

GOLD COMPLEXES FOR HOMOGENEOUS CROSS- COUPLING CATALYSIS AND MIGRATORY INSERTION REACTIONS

Jordi Serra Parareda

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DOCTORAL THESIS

**Gold complexes for homogeneous cross-coupling
catalysis and migratory insertion reactions**

Jordi Serra Parareda

2018

Doctoral programme in Chemistry

Supervised by: Dr. Xavi Ribas Salamaña

Tutor: Dr. Xavi Ribas Salamaña

Presented in partial fulfillment of the requirements for a doctoral
degree from the University of Girona



Dr. Xavi Ribas Salamaña, from the Universitat de Girona,

I DECLARE:

That the thesis entitled “Gold complexes for homogeneous cross-coupling catalysis and migratory insertion reactions” presented by Jordi Serra Parareda to obtain a doctoral degree, has been completed under my supervision and meets the requirements to opt for an International Doctorate.

For all intents and purposes, I hereby sign this document.

A handwritten signature in blue ink, consisting of stylized, overlapping loops and strokes.

Dr. Xavi Ribas Salamaña

Girona, May 21st 2018

A la meva mare i el meu germà

A l'Òscar

I sobretot a tu, pare

*“This above all: to thine own self be true
And it must follow, as the night the day,
Thou canst not then be false to any man.”¹*

SHAKESPEARE, *Hamlet*

¹“I sobretot sigues sincer amb tu mateix / que a això seguirà, com la nit al dia, / el que siguis sincer amb tots els altres.”

FULL LIST OF PUBLICATIONS

This thesis is based on a compendium of the followed publications:

Chapter III

Oxidant-Free Au(I)-Catalyzed Halide Exchange and C_{sp2}-O Bond Forming Reactions. Serra, J.; Whiteoak, C. J.; Acuña-Parés, F.; Font, M.; Luis, J. M.; Lloret-Fillol, J.; Ribas, X. *J. Am. Chem. Soc.* **2015**, *137*, 13389-13397. (DOI: 10.1021/jacs.5b08756). (Impact factor: 13.858, 1st quartile).

Chapter IV

Au(III)-Aryl Intermediates in Oxidant-Free C-O and C-N Cross-Coupling Catalysis. Serra, J.; Parella, T.; Ribas, X. *Chem. Sci.* **2017**, *8*, 946-952. (DOI: 10.1039/c6sc03699f). (Impact factor: 8.668, 1st quartile).

Chapter V

Cyclometalated Gold(III) Complexes: Noticeable Differences between (N,C) and (P,C) Ligands in Migratory Insertion. Serra, J.; Font, P.; Daiann Sosa Carrizo, E.; Mallet-Ladeira, S.; Massou, S.; Parella, T.; Miqueu, K.; Amgoune, A.; Ribas, X.; Bourissou, D. *Chem. Sci.* **2018** (DOI: 10.1039/C7SC04899H). (Impact factor: 8.668, 1st quartile).

All these papers have been published in journals that belong to the first quartile according to JCR.

LIST OF ABBREVIATIONS

°C	Degree(s) Celsius
Å	Angstrom(s)
Ac	Acetyl
Ar	Aryl
B	Base
bhq	benzo[<i>h</i>]quinoline
cat	Catalyst
COSY	Correlation Spectroscopy
DFT	Density Functional Theory
DMSO	Dimethyl Sulfoxide
E ⁰	Standard oxidation potential
EDG	Electron-Donating Group
ESI	Electrospray Ionization
EWG	Electron-Withdrawing Group
EXAFS	Extended X-ray Absorption Fine Structure
equiv	Equivalent(s)
Et	Ethyl
eV	Electronvolt(s)
G	Gibbs free energy
GC	Gas Chromatography
GIAO	Gauge-Including Atomic Orbital
h	Hour(s)
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
Hz	Hertz
IPr	1,3-bis(diisopropylphenyl)imidazole-2-ylidene
K	Degree(s) Kelvin
Kcal	Kilocalorie
L	Generic neutral, 2-electron donor ligand
LUMO	Lowest Unoccupied Molecular Orbital
M	Molar
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Min	Minute(s)
mL	Millilitre(s)
mM	Millimolar
<i>m/z</i>	Mass/charge
NBO	Natural Bond Orbital
<i>n</i> Bu	<i>n</i> Butyl

NHC	<i>N</i> -Heterocyclic Carbene
NLMO	Natural Localized Molecular Orbital
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
OTf	Trifluoromethanesulphonic anion
PCM	Polarizable Continuous solvation Model
Ph	Phenyl
ppm	Part(s) per million
ppy	2-phenylpyridine
py	Pyridine
rds	Rate determining step
rt	Room temperature
s	Second(s)
S _E Ar	Electrophilic Aromatic Substitution
t	Time
T	Temperature
TBA	Tetrabutylammonium
<i>t</i> Bu	<i>Tert</i> -butyl
TM	Transition Metal
tpy	2-(<i>p</i> -tolyl)pyridine
TS	Transition State
V	Volt(s)
XAS	X-Ray Absorption Spectroscopy
XRD	X-Ray Diffraction

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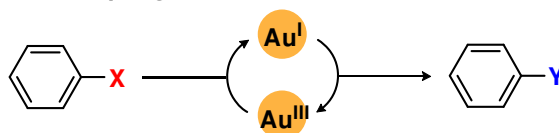
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GRAPHICAL ABSTRACT

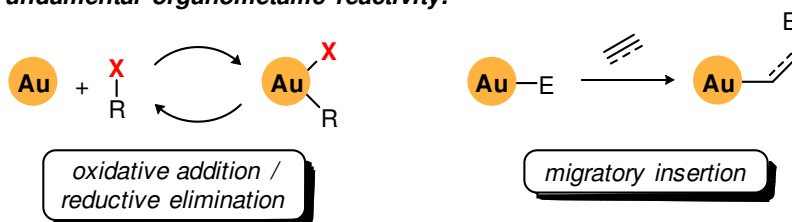
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Chapter I. General Introduction (p. 4)

Oxidative cross-couplings:

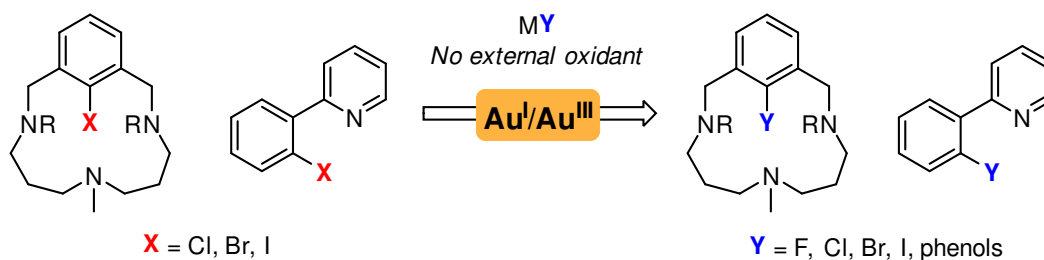


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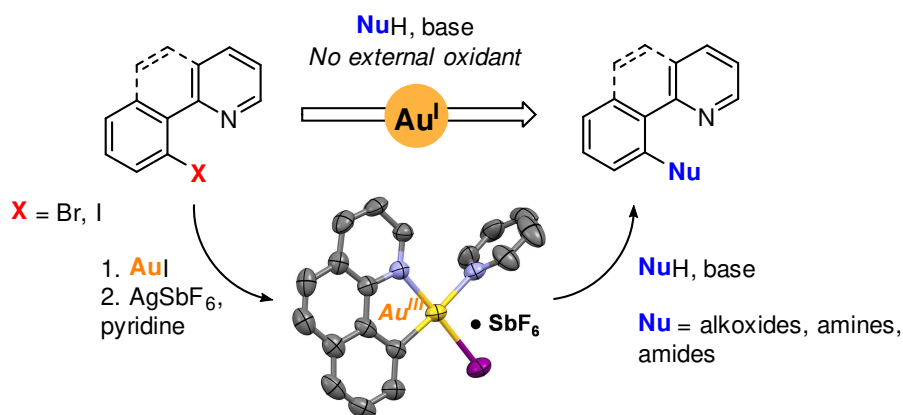


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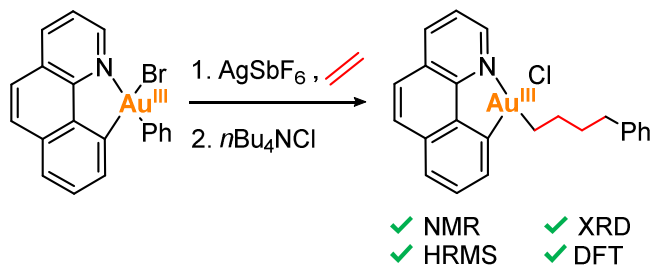
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SUMMARY

Most of the different homogeneous reactions catalyzed by gold have been developed in the past fifteen years and stem from the ability of both Au(I) and Au(III) complexes to coordinate and activate carbon-carbon double and triple bonds, triggering an extensive palette of reactions. In addition to its rich reactivity, several advantages in the use of gold can be easily reckoned, such as its high tolerance to functional groups, air and water. Moreover, the catalyst can be recovered at the end of the reaction in most cases, since no redox chemistry is associated with it. However, and related to this aspect, the high ionization potential of gold has long hindered Au(I)/Au(III) catalytic cycles under homogeneous conditions, an underdeveloped field compared to classical cross-coupling methodologies. Although direct evidence for the main elementary steps of organometallic chemistry has been obtained very recently, their scope is still limited and much remains to be done before our knowledge on gold reaches that of other transition metals, especially of groups 9 and 10. Therefore, the unifying motivation behind the different research topics presented in this doctoral dissertation is to enhance our expertise concerning the factors governing the reactivity of gold complexes, with oxidative addition and migratory insertion particularly under the spotlight.

The first part of the thesis deals with gold-catalyzed C-halide and C-O bond formation within aryl halide model substrates bearing a triazamacrocyclic appendage. This platform previously set rational ground for the implication of aryl-M(III) complexes (M = Cu, Ag) in similar processes, and in the case of gold served to prove that cross-coupling events without external oxidants are feasible. The same reactivity was successfully transferred to monodirecting 2-(2-halophenyl)pyridine substrates. The results obtained, accompanied by DFT calculations, also pinpointed the intermediacy of Au(III) species and paved the way to a more general cross-coupling methodology.

Oxidant-free C-heteroatom bond formation was not only transferred to 2-(2-halophenyl)pyridine substrates, but the nucleophile scope could also be expanded to a range of amines and amides. Remarkably, the square planar environment for a rigidized 10-iodobenzobenzotriazoloquinoline based (C,N)-chelating ligands was able to support crystallographically the formation of (C,N)-Au(III) complexes *via* oxidative addition for the first time and demonstrate as well their involvement as competent catalytic intermediate species.

In the last part of the thesis we turned our attention to another fundamental organometallic step rather elusive with gold: the migratory *syn* insertion of olefins into Au(III)-carbon bonds. We envisioned that the (C,N)-cyclometalated gold(III) complexes previously prepared might be good candidates, and this strategy was exploited to generate a cationic gold(III) phenyl complex with a free coordination site. This complex was shown to display unique reactivity toward migratory insertion of ethylene. The experimental results were combined with computational studies and pointed out striking differences with those observed for the pioneering (C,P)-cyclometalated complexes.

RESUM

La majoria de reaccions homogènies catalitzades per or han estat desenvolupades al llarg dels darrers quinze anys, i aprofiten la capacitat dels complexos d'Au(I) i Au(III) per coordinar i activar enllaços carboni-carboni dobles i triples, possibilitant una extensa varietat de reaccions. A banda d'una rica reactivitat, l'ús de l'or implica bastants avantatges, com ara la seva alta tolerància als grups funcionals, l'aire i l'aigua. A més a més, sovint el catalitzador pot ser recuperat al final de la reacció, ja que no s'hi associa química redox. No obstant, i relacionat amb aquest darrer aspecte, l'elevat potencial de ionització de l'or ha privat l'accés a cicles catalítics del tipus Au(I)/Au(III) en condicions homogènies, un camp subdesenvolupat en comparació amb d'altres metodologies d'acoblament creuat clàssiques. Malgrat que recentment els processos fonamentals en química organometàl·lica han estat evidenciats, el seu abast és encara limitat i queda molt per recórrer abans que el nostre coneixement en or assoleixi el d'altres metalls de transició, en especial dels grups 9 i 10. Així doncs, la motivació principal rere els projectes de recerca presentats en aquesta tesi doctoral és incrementar la nostra expertesa pel que fa als factors que governen les reactivitat dels complexos d'or, amb especial incidència en l'addició oxidant i la inserció migratòria.

La primera part de la tesi se centra en la formació d'enllaços C-halur i C-O en substrats model d'halur d'aril que contenen un apèndix macrocíclic amb tres nitrògens. Prèviament aquesta estratègia ja fou útil per demostrar la implicació d'espècies aril-M(III) (M = Cu, Ag) en processos similars, i pel que fa a l'or ens ha permès provar que les reaccions d'acoblament creuat també són possibles sense oxidants externs. La mateixa reactivitat fou transferida exitosament a substrats del tipus 2-(2-halofenil)piridina amb només un grup director. Els resultats obtinguts, acompanyats per càlculs DFT, també han determinat la intermediació d'espècies d'Au(III) i han possibilitat la generalització de la metodologia d'acoblament creuat.

La formació d'enllaços C-heteroàtom no només es va transferir a substrats 2-(2-halofenil)piridina, sinó que els nucleòfils compatibles també es va poder estendre a amines i amides. Notablement, l'entorn pla-quadrat dels lligands rígids 10-iodobenzo[h]quinolina basats en quelats (C,N) va possibilitar la formació cristal·logràfica de complexos d'Au(III) per primer cop a través d'una addició oxidant, la qual cosa va corroborar la seva implicació com a intermedis catalítics competents.

Finalment, en la darrera part de la tesi vam centrar-nos en un altre procés organometàl·lic elemental fins fa poc esquiava amb l'or: la inserció migratòria d'olefines en enllaços Au(III)-carboni. Per dur-ho a terme, vam considerar que els complexos d'or(III) (C,N)-ciclometal·lats sintetitzats anteriorment podrien ser bons candidats, i aquesta estratègia va ser explotada per generar un complex catiònic d'or(III) fenil amb un punt de coordinació lliure. El complex esmentat va presentar una reactivitat única en front a la inserció migratòria d'etilè. Els resultats experimentals es van combinar amb estudis computacionals i van assenyalar diferències remarcables en comparació amb els complexos (C,P)-ciclometal·lats pioners.

RESUMEN

La mayoría de reacciones homogéneas catalizadas por oro han sido desarrolladas a lo largo de los últimos quince años, y parten de la capacidad de los complejos de Au(I) y Au(III) para coordinar y activar enlaces carbono-carbono dobles y triples, posibilitando una extensa variedad de reacciones. Aparte de una rica reactividad, el uso del oro implica ventajas tales como su alta tolerancia a los grupos funcionales, el aire y el agua. Además, a menudo el catalizador puede ser recuperado al final de la reacción, ya que no lleva asociado química redox. No obstante, y relacionado con este último aspecto, el elevado potencial de ionización del oro ha privado del acceso a ciclos catalíticos del tipo Au(I)/Au(III) en condiciones homogéneas, un campo subdesarrollado en comparación con metodologías clásicas de acoplamiento cruzado. A pesar de que recientemente los procesos fundamentales en química organometálica han sido evidenciados, su alcance es todavía limitado y queda mucho por recorrer antes de que nuestro conocimiento en oro alcance el de otros metales de transición. Así pues, la motivación principal tras los proyectos de investigación presentados en esta tesis doctoral es incrementar nuestro entendimiento en cuanto a los factores que gobiernan la reactividad de los complejos de oro, con especial atención a la adición oxidante y la inserción migratoria.

La primera parte de la tesis se centra en la formación de enlaces C-haluro y C-O en sustratos modelo de haluro de arilo que contienen un apéndice macrocíclico con tres nitrógenos. Esta estrategia ya fue útil previamente para demostrar la implicación de especies arilo-M (III) ($M = \text{Cu}, \text{Ag}$) en procesos similares, y en el caso del oro nos ha permitido probar que las reacciones de acoplamiento cruzado también son factibles sin oxidantes externos. La misma reactividad fue transferida con éxito a sustratos del tipo 2-(2-halofenil)piridina con solo un grupo director. Los resultados obtenidos, acompañados por cálculos DFT, también han determinado la intermediación de especies de Au(III) y han posibilitado la generalización de la metodología de acoplamiento cruzado.

La formación de enlaces C-heteroátomo no sólo se transfirió a sustratos 2-(2-halofenil)piridina, sino que los nucleófilos compatibles también se extendieron a aminas y amidas. Notablemente, el entorno plano-cuadrado de los ligandos rígidos 10-iodobenzo[h]quinolina basados en quelatos (C,N) posibilitó la formación cristalográfica de complejos de Au(III) por primera vez a través de una adición oxidante, lo que corroboró su implicación como intermedios catalíticos competentes.

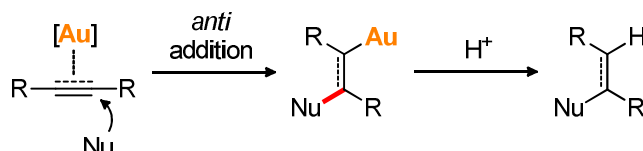
Finalmente, en la última parte de la tesis nos centramos en otro proceso organometálico elemental hasta hace poco esquivo con el oro: la inserción migratoria de olefinas en enlaces Au (III)-carbono. Para este objetivo consideramos que los complejos de oro(III) (C,N)-ciclometalados sintetizados anteriormente podrían ser buenos candidatos, y esta estrategia fue explotada para generar un complejo catiónico de oro(III) fenil con un lado de coordinación libre. El complejo mencionado presentó una reactividad única frente a la inserción migratoria de etileno. Los resultados experimentales se combinaron con estudios computacionales y señalaron diferencias destacables en comparación a los complejos pioneros (C,P)-ciclometalados.

CHAPTER I

GENERAL INTRODUCTION

I. OPENING REMARKS

Gold was one of the first metals widely known to mankind. Its aesthetic appearance and intrinsic durability concealed the attention of the ancient cultures first and alchemists later.¹ In contrast to the other metals, gold could not be transformed or damaged in the presence of acids or any other known reagents, and hence alchemy established its prime goal at the transmutation of common metals into gold. However, this link got lost during the naissance of modern chemistry: gold species were deemed chemically inert and therefore their use in stoichiometric and catalytic reactions was neglected for a long time.² This paradigm changed completely at the end of the 20th century, when gold complexes emerged as unique carbophilic Lewis acids able to activate the C-C multiple bonds of alkynes, allenes or olefins towards nucleophiles (Scheme 1.1).^{3,4} Thus, within less than two decades, gold catalysis witnessed an impressive development as a very efficient method in organic synthesis capable of building molecular complexity, as illustrated in Figure 1.1.⁵



Scheme 1.1: General mechanism for gold-catalyzed nucleophilic addition to π -C-C multiple bonds in organic substrates.

The advent and rise of organogold chemistry led to a deeper understanding of its coordination properties and reactivity and also evidenced important differences compared to the other d-block elements. The unusual high redox stability of Au(I) complexes translates into a prominent tolerance to functional groups, air and water, but also hampers the access to high-valent Au(III) species and traditional oxidative addition/reductive elimination cycles so prevalent in late transition-metal catalysis.

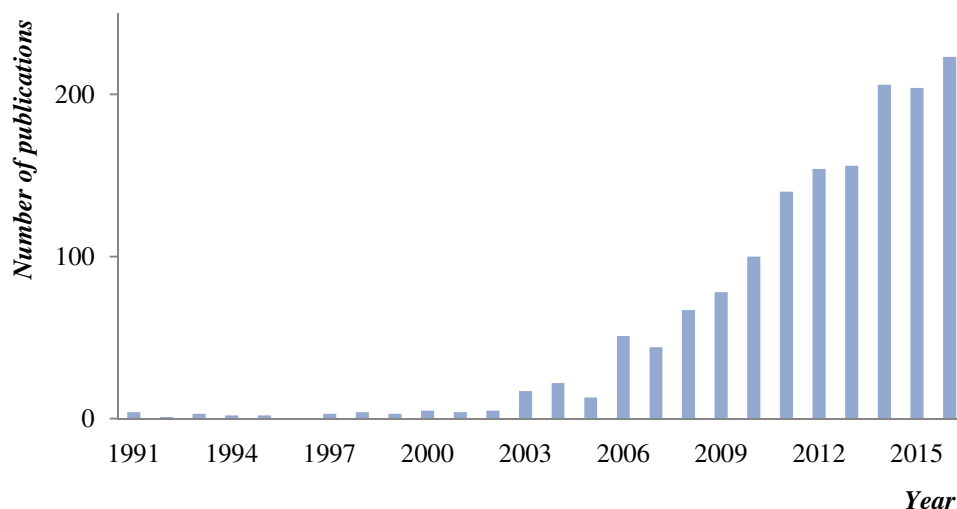


Figure 1.1: Academic publications on both homogeneous and heterogeneous gold catalysis by year, based on the "Web of Science" database (August 2017).

Most of gold's singularities arise in large part from the strong relativistic effects that govern its electronic structure (see section 1.2.1 for details).⁶ On the contrary to the neighboring isoelectronic Pd(0)/Pd(II) and Pt(0)/Pt(II) couples, and despite +3 is a stable and available oxidation state for gold, Au(I) and Au(III) complexes do not easily interconvert between oxidation states. This averseness to engage in two-electron redox oxidations is due to the high oxidation potential of the Au(I)/Au(III) redox couple ($E^0 = + 1.41$ V in water, vs Pd(0)/Pd(II) $E^0 = + 0.987$ V).^{7,8} To overcome the reluctance of gold to undergo oxidative addition to organic (pseudo)halides,^{9,10} the field evolved towards oxidative coupling transformations in which a strong external oxidant drives the first oxidation step to produce the key Au(III) species, thereby allowing the access to Au(I)/Au(III) catalytic cycles.¹¹

With regard to other fundamental organometallic steps (chiefly olefin migratory insertion and β -hydride elimination), as often encountered and substantially understood for most transition metal compounds, are also rather unusual and seldom investigated in the case of gold.

In recent years, however, first insights have evidenced that the reactivity of gold complexes is indeed much more versatile than anticipated and goes far beyond π -bond activation processes. Several groups have supported the ability of gold to undergo these elementary steps,¹² and it is nowadays a very active field of research with many experimental and theoretical contributions.

In this context, the aim of the research projects presented in this dissertation was to gain further knowledge concerning fundamental reactions of gold, with especial focus on Au(I)/Au(III) redox cycles in coupling catalysis and migratory insertion processes. This objective has been approached by the rational design and synthesis of the complexes and the study of their reactivity. The experimental part was also accompanied in close contact by theoretical calculations, which provided an indispensable contribution to the mechanistic understanding of the studied reactions.

1.1 GOLD CATALYSIS IN ORGANIC SYNTHESIS

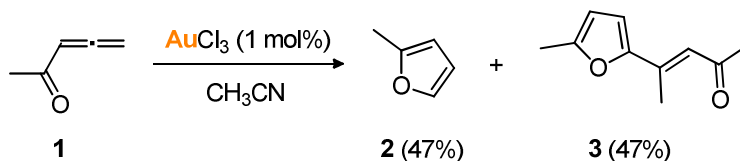
The development of homogeneous gold catalysis for organic synthesis has been extraordinarily rapid since the discovery of the catalytic potential of this metal at the end of the 1990's. Gold exhibits a strong air- and moisture-stable Lewis acidity toward unsaturated C-C bonds, and this intrinsic property has been intensely exploited to yield an array of mild and selective methods for the formation of carbon-carbon and carbon-heteroatom bonds. This mode of reactivity does not imply changes in the oxidation state of the metal center, in contrast to that generally observed in well-known coupling reactions catalyzed by late transition metals such as palladium, nickel and rhodium.

The last lustrum, however, has also witnessed the appearance of cross-coupling reactions proceeding through Au(I)/Au(III) catalytic cycles. Indeed, it has been demonstrated that in the presence of highly electrophilic reagents Au(I) can be oxidized to Au(III) allowing to complete catalytic cycles based on gold. Strikingly, continued efforts pursuing oxidant-free gold-catalyzed cross-coupling methodologies culminated in the first examples in 2014 and 2015.

This chapter will provide a brief bibliographic overview that summarizes the state-of-the-art concerning redox-neutral gold-catalyzed π -bond activation processes and two-electron redox C-C and C-heteroatom couplings. Relevant examples of nucleophilic attack on gold π -complexes under homogeneous conditions are outlined in section 1.1.1, while gold-catalyzed protocols, with and without external oxidants, for classical cross-coupling transformations will be described in section 1.1.2.

1.1.1 Redox-Neutral Homogeneous Gold Catalysis

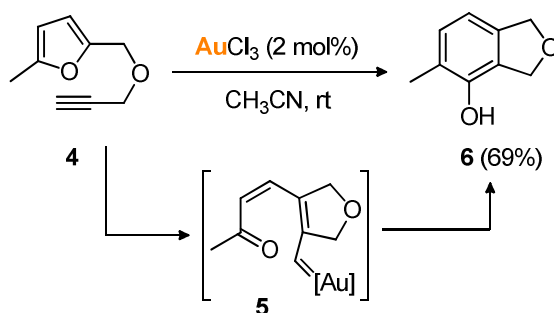
After an initial period between 1986 and 1998 of only occasional activity, in which the most notable examples are some additions of O- or N-nucleophiles to alkenes or alkynes, as developed by Utimoto and Teles,^{13,14} as well as catalytic asymmetric aldol reactions reported by Ito, Sawamura, Hayashi and Togni,^{15,16} a true breakthrough was achieved by Hashmi *et al.* who demonstrated that allenyl and α,β -unsaturated ketones can efficiently cyclize to furans with remarkably high kinetics compared to the analogous Pd and Ag catalysts (Scheme 1.2).¹⁷ In the same publication, the first gold-catalyzed intramolecular addition of a hydroxy group to an activated alkene to form spirocycles was reported. Mechanistically, these reactions proceed by *anti* attack on the gold-activated C-C multiple bond to deliver an intermediate σ -complex that liberates the addition product and the gold catalyst by protodemetalation (see Scheme 1.1 above).



Scheme 1.2: The cycloisomerization of allenyl ketones, with the carbonyl oxygen atom serving as an intramolecular nucleophile.

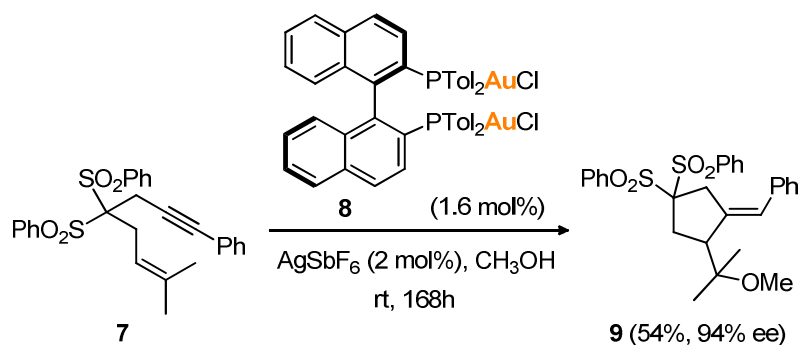
Soon after Hashmi and Teles' initial reports, gold-catalyzed C-C functionalization was extended to a range of nucleophiles, as well as to other alkyne, alkene and allene substrates. Among the many examples reported between 2000 and 2007, it is worth mentioning the first paper on hydroamination of allenes. In analogy to allenyl ketones and alcohols, Morita and Krause shown in 2004 that different related amines can also be cyclized.¹⁸ With regard to alkenes, and although initially Teles had observed that they do not react with gold catalysts, He and Yang succeeded in the intermolecular addition of weak nucleophiles such as phenols and carboxylates to inactivated terminal alkenes.¹⁹

The field moved forward to another class of reactions, skeletal rearrangements, including cycloadditions, cycloisomerizations and other carbocyclization reactions. From a mechanistic point of view, these cyclization reactions are similar to the hydrofunctionalizations in that the activation of an alkyne or allene occurs initially, followed by an attack of a pendant unsaturated C-C bond which leads to a multitude of rearrangement steps. In 2000, Hashmi *et al.* reported the Au(III)-catalyzed intramolecular reaction of a furan with a terminal alkyne moiety to yield highly substituted phenols **6** (Scheme 1.3).²⁰ Later on, it was revealed that this type of reactions, proceeding through gold carbenoid intermediates, could also be initiated in an intermolecular fashion with a binuclear gold(I) catalyst.²¹



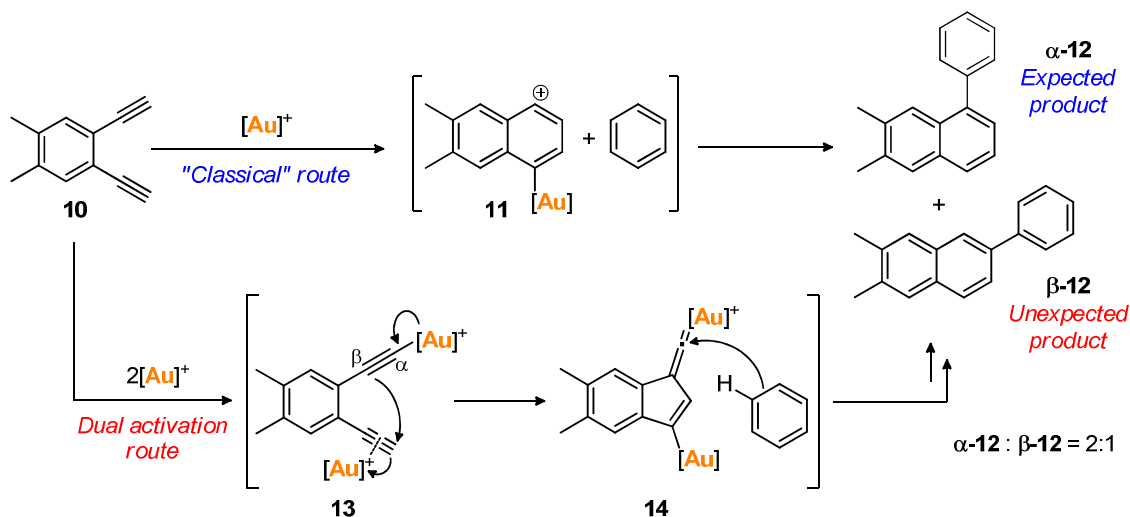
Scheme 1.3: Intramolecular cycloisomerization of a furan with a terminal alkyne unit.

This rapid progress was early accompanied by efforts to develop enantioselective versions of the gold-catalyzed reactions with the aim to expand the synthetic utility of these transformations. Thus, shortly after disclosing highly efficient cationic Au(I)-catalyzed cycloisomerization of 1,6-enynes,²² Echavarren's group made the first attempts in rendering this reaction enantioselective through the synthesis of chiral bis(phosphine)digold(I) dichlorides **8** as precatalysts (Scheme 1.4).²³ To furnish the steric environment required to enclose the gold center and exert chirality, some strategies have been developed by several groups, including the above-mentioned use of sterically encumbered bisphosphinedigold(I) complexes, but also the modification of the weakly coordinating ligand or counterion on gold and the development of other ligands besides bisphosphines.²⁴ Notably, intermolecular variants of the enantioselective reactions continue to pose challenges, and catalysis that relies on the higher oxidation states of gold has yet to be achieved.



Scheme 1.4: Enantioselective 1,6-enyne alkoxy cyclization.

Finally, a new family of reactions that involve the activation of organic substrates by simultaneously two gold centers emerged in 2012. The unexpected formation of product **β -12** from diynes **10** indeed suggested the involvement of an unprecedented mechanism (Scheme 1.5).²⁵ A series of experimental and computational reports indicated that one gold complex is σ -bonded to a terminal alkynyl group in the substrate to form a gold(I) acetylide **13**, while a second Au(I) π -coordinates to the other triple bond and activates the system for an electrophilic attack in β -position of the gold acetylide; afterwards, a gold(I) vinylidene-like intermediate **14** is formed before insertion into the C-H bond of a benzene solvent molecule takes place. Eventually, several rearrangement steps and a protodeauration by the terminal alkyne of the next substrate molecule **10** delivers the product **β -12**.²⁶ This mode of reactivity opened up many innovative synthetic perspectives and further substantiated the versatility of gold in organometallic chemistry.



Scheme 1.5: Enantioselective 1,6-enyne alkoxy cyclization *via* dual Au(I) catalysis.

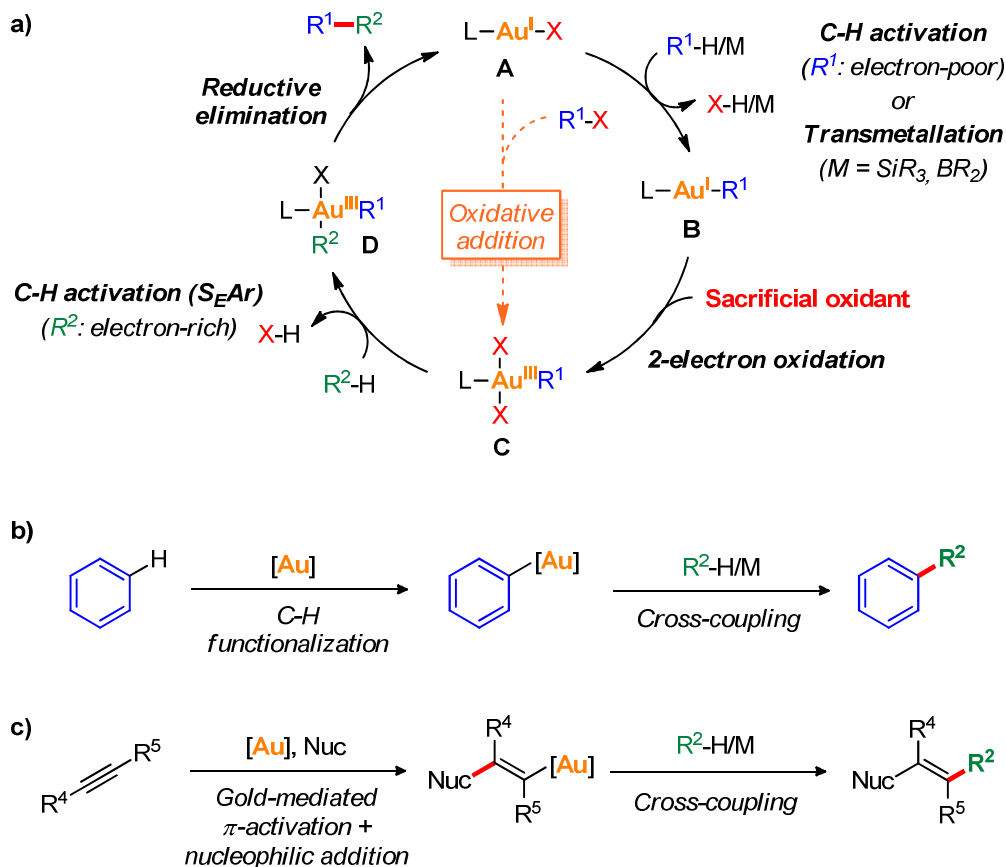
1.1.2 Gold-Catalyzed Oxidative Coupling Reactions

Cross-coupling processes consist of the assembling of two coupling partners, namely an alkyl, aryl or vinyl (pseudo)halide and a nucleophile, assisted by a transition metal promoter. This type of reactions is a cornerstone in modern chemistry, in terms of both

academic research and industrial applications.^{27–29} Although they have been known for more than one century, it was not until the beginning of the 1970's, with the first reports on palladium-catalyzed cross-coupling reactions, that the enormous potential of this transformations in synthetic chemistry was unveiled. Since then, cross-coupling processes have revolutionized organic synthesis by providing a new approach for the synthesis of molecules of interest such as agrochemicals, pharmaceuticals or polymers. In particular, the pioneering palladium-catalyzed C-C bond forming methodologies such as the Mizoroki-Heck, Negishi, and Suzuki-Miyaura reactions were recently recognized with the 2010 Nobel Prize in Chemistry.^{30,31} More recently, the groups of Buchwald and Hartwig made significant contributions to the area, developing protocols for the formation of C-N bonds, specifically for the arylation of amines, extending the number of the architectures accessible.^{32,33} While palladium has received the most research attention, since the beginning of the 21st century other transition metals, most frequently nickel, copper and rhodium, have also been shown to exhibit similar performance.^{34,35} Nevertheless, cross-coupling reactions catalyzed by gold complexes have been much less widely reported.

These transformations typically proceed through M^n/M^{n+2} redox cycles in which the transition metal catalyst undergoes a formal two-electron oxidation and reduction. Due to its redox-neutral character, the oxidation of gold(I) to gold(III) necessary for catalytic coupling reactions is a challenging process. For a long time, the high electronegativity and ionization potential of the Au(I)/Au(III) couple ($E^0 = +1.41$ V) seemed to preclude an oxidative addition step of gold(I) complexes, the general entry point to cross-coupling protocols. An alternative approach to access Au(I)/Au(III) turnovers under homogeneous conditions has relied on the use of a strong oxidant to enable the oxidation of the metal followed or preceded by the coordination of an additional organic fragment (Scheme 1.6, a). Indeed, by means of this strategy, Au(I)/Au(III) redox catalytic cycles have bloomed in the last decade and synthetic applications have also been conceived.^{11,36,37} Taking advantage of the unique properties of gold, these reactions combine the oxidative couplings with the direct C-H bond functionalization of non-activated arenes (Scheme 1.6, b) or the hydrofunctionalization of C-C multiple bonds driven by π -activation (Scheme 1.6, c), enabling the construction of molecular complexity in a very step-economical manner that is not easily accessed using alternative catalysts.

Direct C-H auration with Au(I) compounds (**A** in Scheme 1.6, a) is specific for electron-poor substrates such as arenes and heteroarenes, with regioselectivity favoring the most acidic C-H bond, indicative of concerted metalation-deprotonation (CMD). Alternatively, the Au(I) precursor **A** can undergo a transmetalation event with a pre-functionalized arene, generally arylsilanes or aryl boranes. On the other hand, the Au(III) species formed upon oxidation (**C** in Scheme 1.6, a) display selectivity for C-H activation of electron-rich arenes, characteristic of an electrophilic aromatic substitution (S_EAr). Final reductive elimination of the two coupling partners results in the formation of the new C-C or C-heteroatom bond and regeneration of the Au(I) catalyst.

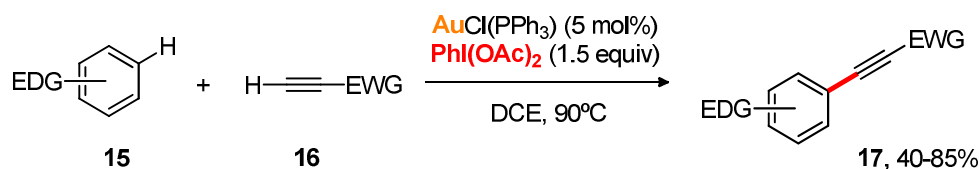


Scheme 1.6: Typical 2-electron redox mechanistic cycle in Au(I)/Au(III) oxidative coupling catalysis, featuring in orange the alternative oxidative addition step to Au(III) intermediates (a). Gold-catalyzed oxidative coupling methodologies combining aryl C-H functionalization (b) or nucleophilic addition (c), both requiring external oxidants.

