stirred with 6N HCl for 2 hours. Both layers were separated and the organic solvent was eliminated at reduced pressure. 5 mL of toluene were added and evaporated again, and this was repeated 5 times in order to eliminate water traces from the solid. A pale yellow solid was obtained (1.82 g, 57% yield).[190]

Chiral acids **H(X4-5)** were prepared according to the procedure described by List et al. (Scheme III.24).[163a]



Scheme III.24: Synthetic pathway for the preparation of compounds **H(X4)** and **H(X5)**.

Preparation of **H(X4)** *and* **H(X5)**

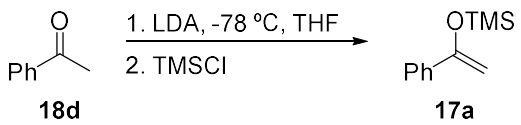
0.40 g of **H(X3)** (1 mmol, 1 equiv) were solved in 10 mL of THF. Subsequently, 525 μL of tetramethylethylenediamine (TMEDA) (3.5 mmol, 3.5 equiv) were added, and the mixture was stirred at room temperature for 30 min. Afterwards, it was cooled to -78 ºC and 2.5 mL of a 1.4 M *sec*-BuLi solution in cyclohexane were slowly added. The mixture was stirred at -78 ºC for 3 hours. Then, the corresponding diarylketone (4 mmol, 4 equiv) was solved in 9 mL of THF and added dropwise at -78 ºC. The mixture was allowed to warm up to room temperature and stirred for 2 more hours.

The reaction was quenched with water at 0 ºC, dichloromethane was added and both layers separated. The aqueous layer was extracted with dichloromethane twice. The organic layers were combined and dried over sodium sulfate. Solvents were evaporated under reduced pressure. The solid crude mixture was separated by column chromatography (silica gel, first diethyl ether to recover the excess of the ketone, then ethyl acetate/IPA 20:1). The recovered ketone can be recrystallized in methanol and reused.

The solid product was solved in chloroform and stirred along with a 6N HCl aqueous solution. Both layers were separated and chloroform was evaporated under reduced pressure. 5 mL of toluene were added and evaporated again, and this was repeated 5 times in order to eliminate water traces from the solid. A pale yellow solid was obtained in both cases.[193]

Silyl Enol Ethers 17a *and* 17b

Substrate **17b** was obtained from commercial suppliers. Substrate **17a** was prepared as follows (Scheme III.25):



18d **17a**

Scheme III.25: Synthesis of **17a**.

[193] For spectroscopic data see ref. 163a.

2 mL of diisopropylamine (DIPA, 15 mmol, 1.25 equiv) were solved in 40 mL of THF. The mixture was cooled to 0ºC and 9.4 mL of a 1.6 M BuLi solution in hexanes (15 mmol, 1.25 equiv) were added. The reaction mixture was allowed to warm up to room temperatureand stirred for 15 min. Afterwards, it was cooled to -78 ºC and 1.4 mL of acetophenone (12 mmol, 1 equiv) were added. It was stirred at -78 ºC for 1 hour, and then 2.0 mL of TMSCl were added. The reaction mixture was allowed to slowly warm up to room temperature overnight. THF was evaporated under vacuum and the residue was kept under argon atmosphere. 5 mL of dry pentane were added. The suspension was filtered through a Celite® path and under argon atmosphere. Pentane was removed under vacuum and the product was distilled at reduced pressure (b.p. 88-89 ºC/11 mmHg). It was obtained as a colourless liquid (2.08 g, 90% yield) and kept under argon atmosphere.

2. S_N1 Reactions

General Procedures for the S_N1 Reactions

General procedure for allylation reactions

0.2 mmol (1 equiv) of the corresponding substrate **8** and 0.8 mmol (4 equiv) of the corresponding nucleophile **2a** or **10a** were solved in 0.4 mL of the corresponding solvent or solvent mixture (see Table II.12). The corresponding reaction temperature was set, and 0.01 mmol (0.05 equiv) of the pre-catalyst **H(X4)** or **H(X5)** were added. The mixture was stirred until total conversion of the starting material. Then, pentane or toluene were evaporated under reduced pressure, whereas mesitylene[194] remained in the crude mixture, which was separated by column chromatography (silica gel, hexanes).

General procedure for reactions using silyl enol ethers or silyl enol esters

0.2 mmol (1 equiv) of the corresponding substrate **8** and 0.8 mmol (4 equiv) of the corresponding nucleophile **17** were solved in 0.4 mL of the corresponding solvent or solvent mixture (see Tables II.13 and II.14). The corresponding reaction temperature was set, and 0.01 mmol (0.05 equiv) of the pre-catalyst **H(X4)** or **H(X5)** were added. The mixture was stirred until total conversion of the starting material. Then, pentane or toluene

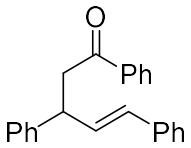
[194] Mesitylene was dried over calcium hydride and distilled under an argon atmosphere prior its use.

were evaporated under reduced pressure, whereas mesitylene remained in the crude mixture, which was separated by column chromatography (silica gel, first hexanes, then hexanes/ethyl acetate 20:1).[195]

Characterisation Data of Products **18** *and* **19**

Products **18**[196]

18b: (*E*)-1,3,5-triphenylpent-4-en-1-one



Appearance: White solid

m.p. 89.3.5-92.6 ºC (decomp.)

Yield/%ee: 93%/24%ee (using **H(X4)**), 87%/34%ee (opposite enantiomer, using **H(X5)**)

HPLC separation conditions: Chiracel® AD-H, hexane/isopropanol 99:1, 0.8 mL/min

HRMS calcd. for $C_{23}H_{20}NaO$ (M+23): 335.1390

HRMS (EI) found: 335.1405

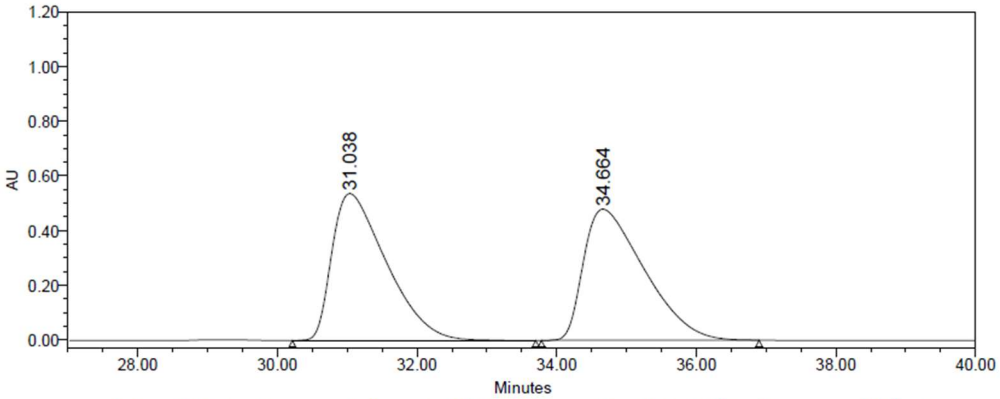
^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.98 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.42-7.14 (m, 10H), 6.55-6.35 (m, 2H), 4.35 (q, *J* = 6.2 Hz, 1H), 3.54 (dd, *J* = 6.9, 3.0 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 198.3 (C), 143.5 (C), 137.4 (C), 137.3 (C), 133.2 (CH), 132.8 (CH), 130.2 (CH), 128.85 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 127.4 (CH), 126.8 (CH), 126.4 (CH), 44.7 (CH_2), 44.1 (CH).

[195] Mesitylene was recovered from the crude mixture using hexanes as eluent. Several portions of recovered mesitylene could be combined, dried over calcium hydride and redistilled under argon an atmosphere to reuse it as solvent.

[196] For spectral data of compound **18a** see C.-F. Yang, J.-Y. Wang, S.-K. Tian, *Chem. Commun.* **2011**, *47*, 8343–8345.

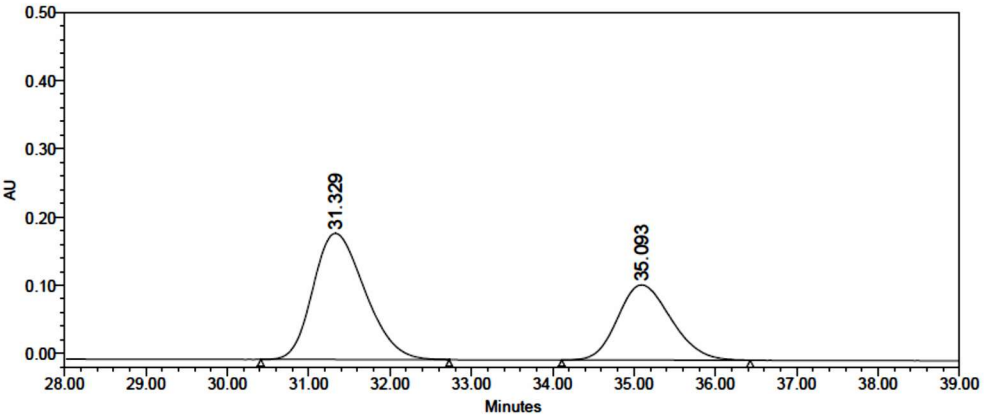
HPLC Chromatograms for racemic product **18b** *and the same compound obtained using* **H(X4)** *and* **H(X5)**, *respectively*



Channel: 996 ; Processed Channel: PDA 246.1 nm; Result Id: 2390; Processing Method: BR1157_2

Processed Channel Descr.: PDA 246.1 nm

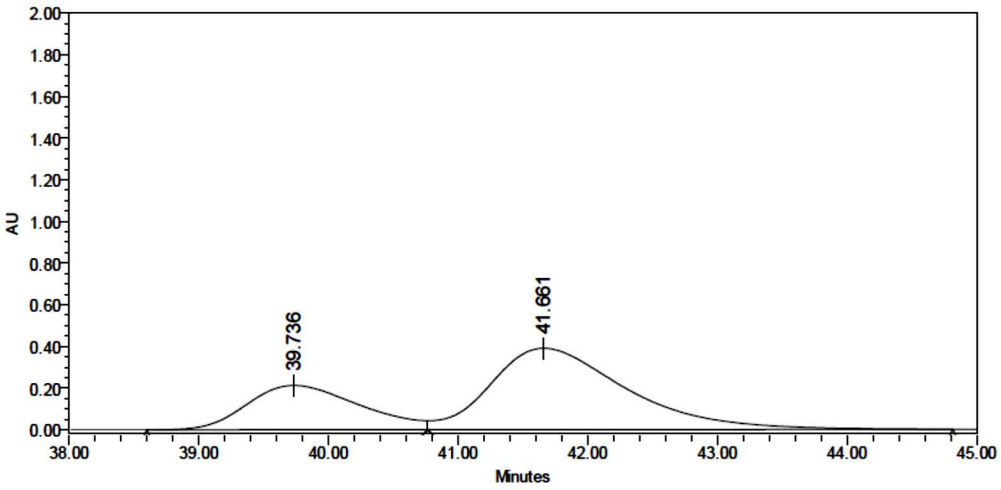
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 246.1 nm	31.038	29016186	50.04	536653
2	PDA 246.1 nm	34.664	28966773	49.96	479540



Channel: 996 ; Processed Channel: PDA 246.1 nm; Result Id: 2382; Processing Method: BR1242

Processed Channel Descr.: PDA 246.1 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 246.1 nm	31.329	8192719	61.99	184869
2	PDA 246.1 nm	35.093	5024083	38.01	110126



Peak Results

	Name	RT	% Area	Area	Height	Amount	Units
1		39.736	31.10	12849065	212831		
2		41.661	68.90	28462540	390560		

Products **19**

19a: methyl (*E*)-2,2-dimethyl-3,5-diphenylpent-4-enoate

Appearance: Slightly yellowish oil

Yield/%ee: 94%/6%ee (using **H(X5)**)

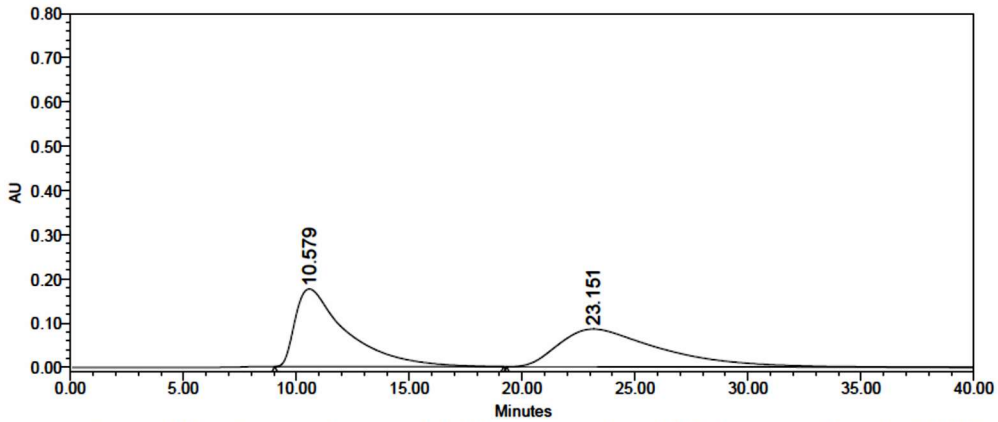
HPLC separation conditions: Chiracel® OB-H, hexane/ethanol 90:10, 0.7 mL/min

HRMS calcd. for $C_{20}H_{22}NaO_2$ (M+23): 317.1512
HRMS (EI) found: 317.1512

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.43-7.11 (m, 10H), 6.63 (dd, *J* = 15.7, 9.4 Hz, 1H), 6.47 (d, *J* = 15.5 Hz, 1H), 3.77 (d, *J* = 9.4 Hz, 1H), 3.62 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 177.5 (C), 140.7 (C), 137.5 (C), 132.7 (CH), 129.3 (CH), 128.9 (CH), 128.6 (CH), 128.3 (CH), 127.5 (CH), 127.0 (CH), 126.5 (CH), 57.2 (CH), 51.8 (CH_3), 47.5 (C), 23.5 (CH_3), 22.8 (CH_3).

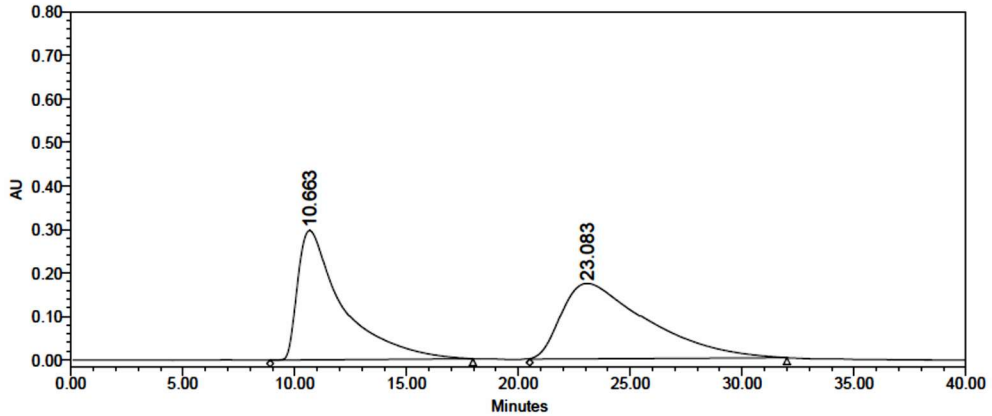
HPLC Chromatograms for racemic product **18b** *and the same compound obtained using* **H(X5)**, *respectively*



Channel: 996 ; Processed Channel: PDA 250.8 nm; Result Id: 2404; Processing Method: BR1190

Processed Channel Descr.: PDA 250.8 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.8 nm	10.579	27744440	50.87	175326
2	PDA 250.8 nm	23.151	26790509	49.13	85345



Channel: 996 ; Processed Channel: PDA 250.8 nm; Result Id: 2394; Processing Method: BR1243

Processed Channel Descr.: PDA 250.8 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.8 nm	10.663	41227202	47.18	296844
2	PDA 250.8 nm	23.083	46159478	52.82	173186

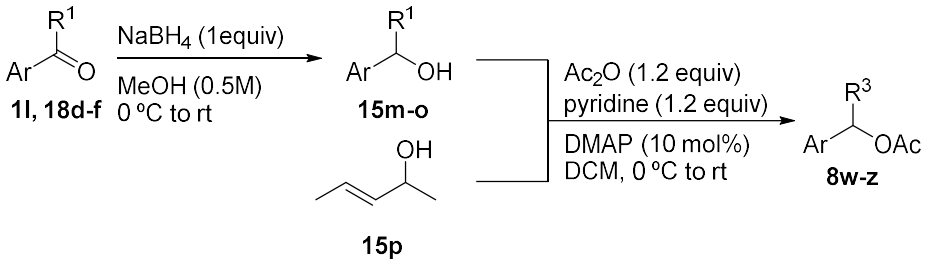
Experimental Remarks for the Synthesis of Benzylic Ethers by Nucleophilic Substitution on Acetates Using Silyl Ethers as Nucleophiles

1. Starting Materials

Preparation of $HNTf_2$

Catalyst $HNTf_2$ was freshly prepared (p. 233) and kept in a 0.1 M solution in DCE prior its use.

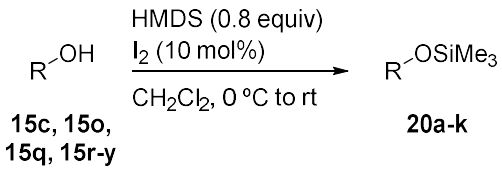
Acetates 8w-z



Scheme III.26: General synthetic pathway for substrates **8w-z**.

Alcohols **15m-o** were prepared by reduction of the corresponding aldehyde or ketone, as described for alcohols **15c-f**, **15h** and **15l** in p. 200. Alcohol **15p** was obtained from commercial suppliers. Also, acetates **8w-z** were synthesised following the same method as for compounds **8f-m** (see p. 208).

Silyl Ethers 20



Scheme III.27: Synthesis of silyl ethers **20**.

Compounds **20** were prepared from the corresponding alcohols using a procedure previously described in literature.[197] Alcohols **15r-t**, **15v**, **15x** and **15y** were obtained from commercial suppliers, and alcohols **15c** and **15o** were prepared as reported in previous pages. Alcohols **15q** and **15w** were obtained upon reduction of 4-bromobenzaldehyde and 2-adamantanone, respectively, with sodium borohydride, as described for other alcohols **15** in p. 208. Alcohol **15u** was synthesised by transesterification of δ-valerolactone with methanol.[198]

2. Synthesis of Benzylic Ethers

General Procedure for the Preparation of Compounds 21

0.2 mmol of the corresponding acetate **8** and 0.8 mmol (4equiv) of the corresponding silyl ether **20** were solved in 0.3 mL of DCE at room temperature. The mixture was cooled to 0 ºC. Subsequently, 0.1 mL of a 0.1 M solution of $HNTf_2$ (0.01 mmol, 0.05 equiv) in DCE was added slowly. After 5 min stirring at 0 ºC, the mixture was allowed to warm up to room temperature. The stirring continued during the time indicated in Tables II.16 and II.17. Afterwards, the solution was filtered through a short path of basic alumina in order to remove the catalyst and convert the excess of compound **20** into the corresponding alcohol.[199] Products **19** were purified by column chromatography (silica gel, hexanes/ethyl acetate 100:1), and obtained in the yields indicated in Tables II.16 and II.17.

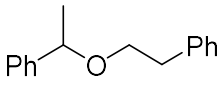
[197] B. Karimi, B. Golshani, *J. Org. Chem.* **2000**, *65*, 7228–7230.

[198] J. Weng, S. Wang, L.-J. Huang, Z.-Y. Luo, G. Lu, *Chem. Commun.* **2015**, *51*, 10170–10173.

[199] This treatment was observed to have no influence in the yield, but to considerably ease the purification of the corresponding product, which is obtained in a mixture with the excess of compound **20** otherwise.

Characterisation Data of Products **21**

21a: 1-phenylethyl 2-phenylethyl ether



Appearance: Colourless liquid

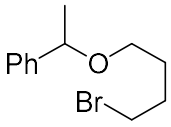
Yield: 67%

HRMS calcd. for $C_{16}H_{18}NaO$ (M+23): 249.1250

HRMS (EI) found: 294.1249

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.45-7.18 (m, 10H), 4.46 (q, *J* = 6.4 Hz, 1H), 3.57 (t, *J* = 7.3 Hz, 2H), 3.06-2.82 (m, 2H), 1.49 (d, *J* = 6.4 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 144.1 (C), 139.2 (C), 129.1 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 126.3 (CH), 126.25 (CH), 78.3 (CH), 69.8 (CH_2), 36.7 (CH_2), 24.3 (CH_3).

21b: 4-bromo-1-butyl 1-phenylethyl ether



Appearance: Colourless liquid

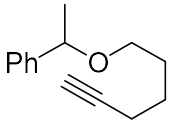
Yield: 79%

HRMS calcd. for $C_{12}H_{17}BrNaO$ (M+23): 279.0355

HRMS (EI) found: 279.0356

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.44-7.20 (m, 5H), 4.40 (q, *J* = 6.5 Hz, 1H), 3.43 (t, *J* = 6.8 Hz, 2H), 3.34 (dt, *J* = 6.4, 3.2 Hz, 2H), 2.07-1.84 (m, 2H), 1.81-1.64 (m, 2H), 1.46 (d, *J* = 6.4 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 144.2 (C), 128.6 (CH), 127.6 (CH), 126.3 (CH), 78.2 (CH), 67.6 (CH_2), 34.0 (CH_2), 29.9 (CH_2), 28.7 (CH_2), 24.3 (CH_3).

21c: hex-5-yn-1-yl 1-phenylethyl ether



Appearance: Colourless liquid

Yield: 54%

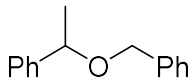
HRMS calcd. for $C_{14}H_{18}NaO$ (M+23): 225.1250

HRMS (EI) found: 225.1254

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.45-7.16 (m, 5H), 4.38 (q, *J* = 6.5 Hz, 1H), 3.31 (t, *J* = 6.0 Hz, 2H), 2.26-2.10 (m, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.76-1.49 (m, 4H), 1.43 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 144.3 (C), 128.6 (CH), 127.5 (CH), 126.3 (CH), 84.6 (C), 78.1 (CH), 68.5 (CH), 68.1 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 24.4 (CH_3), 18.4 (CH_2).

21e: benzyl 1-phenylethyl ether



Appearance: Colourless liquid

Yield: 75%

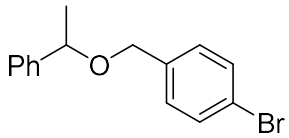
HRMS calcd. for $C_{15}H_{16}NaO$ (M+23): 235.1093

HRMS (EI) found: 235.1094

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.46-7.25 (m, 10H), 4.58-4.43 (m, 2H), 4.32 (d, *J* = 11.3 Hz, 1H), 1.51 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 143.9 (C), 138.8 (C), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 126.5 (CH), 77.4 (CH), 70.5 (CH_2), 24.4 (CH_3).

21f: 4-bromophenylmethyl 1-phenylethyl ether



Appearance: Colourless liquid

Yield: 75%

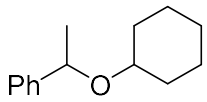
HRMS calcd. for $C_{15}H_{15}BrNaO$ (M+23): 313.0198

HRMS (EI) found: 313.0193

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC) δ (ppm) 7.49 (d, *J* = 8.0 Hz, 2H), 7.45-7.10 (m, 5H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.51 (q, *J* = 6.5 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.28 (d, 12.0 Hz, 1H), 1.51 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC) δ (ppm) 143.6 (C), 137.8 (C), 131.6 (CH),129.5 (CH), 128.7 (CH), 127.8 (CH), 126.5 (CH), 121.5 (C), 77.6 (CH), 69.7 (CH_2), 24.3 (CH_3).

21h: cyclohexyl 1-phenylmethyl ether



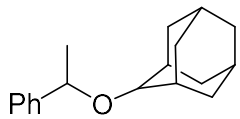
Appearance: Colourless liquid

Yield: 43%

HRMS calcd. for $C_{14}H_{20}NaO$ (M+23): 227.1406
HRMS (EI) found: 227.1408

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.40-7.15 (m, 5H), 4.60 (q, *J* = 6.5 Hz, 1H), 3.16 (tt, *J* = 9.8, 3.8 Hz, 1H), 2.07-1.90 (m, 1H), 1.83-1.60 (m, 3H), 1.57-1.45 (m, 1H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.37-1.00 (m, 5H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 145.2 (C), 128.5 (CH), 127.3 (CH), 126.2 (CH), 75.0 (CH), 74.4 (CH), 33.7 (CH_2), 32.0 (CH_2), 26.0 (CH_2), 25.1 (CH_3), 24.6 (CH_2), 24.4 (CH_2).

21i: 2-adamantyl 1-phenylethyl ether



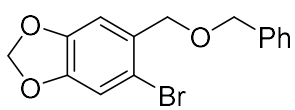
Appearance: Colourless liquid

Yield: 43%

HRMS calcd. for $C_{18}H_{24}NaO$ (M+23): 279.1719
HRMS (EI) found: 279.1723

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.40-7.15 (m, 5H), 4.58 (q, *J* = 6.5 Hz, 1H), 3.38 (brs, 1H), 2.23-2.03 (m, 1H), 1.83-1.60 (m, 3H), 1.91-1.63 (m, 7H), 1.61-1.45 (m, 4H), 1.43 (d, *J* = 6.4 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 145.4 (C), 128.4 (CH), 127.1 (CH), 126.2 (CH), 78.8 (CH), 73.7 (CH), 37.8 (CH_2), 36.9 (CH_2), 36.6 (CH_2), 33.3 (CH), 32.0 (CH_2), 31.8 (CH_2), 31.1 (CH), 27.7 (CH), 27.65 (CH), 25.0 (CH_3).

21m: benzyl (6-bromobenzo[*d*][1,3]dioxol-5-yl)methyl ether



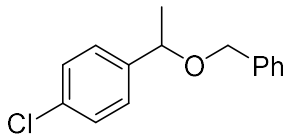
Appearance: Colourless liquid

Yield: 66%

HRMS calcd. for $C_{15}H_{13}BrNaO_3$ (M+23): 342.9940
HRMS (EI) found: 342.9940

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.47-7.27 (m, 5H), 7.03 (s, 1H), 7.01 (s, 1H), 5.97 (s, 2H), 4.61 (s, 2H), 4.54 (s, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 147.8 (C), 147.6 (C), 138.2 (C), 131.1 (C), 128.6 (CH), 127.95 (CH), 127.9 (CH), 113.4 (C), 112.7 (CH), 109.4 (CH), 101.9 (CH_2), 72.7 (CH_2), 71.6 (CH_2).

21n: benzyl 1-(4-chlorophenyl)ethyl ether



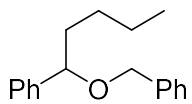
Appearance: Colourless liquid

Yield: 83%

HRMS calcd. for $C_{15}H_{18}ClNO$ (M+17): 264.1150
HRMS (EI) found: 264.1151

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.43-7.24 (m, 9H), 4.49 (q, *J* = 6.5 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.31 (d, *J* = 11.8 Hz, 1H), 1.47 (d, *J* = 6.4 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 142.4 (C), 138.5 (C), 133.3 (C), 128.9 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 127.75 (CH), 76.7 (CH), 70.6 (CH_2), 24.3 (CH_3).

21p: benzyl 1-(4-chlorophenyl)ethyl ether



Appearance: Colourless liquid

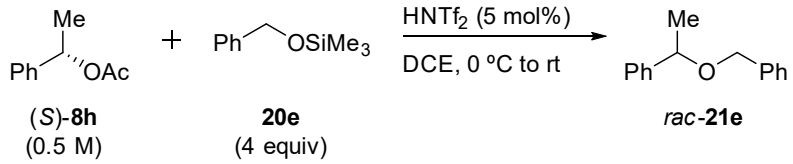
Yield: 83%

HRMS calcd. for $C_{18}H_{22}NaO$ (M+23): 277.1563
HRMS (EI) found: 277.1549

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm) 7.43-7.22 (m, 10H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.34-4.22 (m, 2H), 1.97-1.80 (m, 1H), 1.74-1.58 (m, 1H), 1.51-1.24 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm) 143.0 (C), 138.9 (C), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.65 (CH), 127.6 (CH), 127.0 (CH), 81.8 (CH), 70.6 (CH_2), 38.3 (CH_2), 28.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3).

3. Mechanistic Studies

*Chromatograms for Compound rac-***21e** *Obtained from* **(*S*)-8h**

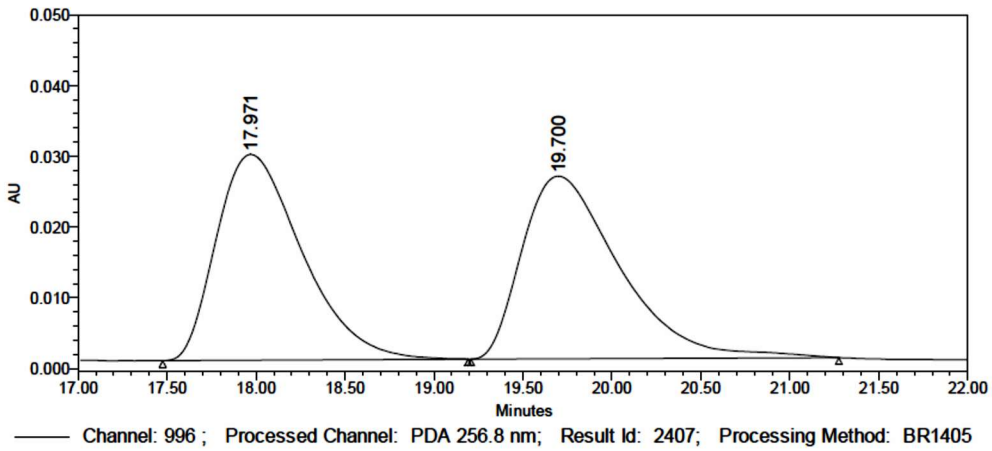


(*S*)-**8h** (0.5 M) + **20e** (4 equiv) → *rac*-**21e**

Scheme III.28: Reaction of (*S*)-**8h** with **20e** to afford racemic **21e**.

The enantiomeric excess of compound *rac*-**21e** obtained from substrate (*S*)-**8h** was analysed by HPLC and found to be racemic. Racemic substrate **21e** was used as reference. The corresponding chromatogram is shown below.

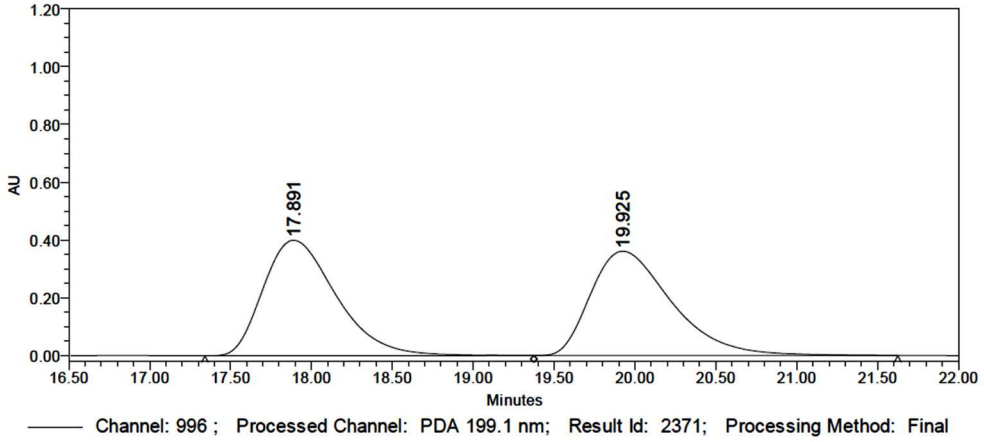
*Compound rac-***21e**



Processed Channel Descr.: PDA 256.8 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 256.8 nm	17.971	973967	49.83	29108
2	PDA 256.8 nm	19.700	980493	50.17	25822

*Compound rac-***21e** *obtained from (S)-***8h**

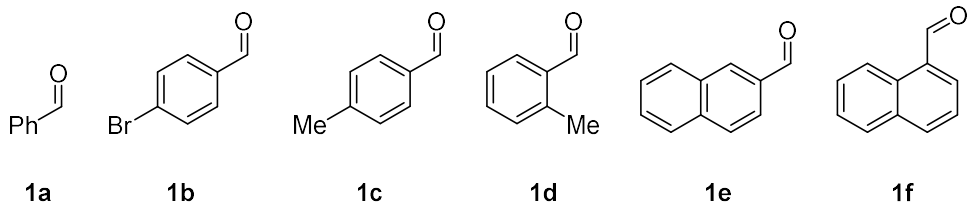


Processed Channel Descr.: PDA 199.1 nm

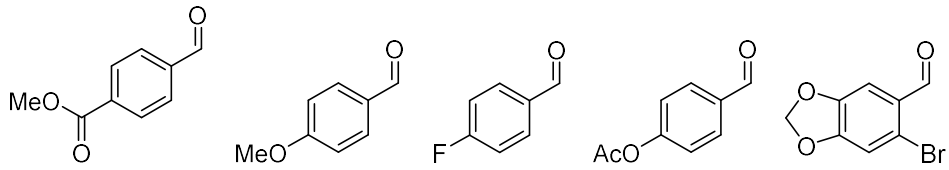
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 199.1 nm	17.891	12537528	49.85	399975
2	PDA 199.1 nm	19.925	12615076	50.15	361523

Index of Structures

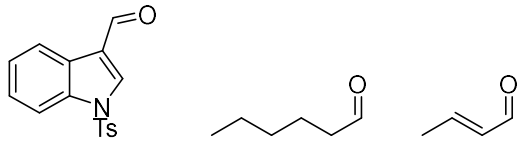
Aldehydes 1



1a **1b** **1c** **1d** **1e** **1f**

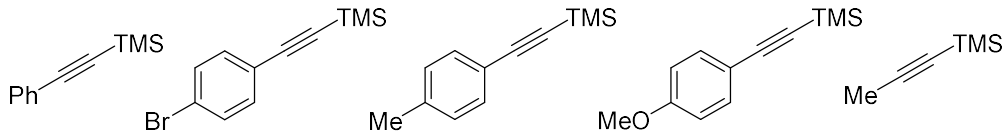


1g **1h** **1i** **1k** **1l**

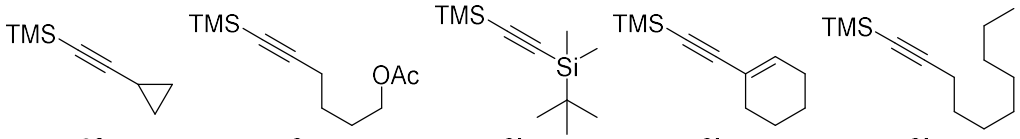


1m **1n** **1o**

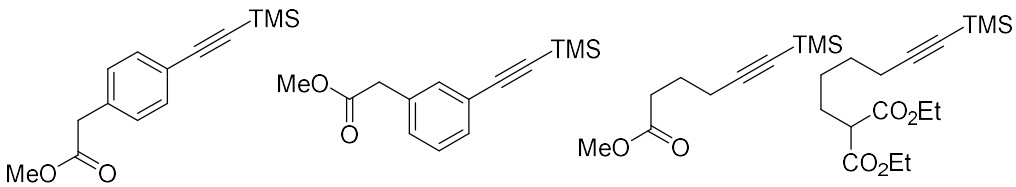
Alkynes 2



2a **2b** **2c** **2d** **2e**



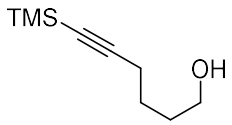
2f **2g** **2h** **2i** **2j**



2k **2l** **2m** **2n**

2o

2p



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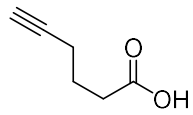
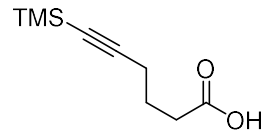
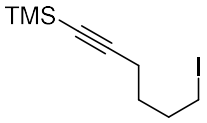


2r

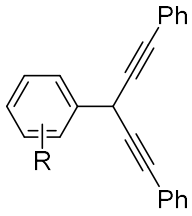


2s

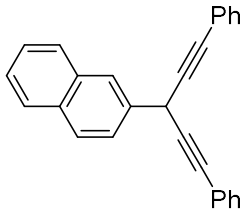


2t

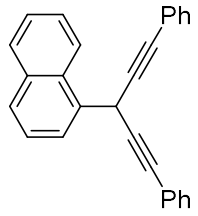
1,4-Diines 3



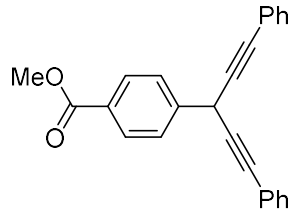
3a (R = H)
3b (R = 4-Br)
3c (R = 4-Me)
3d (R = 2-Me)



3e



3f



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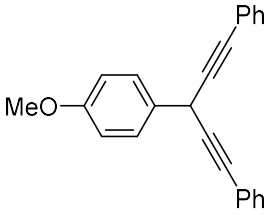
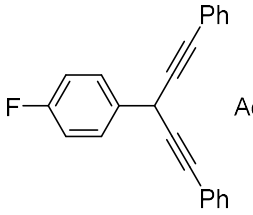


3h



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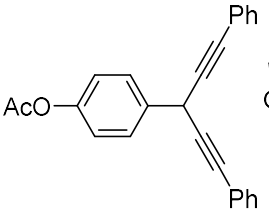

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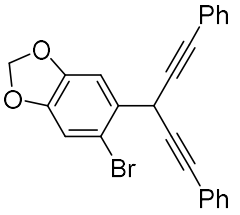

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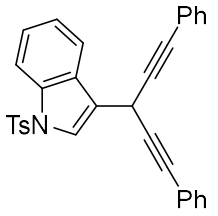

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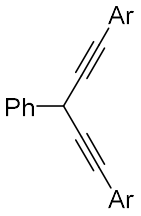
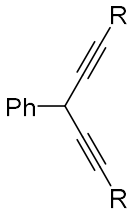
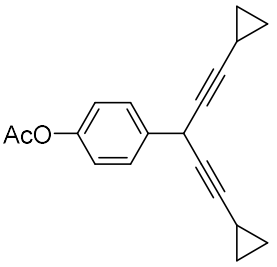


3m (Ar = 4-Br(C_6H_4)
3n (Ar = 4-Me(C_6H_4)
3o (Ar = 4-MeO(C_6H_4)

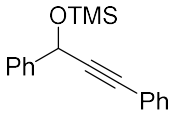


3p (R = Me)
3r (R = $(CH_2)_4OAc$)
3s (R = TBS)

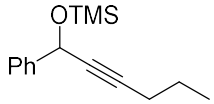


3q

Propargyl Ethers 4



4a



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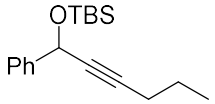

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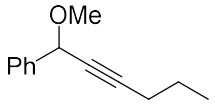

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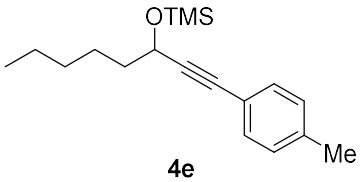
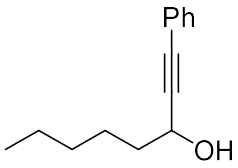
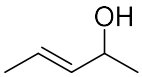


4e

Propargylic and Allylic Alcohols 5

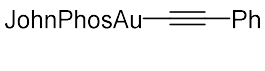


5a



5b

Gold Complexes 6 *and* 7



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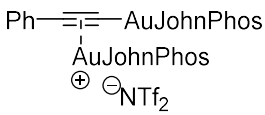

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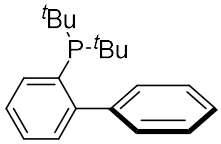
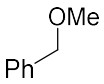


JohnPhos

Acetates and Ether Substrates 8



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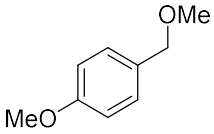

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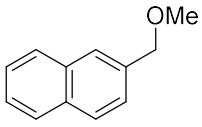

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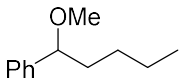

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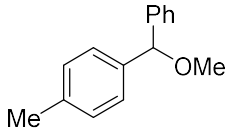

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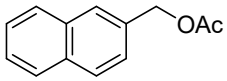

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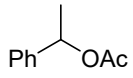

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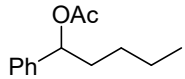

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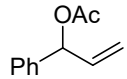

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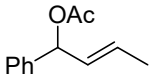

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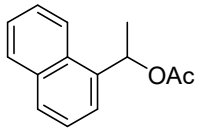

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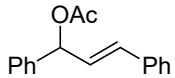

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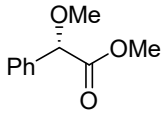

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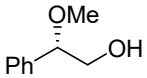

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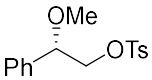

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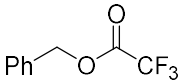

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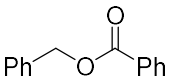

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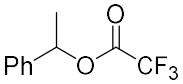

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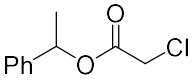

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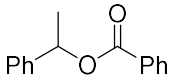

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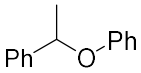

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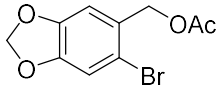

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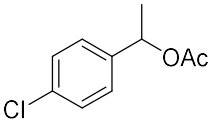

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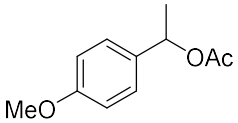

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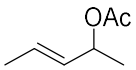

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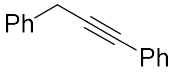
Coupling Products **9**



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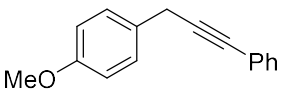

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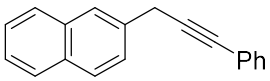

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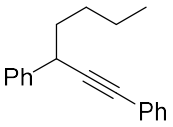

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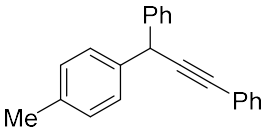

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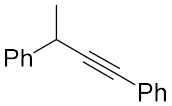

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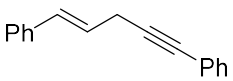

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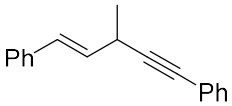

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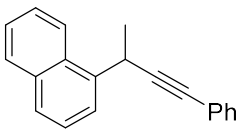

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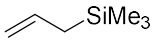
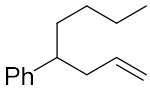
Allyltrimethylsilane 10



10a

Coupling Products 11



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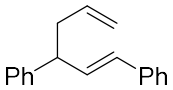

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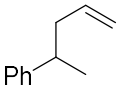
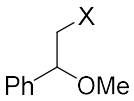


11c

β-*Haloethers* 12



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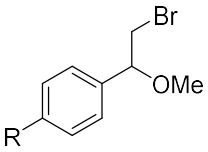
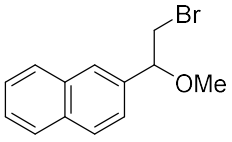
12c, X = I



12d, R = OMe
12e, R = Me
12f, R = Br
12g, R = CO_2Me
12h, R = F



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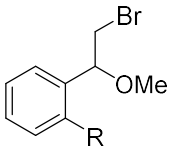
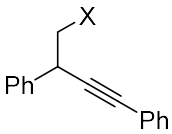
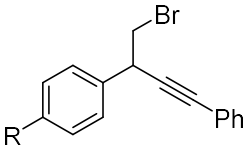


12j, R = OMe
12k, R = Me

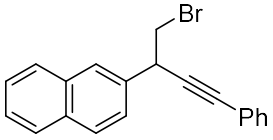
Coupling Products 13



13a, X = Cl
13b, X = Br
13c, X = I



13d, R = OMe
13e, R = Me
13f, R = Br
13g, R = CO_2Me
13h, R = F



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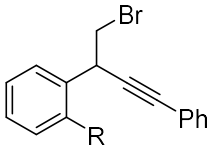
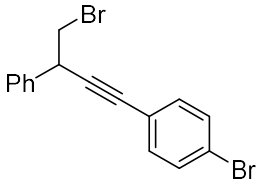


13j, R = OMe
13k, R = Me



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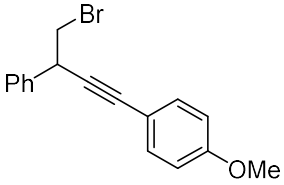

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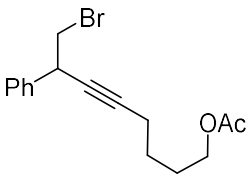

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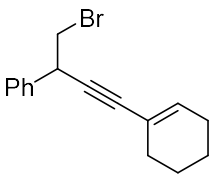

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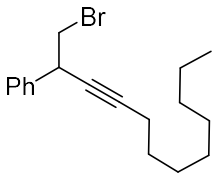

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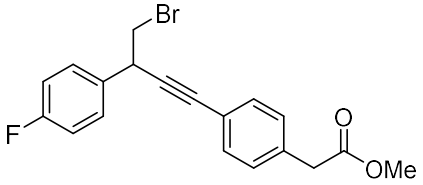

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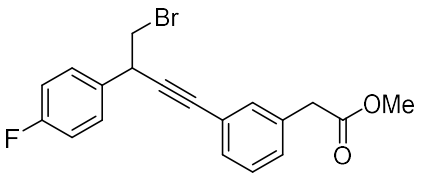

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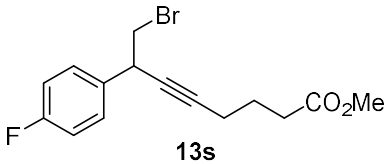

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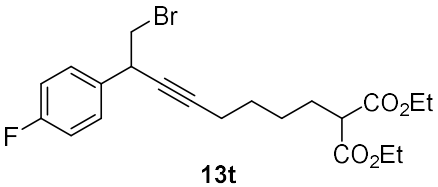
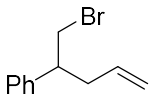


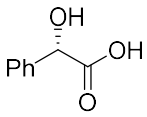
13t

Coupling Products 14



14a

Alcohols 15



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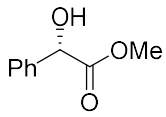

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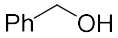

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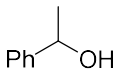

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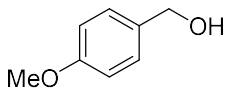

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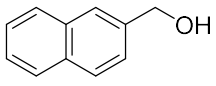

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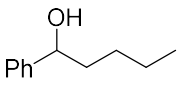

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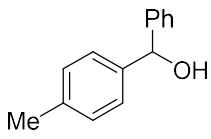

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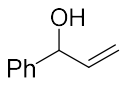

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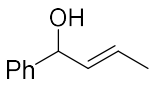

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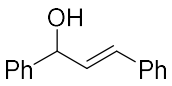

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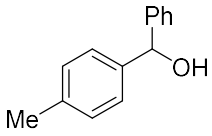

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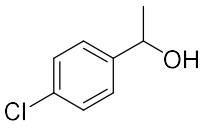

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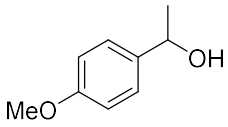

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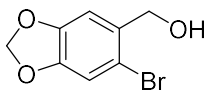

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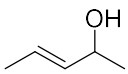

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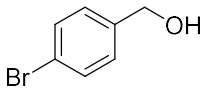

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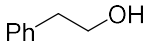

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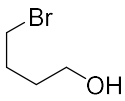

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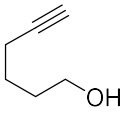

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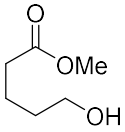

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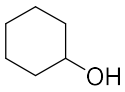

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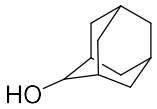

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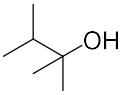
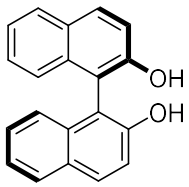


15x

15y

***BINOL Derivatives* 16**



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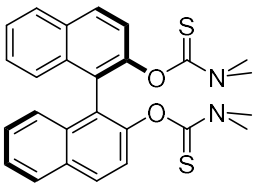

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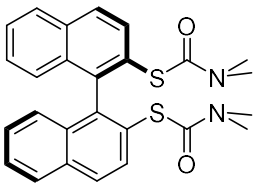

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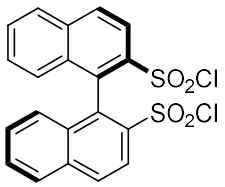

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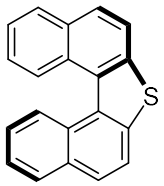
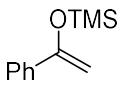


16e

Silyl Enol Ethers and Esters 17



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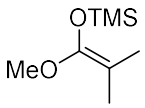
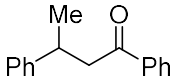


17b

Ketones 18



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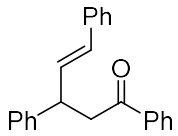

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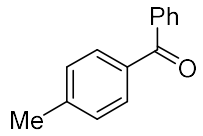

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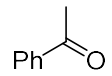

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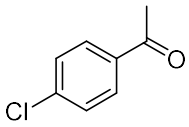

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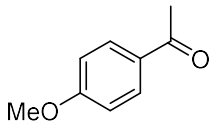

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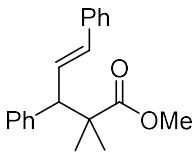
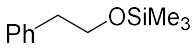
Esters 19



19a

Silyl Ethers 20



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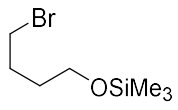

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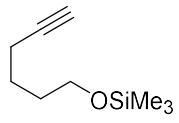

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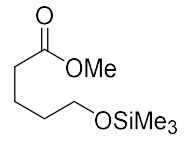

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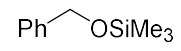

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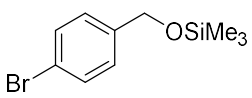

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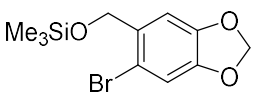

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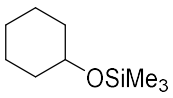

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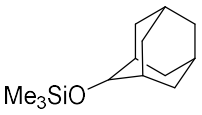

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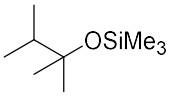

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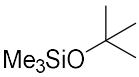

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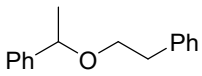

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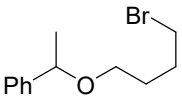

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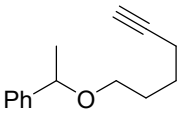

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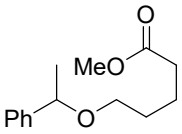

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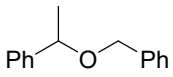

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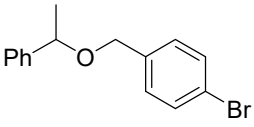

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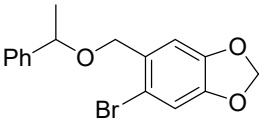

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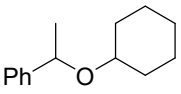

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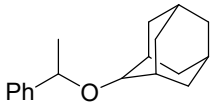

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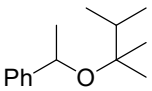

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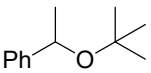

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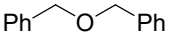

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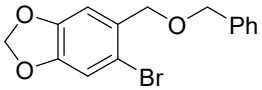

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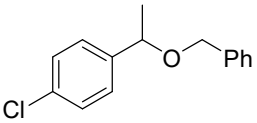

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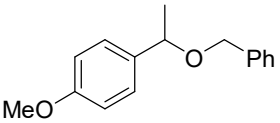

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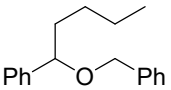

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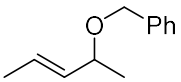

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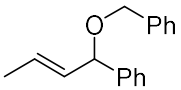

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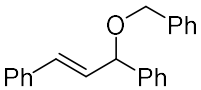

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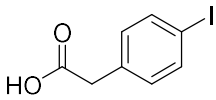
Aryl Iodides 22 *and* 23



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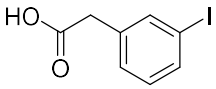

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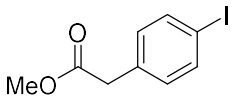

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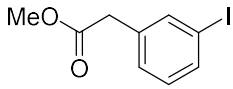
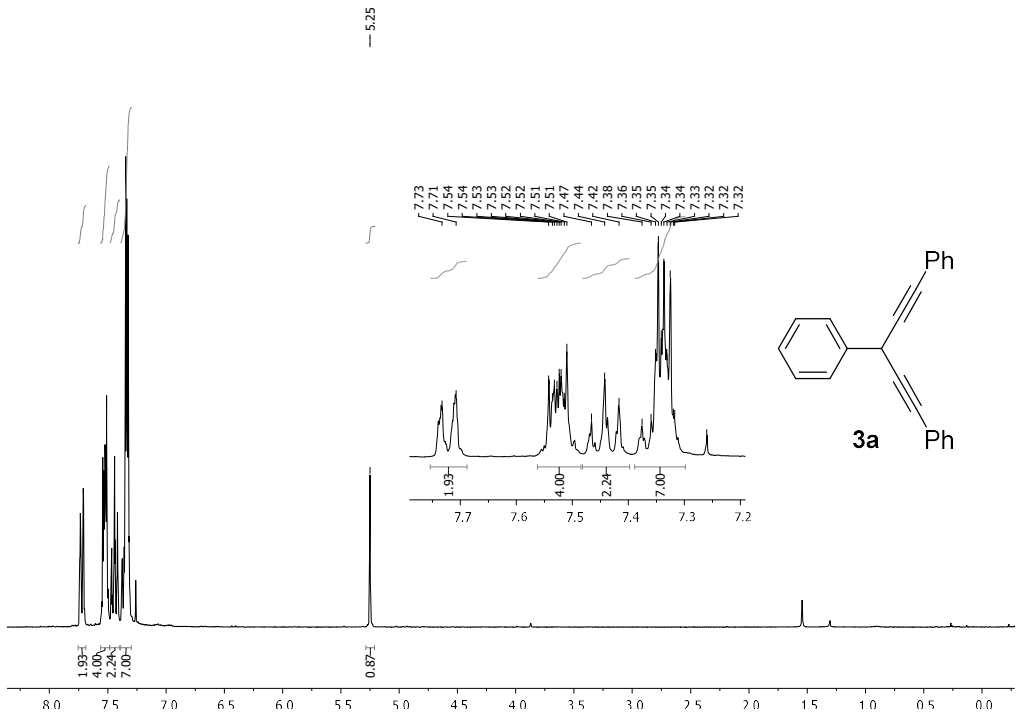