1.1.2.1. Oxidative Couplings Employing External Oxidants

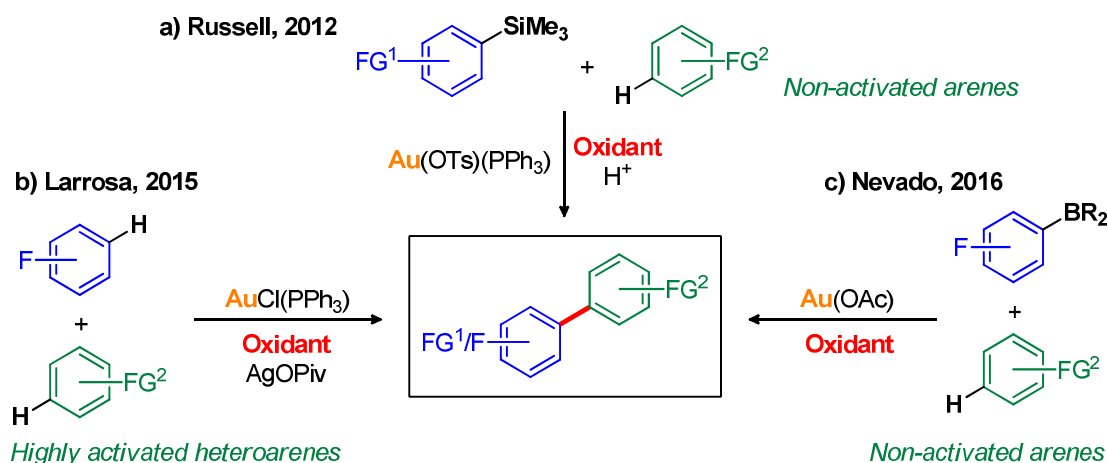
The first gold-catalyzed C-C coupling reaction was reported by Tse and co-workers in 2008.³⁸ Using 2 mol% Au(III) in the presence of $PhI(OAc)_2$ as a sacrificial external oxidant, a series of simple arenes could be homodimerized. It is worth pointing out that this procedure to prepare biaryls directly from simple arenes by C_{sp^2} -H functionalization does not require pre-activation of each coupling partner by metalation or halogenation, in contrast to the so-called Pd-catalyzed Suzuki-Miyaura couplings.

The biaryls synthesized in this reaction are by definition symmetrical and therefore of limited value. This was tackled in 2010 by de Haro and Nevado, who reported the successful synthesis of arylacetylenes from arenes and electron-deficient terminal alkynes.³⁹ In analogy to the copper acetylides found in the Sonogashira reaction, gold(I)-alkynyl species were formed *in situ* and, in the presence of iodine (III) oxidant, a gold(III)-alkynyl intermediate was generated. Electron-rich arenes **15** then reacted with the highly electrophilic Au(III) complex, which upon reductive elimination generate the new C_{sp^2} - C_{sp} bond (Scheme 1.7). Notably, no biaryls resulting from oxidative homodimerization of the arene were formed.



Scheme 1.7: Gold-catalyzed oxidative alkylation of arenes.

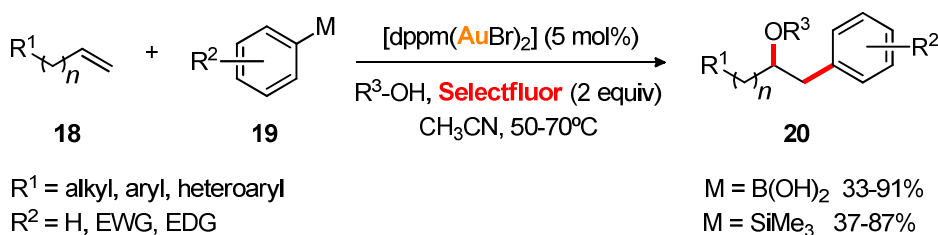
In two pioneering examples, Russell and co-workers demonstrated that electron-deprived arylsilanes can also be employed as coupling fragments in gold-catalyzed arylation reactions (Scheme 1.8, a).^{40,41} Arylsilanes afforded orthogonality to traditional cross-coupling strategies, and their easy synthesis and handling and lack of toxicity renders them valuable substrates. The performance of this process was improved by Larrosa *et al.* in the direct coupling of perfluorinated arenes with highly electronically activated heteroarenes (Scheme 1.8, b).⁴² Although substoichiometric amounts of silver salts were required, the system suppresses the formation of undesired homo-coupling products even without a large excess of one of the coupling partners. In 2016, Nevado and co-workers offered an alternative orthogonal approach to the previously described methods with strong electron-deficient boronic esters (Scheme 1.8, c).⁴³ Interestingly, the use of a gold(I) catalyst bearing an acetato ligand as internal base enabled to work under base-free conditions and avoided the potential deactivation of aryl boranes in basic media.



Scheme 1.8: Gold-catalyzed oxidative synthesis of nonsymmetric biaryls.

On the other hand, numerous gold-catalyzed coupling processes have been reported in which one coupling partner is delivered following the attack of a nucleophile onto a C-C multiple bond. Differently from classical hydrofunctionalization reactions, in which the organogold complex generated upon nucleophilic addition undergoes protodeauration to yield the product, in these tandem reactions the gold catalyst mediates the formation of a new C-C bond by oxidative coupling after it is liberated from the organogold intermediate (Scheme 1.6, c).

Two notorious examples of these cascade nucleophilic addition-oxidative coupling processes were described in 2010. First, in a work by Zhang and co-workers,⁴⁴ less reactive alkenes were hydrofunctionalized under oxidative coupling conditions with arylboronic acids and Selectfluor as oxidant, furnishing different benzyl-substituted heterocycles depending on the nature and position of the intramolecular nucleophile. Strikingly, no alkene products were isolated resulting from β -hydride elimination, a competitive side-reaction recurrent in palladium catalysis. This reactivity was extended to intermolecular systems by Toste and co-workers. A bimetallic gold(I) catalyst was key to prepare highly functionalized alkylated arene products directly from terminal alkenes with simple alcohols, carboxylic acids or water as nucleophiles (Scheme 1.9).⁴⁵ As a follow-up work, the same group successfully employed aryltrimethylsilanes as aryl coupling partners.⁴⁶



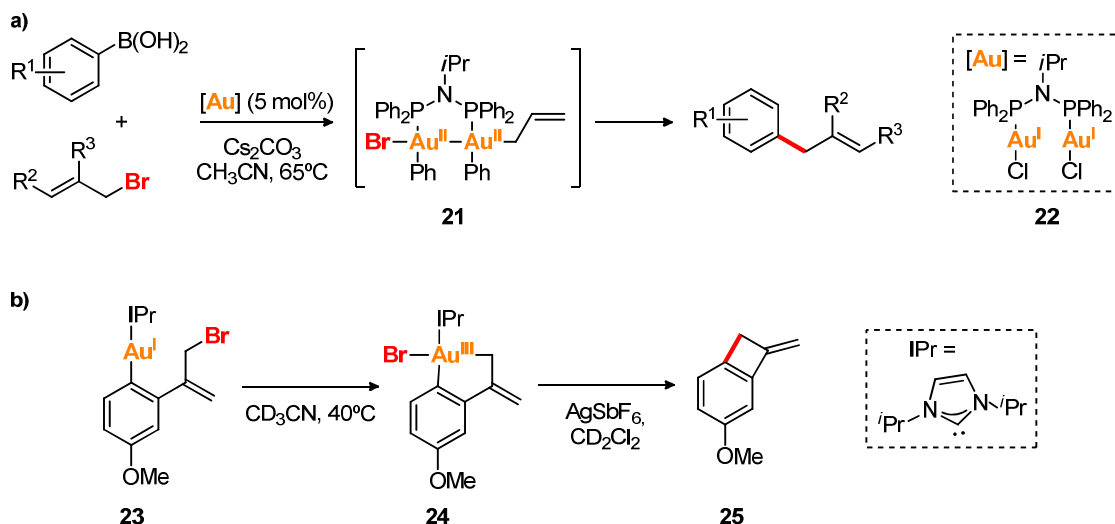
Scheme 1.9: Gold-catalyzed cascade intermolecular heterofunctionalization of alkenes.

1.1.2.2. Oxidative Couplings Employing External Oxidants

In striking contrast to the above cases, gold-catalyzed cross-coupling methodologies without the requirement of sacrificial oxidants arguably represent a challenge owing to the sluggish oxidative addition of alkyl and aryl halides to gold(I).⁴⁷ Although Sonogashira and Suzuki-Miyaura cross-coupling reactions with aryl iodides were described,^{48,49} the involvement of Au(I)/Au(III) redox cycles in these processes occasioned intense debate. It was first suggested that the presence of palladium as a contaminant of gold was responsible for the catalytic activity.⁵⁰ Significantly, it was then discovered that Au(I) salts and related complexes decompose thermally leading to the formation of gold clusters.⁵¹ These gold nanoparticles proved capable of catalyzing Suzuki and Sonogashira couplings in an heterogeneous manner, which explained the observed reactivity under scrupulous Pd-free conditions.⁵²

Continued efforts seeking to overcome these impediments resulted in the first allylation of arylboronic acids reported by Toste in 2014.⁵³ In this seminal work, allyl bromides were acting as the oxidizing equivalents, which oxidatively add to a phosphine gold(I) aryl complex **22** to generate bimetallic Au(II)-Au(II) key intermediates **21** rather than the discrete Au(III) species, followed by an unusually fast C_{sp2}-C_{sp3} reductive elimination (Scheme 1.10, a). Albeit the authors were unable to detect the putative intermediate species, a tethered Au(I) aryl complex **23** bearing an allyl bromide moiety allowed to support the mechanistic proposal under intramolecular conditions. Consequently, after C_{sp2}-Br oxidative addition to Au(I), complex **24**

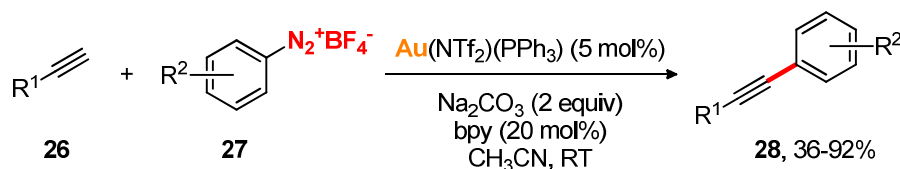
undergoes spontaneous reductive elimination in the presence of a halide abstractor to afford the intramolecular coupling product **25** (Scheme 1.10, b). It is noteworthy that the formation of the benzocyclobutane was quantitative despite the strain of the resulting four-membered ring.



Scheme 1.10: Intermolecular allylation of arylboronic acids proposed to operate *via* Au(II)-Au(II) bimetallic intermediate species **21** (a). Model intramolecular monometallic oxidative addition of allyl bromides and subsequent reductive elimination upon bromide abstraction from a cyclometalated Au(III) complex **24** (b).

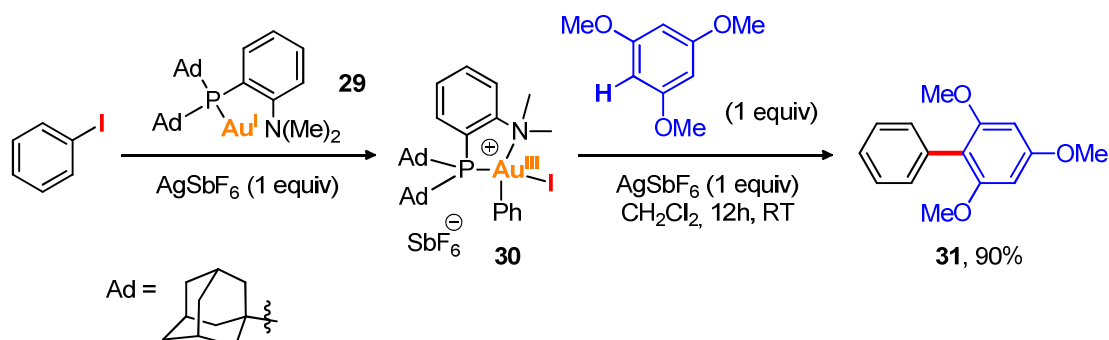
A surrogate strategy to access the requisite gold(III) intermediates within Au(I)/Au(III) catalytic cycles is the visible light-promoted oxidative addition of diazonium salts. In this system, first disclosed by the groups of Glorius and Toste,^{54,55} the high electrophilicity of the aryl radicals photogenerated from aryldiazonium salts is used as a platform to bring gold(I) to gold(III) intermediates. According to the authors, the oxidation of the Au(I) precursor is attained through Ru-catalyzed photoredox decomposition of the diazonium salt, and sequential single-electron transfer from the resulting gold(II) intermediate to the photocatalyst. Later on, Glorius and co-workers provided direct experimental evidence for the involvement of such steps in generating the key Au(III) complexes.⁵⁶ Under the same conditions as those applied in dual gold/photoredox catalysis, well-defined cyclometalated gold(III) species bearing a 2-phenylpyridine ligand scaffold were isolated (see section 1.3.1).

Complementary to these reports, Chen and Shi developed a methodology in which diazonium activation can be achieved without light. Instead, in their gold-catalyzed coupling reaction between alkynes and aryldiazonium salts, bipyridine-assisted nitrogen extrusion was followed by rapid $Au(III)C_{sp}-C_{sp2}$ (Scheme 1.11) and $C_{sp2}-C_{sp2}$ reductive elimination.⁵⁷ Moreover, nucleophiles were also shown to act as diazonium activators for promoting Au(I) oxidation in C-Br, C-S and C-P bond forming reactions.⁵⁸



Scheme 1.11: Ligand-promoted gold redox catalysis with aryldiazonium salts in $C_{sp}-C_{sp^2}$ bond formation.

The latest example dealing with gold(I)-catalyzed C-C cross-coupling with aryl halides in an intermolecular fashion was reported by Bourissou, Zeineddine and co-workers.⁶³ In this work, the authors envisaged to incorporate a (P,N) bidentate phosphine ligand with an hemilabile amino group that promotes the oxidative addition of aryl halides and eventually coordinates the resulting hard Au(III) center (Scheme 1.12). This interaction has been evidenced by both X-ray diffraction analysis and DFT calculations. Subsequently, the highly electrophilic complex **30** reacts with electron-rich arenes, such as trimethoxybenzene and 1-phenylpyrrole, *via* facile $C_{sp^2}-H$ activation and reductively eliminates the corresponding biaryls products **31**. This transformation proved to be effective in a catalytic manner by adding one equivalent of $AgSbF_6$ to generate a more electrophilic Au(III) species that aided the advent of Au(I)/Au(III) cycles.



Scheme 1.12: Amino-assisted intermolecular oxidative addition of iodobenzene to gold(I) and further cross-coupling with 1,3,5-trimethoxybenzene.

1.2 FUNDAMENTAL ORGANOMETALLIC TRANSFORMATIONS WITH GOLD

The factors governing the properties of gold complexes do not periodically mirror those of the other transition metals. Common elementary steps in transition metal mediated reactions, such as oxidative addition, reductive elimination, migratory insertion or β -hydride elimination, are much less evidenced in the case of gold, some of them being noticeably rare. In that sense, relativistic effects provide a theoretical scheme for rationalizing its abnormal coordination chemistry and reactivity.

Nonetheless, some of these fundamental reactions have been deeply investigated and corroborated in the recent years, with remarkable contributions especially on oxidative addition and reductive elimination processes. It is the aim of this chapter to give a comprehensive overview concerning elementary organometallic steps of gold complexes. The focus will be set specifically on the transformations mostly studied within this thesis (the oxidative addition, reductive elimination and the migratory insertion), while transmetalation and β -hydride elimination will be more briefly discussed.

1.2.1 Relativistic Effects in Gold Coordination Chemistry

The term “relativistic effect” arises from the necessity to take special relativity into account in the quantum chemical treatment of heavy elements, permitting solutions to systems in which electrons move at velocities approaching the speed of light. The electrons that penetrate the nucleus (the *s* electrons) increase their average speed as the atomic nuclear charge (*Z*) of a given atom increases. A basic consequence of special relativity is that this increase in velocity results also in a mass increase. Because the Bohr radius of an electron is inversely proportional to its mass, the increase in mass causes the *s* electrons to be in smaller orbitals than if this effect was absent. This is also known as direct relativistic effect, and is valid, to a lesser extent, to the *p* electrons.^{6,64}

This phenomenon is not negligible for the heavy elements. In them, the *s* electrons are more strongly bound and shield the nuclear charge from the other electrons, in particular those in the *d* and *f* orbitals. Therefore, they see a weaker nuclear attraction and occupy larger orbitals. The *d*-orbital expansion in gold enhances in turn the stability (stronger binding) of the *s* electrons (Figure 1.2). This is called indirect relativistic effect or lanthanide contraction, and reaches its maximum for a filled *d*-shell, which explains why platinum, gold and mercury (located at the end of the 5*d* orbital filling) exhibit the largest impact of this relativistic effect (Figure 1.3).^{65–67}

A direct consequence of the significant 6*s* and 6*p* orbital contraction is the characteristic bright yellow color of gold metal. The excitation of 5*d* electrons and the lowering of the valence 6*s* energies, which decreases the energy gap between the 5*d* and 6*s* levels to 2.38 eV, causes blue visible light to be absorbed. By contrast, the related absorption in silver is shifted in the ultraviolet due to a larger 4*d*-5*s* bandgap at ~3.7 eV, and therefore this metal is colorless.⁶⁸

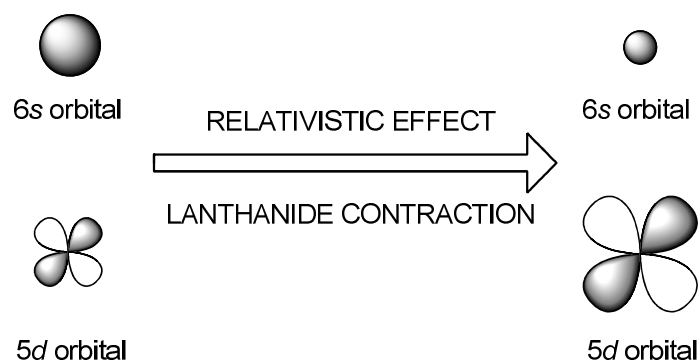


Figure 1.2: Contraction of the outer-shell 6s orbital and subsequent size and energy level increase of the 5d orbital, caused by indirect relativistic effects. Taken from ref. 72.

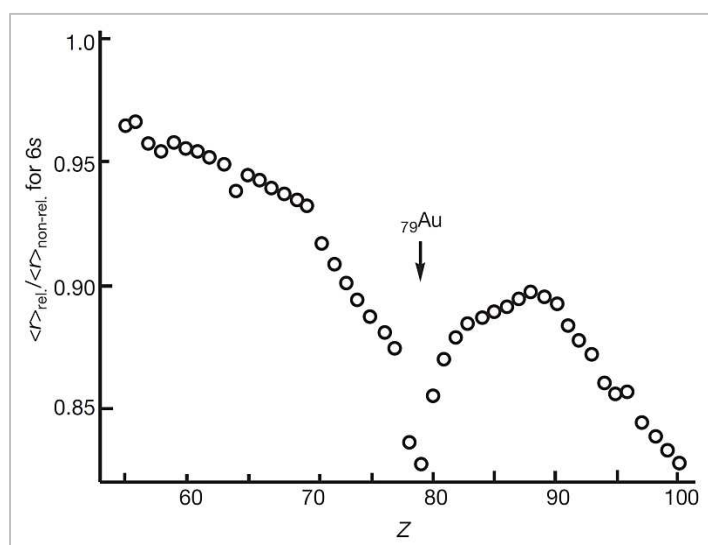


Figure 1.3: Relationship between the relativistic and non-relativistic 6s orbital radii (y-axis) and the atomic number Z (x-axis). Taken from ref. 6.

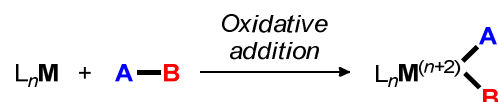
The coordination chemistry of gold is also well linked to relativistic effects. The contraction of the 6s orbital translates into a small size of the gold atom (for comparison, the covalent radii for copper, silver and gold are 1.32 Å, 1.45 Å and 1.36 Å, respectively)⁶⁹ and extraordinarily strong Au-L bonds, where L is the ligand. As a result, the vast majority of Au(I) complexes are dicoordinated and adopt a linear geometry, while tricoordinate and tetracoordinate Cu(I) and Ag(I) complexes are prevalent.⁷⁰ The stability of neutral bicoordinate Au(I) complexes explains the need to abstract a ligand in order to trigger reactivity.

In terms of reactivity, the decrease in size and energy level of the 6s and 6p orbitals increases the Lewis acidity and π -backbonding of the Au(I) complexes (which feature an empty 6s⁰ and full 5d¹⁰ valence shell configuration).⁷¹ As a result, soft gold(I) cations are well-suited for the activation of soft electrophiles such as alkynes, alkenes and allenes. The strong π -acidity also correlates with the unusually high electronegativity of Au(I) species (2.4 on the Pauling scale versus 1.9 for Ag)⁷² and with a high first

ionization energy (9.223 eV, compared with 7.57 eV for Ag).⁶ Accordingly, gold is difficult to oxidize ($E^0 \text{ Au(I)/Au(III)} = +1.41 \text{ V}$ in water).⁷ In this regard, the low electron-electron repulsion in the diffuse $5d$ orbitals has been associated to an increased effective attraction to the nucleus, resulting in insufficient nucleophilicity species to undergo oxidative addition.⁷³ On the other hand, the $5d$ electrons in gold are held with greater energy than the Cu $3d$ and Ag $4d$ electrons due to the expansion of the $5d$ -orbital, which enhances the thermodynamic stability of Au(III) complexes. Comparatively, the +3 oxidation state is less frequently encountered in copper and silver compounds.

1.2.2 Oxidative Addition

Oxidative addition is a crucial step in many cross-coupling reactions. It consists of the metal-assisted cleavage of a bond in an organic or main group reagent, forming a product containing two additional ligands. Consequently, this process leads to an increase in the oxidation state of the metal promoter by two (Scheme 1.13).⁷⁴

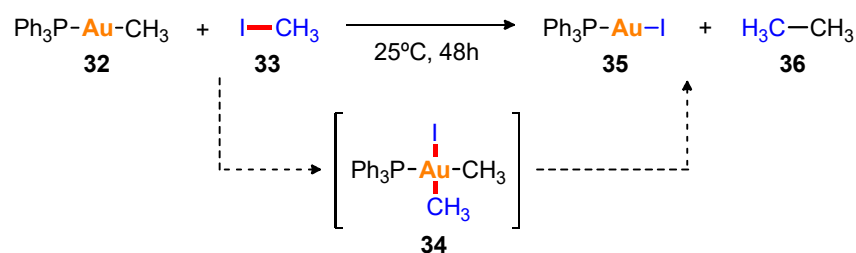


Scheme 1.13: General oxidative addition of a mononuclear complex and an organic fragment. Taken from ref. 74.

From a historic point of view, it was assumed that the redox-neutral character of gold, rooted in the strong relativistic effects governing its electronic structure, hindered such two-electron oxidations and therefore rendered Au(I) complexes inert towards oxidative addition processes. However, in the early 1970's, and particularly in the past three years, it has become evident that the transition from Au(I) to Au(III)-species is possible under certain circumstances.

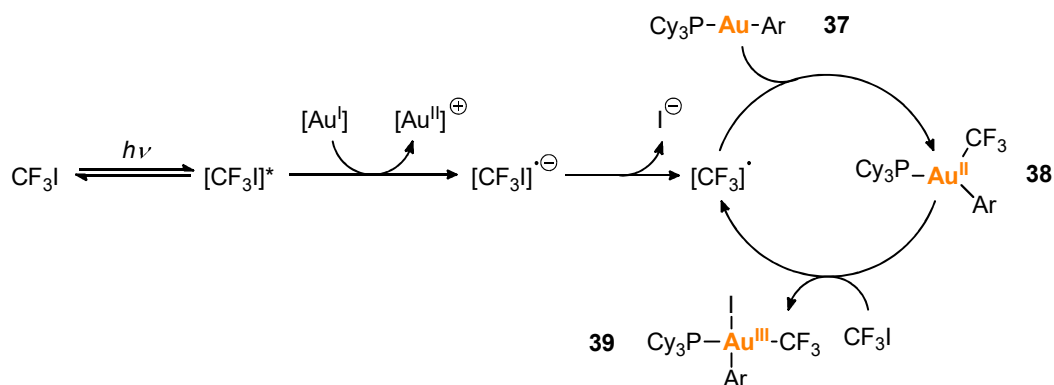
1.2.2.1 Oxidative Addition of Polar Reagents: Alkyl and Aryl Halides

In the early 1970's Kochi and Schmidbaur independently observed that phosphine gold(I) methyl complexes react slowly with methyl iodide to form ethane and phosphine gold(I) iodide (Scheme 1.14).^{75,76} Detailed investigations on the reaction mechanism showed that oxidative addition of the $\text{C}_{\text{sp}^3}\text{-I}$ bond to gold takes place initially, which is generally accepted to proceed *via* an $\text{S}_{\text{N}}2$ -type mechanism.⁷⁷ In some cases, the ensuing gold(III) complexes have been spectroscopically characterized, depending on the substitution pattern of the phosphine donor ligand.⁷⁸ Then, $\text{CH}_3\text{-I}$ transmetalation between the starting methylgold(I) complex **32** and the intermediate dimethylgold(III) iodide complex **34** takes place, followed by decoordination of the phosphine ligand from the resulting phosphine trimethylgold(III) complex and reductive elimination to liberate ethane.



Scheme 1.14: Ethane formation by reaction of a phosphine gold(I) methyl complex with methyl iodide.

The field of C_{sp^3} -X activations remained dormant for more than four decades until Toste and co-workers reported the oxidative addition of trifluoroiodomethane to phosphine gold(I) aryl complexes.⁷⁹ Mechanistic investigations pointed at a radical chain mechanism initiated by near-ultraviolet light (Scheme 1.15). Photoexcited CF_3I is responsible for oxidizing the arylgold(I) complex **37** to intermediate gold(II) species **38**, and the resulting radical-anion $[CF_3I]^{-\bullet}$ undergoes homolytic bond cleavage generating I^- and $[CF_3]^{\bullet}$. The latter reacts with the tricyclohexylphosphine gold(I)aryl complex forming a tricoordinate gold(II) intermediate which is then further oxidized by CF_3I to yield the trifluoromethyl aryl gold(III) product **39** and a $[CF_3I]^{-\bullet}$ radical that closes the propagating cycle. The same group, in order to shed light on the mechanism of oxidant-free allylation of arylboronic acids, designed a substrate featuring a tethered allyl bromide arm that places the gold(I) centre close to the targeted C_{sp^3} -Br bond, enabling the formation of the corresponding gold(III) complex **24** and its characterization by single crystal X-ray diffraction (see scheme 1.10).⁵³

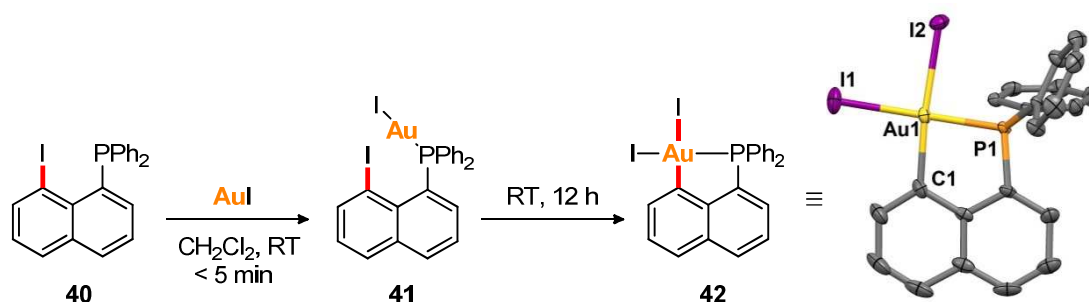


Scheme 1.15: Radical chain mechanism postulated for the oxidative addition of CF_3I to phosphine gold(I) aryl complexes.

With regard to aryl halides, in the course of the controversy concerning the ability of homogeneous gold(I) to catalyze cross-coupling reactions of aryl iodides with arylboronic acids or phenylacetylenes (see section 1.1.2.2.), O'Hair and co-workers investigated the reaction of iodobenzene with gold(I) complexes and small gold clusters by combining mass spectrometry experiments and DFT calculations.⁸⁰ While oxidative addition of iodobenzene to the mononuclear complex Me_3PAuI has a very high activation energy ($31.6 \text{ kcal}\cdot\text{mol}^{-1}$), the related reaction for the bare gold cluster Au_{38} has a substantially

lower barrier ($11.3 \text{ kcal}\cdot\text{mol}^{-1}$). In a similar manner, a range of bisphosphine ligated small gold clusters $[\text{Au}_3\text{L}_5]^+$ and $[\text{Au}_3\text{L}_6]^+$ were proved effective in gas phase C-I bond activation.

At this stage it appeared that the activation of aryl halides to linear two-coordinate gold(I) complexes was highly disfavored and limited only to polymetallic heterogeneous species (clusters, nanoparticles, surfaces). This sparked the interest in alternative strategies that could eventually induce the activation of $\text{C}_{\text{sp}^2}\text{-X}$ bonds at gold. In this line, Bourissou and co-workers designed 8-halonaphthyl phosphines **40** with the aim to position the $\text{C}_{\text{sp}^2}\text{-X}$ bond to be activated in close proximity to the Au(I) center and thereby provide suitable conditions to generate and stabilize the oxidative addition products. This methodology was successful and the authors reported a clear-cut proof on the aryl iodide oxidative addition at Au(I), providing the crystal structure of the aryl-Au(III)-I product **42** (Scheme 1.16).⁸¹ While the $\text{C}_{\text{sp}^2}\text{-I}$ bond oxidatively adds to the metal center at room temperature, activation of the analogous $\text{C}_{\text{sp}^2}\text{-Br}$ bond necessitates temperatures as high as 130°C and oxidative addition of the $\text{C}_{\text{sp}^2}\text{-Cl}$ bond was not observed even at elevated temperatures. According to DFT calculations, the activation barrier for the Ar-I bond activation is $10\text{-}15 \text{ kcal}\cdot\text{mol}^{-1}$ lower than that predicted for related intermolecular reactions with two-coordinate gold(I) complexes.

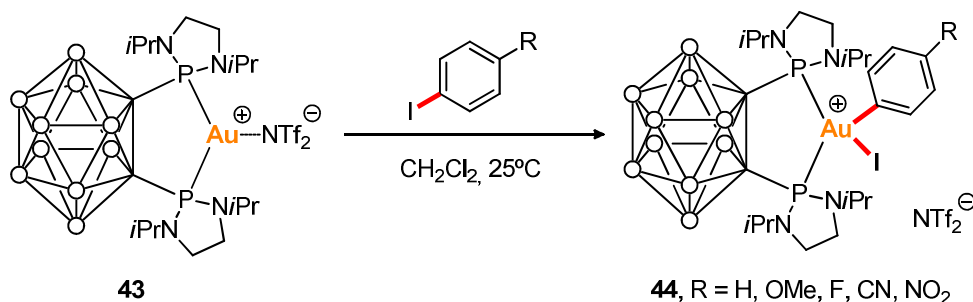


Scheme 1.16: Right: Coordination of 8-iodonaphthyl phosphine to Au(I) and subsequent intramolecular Ar-I oxidative addition. Right: Molecular structure determined by single crystal X-ray diffraction of the stable Au(III) complex **42**.

The same group showed that activation of the $\text{C}_{\text{sp}^2}\text{-Br}$ bond is feasible under milder conditions when the aryl bromide bears two phosphine chelating groups, resulting in the synthesis of original Au(III) “PCP” pincer complexes.⁸¹ Again, $\text{C}_{\text{sp}^2}\text{-Cl}$ bond activation could not be achieved for the respective ligand. The importance of a second phosphine buttress for the oxidative addition of an Ar-Br bond was corroborated by theoretical calculations from Echavarren, Maseras *et al.*⁴⁷

A different strategy to trigger oxidative addition to inert linear Au(I) in intermolecular reactions was also reported by Bourissou, Amgoune and co-workers.⁸² Carborane diphosphines were employed to chelate gold(I) with bent P-Au-P angles (100°) that preorganize the linear Au(I) fragment to the square-planar geometry of the Au(III) oxidative addition product **44** (Scheme 1.17). The prominent role of bending was substantiated by reacting various *p*-substituted iodobenzenes under incredibly mild

conditions, and the ensuing aryl Au(III) complexes were characterized by X-ray diffraction.

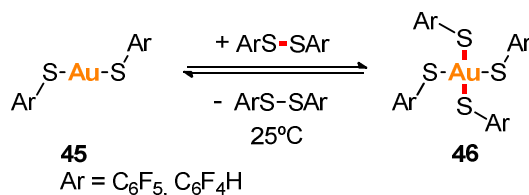


Scheme 1.17: Oxidative addition of iodobenzenes to bent tricoordinate carborane diphosphine Au(I) complexes with a labile triflimide ligand (NTf_2^-).

1.2.2.2 Oxidative Addition of Nonpolar Reagents

Less effort has been devoted to investigate the ability of molecular gold(I) complexes to activate less or even non-polarized bonds. Until the beginning of this decade almost no examples were known, but with the recent upsurge of interest in the oxidative addition of alkyl and aryl halides, the activation of nonpolar σ -bonds by mononuclear gold(I) complexes has also been revisited.

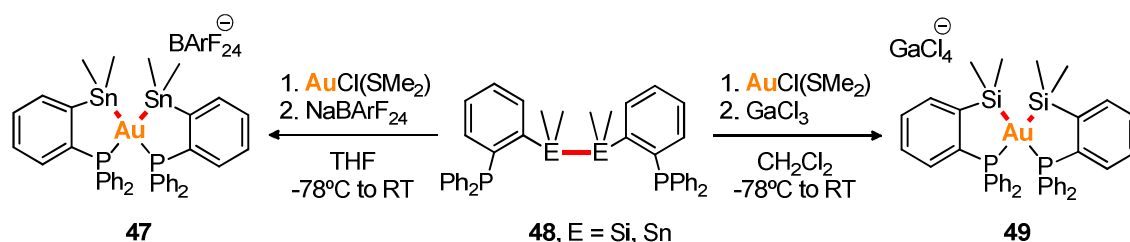
The first contribution, back to the late 1960's, covered the activation of disulfides to yield thiolate Au(III) complexes. Davison *et al.* reported the formation of a chlorotriphenylphosphonium tetrathiolauroate by reacting bis(trifluoromethyl)-1,2-dithiethene with (triphenylphosphine)gold(I) chloride.⁸⁴ The next example did not appear until 2008, when Bachman *et al.* reported that highly activated disulfides undergo facile and reversible oxidative addition to linear dithiolate gold(I) complexes **45** (Scheme 1.18).⁸⁵ Both the homoleptic gold(I) and the gold(III) thiolate complexes were structurally characterized. This work represents a notable exception of the inert character of linear two-coordinate Au(I) complexes towards oxidative addition.



Scheme 1.18: Reversible reductive elimination/oxidative addition of disulfides at electron-rich aurate species.

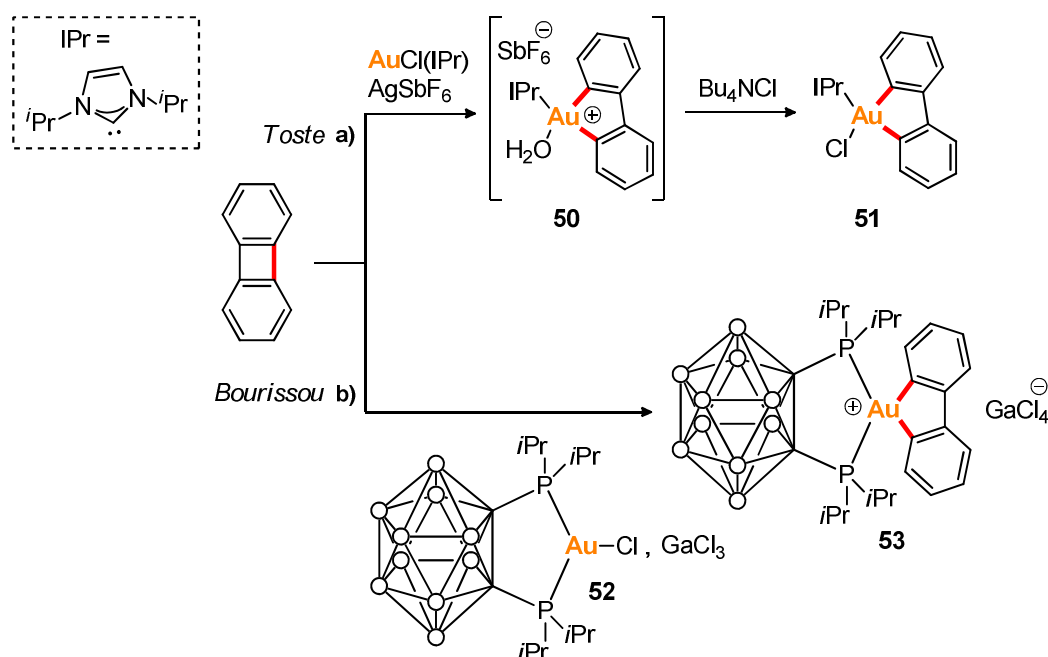
Shortly after, the group of Bourissou published the spontaneous intramolecular oxidative addition of Si-Si and Sn-Sn bonds tethered to a diphosphine ligand by coordination to gold(I), generating bis(silyl) and bis(stannyl)gold(III) complexes, respectively (Scheme 1.19).^{86,87} These Au(III) complexes were fully characterized by multinuclear NMR spectroscopy and X-ray diffraction crystallography. Computational analyses of both processes indicated concerted σ -bond activation pathways with

symmetric geometries in the transition state, featuring low activation barriers of 10.4 kcal·mol⁻¹ for the Si-Si and only 4.1 kcal·mol⁻¹ for the Sn-Sn bond, in agreement with the mildness of the reaction conditions (-78°C) and the weaker bond strength of the latter. Bourissou, Amgoune and co-workers extended the oxidative addition of σ -Si-Si bonds to intermolecular conditions using disilanes.⁸⁸ The formation of cationic phosphine Au(I) complexes upon chloride abstraction was found crucial for the reaction to proceed.



Scheme 1.19: Synthesis of bis(stannyl)- and bis(silyl) gold(III) complexes **47** and **49** by oxidative addition of Si-Si or Sn-Sn bonds to Au(I).

In 2015 the field took an important step forward with the first examples of C-C bond activation. Toste and co-workers described the oxidative addition of biphenylenes to coordinatively unsaturated *N*-heterocyclic carbene (NHC) Au(I) cationic complexes.⁸⁹ The generation of a vacant coordination site upon treatment with AgSbF₆ afforded the [(IPr)Au(biphenylene)]⁺ adduct, which readily reacts with the strained C-C bond of biphenylene. The ensuing cationic Au(III) aqua-complex **50** was trapped with ammonium chloride to generate the more stable tetracoordinate chloro Au(III) complex **51** (Scheme 1.20, a).



Scheme 1.20: Preparation of stable gold(III) complexes *via* oxidative addition of strained C-C bonds to cationic NHC-Au(I) (a) and DCPb-Au(I) complexes (b).

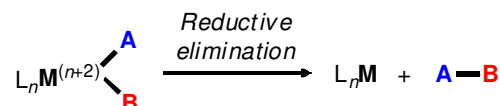
The use of a multidentate ligand with two strong Au-C bonds and an NHC ligand confers prominent stability to the metal center. Furthermore, it was shown that by adding a polar substrate (DMF) coordination of the oxygen at the metal center takes place, denoting an oxophilic and hard Lewis acid character of this gold(III) complex, complementary to the soft character of the gold(I) complexes. Thanks to these properties, complex **51** proved to be a very efficient catalyst for Michael additions, [4+2] and [2+2] cycloadditions to σ,β -unsaturated carbonyl compounds, with good yields and excellent selectivities.

In parallel, Amgoune, Bourissou and co-workers took profit of the carborane diphosphine (DCPb) platform to promote the oxidative addition of the strained C-C bond of biphenylene (Scheme 1.20, b).⁹⁰ Additionally, the bent two-coordinate complex $[(\text{DCPb})\text{Au}]^+$ also activates the $\text{C}_{\text{sp}^2}\text{-C}(\text{O})$ or the $\text{C}_{\text{sp}^3}\text{-C}(\text{O})$ bond of benzocyclobutenone as the result of kinetic/thermodynamic control, respectively.

Interestingly, recent examples have highlighted the major role of hemilabile ligands, bearing either imine⁹¹ or amino⁶³ groups, in stabilizing the gold(III) center resulting from the oxidative addition of biphenylene.

1.2.3 Reductive Elimination

The reductive elimination is intimately linked to the oxidative addition as its microscopic reverse. In consequence, the oxidation state of the metal center decreases by two while forming a new covalent bond between two fragments. It is the product-forming step in many catalytic processes, in particular cross-coupling reactions (Scheme 1.21).⁷⁴



Scheme 1.21: General reductive elimination of a mononuclear complex and an organic fragment. Taken from ref. 74.

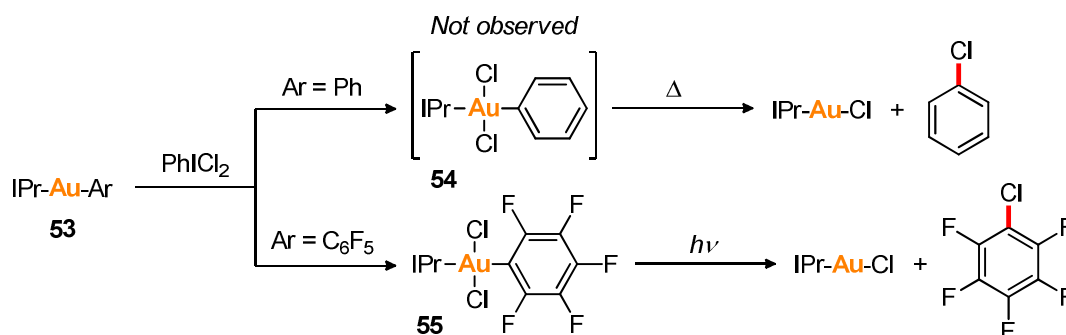
In contrast to the oxidative addition, reductive elimination at gold(III) was substantiated experimentally early on and has never been questioned. Indeed, under certain circumstances, it has been revealed to be more feasible than at other transition metals. Over the past few years, thanks to the landmark advances in the generation of well-defined organogold(III) complexes, important mechanistic insights have been gained and the library of coupling products has also been expanded.

1.2.3.1 C-Halide Bond Formation

The earliest evidence for an Au(III)-Au(I) redox process dates back to 1934. Burawoy and Gibson noticed that $[(\text{AuBr}_2\text{Et})_2]$ undergoes $\text{C}_{\text{sp}^3}\text{-Br}$ reductive elimination upon heating to yield ethyl bromide and Au(I) bromide, as detected by elemental analyses.⁹²

Four decades later, Aresta and Vasapollo reported the spontaneous formation of a $\text{C}_{\text{sp}^2}\text{-Br}$ bond at room temperature from a phosphine dibromogold(III) aryl complex, which was accessed by low-temperature oxidation of $(\text{Ph}_3\text{P})\text{Au-Ar}$ with Br_2 .⁹³ Similar aryl halide formations were also observed upon reaction of several perhalophenyl phosphine or arsine gold(I) complexes with dihalogens (Cl_2 , Br_2 , I_2), although the putative intermediate gold(III) complexes were not characterized.⁹⁴

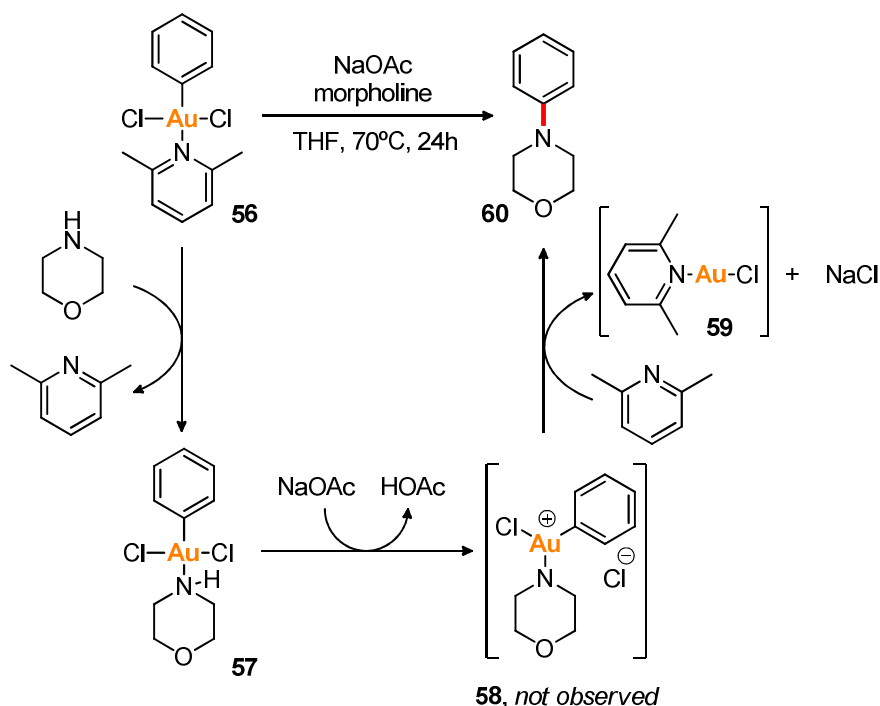
Rosenthal and co-workers investigated recently the generation of aryl chloride bonds *via* reductive elimination from (IPr)arylgold(III) dichlorides. (IPr)Au-Ar complexes **53** were oxidized with PhICl_2 and, depending on the electronic properties of the aryl group, either thermal ($\text{Ar} = \text{Ph}$) or photochemical ($\text{Ar} = \text{C}_6\text{F}_5$) $\text{C}_{\text{sp}^2}\text{-Cl}$ formation was observed (Scheme 1.22). The intermediacy of highly reactive gold(III) tricoordinated species formed by decoordination of chloride was proposed.⁹⁵



Scheme 1.22: $\text{C}_{\text{sp}^2}\text{-Cl}$ bond-forming reactions through thermal or photochemical treatment of dichloroarylgold(III) complexes.

1.2.3.2 C-N and C-O Bond Formation

Fewer reports are known concerning C-N and C-O bond formation. In 2010, Limbach *et al.* investigated the stoichiometric C-H bond activation mediated by gold(III) complexes followed by $\text{C}_{\text{sp}^2}\text{-N}$ bond reductive elimination.⁹⁶ A four-coordinate dichloro(morpholine)phenylgold(III) complex **57** was isolated and characterized (Scheme 1.23). Upon addition of a base (NaOAc), the morpholine ligand is deprotonated and chloride dissociation occurs subsequently from a dichloro(morpholide)phenylgold(III) complex. The transient three-coordinate gold(III) intermediate **58** undergoes fast reductive elimination yielding the aniline **60** as the cross-coupled product and a gold(I) complex **59**. None of the proposed key intermediates, nor the final Au(I) product, could be detected.



Scheme 1.23: Mechanistic rationale for a C_{sp^2} -N bond-forming reaction *via* reductive elimination from an Au(III) complex.

1.2.3.3 C-C and C-P Bond Formation

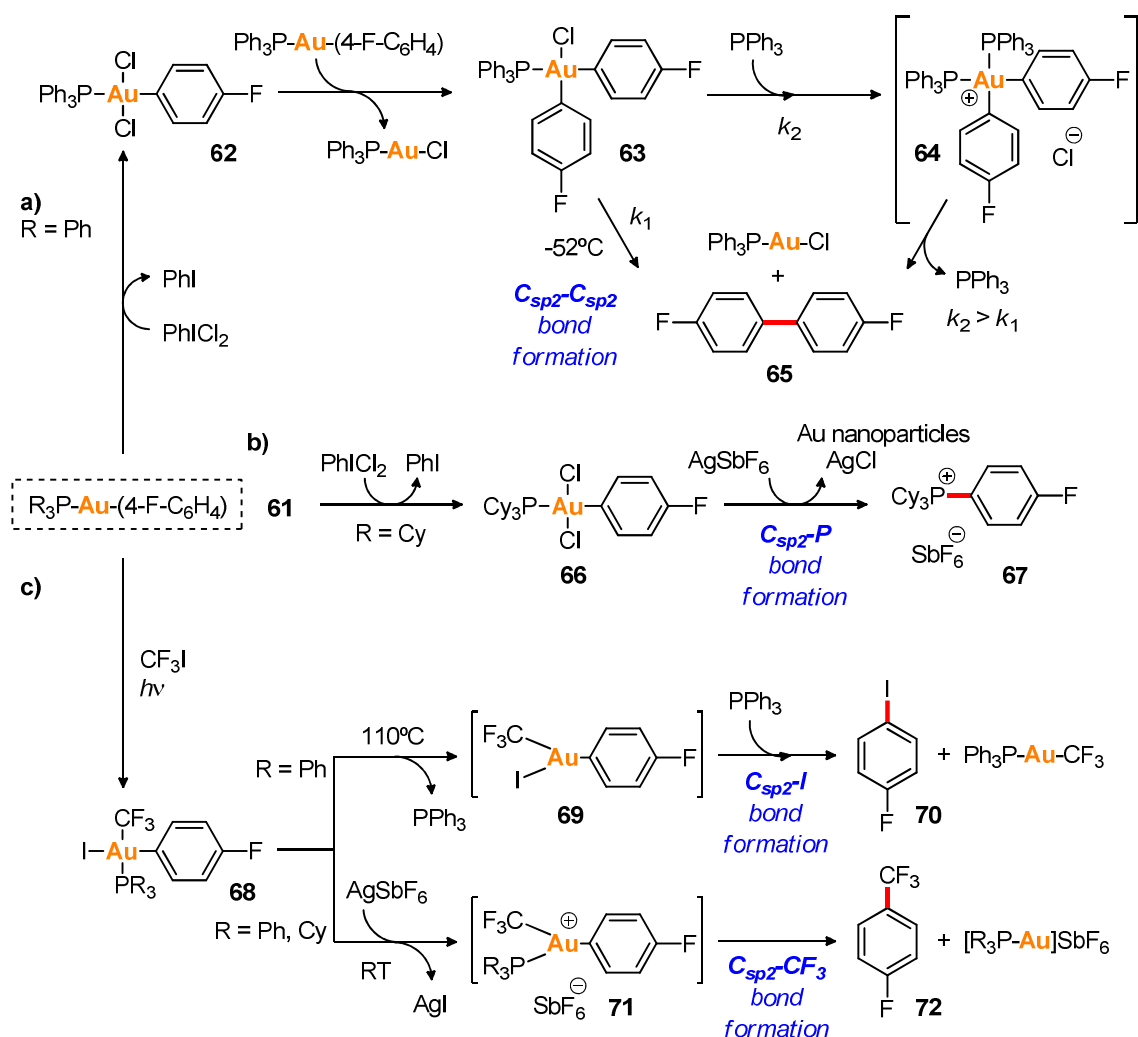
From a broad perspective, Toste's group contributions on C-C bond-forming reactions merit special consideration. In 2013 they reported exceedingly fast C_{sp^2} - C_{sp^2} bond reductive elimination rates from a *cis*-bis(aryl)gold(III) complex.⁹⁷ *In situ* oxidation of $[Au(4-F-C_6H_4)(PPh_3)]$ complex **61** with phenyliodoso dichloride led to the formation of the bis(aryl)gold(III) complex **62**, which further transmetalated with another equivalent of arylgold(I) complex **61** at $-78^\circ C$ (Scheme 1.24, a). *cis*- $[AuCl(4-F-C_6H_4)_2Cl(PPh_3)]$ intermediate **63** was identified by ^{31}P and ^{19}F NMR spectroscopy and shown to decompose to $[AuCl(PPh_3)]$ and difluorobiphenyl **65** at $-52^\circ C$.

It is noteworthy that the addition of an excess of triphenylphosphine increased significantly the rate of product formation. This observation is rationalized by fast chloride to phosphine ligand exchange, followed by even more facile reductive elimination at the resulting cationic (diphosphine)bis(aryl)gold(III) species **64**. These results suggest that reductive elimination of aryl groups at gold(III) to form biaryls can also happen at a four-coordinate gold(III) center.

The use of bulky, strongly donating trialkylphosphines avoids the aryl transmetalation from Au(I) to Au(III) observed in the triphenylphosphine version of complex **61**, resulting in quantitative oxidation of the starting material. In another work, the Toste group showed that the ensuing complex **66** undergoes facile C_{sp^2} -P reductive elimination to yield phosphonium salts **67** from tricoordinate Au(III) species, but also from neutral four- and five-coordinate intermediates under specific circumstances (Scheme 1.24, b).⁹⁸

As discussed above (see section 1.2.2.1., Scheme 1.15), Toste and co-workers showed that photoexcited CF_3I can alternatively oxidize the two-coordinate phosphine Au(I) aryl complexes **61** *via* a radical chain mechanism (Scheme 1.24, c).⁷⁹ The ensuing four-coordinate gold(III) complex $[\text{Au}(4\text{-F-C}_6\text{H}_4)(\text{CF}_3)\text{I}(\text{PPh}_3)]$ **68** leads to $\text{C}_{\text{sp}^2}\text{-I}$ bond formation upon heating.⁹⁹ Moreover, sonicating the Au(III) complex **68** with excess of AgX ($\text{X} = \text{F}, \text{Cl}, \text{Br}$) salts affords the corresponding metathesis products in high yields. The thermolyses of these complexes generate $\text{C}_{\text{sp}^2}\text{-X}$ and/or $\text{C}_{\text{sp}^2}\text{-CF}_3$ reductive elimination products, with selectivities for the C-X bond formation decreasing from heavier to lighter halides. Thereby, C-CF_3 reductive elimination is only observed upon iodide abstraction by a silver salt or applying high temperatures (122°C) when $\text{X} = \text{F}$.

Reductive elimination takes place likely at tricoordinated intermediates **69** and **71**, formed upon dissociation of the phosphine ligand. This finds support in the fact that $[\text{Au}(4\text{-F-C}_6\text{H}_4)(\text{CF}_3)\text{I}(\text{PR}_3)]$ ($\text{R} = \text{Cy}$) does not undergo thermal reductive elimination, likely due to the better σ -donor properties of PCy_3 , preventing the dissociation from gold(III). Free triphenylphosphine ligand in the reaction media led to complete inhibition of the reductive elimination at $[\text{Au}(4\text{-F-C}_6\text{H}_4)(\text{CF}_3)\text{I}(\text{PPh}_3)]$.

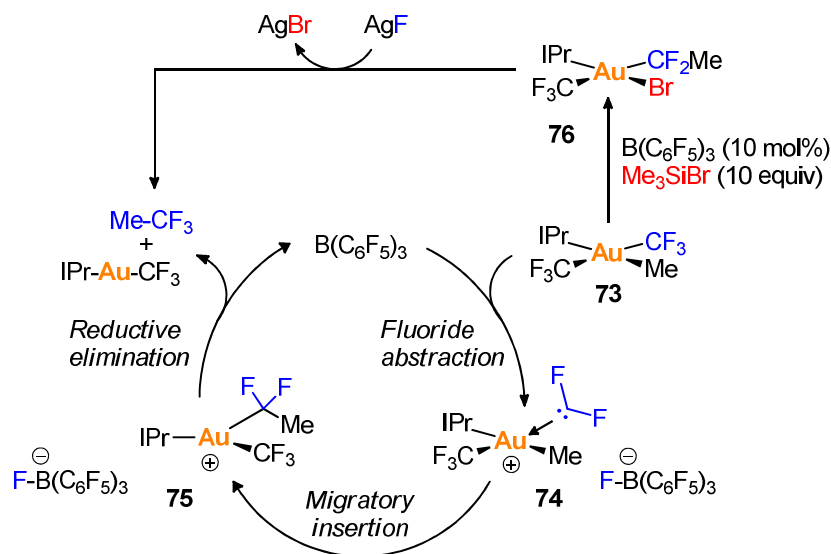


Scheme 1.24: Reductive elimination of $\text{C}_{\text{sp}^2}\text{-C}_{\text{sp}^2}$ (a), $\text{C}_{\text{sp}^2}\text{-P}$ (b) and $\text{C}_{\text{sp}^2}\text{-I}$ or $\text{C}_{\text{sp}^2}\text{-CF}_3$ (b) bonds from arylgold(III) phosphine complexes, generated by chemical (a and b) or photoinduced (c) oxidations.

$C_{sp^3}-C_{sp^2}$ bond formation has also been investigated by the same group (see Scheme 1.10, b).⁵³ The cyclometalated gold(III) complex **24** displays high stability and no reductive elimination is detected upon heating. However, abstraction of the bromide by $AgSbF_6$ induces spontaneous intramolecular C-C bond formation, proceeding through a putative cationic three-coordinate intermediate.

Very recently, Toste and co-workers have published a remarkable contribution on formal $C_{sp^3}-CF_3$ bond construction, which also implies rare migratory insertion at Au(III).¹⁰⁰ In this work, the unexpected formation of trifluoroethane was observed upon treatment of complex $[Au(CH_3)(CF_3)_2(L)]$ ($L = IPr$ or PCy_3) **73** with $B(C_6F_5)_3$ (Scheme 1.25). The reaction also occurs at catalytic loadings of borane, which is responsible for abstracting a fluoride from a CF_3 moiety, generating a difluorocarbene intermediate **74**. This undergoes migratory insertion of the alkyl fragment, followed by net C-F reductive elimination to yield trifluoroethane. This mechanism is supported by the isolation of a rearranged gold(III) complex **76** bearing a bromide and α,α -difluoroethyl substituents upon reaction with bromotrimethylsilane, which leads as well to the gradual formation of CH_3-CF_3 and $[Au(CF_3)IPr]$ by AgF treatment.

This synthetic protocol is exceptional because it merges extremely rare $C_{sp^3}-CF_3$ reductive elimination through a catalytic process involving disassembly and reassembly of the CF_3 moiety, and enables the radio synthesis of ^{18}F -labeled aliphatic CF_3 -containing compounds for their application in positron emission tomography (PET).



Scheme 1.25: Proposed catalytic cycle of the borane-mediated reductive elimination of trifluoroethane.

1.2.4 Transmetalation

The transmetalation is the bridging reaction between the oxidative addition and the reductive elimination in metal catalyzed cross-coupling processes, in which an organic fragment is transferred from a coupling reagent to a transition-metal species.^{12,74}

A variety of transmetalation events have been documented with gold, ranging from simple salt metathesis reactions with gold halides and organolithium or Grignard

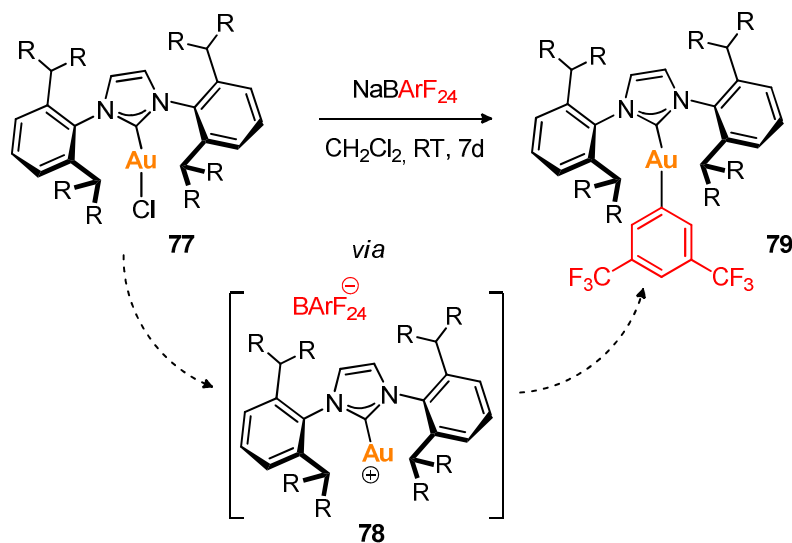
reagents, to transmetalations involving other transition metals and p-block elements (boron, silicon and tin). Thus far, the scope of organic moieties transferred from p-block elements to gold is almost exclusively limited to aryl fragments and, sporadically, to vinyl ones. Access to alkyl gold species by transmetalation needs still to be developed.

For the sake of conciseness, the following section only covers the most relevant literature with regard to transmetalation reactions from boron to gold, the p-block element with more examples disclosed. Direct C-H auration reactions have been discussed before (see section 1.1.2.1.).

1.2.4.1 Borate Salts

Boron-to-gold aryl transfer was documented in the mid-1990's between phosphine Au(I) complexes and NaBPh₄ salts under stoichiometric conditions by the groups of Schmidbaur and Fackler.^{101,102}

A closely related reactivity was reported by Straub and co-workers using NaBArF₂₄.¹⁰³ The attempt to isolate a sterically encumbered cationic NHC-Au(I) complex with the weakly coordinating tetrakis[bis(3,5-trifluoromethyl)phenyl]borate counteranion (BArF₂₄[−]) **78** resulted in the slow abstraction of a (trifluoromethyl)phenyl group and consequent transfer to gold (Scheme 1.26).

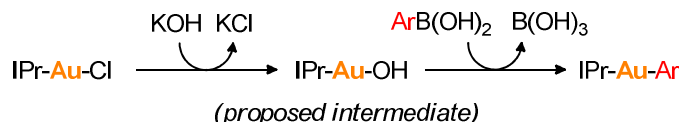


Scheme 1.26: Transfer of a bis(trifluoromethyl)phenyl group from boron to Au(I).

1.2.4.2 Boronic Acids

Transmetalation from arylboronic acids to gold has also been demonstrated with phosphine or *N*-heterocyclic carbene Au(I) complexes. Gray and co-workers showed that they react with arylboronic acids in the presence of a mild base in alcoholic media, applying conventional heating or microwave irradiation.^{104–106} Shortly after, the Nolan group improved the synthetic protocol with AuCl(IPr) by using potassium hydroxide as

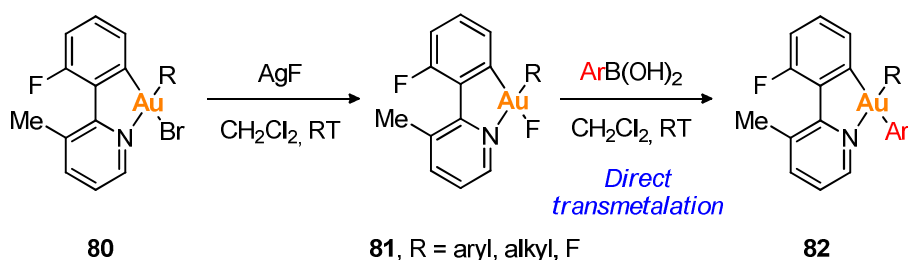
a base, allowing for the transmetalation to be performed at room temperature.¹⁰⁷ The mechanism for this transformation was investigated by experimental and computational means, and found to involve most likely a gold(I) hydroxo species as the key intermediate (Scheme 1.27).



Scheme 1.27: Reaction of gold chloride complexes with arylboronic acids in the presence of a base.

Examples of Au(III)-B transmetalation are less abundant. In a seminal work, Bochmann and co-workers showed that (C,N,C)-pincer gold(III)-OH complexes react smoothly with either electron-rich or electron-poor boronic acids without an external base to afford the corresponding arylation products.^{108,109} In a subsequent study, the group of Nevado treated $[\text{Au}(\text{C}_6\text{F}_5)\text{Cl}_2(\text{PPh}_3)]$ complexes with electron-deficient arylboronic acids in the absence of a base to form stable $[\text{Au}(\text{C}_6\text{F}_5)(\text{Ar}^{\text{F}})\text{Cl}(\text{PPh}_3)]$ products. The reaction requires forcing conditions (150°C) and does not proceed with arylboronic acids lacking electron-withdrawing substituents on the aromatic ring.¹¹⁰

You and co-workers recently disclosed a catalytic cycle in which 2-(aryl)pyridine substrates react with Au(III) salts in the presence of *N*-fluorobenzenesulfonimide (NFSI) as a fluoride source and arylboronic acids to produce the corresponding $\text{C}_{\text{sp}^2}\text{-C}_{\text{sp}^2}$ coupling product on biaryl Au(III) intermediates.¹¹¹ The fluoride source was proposed to assist B-to-Au transmetalation *via* the formation of (a) Au(III)-F species or (b) through C-B bond cleavage assisted by noncoordinated fluoride anions. In seeking to ascertain the operating mechanism, Nevado and co-workers later on provided experimental evidence for a direct Au(III)-F/B transmetalation event preceding the $\text{C}_{\text{sp}^2}\text{-C}_{\text{sp}^2}$ bond formation.¹¹² Novel cyclometalated Au(III) complexes $[(\text{C},\text{N})\text{AuF}_2]$ and $[(\text{C},\text{N})\text{AuRF}]$ (R = aryl, alkyl) **81** were synthesized and the corresponding transmetalation products **82** between arylboronic acids were isolated (Scheme 1.28). Moreover, depending on the electronic and steric features of the boron counterpart and the electronic nature of the cycloaurated complex, either intra- or intermolecular reductive elimination products could be observed alongside.

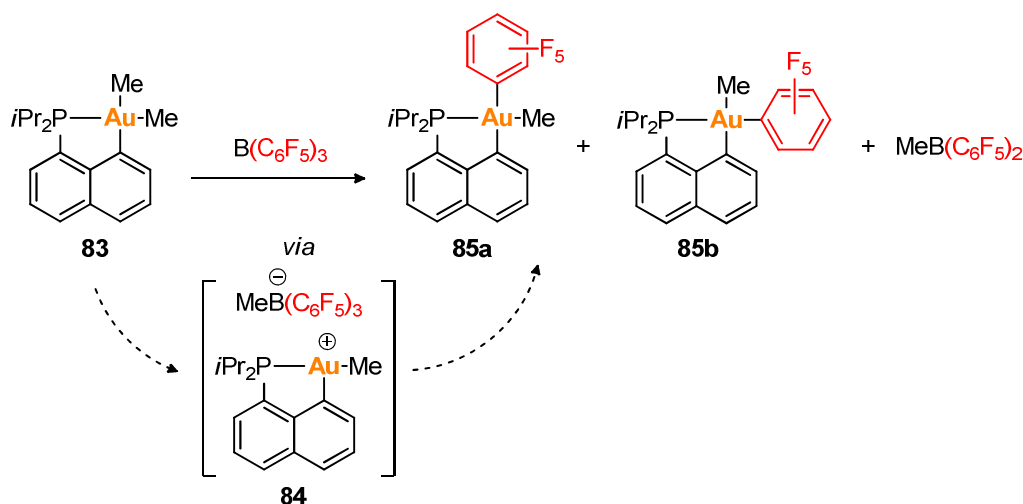


Scheme 1.28: Reaction of (C,N)-cyclometalated Au(III)-F complexes with arylboronic acids.

1.2.4.3 Boranes

Hansmann, Stephan, and Hashmi explored the reactivity of organogold species with the strong Lewis acid tris(pentafluorophenyl)borane $\text{B}(\text{C}_6\text{F}_5)_3$.¹¹³ In this work, an alkynyl fragment is abstracted by $\text{B}(\text{C}_6\text{F}_5)_3$ from L-gold(I) acetylides ($\text{L}=\text{NHC}$ or phosphine) to yield the corresponding alkynyl borate species, in which the alkyne is π -coordinated to the $[(\text{L})\text{Au}]^+$ fragment as characterized by different techniques. Upon prolonged heating at 60°C , these compounds undergo a slow C_6F_5 group transfer to the cationic gold fragment affording $(\text{NHC})\text{-AuC}_6\text{F}_5$ species.

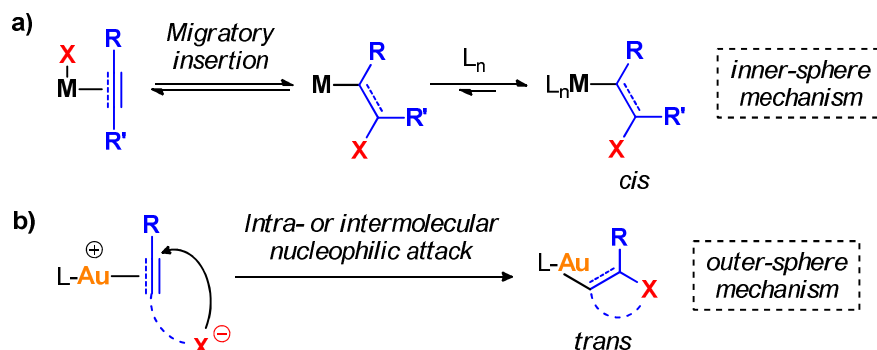
As a surrogate strategy to halide abstraction with silver salts to access cationic gold(III) methyl species with a free coordination site, Bourissou, Amgoune and co-workers investigated the reaction of a (C,P)-cyclometalated $\text{Au}(\text{III})\text{-(Me)}_2$ complex **83** with $\text{B}(\text{C}_6\text{F}_5)_3$ (Scheme 1.29).¹¹⁴ Instead, $\text{Me}/\text{C}_6\text{F}_5$ redistribution between gold and boron was observed, resulting in the net formation of two $[(\text{C,P})\text{AuMe}(\text{C}_6\text{F}_5)]$ isomers and $\text{MeB}(\text{C}_6\text{F}_5)_2$ by aryl group transfer from boron to gold. The formation of complexes **85a/85b** is thought to involve a tricoordinate cationic gold(III) methyl complex **84** and borate counteranion intermediates.



Scheme 1.29: Formation of neutral $\text{Au}(\text{III})$ complexes by $\text{Me}/\text{C}_6\text{F}_5$ redistribution between a (C,P)-cyclometalated $\text{Au}(\text{III})\text{-(Me)}_2$ and $\text{B}(\text{C}_6\text{F}_5)_3$.

1.2.5 Migratory Insertion

Transition metals react by the insertion of an unsaturated substrate (i.e. alkenes, alkynes, ketones, CO and related compounds) into and adjacent metal-ligand bond, $M\text{-X}$ (Scheme 1.30, a). The vacant coordination site created is generally filled by a Lewis base L .⁷⁴ These insertion processes take place within the coordination sphere of the metal center in a *syn* manner, with the X-type ligand ending up in *cis* position.



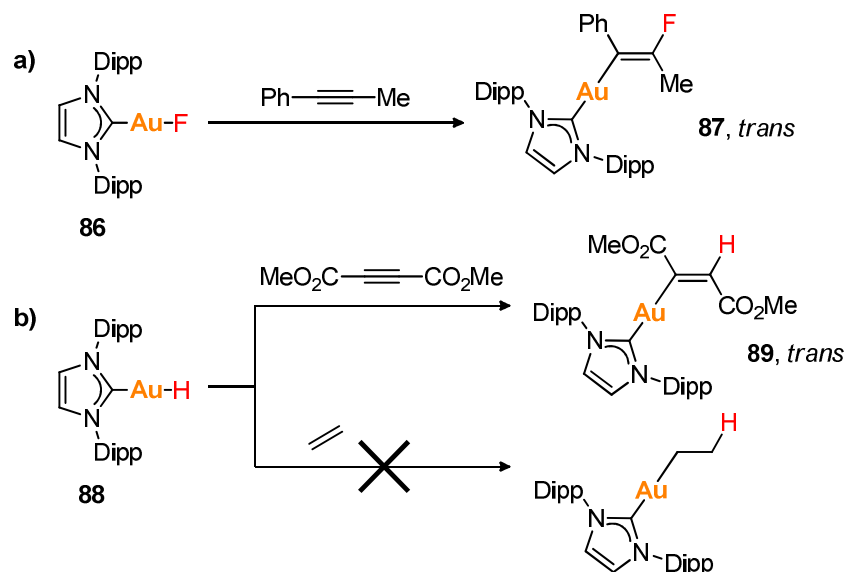
Scheme 1.30: General migratory insertion scheme of an unsaturated ligand at a transition metal (a) and gold-mediated addition of nucleophiles to C-C multiple bonds (b).

Whereas migratory *syn* insertion reactions are known for all transition metals, it remained elusive for gold complexes until 2015. Instead, cationic gold species activate C-C multiple bonds towards intra- or intermolecular nucleophilic attack rendering *trans* configured products, which is typical for outer-sphere and *anti* selective additions (Scheme 1.30, b).^{12,71} Although in some reports a *syn* addition/isomerization scheme was postulated in order to rationalize the observed *E*-selectivities in gold-catalyzed hydroamination of alkynes, allenes and alkenes,^{115–118} no experimental evidence for this pathway is available. Moreover, *E-Z* isomerization might also explain the obtained results.^{119,120}

1.2.5.1 Anti-Addition Reactions with Au(I) Complexes

Among the relevant literature on this topic, Sadighi and co-workers studied the reversible addition of a (NHC)-Au(I) fluoride complex **86** across several alkynes (Scheme 1.31, a).¹²¹ The vinylgold complex **87** isolated from the reaction with phenylacetylene displays a *trans* arrangement of the gold and fluoride atoms, which is in accordance with an outer-sphere mechanism proceeding *via* displacement of the fluoride, followed by nucleophilic *anti* addition to the π -coordinated alkyne.

In likewise manner, the same group reported the insertion of electron-deficient alkynes into the Au-H bond of a (NHC)-Au(I) hydride complex **88** (Scheme 1.31, b, top).¹²² The same stereochemical configuration was observed in the resulting vinylgold complexes **89**, which was tentatively rationalized either by a radical mechanism or by a *syn* insertion of the alkyne into the Au-H bond with subsequent isomerization. However, experimental data to support this mechanistic proposal is unavailable.



Scheme 1.31: Stoichiometric reactions between alkynes and (NHC)-Au(I) fluoride (a) and hydride (b, top) complexes. Attempted ethylene insertion into the Au-H bond of a (NHC)-Au(I) hydride complex (b, bottom). Dipp = (2,6-diisopropyl)phenyl.

In a combined experimental and theoretical study, the groups of Hashmi and Köppel concluded that terminal and non-activated alkynes, as well as olefins such as ethylene or norbornene, do not insert into the Au-H bond of the (NHC)-Au(I) hydride complex **88** even upon heating (Scheme 1.31, b, bottom).¹²³

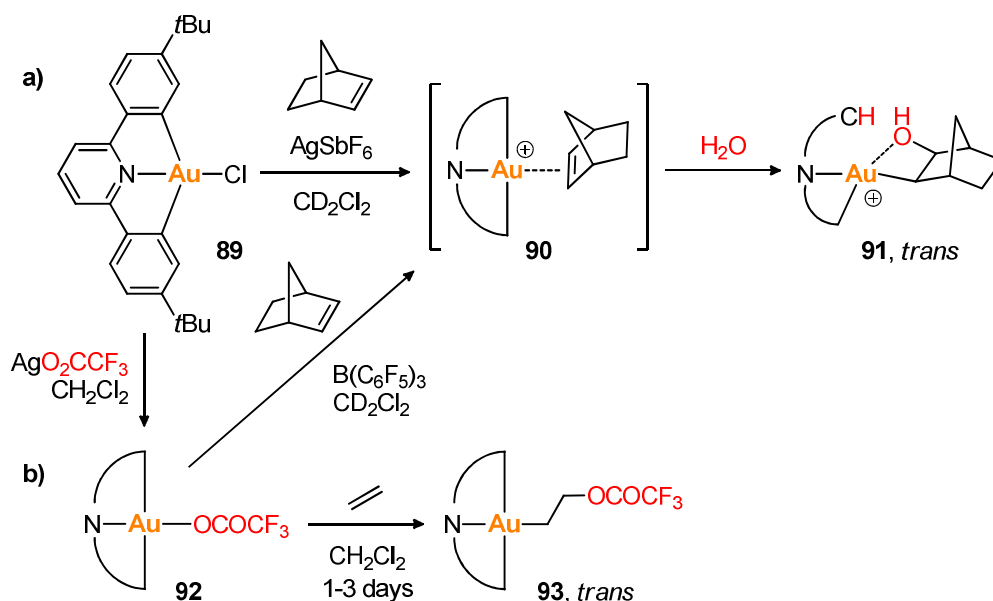
1.2.5.2 Anti-Addition Reactions with Au(III) Complexes

The d⁸ configuration of Au(III) species makes them better candidates for the insertion of insaturations. Several groups have developed strongly chelating ligand-embedded Au(III) complexes with the aim of enhancing their stability and gaining insights into the properties of the addition process.

Bochmann *et al.* reported on a gold(III) hydride (C,N,C)-pincer complex that is unreactive towards several alkynes and alkenes, in contrast to Sadighi's Au(I) hydride complex, but undergoes insertion reactions with allenes, yielding regioselectively Au(III)-vinyl complexes.¹²⁴ Notably, substitution of the hydride by a more labile trifluoroacetate ligand permits the slow but quantitative insertion of ethylene into the Au(III)-OCOCF₃ bond at room temperature (Scheme 1.32, b).¹²⁵

A different synthetic approach was tried in order to achieve olefin insertion. An analogous (C,N,C)-Au(III)Cl complex **89** was reacted with AgSbF₆ at -40°C, and the available coordination site generated was occupied by norbornene (Scheme 1.32, a). Upon heating up to room temperature the norbornolyl complex **91** was obtained after nucleophilic attack by OH⁻ (coming from adventitious water) on the coordinated norbornene, while the Au-Ph bond was acidically cleaved. The solid-state structure of **91** shows that the norbornene is bonded by its *exo* face, as is usually observed in outer-

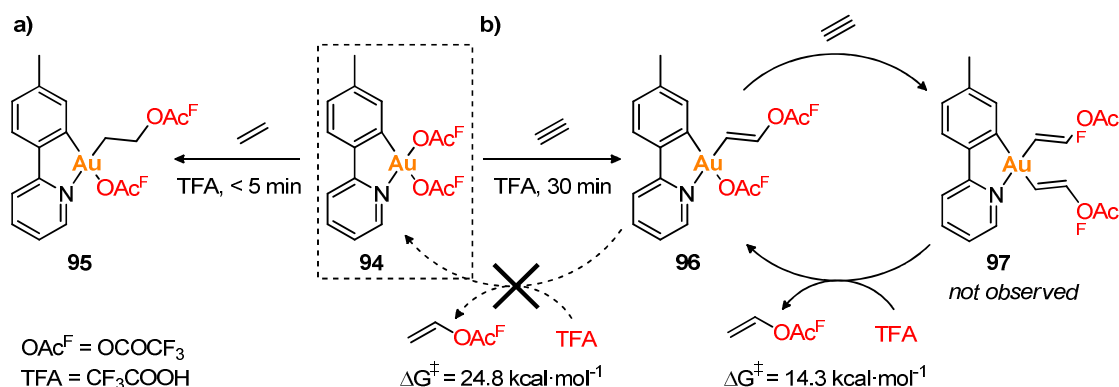
sphere mechanisms. Overall, the (C,N,C)-pincer complexes do not appear to be suitable for migratory *syn* insertions because they lack the requisite vacant site for a coordination/addition process.



Scheme 1.32: Nucleophilic attack on an Au(III)-norbornene complex (a) and insertion of ethylene into an Au(III)-trifluoroacetate bond (b).