23b

NMR Spectra

Products 3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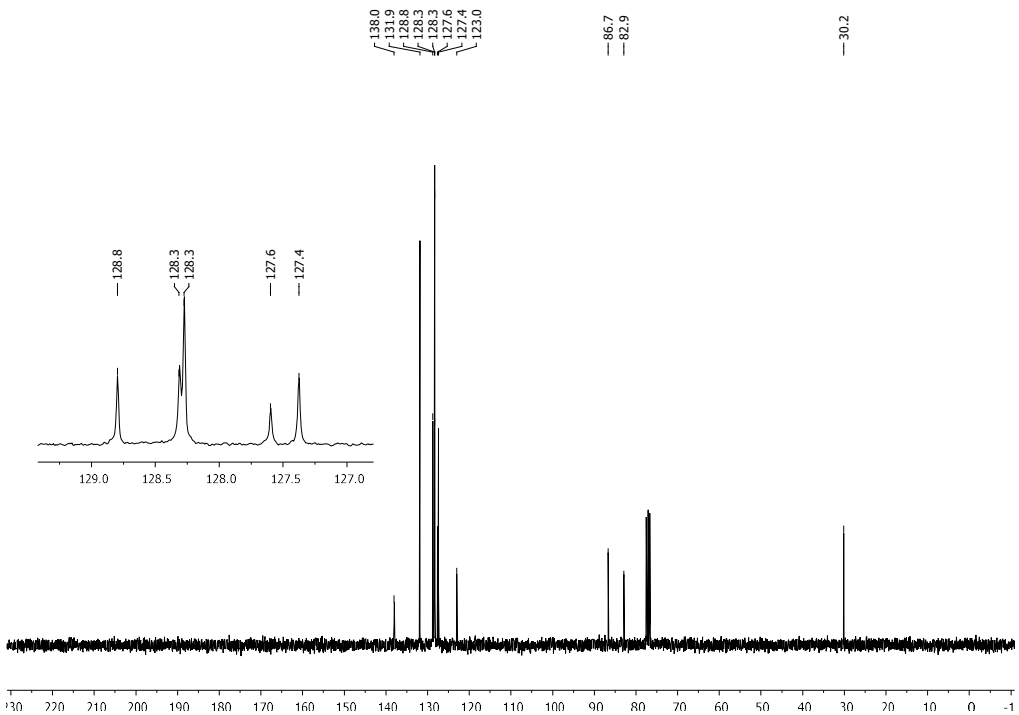
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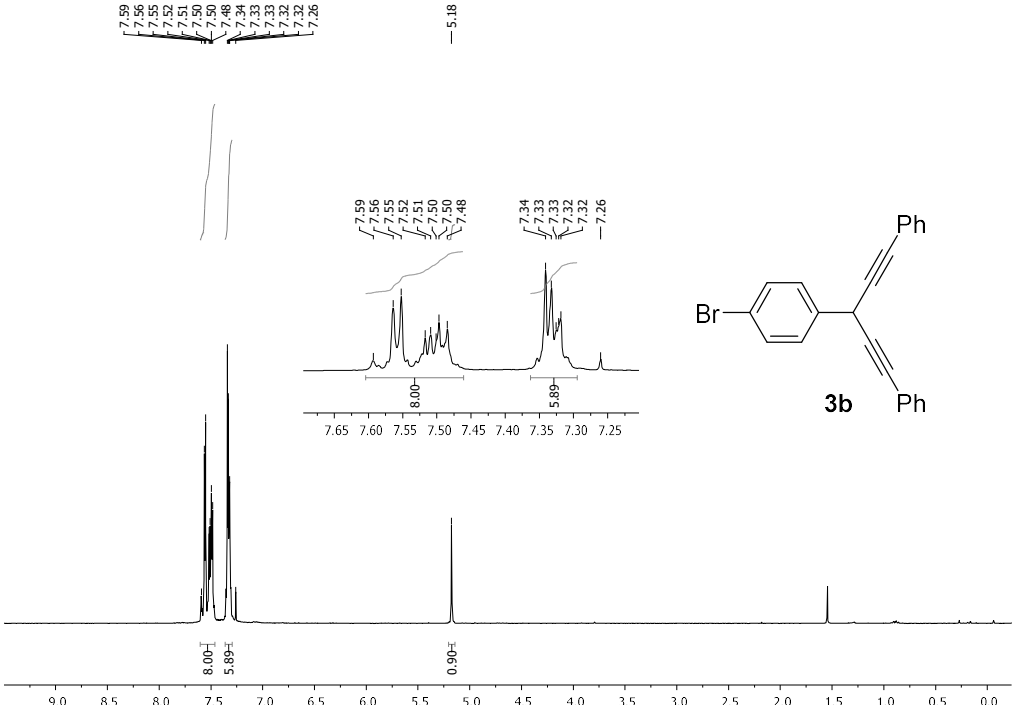
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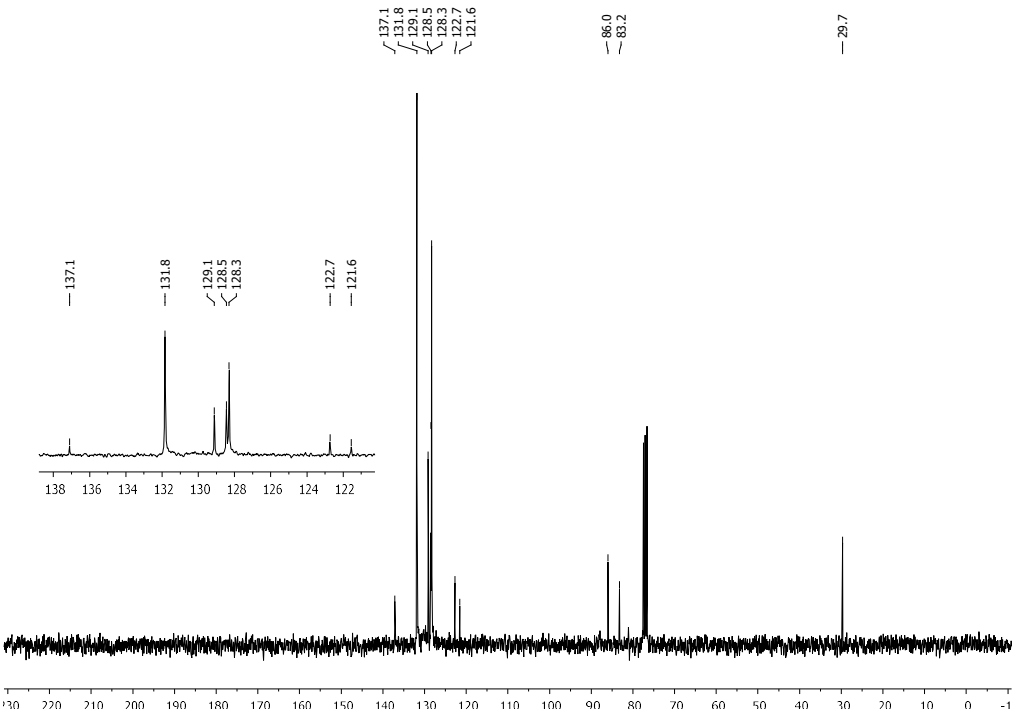
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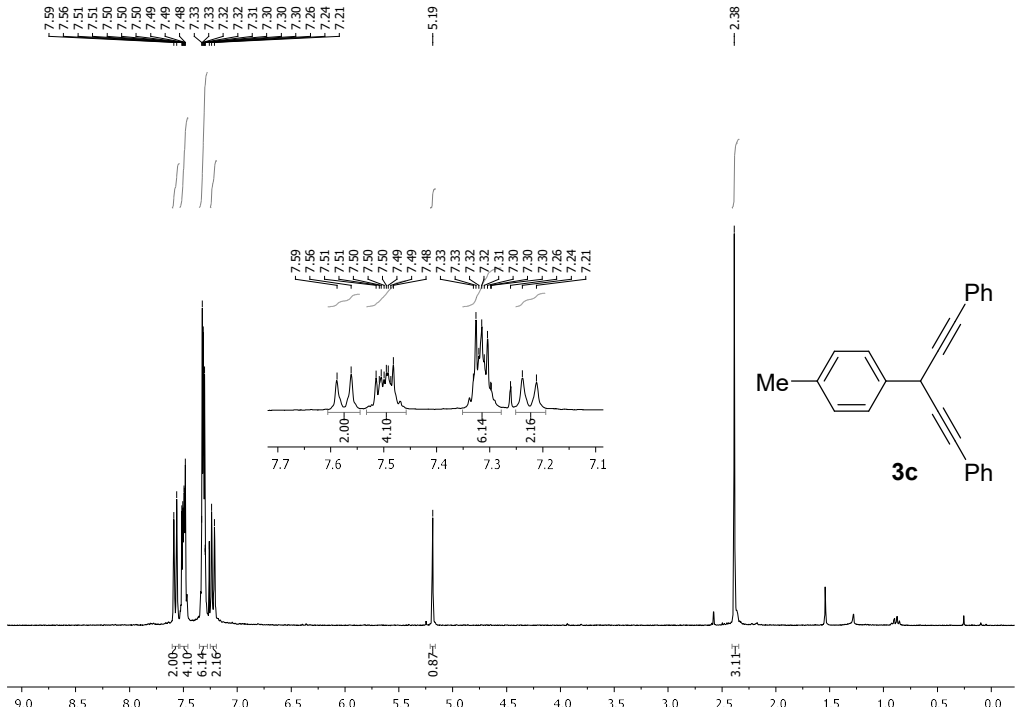
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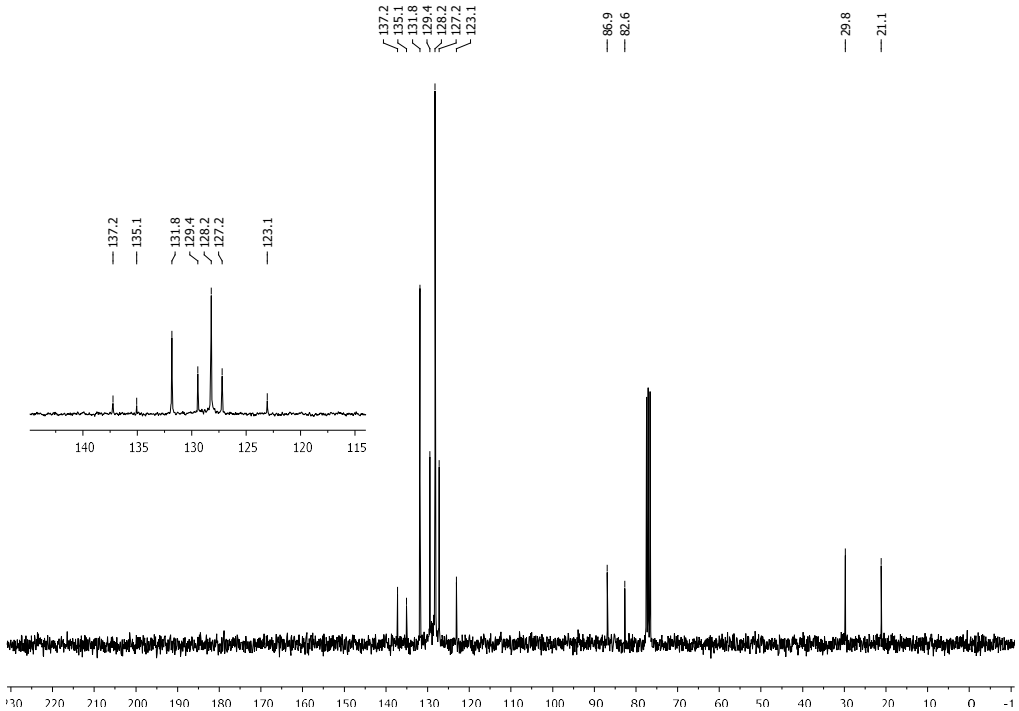
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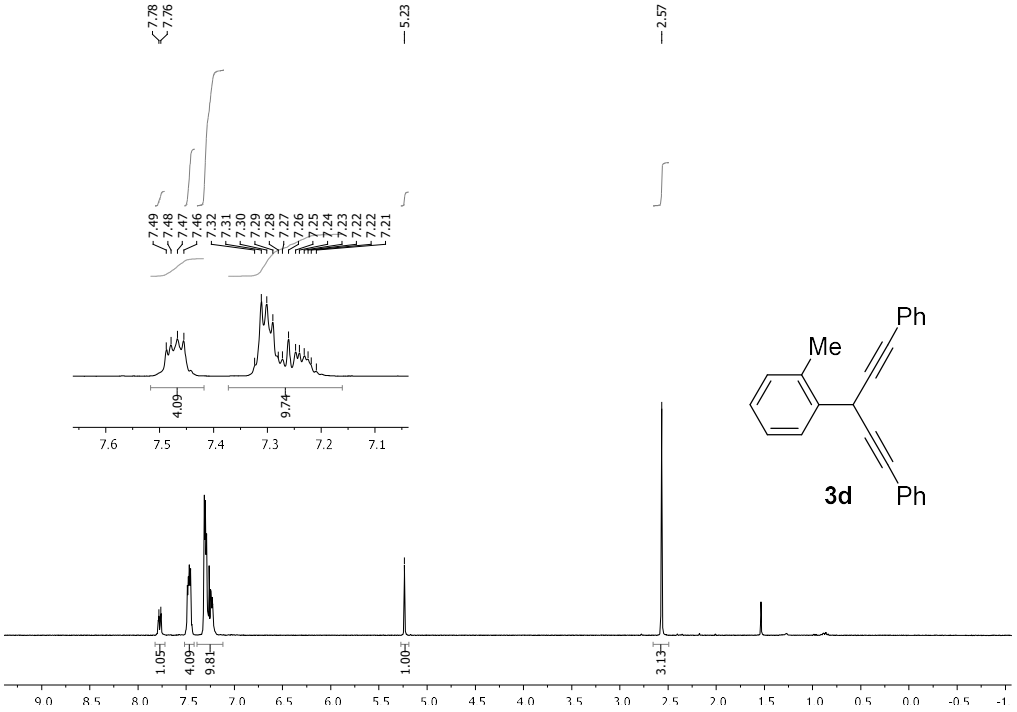
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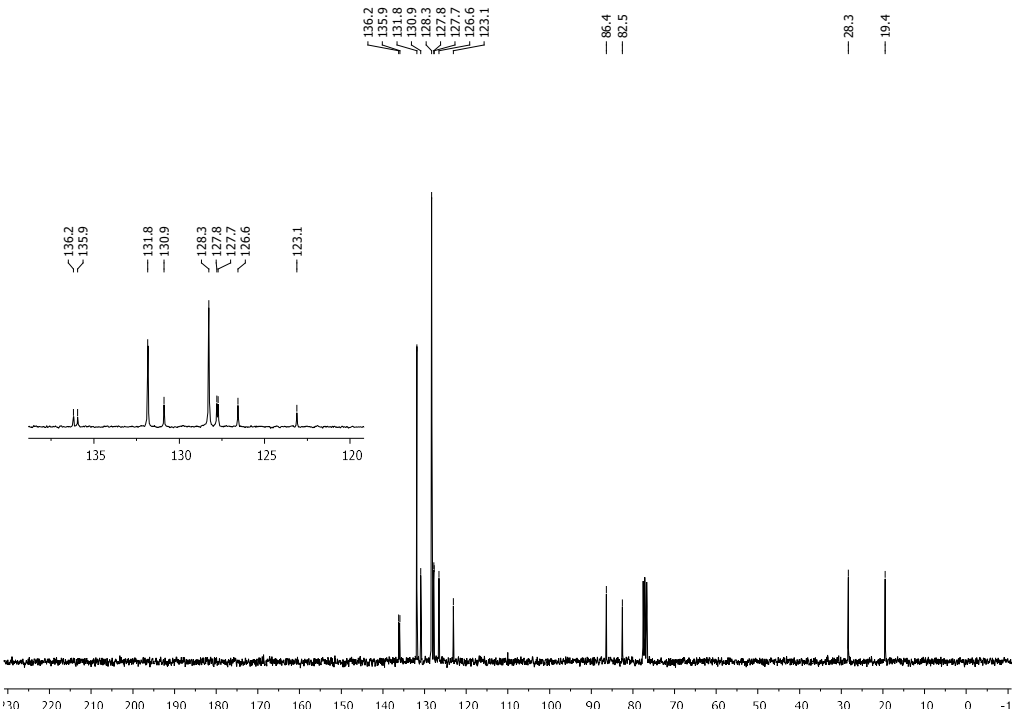
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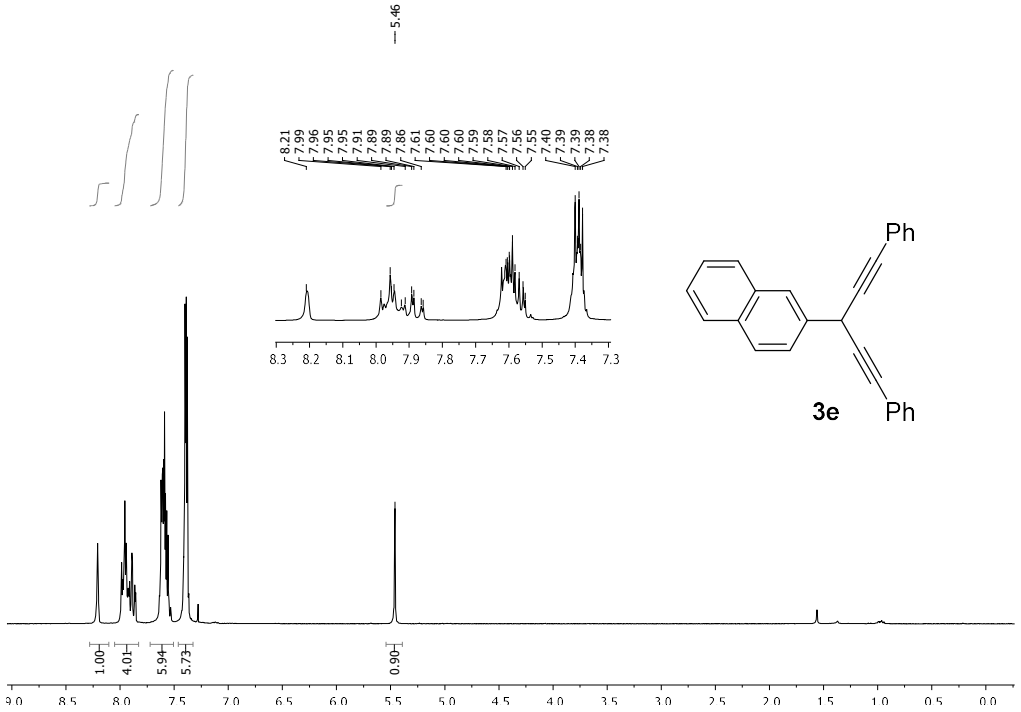
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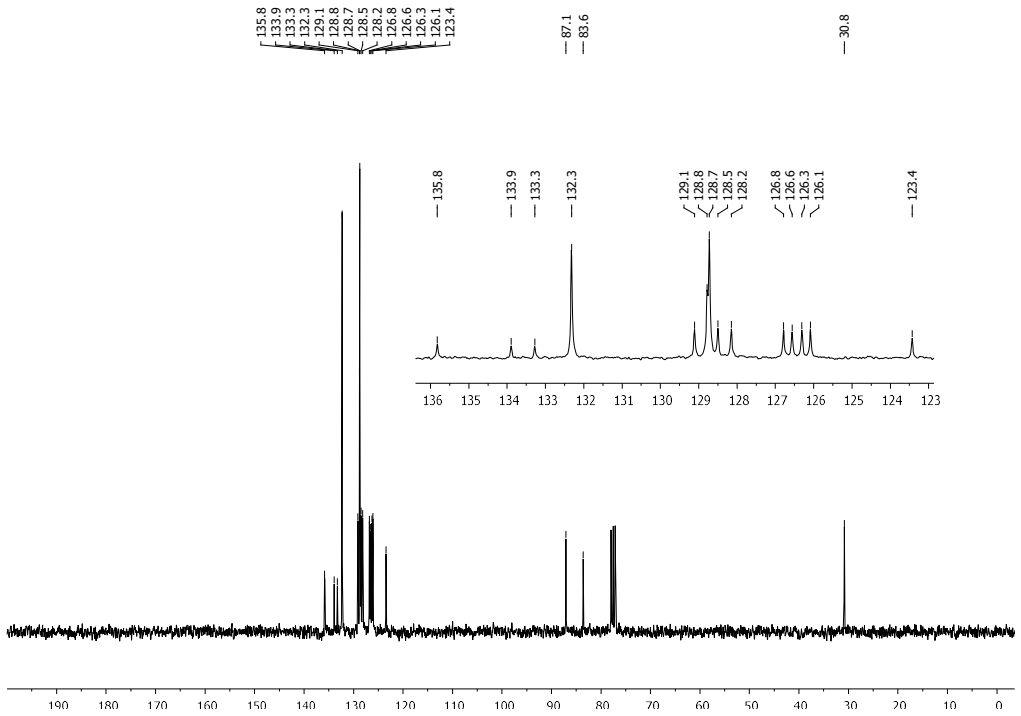
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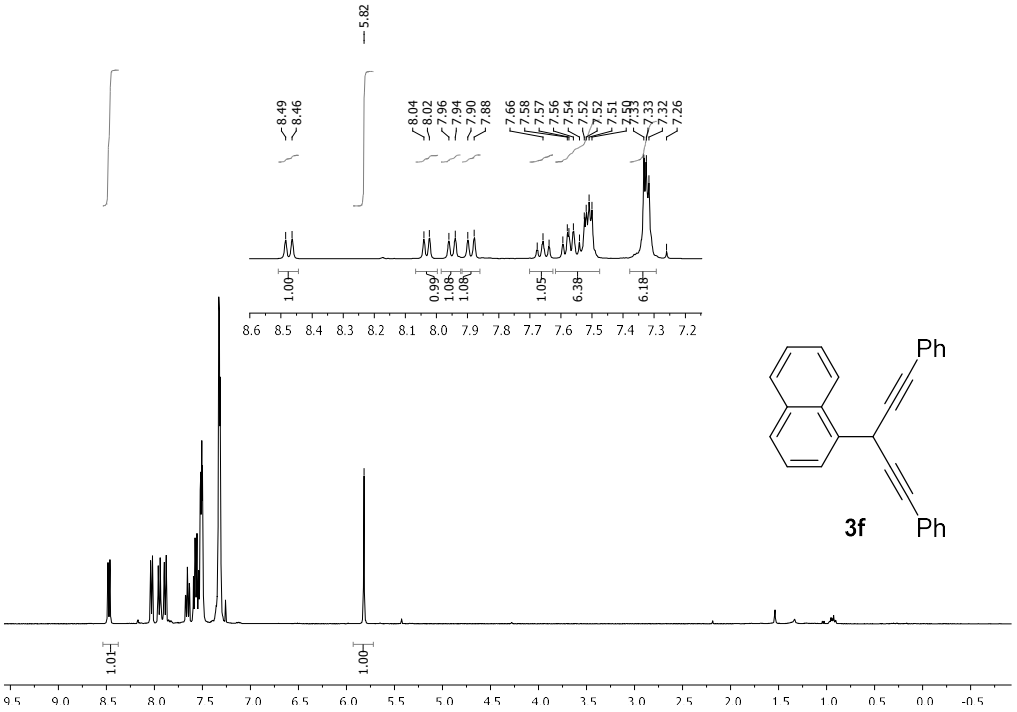
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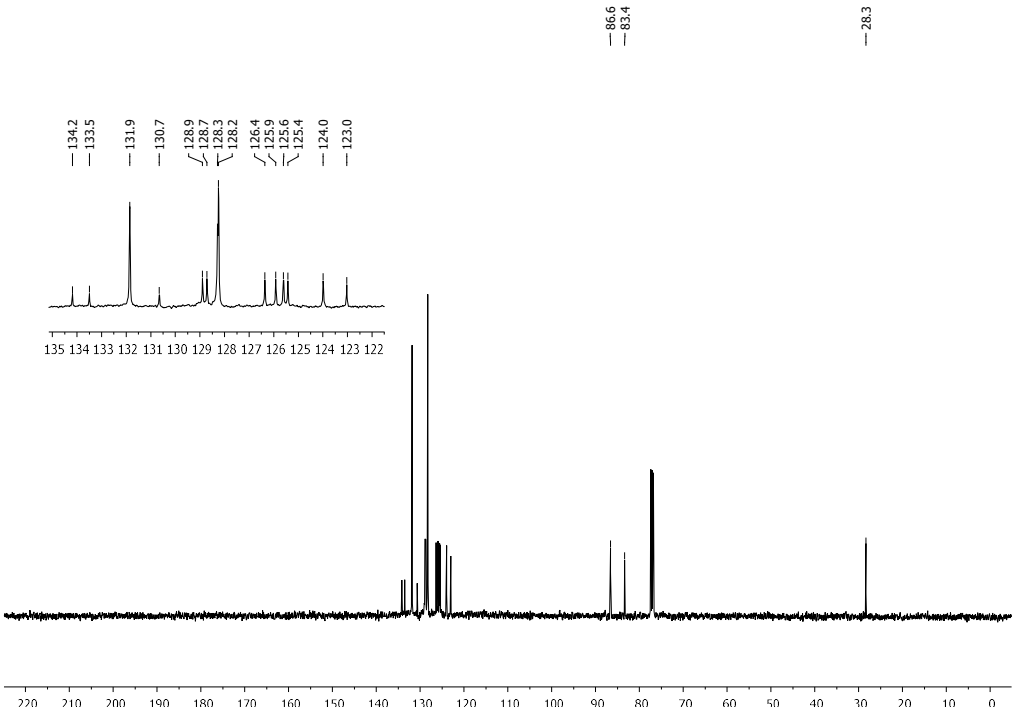
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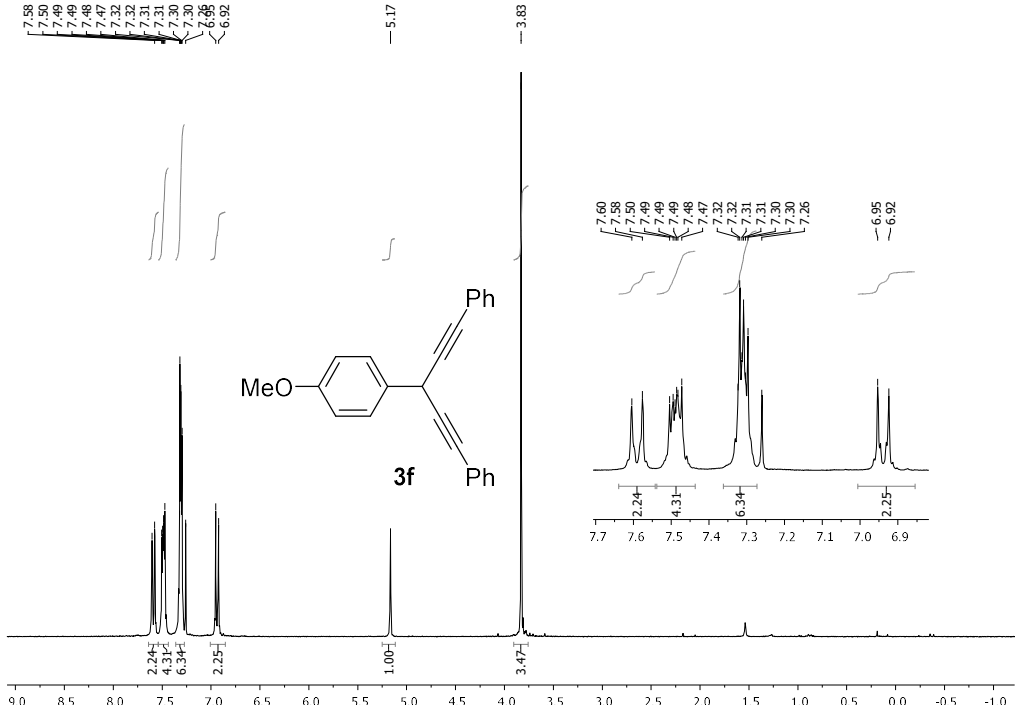
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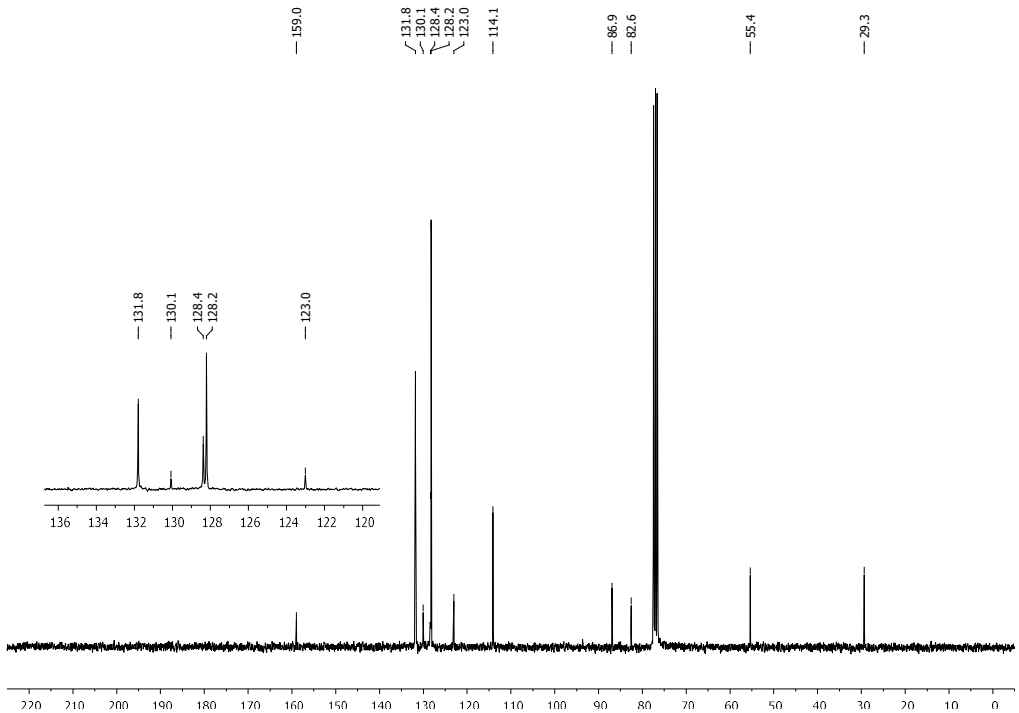
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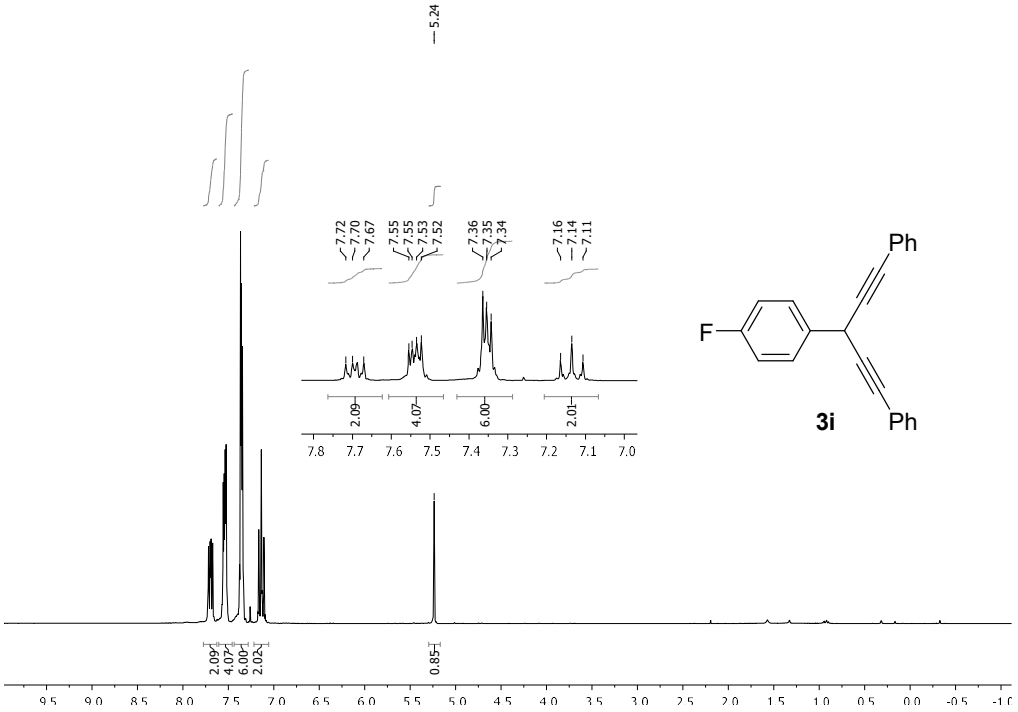
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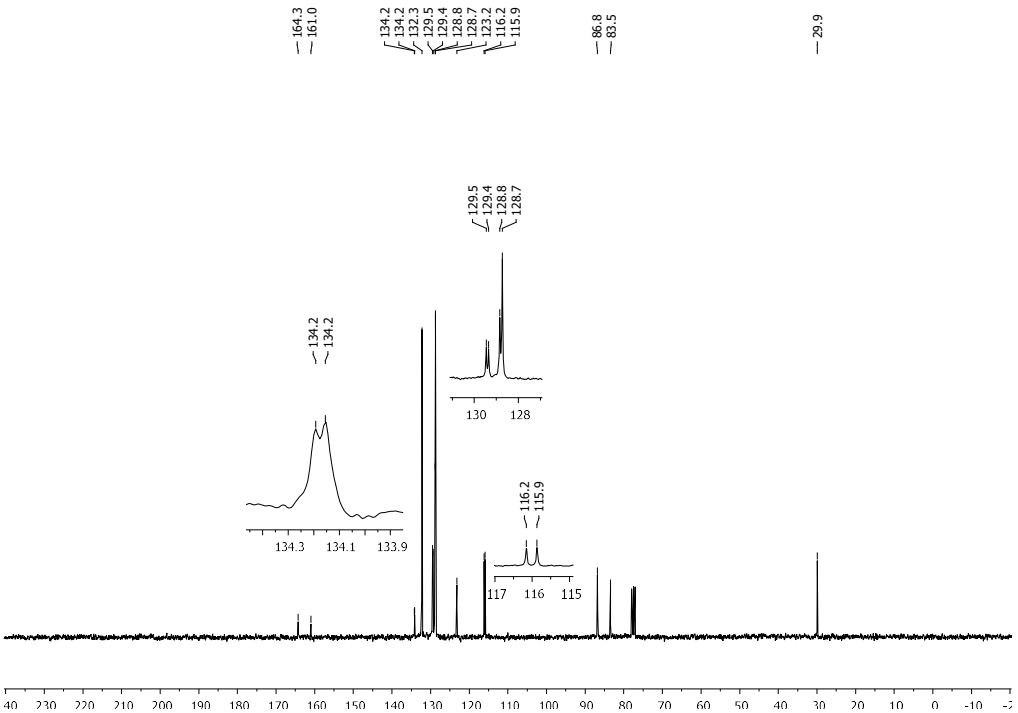
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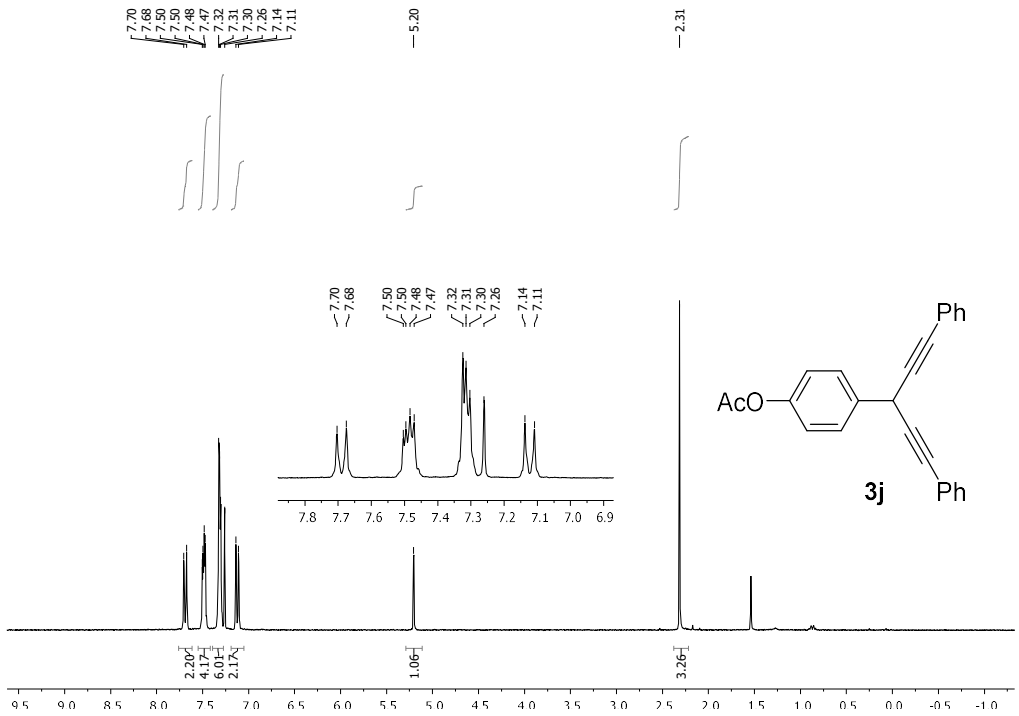
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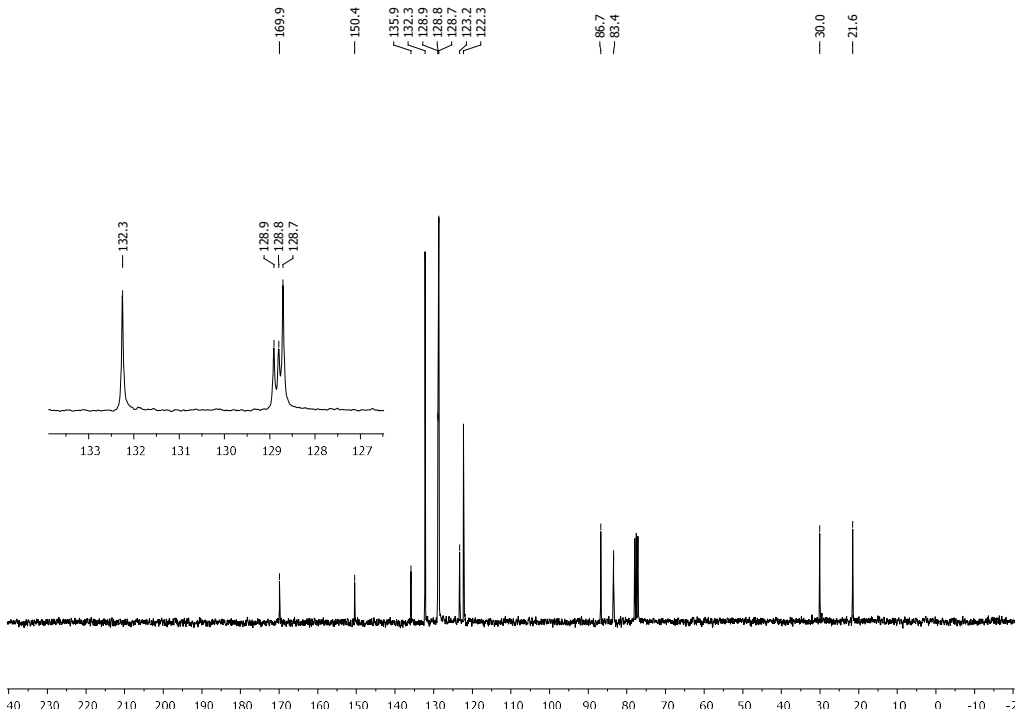
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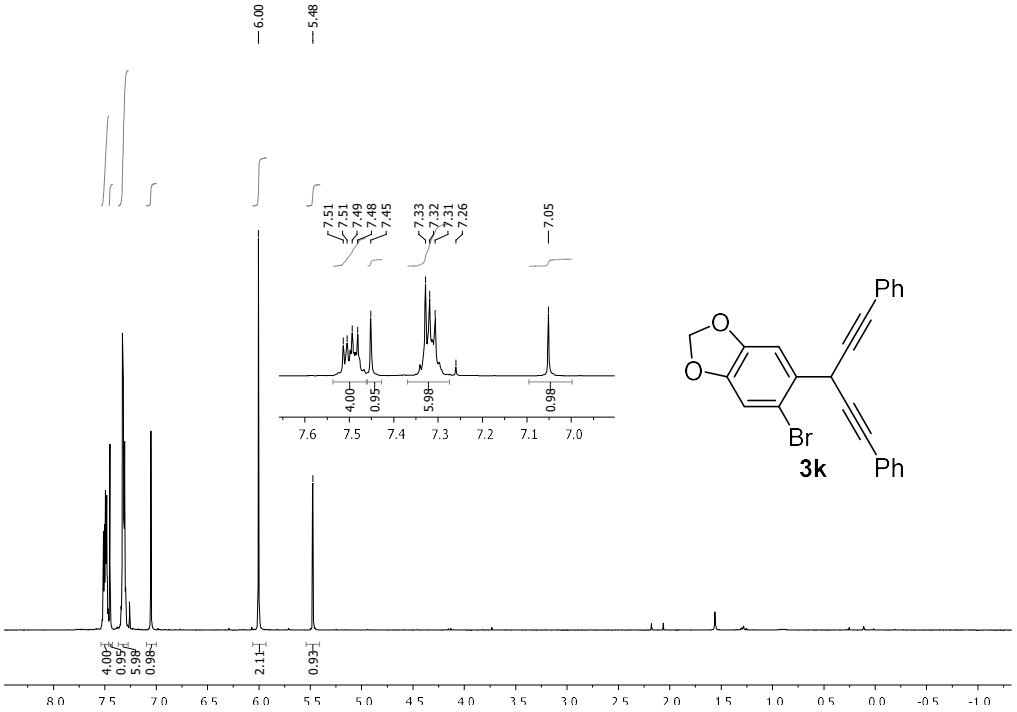
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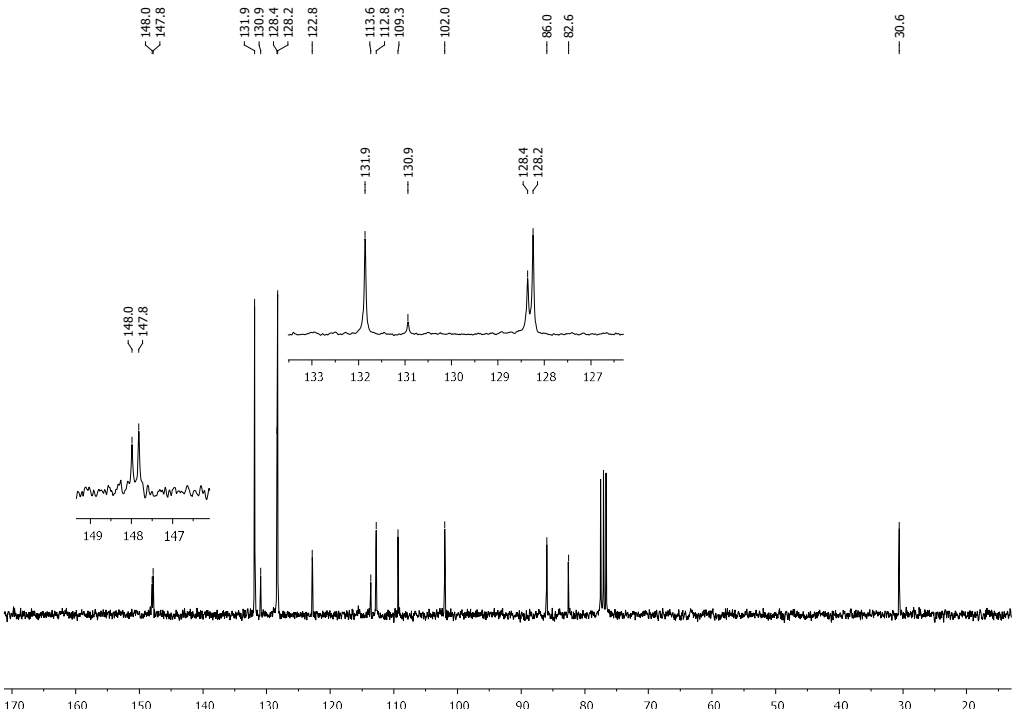
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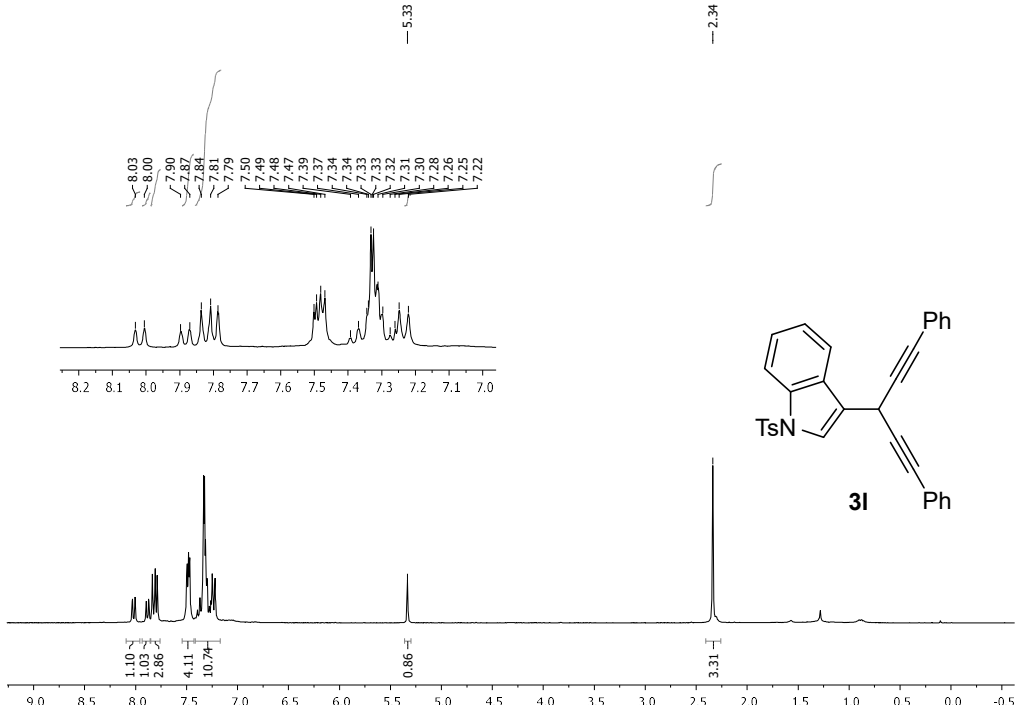
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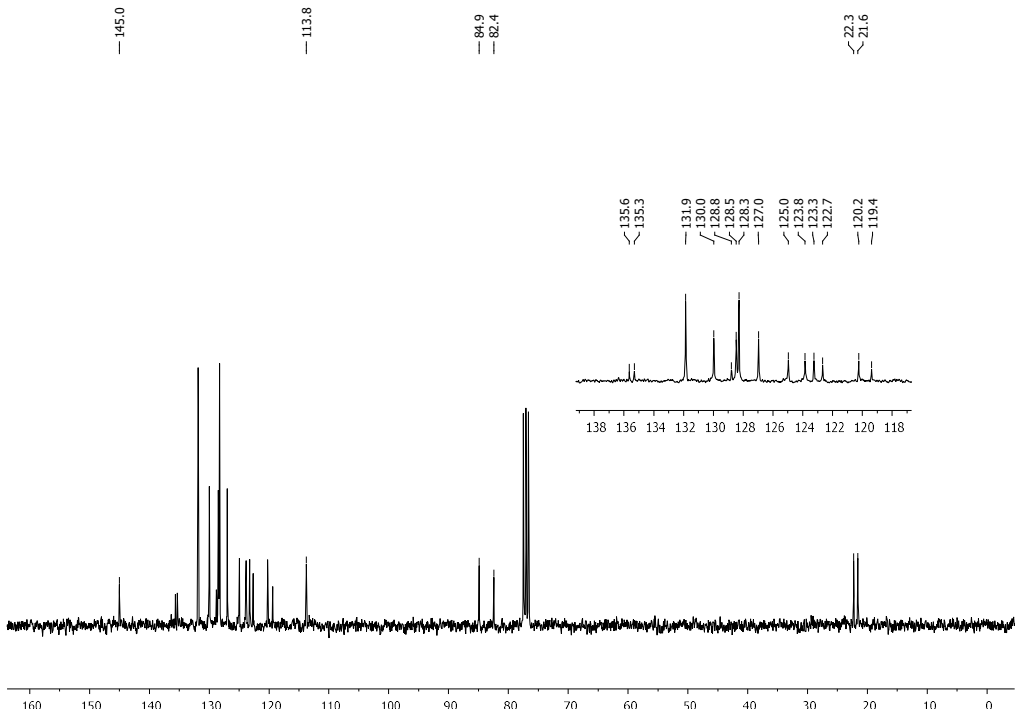
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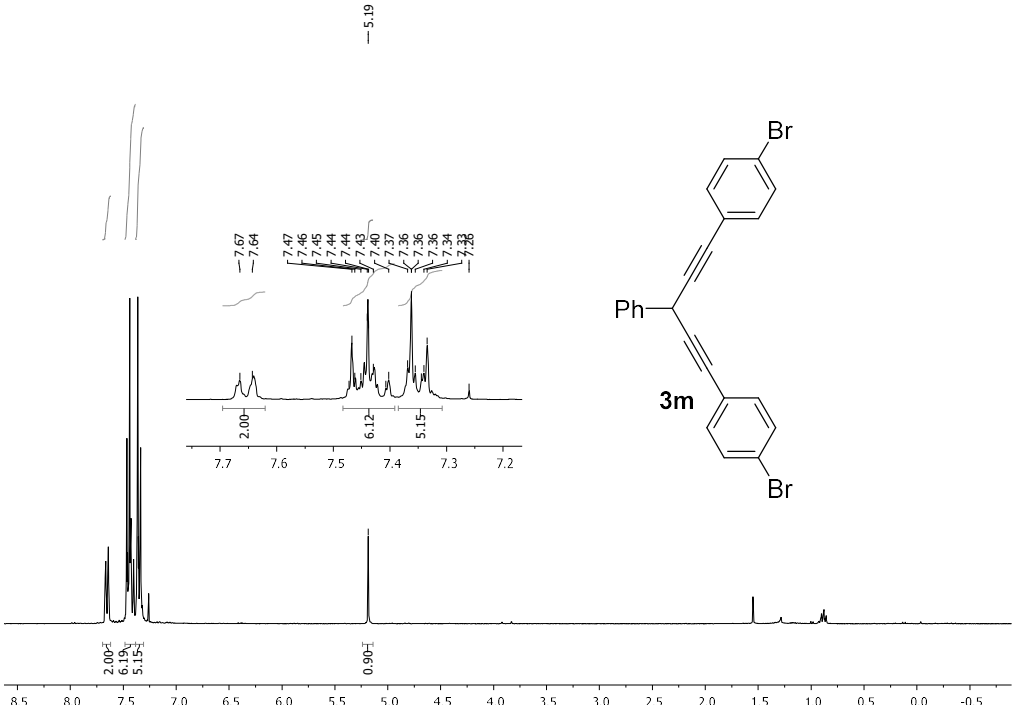
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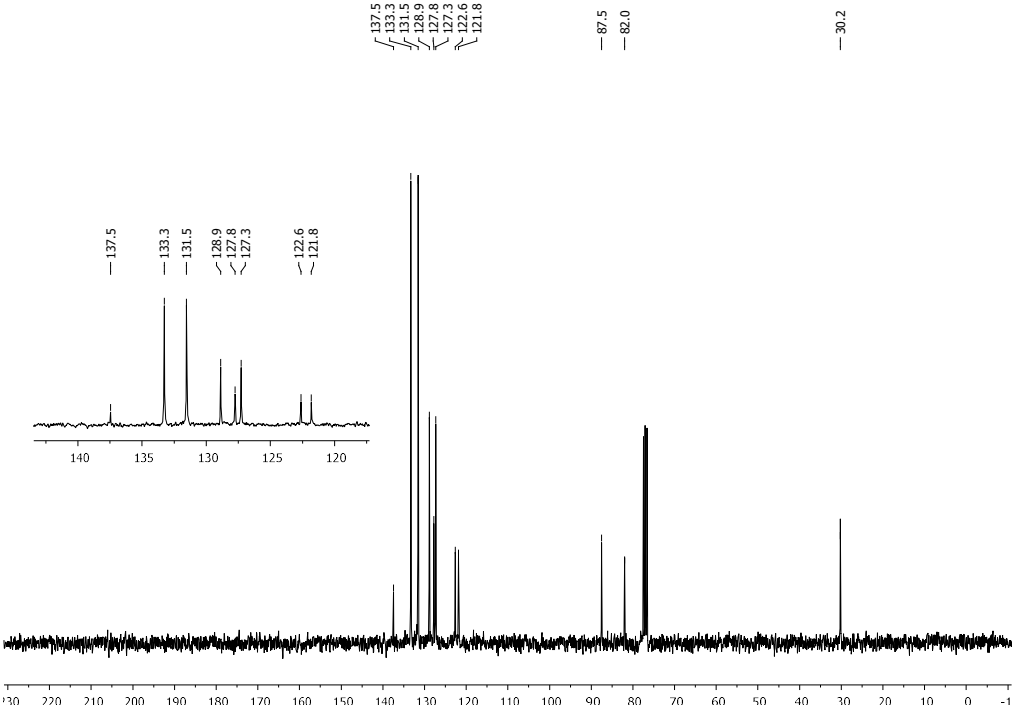
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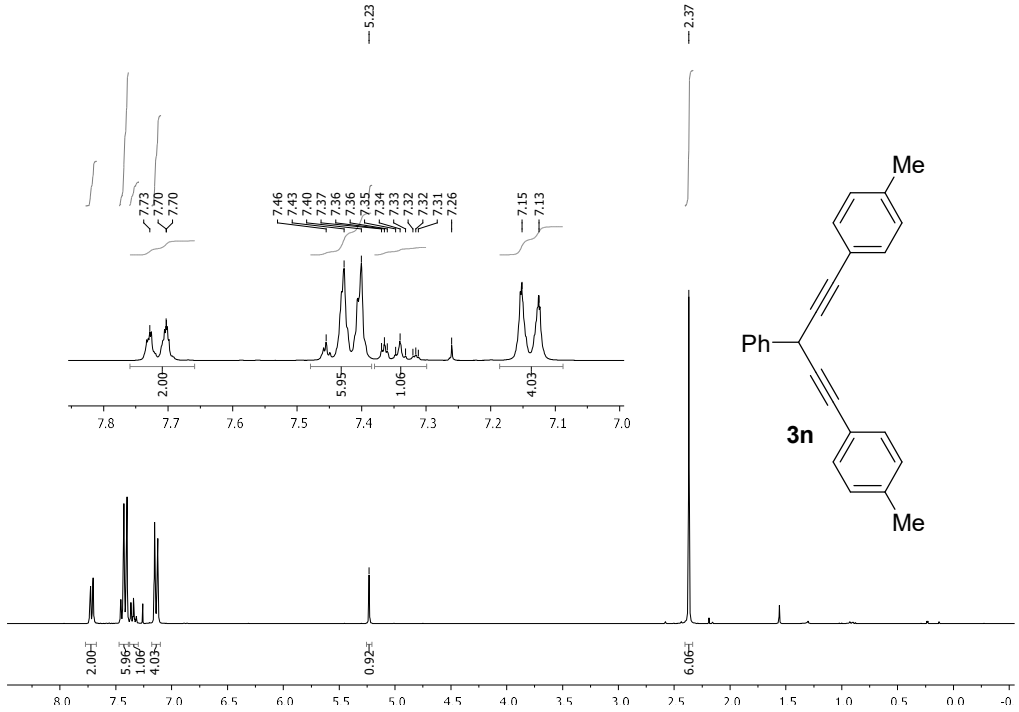
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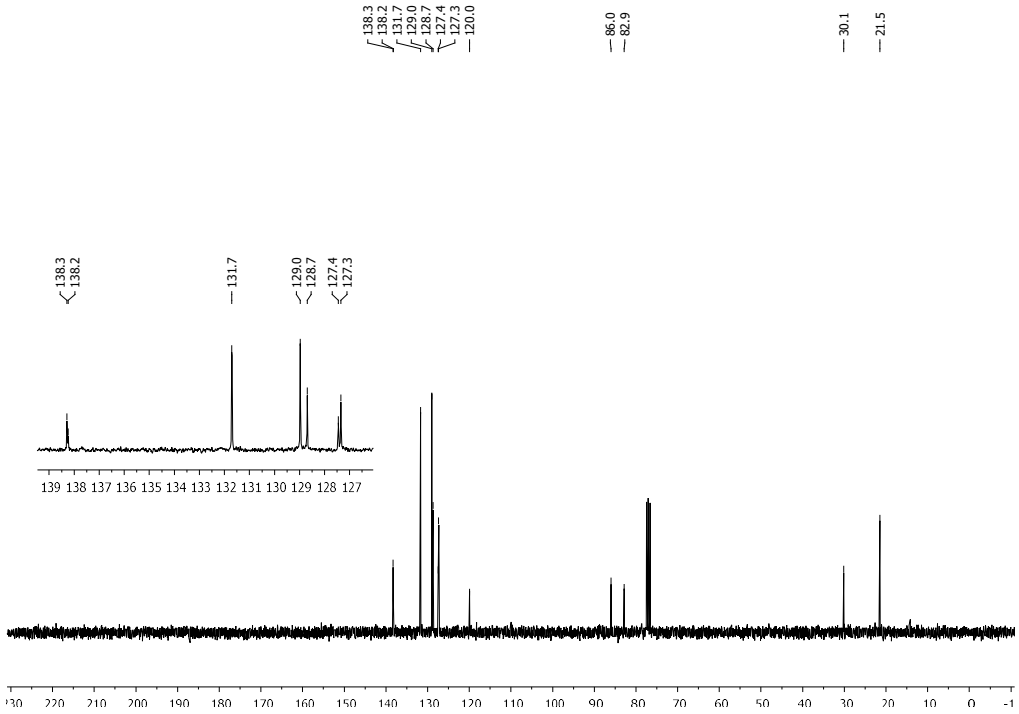
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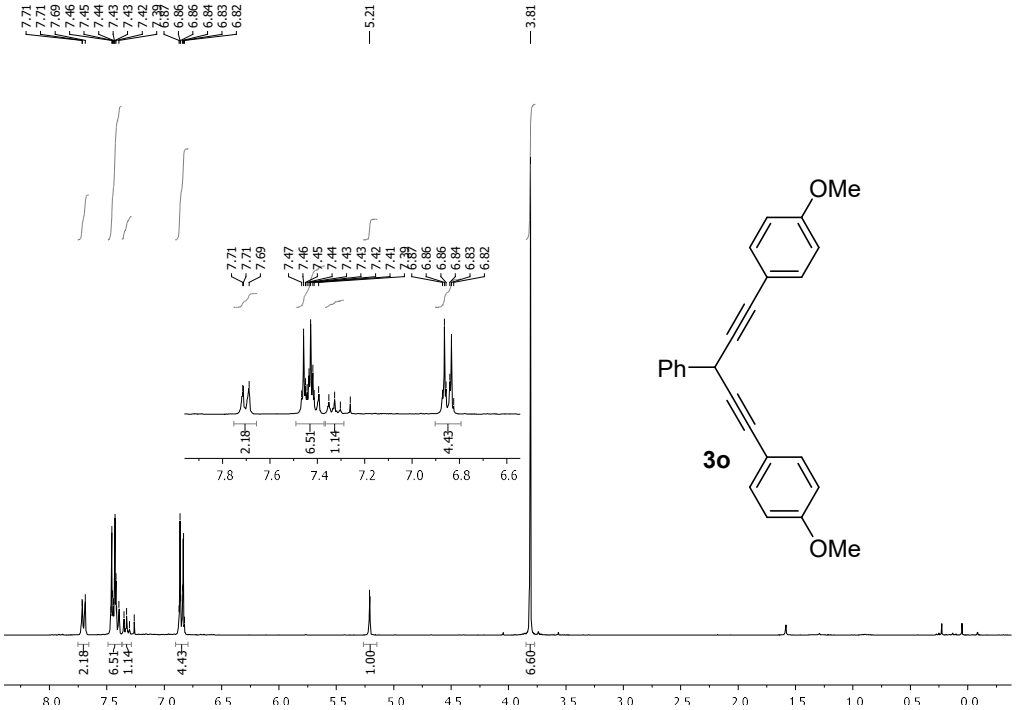
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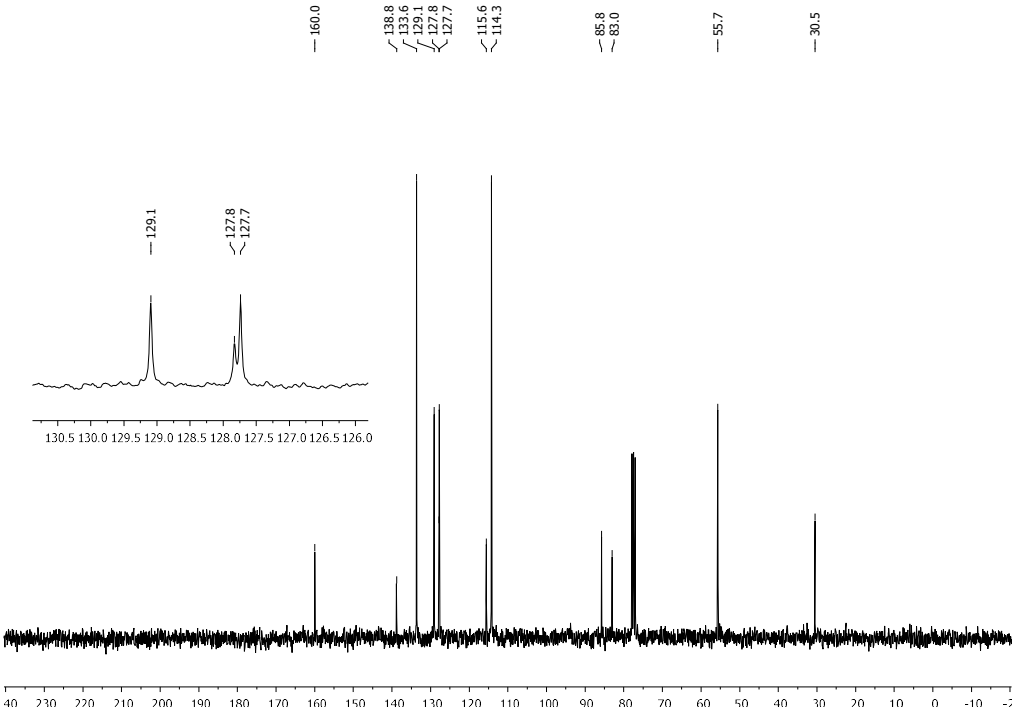
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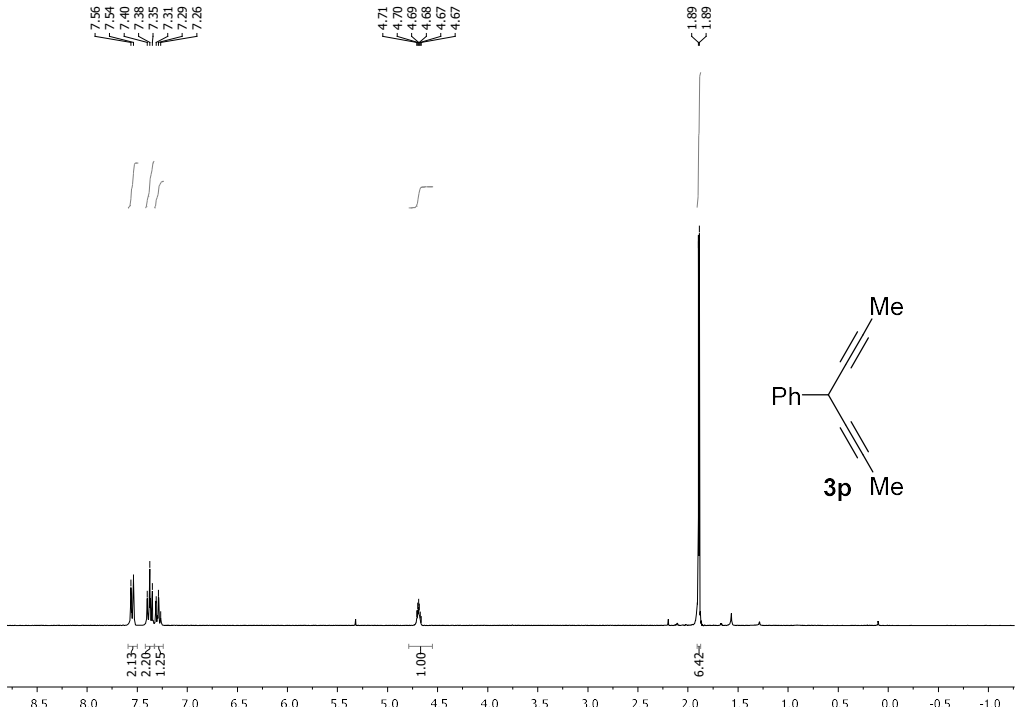
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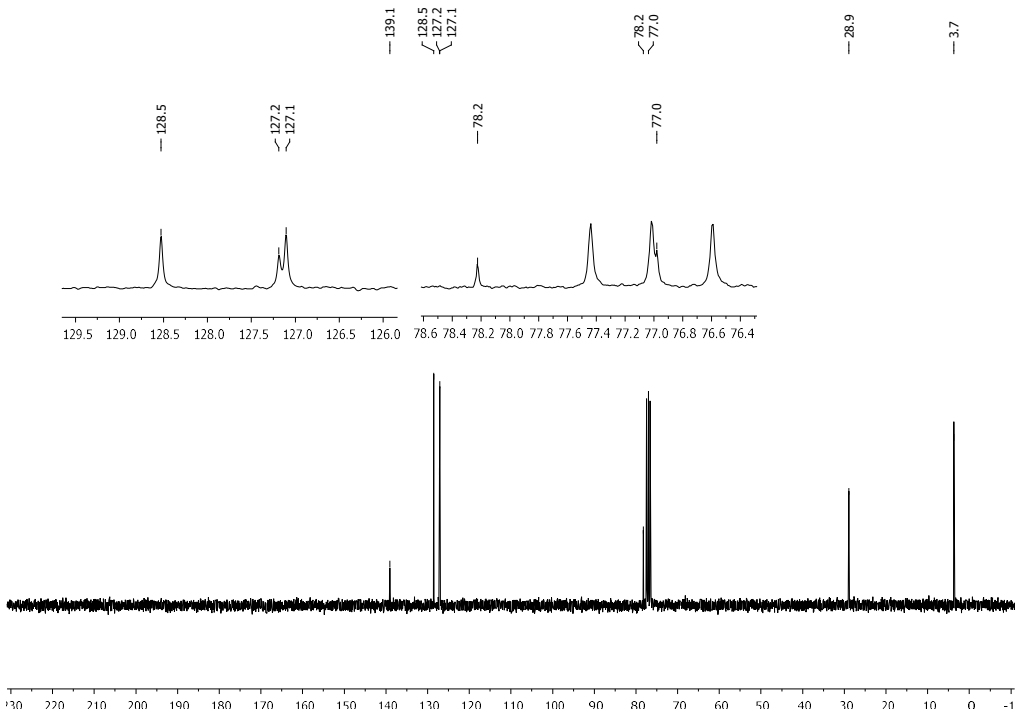
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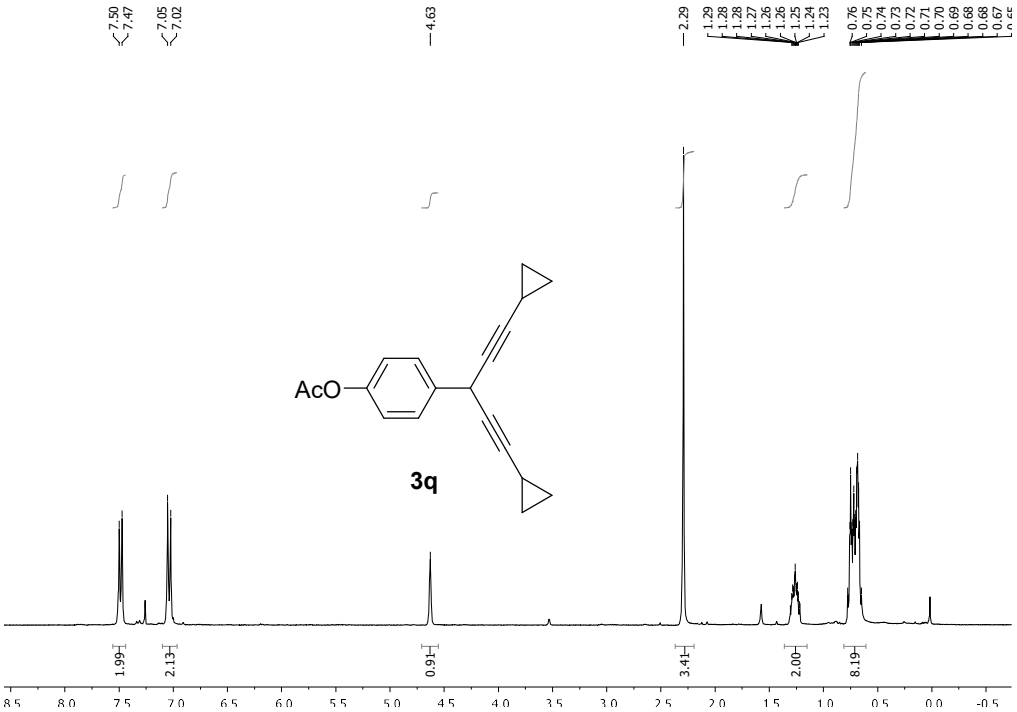
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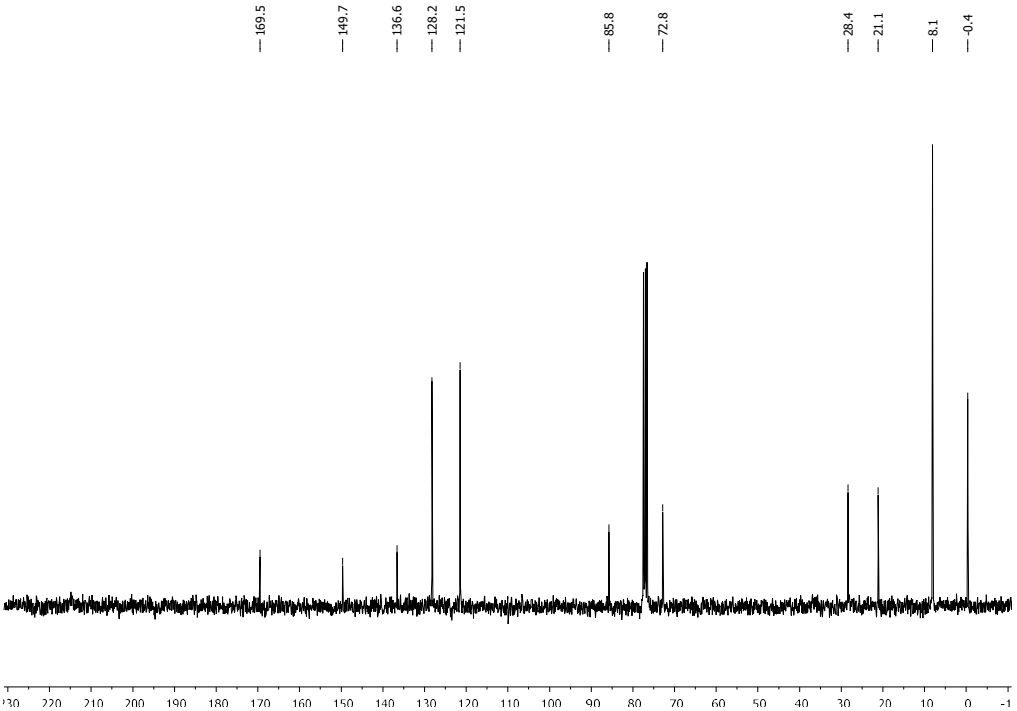
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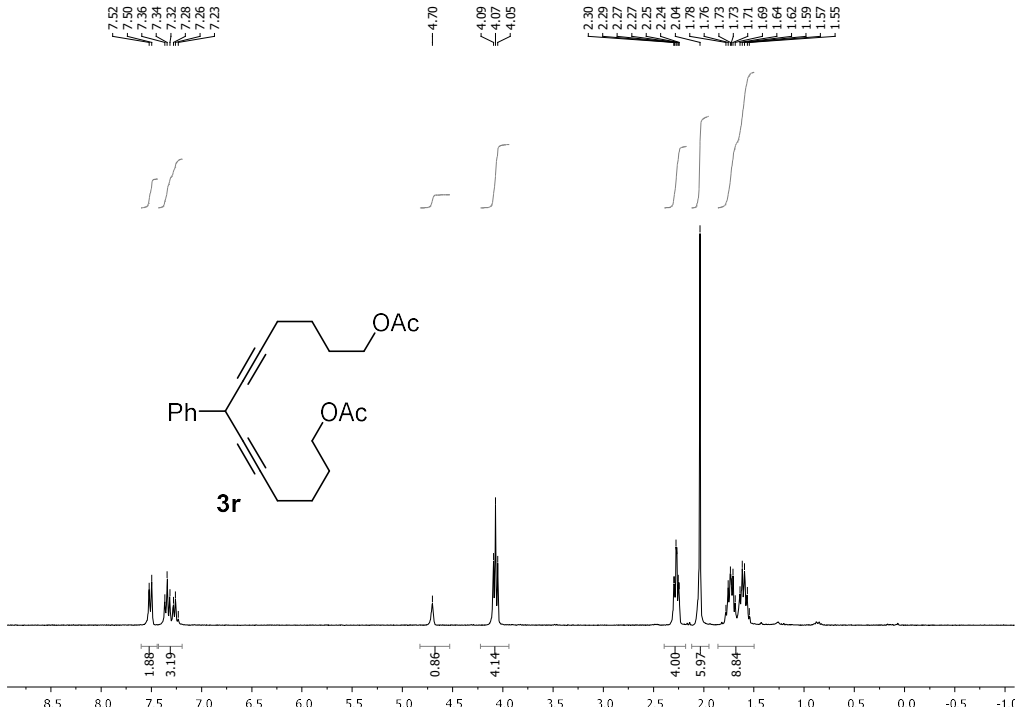
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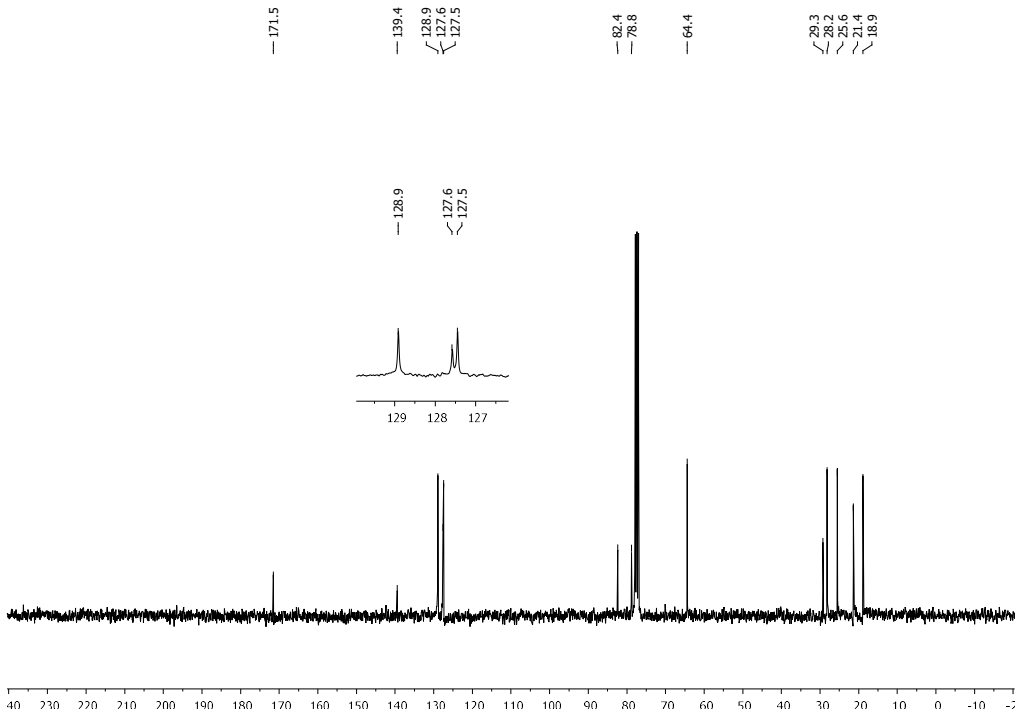
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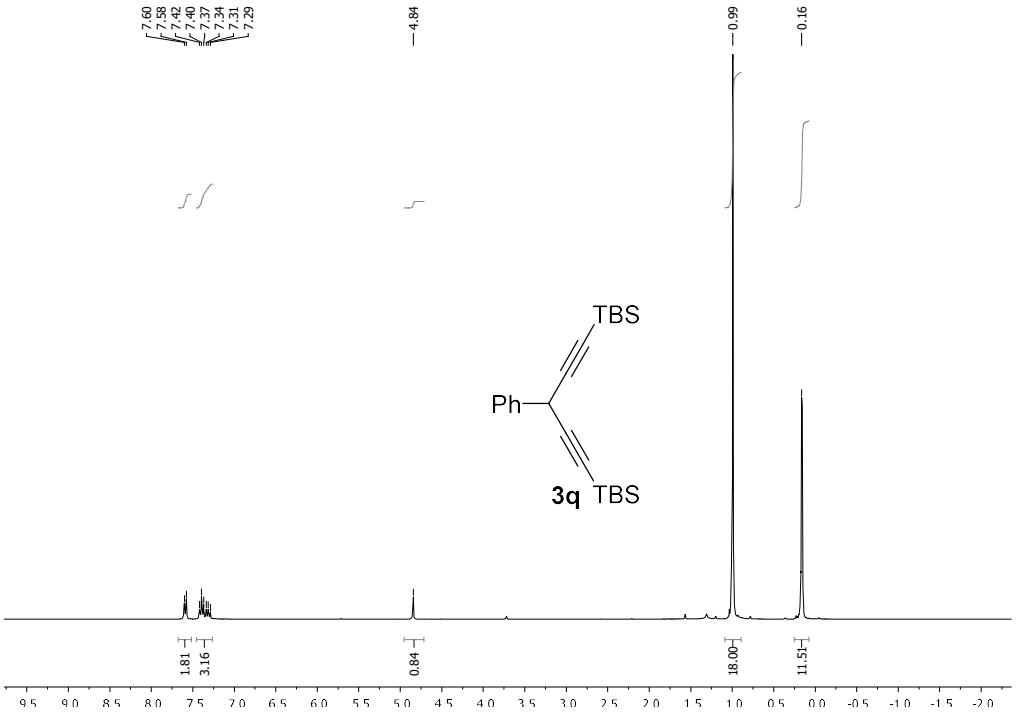
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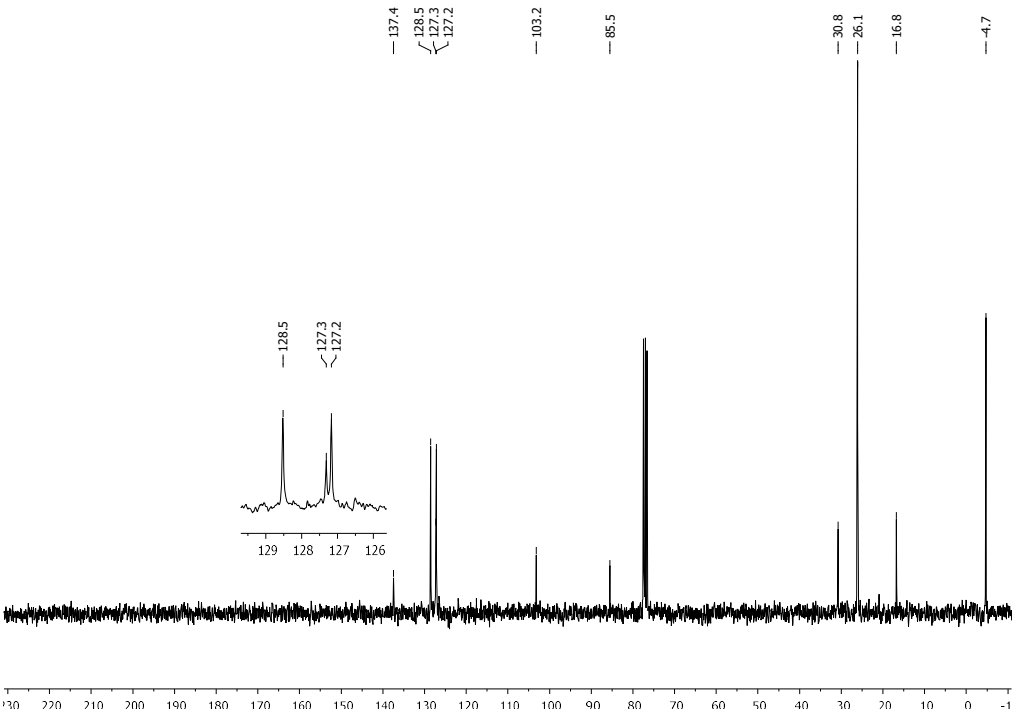
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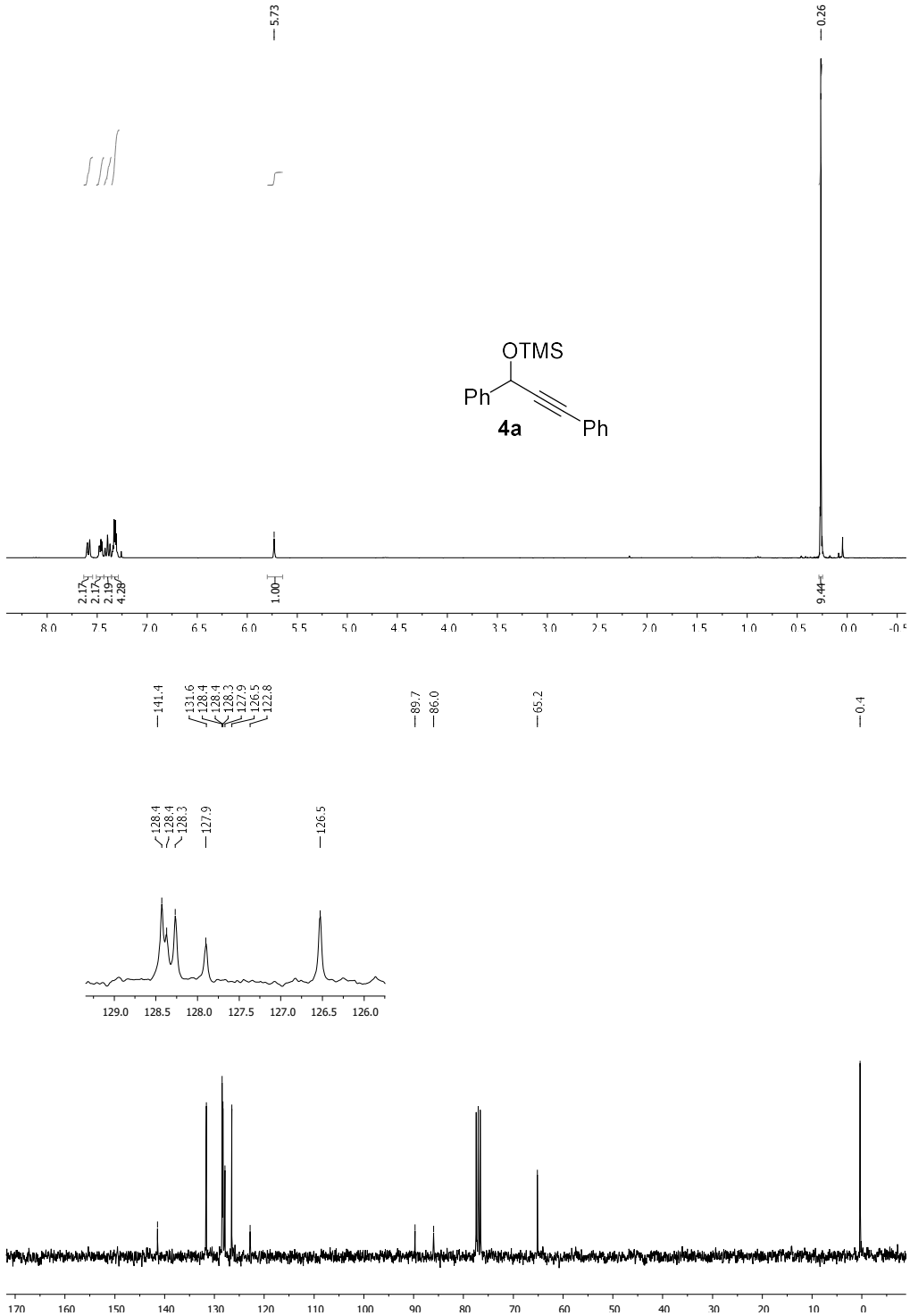
***Substrate* 4a**