The mechanism for the insertion of ethylene into an Au-O bond of the (C,N)-cyclometalated $[\text{Au}(\text{tpy})(\text{OCOCF}_3)_2]$ complex **94** (tpy = 2-(*p*-tolyl)pyridine) was deeply explored by the group of Tilset by combining experimental and theoretical investigations (Scheme 1.33, a).¹²⁶ According to deuterium-labeling experiments, ethylene *anti* inserts into the Au-O bond *trans* to N of the chelating ligand after the trifluoroacetate ligand is displaced by ethylene *via* an associative mechanism. In contrast, *syn* insertion of the coordinated ethylene through an inner-sphere pathway was found to be much less favorable. Strikingly, a catalytic process was not accessible because complex **95** resists protolytic cleavage of the Au-C_{sp3} bond.

In a recent study, however, the same group revealed that the $[\text{Au}(\text{tpy})(\text{OCOCF}_3)_2]$ complex **94** can catalyze the *anti* addition of trifluoroacetic acid to acetylene.¹²⁷ The detailed empirical and computational evidence gathered suggests initial formal acetylene insertion (i.e., coordination and nucleophilic attack of the dissociated trifluoroacetate at the site *trans* to tpy-N) to furnish complex **96** (Scheme 1.33, b). Interestingly, protolytic cleavage of the vinyl group in **96** does not occur, and thus a second insertion of acetylene *trans* to tpy-C is required, yielding an undetected Au(III) divinyl species **97** as a crucial intermediate for which the true catalytic activity occurs at the site *trans* to tpy-C. The more facile protolytic cleavage of the Au-vinyl bond *trans* to tpy-C ($\Delta G^\ddagger = 14.3 \text{ kcal}\cdot\text{mol}^{-1}$) as compared to that *trans* to tpy-N ($\Delta G^\ddagger = 26.8 \text{ kcal}\cdot\text{mol}^{-1}$) in **97** is a result of the higher *trans* effect of tpy-C versus tpy-N on each reaction step.



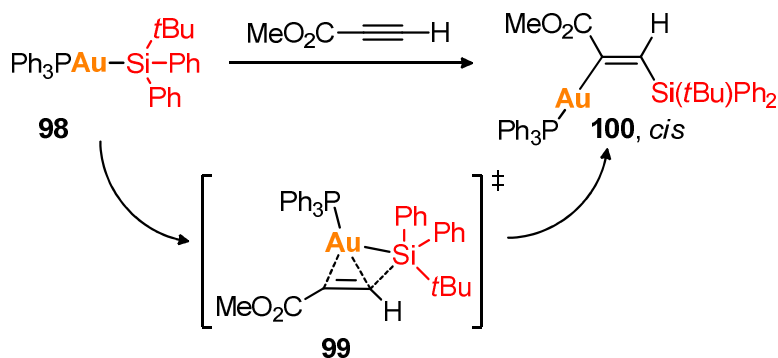
Scheme 1.33: Formal insertion of ethylene at $[\text{Au}(\text{tpy})(\text{OAc}^F)_2]$ (a) and double insertion mechanism for the catalytic trifluoroacetylation of acetylene (b).

1.2.5.3 Migratory Syn Insertions with Au(I) Complexes

As commented in the previous sections, the coordination of a third ligand to linear two-coordinate Au(I) complexes is disfavored owing to a high deformation energy. This represents a major hurdle for the implementation of migratory *syn* insertions at Au(I) complexes.

There is, however, a marked exception to this trend. Amgoune, Bourissou and co-workers provided evidence that internal and terminal alkynes, as well as allenes, can insert readily into the Au-Si bonds of $[\text{Au}(\text{SiPh}_2\text{R})(\text{PPh}_3)]$ complexes in a *syn* fashion.¹²⁸ The reaction is broad in scope and gives access to a variety of stable β -silyl vinylgold compounds, with a *cis* arrangement of the gold and silicon atoms in all cases.

Joint experimental and computational studies give credence to an inner-sphere mechanism for the insertion reaction.¹²⁹ π -Coordination of the alkyne to the silylgold complex **98** gives rise to a three-coordinate intermediate **99**, which then forms the vinylgold complex **100** by migration of the silyl moiety onto the alkyne with concomitant Au-C bond formation (Scheme 1.34). This particularly unusual reactivity may have its origin in the distinct electronic properties of the silyl ligand, especially in its strong σ -donor character.

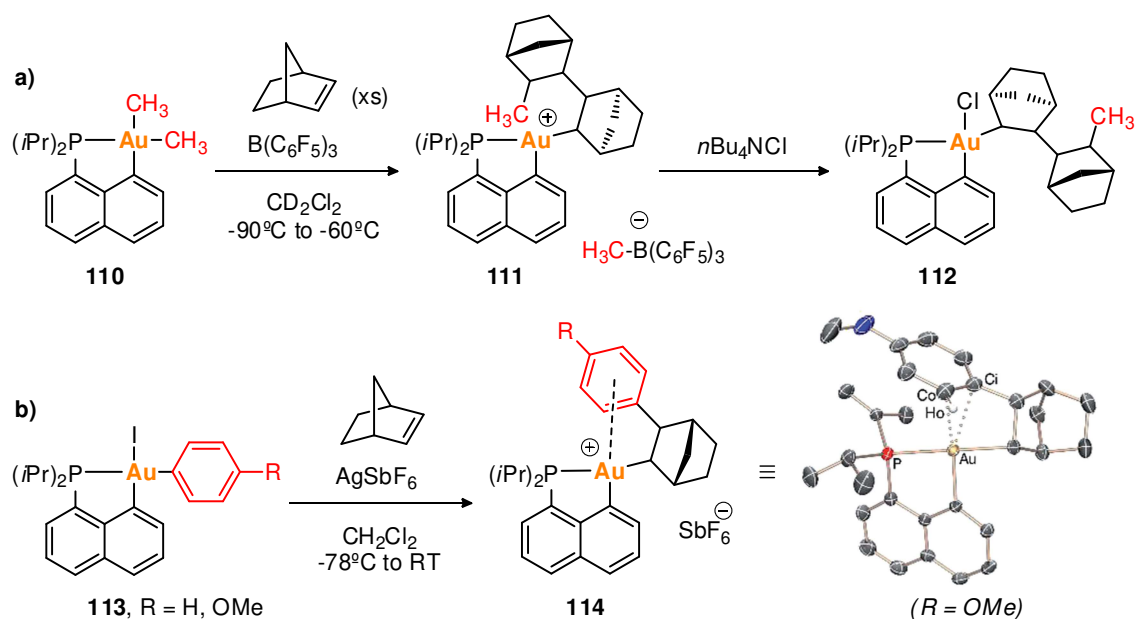


Scheme 1.34: *Syn* insertion of methyl propiolate into an Au-Si bond and computed transition state.

1.2.5.4 Migratory *Syn* Insertions with Au(III) Complexes

Similarly to Au(I) complexes, migratory *syn* insertions of Au(III) species remained unprecedented until 2015. From then on, however, a series of results corroborate that Au(III) complexes hold promise to open up new avenues into gold-mediated *syn* insertion processes.

In the pioneering example, the group of Bourissou abstracted a methide from a discrete (C,P)-cyclometalated gold(III) dimethyl complex **110** with B(C₆F₅)₃ (Scheme 1.35, a).¹¹⁴ As mentioned before (section 1.2.4.3), the cationic complex generated is highly reactive and evolves spontaneously by C₆F₅ transfer from boron. While in the presence of olefins such as ethylene and styrene no further reactivity was observed, norbornene easily inserts into the Au-methyl bond at -60°C. The ensuing norbornyl complex **111** decomposes rapidly at low temperature (despite its stabilization by γ -CH agostic interaction),¹³⁰ and hence trapping by pyridine or chloride to give thermally stable four-coordinate adducts **112** was required. The crystal structure of the chloride complex revealed that two norbornene units inserted on the *exo* face and in a *syn* manner, consistent with an inner-sphere mechanism. The double insertion of norbornene gives access to a more thermodynamically stable complex bearing the Au-norbornyl bond in the *trans* position relative to P (weaker *trans* influence).¹³¹



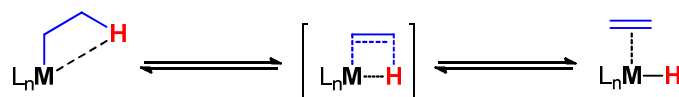
Scheme 1.35: Formation of gold(III) norbornyl complexes upon insertion of norbornene into an Au-Me (a) and an Au-Ph bond (b). Right, bottom: Molecular structure determined by single crystal X-ray diffraction of complex **114**, displaying the η^2 -coordination of the remote aryl ring to the Au(III) center.

The same (C,P) chelate framework has been utilized to investigate the insertion of norbornene and also ethylene into Au(III)-aryl bonds (Scheme 1.35, b).¹³² The formation of the active tricoordinate intermediate was achieved in this case with halide scavenger AgSbF₆. Both olefins mono-insert (the barrier for isomerization is lower than for a second insertion, in contrast to the Au(III) dimethyl complex). Besides, it is worth

mentioning that, in the case of ethylene, β -hydride elimination leading to the release and reinsertion of styrene was observed (see following section). Remarkably, the resulting Au(III) alkyl complexes **114** exhibit higher stability than the previous Au(III) methyl derivative due to intramolecular η^2 -coordination of the remote aryl ring to gold. This interaction was substantiated by different techniques, including X-ray diffraction analysis (see Scheme 1.35, b).

1.2.6 β -Hydride Elimination

β -Hydrogen elimination from metal-alkyl complexes is the microscopic reverse of migratory insertion of alkenes into M-H bonds, and therefore it generates a metal hydride species and an olefin.⁷⁴ β -Hydrogen eliminations require the presence of an open coordination site at the metal prior to the C-H bond cleavage step, which explains the reluctance to undergo such a process of coordinatively saturated transition metal-alkyl complexes lacking a *cis* coordination site.



Scheme 1.36: General mechanism of β -Hydride elimination.

Contrary to the other transition metals, gold(I) generally does not engage in β -elimination or migratory insertion processes,³ which is demonstrated by the isolation and thermal stability of numerous gold alkyl complexes, further inhibiting Au(I)/Au(III) cycles from operating.^{133,134}

The low propensity of Au(I) alkyl complexes to undergo β -hydride elimination was corroborated by Köppel, Hashmi and co-workers, who studied experimentally and computationally the elimination of ethylene from an (NHC)-Au(I) ethyl complex (the reverse reaction of the aforementioned migratory insertion, see Scheme 1.31).¹³³ DFT calculations predicted a prohibitively high barrier ($\Delta G^\ddagger = 49.7 \text{ kcal}\cdot\text{mol}^{-1}$) for this process, with formation of a transient high-energy tricoordinate Au(I) hydride ethylene species ($\Delta G = 33.0 \text{ kcal}\cdot\text{mol}^{-1}$) (Figure 1.4). The [Au(Et)(IPr)] complex decomposed at around 180°C, but not through the envisioned β -hydride elimination route.

The absence of reactivity was attributed to the filled 5*d*-shell of Au(I) complexes, preventing the hydrogen-metal interaction necessary for the elimination to occur. Nonetheless, these interactions might exist in case of Au(III) compounds, for which empty 5*d* orbitals are available. Indeed, this hypothesis found preliminary support in an example by Toste and Mankad, in which the authors reported the formation of alkenes derived from a formal β -hydride elimination process at an NHC alkylgold(III) fluoride complex, albeit the corresponding NHC-Au(III)-hydride was not detected.¹³⁵

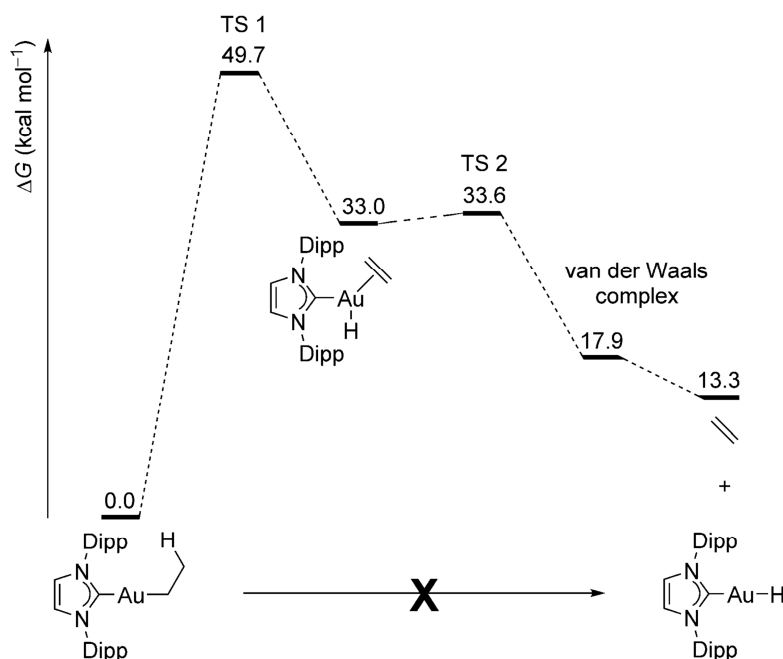
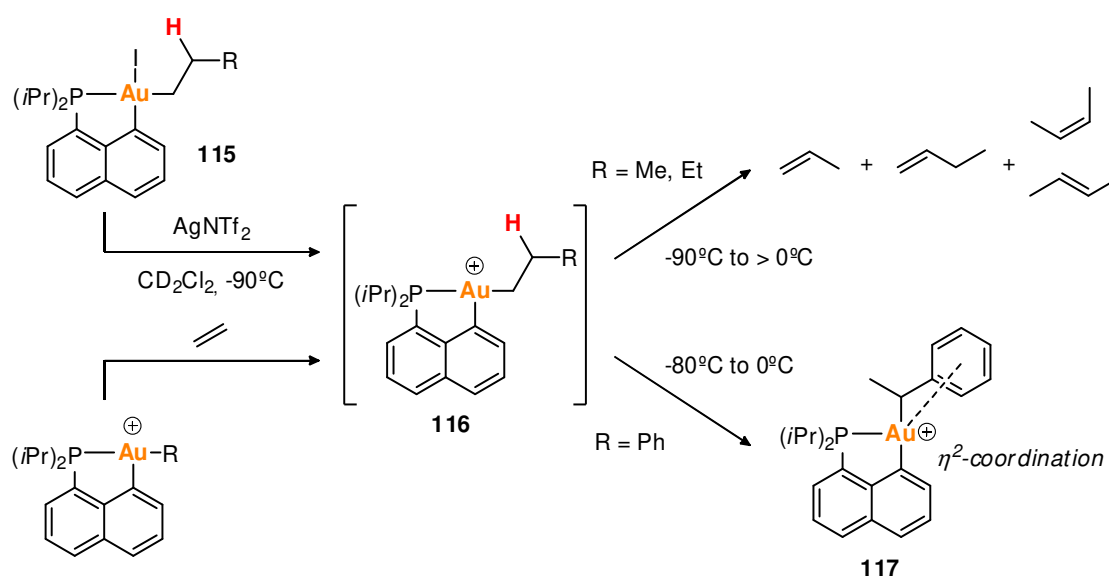


Figure 1.4: Computed reaction profile for β -hydride elimination from an (NHC)-Au(I) ethyl complex. Taken from ref. 12. Dipp = (2,6-diisopropyl)phenyl.

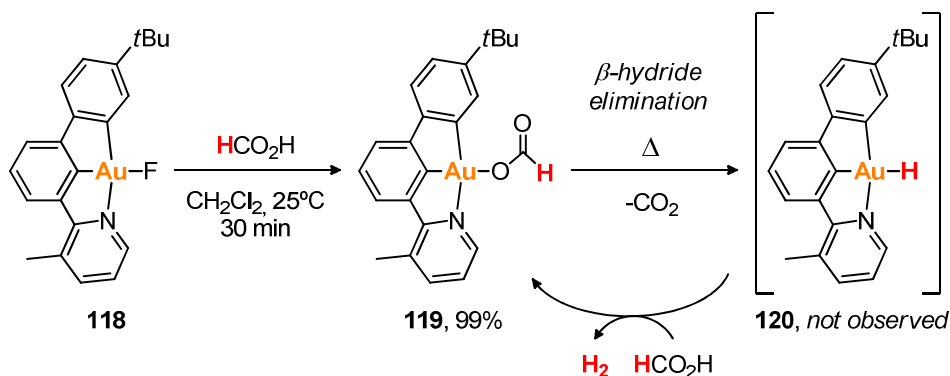
The occurrence of β -hydride elimination at Au(III) complexes received a major boost in 2016. Taking advantage of a phosphino-naphthyl (C,P) chelate, the group of Bourissou prepared cationic gold(III) alkyl complexes **116** and systematically investigated their fate by means of variable temperature NMR spectroscopy (Scheme 1.37).¹³⁶ The formation of propylene, 1-butene and 2-butenes from the Au(III) *n*-propyl and *n*-butyl complexes validates their decomposition *via* a β -hydride elimination pathway. In the case of the gold(III) *n*-butyl complex, olefin isomerization takes place after β -hydride elimination through sequential reinsertion into the Au-H bond.



Scheme 1.37: Formation of cationic Au(III) alkyl complexes **116** and reaction outcomes upon β -hydride elimination/reinsertion sequences.

β -Hydride elimination has also been observed after insertion of ethylene into cationic gold(III) methyl and gold(III) phenyl complexes. With regard to the first complex, propylene and 1-butene were formed, the latter resulting from two successive reinsertions of ethylene into Au-H and then Au-Et bonds, followed by β -hydride elimination. Concerning the Au(III) phenyl complex, it eliminates styrene and subsequently reinserts it into the Au-H to generate complex **117** (Scheme 1.37).¹³² Note that the arene coordination to the Au(III) center disfavors further β -hydride elimination from complex **117**.

Last, in a very recent work the group of Nevado has presented the synthesis of a gold(III)-formate complex **119** from a gold(III)-fluoride precursor **118** stabilized by a (N,C,C) pincer ligand and acid formic (Scheme 1.38).¹³⁷ This complex undergoes β -hydride elimination upon heating, leading to carbon dioxide liberation and a putative gold(III) hydride species **120** that was not experimentally detected. Interestingly, a catalytic system for the dehydrogenation of formic acid could also be designed, in which the highly reactive gold(III)-hydride reacts with formic acid to release molecular hydrogen and regenerate the gold(III)-formate complex, thereby closing the catalytic cycle.

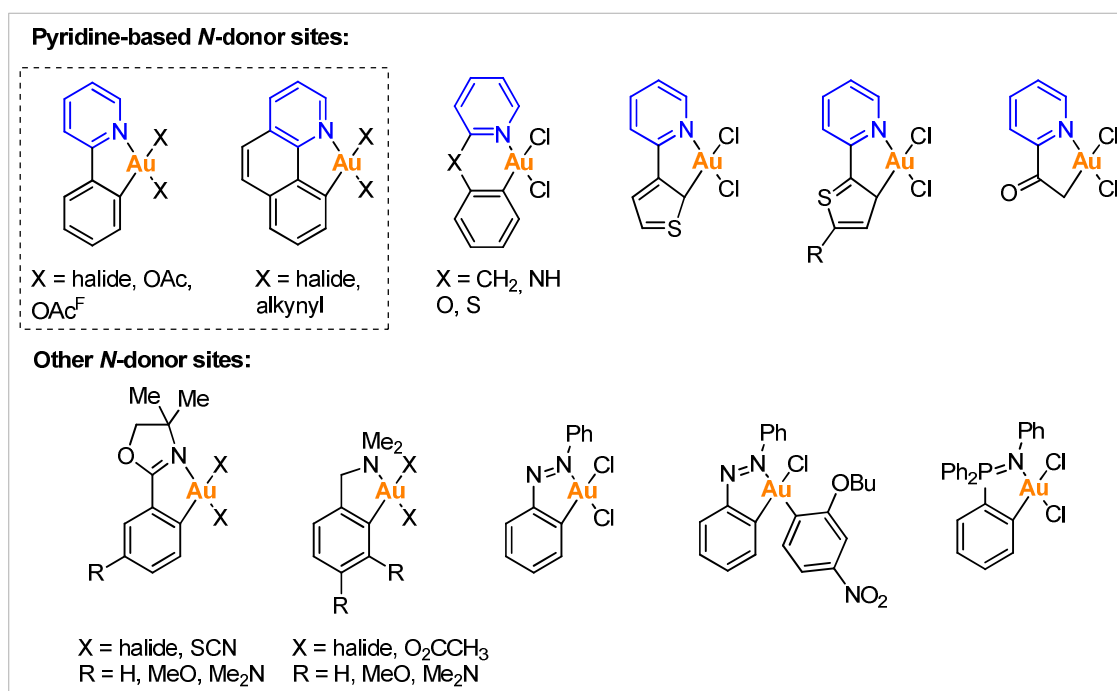


Scheme 1.38: Synthesis of (N,C,C)-Au(III)-formate complex **119** and catalytic dehydrogenation of formic acid mediated by a putative (N,C,C)-Au(III)-hydride intermediate **120**.

1.3 (C,N)-CYCLOMETALATED Au(III) COMPLEXES

The propensity of Au(III) complexes towards reduction to Au(I) and the challenges associated with their synthesis has limited their exploration in the field of organometallic chemistry.^{138,139} In this perspective, ligand templates play a critical role in enabling the stabilization of high-valent Au(III) in the form of cyclometalated complexes. Cycloauration reactions afford products featuring usually five- or, less frequently, six-membered rings, analogous to the broadly studied d^8 -square planar Pd(II) and Pt(II) systems L_2MCl_2 . The exquisite balance between stabilization and reactivity granted by cyclometalating ligands has led to the development of novel gold(III) species with properties transcending multiple research disciplines, including catalysis, medicinal chemistry and material science.^{2,140}

Two areas of research gaining prominence comprehend the extensive studies on the potential antitumour activity and photophysical properties of gold(III) complexes. Au(III) compounds are intrinsically four-coordinate and feature square planar geometries, as also found for $[PtCl_2(NH_3)_2]$ (cisplatin), so that a related mechanism of action (i.e., interaction with DNA and disruption of normal cell division processes) might be assumed for these compounds. Since Au(III) is usually regarded as oxidizing, a key factor that needs to be overcome is their tendency to decompose in the reducing mammalian environment.¹⁴¹ In this regard, judicious choice of cyclometalating ligands can impart stability to the higher oxidation state of gold. On the other hand, investigations have been carried out concerning the luminescent properties of Au(III) species, which can serve as dopants for OLEDs (organic light-emitting diodes).¹⁴² The presence of low-lying metal-centered orbitals in the gold(III) complexes makes them quite susceptible for thermal population at ambient temperatures leading to nonradiative relaxation of the excited state.¹⁴³

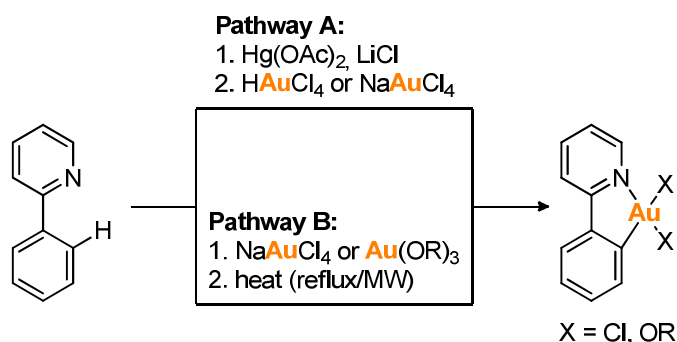


Scheme 1.39: Representative examples of five- or six-membered[(C,N)AuX₂]cyclometalated complexes.

A myriad of cyclometalated complexes have been disclosed in the past decades, most commonly containing an Au(III)-aryl bond, with (C,N,C)¹⁴⁴ and (N,C,C)¹⁴⁵ pincer ligands representing the most profusely investigated scaffolds. Other templates comprise prevalent (C,N)¹⁴⁶ and (N,N)¹⁴⁷ or rarer (C,C)¹⁴⁸ and (C,P)⁸¹ chelates, giving access to mono-cyclometalated Au(III) species.⁸³ Among the chelating (C,N)-type ligands, 2-aryl substituted pyridines have been predominantly used, although metalation sites have also been expanded to C_{sp3}-hybridized atoms or thiophene pendant groups, and *N*-donor sites from amines, imines, oxazoline and diazo compounds (representative overview in Scheme 1.39). In the forthcoming section, only five-membered (C,N)-Au(III) complexes arising from 2-phenyl substituted pyridine ligands are surveyed, since their synthesis and reactivity is in part a subject of investigation in this thesis. The discussion covers general aspects of their synthesis and reactivity.

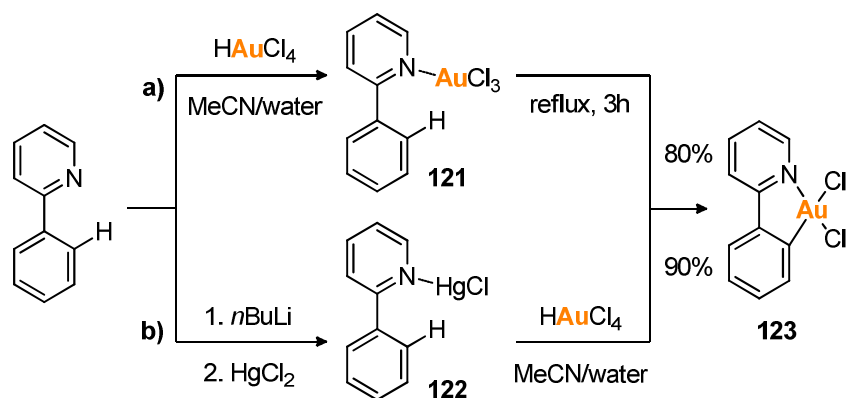
1.3.1 Synthetic Approaches

Essentially, two main synthetic routes have been applied in order to access (C,N)-cyclometalated Au(III) complexes (Scheme 1.40): (a) transmetalation reactions involving an organomercury precursor and (b) pyridine-coordination followed by direct C-H auration upon heating or microwave conditions, both strategies employing Au(III) salts as gold source. Notably, in the past two years oxidative addition of aryl iodides and aryl diazonium salts to Au(I) has been devised as an alternative pathway.



Scheme 1.40: Synthetic methodologies to cycloaurated phenylpyridine complexes.

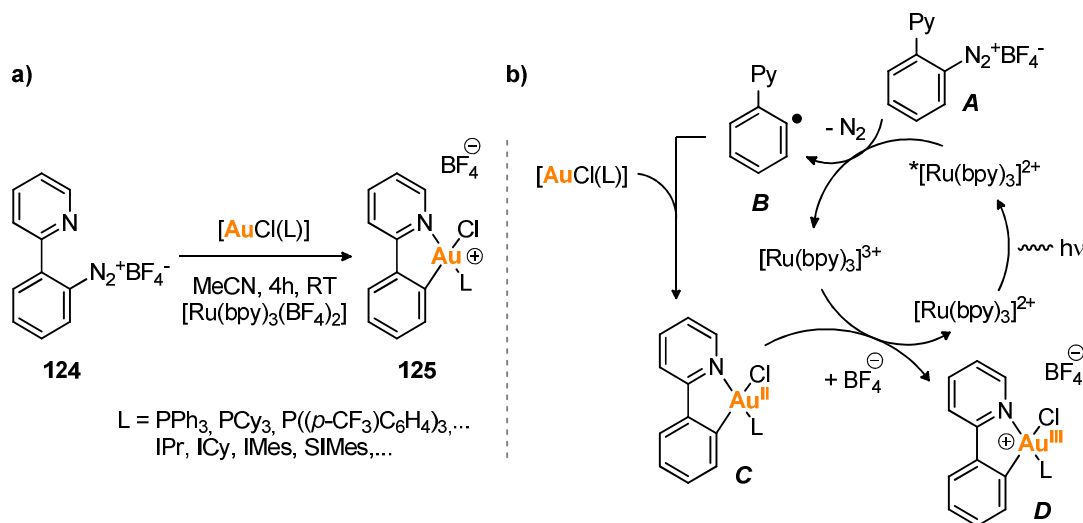
The first contribution in this area was reported by Constable and Leese in the late 1980's.¹⁴⁹ 2-phenylpyridine was treated at room temperature with HAuCl₄ or NaAuCl₄, leading to the formation of the yellow *N*-coordinated complex **121** (Scheme 1.41, a). Upon heating in aqueous acetonitrile the cyclometalated complex **123** was obtained. In the same work, the authors showed that this complex can also be prepared by transmetalation of HAuCl₄ with (ppy)HgCl **122** (ppy = 2-phenylpyridine) (Scheme 1.41, b). The organomercury compound was prepared by reaction of the starting ligand with *n*-butyl lithium, followed by treatment of the resulting organolithium with HgCl₂. This strategy was extended by Parish *et al.* to the synthesis of a range of complexes containing various substituents on the pyridine ring.¹⁵⁰ The inherent toxicity of the organomercury derivatives represents the main drawback of this methodology.



Scheme 1.41: C-H auration (a) and transmetalation with organomercury compounds (b) to [Au(ppy)Cl₂].

Similar dihaloauracycles [Au(tpy)X₂] (tpy = 2-(*o*-tolyl)pyridine, X = Cl, Br) can be easily accessed by small modifications of the established protocol, for instance by using AuX₃ in *t*-BuOH solvent and warming up to 130°C in a MeCN/water mixture.¹⁵¹ On the other hand, and apart from classical heating conditions, Tilset and co-workers have successfully synthesized [Au(OAc^F)₂(tpy)] complex using microwave heating procedure (see Scheme 1.40, pathway B).^{152,153} Under the reaction conditions described, the acetate ligands of the gold source Au(OAc)₃ exchanged with more labile trifluoroacetate ligands coming from the TFA solvent.

As an alternative approach to these protocols, Glorius *et al.* devised a method to access (C,N)-cyclometalated Au(III) complexes through photomediated oxidative addition of aryldiazonium salts **124** with a 2-(pyridin-2-yl) pendant group to Au(I) complexes (Scheme 1.42, a).⁵⁶ Upon irradiation with visible-light and in the presence of [Ru(bpy)₃](BF₄)₂ photocatalyst, the authors synthesized several cationic complexes **125** bearing a variety of phosphine and *N*-heterocyclic carbene ligands. Furthermore, this mild methodology provides direct experimental support to the key proposed sequential oxidative addition to Au(I) in dual gold/photoredox catalysis (see section 1.1.2.2.).^{54,55}



Scheme 1.42: Photoredox-initiated oxidative addition of aryldiazonium salts to different Au(I) chlorides (a), and mechanistic proposal (b).

A rather unusual mechanistic hypothesis was postulated by the authors (Scheme 1.42, b). In this scenario, aryl radicals **B** are formed upon Ru-catalyzed photoredox decomposition of the aryldiazonium salt **A**. The photogenerated aryl radical **B** then adds to the Au(I) precursor to afford the open-shell Au(II) intermediate **C**. This unstable species is expected to rapidly donate an electron to oxidized Ru(III), regenerating the Ru(II) catalyst and affording a highly electrophilic Au(III) species **D**.

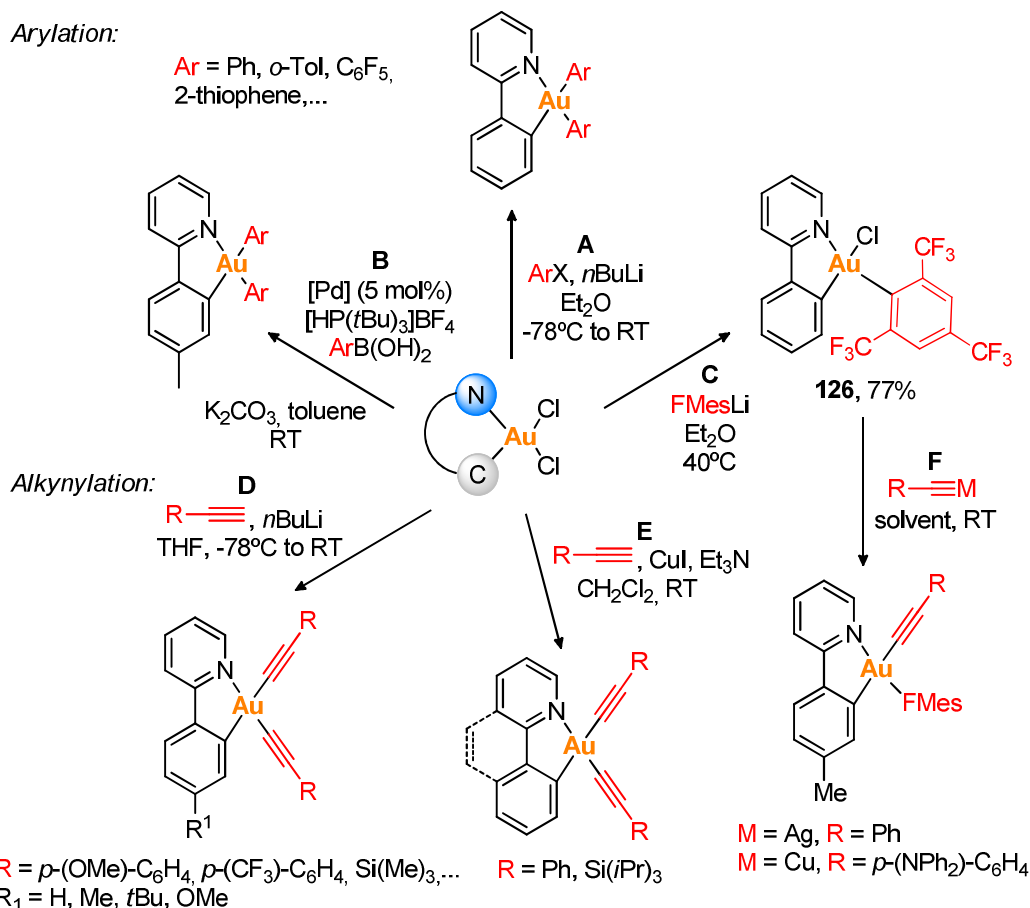
1.3.2 Reactivity

1.3.2.1 Arylation, Alkylation and Alkynylation

Cyclometalated complexes of the type $[\text{Au}(\text{L})\text{Cl}_2]$ (L = derivatives of 2-phenylpyridine) can be functionalized by replacement of the chloride ligands by aryl, alkyl and alkynyl groups in very straightforward manners.

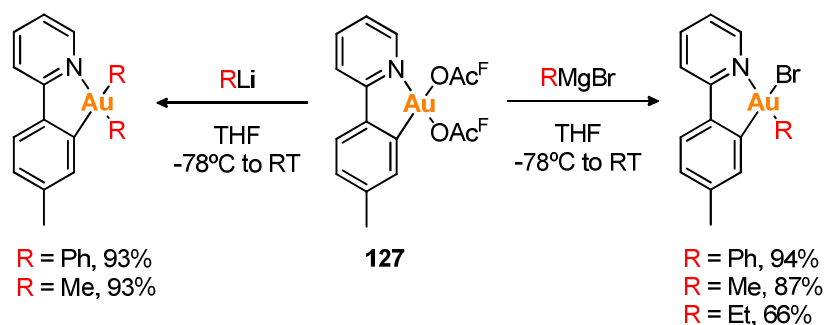
Preliminary investigations by Vicente *et al.* enabled the synthesis of biaryl-substituted complexes from stable $[\text{Au}(\text{ppy})\text{Cl}_2]$ precursors by reaction with the corresponding lithiated arenes in dry diethyl ether at -78°C (Scheme 1.43, pathway **A**).¹⁵⁴ The complexes obtained were deemed susceptible to undergo reductive elimination yielding biaryls and Au(I) species.¹⁵⁵ Higher stabilities were sought by using electron-poor arene sources.¹⁵⁶ In a similar manner, reaction of lithiated 2,4,6-tris(trifluoromethyl)phenyl (FMesLi) with $[\text{Au}(\text{ppy})\text{Cl}_2]$ yields the monoarylated complex **126** (Scheme 1.43, pathway **C**).¹⁵⁷ The chloride can be further displaced by Cu(I) and Ag(I) acetylides generated in situ, delivering complexes with emission properties (Scheme 1.43, pathway **F**). Alternatively, arylation of $[\text{Au}(\text{tpy})\text{Cl}_2]$ can be attained *via* a Pd-catalyzed Suzuki-Miyaura coupling of arylboronic acids (Scheme 1.43, pathway **B**).¹⁵⁸ The protocol works under mild operating conditions and tolerates a broad range of substituents on the arylboronic acid counterpart.

The alkynylation of dichloride complex $[\text{Au}(\text{ppy})\text{Cl}_2]$ follows a route equivalent to that described for the arylation but using Li-alkynyl species to produce luminescent dialkynyl complexes with low to moderate yields (Scheme 1.43, pathway **D**).¹⁵⁹ Related compounds were obtained employing terminal alkynes in the presence of triethylamine and a catalytic amount of CuI to achieve the desired ligand exchange (Scheme 1.43, pathway **E**), analogously to pathway **F**.¹⁶⁰



Scheme 1.43: Arylation and alkynylation procedures of dichloride $[\text{Au}(\text{ppy})\text{Cl}_2]$ complex.

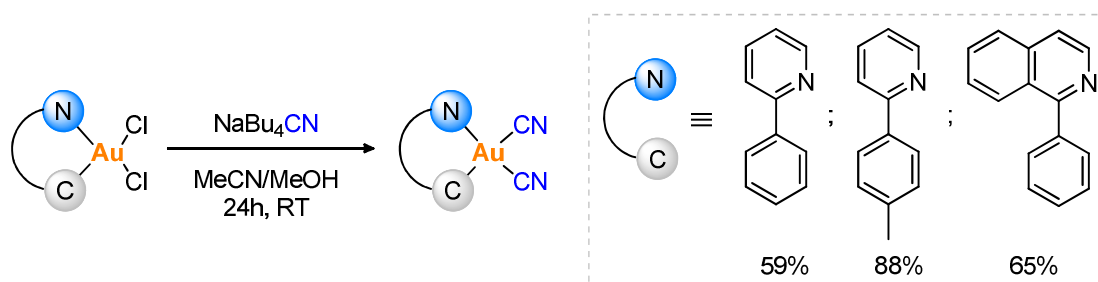
In order to improve the reaction outcomes of the preceding arylation protocols, chloride ligands can be replaced by more labile trifluoroacetato ligands. Tilset and co-workers reported the selective mono- and diarylation of complex $[\text{Au}(\text{tpy})(\text{OAc}^{\text{F}})_2]$ **127** with Grignard or lithium reagents, respectively, at low temperature (Scheme 1.44).¹⁵³ This methodology also gives access to mono- and dialkylated complexes. As expected, when $[\text{Au}(\text{tpy})(\text{Cl})_2]$ was subjected to the same conditions, longer reaction times were required with lithium reagents compared to starting from $[\text{Au}(\text{tpy})(\text{OAc}^{\text{F}})_2]$, whereas much poorer selectivity and yield were observed with the Grignard reagents.



Scheme 1.44: Selective mono- and dialkylation of complex $[\text{Au}(\text{tpy})(\text{OAc}^{\text{F}})_2]$.

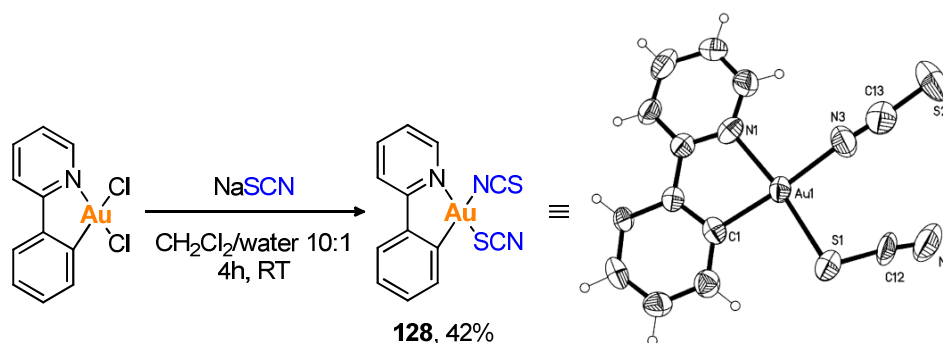
1.3.2.2 Cyanation and Thiocyanation

A well-recognized strategy to enhance the luminescent properties of (C,N)-cyclometalated Au(III) complexes is the incorporation of strong σ -donor ligands, which results in increased splitting of non-emissive d-d states. In this context, the use of cyanides represents an attractive option: their strong σ -donor character also stabilizes the complexes through a reasonable extent of π -back bonding and therefore prevents reductive elimination. As reported recently, these complexes can be readily prepared by reaction of the corresponding Au(III)-dichloro precursors with tetrabutylammonium cyanide in a MeCN/MeOH mixture (Scheme 1.45).¹⁶¹ The ensuing complexes are bench-top stable and easy to handle, contrary to the diaryl and dialkynyl complexes previously mentioned, where electronic modification with functional groups was necessary to impart stability.



Scheme 1.45: Synthetic procedure for Au(III) dicyano complexes featuring different pyridine-based cyclometalating ligands.

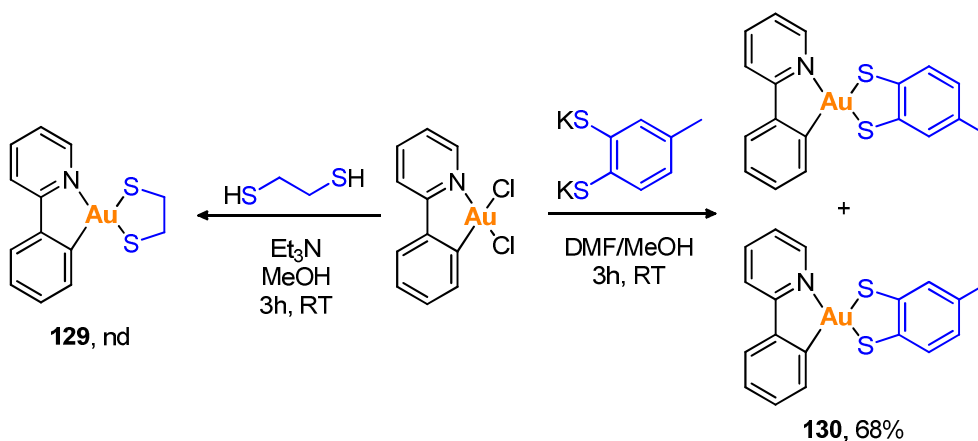
In likewise manner, reaction of [Au(ppy)(Cl)₂] with NaSCN affords the bis(thiocyanato) complex [Au(ppy)(SCN)₂] **128** (Scheme 1.46).¹⁶² Interestingly, X-ray diffraction analysis showed the two thiocyanate ions in their ambidentate nature (Scheme 1.46, right). Hence, the thiocyanate *cis* to the high *trans*-influence aryl carbon is S-bonded, while the other thiocyanate is N-bonded, with the Au-NCS group linear whereas the Au-SCN is bent. This complex exhibited promising *in vivo* cytotoxicity against human leukemia cells.



Scheme 1.46: Thiocyanation of [Au(ppy)(Cl)₂] (left), and ORTEP diagram showing the two binding modes of thiocyanate ions (right).

1.3.2.3 Dithiolation

A number of derivatives formed by reaction of (C,N)-cyclometalated Au(III) dihalide complexes with dithiol-based chelating ligands have been synthesized, generally starting from $[\text{Au}(\text{ppy})(\text{Cl})_2]$ precursor. The standard protocol involves either treatment with the corresponding dithiol in the presence of a mild base,¹⁶³ or reaction with direct 3,4-toluenedithiolate potassium salts, the latter giving the mixture of isomers **130** (Scheme 1.47).¹⁶⁴ X-ray structure determinations on the ensuing complexes revealed that the Au-S bond *trans* to the Au-C bond is longer than that *trans* to the pyridine moiety, as a result of the high *trans*-influence of the aryl donor. Neither Au(III) complex displays emissive properties.



Scheme 1.47: Synthesis of different (C,N)-cyclometalated Au(III) complexes with dithiolate donor ligands.

1.4 References

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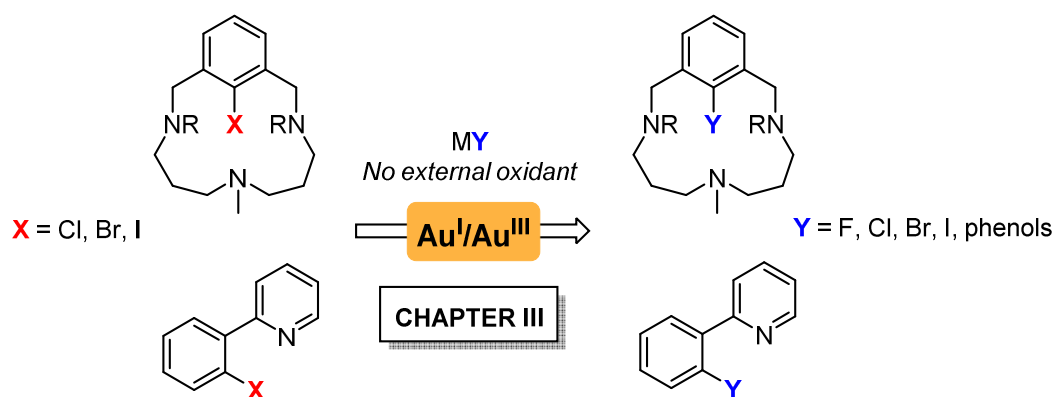
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CHAPTER II

OBJECTIVES

As illustrated in the introduction, the in-depth comprehension of the precise aspects controlling the reactivity of gold complexes has been restricted for a long time. Fundamental organometallic reactions such as C-X bond activation processes *via* oxidative addition, migratory insertions or β -hydride elimination, well known for the adjacent group-10 metals and often encountered in many catalytic cycles, have only been substantiated for gold complexes in the very recent years. However, due to the challenging access to the high-valent Au(III) intermediate species operating in these processes, our knowledge on the factors governing the reactivity of gold complexes is still scarce or even non-existent. Therefore, the aim of the research projects presented in this dissertation was to gain further knowledge in regard of these elementary reactions and their mechanistic insights.

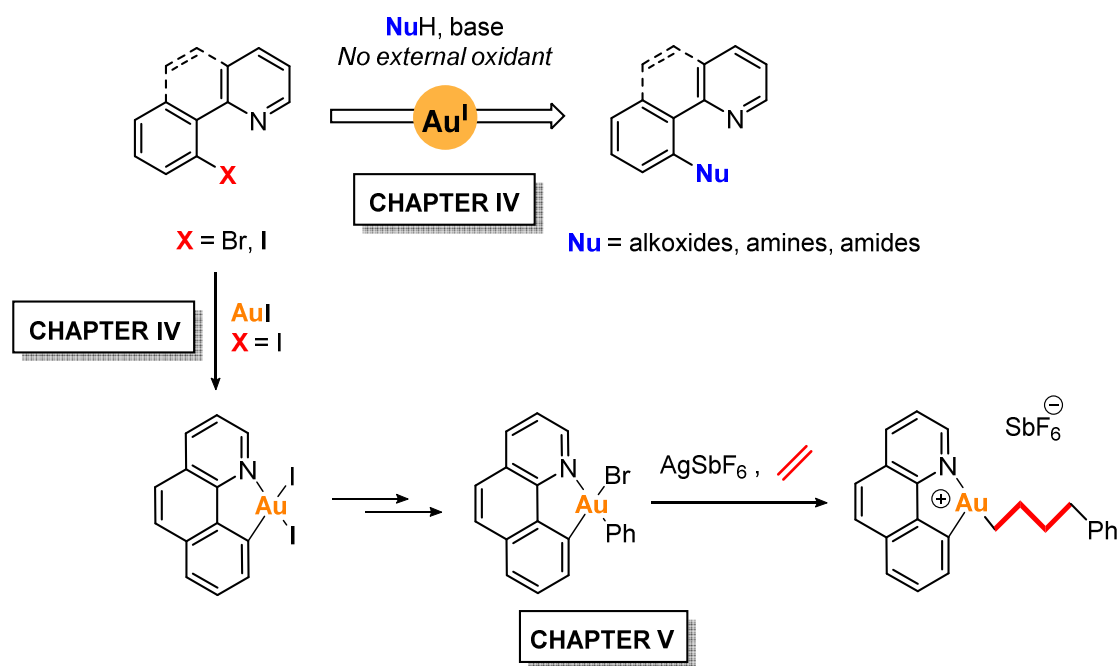
In the first place (Chapter III) we strived to evaluate the plausibility of two-electron processes involving oxidative addition and reductive elimination in oxidant-free gold-catalyzed cross-coupling reactions. For this purpose, we followed a strategy based on attaching an appendage to aryl halide substrates featuring three nitrogen coordination sites available to assist the stabilization of putative Au(III) species by chelation. Indeed, this approach has proven fruitful in our group in isolating pyramidal aryl-Cu(III) and aryl-Ag(III) complexes and validating their intermediacy in thermally-driven coupling reactions with a wide range of nucleophiles.^{1,2} The same reactivity was successfully transferred to monodirecting 2-(2-halophenyl)pyridine substrates. Although the high-valent complexes pursued could not be observed for gold, we managed to develop the first example of oxidant-free Au(I)-catalyzed carbon-X (X = halides, phenols) bond formation in the absence of external oxidants.



In the second part of the thesis (Chapter IV) we explored the expansion of the nucleophile scope using different amines and amides to target the C-N bond forming couplings in 2-(2-halophenyl)pyridines substrates. Moreover, in the course of this investigation we became aware that the square-planar coordination geometry defined by the 2-phenylpyridine framework might be suitable for stabilizing a five-membered ring Au(III) intermediate stemming from oxidative addition of aryl halides at Au(I). Indeed, the addition of a third aromatic ring to 2-(2-iodophenyl)pyridines in the form of 10-iodobenzo[*h*]quinoline substrate to avoid rotation of the pyridyl group was crucial to

access the targeted cycloaurated complex. An analogous cationic complex is a competent catalytic intermediate species in the C-O and C-N bond forming reactions, which calls the often assumed redox-neutral behavior of gold complexes without external oxidants into question.

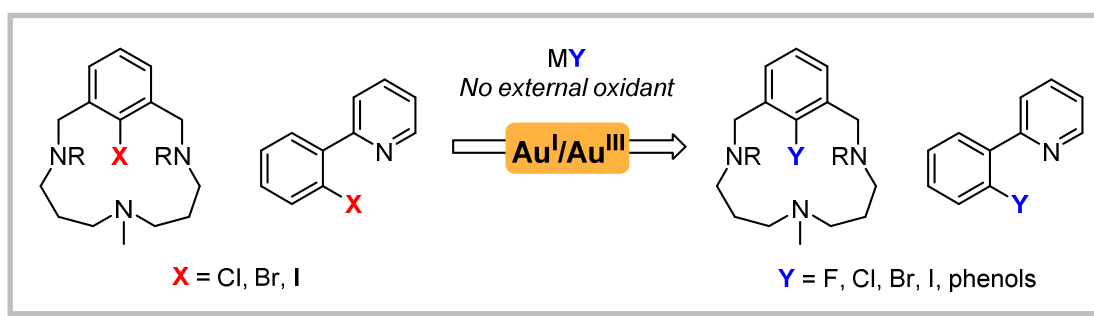
Finally, we aimed at the exploration of migratory *syn* insertions, another important organometallic step rather unexplored for gold (Chapter V). The well-defined (C,N)-cyclometalated Au(III) complex synthesized previously was used as a precursor to prepare highly reactive tricoordinate cationic complex bearing an aryl-Au(III) bond. The reactivity of this complex towards an inert olefin (ethylene) was exhaustively studied and compared with that of related (C,P)-cyclometalated Au(III) complexes.^{4,5} The experimental work was accompanied in close contact by theoretical calculations. The results obtained highlight the influence of the ancillary ligand on the properties of the gold center, and stress the importance of the coordination environment on the reaction outcome.



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CHAPTER III

Oxidant-Free Au(I)-Catalyzed Halide Exchange and C_{sp2}-O Bond Forming Reactions



This chapter corresponds to the following publication:

Serra, J.; Whiteoak, C. J.; Acuña-Parés, F.; Font, M.; Luis, J. M.; Lloret-Fillol, J.; Ribas, X. *J. Am. Chem. Soc.* **2015**, *137*, 13389-13397. DOI: 10.1021/jacs.5b08756.

J. S. performed all the experimental work concerning with this publication. Besides, he was involved in argumentations, discussions and writing of the manuscript. J. M. L. and J. Ll.-F. supervised the DFT studies. J. S. contributed in approximately 65%.

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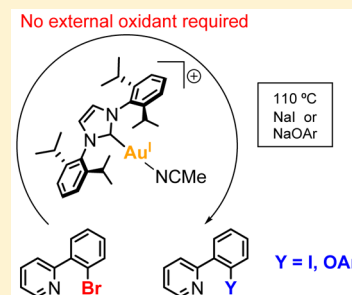
Oxidant-Free Au(I)-Catalyzed Halide Exchange and C_{sp2}–O Bond Forming Reactions

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S Supporting Information

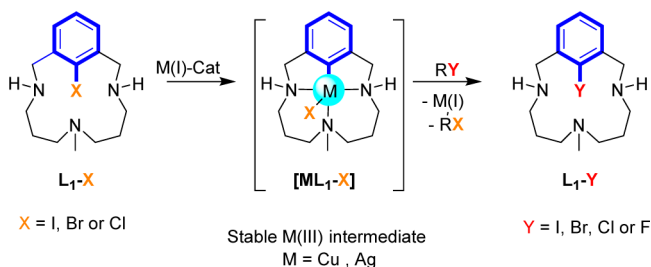
ABSTRACT: Au has been demonstrated to mediate a number of organic transformations through the utilization of its π Lewis acid character, Au(I)/Au(III) redox properties or a combination of both. As a result of the high oxidation potential of the Au(I)/Au(III) couple, redox catalysis involving Au typically requires the use of a strong external oxidant. This study demonstrates unusual external oxidant-free Au(I)-catalyzed halide exchange (including fluorination) and C_{sp2}–O bond formation reactions utilizing a model aryl halide macrocyclic substrate. Additionally, the halide exchange and C_{sp2}–O coupling reactivity could also be extrapolated to substrates bearing a single chelating group, providing further insight into the reaction mechanism. This work provides the first examples of external oxidant-free Au(I)-catalyzed carbon–heteroatom cross-coupling reactions.



INTRODUCTION

Metal-mediated transformations in organic synthesis have revolutionized the design of retro-synthetic strategies for the preparation of new organic compounds.^{1,2} Among these strategies, carbon–carbon (C–C) and carbon–heteroatom (C–X) forming cross-coupling reactions mediated by Pd and Cu have become the most established options.^{3–12} Nevertheless, the discovery of new methodologies involving other transition metals with the possibility of providing new selectivities is highly desirable. Recently, during screening of the redox chemistry of coinage metals with a model aryl macrocyclic ligand, we have provided experimental evidence regarding the unexpected feasibility of Ag(I)/Ag(III) two-electron redox cycles in C–C and C–heteroatom cross-coupling catalysis,¹³ operating analogously to Cu(I)/Cu(III) catalysis (Scheme 1).^{14,15} In contrast

Scheme 1. Previously Reported M(I) (M = Cu or Ag) Catalyzed Halide Exchange Reactions in Model Aryl Halide Macrocyclic Substrates



to the other coinage metals, Au-catalyzed cross-coupling catalysis has only been observed in the presence of external oxidants.^{16–20} This difference in reactivity is due to the high

oxidation potential of the Au(I)/Au(III) redox couple ($E_0 = +1.41$ V in water),²¹ and, as a result, Au(I)-catalyzed C–C bond forming reactions utilizing the π Lewis acid properties of Au are more common.^{22–29}

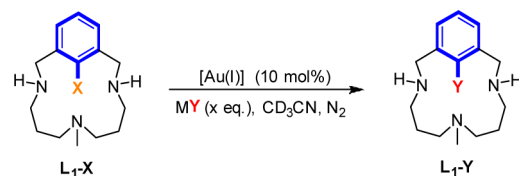
The engagement of Au(I) catalysis in aryl halide oxidative addition has been a matter of controversy over the past few years. In 2007 Corma and co-workers reported what they considered to be the first example of Au(I)-catalyzed Sonogashira couplings using aryl iodides without the need for an external oxidant,³⁰ but in 2010, Espinet, Echavarren and co-workers provided evidence on the unlikelihood that these Au(I)-catalyzed Sonogashira coupling reactions proceeded in the absence of Pd impurities.^{31,32} Around the same time, Lambert and co-workers provided further evidence that the activity observed in these Au-catalyzed Sonogashira couplings was a consequence of the presence of Au nanoparticles.³³ The latter observation was also later reported by Corma and co-workers in 2011.³⁴

The viability of the oxidative addition of aryl halides at Au(I) has recently attracted renewed interest, particularly in work reported by Bourissou and co-workers whereby the crystal structures of aryl-Au(III)-I oxidative addition products have been reported.³⁵ These compounds are reported to be extremely stable and no further reactivity was observed. In addition, Toste recently reported Au(I) oxidative addition using biphenylene to obtain [IPrAu(III)(biphenyl)]⁺, where its Lewis acid properties are further exploited.³⁶ Reductive elimination from Au(III) for C–C bond formation has long been known, particularly from the groups of Kochi, Tobias and Vincent, reporting reductive eliminations from dialkyl–Au(III) complexes, although not in a

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Table 1. Catalytic Halide Exchange Reactions with L_1 -X in CD_3CN under N_2 ^a


entry	L_1 -X	MY (equiv)	Au(I) (10 mol %)	T (°C)	t (h)	yield L_1 -Y (%) ^b
1	L_1 -I	Bu_4N -Cl (2)	$AuCl(PPh_3)$	40	48	>99
2			$Au(NTf_2)PPh_3$	40	48	97
3			$[Au(NCMe)IPr]^+$	40	6	>99 ^c
4			-	40	48	2
5		NaBr (10)	$AuCl(PPh_3)$	40	48	5 (94) ^d
6			$Au(NTf_2)PPh_3$	40	48	9 (96) ^d
7			$[Au(NCMe)IPr]^+$	40	30	15 (97) ^d
8			-	40	48	0 (36) ^d
9	L_1 -Br	Bu_4N -Cl (2)	$AuCl(PPh_3)$	40	60	98
10			$Au(NTf_2)PPh_3$	40	60	99
11			$[Au(NCMe)IPr]^+$	40	12	99
12			-	40	60	trace
13		NaI (10)	$AuCl(PPh_3)$	70	18	95
14			$Au(NTf_2)PPh_3$	70	8	92
15			$[Au(NCMe)IPr]^+$	70	4	94
16			-	70	18	23
17	L_1 -Cl	NaBr (10)	$AuCl(PPh_3)$	70	72	30 (56) ^e
18			$Au(NTf_2)PPh_3$	70	72	34
19			$[Au(NCMe)IPr]^+$	70	72	46 (59) ^e
20			-	70	72	trace
21		NaI (10)	$AuCl(PPh_3)$	70	100	42 (64) ^f
22			$Au(NTf_2)PPh_3$	70	100	48
23			$[Au(NCMe)IPr]^+$	70	48	67
24			-	70	100	16

^aConditions: 15.3 μ mol L_1 -X, 10 mol % Au(I), MY, 0.5 mL CD_3CN , N_2 ; see Au(I) catalyst structures in Scheme 2. ^bYields calculated using ^1H NMR spectra, with 1,3,5-trimethoxybenzene as internal standard. ^cQuantitative yield after 30 h using 5 mol % of Au(I) cat. ^dIn parentheses, experiments at 70 °C. ^eIn parentheses, LiBr (10 equiv) as bromide source. ^fIn parentheses, yield after 350 h.

catalytic fashion.^{37–40} More recently, Toste and co-workers have also described an extremely fast reductive elimination from Au(III) complexes forming biaryl compounds.⁴¹ These oxidative addition and reductive elimination steps have been combined in a stepwise stoichiometric intramolecular Au-mediated allylation of arylboronic acids proceeding through an isolable Au(III) intermediate indicating the feasibility of these conversions.^{36,42,43}

Inspired by these reports, we decided to investigate the possibility of external oxidant-free Au(I)-catalyzed cross-coupling reactions using our model systems and to study the intrinsic differences of Au reactivity compared to the previously reported two-electron redox catalysis with Ag and Cu.^{8,13,15}

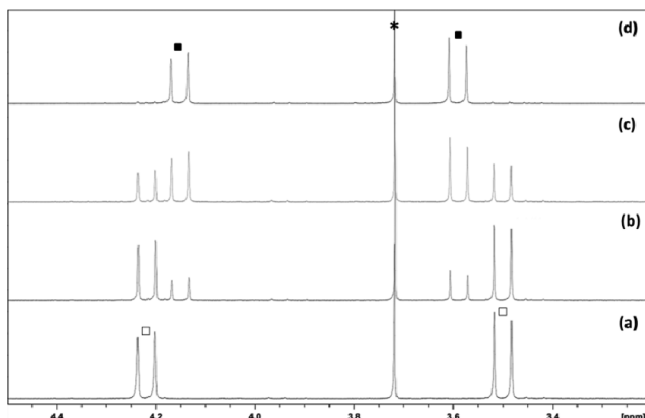
RESULTS AND DISCUSSION

Au(I)-Catalyzed Halide Exchange in Aryl-X Model Substrates (X = Cl, Br, I). In analogy to our previous works on Ag and Cu based halide exchange reactions, we first attempted a stoichiometric reaction by adding 1 equiv of a Au(I) source, $[AuCl(SMe_2)]$, to a CD_3CN solution of L_1 -Br (1 equiv) in which we observed the immediate formation of a precipitate as well as a change in the color of the solution to pale violet, indicating the decomposition of the Au(I) precursor to Au(0) in the form of Au nanoparticles. This result suggested that the soft nature of the Au(I) cation could not be stabilized by the secondary and tertiary amines of the model aryl halide macrocycle in contrast to our previous examples using Cu and Ag.

Also, we realized that Au(I) was prone to disproportionation to form metallic Au; therefore, a strongly coordinating ligand should be used to stabilize Au(I) in solution to avoid this detrimental side reaction.

We decided to first investigate the potential for catalytic halide exchange in the aryl halide macrocycle mediated by $[AuCl(PPh_3)]$. Initially, we focused on L_1 -I in the presence of a catalytic amount of $[AuCl(PPh_3)]$ (10 mol %) and 2 equiv of tetrabutylammonium chloride (nBu_4N -Cl) in CD_3CN , and we were pleased to observe clean and quantitative conversion to the halide exchanged product, L_1 -Cl in 48 h at 40 °C (Table 1, entry 1). Importantly, in the absence of Au(I), only traces of halide exchange product were observed, confirming the role of Au(I) as catalyst (Table 1, entry 4). Conversion of L_1 -I to L_1 -Br was also cleanly achieved, although the optimization process rendered improved results using slightly higher temperatures (70 °C; Table 1, entries 5–8). Subsequently, the study was extended to the bromide containing aryl macrocycle, L_1 -Br. This conversion is analogous to the well-known Cu-catalyzed Buchwald transformation of aryl-bromides to the corresponding aryl-iodides,⁴⁴ and again it was possible to cleanly realize the Cl and I exchanged products (Table 1, entries 9–16). As can be seen in a ^1H NMR monitoring experiment (Scheme 2), the reactions proceeded cleanly and showed no presence of intermediates during the catalytic transformation of L_1 -Br to L_1 -I. Halide exchange reactions

Scheme 2. ^1H NMR Spectra of the Evolution of the Benzylic Region during the Halide Exchange Reaction from $\text{L}_1\text{-Br}$ to $\text{L}_1\text{-I}$ (Table 1, entry 13) in CD_3CN ^a

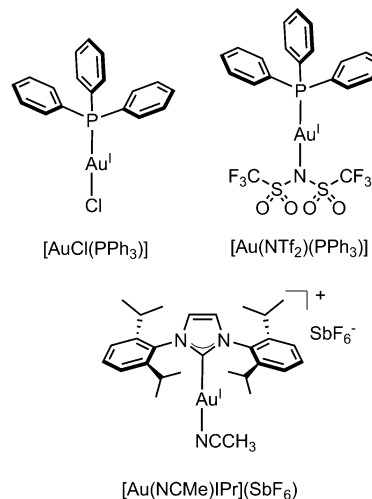


^a(a) $t = 0$ h, (b) $t = 2$ h, (c) $t = 8$ h and (d) $t = 18$ h. $\square$ $\text{L}_1\text{-I}$, $\blacksquare$ $\text{L}_1\text{-Br}$, and * 1,3,5-trimethoxybenzene (internal standard).

starting from $\text{L}_1\text{-Cl}$ (Table 1, entries 17–24) proved to be significantly more challenging than those with $\text{L}_1\text{-I}$ and $\text{L}_1\text{-Br}$, likely as a result of the stronger Ar-X bond ($\text{Ar-Cl} = 97.3 \text{ kcal}\cdot\text{mol}^{-1}$, $\text{Ar-Br} = 82.7 \text{ kcal}\cdot\text{mol}^{-1}$ and $\text{Ar-I} = 66.9 \text{ kcal}\cdot\text{mol}^{-1}$).⁴⁵ With respect to the iodination of $\text{L}_1\text{-Cl}$, even after prolonged reaction times of up to 350 h (Table 1, entry 21), we were unable to realize quantitative conversions. The low conversion of $\text{L}_1\text{-Cl}$ to $\text{L}_1\text{-Br}$ using NaBr (30% yield, Table 1, entry 17) may be also attributed to the low solubility of the initial halide salt in acetonitrile. The use of more soluble LiBr improved the yield of $\text{L}_1\text{-Br}$ to 56% (Table 1, entry 17). The precipitation of the sodium salts (NaCl and NaBr) from the CD_3CN solution may be key to understanding the catalytic cycle turnover towards heavier halide products;¹⁴ no halide exchange reaction is observed in the exchange of aryl chloride toward aryl bromide or aryl iodide when using soluble $n\text{Bu}_4\text{NBr}$ or $n\text{Bu}_4\text{NI}$, respectively.

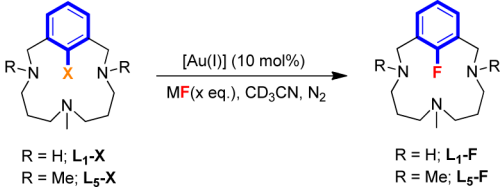
In general, although the halide exchange reactions catalyzed by $[\text{AuCl}(\text{PPh}_3)]$ were effective, in some cases they struggled to reach completion after extended periods of time (days). To tackle the poor reactivity of $\text{AuCl}(\text{PPh}_3)$, we hypothesized that the availability of the coordination site on the Au(I) center might have an important effect on the reaction outcome. Recently, theoretical calculations have suggested that a putative oxidative addition of aryl halides to Au(I) would be much easier when employing $[\text{Au(I)L}]^+$ complexes.⁴⁶ Although these kind of cationic Au(I) complexes have proven very unstable, the use of a weakly coordinating counterion can prevent such decomposition. In view of this, we tested the efficiency of $[\text{Au}(\text{NTf}_2)(\text{PPh}_3)]$ ($\text{NTf}_2 = \text{bis}(\text{trifluoromethanesulfonyl})\text{imide}$) as Au(I) catalyst in the previously described halide exchange transformations (Scheme 3).^{47,48} The results obtained were comparable to those using $[\text{AuCl}(\text{PPh}_3)]$ (see Table 1), except for the iodination of $\text{L}_1\text{-Br}$, which was accomplished in the same excellent yields in only 8 h (Table 1, entry 14). We also attempted the chloride abstraction from $\text{AuCl}(\text{PPh}_3)$ by silver salts with an accompanying noncoordinating anion, such as BF_4^- or SbF_6^- in acetonitrile solution, to occupy the vacant coordination site by a labile solvent molecule.^{49,50} $[\text{Au}(\text{NCMe})(\text{PPh}_3)]\text{SbF}_6$ was synthesized, but its use as a catalyst proved unsuccessful due to rapid decomposition into $[\text{Ph}_3\text{P-Au-PPh}_3]^+$ species and Au(0) in solution at temperatures above 25°C .

Scheme 3. Au(I) Catalysts Used in This Work



In view of the difficulties in isolating an alternative triphenylphosphine-based Au complex that shows improved reactivity, we sought another ancillary ligand. Over the past few years, Nolan and co-workers have prepared a range of complexes with N -heterocyclic donor ligands (NHC) replacing the common phosphines.^{49–52} This type of ligand has been reported to stabilize cationic Au(I) much more effectively than PPh_3 , while maintaining its catalytic properties. Hence, we prepared $[\text{Au}(\text{NCMe})\text{IPr}]\text{SbF}_6$ ($\text{IPr} = 1,3\text{-bis}(\text{di-isopropylphenyl})\text{-imidazol-2-ylidene}$) starting from commercially available $\text{AuCl}(\text{IPr})$ (Scheme 3). Subsequently, we tested its catalytic efficacy towards halide exchange reactions within the aryl halide macrocyclic substrates (Table 1). To our delight, good to excellent yields were also attained employing significantly shorter reaction times, especially for the chlorination of $\text{L}_1\text{-I}$ and $\text{L}_1\text{-Br}$ (Table 1, entries 3 and 11) and the iodination of $\text{L}_1\text{-Br}$ and $\text{L}_1\text{-Cl}$ (Table 1, entries 15 and 23). For comparison, in some reactions $\text{AuCl}(\text{IPr})$ or $\text{AuBr}(\text{IPr})$ were used instead of $[\text{Au}(\text{NCMe})\text{IPr}]\text{SbF}_6$ and the same results were obtained (see Table S3). This is an important indication that the catalytic activity of a Au(I) complex, namely $[\text{AuX(L)}]$, is predominantly governed by the nature of the ancillary ligand L rather than the counteranion X .

Au(I) -Catalyzed C–F Bond Forming Reactions with Model Macrocyclic Substrates. Since catalytic halide exchange reactions mediated by Au(I) were shown to be successful with the combination of any pair of $\text{L}_1\text{-X}$ and MY (where $\text{X}, \text{Y} = \text{Cl}, \text{Br}, \text{I}$), we then sought to investigate the possibility of halide exchange for the realization of fluorination products using $\text{AuCl}(\text{PPh}_3)$, $\text{Au}(\text{NTf}_2)(\text{PPh}_3)$ or $[\text{Au}(\text{NCMe})\text{IPr}]\text{SbF}_6$ as catalysts. Initially, we tested Bu_4NF as fluoride source, but we found it to be completely ineffective. In contrast, addition of 2 equiv of AgF , a typical fluoride source for catalytic fluorination reactions,⁵³ to a solution of ligand $\text{L}_1\text{-Cl}$ and 10 mol % of $\text{AuCl}(\text{PPh}_3)$ or $\text{Au}(\text{NTf}_2)(\text{PPh}_3)$ at 70°C afforded the desired fluorination product, $\text{L}_1\text{-F}$ (Table 2, entries 1–2), albeit in low but encouraging 32% and 36% yields, respectively. Changing $\text{L}_1\text{-Cl}$ for $\text{L}_1\text{-Br}$ or $\text{L}_1\text{-I}$ as starting substrate provided improved yields in shorter reaction times (Table 2, entries 10 and 19), although the background reaction (blank experiments, Table 2 entries 4, 9, 13, 18, 20) becomes more significant than when using $\text{L}_1\text{-Cl}$, which can be explained by the previously demonstrated Ag -mediated fluorination catalysis operating with the intermediacy of an aryl-Ag(III) species.¹³ The permethylated

Table 2. Catalytic Fluorination Reactions with L₁-X and L₅-X in CD₃CN under N₂^a


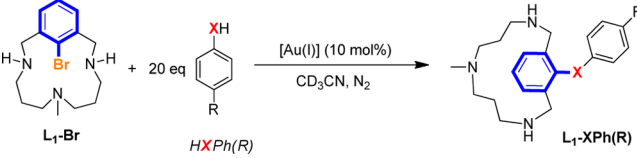
entry	L _n -X	MF (equiv)	Au(I) (10 mol %)	T (°C)	t (h)	yield L _n -F (%) ^b
1	L ₁ -Cl	AgF (2)	AuCl(PPh ₃)	70	72	32 ^c
2		AgF (2)	Au(NTf ₂)PPh ₃	70	72	36 ^c
3		AgF (2)	[Au(NCMe)IPr] ⁺	70	24	64 ^d
4		AgF (2)	-	70	72	6
5	L ₅ -Cl	KF (5)	[Au(NCMe)IPr] ⁺	70	72	14 ^e
6		AgF (2)	AuCl(PPh ₃)	70	72	51
7		AgF (2)	Au(NTf ₂)PPh ₃	70	72	50
8		AgF (2)	[Au(NCMe)IPr] ⁺	70	12	98
9		AgF (2)	-	70	72	4
10	L ₁ -Br	AgF (2)	AuCl(PPh ₃)	40	48	49 ^f
11		AgF (2)	Au(NTf ₂)PPh ₃	40	48	54 ^g
12		AgF (2)	[Au(NCMe)IPr] ⁺	40	48	68 ^h
13		AgF (2)	-	40	48	42
14	L ₅ -Br	KF (5)	[Au(NCMe)IPr] ⁺	70	48	23 ^e
15		AgF (2)	AuCl(PPh ₃)	40	48	100
16		AgF (2)	Au(NTf ₂)PPh ₃	40	48	100
17		AgF (2)	[Au(NCMe)IPr] ⁺	40	6	100
18		AgF (2)	-	40	48	100
19	L ₁ -I	AgF (2)	AuCl(PPh ₃)	40	24	56 ⁱ
20		AgF (2)	-	40	24	54

^aConditions: 15.3 μmol L₁-X or L₅-X, 10 mol % Au(I), MF, 0.5 mL CD₃CN, N₂. ^bYields calculated using ¹H NMR spectra, with 1,3,5-trimethoxybenzene as internal standard. ^c6% of L₁-N-intra observed. ^d5% of L₁-N-intra observed. ^e0% yield when Au(I) source is absent. ^f7% of L₁-N-intra observed. ^g9% of L₁-N-intra observed. ^h8% of L₁-N-intra observed. ⁱ5% of L₁-N-intra observed.

macrocyclic substrates, L₅-X (X = Cl, Br), exhibited significantly enhanced fluorination yields when compared to their L₁-X analogues (Table 2, entries 5–9 and 14–18), which suggested that the strong basicity of the F[−] anion directly affected the secondary amines in the reactions using L₁-X. It is known that the secondary amines of the macrocyclic L₁-X ligand are relatively easily deprotonated upon formation of aryl–Cu(III) and aryl–Ag(III) species,^{13,54} triggering the formation of side-products such as intramolecular C–N coupling products. The presence of L₁-N-intra compound^{13,14,55} as a byproduct (Table 2) may suggest the formation of an organometallic Au–C_{aryl} bond (see Mechanistic Insight section for discussion). In the case of L₁-Cl and L₅-Cl, only residual fluorination is observed if Au(I) is excluded (Table 2, entries 4 and 9), thus demonstrating a distinctive genuine reactivity for Au catalysis compared to Ag-mediated transformations. Interestingly, 14% and 23% of L₅-F were obtained using KF as the fluoride source when fluorinating L₅-Cl and L₅-Br, respectively (Table 2, entries 5 and 14), suggesting that Au has a central role in this fluorination catalysis.

Au(I)-Catalyzed C–O Bond Forming Reactions Using Phenols with Model Macrocyclic Substrates. To the best of our knowledge, there are no reported examples of Au-catalyzed Ullmann-type coupling reactions, and therefore, to further expand the substrate scope and applicability of the

catalyst system, we decided to investigate the potential for C–O and C–S bond formation using a range of substituted phenols and thiophenol. We were pleased to observe that with the phenolic substrates it was possible to form the desired coupling products (Table 3, entries 2–8). We found it

Table 3. Catalytic C–O Bond Forming Reactions with L₁-Br and L₅-Br in CD₃CN under N₂^a


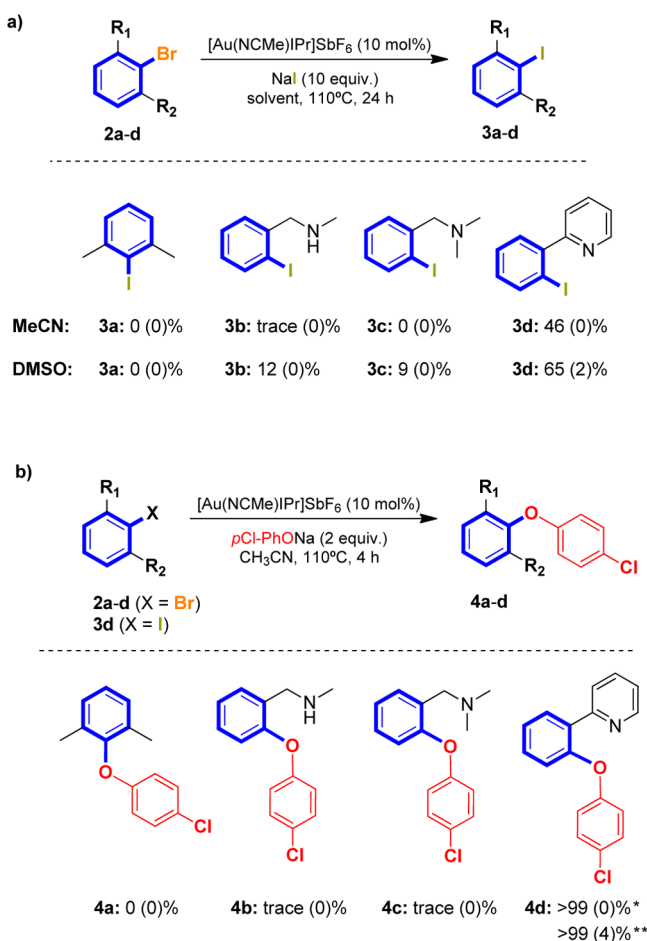
Entry	X	R	Au(I) (10 mol %)	Yield L ₁ -XPh(R) (%) ^b		
				25 °C	40 °C	70 °C
1	O	H	AuCl(PPh ₃)	-	-	34 ^c
2		H	Au(NTf ₂)PPh ₃	-	51	75
3		Me	Au(NTf ₂)PPh ₃	-	41	71
4		OMe	Au(NTf ₂)PPh ₃	-	45 ^d	89 ^e
5		OMe	[Au(NCMe)IPr] ⁺	-	44 ^f	87 ^g
6		NO ₂	Au(NTf ₂)PPh ₃	-	15	35
7		CF ₃	Au(NTf ₂)PPh ₃	-	32	56
8		Cl	Au(NTf ₂)PPh ₃	29	52	79 (61) ^h
9		Cl	[Au(NCMe)IPr] ⁺	42	61	84 (83) ^h
10		Cl	-	<1	15	45
11	S	H	Au(NTf ₂)PPh ₃	-	0	0

^aConditions: 15.3 μmol L₁-Br or L₅-Br, 10 mol % Au(I), nucleophile, 0.5 mL CD₃CN, N₂, 24 h. ^bYields calculated using ¹H NMR spectra, with 1,3,5-trimethoxybenzene as internal standard. ^c10% L₁-Cl observed in addition to C–O coupling product. ^d2% of L₁-H observed. ^e9% of L₁-H observed. ^f4% of L₁-H observed. ^g10% of L₁-H observed. ^hYield after 8 h in parentheses.

necessary to use Au(NTf₂)PPh₃ as Au(I) source for this study, as during experiments using AuCl(PPh₃) we observed rapid formation of the Cl-exchanged product. The amount of L₁-Cl formed did not exceed 10% yield, confirming that the chloride source was the Au(I) salt, and thus strongly suggesting that C–Br bond activation mediated by Au had occurred (Table 3, entry 1, and Figure S17 in Supporting Information). On the other hand, it can be seen that variation of the electronic properties of the phenol has an important effect on the yield, with electron-donating substituents typically giving higher yields (e.g., *p*-methoxyphenol = 89%, Table 3, entry 4) compared with phenols with strongly electron-withdrawing groups (e.g., *p*-nitrophenol = 35%, Table 3, entry 6). Finally, we found that the nature of the Au(I) catalyst has a clear impact on the yields and temperatures where reactions can be conducted. When [Au(NCMe)IPr](SbF₆) was used as catalyst, coupling with *p*-chlorophenol could be achieved in moderate yields at room temperature, conditions where the background reaction is absent (Table 3, entries 9–10). When using thiophenol, we were unable to detect any C–S coupling product (Table 3, entry 11), probably due to the affinity of thiols to coordinate to Au(I), thus blocking the catalyst. It is also interesting to highlight the presence of a small amount of L₁-H byproduct in some of the C–O catalysis in Table 3, which again suggests the intermediacy of an Au–C_{aryl} bond.