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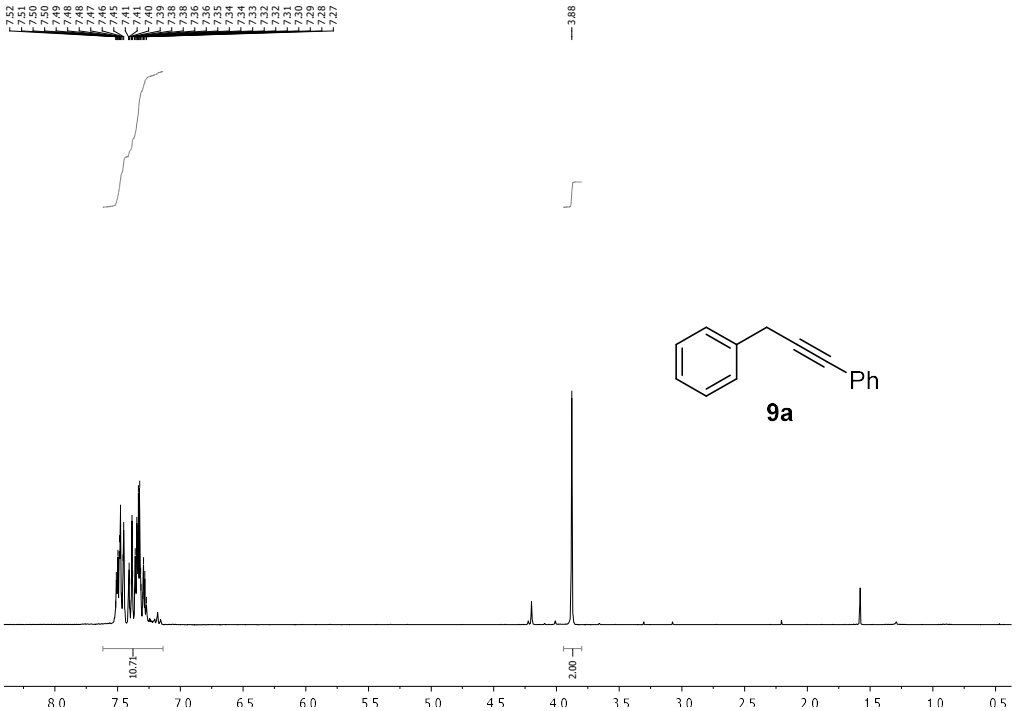

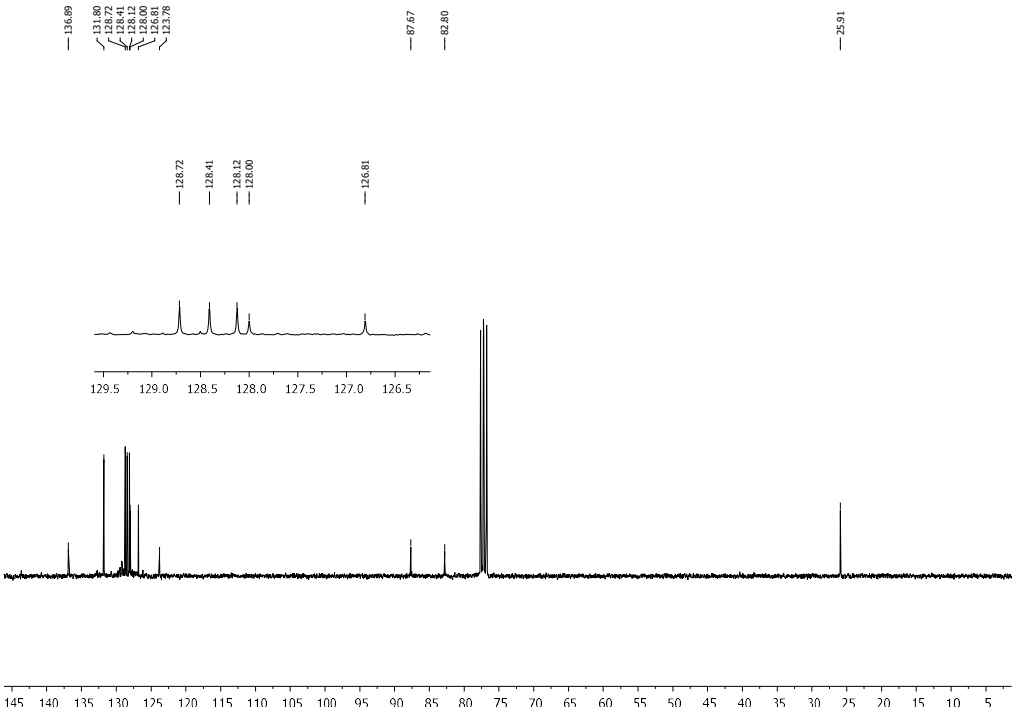

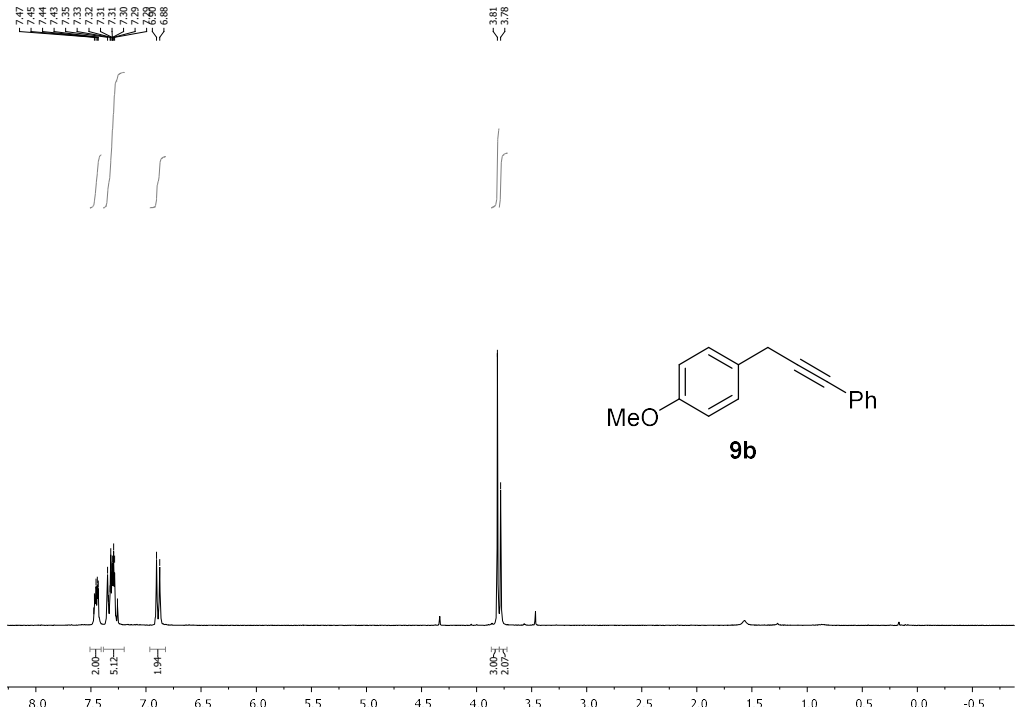
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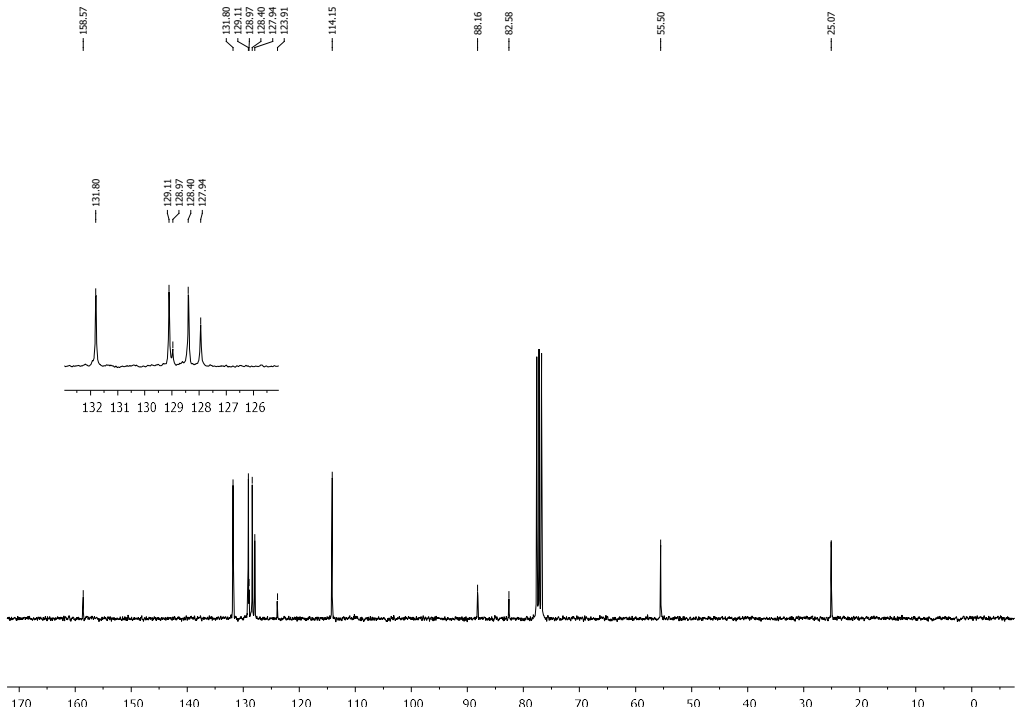
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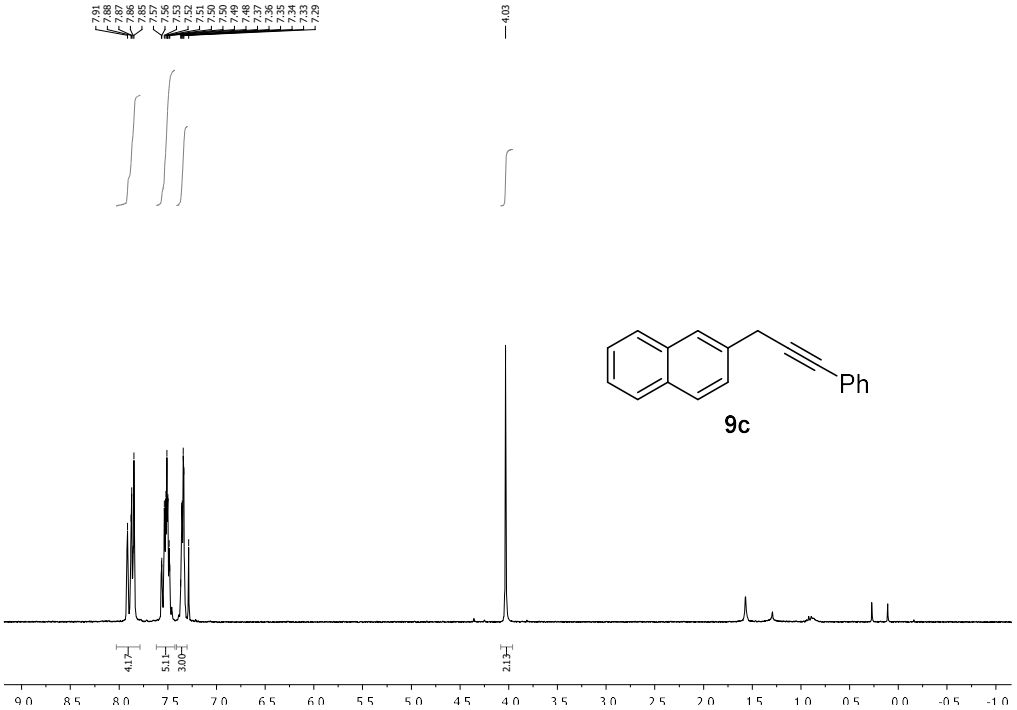
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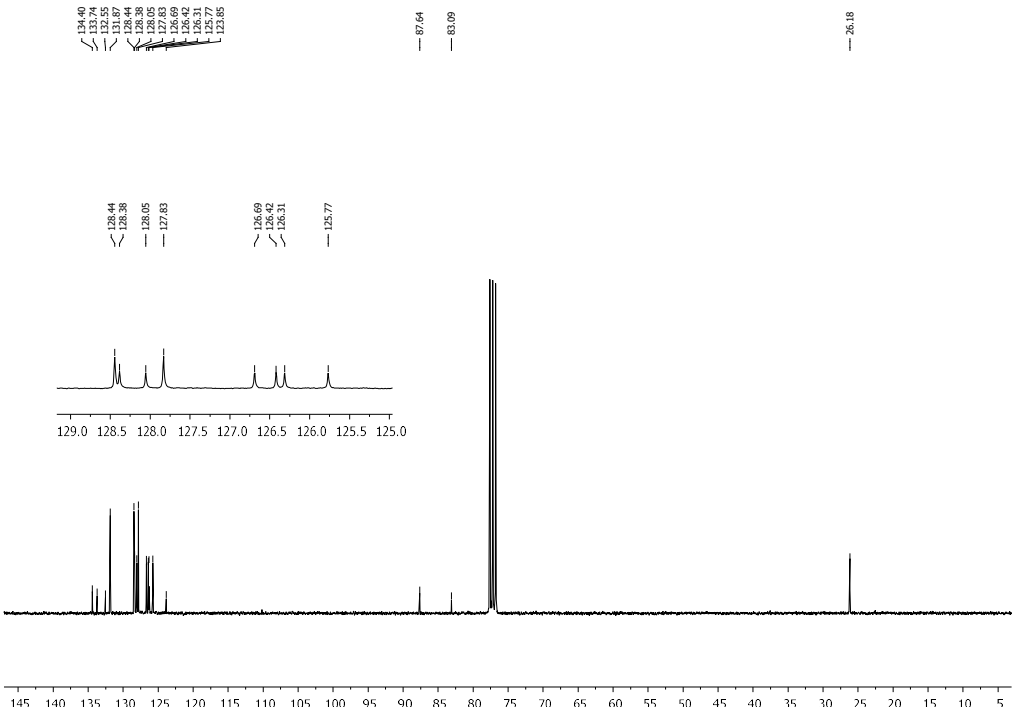
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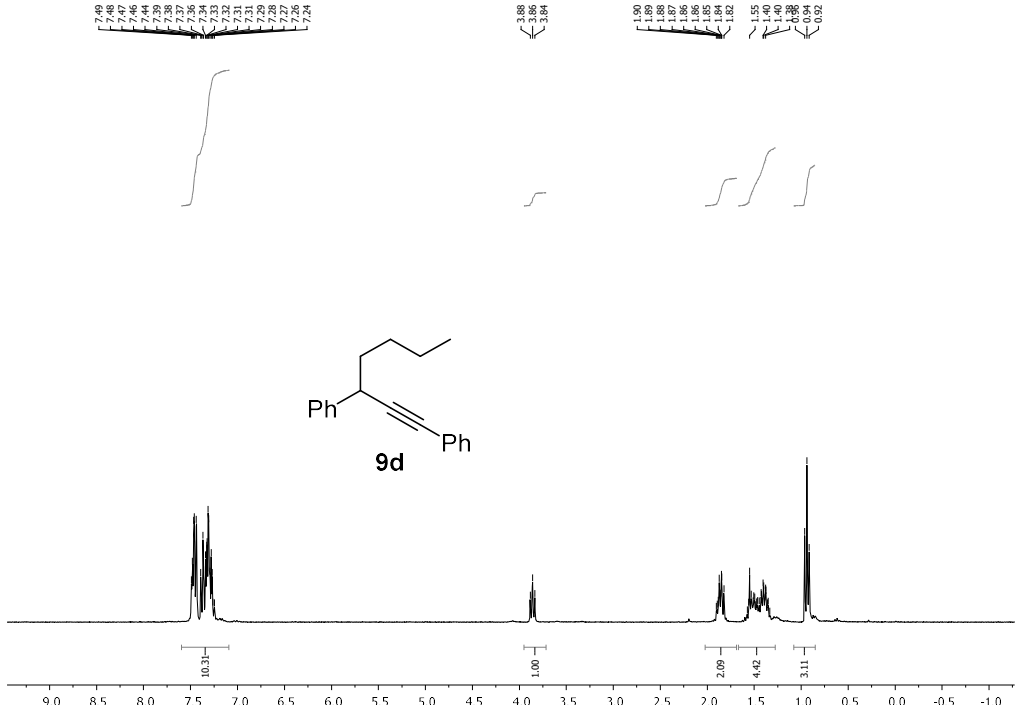
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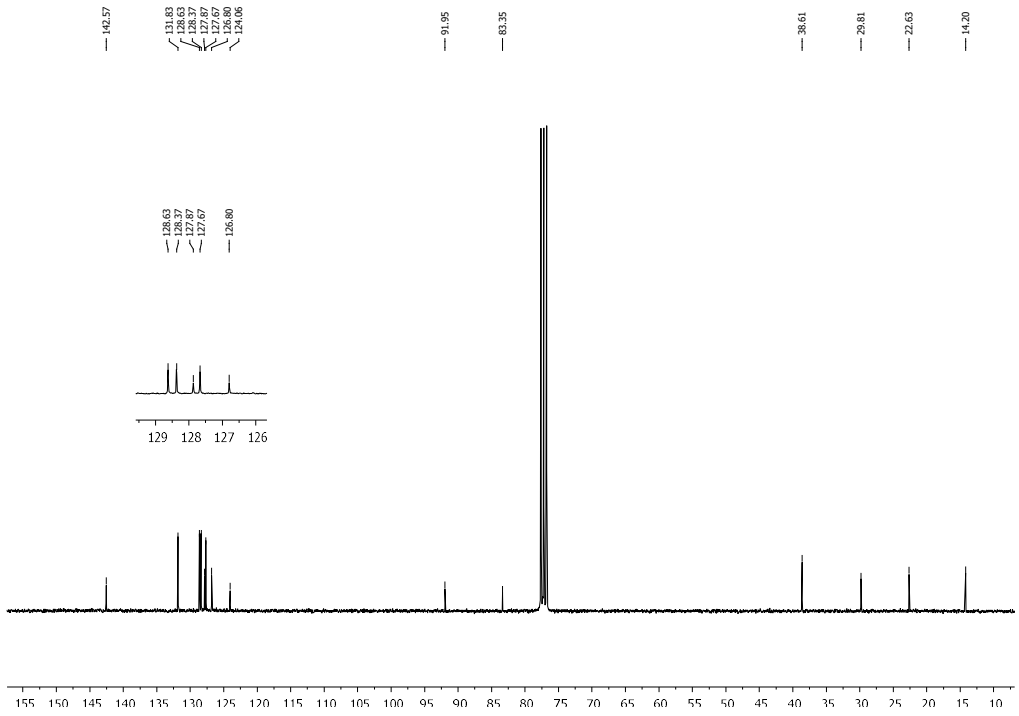
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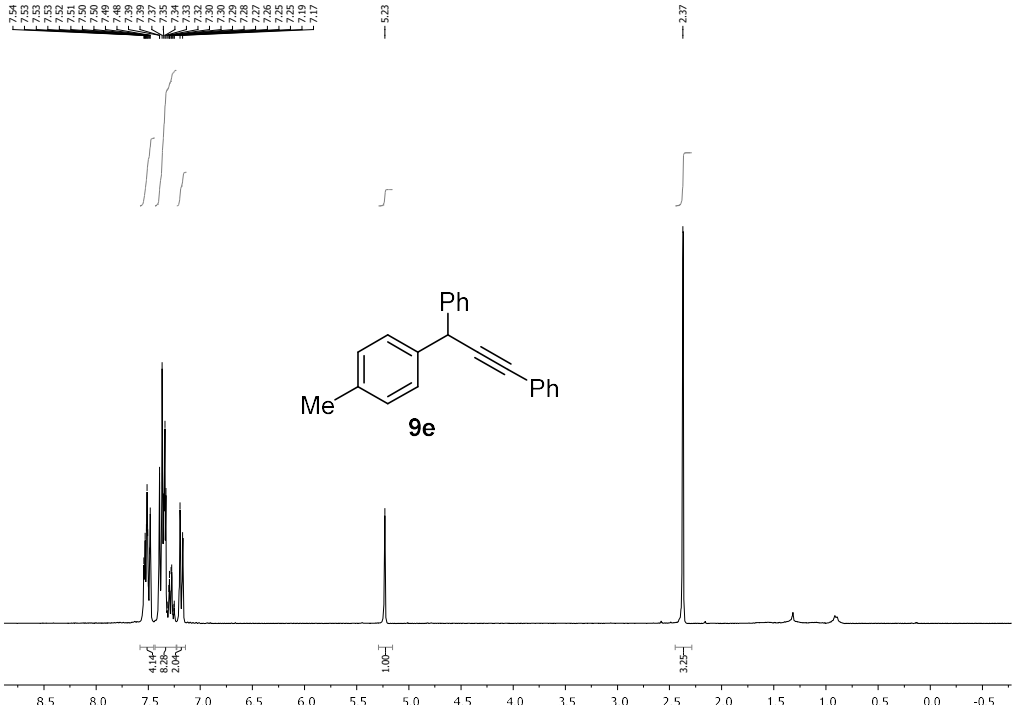
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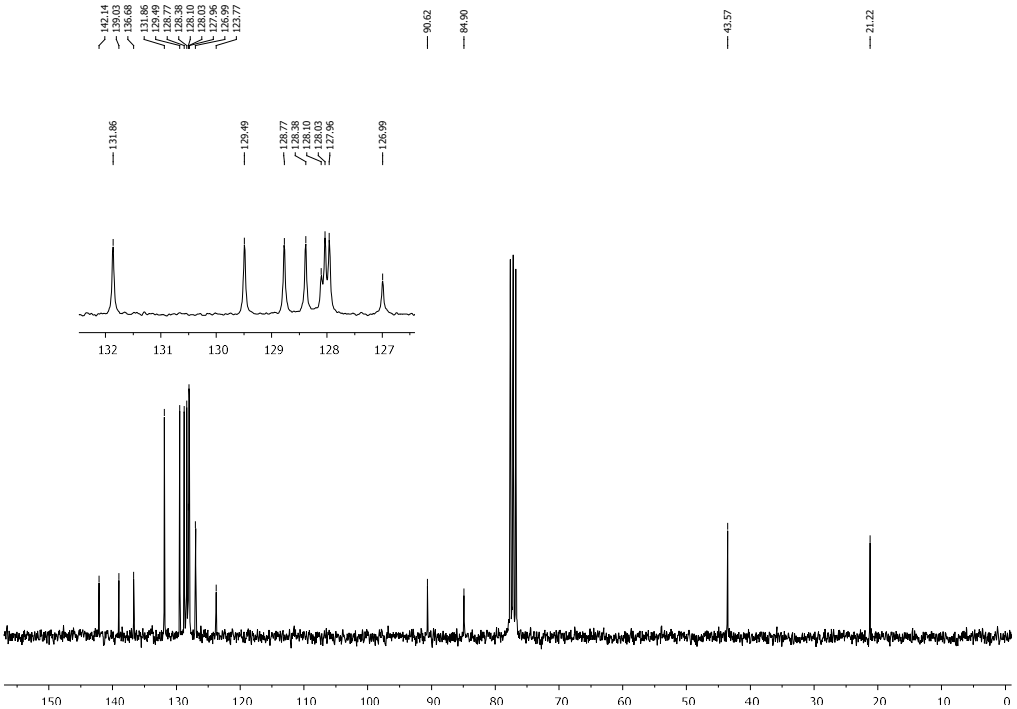