Au(I)-Catalyzed Halide Exchange and C–O Bond Forming Reactions with Nonmacrocyclic Substrates. Following these successful studies, we attempted to transfer

Scheme 4. Screening of *ortho*-Chelating Groups (Yields for Blank Experiments without Au Catalyst in Parentheses) for (a) Bromide to Iodide Exchange (Yields Calculated by GC Analysis) and (b) C–O Coupling with Sodium *p*-Chlorophenolate (Yields Calculated by ^1H NMR)



*X = Br, 65% yield after 24 h at 90 °C; **X = I, yield at 90 °C.

the reactivity from the aryl halide macrocyclic model substrates to other compounds in order to gain further insight into the mechanism and also demonstrate further reactivity (Scheme 4). Since the strongly coordinating ligands PPh_3 and IPr required to achieve the catalysis shown above are likely to remain coordinated to the Au center throughout the course of the reaction, we wondered if the macrocyclic triamine chain was necessary for the reaction to proceed. Therefore, we explored the representative catalytic performance of halide exchange and C–O coupling with three different aryl halide substrates containing a single chelation site (N atom) and one without (2a–d, Scheme 4). Among the different Au(I) sources used previously, the cationic $[\text{Au}(\text{NCMe})\text{IPr}]\text{SbF}_6$ complex was selected for this study as it allowed vastly improved results. Attempts towards bromide to iodide exchange with 2-bromo-1,3-dimethylbenzene (3a) afforded no product, suggesting that Au is not catalyzing the halide exchange reactions through its Lewis acid character and that a chelating group is crucial for catalysis to occur. Subsequently, aliphatic amine chelating groups (both secondary and tertiary amines in analogy to the aryl halide macrocycles $\text{L}_1\text{–Br}$ and $\text{L}_5\text{–Br}$, respectively) were introduced and again little or no halide exchange was observed when acetonitrile was employed as solvent (Scheme 4a, 3b and 3c).

Upon replacement of the aliphatic amine moieties with a pyridyl chelating group, we were pleased to observe 46% of the halide exchanged product (Scheme 4a, 3d). Importantly, 0% conversion was obtained in the absence of Au. The pyridyl chelating groups are significantly different in terms of their electronic properties to amine chelating groups. However, we propose that the higher activity observed with the pyridyl group is a consequence of the increased rigidity of the resulting chelate enabling the required disposition of the Au(I) reactive intermediate to activate the C–X bond of the substrate. These results demonstrate the importance of rigid chelation and highlight the beneficial nature of the rigid aryl halide macrocycle used in this study. Changing the solvent to DMSO provided increased yields of the halide exchanged products except in the case of the nonchelate containing substrate, 3a, (Scheme 4a), thus following a similar trend as in acetonitrile.

The C–O coupling reactions were also investigated with the nonmacroyclic substrates and the same trend as for the halide exchange reaction was obtained. The more rigid 2-(2-bromophenyl)pyridine (2d) afford quantitative yields for the biaryl ether 4d, whereas minor or no conversion was achieved when using substrates 2a–c (Scheme 4b). It is worth noting that the reaction requires the presence of a base to achieve initial deprotonation of the phenol-derivative. Nevertheless, the use of the corresponding independently prepared sodium *p*-chlorophenolate proved more beneficial to the reaction outcome (Scheme 4b).

Thereafter, we explored the substrate scope to evaluate the potential of these transformations and to gain mechanistic insight. We expanded the scope of the nonmacroyclic substrates, preparing 2da and 2db, which contain an electron-withdrawing group (pCF_3 , 2da) or an electron-donating group (pOMe , 2db) in the *para*-position with respect to the bromine atom. Both substrates were tested in the Au(I)-catalyzed iodination of aryl bromides as well as the C–O bond formation to form the biaryl ether using *p*Cl-phenolate as nucleophile (Scheme 5a). The halide exchange reactions afforded similar yields of the iodinated product 3da and 3db under the same experimental conditions as when using 2d, and also excellent outcomes were found for the formation of the corresponding biaryl ether products 4da and 4db. Kinetic studies at the early stages of the C–O coupling reactions reveal higher yields for the *p*-trifluoromethyl substituted substrate (4da), although no unambiguous mechanistic information can be ascertained from the values obtained (Table 4). In addition, in order to explore the utility of this methodology towards the synthesis of other products, 2d was reacted with sodium methoxide as nucleophile, providing the aryl methyl ether 5d again in quantitative yields (Scheme 5b). These results suggest that other substrates, nucleophiles and reaction conditions might be found for a more general and applicable oxidant-free Au-catalyzed reaction that leads to the formation of new products of interest.

Mechanistic Insights. The results obtained permit some insights into the reaction mechanism although we have not been able to detect a putative aryl–Au(III) species analogous to the previously reported aryl–Cu(III) and aryl–Ag(III).^{8,13,15} The difficulty in isolating this key intermediate is likely related to the challenge in avoiding Au(I) disproportionation when weak ligands are used to stabilize Au(I), i.e., $\text{AuCl}(\text{SMe}_2)$ or bare AuI. The use of more stabilizing PPh_3 or IPr ligands enhance catalytic turnover but do not allow the detection of a putative square-planar aryl–Au(III), since PPh_3 or IPr ligands are likely not detached from Au(I) center during the catalytic cycle. The latter is in agreement with the fact that one chelating

Scheme 5. Substrate Scope of the Au(I)-Catalyzed C-Heteroatom Bond Forming Reactions (Conversions in Parentheses)

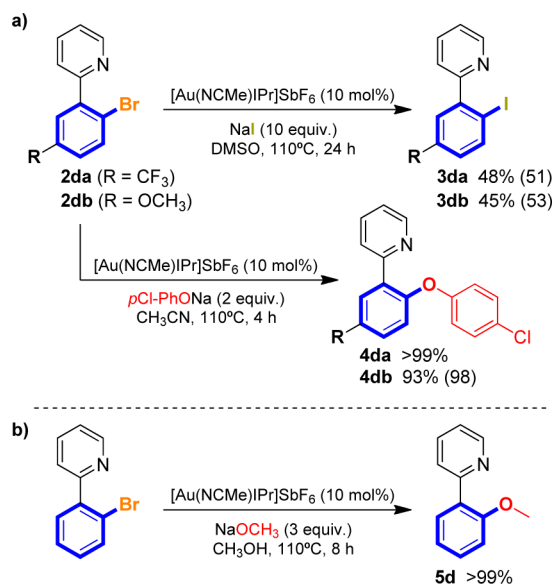


Table 4. Yields Obtained during the Initial Stages of the *p*Cl-Phenolate Coupling to 2d and Its *p*-Substituted Derivatives

<i>t</i> (h)	yield (%)		
	R = H (4d)	R = CF ₃ (4da)	R = OCH ₃ (4db)
1	35	78	41
2	61	>99	73
4	>99	>99	93

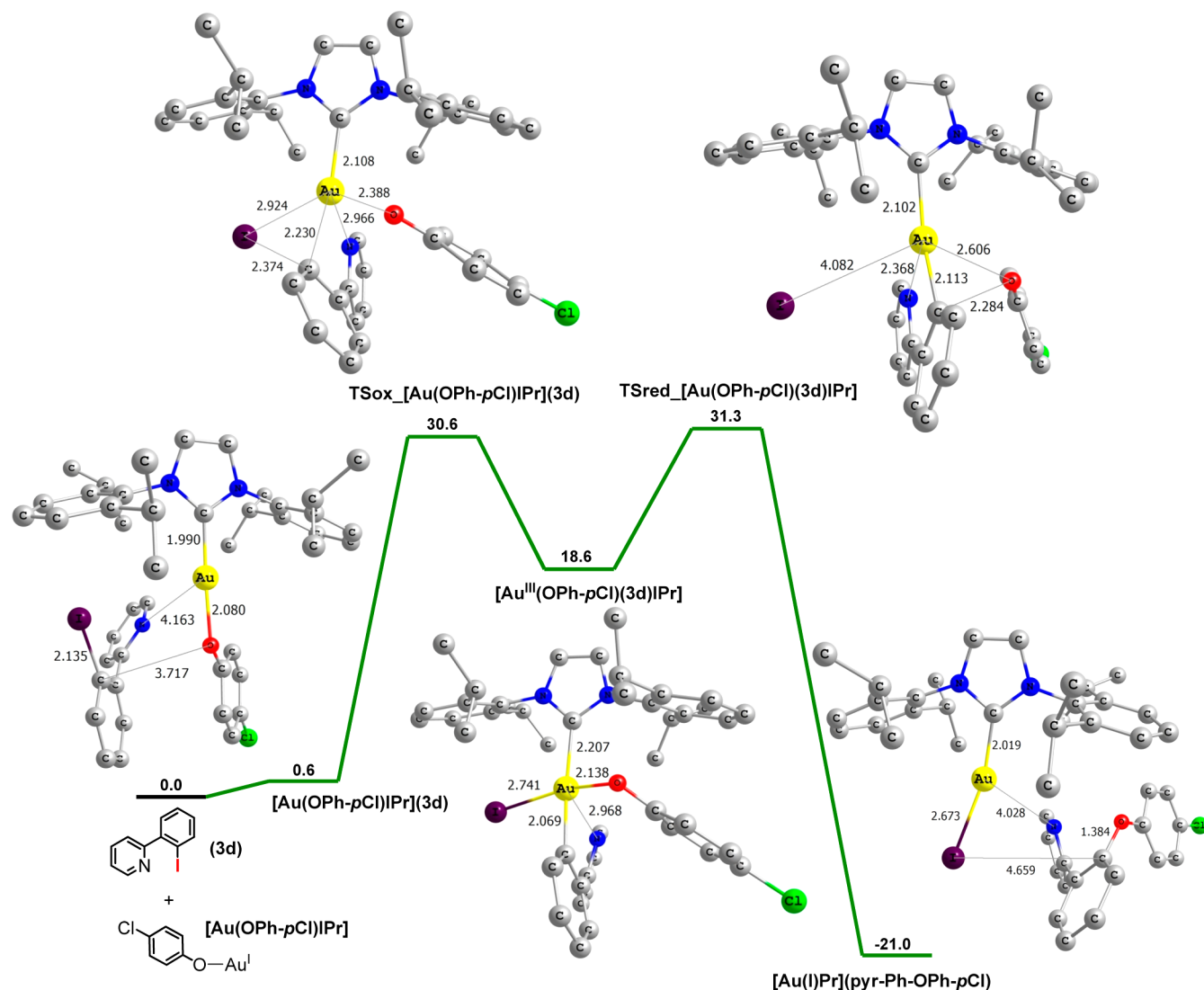
group is sufficient to translate the catalytic performance from the macrocyclic substrate to the more simple substrates (Scheme 4). The coordination of the [Au(NCMe)IPr]SbF₆ to L₁-Br or 2d can be observed experimentally by means of ¹H NMR and ESI-MS (see Supporting Information, Figures S28 and S29). However, a ¹H NMR monitoring experiment of the C–O coupling catalysis of *p*-chlorophenol and 2d shows that under catalytic conditions, i.e., in the presence of excess of phenolate, [Au(OPh-*p*Cl)IPr] forms at room temperature as a catalytic intermediate (see Figures S29 and S32). The reaction only takes place upon heating, and once the catalysis has started, the bromide anion released from 2d in the first catalytic cycle is immediately trapped by Au, forming [Au(Br)IPr] (see Figure S30). With the aim of evaluating if those species are indeed off-cycle intermediates of the reaction, independently prepared [Au(OPh-*p*Cl)IPr] and [Au(Br)IPr] were tested as catalysts in both the halide exchange and C–O bond forming reactions with the macrocyclic and nonmacrocyclic substrates, obtaining the same results as with [Au(NCMe)IPr]SbF₆ (see Table S3), which clearly supports their intermediacy in the reaction mechanism. ¹H NMR monitoring experiments do not prove that any of these Au species coordinate to the substrate, but the observation of reactivity in 2b–d but not 2a suggests that this is a requirement (see Figure S31). Indeed, under HRMS conditions, we can detect the in situ formation of [Au(2d)IPr]⁺ by substitution of the coordinated phenolate or the bromide (Figures S33 and S34), thus providing experimental support to our proposal. Also, species [Au(3d)IPr]⁺ and

[Au(4d)IPr]⁺ are observed in the final crude reaction mixtures (Figures S10 and S30).

The possibility that Au(0) colloids could be the active species responsible for this chemistry was also considered. To assess whether the catalyst is homogeneous or heterogeneous, we ran reactions under identical conditions except for the presence of a large excess of mercury (ca. ~500 equiv with respect to Au catalyst, under heavy stirring), which acts as a poison towards nanoparticles.^{56,57} A quenching of reactivity would strongly suggest colloidal catalysis. However, when performing halide exchange catalysis and C–O coupling using both the aryl–Br macrocyclic model substrate (L₁–Br) and the bromoaryl-pyridine (2d), we did not detect a significant decrease in activities (see Table S2). Somewhat lower yields (10–30% lower) were observed at expense of the formation of side-products, but the previously observed halide exchange reactions and C–O couplings remained as the main transformations occurring in the solution. Notably, ¹H NMR analysis of the reaction crude at the end the catalysis indicates that the entire catalyst remains in solution in the form of [Au(Br)IPr], since authentic samples of free IPr and IPr-HOTf do not match the observed NHC signals, whereas an authentic sample of [Au(Br)IPr] does (Figure S35).

At present we cannot fully discard any mechanism, but as mentioned a Au(I) π -interaction with the aromatic ring is unlikely because only substrates with chelating groups give positive results. In fact, HRMS monitoring shows that [Au(OPh-*p*Cl)IPr] remains unaltered for 24 h under the catalytic conditions used for the reaction of 2a with *p*-chlorophenol, with no conversion (Figure S31). Bourissou and co-workers have previously demonstrated that an oxidative addition step is significantly enhanced if nonlinearity is forced upon Au(I).⁵⁸ Given that one chelating group in the substrate is necessary (see Scheme 4), we hypothesize that this coordination may help in distorting the linearity of the Au(I) resting state, and allows for the reaction to occur upon heating (in the examples described here temperatures of 110 °C need to be applied to overcome the energy barrier). The observation of L₁–N-intra and L₁–H in C–F and C–O coupling catalysis is reminiscent of Cu(I)/Cu(III) and Ag(I)/Ag(III) catalysis when using the macrocyclic model substrates, also pointing towards the existence of a Au(I)/Au(III) catalytic cycle.

We also embarked on a DFT study to gain insight into the mechanism, and specifically we focused on the coupling of *p*Cl-PhO[−] with 3d as the model reaction, using [Au(NCMe)IPr]⁺ as the catalyst (see Supporting Information for computational details). First, we calculated the thermodynamic values of the replacement of a acetonitrile molecule in [Au(NCMe)IPr]⁺ by the *p*Cl-PhO[−] group to form [Au(OPh-*p*Cl)IPr], finding that this is clearly an exergonic process ($\Delta G = -11.4$ kcal·mol^{−1}). The free energy balances for the exchange of the coordinated *p*Cl-PhO[−] ($\Delta G = 2.5$ kcal·mol^{−1}) or iodide ($\Delta G = -1.4$ kcal·mol^{−1}) by 3d allow the formation of [Au(3d)IPr]⁺, and suggest that the generation of the analogous [Au(2d)IPr]⁺ may be feasible under reaction conditions, thus in agreement with the HRMS experiments. Moreover, a complete reaction pathway for the C-halogen functionalization has been successfully computed at M06L level (Scheme 6), showing a transition state for the oxidative addition step (TS_{ox}) at 30.6 kcal/mol, and a TS_{red} for the reductive elimination at 31.3 kcal/mol. Given the fact that reactions are conducted above 90 °C, these barriers are below the kinetic limit, thus in agreement with the experiments performed and the rather slow reactions. DFT calculations indicate that the reductive elimination step is rate limiting;

Scheme 6. DFT Reaction Profile for the Oxidative Addition/Reductive Elimination Steps of $[\text{Au}(\text{OPh-}p\text{Cl})]\text{IPr}$ over 3d Substrate^a

^aRelative Gibbs energy values in acetonitrile solution are given in kcal·mol⁻¹ and selected bond distances in Å (H atoms are omitted for clarity).

however, the fact that both TS are very close in energy suggests that subtle changes may favor switching to a rate limiting oxidative addition. The energetic similarity between both TS could justify the somewhat ambiguous trend among the electronically different *p*-substituted 2-(2-bromophenyl)pyridine substrates (Table 4). We have also determined the oxidative addition/reductive elimination Gibbs energy profile for another Au(I) isomer where the gold cation is coordinated to 3d instead of *p*Cl-PhO⁻. However, the optimized oxidative addition TS (see Figure S37) is about 7 kcal/mol higher in energy than TS_{ox} and TS_{red} described in Scheme 6.

Nucleophilic aromatic substitution was also explored computationally, where the cationic Au(I) would act as a Lewis acid to increase the reactivity of the aryl-I moiety. Remarkably, all the TS searches for the direct attack of the phenolate to 3d actually converged to TS_{ox} (Scheme 6), thus driving the reaction through a Au(III) species and rendering the possibility of a direct nucleophilic attack on the aryl-carbon of 3d unlikely.

This alternative mechanism was also studied experimentally. Having in hand the isolated methoxide insertion product 5d, we studied the cationic Au(I)-mediated displacement of the

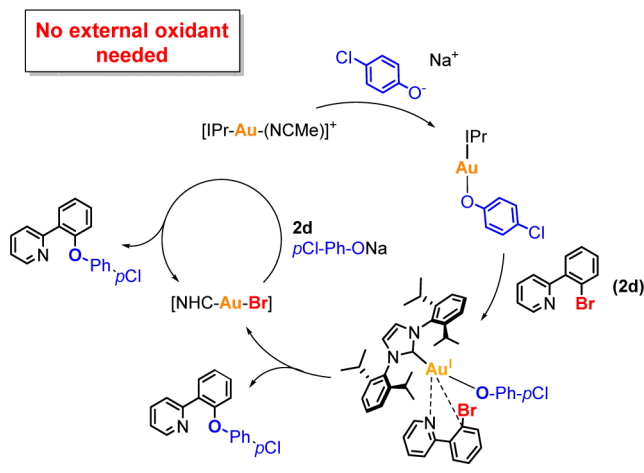
methoxy group in the presence of sodium *p*Cl-phenolate as nucleophile under the same reactions conditions described for 2d. After sufficient time to allow any reaction to proceed, we quantitatively recovered the starting material. This is in contrast to a related nucleophilic aromatic substitution reported by Meyers and co-workers in the late 1970s describing a nucleophilic displacement of the *o*-methoxy group in comparable substrates to 2d by organolithium and Grignard reagents. This suggests that our reported reaction indeed proceeds through a mechanism different to a Au-assisted nucleophilic aromatic substitution.⁵⁹

A preliminary proposal for the Au(I) catalyzed C–O cross coupling based on the experimental and DFT study findings provided above is depicted in Scheme 7, involving the formation of the C–O product 4d via the intermediacy of $[\text{Au}(\text{OPh-}p\text{Cl})\text{IPr}]$ and $[\text{Au}(\text{Br})\text{IPr}]$ resting state forms of the catalyst.

CONCLUDING REMARKS

In summary, to the best of our knowledge, we have described the first examples of oxidant-free Au(I)-catalyzed halide exchange and C–O cross coupling reactions. We have shown that a rigid

Scheme 7. Proposed Mechanism of $[\text{Au}(\text{NCMe})\text{IPr}]^+$ Catalyzed C–O Coupling Reaction with **2d and *p*-Chlorophenol**



chelating group is highly beneficial for the catalysis, either using a triazamacrocyclic substrate ($\text{L}_1\text{--X}$ or $\text{L}_5\text{--X}$) or 2-(2-bromophenyl)pyridine (**2d**). It has been shown that there are intrinsic differences compared to Cu and Ag analogous systems. Indeed, Au(I)-catalyzed fluorination reactions were possible for aryl chloride substrates, whereas Ag is inactive.¹³ The mechanistic insight provided suggests catalysis involving two different resting states for the C–O coupling catalysis, both of which we have observed in situ under catalytic conditions. The halide exchange reactions are thought to proceed through a similar pathway, as the active catalysts should be formed in situ upon addition of excess of the halide. However, further investigations are needed to clarify the exact mechanism. This report is a proof of concept of the viability of oxidant-free Au(I)-catalyzed cross-coupling reactions and is envisioned to open new opportunities in Au catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08756.

Chemical compound full characterization; HRMS and NMR monitoring experiments of the catalytic reactions; complete description of computational details; XYZ coordinates for all DFT calculated molecules (PDF)

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Notes

The authors declare no competing financial interest.

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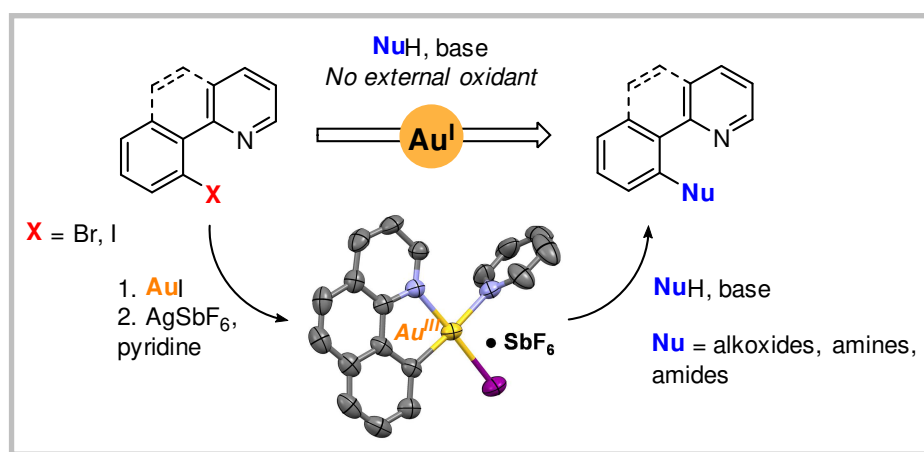
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CHAPTER IV

Au(III)-Aryl Intermediates in Oxidant-Free C-O and C-N Cross-Coupling Catalysis



This chapter corresponds to the following publication:

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For this publication, J. S. performed all the experimental work, wrote the manuscript and was involved in argumentations and discussions. T. P. supervised the NMR experiments and determined the assignment. J. S. contributed in approximately 90%.

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Au(III)-aryl intermediates in oxidant-free C–N and C–O cross-coupling catalysis†

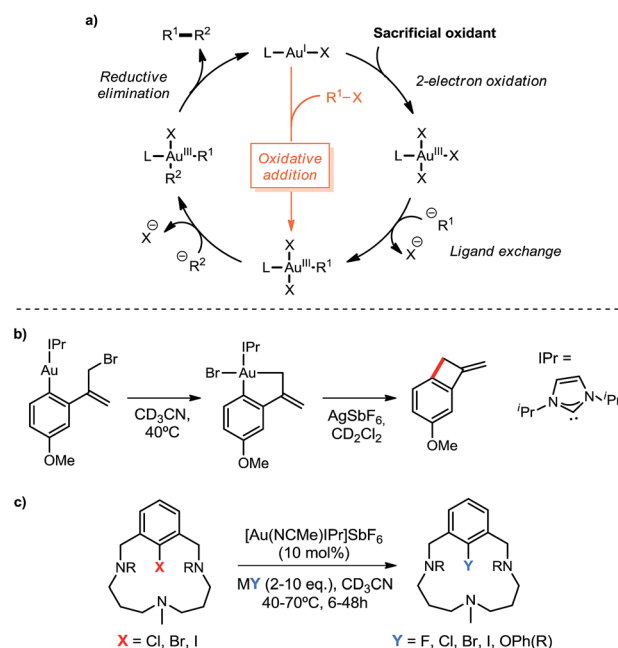
Jordi Serra,^a Teodor Parella^b and Xavi Ribas^{*a}

Au(III)-aryl species have been unequivocally identified as reactive intermediates in oxidant-free C–O and C–N cross coupling catalysis. The crystal structures of cyclometalated neutral and cationic Au(III) species are described and their key role in 2 electron-redox Au(I)/Au(III) catalysis in C–O and C–N cross couplings is shown. Nucleophiles compatible with Au-catalyzed cross couplings include aromatic and aliphatic alcohols and amines, as well as water and amides.

Introduction

In the last few years, the use of gold in homogeneous catalysis has experienced increasing attention and progress. Although typically regarded as superior Lewis acids for the activation of multiple C–C bonds towards nucleophiles,¹ gold complexes have recently found new patterns of reactivity, namely 2-electron redox processes applied to cross-coupling transformations.² In spite of the growing number of examples in this field, the access to key Au(III) intermediates has been limited to harsh sacrificial oxidants, such as I³⁺ derivatives or F⁺ sources (Scheme 1a),³ as well as using highly electrophilic aryldiazonium salts under photoredox conditions or *via* light-driven radical chain reactions.⁴ On the other hand, the straightforward pathway through the oxidative addition of C_{sp}²–X and C_{sp}³–X bonds (X = halide) to Au(I) has generally been regarded as highly reluctant,⁵ markedly differing from other transition-metal chemistry.⁶ However, recent in-depth organometallic investigations have dismissed this conception with remarkable achievements. The first evidence for the intramolecular oxidative addition of aryl halides to gold(I) complexes was disclosed by the Bourissou group in 2014,⁷ showing that phosphine-chelation assistance is key to delivering the C_{sp}²–X bond in close proximity to the gold center, thus promoting the oxidative addition even at room temperature for X = I. The same group later took advantage of the ability of carborane diphosphines to chelate gold(I) with small P–Au–P bite angles, which render

a preorganized architecture closer in energy to the ensuing square-planar geometry of the oxidative addition product. By means of this strategy, intermolecular oxidative addition of aryl iodides and strained C–C bonds under mild conditions was accomplished.⁸ Also in 2014, the Toste group substantiated the ability of gold to perform the elementary steps of organometallic cross-coupling chemistry, including oxidative addition, with the first example of a Au(I)-catalyzed C–C bond formation without the requirement of external oxidants.⁹ A tethered Au(I) aryl complex featuring an allyl bromide moiety allowed to



Scheme 1 (a) Common 2-electron redox mechanistic cycle in Au(I)/Au(III) oxidative catalysis, featuring in orange the alternative oxidative addition pathway to Au(III) intermediates; (b) oxidant-free Toste's allylation of arenes and (c) Ribas' halogen exchange and C–O coupling catalysis.

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† Electronic supplementary information (ESI) available: Detailed synthesis and full characterization of substrates, products and complexes. Crystallographic data for compounds **1ah**, **3a** and **3b**. CCDC 1489676, 1489681 and 1489682, respectively. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc03699f

support this mechanism *via* oxidative addition under intramolecular conditions (Scheme 1b).

In our group we envisioned that a coordinating environment could favor the oxidative addition of Au(I) salts to aryl halides and the following reactivity towards nucleophiles. This strategy, based on attaching a macrocyclic appendage to aryl halide substrates bearing three available nitrogen coordination sites, had actually proved extremely beneficial in the isolation and exhaustive characterization of square pyramidal aryl-Cu(III) and aryl-Ag(III) complexes in the context of $2e^-$ redox M(I)/M(III) cross coupling catalysis.¹⁰ Hence, using this approach we were able to describe the first oxidant-free gold(I)-catalyzed halide exchange and C_{sp^2} -O bond forming reactions (Scheme 1c), additionally transferring this novel chemistry to more easily available substrates such as 2-(2-halophenyl)pyridines.¹¹

In this work we present the expansion of the nucleophile scope from halides and phenols to amines and amides, which stands as the first example of a gold(I)-catalyzed C-N bond formation, resembling the well-known Cu-based Ullmann-type¹² or Pd-based Buchwald-Hartwig cross-coupling catalysis.¹³ Furthermore, the straightforward synthesis and crystallographic characterization of the hitherto new (N,C)-cyclo-metalated Au(III) complexes **3a** and **3b** *via* the oxidative addition of a C_{sp^2} -I bond is also herein described. Their competency as intermediate species in catalytic C-O and C-N couplings is also demonstrated, therefore confirming the redox Au(I)/Au(III) mechanistic cycle previously postulated.

Results and discussion

In the course of our investigations into the oxidant-free gold(I)-catalyzed halogen exchange we found that the applicability of the system could be extended to C-O coupling reactions using sodium *p*-chlorophenolate and, interestingly, sodium methoxide. The latter required its conjugate acid (MeOH) as solvent to proceed, presumably due to the low solubility of the salt in CH_3CN . This prompted us to study the related transformations with other alkoxides and protic solvents. In a similar manner, EtONa was reacted with 2-(2-bromophenyl)pyridine **1a-I** in ethanol (110 °C, $[Au(NCMe)IPr]SbF_6$ as catalyst) and after 24 h a moderate 56% yield of the desired coupling product **1ac** was obtained, which could be increased up to 78% after 48 h (Table 1, entry 6). This can be attributed both to the lower acidity of EtOH compared to MeOH and the larger steric hindrance of the ethoxide. The preference for smaller and more acidic alkoxides was confirmed by carrying out the reaction with MeONa in EtOH, whereby **1ab** was the major product. This trend could be further extrapolated to more sterically demanding alkoxides such as 2-propoxide (**1ad**) and *tert*-butoxide (**1ae**) giving yields of 21% and 4%, respectively (Table 1, entries 7 and 8).

The use of sodium hydroxide as a nucleophile (in H_2O solvent) deserves a special mention. Although in terms of reactivity one might anticipate a similar behavior to sodium methoxide in MeOH (Table 1, entry 3) to readily provide 2-(pyridin-2-yl)phenol **1af**, this was only formed in a 34% yield (Table 1, entry 9). On the contrary, the diaryl ether

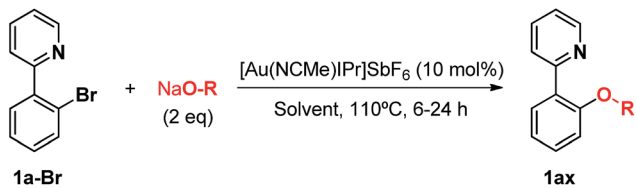
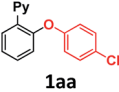
homocoupling product **1ag** was the major product (26% yield). A simple explanation for this outcome involves the deprotonation in basic media of the early-stage generated phenol, which subsequently acts as the preferred nucleophile in the coupling reaction with **1a-Br** starting material. It should be noted that this transformation using NaOH as a base was performed in aqueous media, in the absence of a phase-transfer reagent and without the addition of a co-solvent. In an effort to gain a better understanding of this reactivity, we carried out the same reaction using NaOMe instead of NaOH, and the yield of phenol **1af** increased up to 52% (Table 1, entry 10). These results suggest that control over the selectivity and yield of each product might be achieved by the appropriate modification of the reaction conditions. Notably, the combination of sodium hydroxide and methanol led to the complete formation of the methoxy insertion product **1ab** (Table 1, entry 2).

Overall, we have shown that steric and pH effects play a crucial role in the Au(I)-catalyzed ether and phenol formation, with smaller and more basic alkoxides leading to better results. This methodology allows for the synthesis of 2-(pyridin-2-yl)phenol **1af** in water and 2-(2-methoxyphenyl)pyridine **1ab** and 2-(2-ethoxyphenyl)pyridine **1ac** in moderate to excellent yields, and represents the first example of the Au-catalyzed cross-coupling of aliphatic alcohols to aryl halides. Moreover, gold promotes the coupling of water to form phenols, and the coupling of linear aliphatic alcohols to form ethers, thus presenting a complementary methodology to the Cu-based C-O cross-couplings for these challenging nucleophiles.¹⁴

In light of these promising results, we then sought to expand the Au-catalyzed C-heteroatom reaction scope towards C_{sp^2} -N bond formation through the combination of aryl halides and N-nucleophiles, typically relying on two different approaches: (a) Cu-catalyzed Ullmann-type and (b) Pd-catalyzed Buchwald-Hartwig coupling reactions. As far as we know, this reactivity has only been successfully transferred to nickel.¹⁵ We initially selected *p*-nitroaniline, given its major acidity compared to other amines ($pK_a = 20.9$ in DMSO), as the nucleophile to be reacted with **1a-Br** in the presence of 10 mol% $[Au(NCMe)IPr][SbF_6]$ at 110 °C (Table S1†). Regardless of the base used, in all cases the starting material was recovered. Thus, afterwards, optimization of the solvent was investigated, whereby we obtained a significant and encouraging 39% yield of the desired product in DMSO and with KO*t*-Bu as a base. The same conditions employing the more reactive **1a-I** substrate resulted in almost quantitative yields. The final optimization set the preferred experimental conditions at 110 °C, 24 h and an excess of the nucleophile and 3 equivalents of base for further substrate scoping. It is worth pointing out the high-performance of KO*t*-Bu as a base without competing with *p*-nitroaniline as the nucleophile in the coupling reaction, as foreseen from the C-O bond forming results (Table 1, entry 8). Detailed NMR and X-ray crystallography analysis of the isolated product confirmed the expected structure. Remarkably, a gold-free blank experiment was performed and the reaction did not proceed (0% yield). The sluggishness of the reaction when **1a-Br** is used instead of **1a-I** is in good agreement with a rate-limiting oxidative addition step.



Table 1 Au(i)-catalyzed C–O bond formation with different NaO–R^a

					
Entry	R–ONa	Solvent	Time (h)	Product	Yield ^b (%)
1	<i>p</i> Cl-PhONa	CH ₃ CN	6	 1aa	>99 ^c
2	HONa	MeOH	8	 1ab	>99
3	MeONa	MeOH	8		>99 ^c
4	EtONa	MeOH	24		>99
5	MeONa	EtOH	24	 1ac	86 (9) ^d
6	EtONa	EtOH	24		56 (78) ^e
7	(2-Propoxide)Na ^f	2-Propanol	48	 1ad	21
8	<i>t</i> -BuONa	<i>tert</i> -Butanol	48	 1ae	4
9	HONa	H ₂ O	24	 1af	34 (1af), 26 (1ag)
10	MeONa	H ₂ O	24	 1ag	

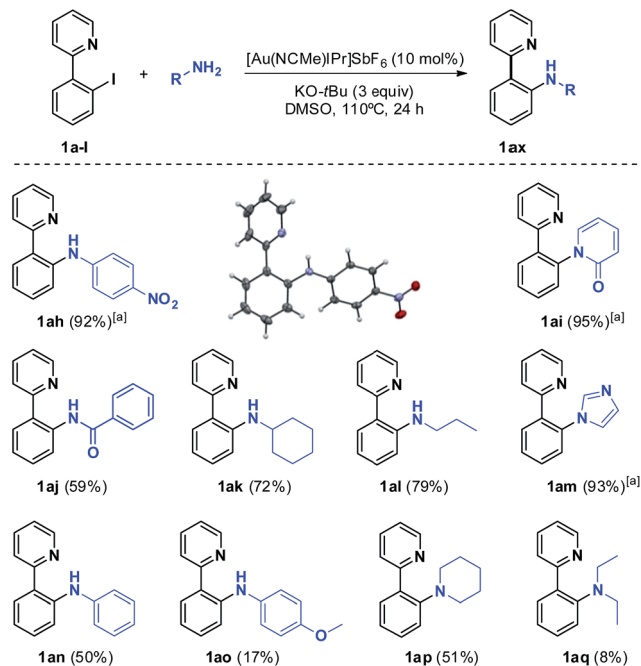
^a General conditions: [2-(2-halophenyl)pyridine] = 20 mM, [alkoxide] = 40 mM, 0.5 mL solvent, 110 °C. ^b Calculated with ¹H-NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. ^c Ref. 11. ^d In parentheses, the yield of the ethoxide insertion product. ^e In parentheses, the yield after 48 h. ^f The alkoxide was generated *in situ* adding 2 equivalents of sodium *tert*-butoxide as a base.

Then the scope of the optimized protocol was examined using different amines and amides. Cyclic aromatic and aliphatic amines and amides (imidazole and 2-hydroxypyridine, Scheme 2, products **1am** and **1ai**) afforded the best results, most likely owing to their superior acidity ($pK_a = 18.6$ and 17.0 in DMSO, respectively).¹⁶ Good outcomes were obtained for primary aliphatic amines (Scheme 2, products **1ak** and **1al**), while secondary amines were less prone to arylation, with moderate and low yields for piperidine (**1ap**) and diethylamine (**1aq**), respectively. Likewise, benzamide was arylated in a moderate yield (59%, **1aj**). Essentially, acidity and steric hindrance seem to be the basis of the observed reactivity trend for the aryl iodide **1a-I**. We then turned our attention to the electronic properties of the *para*-substituents on the aniline ring. In contrast to the excellent results provided by *p*-nitroaniline, aniline did not exceed 50% yield, while *p*-methoxyaniline was poorly arylated (17%, **1ao**). This observation, together

with the data collected for the other N-nucleophiles, indicates sensitivity to less acidic and sterically hindered substrates, which is translated into a decrease in yields. In this system, the Au-based methodology for the arylation of aliphatic amines is superior to Cu-based Ullmann-type couplings.¹⁴

C–N cyclometalated gold(III) complexes have been the subject of deep investigation, ever since the first report of neutral AuCl₂(ppy) containing a 2-phenylpyridine-type ligand by Constable and co-workers.¹⁷ This family of complexes has shown potential anticancer activity¹⁸ and photophysical properties,¹⁹ and their use has benefited from their tolerance to both air and water. The methods to prepare them require either transmetalation from toxic organomercury derivatives or formal C–H auration with gold(III) tri or tetrahalide salts.²⁰ Furthermore, an alternative approach, employing aryldiazonium salts and Au(I) complexes under visible light photoredox conditions, has been developed very recently.^{4c} Nevertheless,

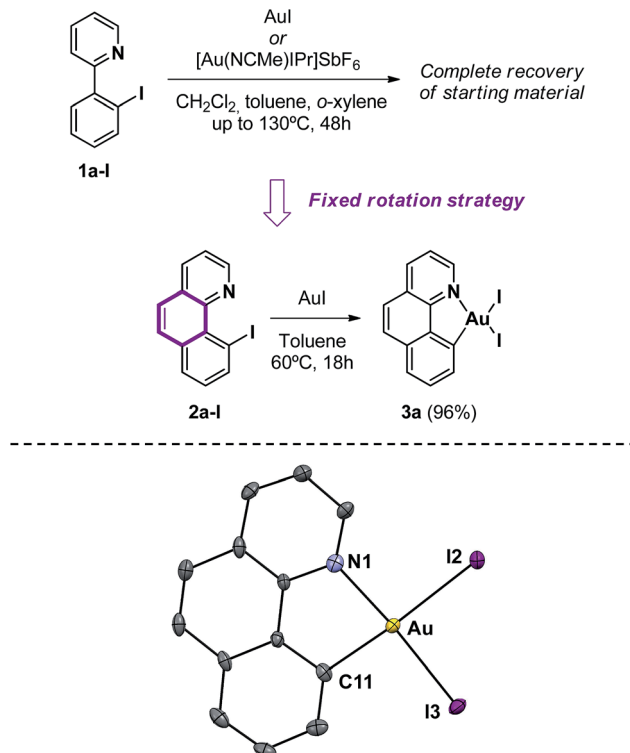




Scheme 2 Substrate scope of the C–N bond forming reactions. ^[a]100 °C.

since their synthesis had not been previously realized *via* the oxidative addition of C_{sp^2} –X bonds, we deemed it worthy to investigate this possibility using the 2-(2-halophenyl)pyridine substrates.