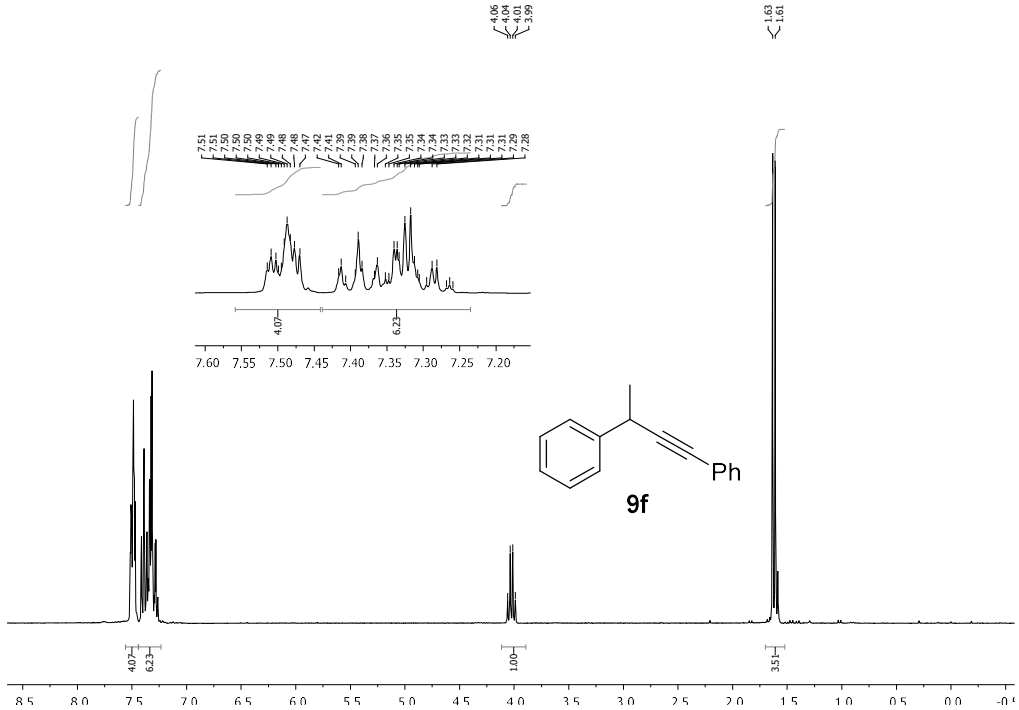
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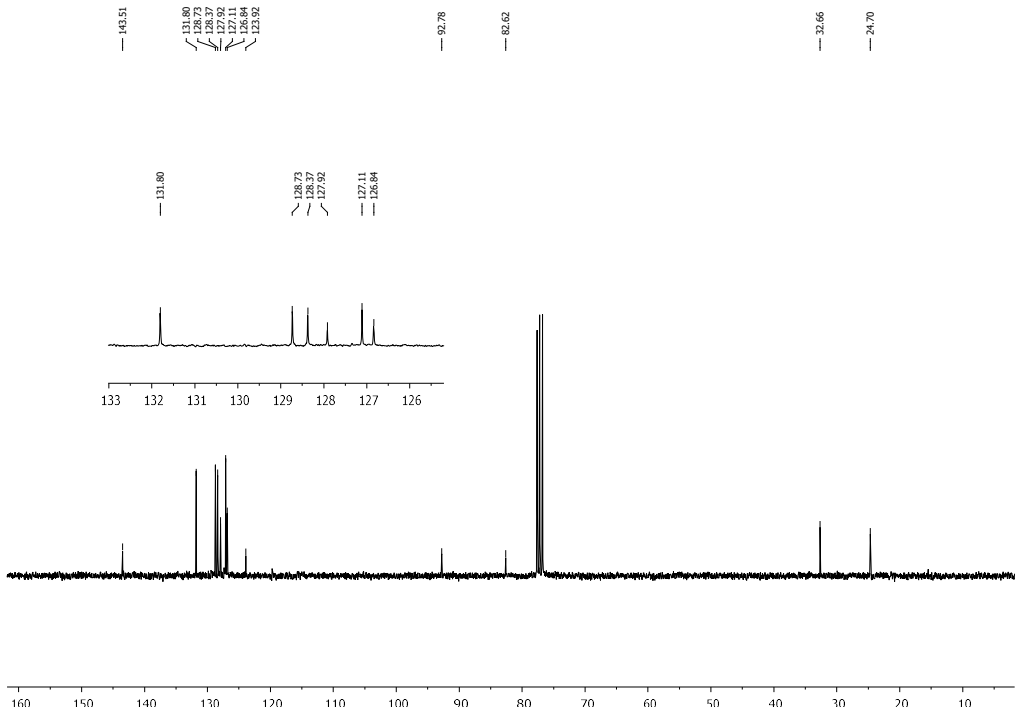
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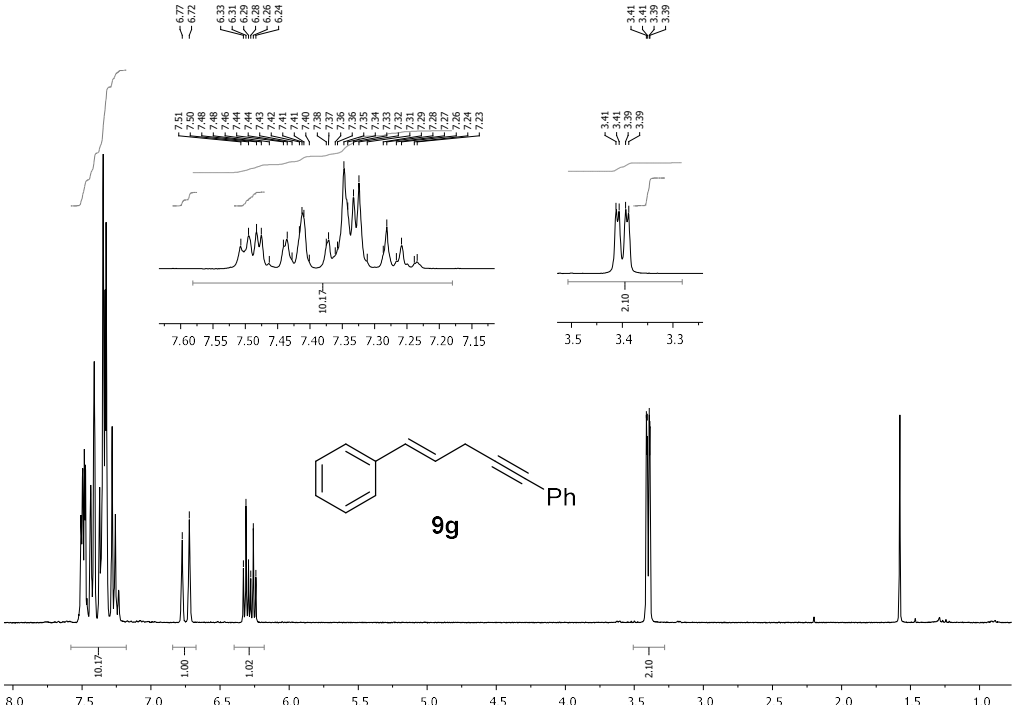
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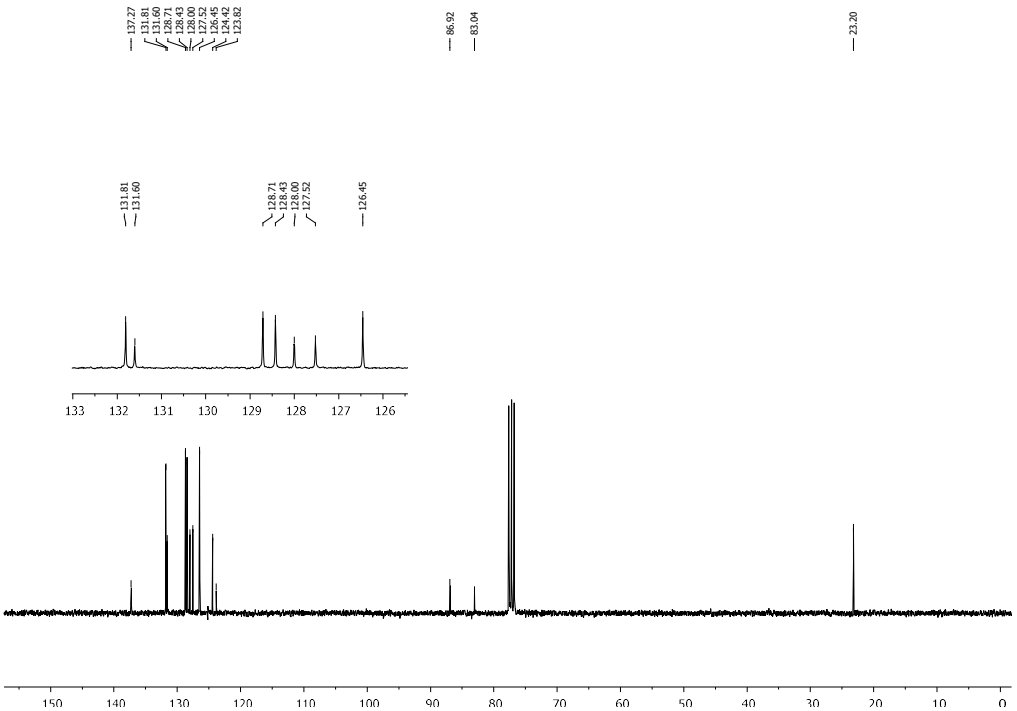
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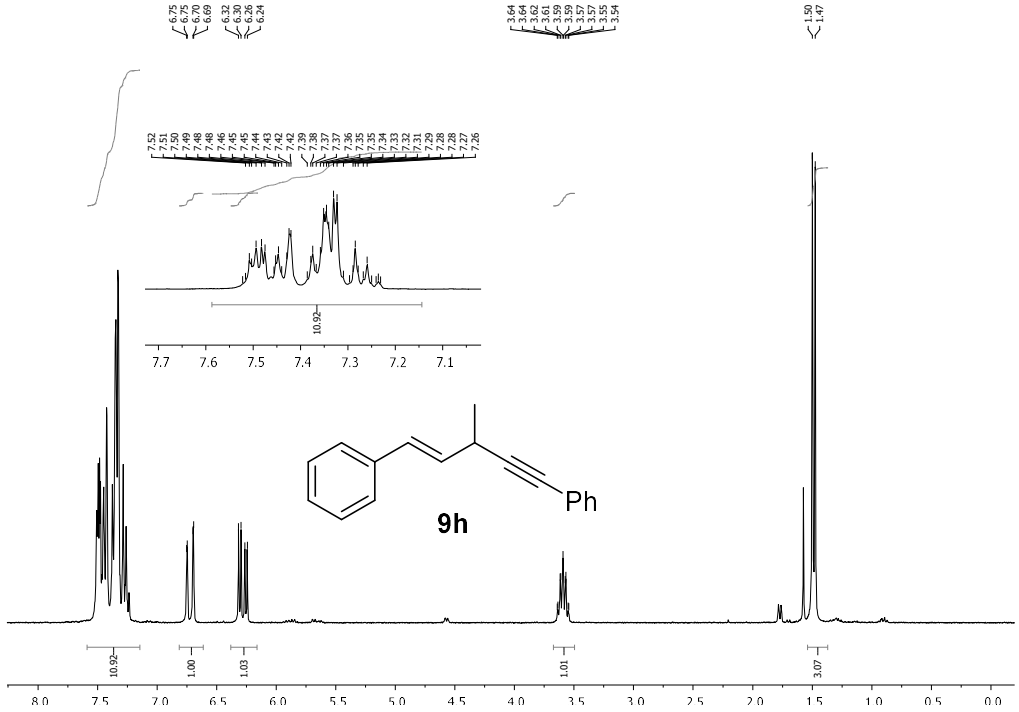
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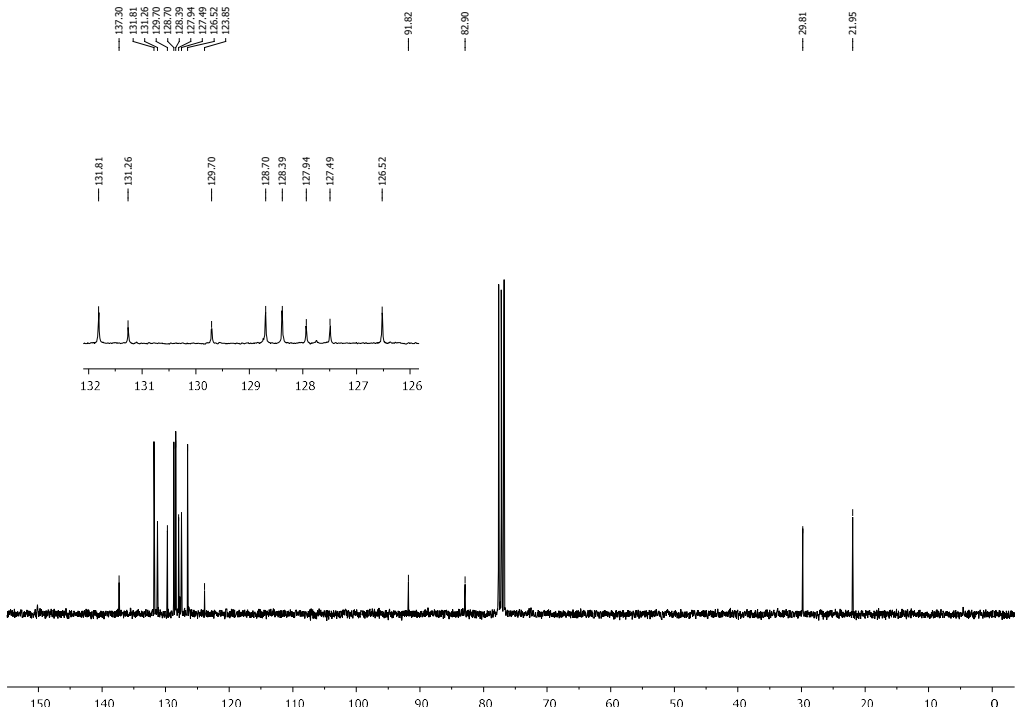
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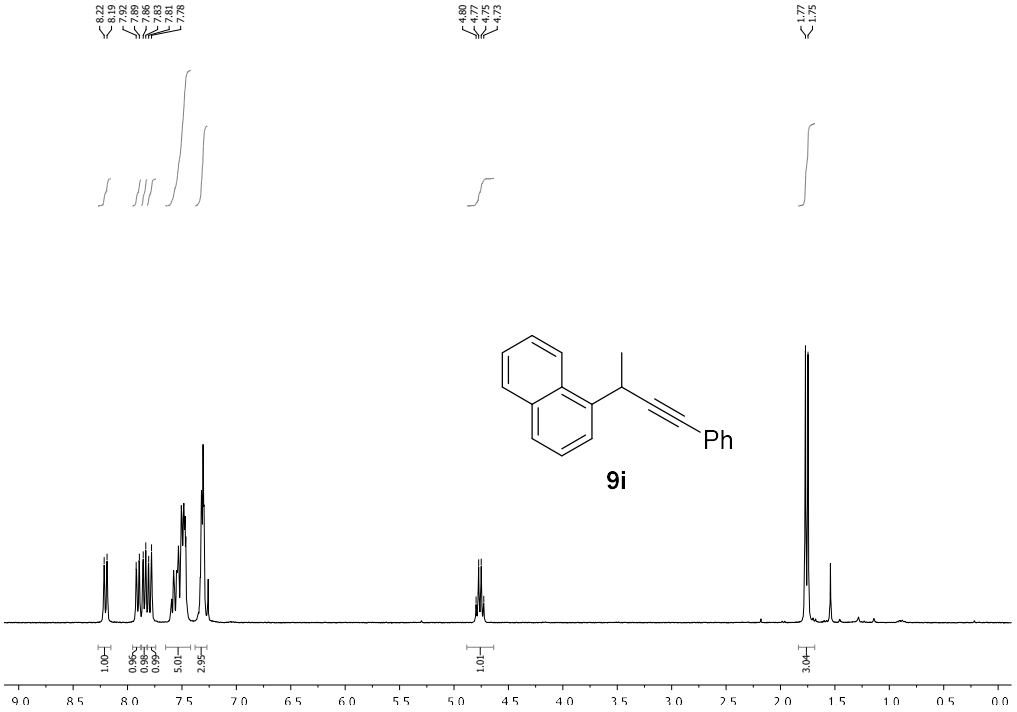
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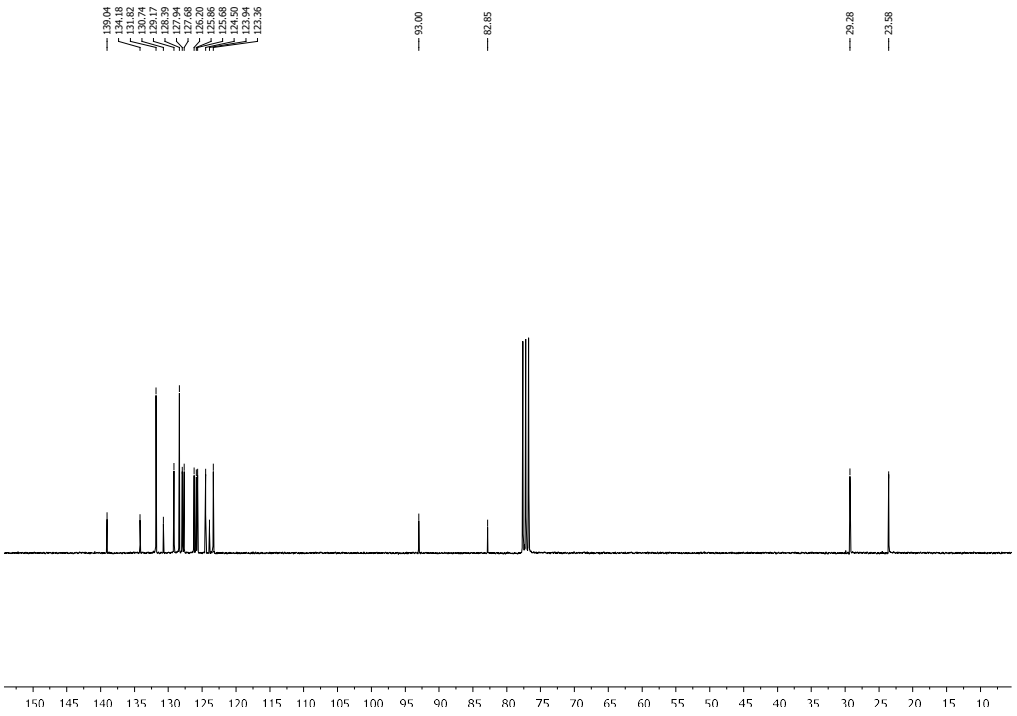
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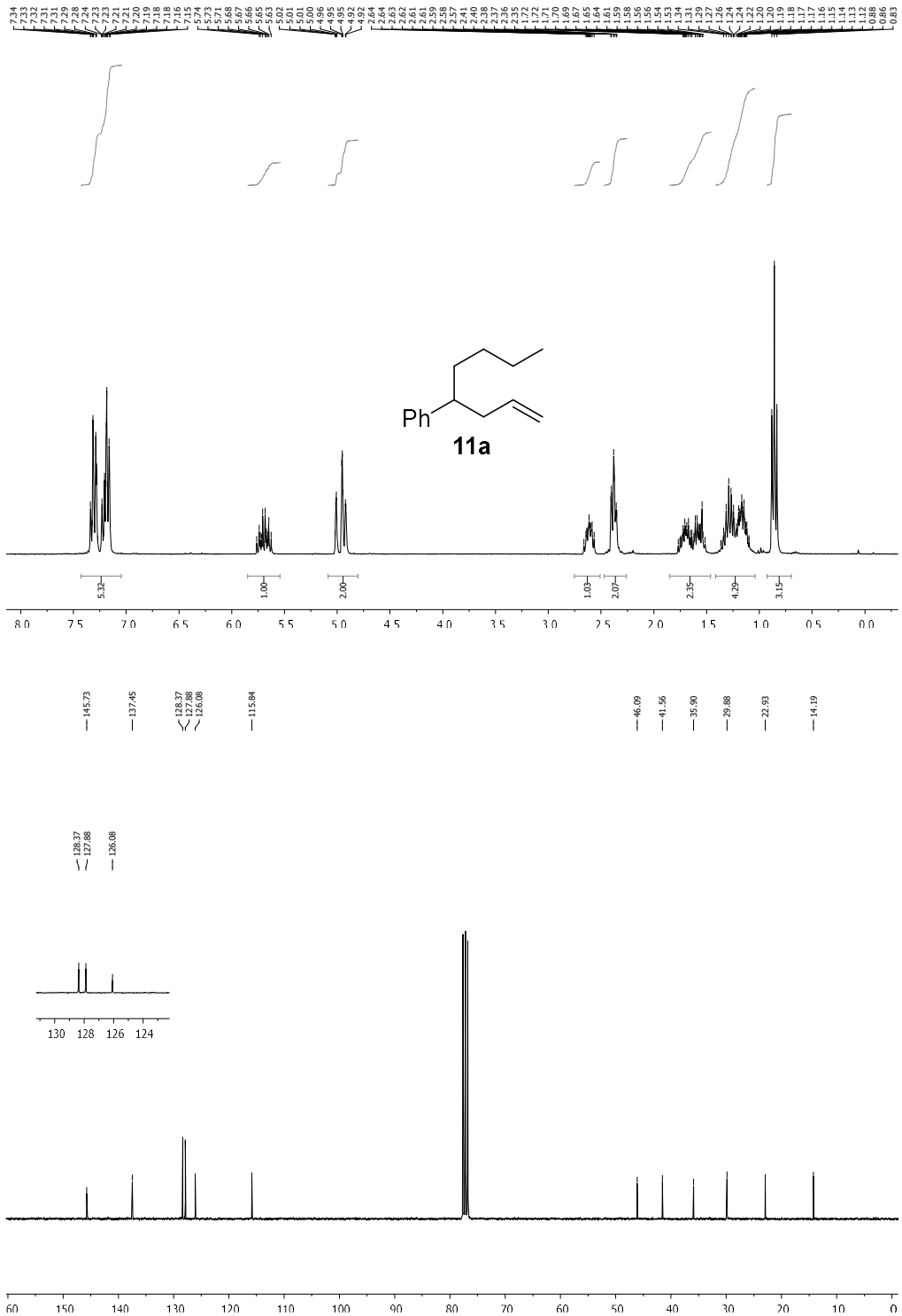

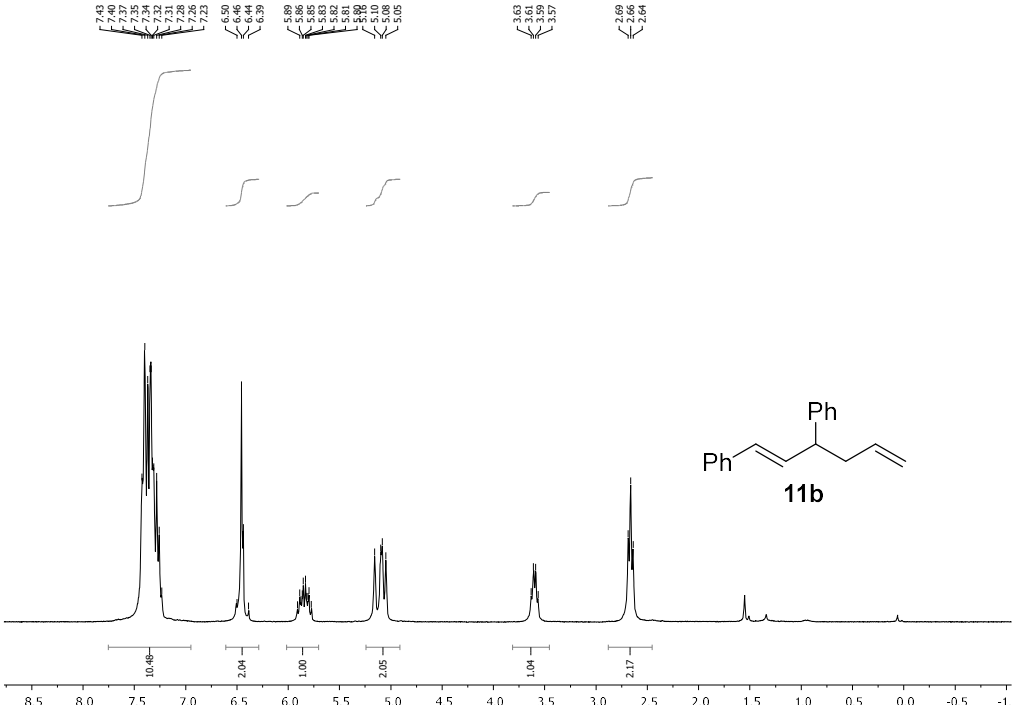
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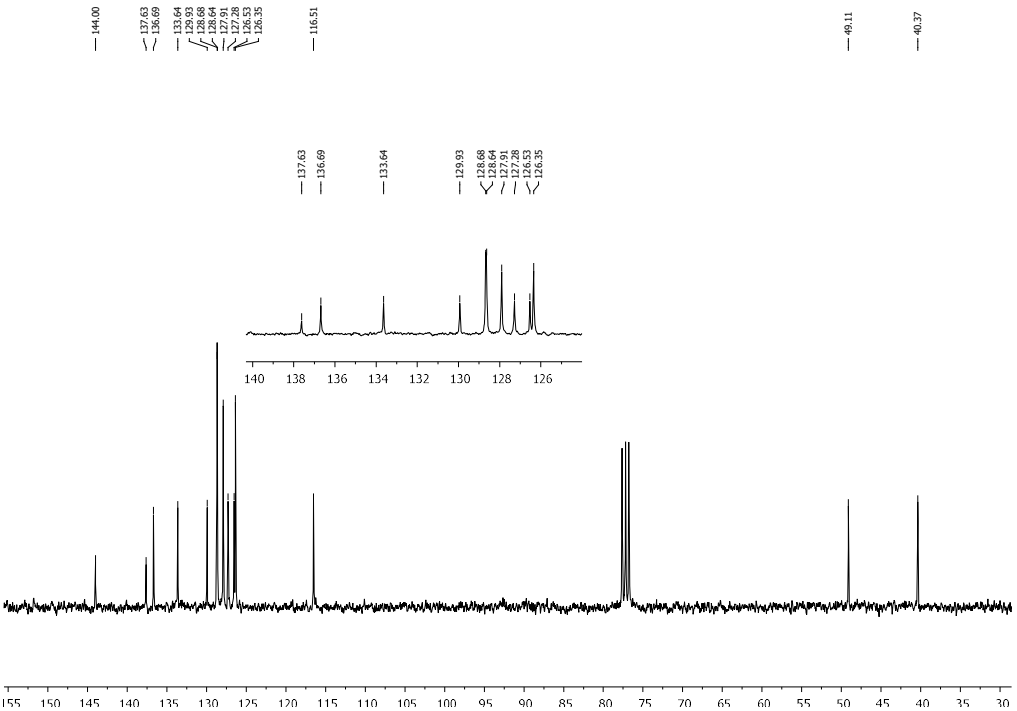
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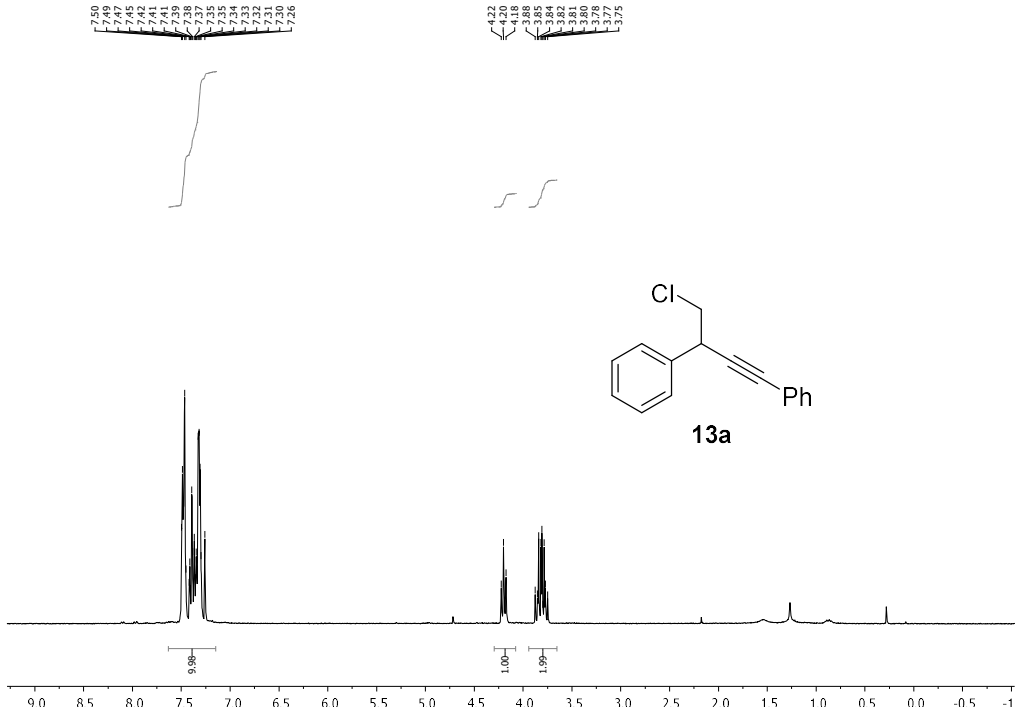
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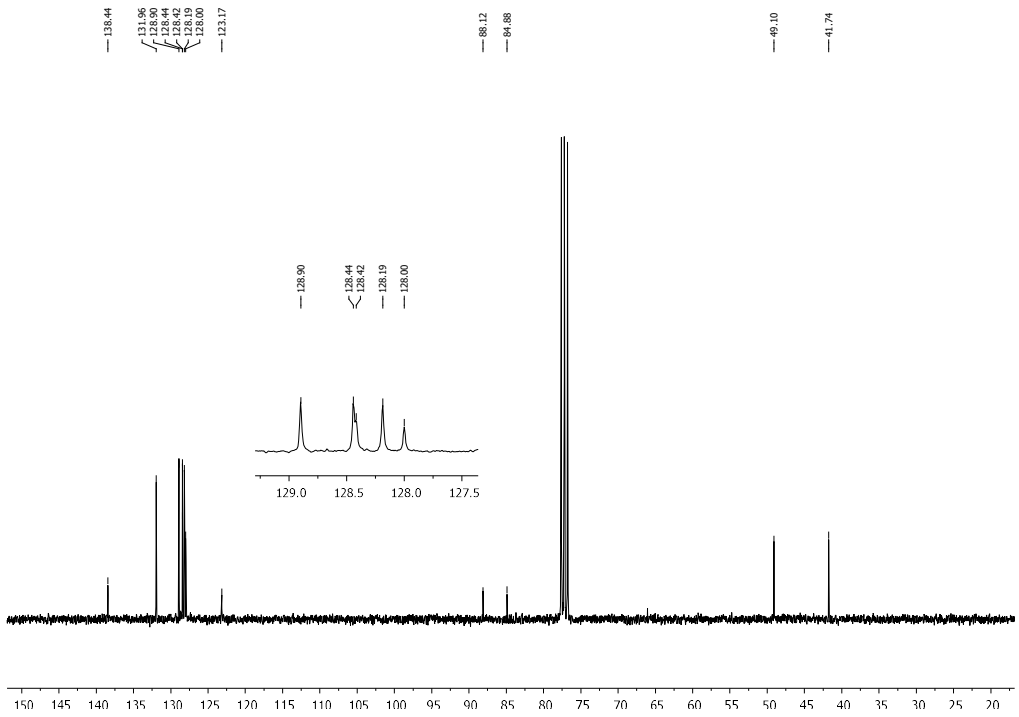
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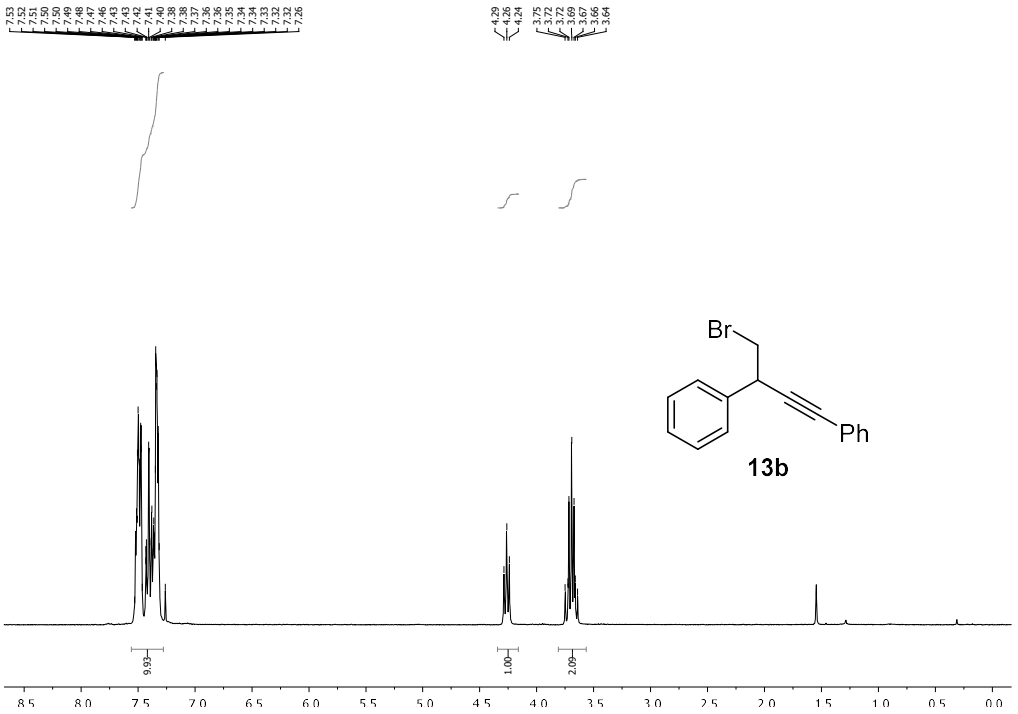
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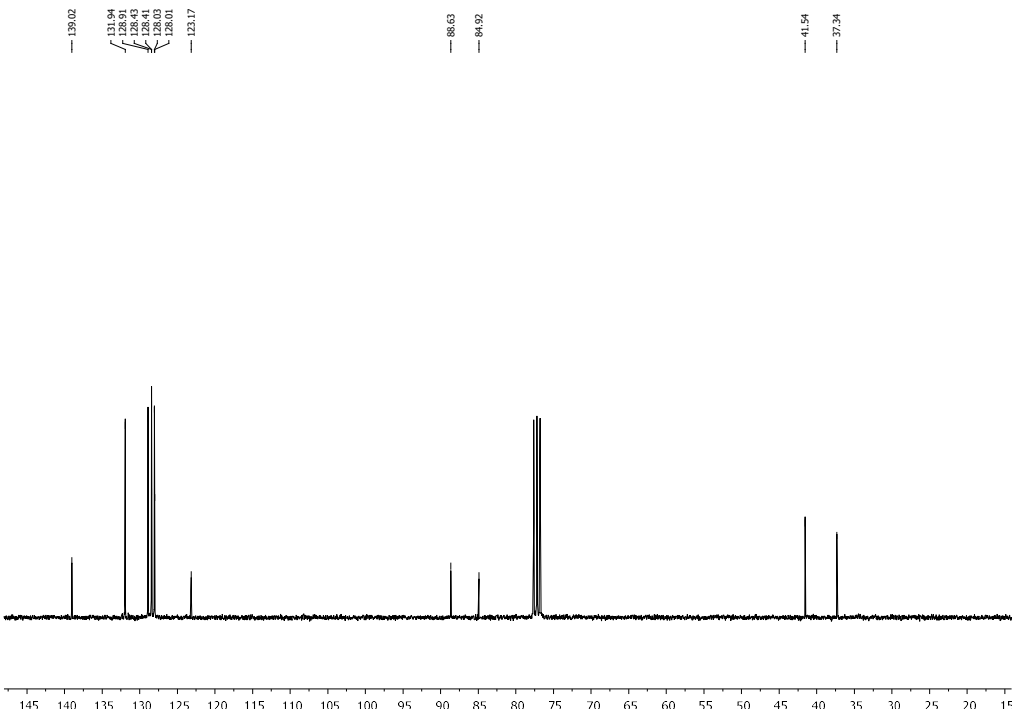

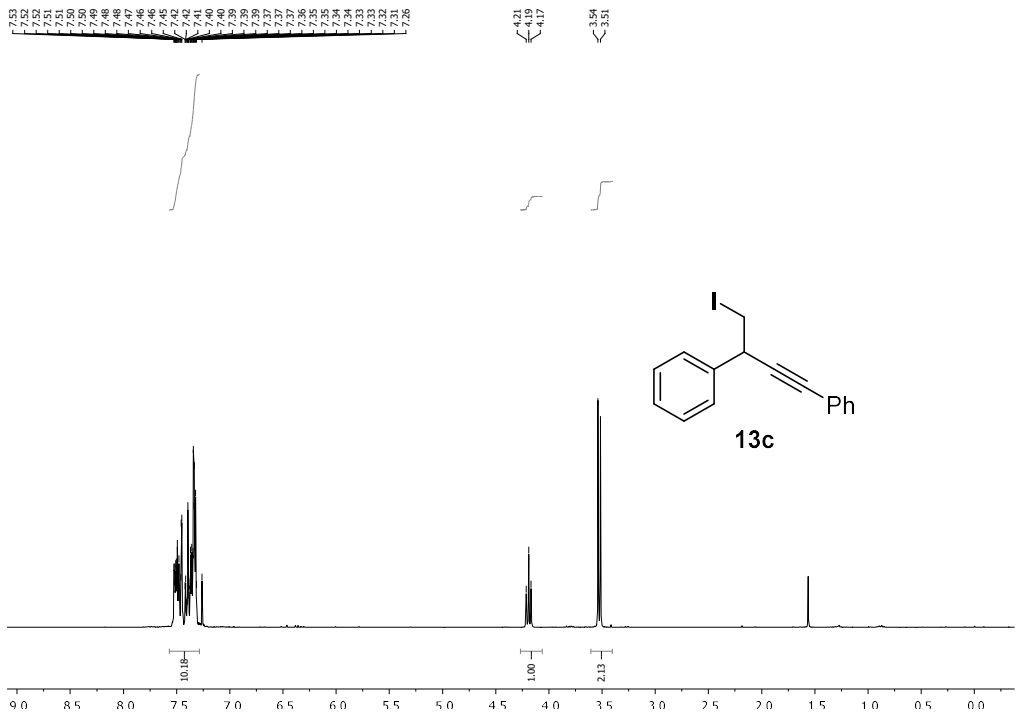
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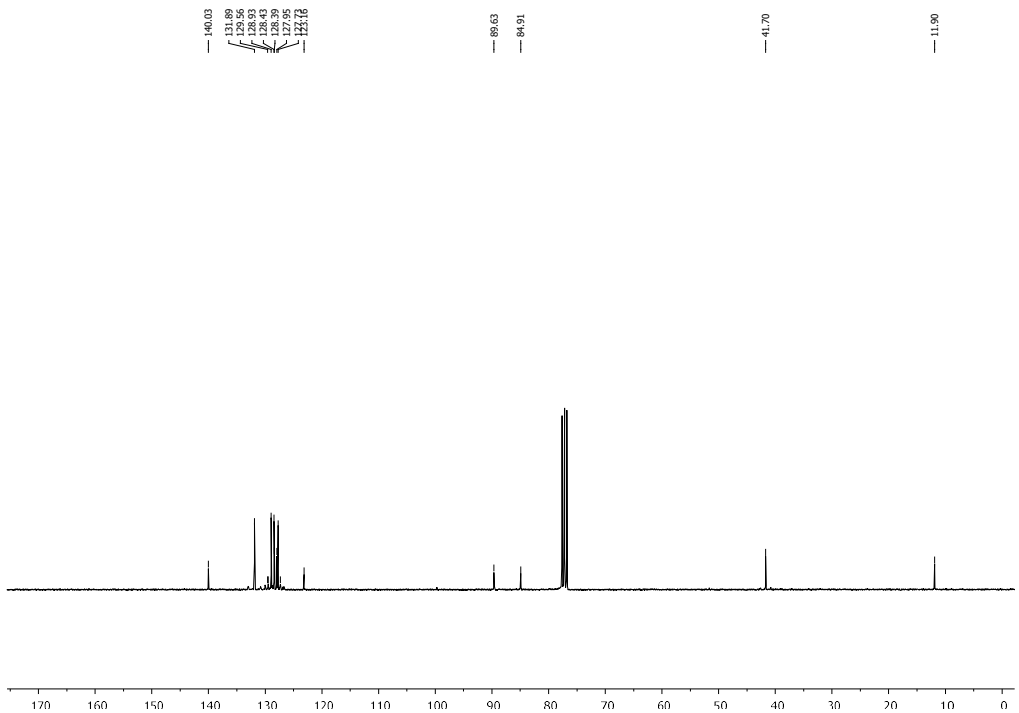
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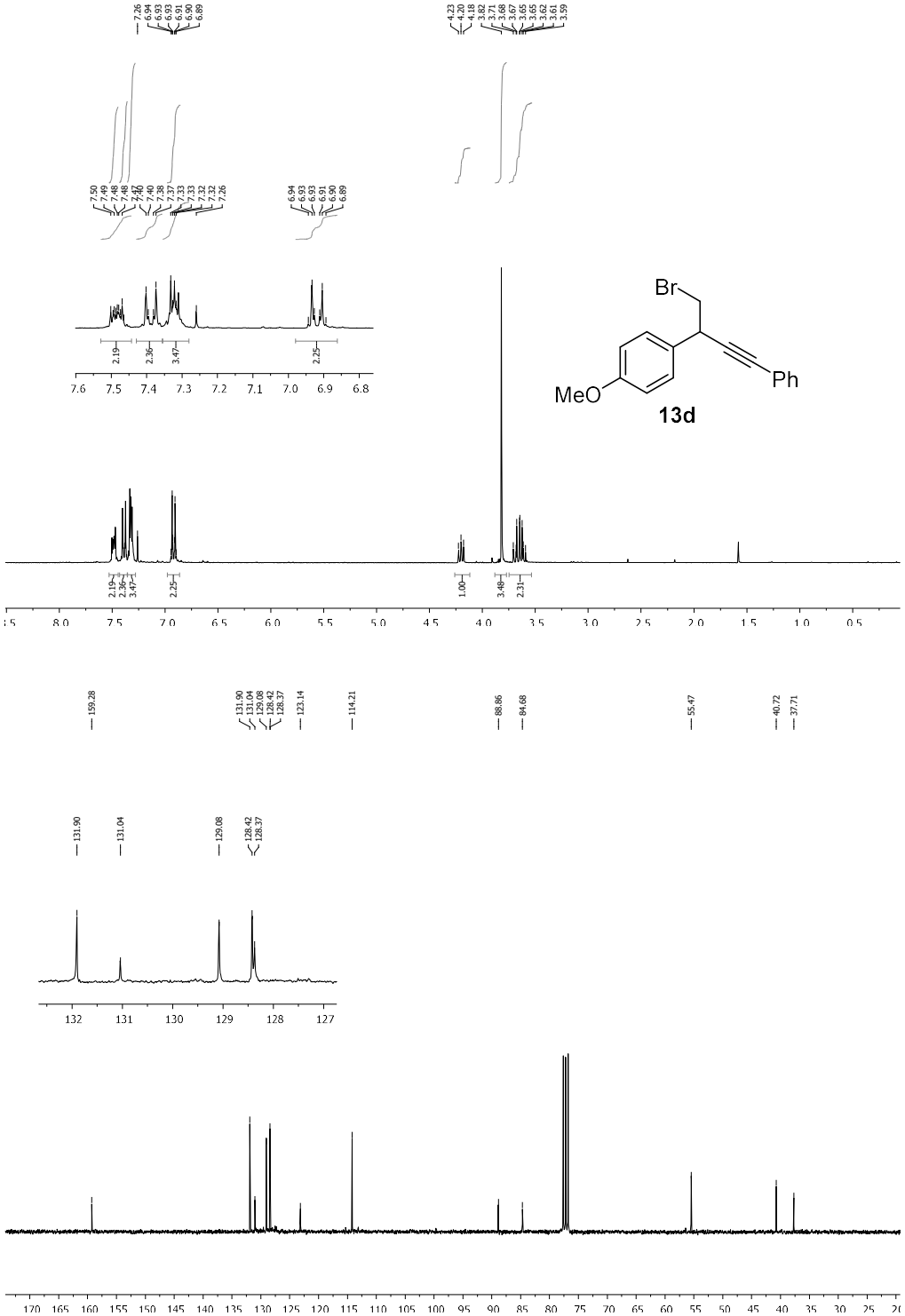
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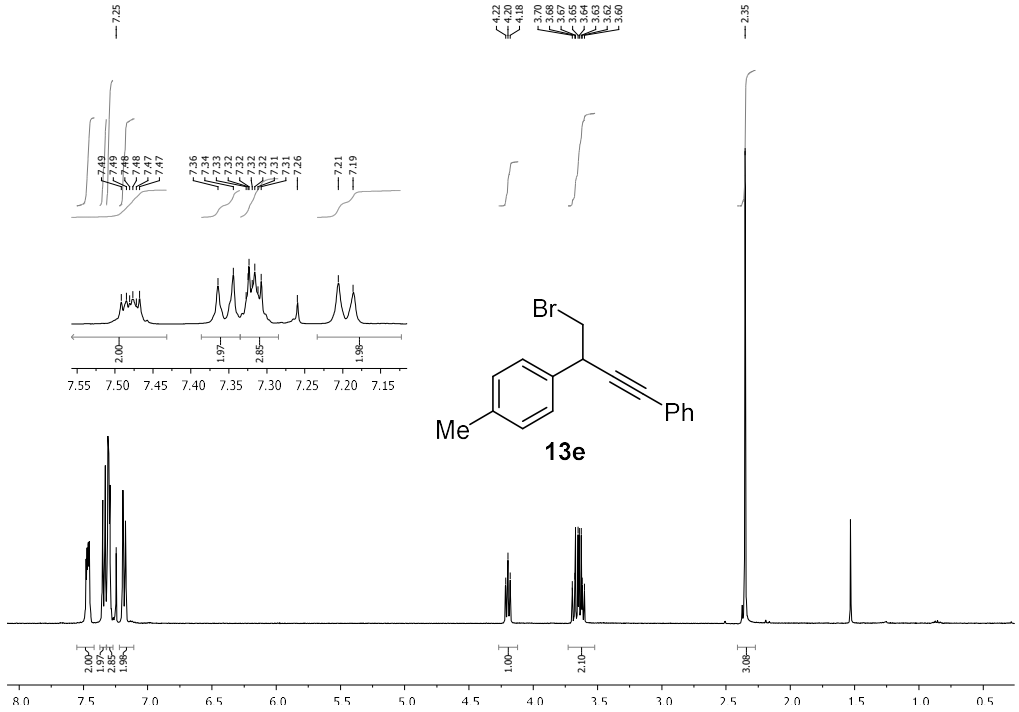
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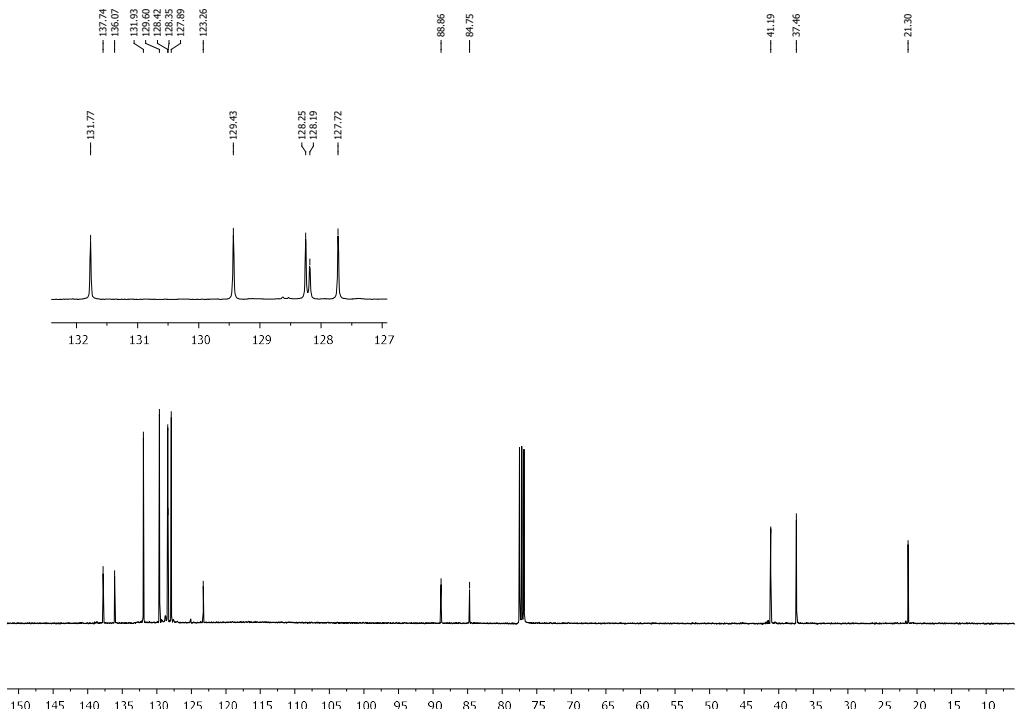