Inspired by the work of Bourissou and co-workers,⁷ we first reacted 2-(2-iodophenyl)pyridine **1a-I** and AuI in dichloromethane at room temperature. However, the complete recovery of the starting materials was observed, even after changing the solvent to toluene and *o*-xylene and heating up to 130 °C. A cationic $[Au(NCCH_3)IPr]SbF_6$ gold(i) source gave identical results, regardless of the reaction conditions. This observation suggests the equilibrium displacement towards more stable reagents (see the ESI,[†] Section 1.6, for details). To tackle the aforementioned difficulties, we envisaged to block the rotation of the pyridine chelating group by incorporating an extra ring into the substrate, aiming at enhancing the stability of the desired product. Consequently, 10-iodobenzo[*h*]quinolone **2a-I** was prepared following a two-step procedure starting from benzo[*h*]quinolone (see the ESI[†]). Gratifyingly, oxidative addition of the C_{Ar} –I bond proceeded readily with AuI at 60 °C for 18 h to give the cyclometalated Au(III) complex **3a** as a red powder (Scheme 3). Complex **3a** withstands air and water indefinitely and is only soluble in CH_2Cl_2 , $CHCl_3$ and DMSO. X-ray-quality crystals were obtained by gently stirring **2a-I** and AuI in CH_2Cl_2 at room temperature for 4 days, followed by slow evaporation of the solvent. The solid-state structure of the complex displays a Au–C bond length of 2.055(7) Å, indicative of a Au(III) center, and a distorted square-planar environment owing to the constraints of the five-membered (N,C) chelate ligand, with a C11–Au–N1 angle of 81.5(3) and an associated N1–Au–I2 angle of 94.8(2).

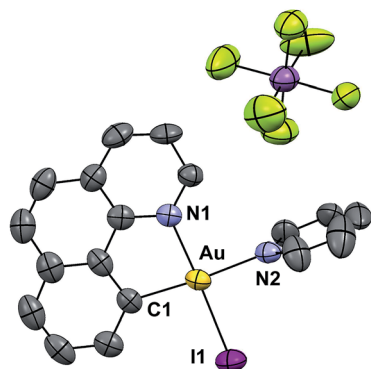
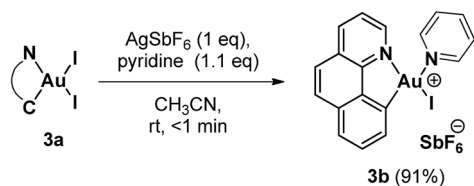


Scheme 3 Synthetic approach to Au(III) complex **3a** and the molecular structure in the solid state. Selected bond lengths [Å] and angles [°]: Au–C(11) = 2.055(7), Au–N(1) = 2.113(8), Au–I(2) = 2.6402(6) and Au–I(3) = 2.5755(7); C(11)–Au–I(3) = 94.5(2), C(11)–Au–N(1) = 81.5(3), I(2)–Au–I(3) = 89.3(2) and N(1)–Au–I(2) = 94.8(2). (Ellipsoids are set at 50% probability; hydrogen atoms have been omitted for clarity).

The bond lengths in **3a** are similar to those reported for the related cyclometalated $[Au(ppy)Cl_2]^{18a}$ and $[Au(tpy)Br_2]^{21}$ complexes. Specifically, the Au–I distances are longer than the analogous Au–Cl and Au–Br ones, consistent with bigger and more labile iodine atoms. The Au–I3 distance (2.5755(7) Å) *trans* to the pyridyl nitrogen is shorter than the Au–I2 distance (2.6402(6) Å) as a result of the greater structural *trans* influence of the aryl group. Most diagnostic of the formation of a C–Au(III) bond is the low-field shift of the ¹H-NMR signal corresponding to the α -proton in the pyridine moiety from δ 9.11 in **2a** to 10.35 ppm, as well as the disappearance of the ¹³C-NMR signal of the C–I atom at δ 88.9 ppm and the appearance of a new signal at δ 153.6 ppm, corresponding to the quaternary carbon ligated to the Au(III) center.

With neutral **3a** in hand, we next investigated the abstraction of iodide using 1 equivalent of AgSbF₆ in order to generate a more soluble and reactive cationic complex (Scheme 4). The reaction was carried out in acetonitrile due to its coordinating properties, but no changes were detected after vigorously stirring for 3 hours at room temperature. At this point we hypothesized that the medium-strength Lewis base character of acetonitrile cannot efficiently stabilize a three-coordinate gold(III) species, and consequently a stronger Lewis base was employed. Upon the addition of pyridine (1.1 equiv.), **3a** was immediately consumed and the solution turned bright yellow

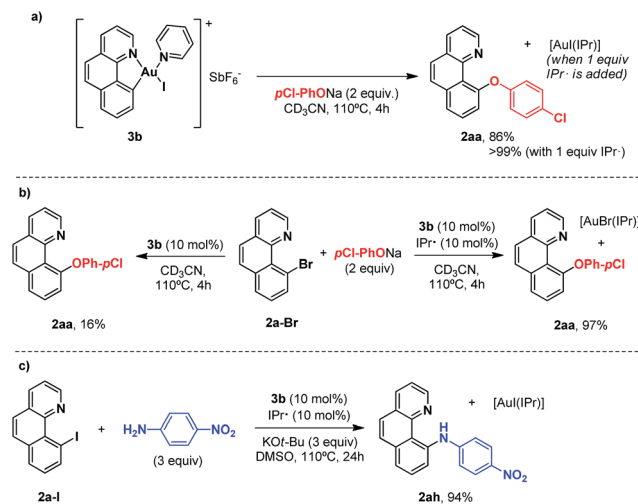




Scheme 4 Synthetic approach to Au(III) complex **3b** and the molecular structure in the solid state. Selected bond lengths [Å] and angles [°]: Au–C(1) = 2.023, Au–N(1) = 2.068(7), Au–N(2) = 2.119(8) and Au–I(1) = 2.556(2); C(1)–Au–I(1) = 95.1(3), C(1)–Au–N(1) = 82.8(3), N(2)–Au–I(1) = 89.2(2) and N(1)–Au–N(2) = 93.0(3). (Ellipsoids are set at 50% probability; hydrogen atoms have been omitted for clarity).

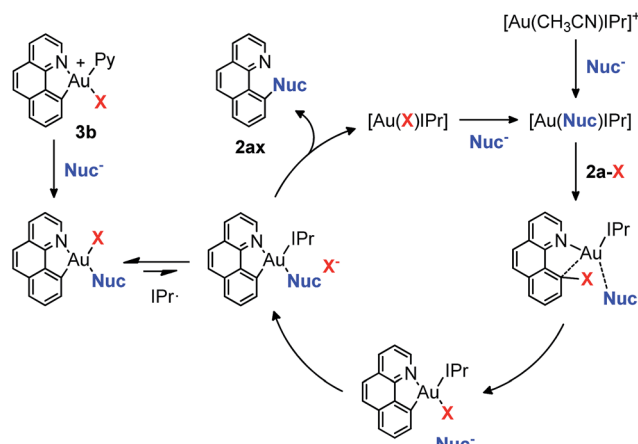
with the formation of an abundant grey precipitate (AgI). Complex **3b** was isolated as an orange powder after filtration and solvent removal (91% yield). **3b** is also air- and moisture-stable and can be stored on the benchtop without noticeable decomposition. The ESI-HRMS mass spectrum of this complex shows one major peak at m/z 580.9782 corresponding to the mass of $[(2a)Au(I)Py]^+$, the cationic fragment of **3b**. Low-temperature ^1H -NMR (248 K) allowed the structural characterization of **3b** in solution (see the ESI†). Crystals of this complex, grown from the slow diffusion of diethyl ether in a CH_3CN solution of the compound, confirmed the removal of the iodide *trans* to the Au–C bond, as expected from the larger *trans* effect (Scheme 4).

In our previous studies on gold(I)-catalyzed halogen exchange and C–O bond formation we proposed a mechanism operating through the general two-electron-based Au(I)/Au(III) cycle (Scheme 6),¹¹ albeit the high-valent $[Au(2a)(IPr)X]$ (X = halide or phenolate) species could not be detected. In this regard we reasoned that the cationic Au(III) complex **3b** might be helpful in trying to unveil the involvement of aryl-Au(III) species in this oxidant-free transformation. First, 1 equivalent of complex **3b** was subjected to the same conditions as used for the *p*-chlorophenolate insertion with 2-(2-bromophenyl)pyridine **1a-I** and the desired 10-(4-chlorophenoxy)benzo[*h*]quinoline **2aa** was obtained in 86% yield (Scheme 5a), validating the feasibility of aryl-Au(III) species in Au(I)-catalyzed cross couplings. Nonetheless, an analogous experiment starting from 10-bromobenzo[*h*]quinolone **2a-Br** and catalytic amounts of **3b** (10 mol%) provided almost 2 catalytic turnovers (16% yield of product **2aa**, Scheme 5b). Therefore, 10 mol% of the N-heterocyclic carbene donor ligand IPr $\cdot$ (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene)



Scheme 5 (a) Stoichiometric reactions of complex **3b** with sodium *p*-chlorophenolate in the absence and in the presence of the NHC ligand IPr. (b) Catalytic version, with and without IPr, starting from **2a-Br**, and (c) analogous coupling of *p*-nitroaniline to **2a-I** with IPr.

employed in the catalytic transformations was also added, and we were pleased to find that virtually quantitative yields of **2aa** were achieved (Scheme 5b). Equal behavior was found with the *p*-nitroaniline insertion to **2a-I** (Scheme 5c), overall unequivocally substantiating the implication of aryl-Au(III) species as competent catalytic intermediates. **3b** rapidly generates the neutral complex $[Au(2a)(Nuc)X]$ (X = Br, I) in the presence of a nucleophile (Scheme 6). Then, the IPr $\cdot$ carbene exchanges one of the anionic ligands to form the less favored $[Au(2a)(IPr)Nuc]$ intermediate, which rapidly reductively eliminates the cross-coupling product (**2ax**) and gold(I) as $[Au(X)IPr]$.¹¹ Strikingly, ^1H -NMR inspection of the crude product proved that all the Au(I) remained in solution in this resting state form. On the other hand, attempts to isolate the $[Au(2a)(IPr)Nuc]$ species generated in solution when IPr $\cdot$ is added were fruitless, supporting their short-lived nature in the catalytic cycle.



Scheme 6 Proposed mechanism of the Au(I)-catalyzed cross-coupling reactions operating via aryl-Au(III) intermediates. X = Br, I.



Conclusions

In conclusion, we have developed the first examples of gold(i)-catalyzed C–N cross-coupling reactions in the absence of sacrificial oxidants, in parallel to the well-established Cu- and Pd-catalyzed methodologies, and extended the previously described C–O coupling catalysis with phenols to aliphatic alcohols and water. This system allows entry to different aryl-amine, arylamide, phenol and aryl-ether products under practical synthetic laboratory conditions, with absolute tolerance for both air and water. In either case, the acidity of the nucleophile is at the basis of the reactivity observed. Moreover, we have synthesized novel neutral and cationic C–N cyclometalated Au(III) complexes through mild oxidative addition of a C_{sp}²–I bond to gold(i) iodide, and presented conclusive evidence of their competence in the C–O and C–N coupling transformations. To the best of our knowledge, this represents the first example in which the intermediacy of Au(III) species in an oxidant-free 2-electron coupling processes is demonstrated, clarifying the proposed mechanism operating *via* oxidative addition and reductive elimination steps. Future work is directed towards investigating other suitable chelating groups for a more versatile system, with special interest in removable directing groups.

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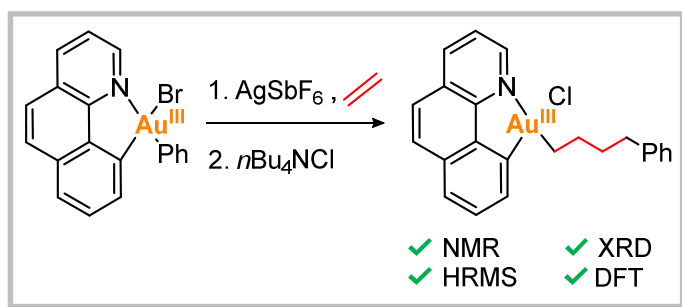


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CHAPTER V

Cyclometalated Gold(III) Complexes: Noticeable Differences between (N,C) and (P,C) Ligands in Migratory Insertion



This chapter corresponds to the following publication:

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J. S. performed most of the experimental work concerning with this publication, was involved in discussions and contributed in writing the manuscript. P. F. carried out the D-labelling experiments with ethylene-*d*₂. S. M.-L. collected and analyzed the XRD data. E. D. S. C. and K. M. performed the DFT studies. J. S. contributed in approximately 50%.

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Cyclometalated gold(III) complexes: noticeable differences between (N,C) and (P,C) ligands in migratory insertion†

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Gold(III) complexes are garnering increasing interest for opto-electronic, therapeutic and catalytic applications. But so far, very little is known about the factors controlling their reactivity and the very influence of the ancillary ligand. This article reports the first comprehensive study on this topic. The reactivity of a cationic (N,C) gold(III) complex, namely **1A**, towards ethylene has been thoroughly studied and compared with that of the related (P,C) complex **1C**. A cationic gold(III) complex **5A** resulting from double insertion of ethylene was selectively obtained. Complex **5A** was found to be remarkably stable. It was trapped with chloride and fully characterized. In marked contrast to that observed with **1C**, no β -H elimination or linear-to-branched rearrangement of the alkyl chain occurred with **1A**. The energy profile for the reactions of **1A** with ethylene has been comprehensively investigated computationally, and the influence of the ancillary ligand has been precisely delineated. Because nitrogen is a weaker donor than carbon (and phosphorus), the (N,C) ligand is very electronically dissymmetric, much more than the (P,C) ligand. This makes the two reactive sites at gold quite different, which noticeably influences the competition between migratory insertion and β -H elimination, and actually changes the outcome of the olefin insertion at gold. This study provides valuable insight into the influence of ancillary ligands on gold(III) reactivity, something critical to further develop Au(III) and Au(I)/Au(III) catalysis.

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Introduction

The past few years have witnessed spectacular development in gold(III) chemistry.^{1–4} Au(III) complexes display very interesting luminescence properties^{5,6} and biological activities,^{7,8} and increasing efforts are made to develop their opto-electronic and therapeutic applications. Au(III) complexes also show unique catalytic properties, for the electrophilic activation of π -CC

bonds and carbonyl compounds, and as intermediates in Au(I)/Au(III) redox cycles.^{3,9–11}

Hard C- and N-based ligands occupy a forefront position in gold(III) chemistry.^{1,12} In particular, (N,C) cyclometalated complexes **A**, and (C,N,C) and (N,C,C) pincer complexes **B** and **B'** offer a unique balance between stability and properties (Scheme 1).^{6,10c,d,13–15} Strikingly, soft P donors have also proved recently to efficiently stabilize gold(III) species.¹⁶ (P,C) cyclometalated gold(III) complexes **C** (which are readily available by chelate-assisted oxidative addition of C–X bonds)^{16a} have been shown to display rich reactivity.^{16b–f} Unprecedented elementary organometallic reactions such as migratory insertion of alkenes^{16b,c,e} and β -hydride elimination^{16d} have been evidenced, enlarging the portfolio of chemical transformations of gold complexes.²

To progress and develop further the chemistry of gold(III) complexes, it is critical to better understand how their properties and reactivity are influenced by ancillary ligands. It was precisely the focus of this work to bridge the gap between widespread (N,C) gold(III) complexes and recently introduced (P,C) gold(III) species, and to try to answer the following questions:

(i) Is the unprecedented reactivity recently evidenced with (P,C) gold(III) complexes specific to this ligand set or is it general? In other words, are (N,C) gold(III) complexes also prone to migratory insertion and β -H elimination?

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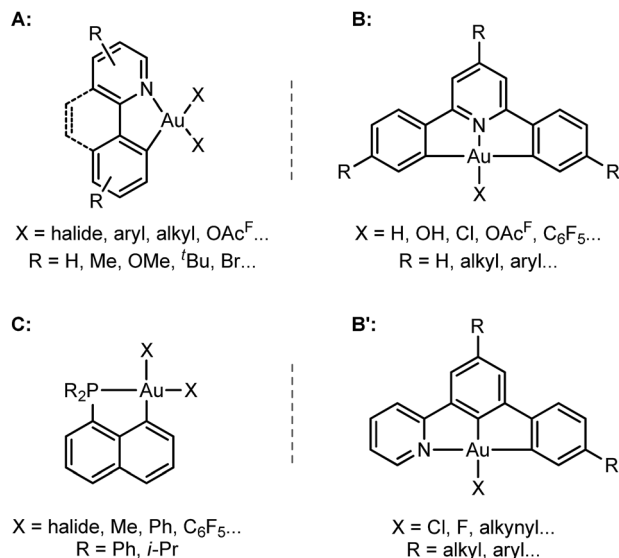
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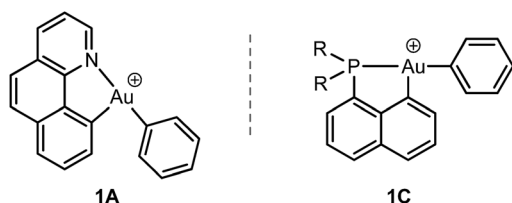
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† Electronic supplementary information (ESI) available: Detailed experimental conditions and procedures, analytical data, theoretical details (PDF), crystallographic data for compounds **5A-H₂O** and **5A-Cl**, and DFT optimized structures (XYZ). CCDC 1574199 and 1574200. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc04899h



Scheme 1 General structures of (N,C), (C,N,C), (N,C,C) and (P,C) gold(III) complexes A–C.



Scheme 2 Structures of the (N,C) and (P,C) cationic gold(III) complexes studied and compared in this work.

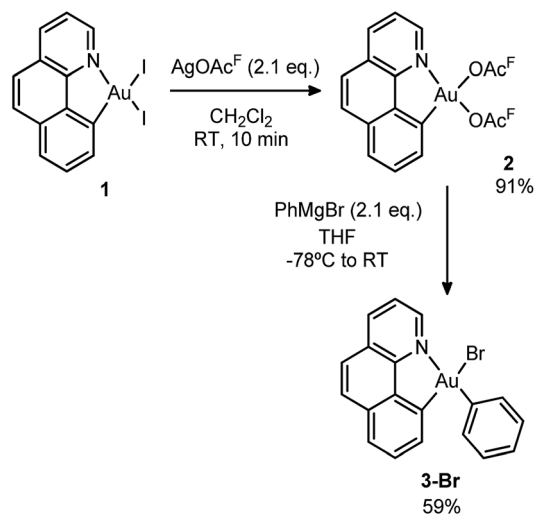
(ii) What is the precise influence of the ancillary ligand on reactions with alkenes? Does it affect the kinetics and thermodynamics? Does it change the mechanism and/or fate of the reaction?

To this end, we studied a cationic tricoordinate (N,C) gold(III) complex, namely $[(\text{N,C})\text{AuPh}]^+ \mathbf{1A}$ (Scheme 2), and we report here a detailed investigation of its reactivity towards ethylene. This study draws some analogies with the related $[(\text{P,C})\text{AuPh}]^+$ complex $\mathbf{1C}$,^{16e} but also reveals noticeable differences. The weaker donicity of N *versus* P makes the (N,C) ligand much more electronically dissymmetric than the (P,C) ligand. As shown by detailed DFT investigations of the reaction profiles, these electronic properties noticeably influence the balance between the different reaction paths and eventually change the outcome of the ethylene insertion at gold. To the best of our knowledge, this is the first time that the impact of ancillary ligands on gold(III) reactivity is thoroughly explored.

Results and discussion

Reaction of the $[(\text{N,C})\text{AuPh}]^+$ complex $\mathbf{1A}$ with ethylene

Initially, we attempted the selective mono-arylation of the $[(\text{N,C})\text{AuI}_2]$ complex $\mathbf{1}$, which was recently prepared *via* $\text{C}_{\text{AR}}\text{--I}$ oxidative addition to Au(I) ,^{13f} following the same synthetic procedure as



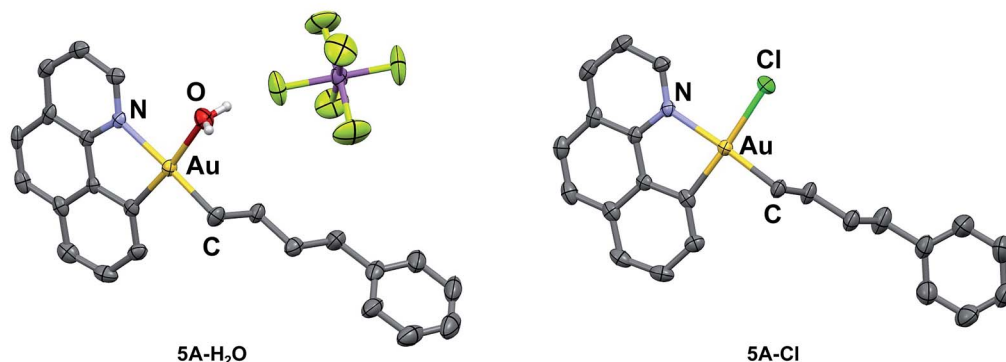
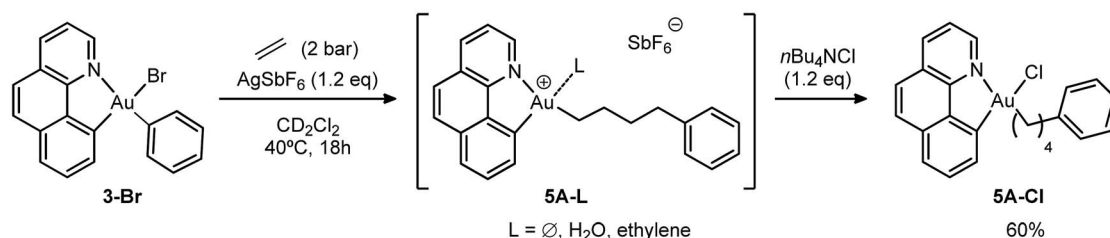
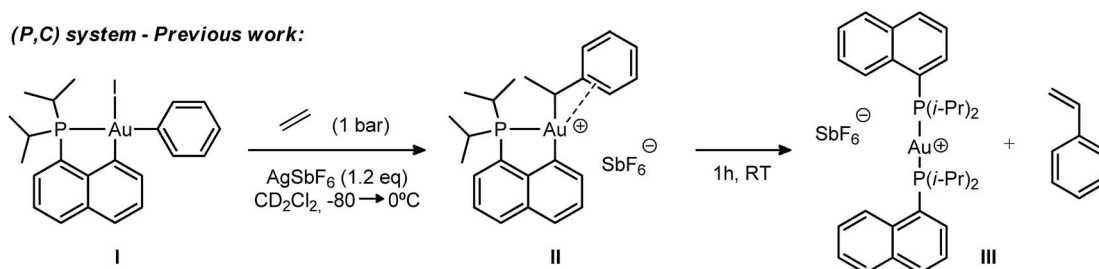
Scheme 3 Synthesis of the Au(III) complex $\mathbf{3-Br}$, precursor to $\mathbf{1A}$.

that described for the $[(\text{P,C})\text{AuI}_2]$ complex.^{16e} However, treatment of $\mathbf{1}$ with PhMgBr led to an intractable mixture of products. Hopefully, exchange of iodines at gold for more labile trifluoroacetate groups (complex $\mathbf{2}$) allowed for the synthesis of the desired $[(\text{N,C})\text{AuBrPh}]$ complex $\mathbf{3-Br}$ (Scheme 3), applying the conditions reported by Tilset and co-workers.¹⁷ Complex $\mathbf{3-Br}$ was isolated as a white powder in 59% yield after column chromatography and characterized by NMR spectroscopy and high-resolution mass spectrometry (HRMS).¹⁸

The cationic $[(\text{N,C})\text{AuPh}]^+$ complex $\mathbf{1A}$ was then generated by abstracting the bromide at the Au(III) atom with AgSbF_6 in dichloromethane under ethylene pressure (2 bar). No changes were observed within 72 h at room temperature, whereas upon heating at 40°C for 18 h, complete conversion into a new species with aliphatic signals above δ 1.8 ppm was achieved (Scheme 4). Moreover, crystals formed spontaneously in small amounts inside the NMR tube, and X-ray diffraction analysis revealed double insertion of ethylene plus coordination of one molecule of adventitious water (Scheme 4). At this point, aiming at generating a more stable neutral four-coordinate gold(III) complex to allow for easier handling and characterization,^{16d,e} we quenched the reaction crude with $n\text{Bu}_4\text{NCl}$. A white solid was isolated in 60% yield and characterized by multinuclear NMR spectroscopy and HRMS as $\mathbf{5A-Cl}$. The relative integration of the aromatic and aliphatic signals in the ^1H NMR spectrum (13 *versus* 8H), and the peak at m/z 508.1346 corresponding to the mass of $[(\text{N,C})\text{AuPh}]^+$ augmented by two ethylene molecules, corroborated the double insertion into the Au–Ph bond. The solid-state structure of the complex $\mathbf{5A-Cl}$ was also determined by X-ray crystallography.¹⁸ The gold atom sits in a square-planar environment formed by the (N,C) chelate ligand, the Cl atom and the $(\text{CH}_2)_4\text{Ph}$ chain located *cis* to the aryl moiety.

The stability of the cationic gold complex $\mathbf{5A}$ generated under these conditions contrasts with the instability of $\mathbf{1A}$. In the absence of ethylene, the latter fully decomposes within 6 h in solution at room temperature into several side-products and metallic gold. At this stage, and without knowing the precise



(N,C) system - This work:**(P,C) system - Previous work:**

Scheme 4 Reactions of the (N,C) and (P,C)-ligated gold(III) complexes **1A** and **1C** with ethylene, and the molecular view of **5A-H₂O** and **5A-Cl** with thermal ellipsoids drawn at the 50% probability level (hydrogen atoms have been omitted for clarity).

structure of **5A** due to its ill-defined ^1H NMR spectrum (the fourth coordination site at gold may be occupied by the SbF_6^- counter anion, the pendant Ph ring, an H_2O or ethylene molecule), it is difficult to rationalize this difference.

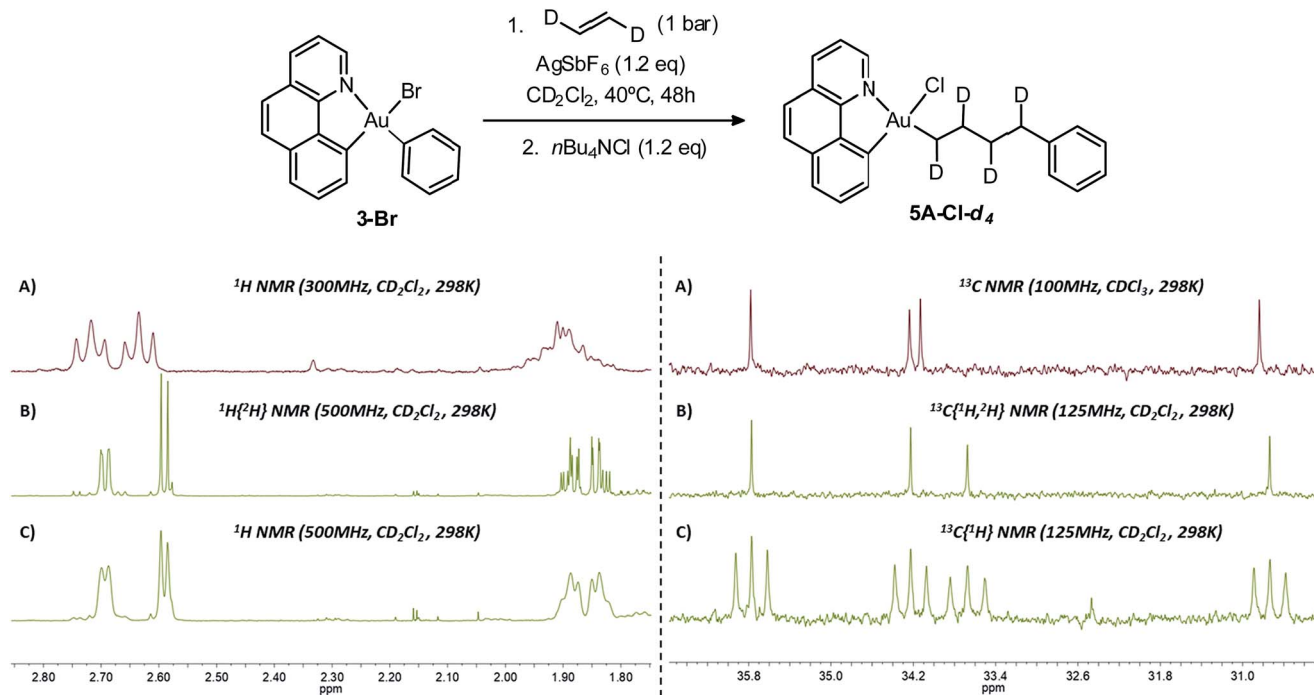
The double addition of ethylene to complex **1A** is reminiscent of the insertion of two norbornene (NB) molecules into the Au–Me bond of the (P,C)-ligated gold(III) dimethyl complex.^{16b,c} In this process, the insertion of a second NB into the Au–C_{norbornyl} bond gives access to a more thermodynamically stable complex, with the Au–C_{norbornyl} bond at the *trans* position relative to phosphorus. In a likewise manner, the strong *trans* influence of the benzoquinolinic carbon in **1A** triggers the migration of the alkyl group by insertion of a second ethylene molecule at the *cis* position relative to the aryl moiety (see DFT calculations below). In spite of the presence of a hydrogen atom at a β position and the tendency of cationic low-coordinate gold(III) alkyl complexes to undergo β -H elimination,^{16d} complex **5A** shows unusual thermal stability and no formation of styrene or higher olefins was detected during the course of the reaction. This is in stark contrast to the behaviour of the [(P,C)AuPh]⁺ complex **1C**, where, after ethylene insertion, a β -H

elimination and re-insertion sequence takes place leading to the gold(III)–arene complex **II**, which after 1 h at room temperature eventually evolves into the linear gold(I) complex **III** by reductive elimination, styrene release and ligand redistribution (Scheme 4, bottom).^{16e}

D-labeling experiment

To assess the possible occurrence of β -H elimination in competition with ethylene insertion, a D-labeling experiment was carried out using *trans*-ethylene- d_2 (Scheme 5). The reaction conditions have been adapted to enable the use of *trans*-ethylene- d_2 which was supplied by Cluzeau Info Labo in a lecture bottle (1 atm, 95.2% D). Using an atmospheric pressure of ethylene, complete conversion was achieved after two ethylene refillings and 2×24 hours heating at 40°C . The reaction was then repeated with *trans*-ethylene- d_2 using the same experimental conditions.¹⁸ The reaction mixture was then trapped with $n\text{Bu}_4\text{NCl}$ and analysed by NMR spectroscopy. The ^1H NMR spectrum shows the expected integration and pattern for the Au(CHD)₄Ph enchainment (Scheme 5): the two terminal





Scheme 5 D-labeling experiment using *trans*-ethylene- d_2 affording selectively the **5A-Cl-d₄** product. Aliphatic ^1H and ^{13}C NMR signals of **5A-Cl** (A) and **5A-Cl-d₄** (B, C), as obtained by the analysis of the reaction crudes. In the case of the complex derived from *trans*-ethylene- d_2 , deuterium-decoupled (B) and deuterium-coupled (C) NMR analyses are shown.

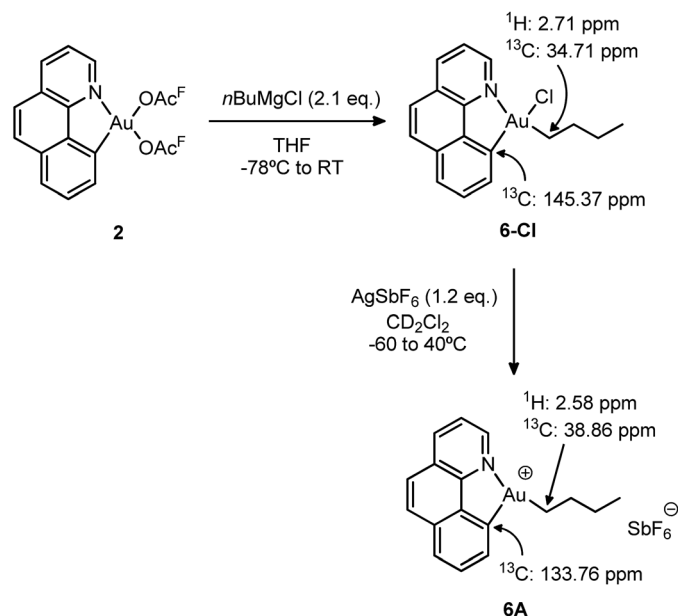
CHD moieties resonate as doublets compared to triplets for the non-deuterated complex (**5A-Cl**). Consistently, the corresponding ^{13}C NMR signals all appear as 1 : 1 : 1 triplets in the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum. There is very little sign of H/D scrambling, if any, confirming that β -H elimination does not occur to a significant extent under these conditions and that ethylene insertion prevails.

Synthesis and characterization of the $[(\text{N,C})\text{Au}(n\text{Bu})]^+$ complex **6A**

To gain a better understanding of the reluctance of complex **5A** to undergo β -H elimination, the analogous gold(III) *n*-butyl complex **6-Cl** was synthesized and the behaviour of its cationic version was investigated (Scheme 6). The selective monoalkylation of $[(\text{N,C})\text{Au}(\text{OAc}^F)_2]$ complex **2** was successfully accomplished using 2.1 equiv. of the Grignard reagent $n\text{BuMgCl}$ under identical conditions to those applied for the preparation of the $[(\text{N,C})\text{AuBrPh}]$ complex **3-Br**. After column chromatography, the target $[(\text{N,C})\text{AuCl}(n\text{Bu})]$ **6-Cl** complex was isolated as a bench-top stable white powder in 73% yield and characterized by multinuclear NMR spectroscopy and high-resolution mass spectrometry.¹⁸

We then proceeded with the generation of the corresponding cationic gold(III) complex **6A** by chloride abstraction with AgSbF_6 in CD_2Cl_2 . As indicated by ^1H NMR, it is instantaneously formed at -60°C and it remains unchanged upon warming up to room temperature. No signs of degradation or β -H elimination (formation of butenes and butane) were observed by ^1H and ^{13}C NMR, even after heating at 40°C for 24 h. In consequence,

the cationic complex was fully characterized by NMR spectroscopy at room temperature without particular precautions. The ^{13}C NMR data reveal a significant shift to high field of the aromatic carbon directly bound to gold upon cationization (from δ 145.37 ppm in the neutral complex **6-Cl** to δ 133.76 ppm in the cationic complex **6A**). On the other hand, the alkylc



Scheme 6 Synthesis of the *n*-butyl complexes **6-Cl** and **6A** and the most diagnostic ^1H and ^{13}C NMR shifts.



carbon of the *n*-butyl chain attached to gold shifts to low field with $\Delta\delta = 4.6$ ppm. Overall, the salient thermal stability of the *n*-butyl cationic complex is in accordance with the lack of β -H elimination in the ethylene insertion reaction of $[(N,C)AuPh]^+$ complex **5A**.

In order to explain the double insertion of ethylene and selective formation of **5A**, and to understand the different outcomes observed with the (N,C) and (P,C) complexes, a thorough DFT study was performed.

Computational investigation of the energy profile for the reaction of **1A** with ethylene

DFT calculations were carried out at the B3PW91/SDD + f(Au),6-31G** (other atoms) level of theory. Solvent effects (DCM) were taken into account by means of a polarizable continuum model (PCM).¹⁸ Two energy minima corresponding to the *cis* and *trans* isomers of **1A** were found on the potential energy surface (PES) (Fig. 1). By convention, *cis* and *trans* refer to the relative position of the phenyl (or alkyl group) at gold with respect to the carbon atom of the benzoquinolinic ligand. The *cis* isomer **1A** is much more thermodynamically stable (by 36.2 kcal mol⁻¹), in line

with the detrimental *trans* arrangement of the phenyl and benzoquinolinic carbon atoms in **t-1A**.

1. First ethylene insertion. Compared to **1A** in its ground-state *cis* geometry, the π -complex of ethylene **2A** is slightly downhill in energy ($\Delta G -3.4$ kcal mol⁻¹) (Fig. 1). The alkene is coordinated in a symmetric fashion (two short Au...C contacts at 2.40 Å). It is oriented perpendicular to the metal coordination plane^{16c,19,20} and the CH₂ moiety atoms remain quasi-planar, in line with strong $\pi(CC) \rightarrow Au$ donation and weak $Au \rightarrow \pi^*(CC)$ backdonation, as apparent from the NBO second order perturbation analysis (stabilization energies for the donor-acceptor interactions of 45.7 and 14.1 kcal mol⁻¹, respectively). Insertion of ethylene into the Au-Ph bond then proceeds *via* a planar 4-center transition state. The resulting Au complex **3A** is stabilized by π -arene coordination *trans* to the weak N donor ($Au \cdots C_{ortho}$ and $Au \cdots C_{ipso}$ contacts of 2.21 and 2.71 Å, respectively and NBO second order stabilization energies for the $\pi(C_{ipso}C_{ortho}) \rightarrow \sigma^*(AuN)$ donor-acceptor interaction of 31.0 kcal mol⁻¹).²¹ The activation barrier for the migratory insertion is 20.7 kcal mol⁻¹ and the reaction is endergonic ($\Delta G +5.6$ kcal mol⁻¹). The involvement of the *trans* isomer **t-1A** was also considered, but as mentioned above, it lies very high in energy (36.2 kcal mol⁻¹ above the *cis* isomer) and is thus very unlikely to participate. Note however that the very unfavourable *trans* arrangement of the two organic fragments makes the coordination-insertion of ethylene into **t-1A** very easy and strongly exergonic. Although the resulting insertion product **c-3A** is more stable than **3A** by 22.0 kcal mol⁻¹, its involvement is unlikely because the barrier for *trans* $\rightarrow$ *cis* isomerization is also very high (28.2 kcal mol⁻¹) due to the necessity to break the strong π -arene interaction.