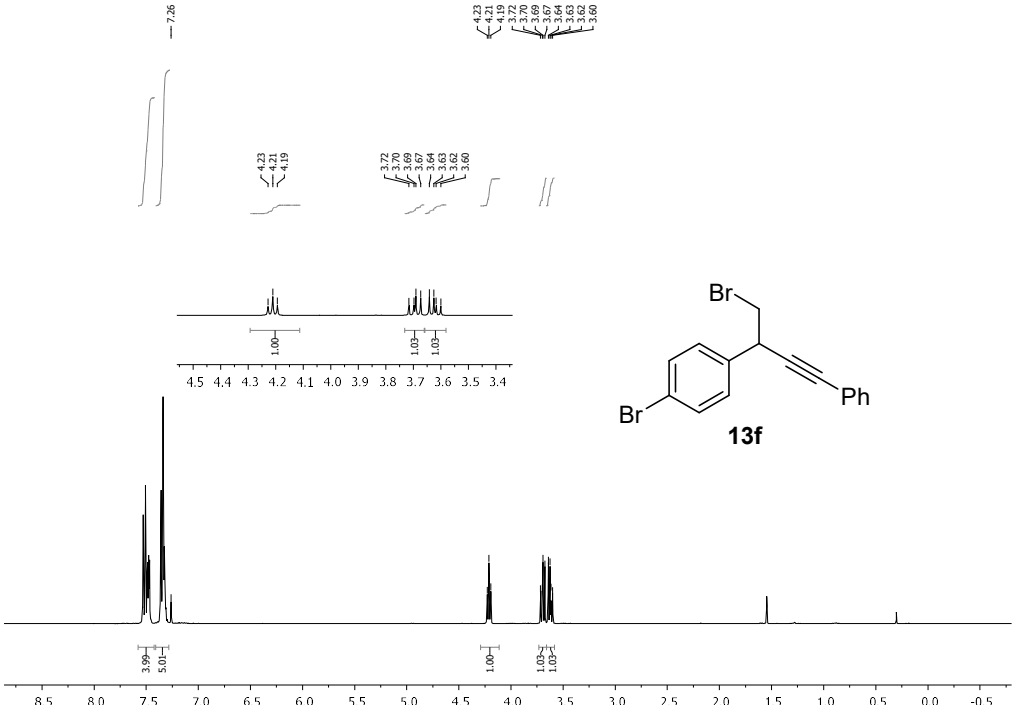
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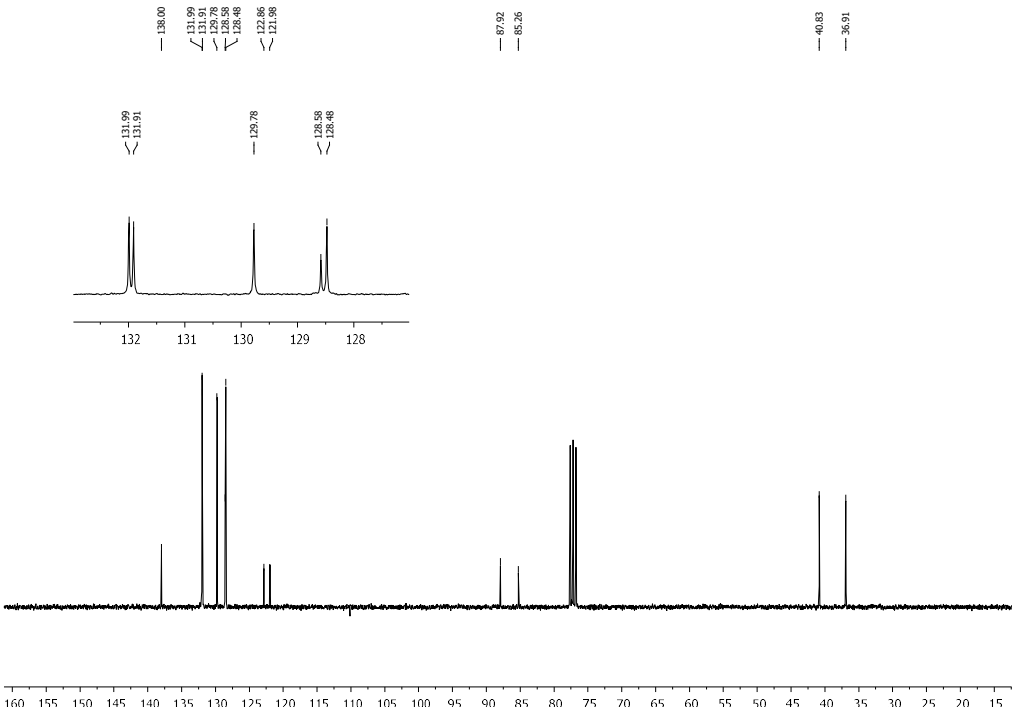
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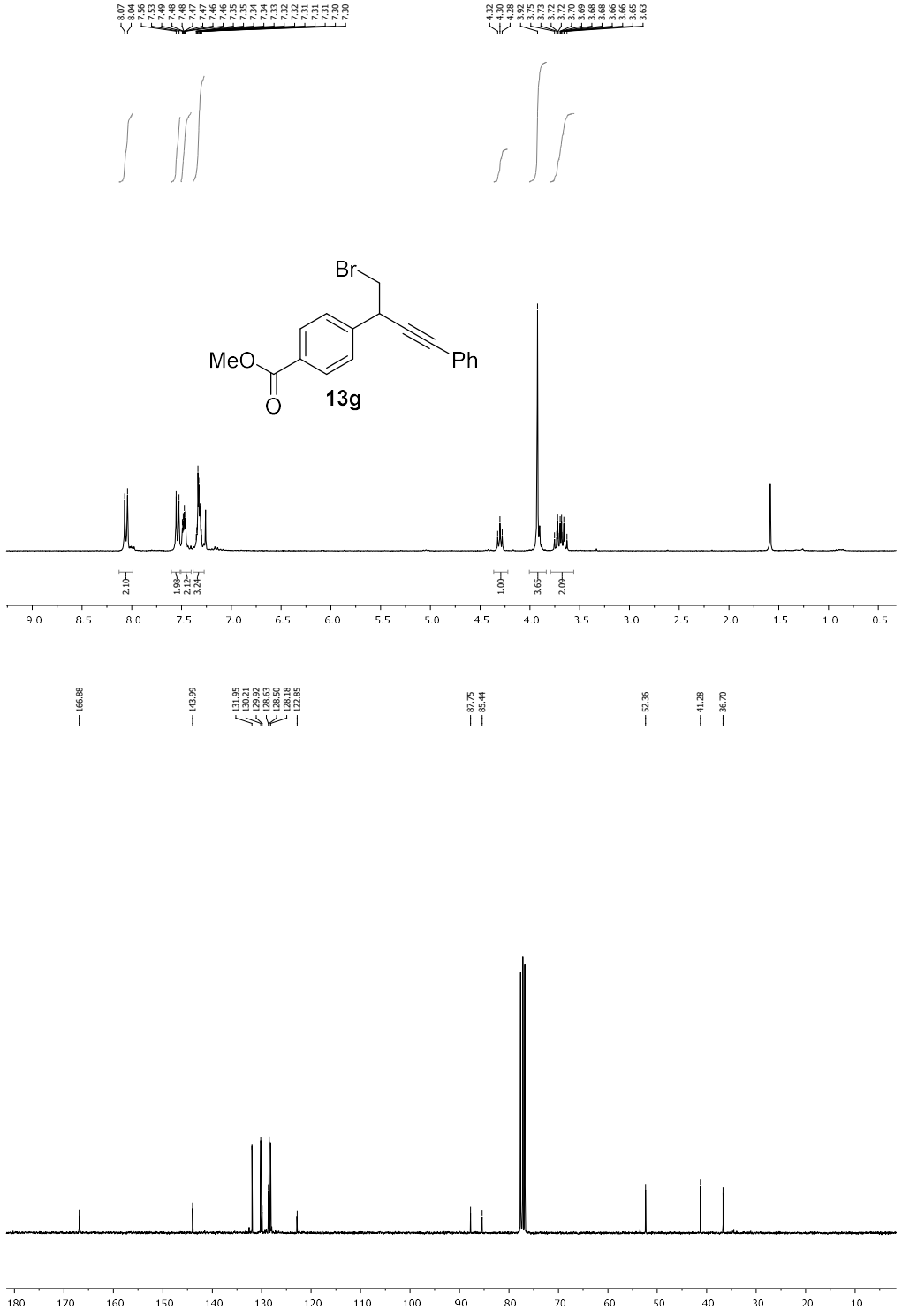
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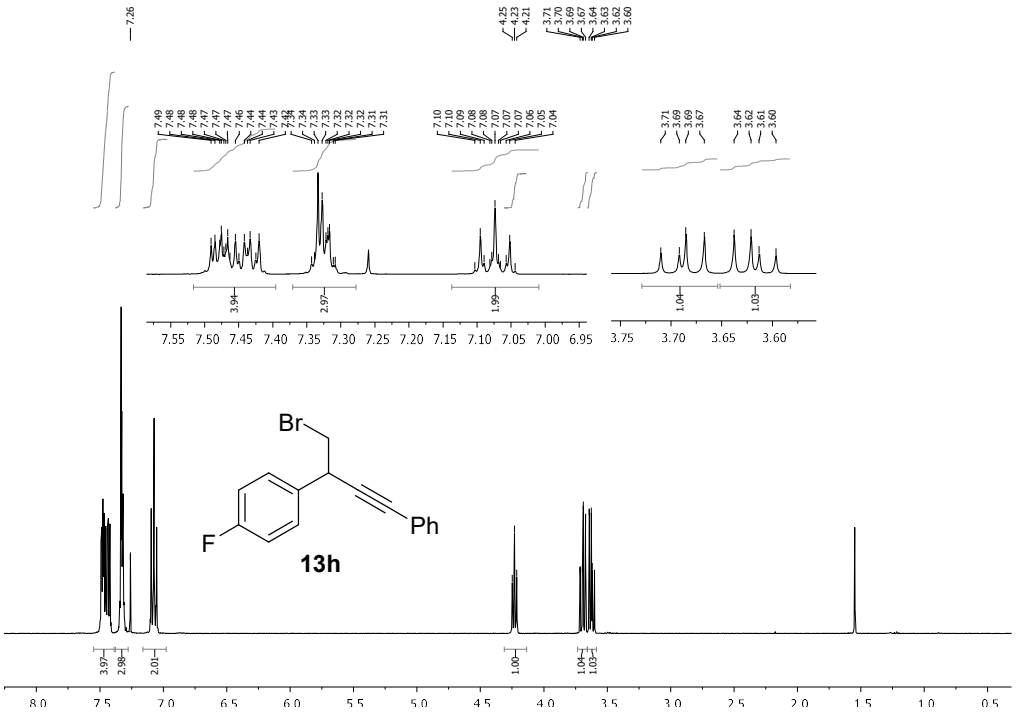
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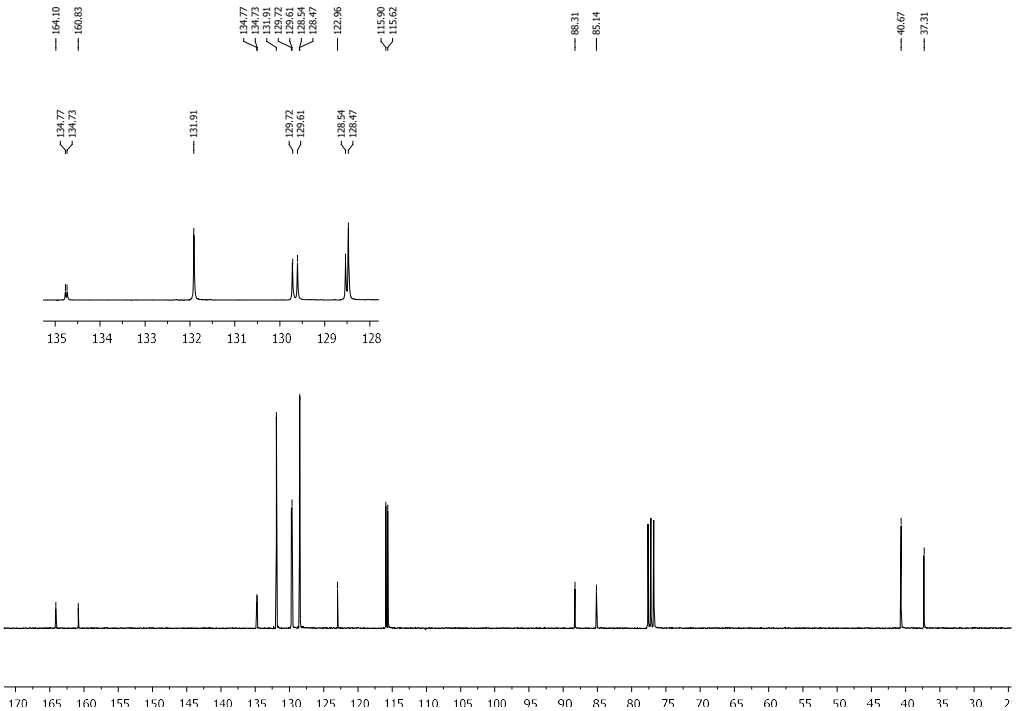

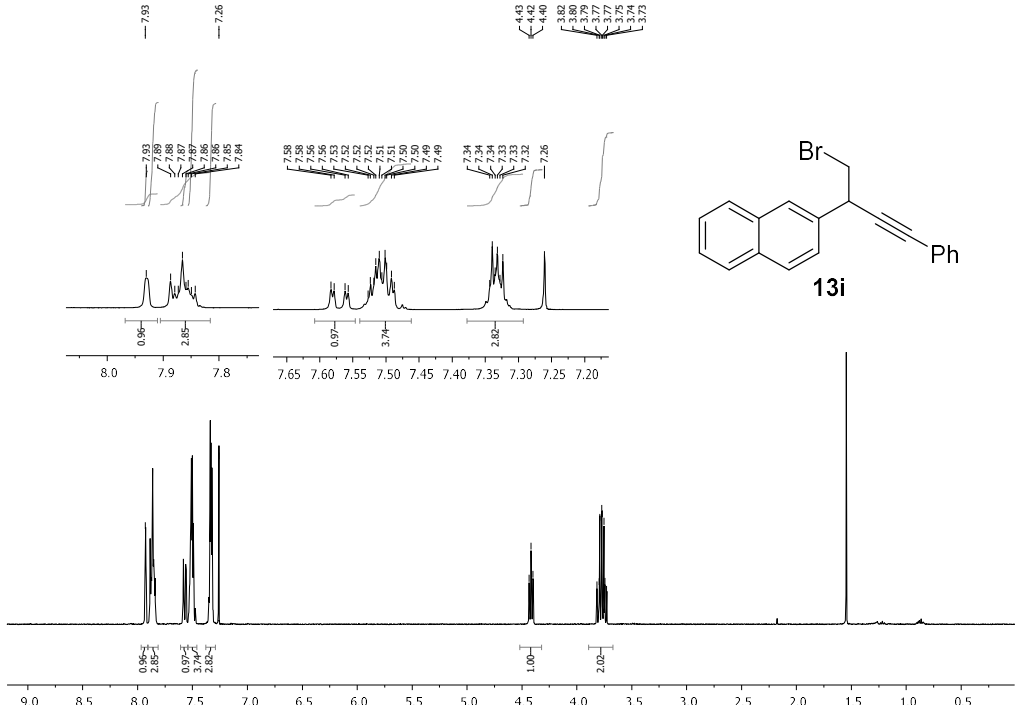
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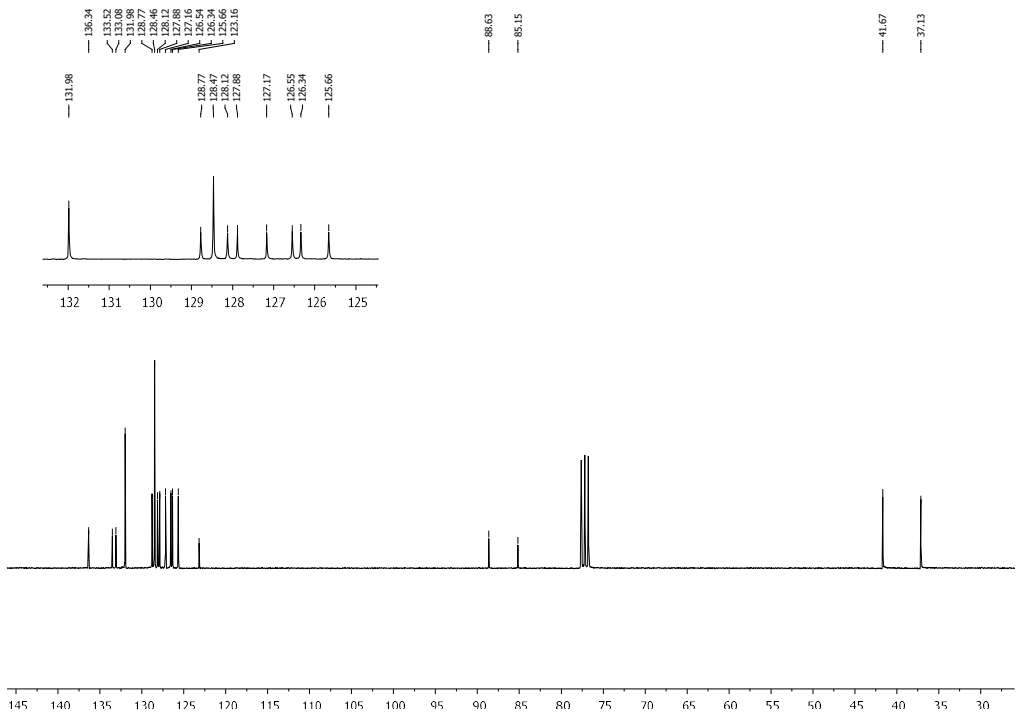

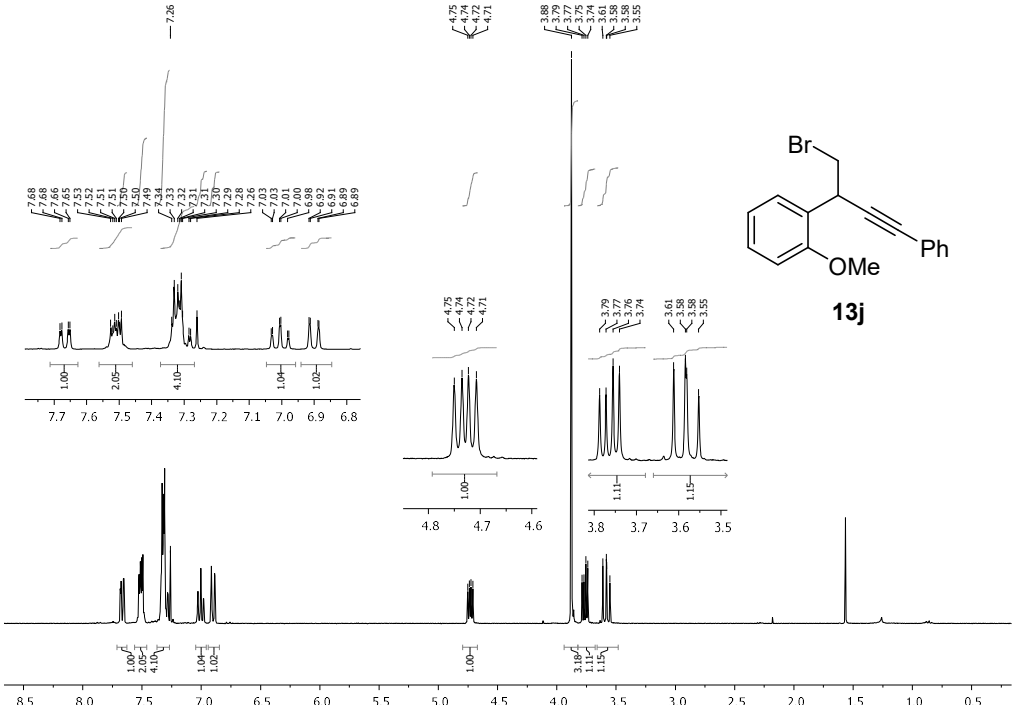

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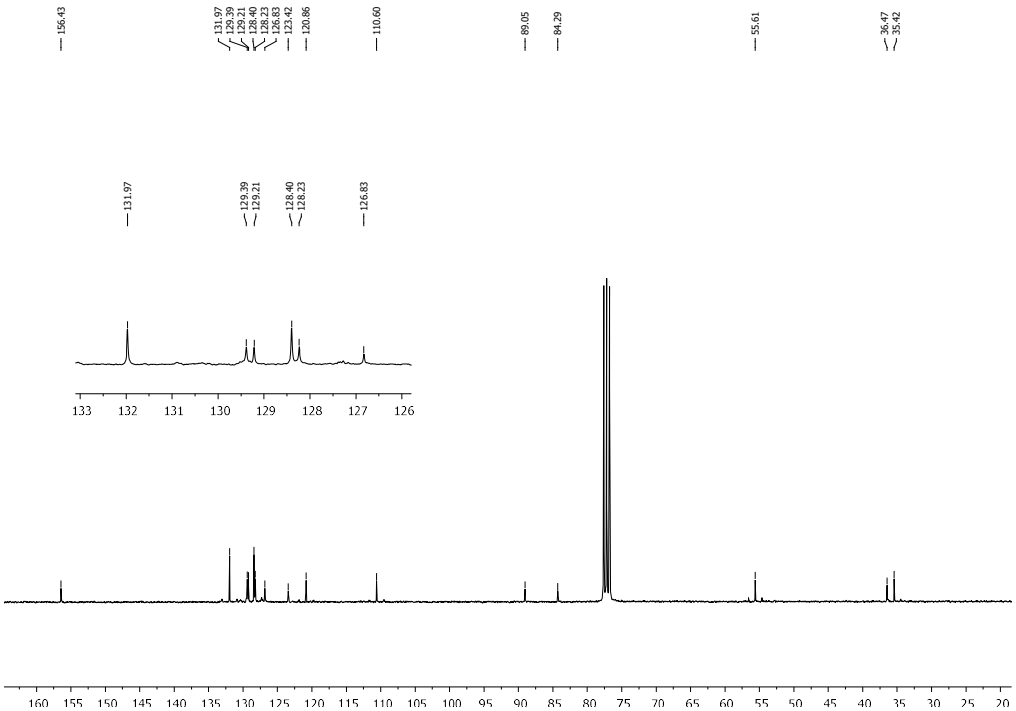

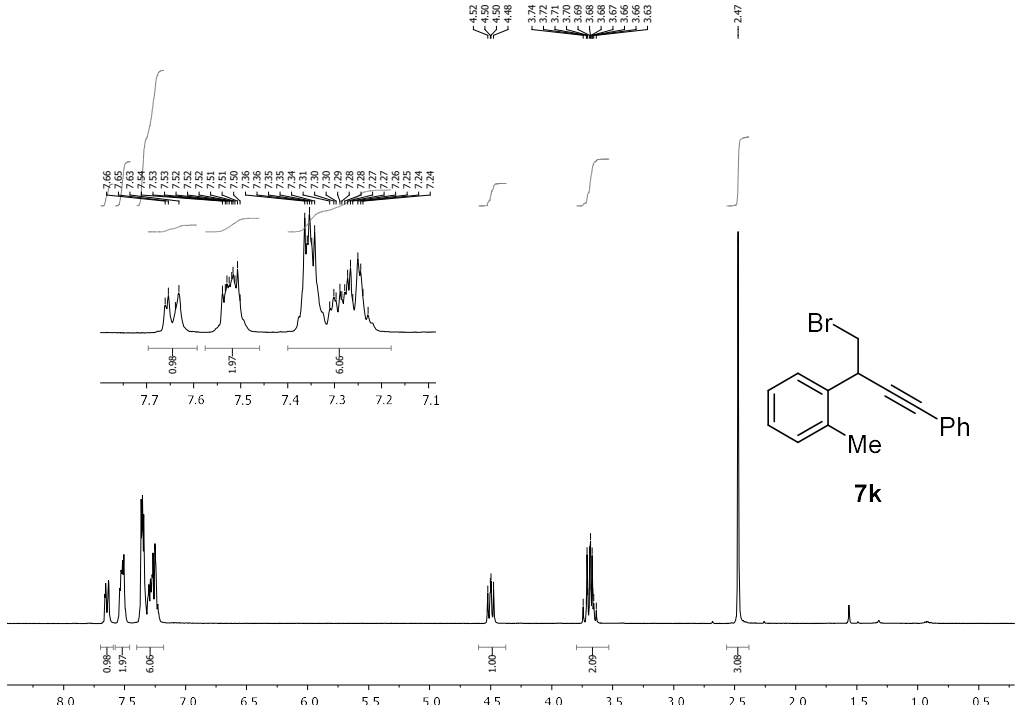
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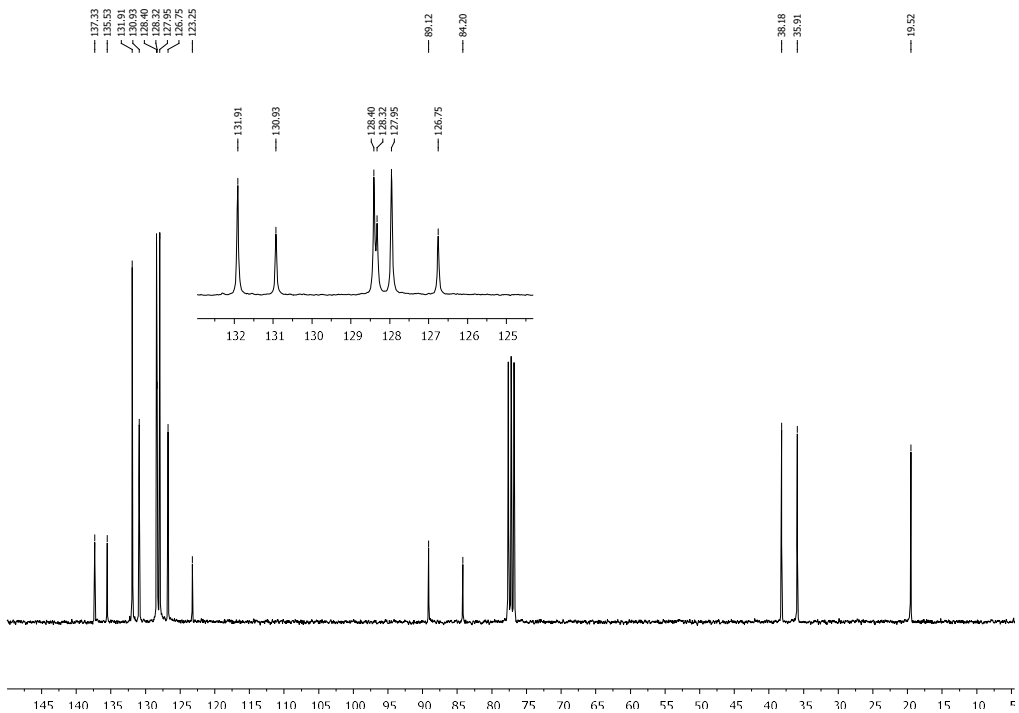

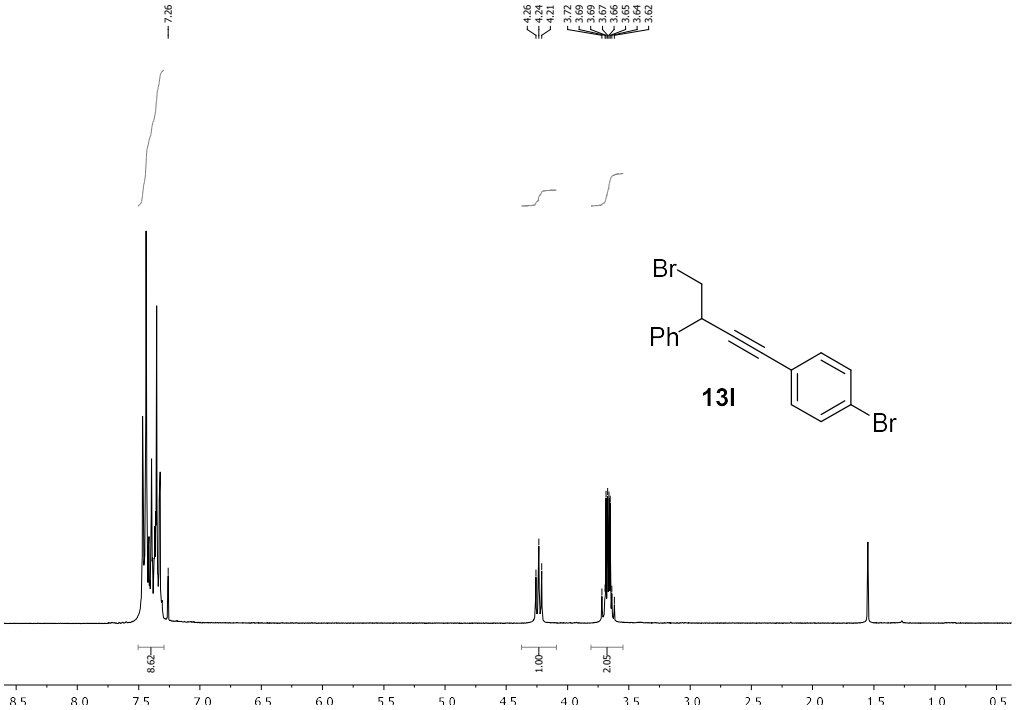
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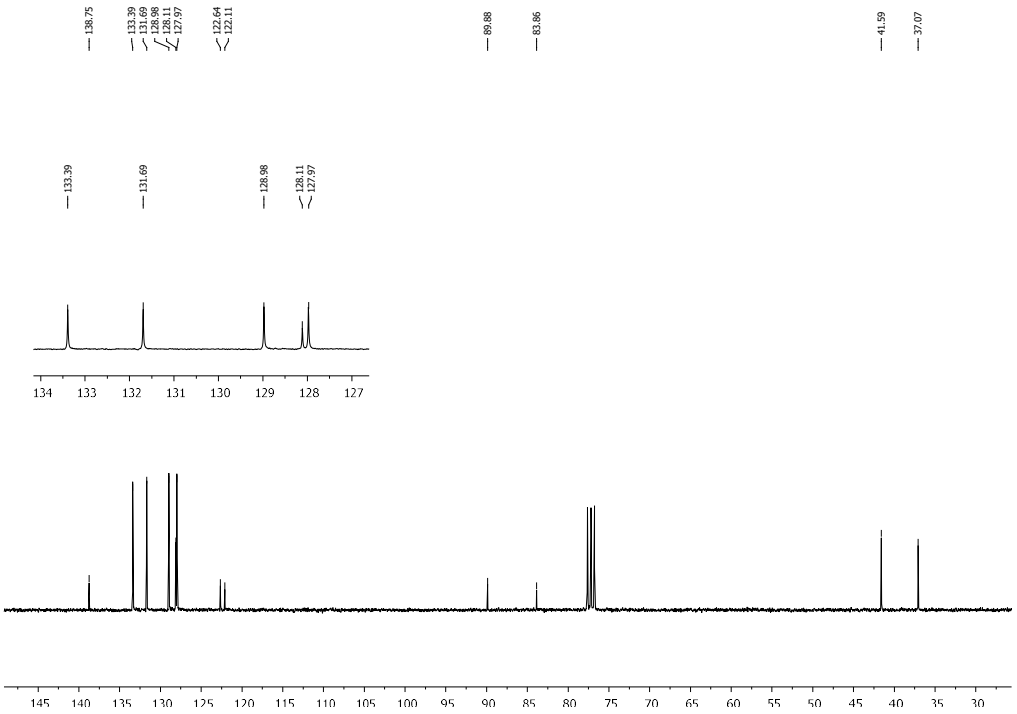
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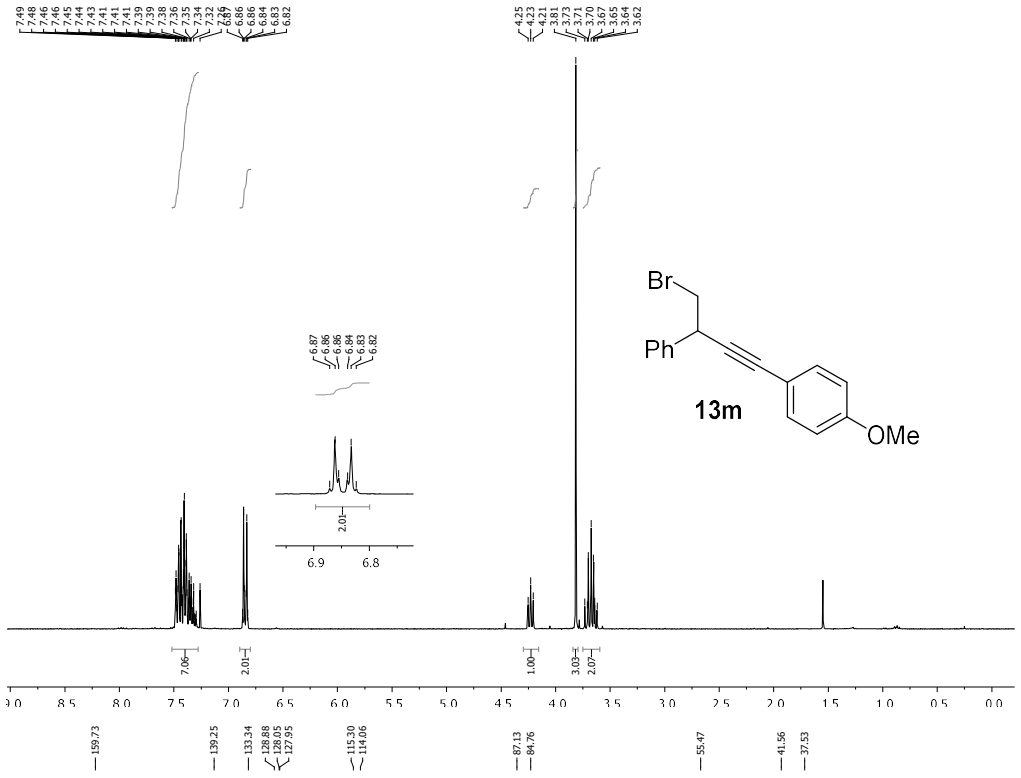
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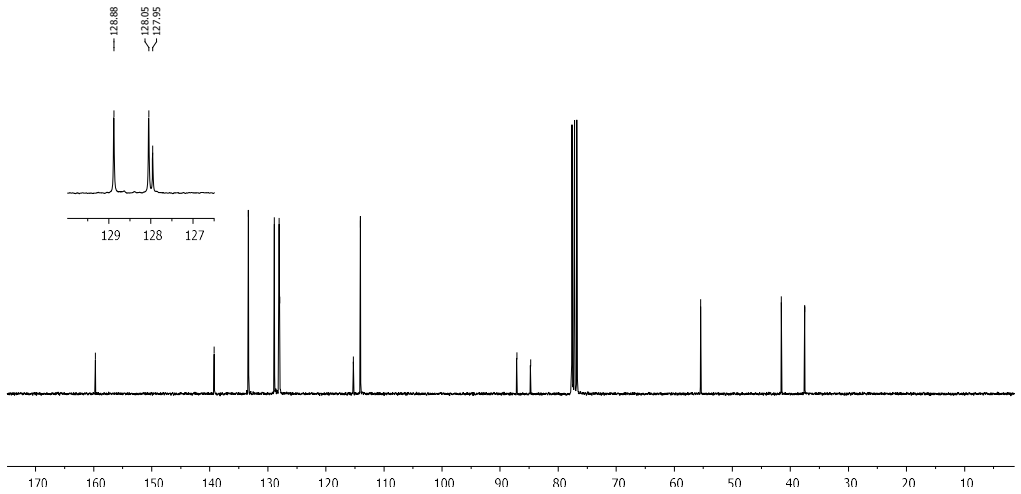

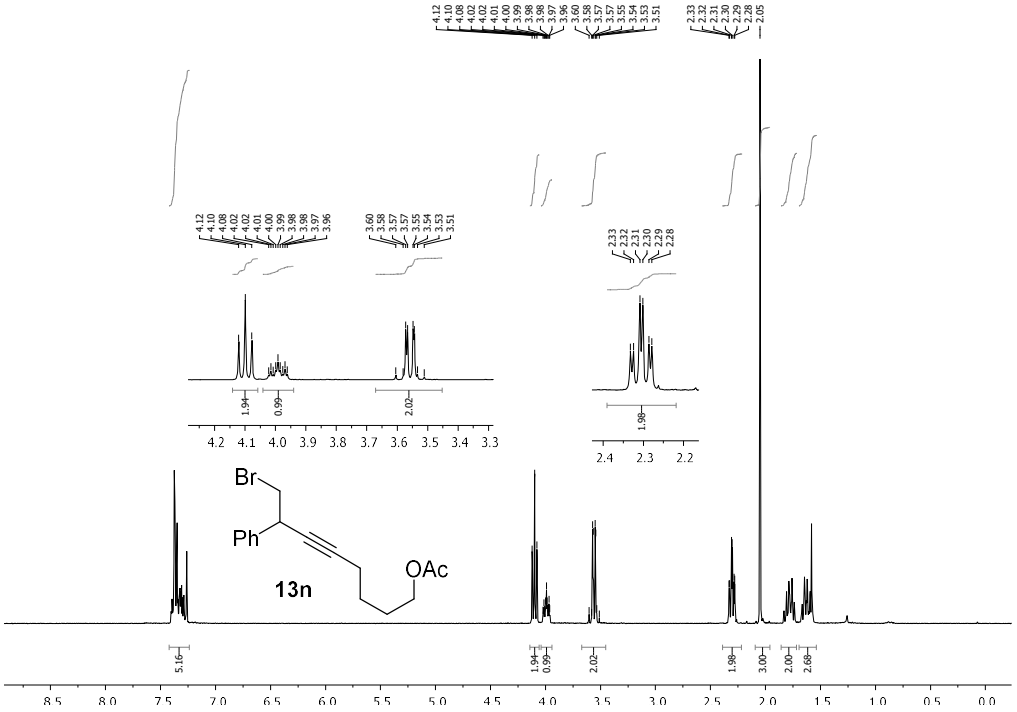
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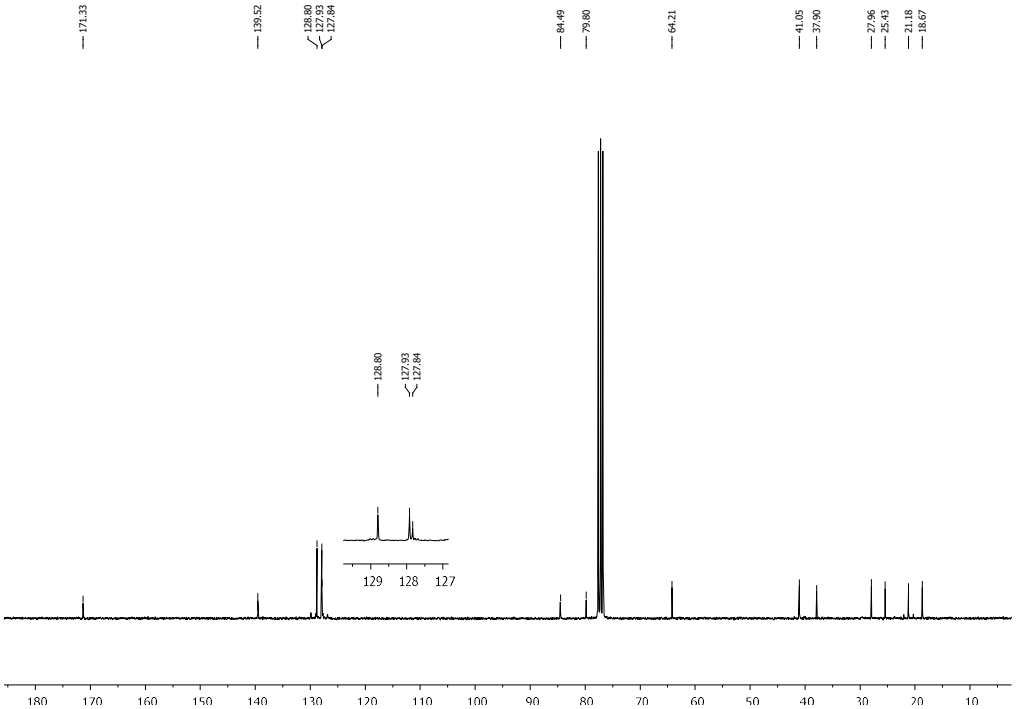

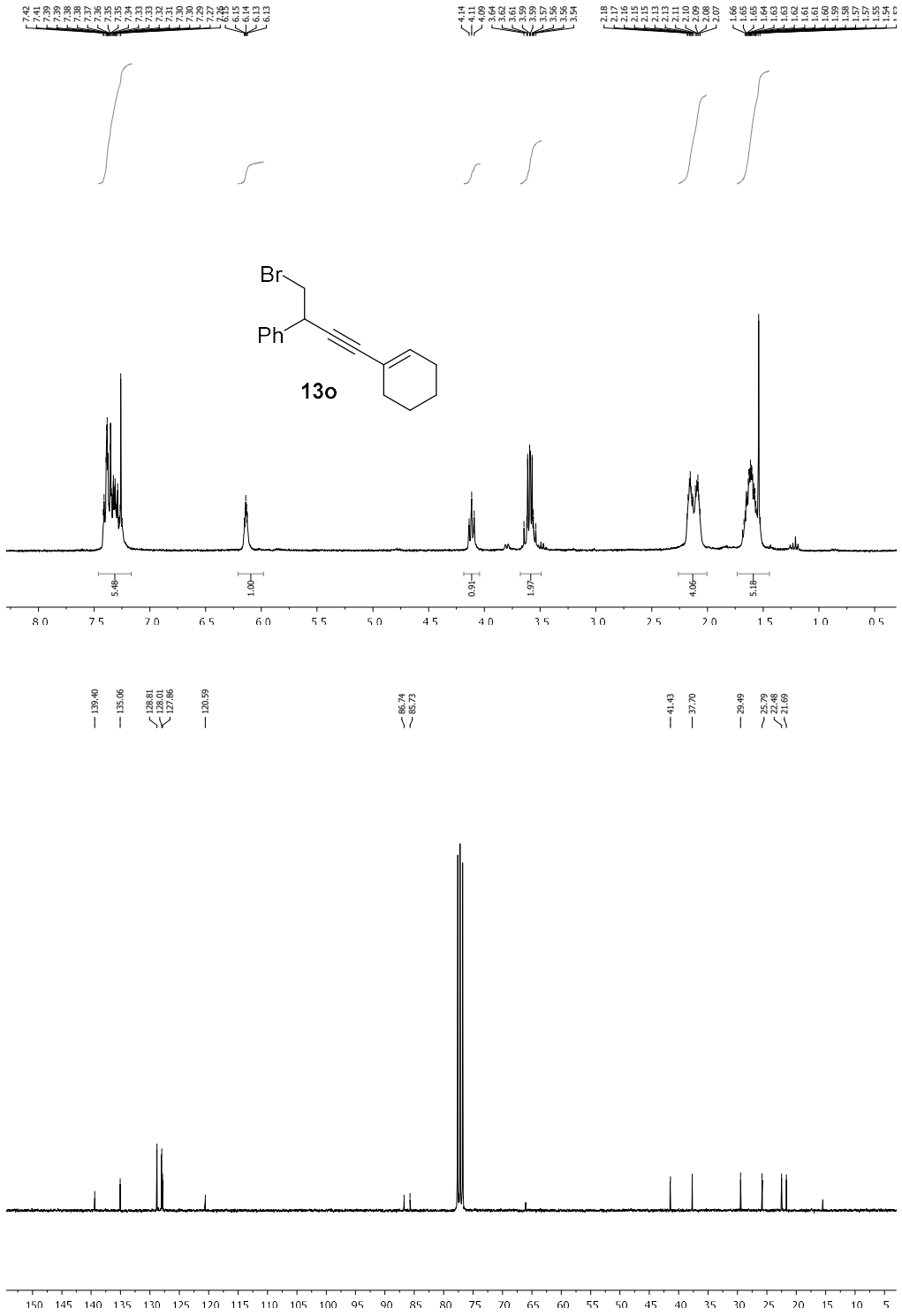
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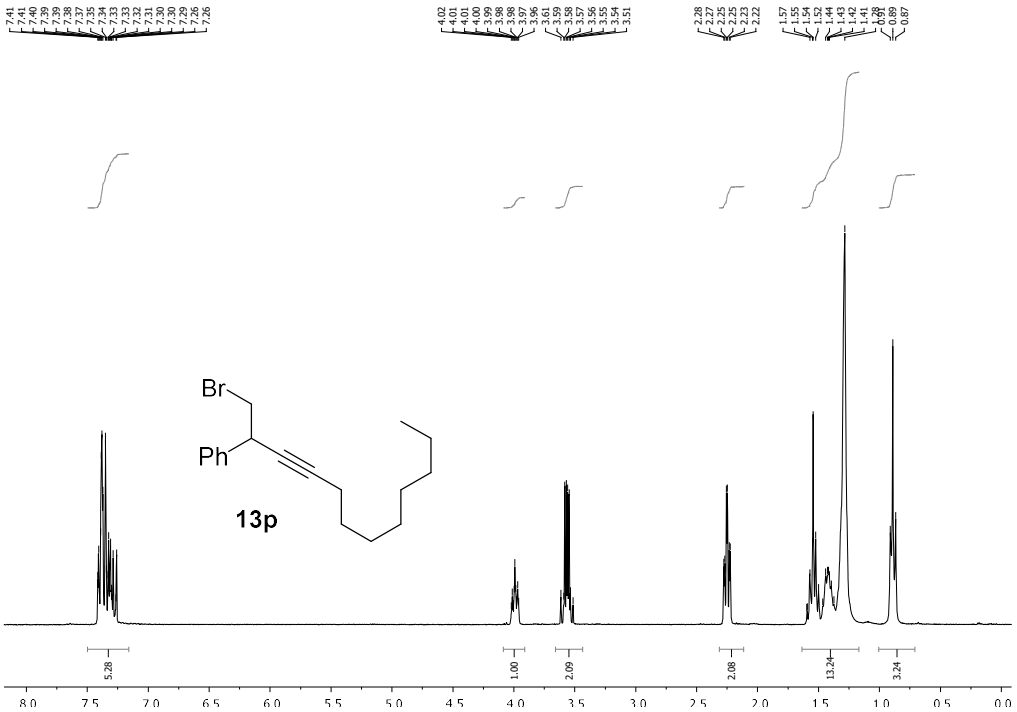
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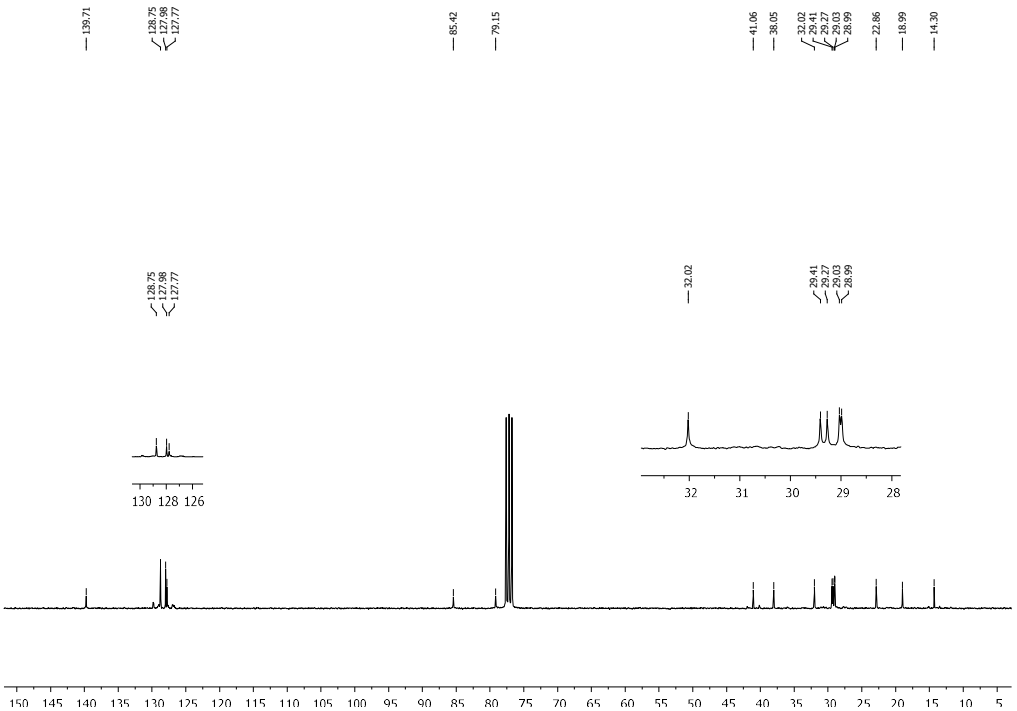

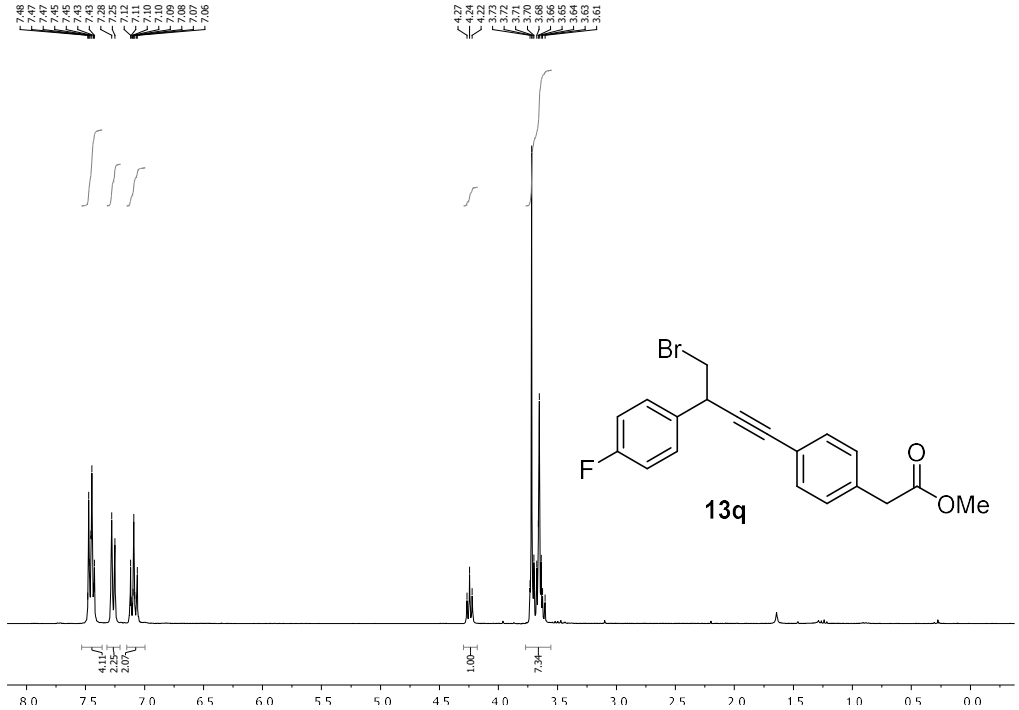
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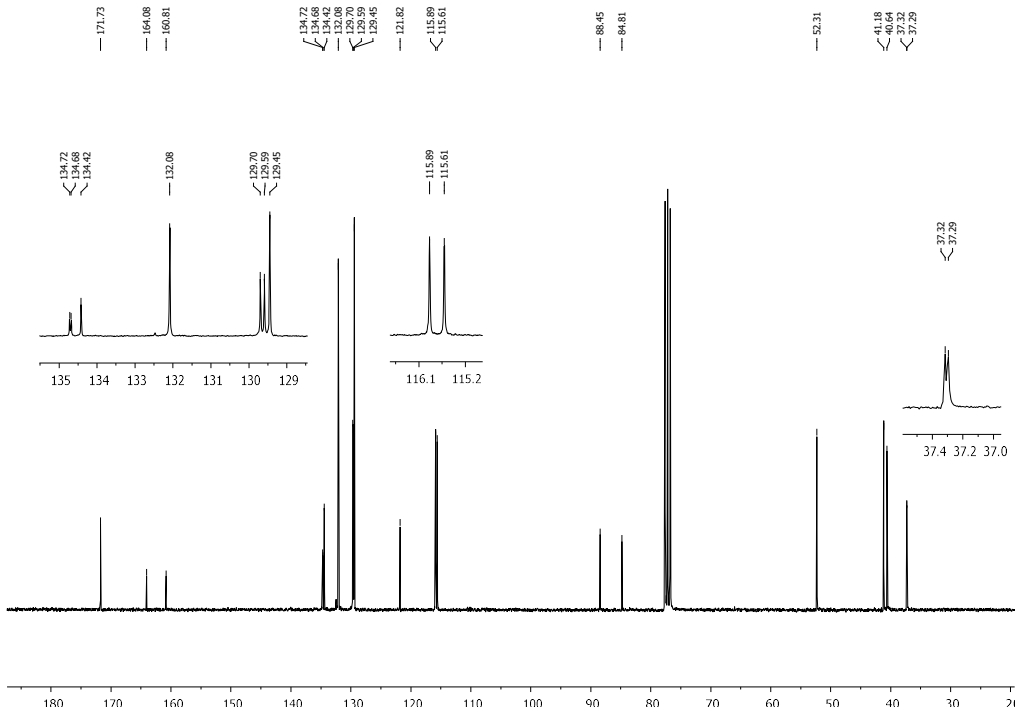

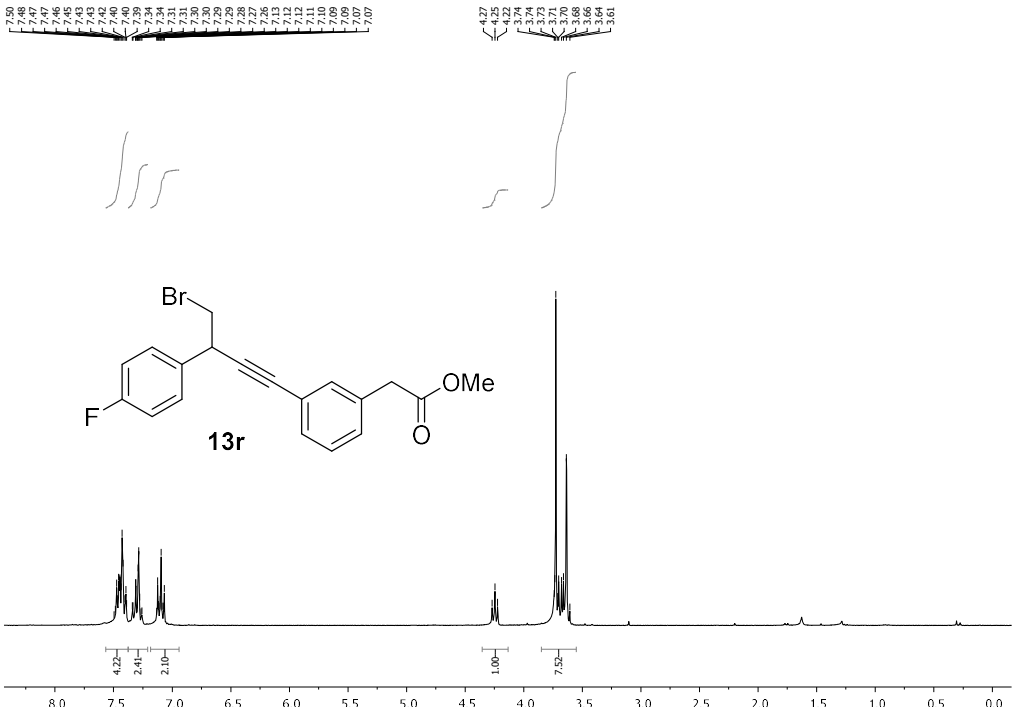
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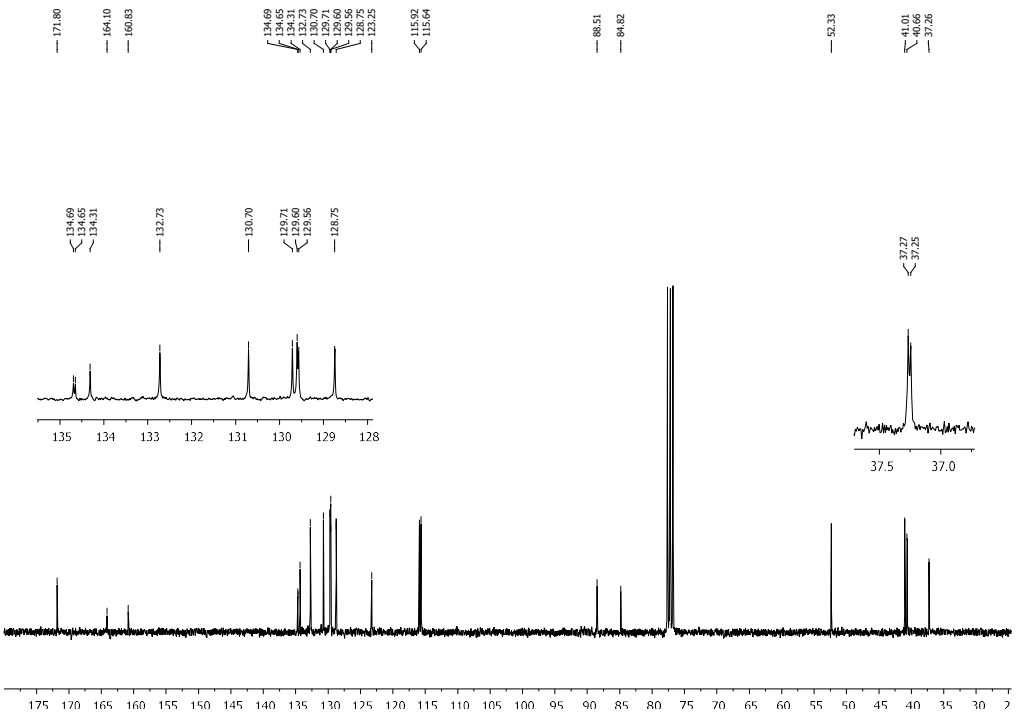

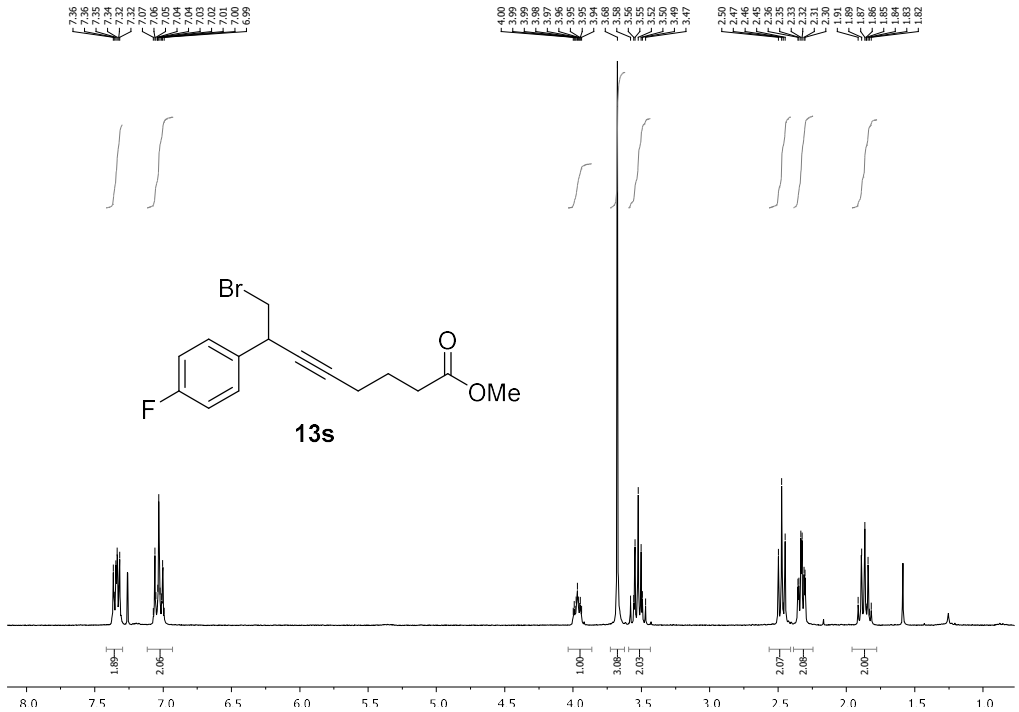
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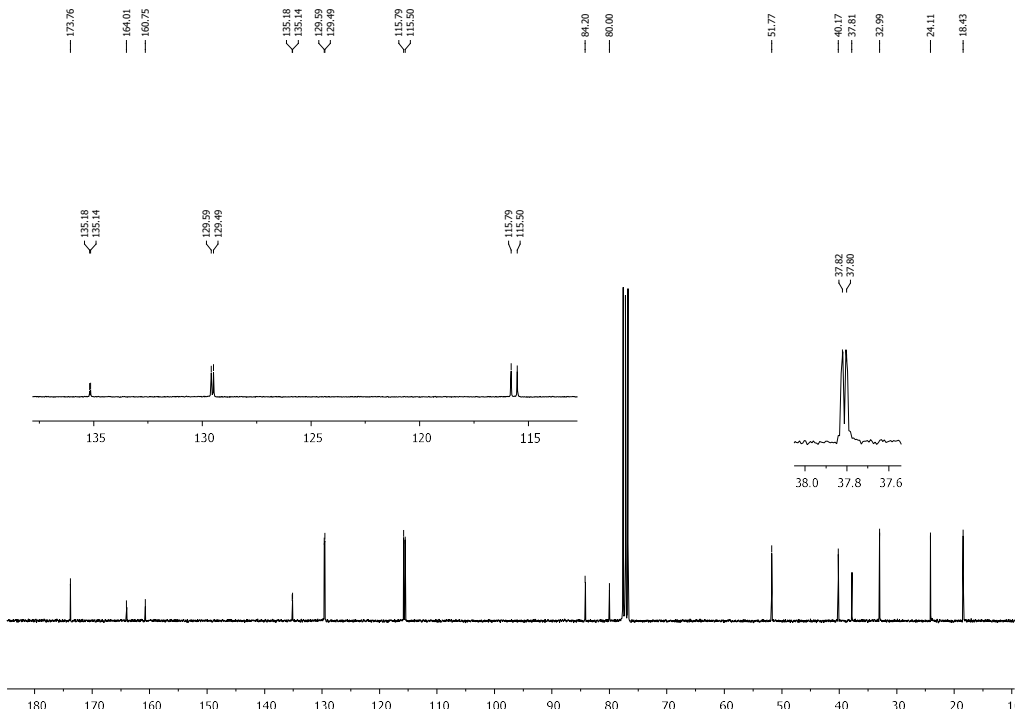

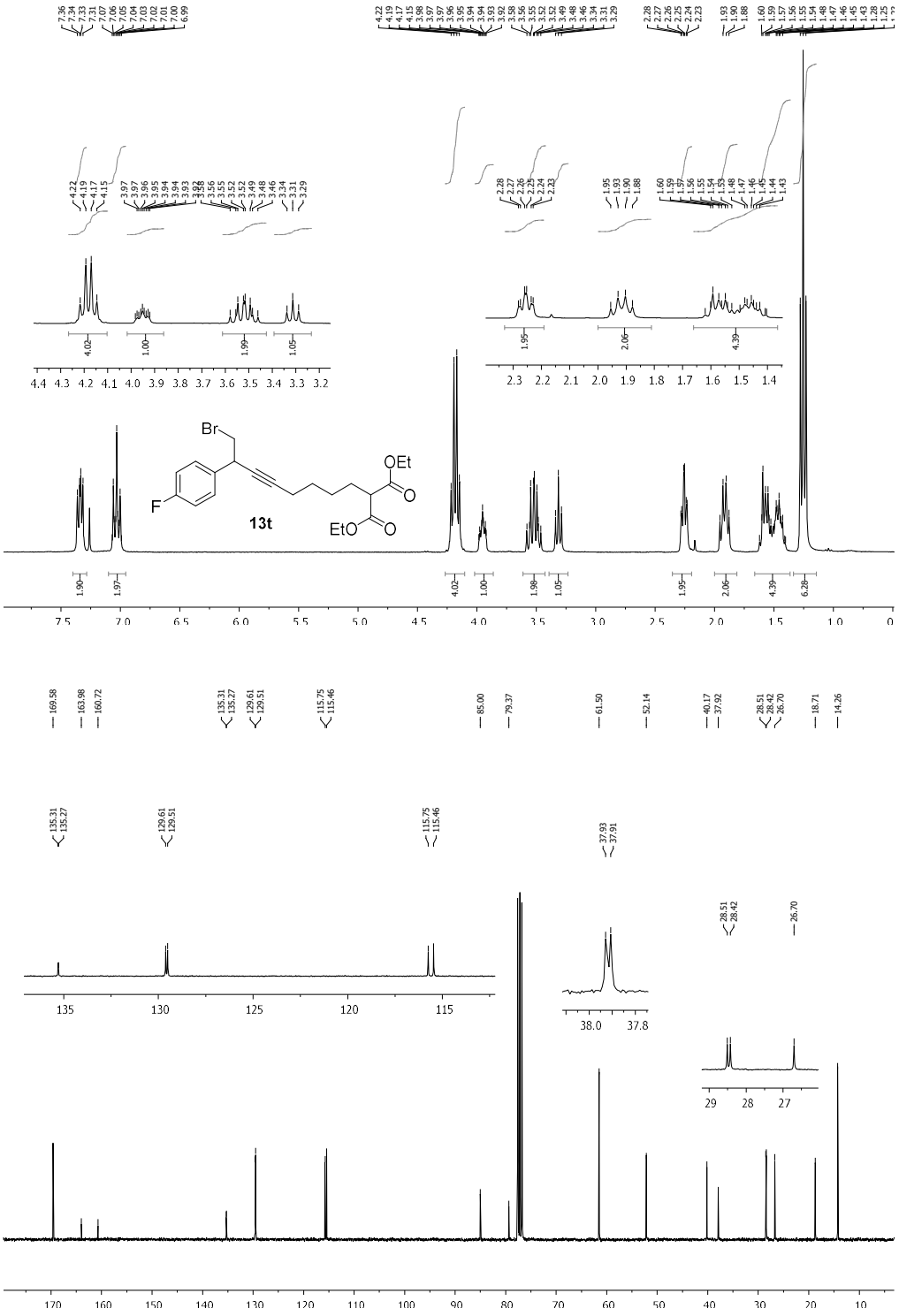
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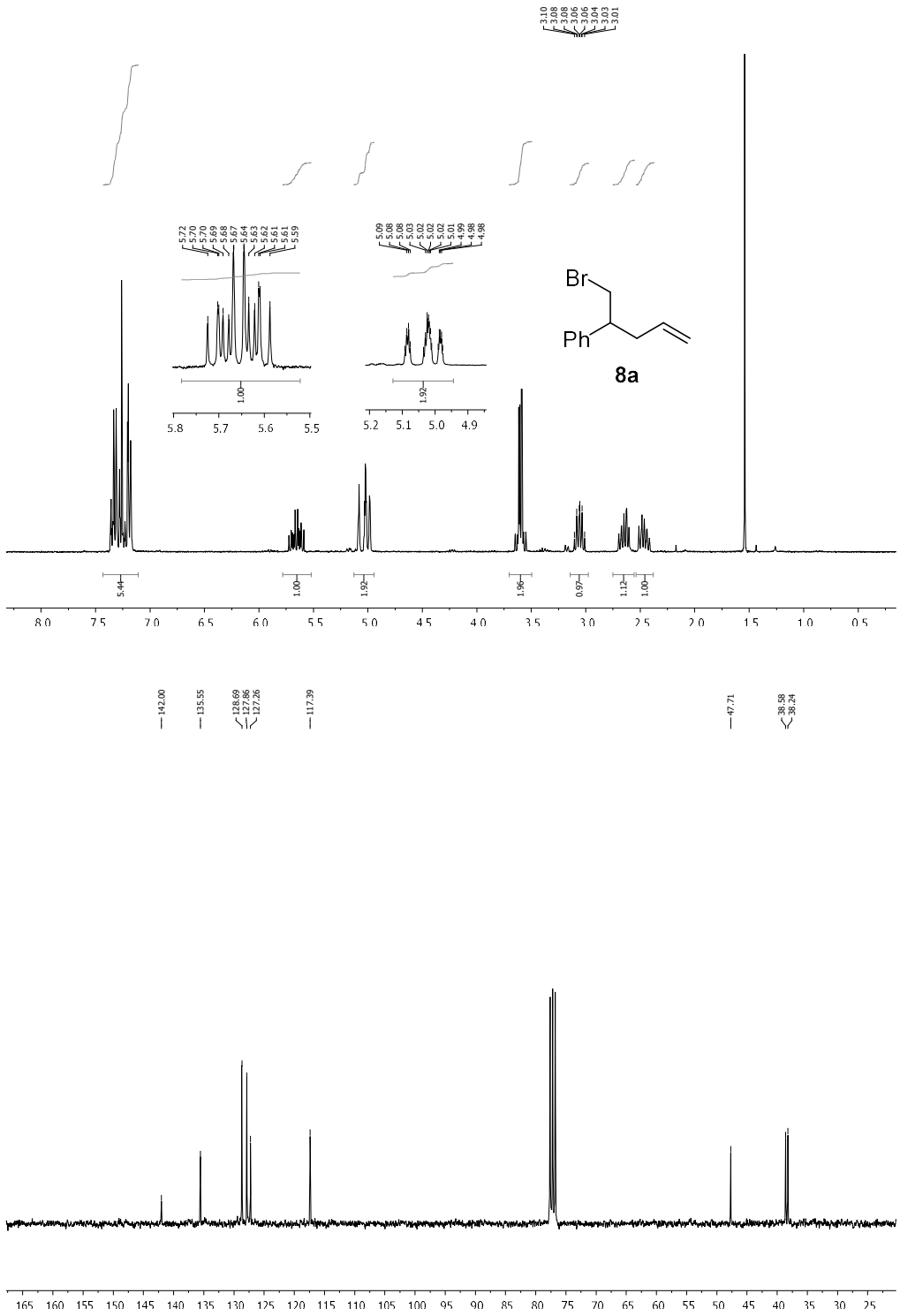

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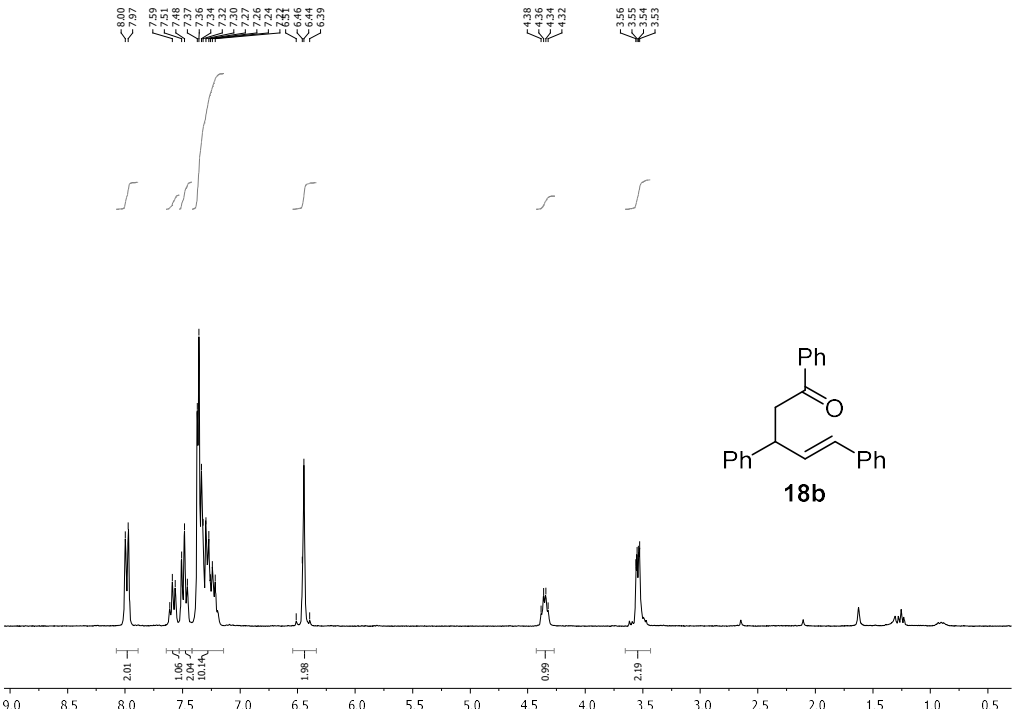
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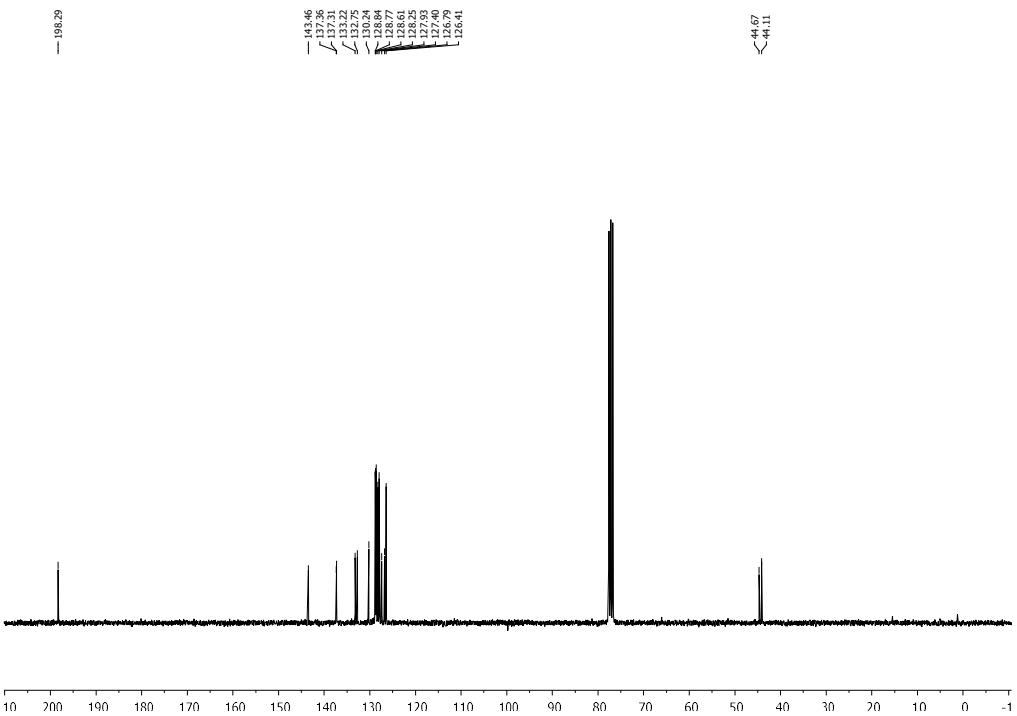
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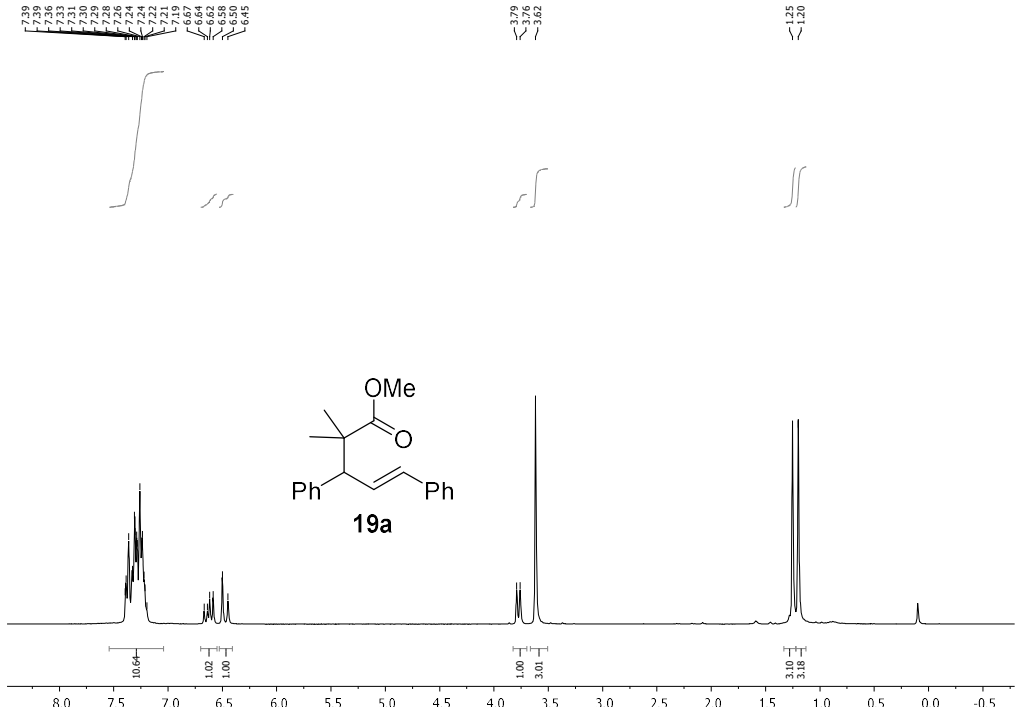
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O
Ph
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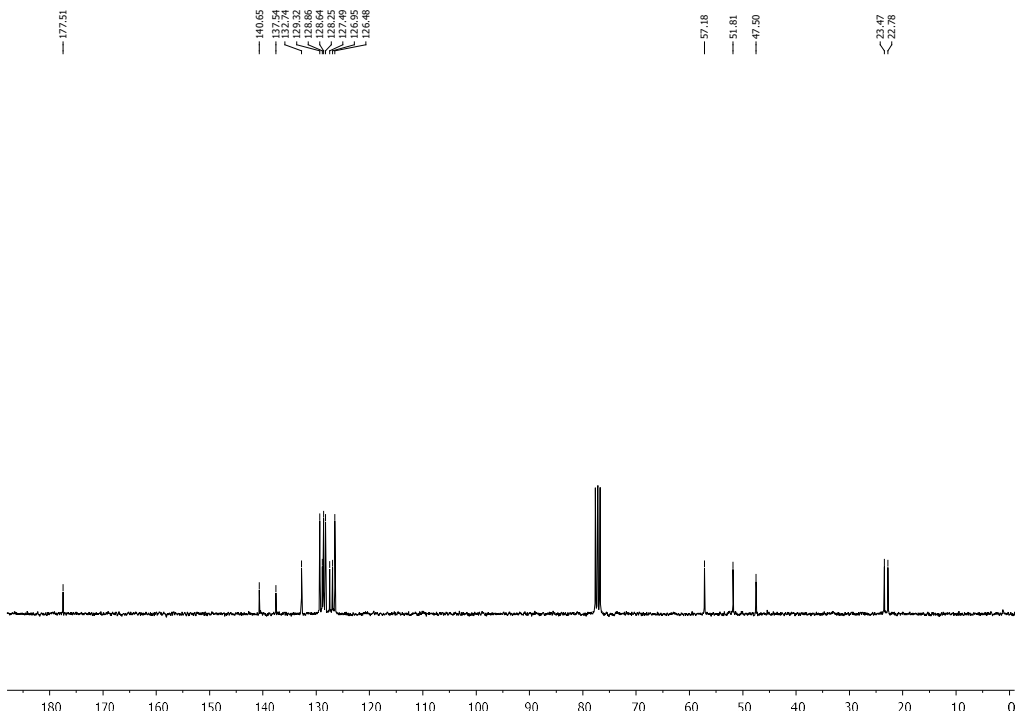
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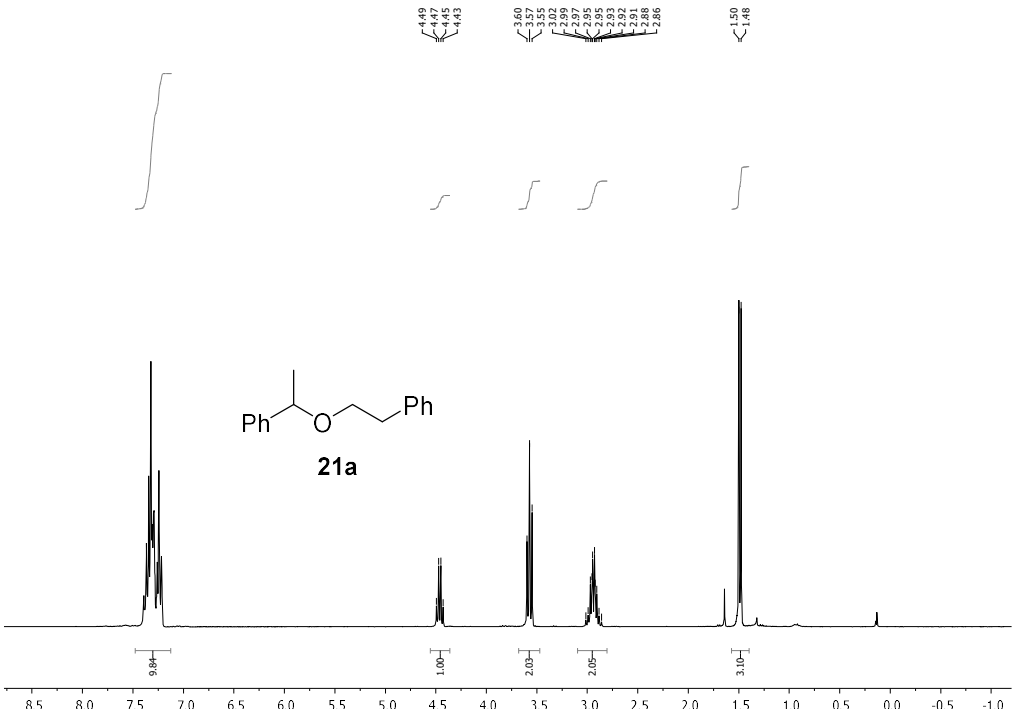
Products 21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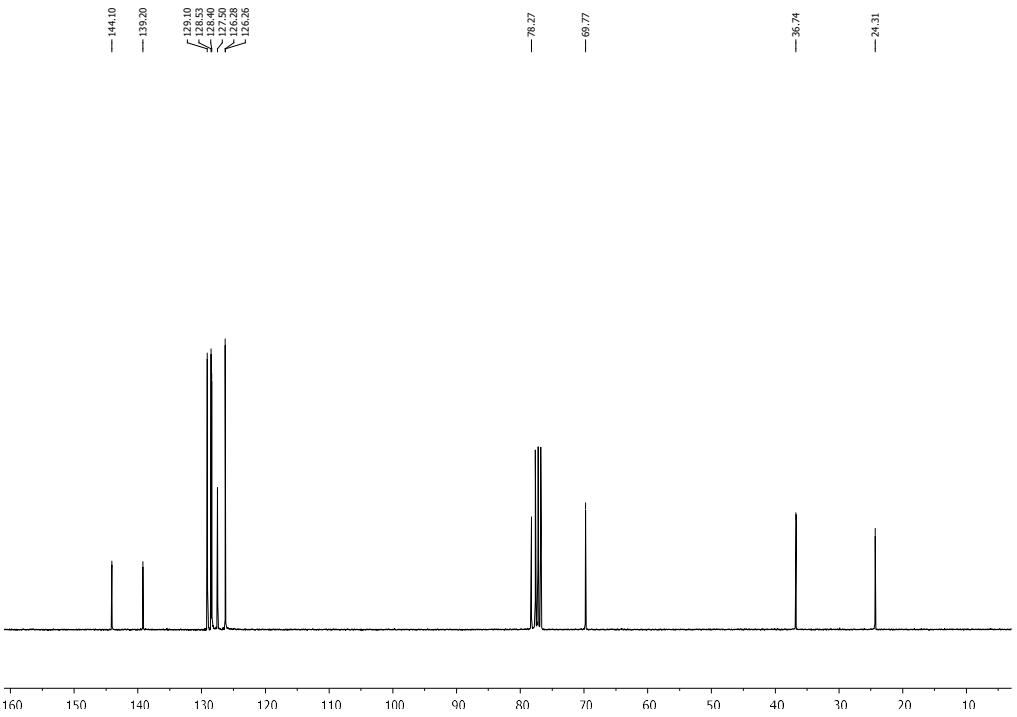
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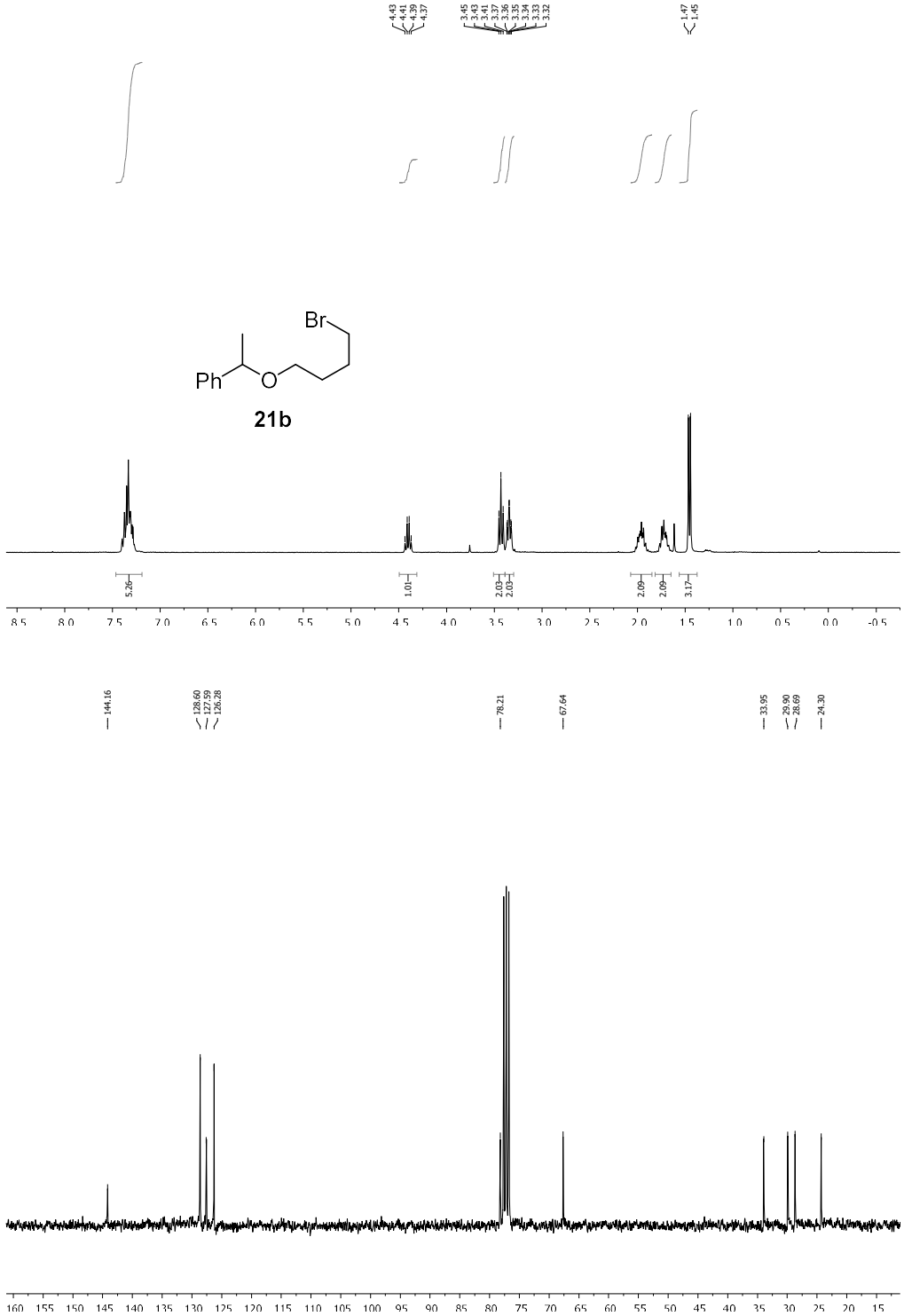
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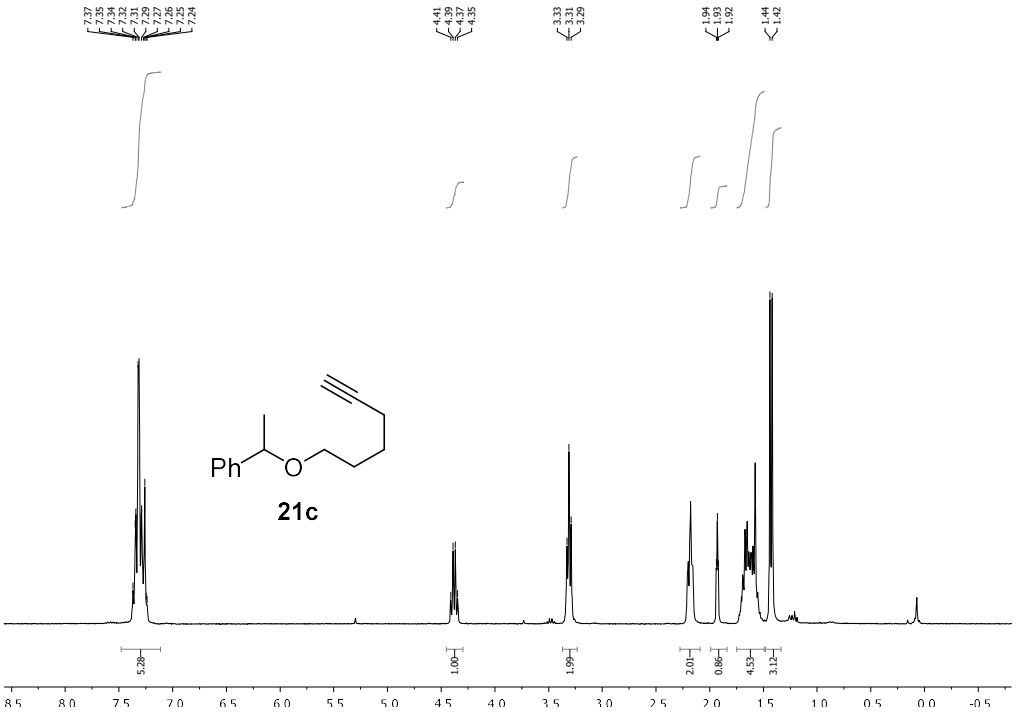
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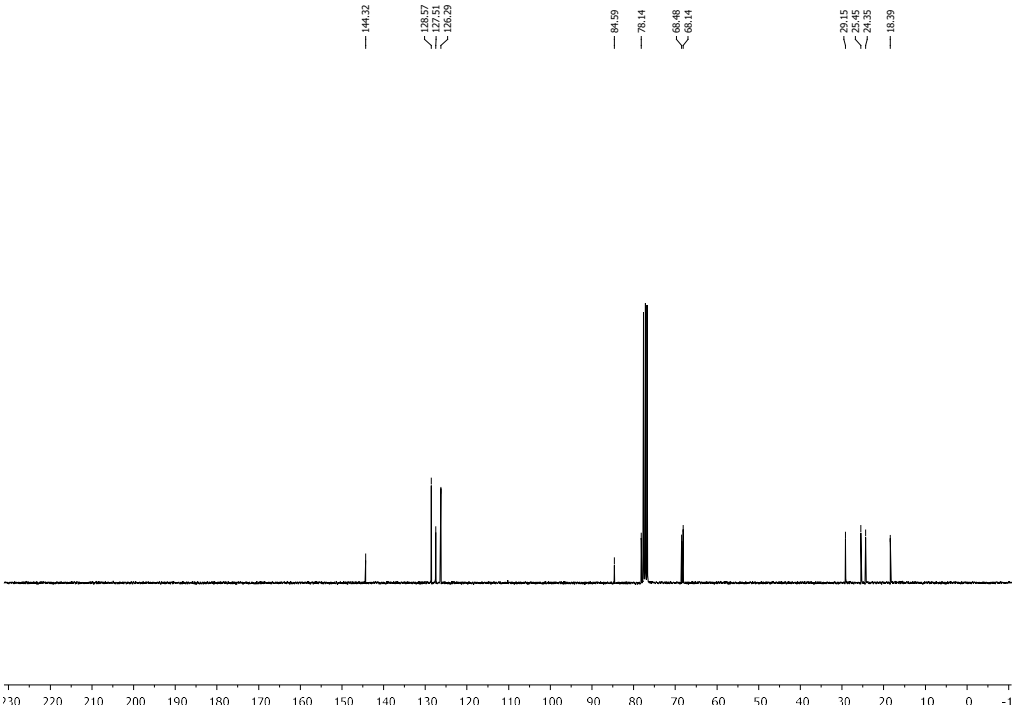
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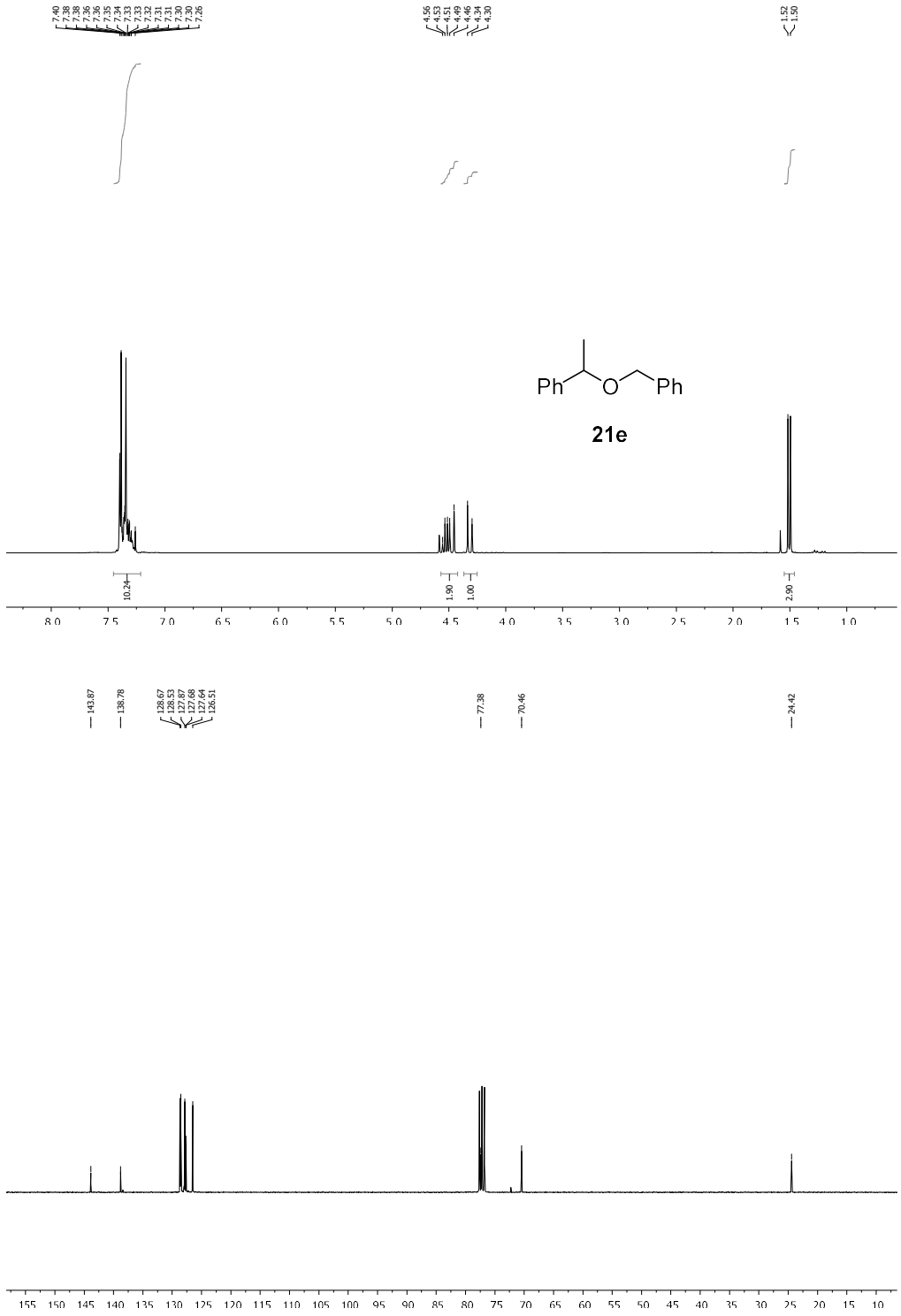
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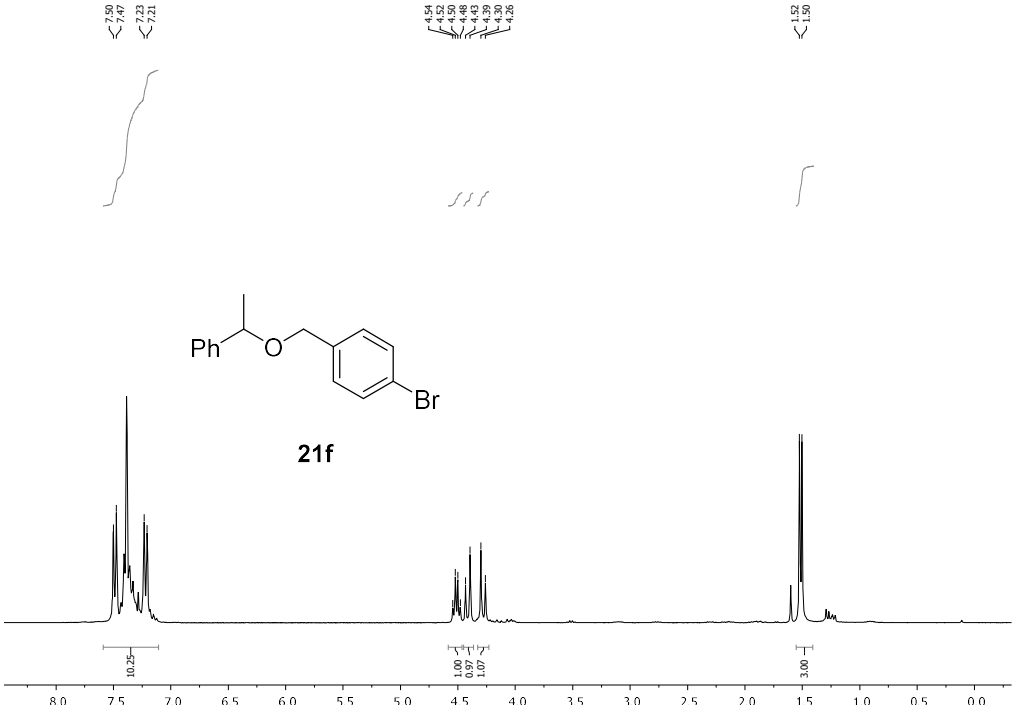
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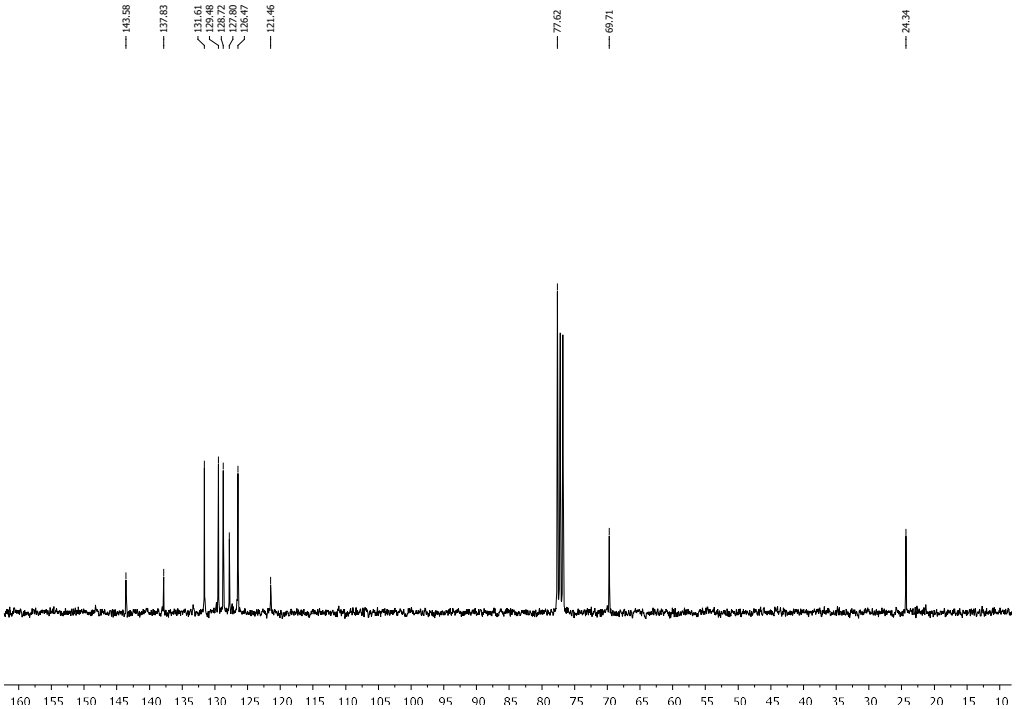
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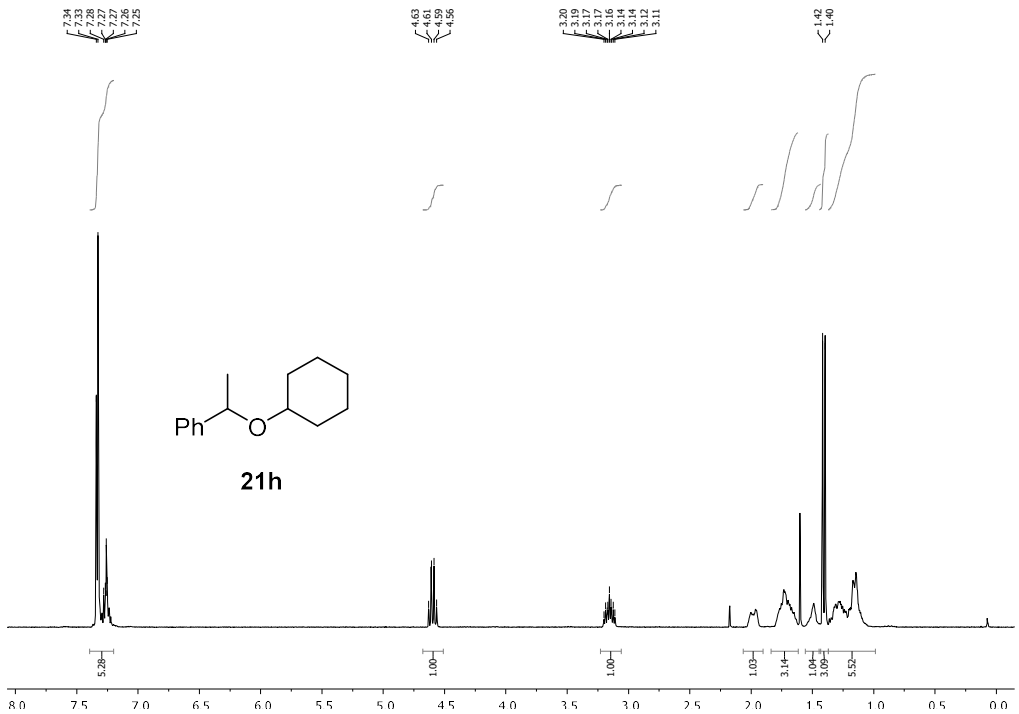
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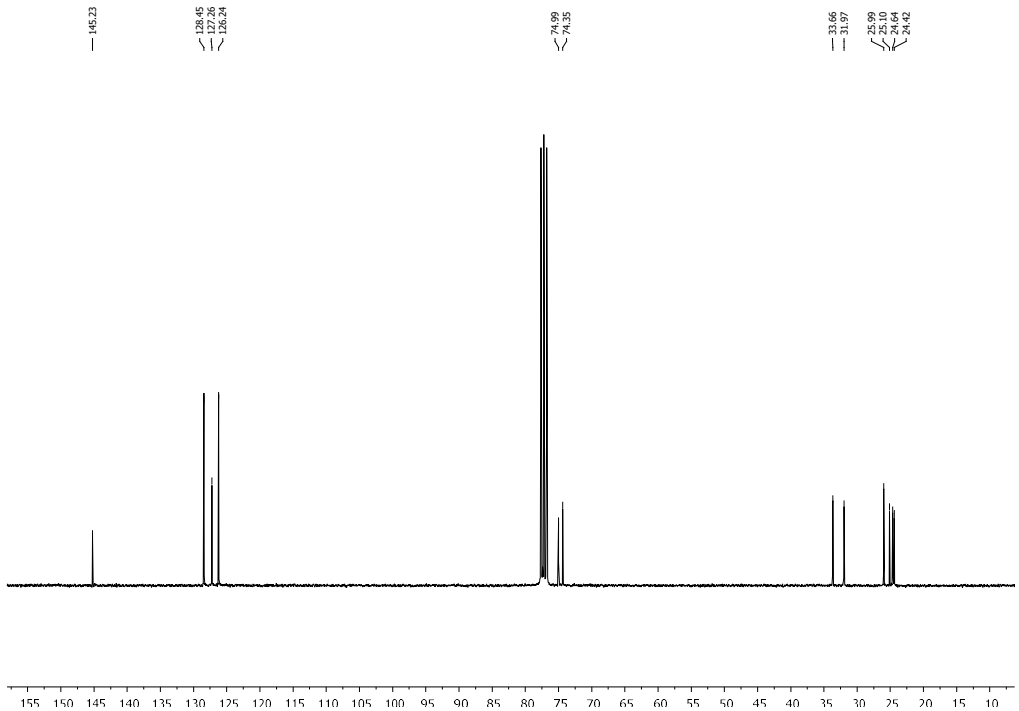
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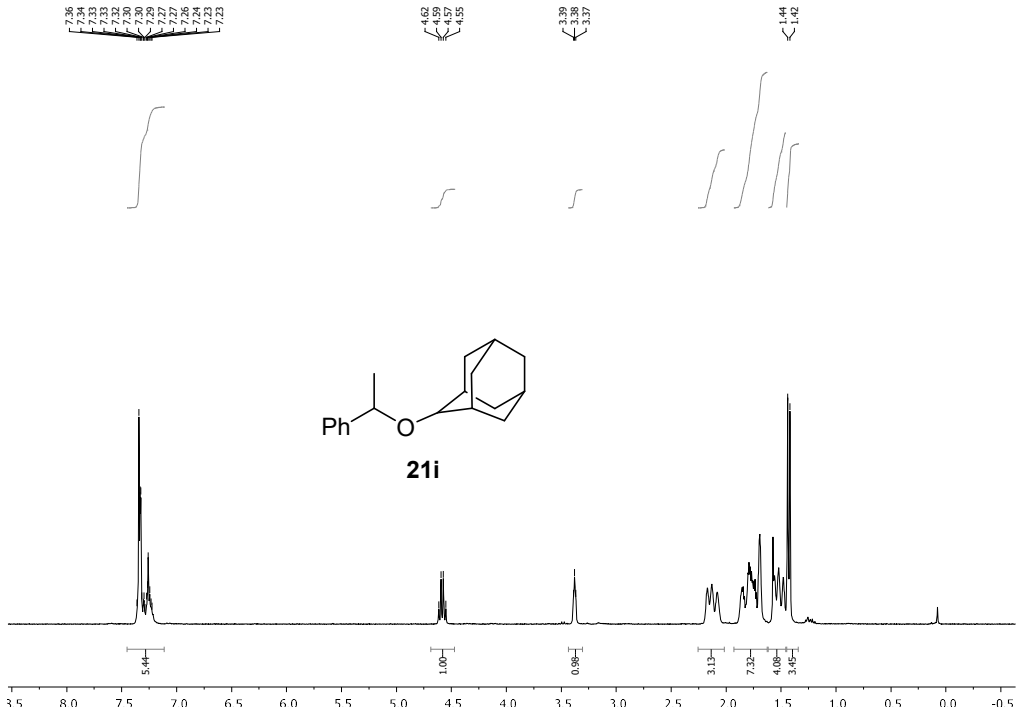
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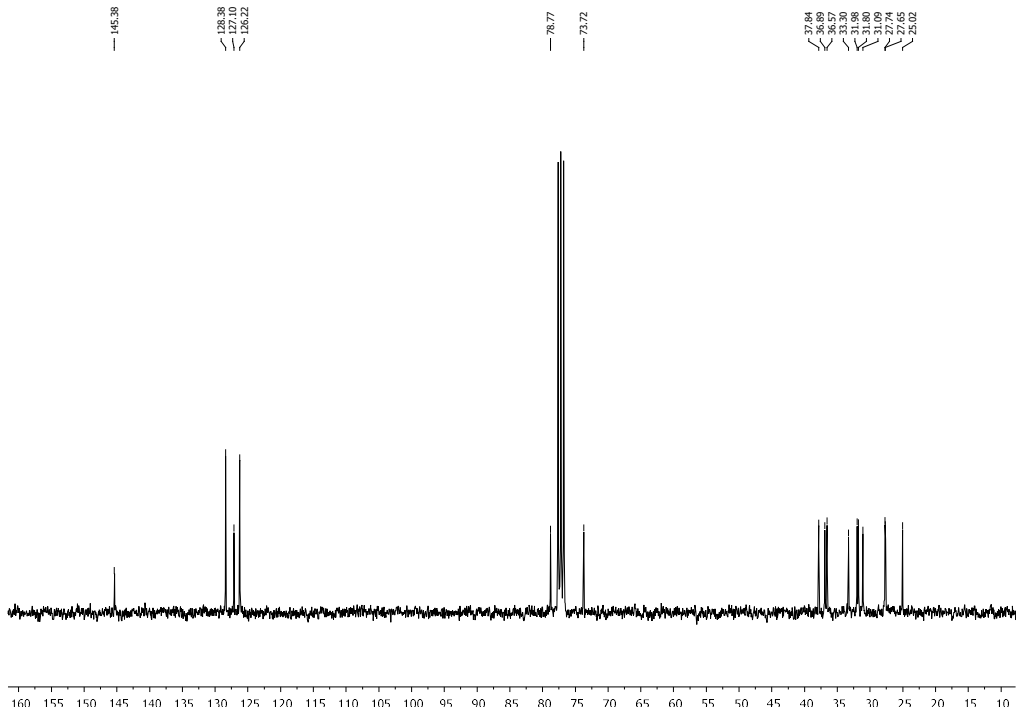
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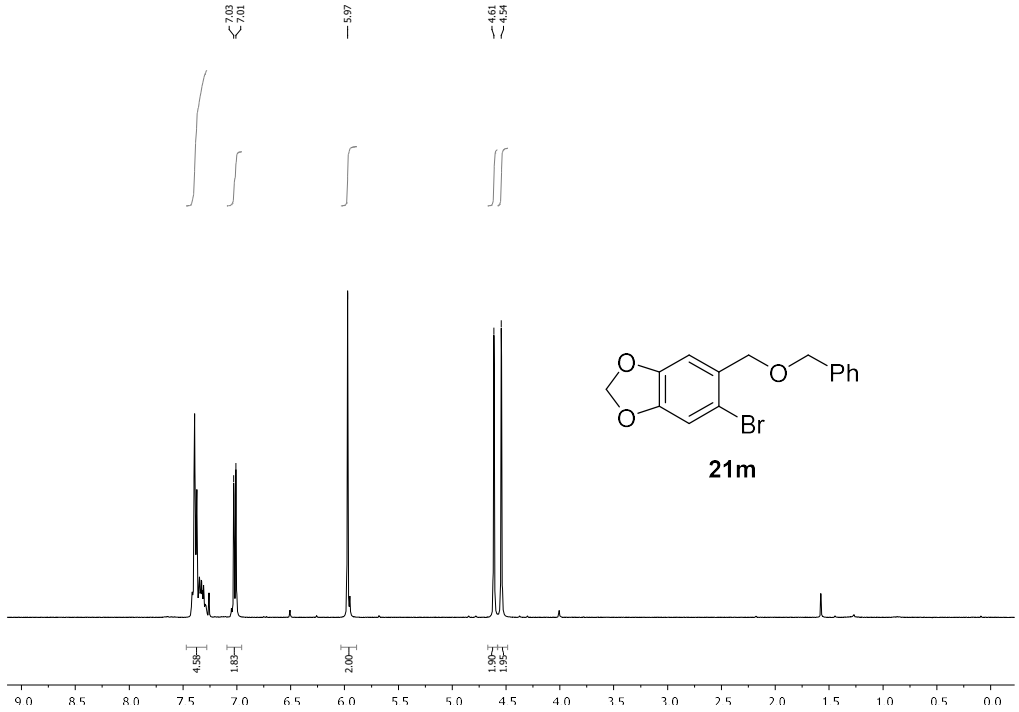
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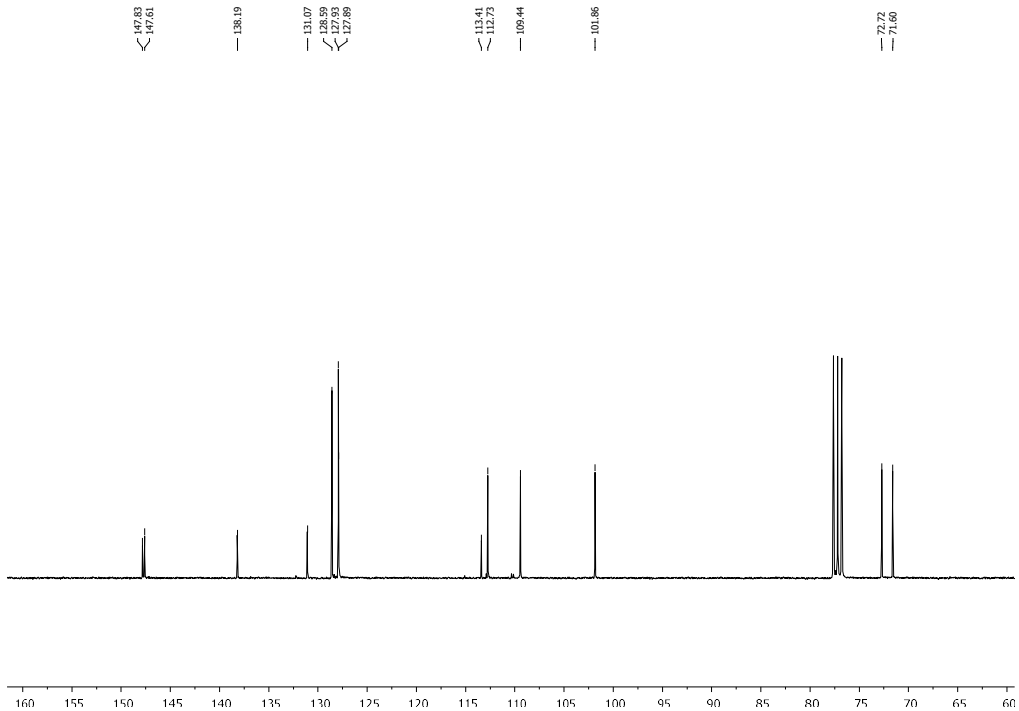
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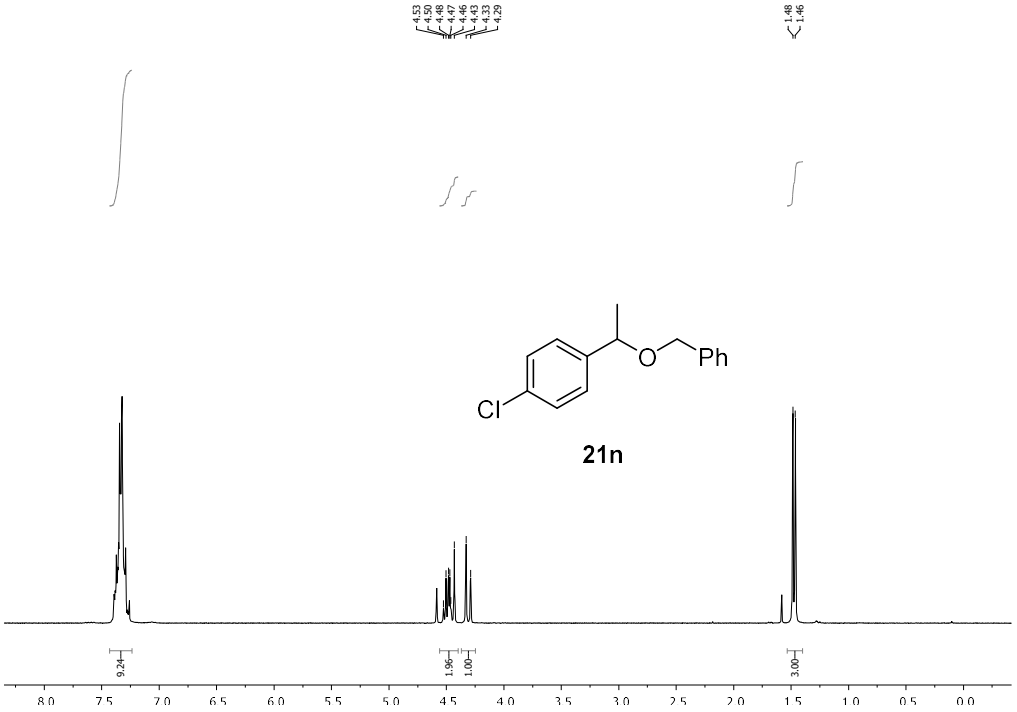
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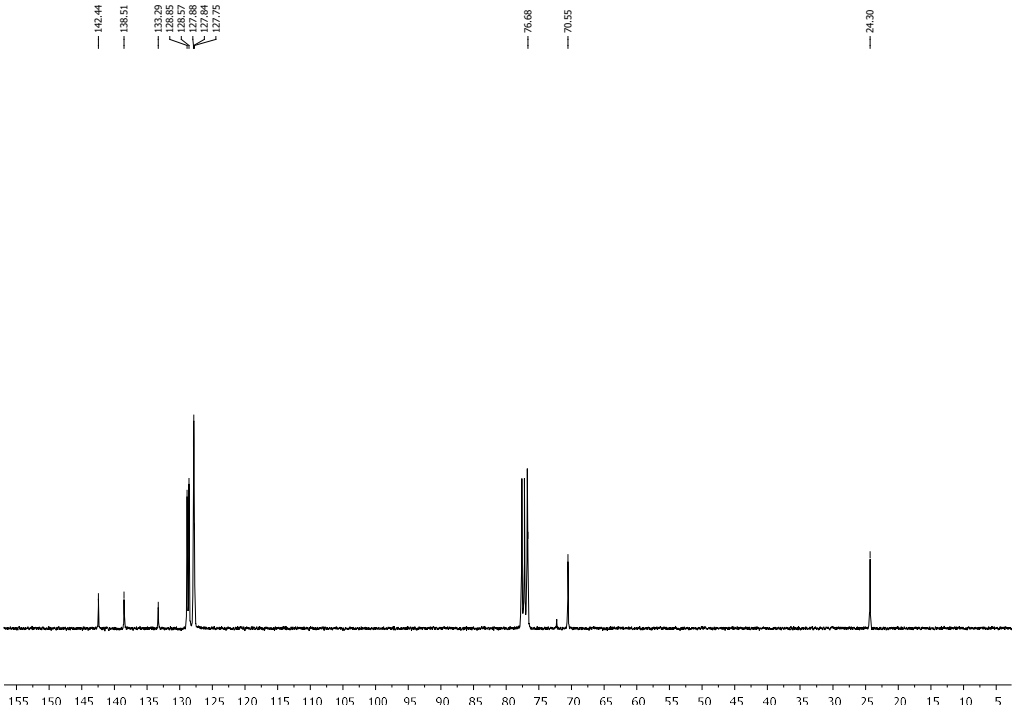
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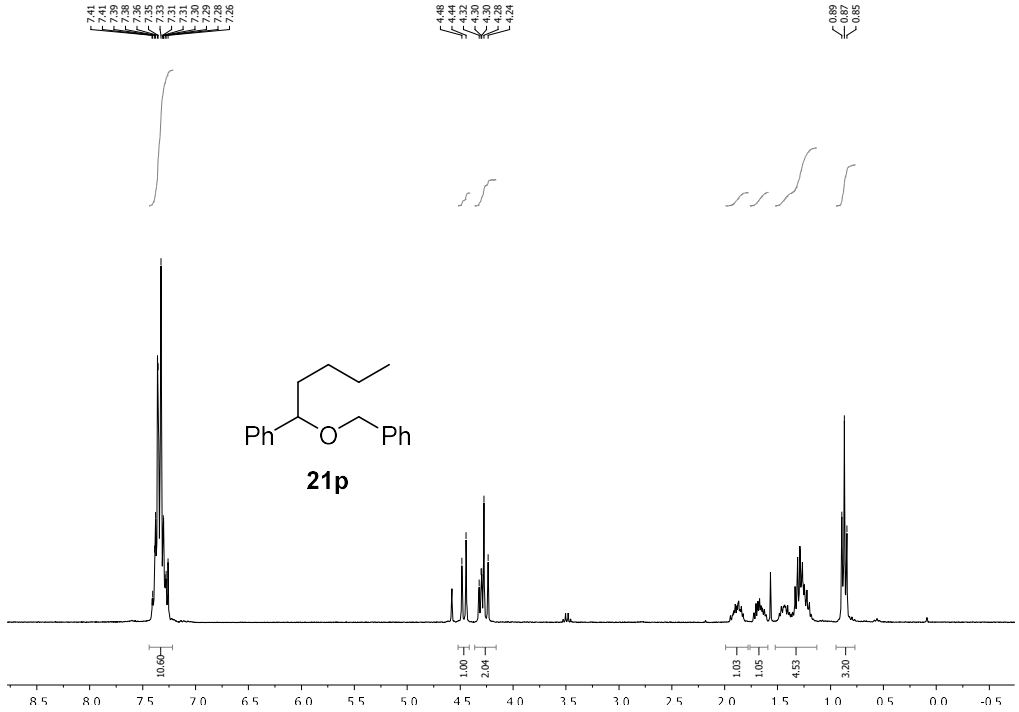
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4.44
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4.30
4.30
4.28
4.24
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Ph
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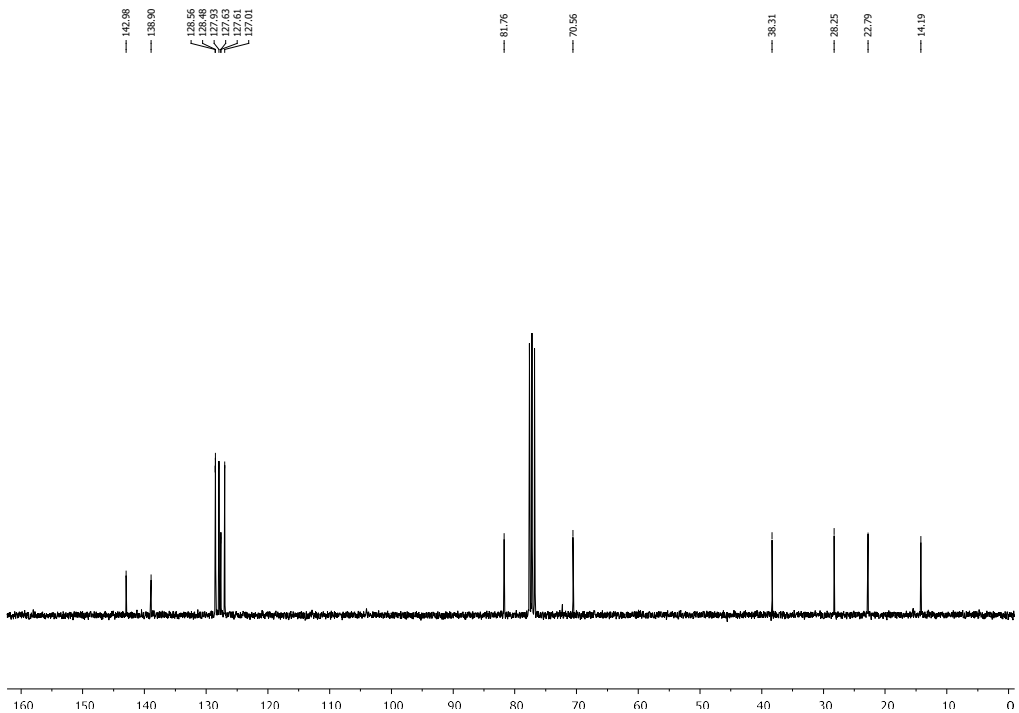
3.20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14.19