2. Second ethylene insertion versus β -H elimination. In line with experimental observations, the insertion of a second ethylene molecule is highly favoured. Displacement of the π -arene coordination at **3A** by ethylene is about thermoneutral and migratory insertion then proceeds with a very low energy barrier (6.6 kcal mol⁻¹ for **3A**) to give the (CH₂)₄Ph complex **5A** (Fig. 2). The extended linear form **5A** is slightly more stable (by 2.5 kcal mol⁻¹) than the γ -CH agostic stabilized one **5A- γ** [$\sigma(CH) \rightarrow \sigma^*(AuC)$ donor-acceptor interaction is found at the second-order perturbation level in NBO].^{18,22} β -H elimination from **3A** was also considered. In line with that observed for $[(P,C)Au(n\text{-alkyl})]^+$ complexes, the activation barrier for β -H elimination is low (only 2.8 kcal mol⁻¹) and because of the unfavourable *trans* arrangement of **3A**, the formation of the gold hydride styrene complex **7A** is thermodynamically favoured (by 14.4 kcal mol⁻¹, ΔG). Rotation of styrene and re-insertion into the Au-H bond may occur to give the branched complex **8A** as in the case of the (P,C) complex, but the corresponding energy barrier is relatively high (20.9 kcal mol⁻¹). From a kinetic viewpoint, the second ethylene insertion and β -H elimination from **3A** are likely to compete, but the absence of noticeable H/D scrambling upon reaction with ethylene-*d*₂ (Scheme 5) indicates a minimal occurrence, if any, of β -H elimination. The easiness of the re-insertion of styrene into **7A** ($\Delta G^\ddagger 17.2$ kcal mol⁻¹) combined with the high exergonic character of the second ethylene insertion into **3A** drives the reaction to the formation of **5A**.

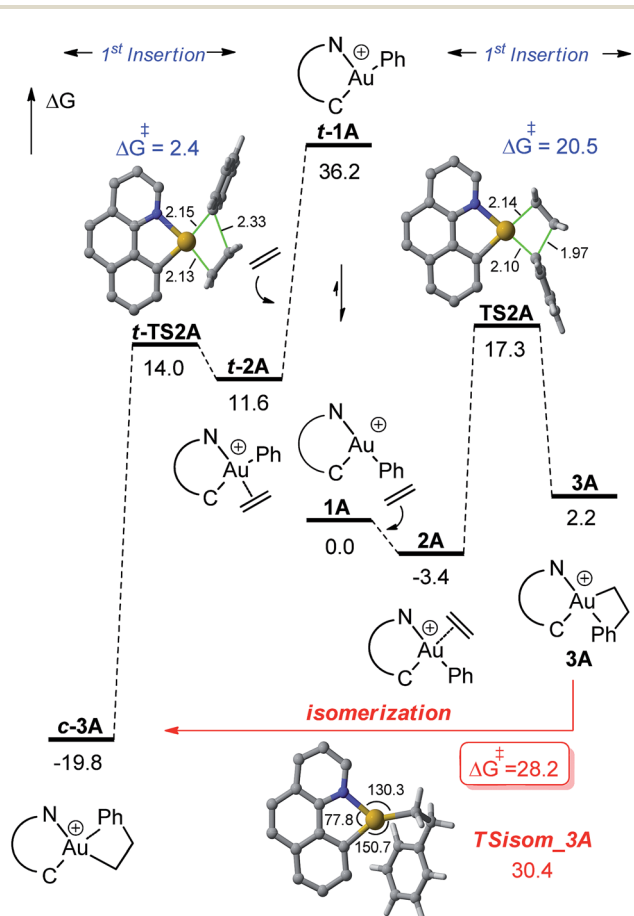


Fig. 1 Energy profile (ΔG in kcal mol⁻¹) computed at the PCM(dichloromethane)-B3PW91/SDD + f(Au)/6-31G** (other atoms) level of theory for the insertion of ethylene into the Au-Ph bond of **1A** (*cis* and *trans* isomers).



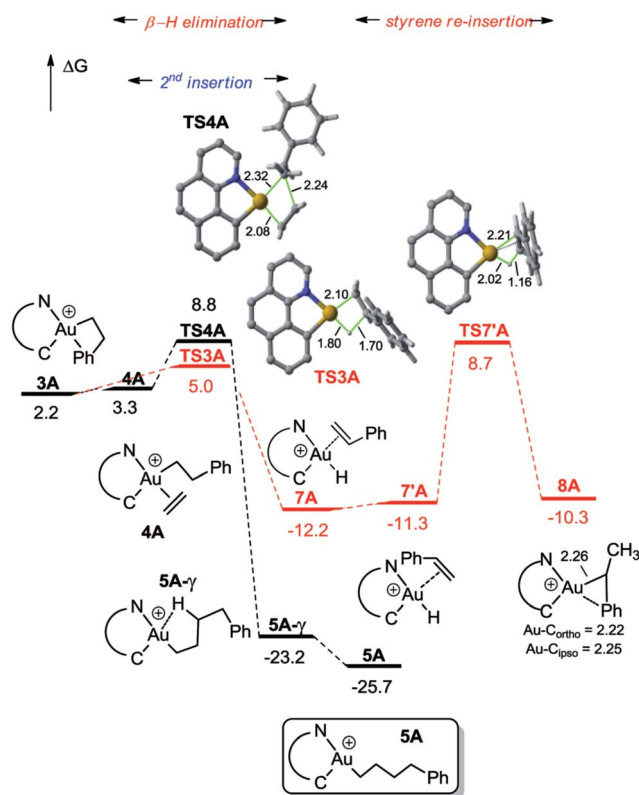


Fig. 2 Energy profile (ΔG in kcal mol⁻¹) computed at the PCM(dichloromethane)-B3PW91/SDD + f(Au)/6-31G**(other atoms) level of theory for the second ethylene insertion and β -H elimination from 3A.

For the sake of completeness, β -H elimination, γ -H transfer and third ethylene insertion into 5A, as well as second ethylene insertion into 8A have been considered but all these transformations were found to be kinetically or thermodynamically

disfavoured (Fig. S7 and S9–S11[†]).¹⁸ The same holds true for the second ethylene insertion and β -H elimination from **c-3A**, the more stable isomer of the first ethylene insertion. It is in particular worth noting that if the activation barrier for β -H elimination from 5A is not prohibitively high (19.0 kcal mol⁻¹), the reaction is strongly endergonic (ΔG 18.5 kcal mol⁻¹) due to the unfavourable *trans* arrangement of the resulting gold hydride olefin complex. This probably explains the stability of the [(N,C)Au(*n*Bu)]⁺ complex 6A noticed experimentally. The activation barrier for the third ethylene insertion is *ca.* 17 kcal mol⁻¹ higher than that of the first insertion, in line with the higher reactivity of the Au–C_{sp}² vs. Au–C_{sp}³ bond, as previously observed with the [(P,C)Ph]⁺ and [(P,C)AuMe]⁺ complexes.^{16d,e}

Comparison of the (N,C) and (P,C) complexes

The above discussion has pointed out noticeable differences between the (N,C) and (P,C)-ligated gold complexes which are mainly associated with the weaker donor character of N *versus* P. As a result, the (N,C) ligand induces significant electronic dissymmetry on gold compared to the (P,C) ligand, and the two reaction sites *trans* to N or C (*cf.* square-planar geometry of the Au(III) complexes) behave quite differently, as previously noticed by Tilset, Nova and co-workers for the tolylpyridine (tpy) ligand.^{13c,d}

To confirm and highlight the difference in the electronic properties of the ligand, calculations were performed on the naked [(N,C)Au]²⁺ and [(P,C)Au]²⁺ fragments (Fig. 3).¹⁸ In both cases, the LUMO corresponds to the vacant orbital at Au at the *trans* position to the N or P [main contribution of the $\sigma^*(\text{Au-N})$ (Au–P) orbitals]. It is significantly lower in energy (by 1 eV) with the (N,C) ligand. In contrast, the LUMO + 1 orbitals of the two fragments, which correspond to the vacant orbitals at Au at the *trans* position to the aryl moiety, lie close in energy. Thus, the

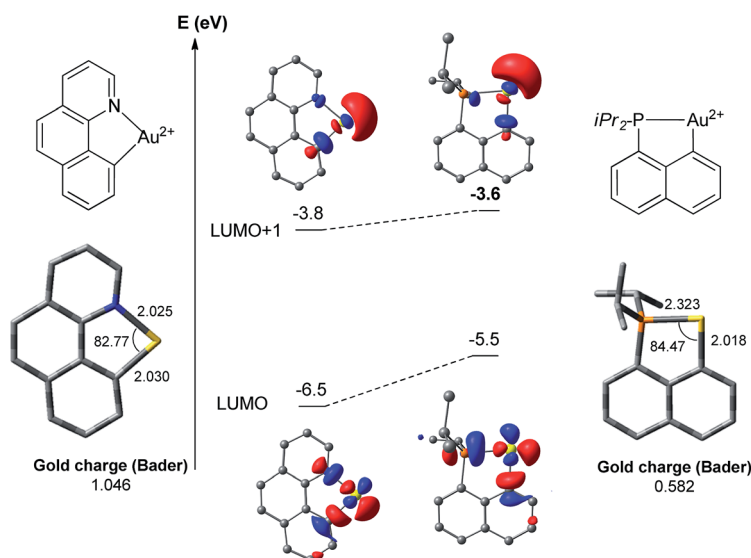


Fig. 3 Optimized structures (with selected geometrical data) and the lowest energy molecular orbitals of the [(N,C)Au]²⁺ and [(P,C)Au]²⁺ fragments computed at the PCM(dichloromethane)-B3PW91/SDD + f(Au)/6-31G**(other atoms) level of theory.



(N,C) ligand induces a significantly larger LUMO–LUMO + 1 gap than the (P,C) ligand and hence a stronger electronic dissymmetry of the coordination sphere at gold. Note also that the weaker donicity of the (N,C) ligand results in a significantly more electrophilic gold center than with the (P,C) ligand: the LUMO is noticeably lower in energy and the Bader atomic charge at gold is much higher (1.05 *versus* 0.58).

To further compare the two systems and pinpoint the differences, calculations on the $[(P,C)AuPh]^+$ complex **1C** were re-performed^{16c} at the same level of theory as for the $[(N,C)AuPh]^+$ complex **1A** and completed to include the second ethylene insertion (Fig. S12†).¹⁸ The difference between the (N,C) and (P,C) ligands is spectacular in the energy gap between the *cis* and *trans* isomers of **1A** and **1C** (as well as of related species). As mentioned above, the *cis* form of **1A** is more stable than the *trans* isomer by 36.2 kcal mol^{−1} (ΔG). The energy gap falls down to 7.1 kcal mol^{−1} for **1C**. The difference is also striking in the first ethylene insertion as well as in the competition between second ethylene insertion and β -H elimination. With the (N,C) ligand, the first ethylene insertion is slightly uphill in energy (ΔG +2.2 kcal mol^{−1}) while the second insertion is strongly exergonic (ΔG −27.9 kcal mol^{−1}) and favoured over β -H elimination. In contrast, ethylene insertion into the (P and C) complex **1C** is downhill in energy (ΔG −10.0 kcal mol^{−1}) but the second ethylene insertion involves a high activation barrier (21.6 kcal mol^{−1} *versus* 15.1 kcal mol^{−1} for the first insertion) and does not compete with β -H elimination/re-insertion leading to the branched product **II**. In addition, reductive elimination of the gold hydride **7A** (C_{sp^2} –H coupling) was found to be significantly more demanding energetically than that of the corresponding (P,C) complex **7C** (the activation barrier is about 10 kcal mol^{−1} higher in energy, see Fig. S14†),¹⁸ in line with the stability of **5A** and fast decomposition of **II** (see Scheme 4).

Conclusions

To sum up, the novel cyclometalated Au(III) complex $[(N,C)AuPh]^+$ **1A** was shown to react with ethylene to selectively give a double insertion product (**5A**), without β -H elimination nor rearrangement of the linear (CH₂)₄Ph chain. Trapping with chloride affords complex **5A-Cl** which has been fully characterized, including by X-ray diffraction. The energy profile for the reactions of **1A** with ethylene has been thoroughly investigated computationally, considering competitive paths, and the influence of the ancillary ligand has been delineated by comparing the (N,C) and (P,C) complexes **1A** and **1C**.

Because of the weak donor character of nitrogen (compared with carbon and even phosphorus), the benzoquinoline ligand is very electronically dissymmetric. As a result, the two reactive sites at gold are quite different. This situation contrasts with the more symmetric nature of the (P,C) chelate and explains the peculiar reactivity of **1A**. The electronic dissymmetry of the (N,C) ligand explains why β -H elimination is not observed upon reaction of **1A** with ethylene, neither upon cationisation of **6-Cl**. The activation barrier for β -H elimination is not prohibitively high, but the reaction is uphill in energy due to the

unfavourable position of the hydride (*trans* to the carbon atom of the ligand) in the resulting complex.

The detailed mechanistic study of migratory insertion and β -H elimination has revealed that the properties of the ancillary ligand, and in particular the electronic dissymmetry that the (N,C) ligand induces at gold play a prominent role in reactivity. This situation is somewhat reminiscent of that arising with phosphine–sulfonate bidentate ligands which, thanks to their strong electronic dissymmetry, bestow unique properties to Pd(II) complexes towards the coordination–insertion polymerization of ethylene and polar olefins.²³

This study reveals that (N,C) Au(III) complexes possess rich reactivity. It generalizes migratory insertion of alkenes at gold, an elementary process unknown with gold until very recently, but involved in many synthetically useful transformations (such as the Mizoroki–Heck reaction, the oligomerization/polymerization of olefins, *etc.*). The ancillary ligand markedly influences the outcome of the reaction and thus, modulation of its structure paves the way for tuning and optimizing the properties of gold(III) complexes.

Accordingly, future work will seek to take advantage of well-defined (N,C) and (P,C) gold(III) complexes in catalysis and to expand further the variety of chelating ligands.

Conflicts of interest

There are no conflicts to declare.

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CHAPTER VI

RESULTS AND DISCUSSION

6.1 GOLD-CATALYZED CROSS-COUPPLING REACTIONS WITHOUT EXTERNAL OXIDANTS

In the last four decades synthetic chemistry has relied on catalytic cross-coupling transformations promoted by most transition metals,¹ although some of them, including gold, have only received interest in the past few years. Previously, the strong Lewis acidity of Au(I) salts found application in activating the π -system of alkenes, alkynes and allenes to promote the nucleophilic attack over the insaturation.²⁻⁴ However, concerning the two-electron transitions involved in cross-coupling protocols, gold holds the most unexplored chemistry among the transition metals commonly employed and its redox chemistry is the least understood.

The high oxidation potential of the Au(I)/Au(III) pair ($E_0 = + 1.41$ V)⁵ seemed to preclude an oxidative addition step of gold(I) complexes. Although Suzuki-Miyaura and Sonogashira cross-coupling reactions have been described using Au(I) salts as catalysts,^{6,7} the activity was then attributed to the presence of Au nanoparticles.⁸ Nevertheless, Au(I)/Au(III) redox catalytic cycles have been developed in the last decade by using strong oxidants to enable the oxidation of the metal.⁹⁻¹¹ Very recently, the ability of Au(I) complexes to undergo oxidative addition events at alkyl and aryl halides has also been demonstrated,^{12,13} albeit their implementation in two-electron catalytic cycles under homogeneous conditions still lacks solid precedent.

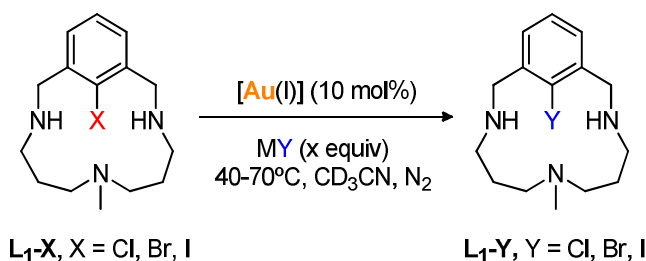
6.1.1 Oxidant-Free Au(I)-Catalyzed Halide Exchange and C_{sp2}-O Bond Forming Reactions

In this regard, we hypothesized that the use of macrocyclic model systems **L₁-X** (see Scheme 6.1) might be beneficial in order to substantiate external oxidant-free Au(I)-catalyzed cross-coupling reactions and provide mechanistic information. These model aryl halide substrates containing three amine coordination sites already served to engage copper and silver in oxidative addition and reductive elimination processes and allowed to unequivocally identify aryl-Cu(III) and aryl-Ag(III) as the key intermediate species in catalytic C-C and C-heteroatom bond forming reactions.^{14,15}

Initially we reacted 1 equivalent of [AuCl(SMe)₂] salt with **L₁-Br** in CD₃CN at 70°C, in an analogous manner to the previous synthesis of aryl-Cu(III) and aryl-Ag(III) complexes. In the case of gold, however, decomposition of the Au(I) source to metallic Au(0) was observed. Notably, this was accompanied by quantitative conversion of the **L₁-Br** substrate to **L₁-Cl** product, suggesting that a bromide to chloride halide exchange event promoted by gold had occurred.

This observation opened the door to explore the catalytic version of this transformation (Scheme 6.1). For this purpose, and in order to avoid Au(I) disproportionation to Au(0), [AuCl(PPh₃)] was tested as the potential catalyst. We started with the thermodynamically favored conversion of the aryl iodide (**L₁-I**) and bromide (**L₁-Br**) ligands to the corresponding aryl chloride (**L₁-Cl**) product. Gratifyingly, nearly quantitative yields were achieved at moderate reactions conditions

using CD₃CN as solvent and Bu₄NCl as chloride source (Table 6.1, entries 1 and 7). A control experiment indicates that gold plays a crucial role in the halide exchange reaction as in its absence very small amounts of halide exchanged product were obtained under the same reaction conditions (Table 6.1, entries 1 and 7, in parentheses). These reactions were monitored by ¹H-NMR spectroscopy and the desired product was also identified by ESI-MS analyses. Similarly, the exchange of iodide to bromide using NaBr afforded the **L₁-Br** product in 97% yield (Table 6.1, entry 4), although an increase in temperature from 40°C to 70°C was required due to the poor solubility of sodium bromide in acetonitrile. We also explored conversion of **L₁-Br** towards **L₁-I** ligand, in a parallelism with the well-known Cu-catalyzed Buchwald's transformation of aryl bromides to the corresponding iodides. Nearly quantitative yields were accomplished at 70°C, with no significant formation of any undesired secondary products (Table 6.1, entry 10), as observed by ¹H-NMR monitoring in CD₃CN, focusing on the signals in the benzylic region to unambiguously follow the exchange transformation (Scheme 6.2).



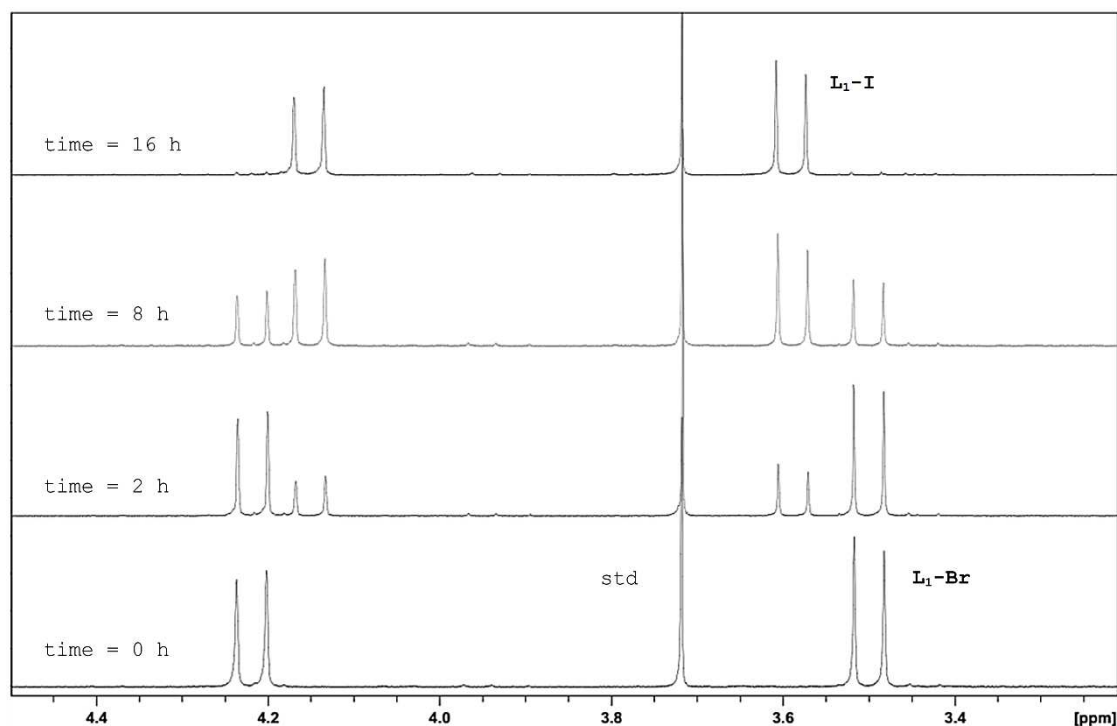
Scheme 6.1: Catalytic halide exchange reactions within model macrocyclic substrates **L₁-X**.

Entry	L ₁ -X	MY (eq)	[Au(I)]	T (°C)	t (h)	Yield L ₁ -Y (%)*		
1	L ₁ -I	TBA-Cl (2)	[AuCl(PPh ₃)]	40	48	>99 (2) ^a		
2			[Au(NTf ₂)(PPh ₃)]		48	97		
3			[Au(NCMe)IPr] ⁺		6	>99 ^b		
4		NaBr (10)	[AuCl(PPh ₃)]	70	48	94 (36) ^a		
5			[Au(NTf ₂)(PPh ₃)]		48	96		
6			[Au(NCMe)IPr] ⁺		30	97 (15) ^c		
7			[AuCl(PPh ₃)]		60	98 (trace) ^a		
8			TBA-Cl (2)		[Au(NTf ₂)(PPh ₃)]	40	60	99
9					[Au(NCMe)IPr] ⁺	12	99	
10	L ₁ -Br	[AuCl(PPh ₃)]		18	95 (23) ^a			
11	NaI (10)	[Au(NTf ₂)(PPh ₃)]	70	8	92			
12		[Au(NCMe)IPr] ⁺		4	94			
13		[AuCl(PPh ₃)]		72	56 (trace) ^a			
14	L ₁ -Cl	LiBr (10)	[Au(NTf ₂)(PPh ₃)]	70	72	54		

15		$[\text{Au}(\text{NCMe})\text{IPr}]^+$	72	59 (46)^d
16		$[\text{AuCl}(\text{PPh}_3)]$	100	42 (16)^a
17		$[\text{Au}(\text{NTf}_2)(\text{PPh}_3)]$	100	48
18	NaI (10)	$[\text{Au}(\text{NCMe})\text{IPr}]^+$	48	67

Table 6.1: Catalytic halide exchange reactions with MY in CD_3CN under N_2 atmosphere. Conditions: 15.3 μmol **L₁-X**, 10 mol% Au(I), 0.5 mL CD_3CN . * ^1H -NMR yield using 1,3,5-trimethoxybenzene as internal standard. ^aIn parentheses, yields in the absence of Au(I) cat. ^bAfter 30h with 5 mol% Au(I) catalyst loading. ^cIn parentheses, at 40°C. ^dIn parentheses, using NaBr (10 equiv).

Later, we moved to reversible halide exchange reactions towards heavier halides and the formation of a weaker $\text{C}_{\text{sp}2}$ -halogen bond. As envisioned, the iodination of **L₁-Cl** demanded longer reaction times, and even after 350 h quantitative conversions could not be attained (Table 6.1, entry 16). The poor conversion of **L₁-Cl** to **L₁-Br** using excess of NaBr might also be attributed to the low solubility of the halide source in acetonitrile. The use of more soluble LiBr improved the yield of **L₁-Br** from 30% up to 56% (Table 6.1, entry 16). The precipitation of the MX salt (X being the removed halide) is key to overcome the reversibility of the aryl-X oxidative addition step, especially with stronger C-X bonds. This is in agreement with the absence of reactivity when employing soluble $n\text{Bu}_4\text{NBr}$ and $n\text{Bu}_4\text{NI}$ halide sources.



Scheme 6.2: ^1H -NMR spectra acquired during the catalytic time-course of the exchange from **L₁-Br** to **L₁-I**. Peak labelled with “std” corresponds to 1,3,5-trimethoxybenzene internal standard.

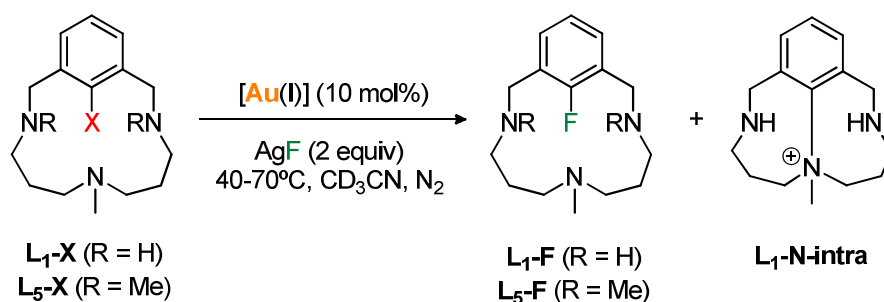
In seeking to improve the catalytic performance of these transformations, we envisaged that mono-coordinated Au(I) complexes could have a significant impact on

the reaction outcome. Indeed, DFT calculations have previously pointed out the inert nature of linear two-coordinate Au(I) complexes towards oxidative addition of aryl halides, and that such step would be much more facile when starting from [LAu](X) complexes, X being a weakly coordinated counterion that prevents detrimental decomposition of the Au(I) salt.¹⁶ Thus, we repeated the halide exchange reactions described above with [Au(NTf₂)(PPh₃)] as catalyst (NTf₂ = bis(trifluoromethanesulfonyl)imide). The yields obtained were virtually the same when using [AuCl(PPh₃)], except for the iodination of **L₁-Br**, in which again yields superior to 90% were accomplished in only 8 h (Table 6.1, entry 11). It is worth mentioning that attempts to prepare an Au(I) catalyst containing a noncoordinating counteranion by chloride abstraction with AgX salts (X = BF₄⁻ or SbF₆⁻) and an acetonitrile molecule as a labile ligand turned into the rapid decomposition of the gold precursor to [Ph₃P-Au-PPh₃]⁺ species and Au(0) at temperatures higher than 25°C.

Since triphenylphosphine-based Au(I) complexes did not exhibit improved reactivity, we then sought to explore the potential of *N*-heterocyclic carbenes (NHC's) as ancillary ligands. Compared to phosphines, they display a stronger σ-donor character, which enables favorable rates of oxidative addition processes, and the presence of sterically encumbering groups bound to the *N*-atoms facilitate reductive elimination of the product from the metal center.^{17,18} In the recent years some groups, especially Nolan and co-workers,^{19–22} have accessed a wide range of new NHC-containing Au(I) complexes and highlighted their benefits in homogeneous catalysis taking advantage of these intrinsic properties. Therefore, we synthesized cationic [Au(NCCH₃)IPr]SbF₆ (IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidene) following a protocol found in the literature.²² Strikingly, when it was tested in the halide exchange reaction, good to excellent yields were also achieved in markedly shorter reaction times. The chlorination of **L₁-Br** and **L₁-I** and the iodination of **L₁-Cl** and **L₁-Br** presented the most salient differences compared to the phosphine-based catalysts (Table 6.1, entries 3 and 9, 12 and 18).

These good results encouraged us to investigate the plausibility of more challenging fluorination reactions. KF and *n*Bu₄NF were initially chosen as fluoride sources, but they proved to be completely inefficient. On the contrary, direct addition of 2 equivalents of AgF to a solution of **L₁-Cl** and 10 mol% of AuCl(PPh₃), Au(NTf₂)(PPh₃) or [Au(NCCH₃)IPr]SbF₆ at 70°C gave the desired aryl fluoride ligand **L₁-F** (Table 6.2, entries 1–3). However, low yields were obtained and the exchange transformations were not clean. Moreover, at this temperature, a competing intramolecular side-reaction involving aryl-amine coupling occurs (**L₁-N-intra**, Scheme 6.3). Changes of **L₁-Cl** ligand by **L₁-Br** and **L₁-I** afforded better yields in shorter reaction times, along with a 5–9% yield of the intramolecular side-product **L₁-N-intra** (Table 6.2, entries 7–9 and 13). Also, similar results were obtained in absence of Au(I) with aryl bromides and iodides (Table 6.2, entries 7 and 13 in parentheses), which suggests that fluoride insertion can also be mediated by Ag(I) through the intermediacy of aryl-Ag(III) species, as previously validated in our group.¹⁵

The reactivity of the permethylated macrocyclic **L₅-X** substrates (X= Cl, Br) exhibited significant differences with regard to the **L₁-X** analogues, indicating that the basicity of the F⁻ anion strongly affects the secondary amines of the **L₁-X** ligands, which might be keen to deprotonation triggering the formation of side-products such as the intramolecular C-N coupling product **L₁-N-intra**. Notably, the [Au(NCCH₃)IPr]SbF₆ complex boosted the reaction outcomes for **L₅-Cl** and **L₅-Br** to a great extent, and also proved effective with KF (Table 6.2, entries 6 and 12 in parentheses). The prominent role of gold is additionally supported by the virtual absence of fluorinated products when Au(I) catalysts are excluded in the chlorinated ligands (Table 6.2, entries 1 and 4 in parentheses).

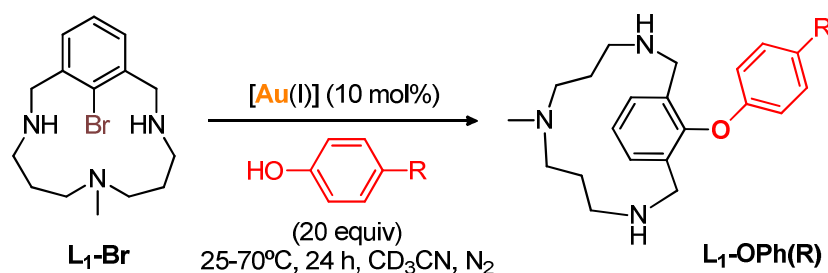


Scheme 6.3: Catalytic fluorination reactions within model macrocyclic substrates **L_n-X**.

entry	L_n-X	[Au(I)]	T (°C)	t (h)	Yield L_n-F (%) [*]	Yield L₁-N-intra (%) [*]
1	L₁-Cl	AuCl(PPh ₃)	70	72	32 (6)^a	6
2		Au(NTf ₂)(PPh ₃)		72	36	6
3		[Au(NCMe)IPr] ⁺		24	64	5
4	L₅-Cl	AuCl(PPh ₃)	70	72	51 (4)^a	-
5		Au(NTf ₂)(PPh ₃)		72	50	-
6		[Au(NCMe)IPr] ⁺		12	98 (14)^b	-
7	L₁-Br	AuCl(PPh ₃)	70	48	49 (42)^a	7
8		Au(NTf ₂)(PPh ₃)		48	54	9
9		[Au(NCMe)IPr] ⁺		48	68	8
10	L₅-Br	AuCl(PPh ₃)	40	48	100 (100)^a	-
11		Au(NTf ₂)(PPh ₃)		48	100	-
12		[Au(NCMe)IPr] ⁺		6	100 (23)^c	-
13	L₁-I	AuCl(PPh ₃)		24	56 (54)^a	5

Table 6.2: Catalytic fluorination reactions with AgF (2 equiv) in CD₃CN under N₂ atmosphere. Conditions: 15.3 μmol **L_n-X**, 10 mol% Au(I), 0.5 mL CD₃CN. ^{*}1H-NMR yield using 1,3,5-trimethoxybenzene as internal standard. ^aIn parentheses, yields in the absence of Au(I) cat. ^bIn parentheses, using KF (5 equiv) for 72 h. ^cIn parentheses, using KF (5 equiv) for 48 h.

Since Ullmann-type C-heteroatom coupling reactions are unprecedented for gold, we deemed it worthy to examine the potential for C-O bond formation within **L₁-Br** employing an excess of differently substituted phenols (Scheme 6.4). For this purpose, we avoided the use of AuCl(PPh₃) catalyst as it led to the formation in preliminary experiments of the chloride-exchanged product in 10% yield. This is a strong indication that Ar-Br bond activation mediated by gold takes place. With Au(NTf₂)(PPh₃) moderate to excellent yields were attained, depending on the electronic nature of the substituent in *para* position of the aromatic ring, with electron-rich phenols giving the best results (e.g., *p*-chlorophenol = 79%, Table 6.3, entry 8). In that case, where the blank experiment at 70°C is not negligible, we found that [Au(NCCH₃)IPr]SbF₆ allows us to conduct the reaction at lower temperatures, thus decreasing the impact of the background reaction. On the other hand, when thiophenol was employed no C-S coupling event was observed, probably due to the S-affinity of gold complexes which may eventually quench the catalyst. Finally, the presence of small amounts of **L₁-H** side-product with *p*-methoxyphenol merits comment, since it suggests again the intermediacy of an Au-C_{sp2} bond cleaved by protodeauration.



Scheme 6.4: Catalytic C-O bond formation with **L₁-Br**.

entry	R	[Au(I)]	Yield (%) [*]		
			25°C	40°C	70°C
1	H	AuCl(PPh ₃)	-	-	34 ^a
2	H	Au(NTf ₂)(PPh ₃)	-	51	75
3	Me	Au(NTf ₂)(PPh ₃)	-	41	71
4	OMe	Au(NTf ₂)(PPh ₃)	-	45 ^b	89 ^c
5	OMe	[Au(NCMe)IPr] ⁺	-	44 ^d	87 ^e
6	NO ₂	Au(NTf ₂)(PPh ₃)	-	15	35
7	CF ₃	Au(NTf ₂)(PPh ₃)	-	32	56
8	Cl	Au(NTf ₂)(PPh ₃)	29	52	79 (61) ^f
9	Cl	[Au(NCMe)IPr] ⁺	42	61	84 (83) ^f
10	Cl	-	<1	15	45

Table 6.3: Catalytic C-O bond forming reactions. Conditions: 15.3 μmol **L₁-Br**, 10 mol% Au(I), 0.5 mL CD₃CN, 24h. ^{*}¹H-NMR yield using 1,3,5-trimethoxybenzene as internal standard. ^a10% **L₁-Cl** observed

as a byproduct. ^b2% **L₁-H** observed. ^c9% **L₁-H** observed. ^d4% **L₁-H** observed. ^e10% **L₁-H** observed. ^fIn parentheses, yields after 8h.

The promising results regarding the Au(I)-catalyzed C-heteroatom bond formation of model aryl halide substrates encouraged us to investigate whether this reactivity can be transferred to more readily available systems featuring only one chelation site (Scheme 6.5). We selected the [Au(NCCH₃)IPr]SbF₆ complex to be evaluated in representative iodination and C-O coupling reactions. To start with, attempts towards bromide to iodide exchange in acetonitrile with non-coordinating 2-bromo-1,3-dimethylbenzene **2a** gave no product, indicating that a chelating position is necessary and that Au(I) is not mediating the halide exchange *via* its Lewis acid nature. Similarly, hard *N*-donor secondary and tertiary amine groups (resembling those found in the macrocyclic **L_n-X** substrates) did not afford the iodinated product. In marked contrast, however, the pyridyl moiety allowed us to achieve 46% yield of the desired product, which could be further increased up to 65% upon solvent replacement by DMSO. The intrinsic differences in terms of electronic properties as well as in the rigidity conferred to the ensuing chelate might explain the observed results. 2-phenylpyridine ligand templates have proven useful in stabilizing a number of (C,N)-cyclometalated Au(III) complexes while maintaining their activity in C-C coupling reactions.^{23,24} A similar trend was obtained when C-O bond forming reactions with the nonmacrocyclic substrates were studied, with quantitative yields for 2-(2-bromophenyl)pyridine. Instead of adding a base in order to deprotonate the phenol-derivative, independently prepared sodium *p*-chlorophenolate was employed as the coupling counterpart, which proved more favorable to the reaction outcome. Strikingly, in all experiments no conversion or residual amounts of product were detected when the Au(I) catalyst was excluded.

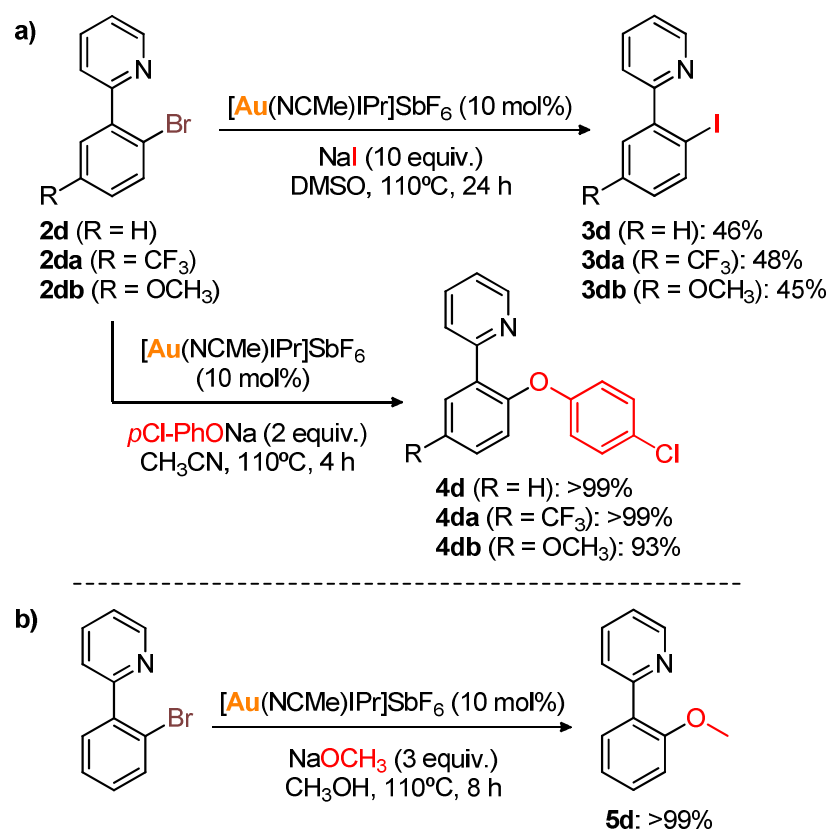
CG₁ = CG₂ =				
H H H				
conditions:	2a	2b	2c	2d

NaI (10 eq.),				
CH ₃ CN, 24h	0%	trace	0%	46 (0)%
DMSO, 24h	0%	12%	9%	65 (2)%
	3a	3b	3c	3d

NaOPh- <i>p</i> Cl (2 eq.)				
CH ₃ CN, 4h	0%	trace	trace	>99 (0)%
	4a	4b	4c	4d

Scheme 6.5: Screening of the *ortho*-chelating groups for iodination of aryl bromides (yields determined by GC analyses) and C-O couplings (yields calculated by ¹H-NMR).

Later on we evaluated the behavior of these transformations with 2-(2-bromophenyl)pyridine bearing an electron-donating group (CF₃, substrate **2da**) and an electron-withdrawing substituent (OMe, substrate **2db**) in the *para*-position with respect to the bromine atom (Scheme 6.6, a). Both iodination and C-O coupling reactions provided similar values as when using **2d**. Therefore, no relevant mechanistic information could be obtained from the final yields, although kinetic studies at the initial stages (after 1 and 2 hours) of the *p*-chlorophenolate coupling suggested higher preference for the *p*-trifluoromethyl substituted derivative (Table 6.4). Interestingly, sodium methoxide could also be inserted quantitatively under this working protocol giving the aryl methyl ether **5d** (Scheme 6.6, b), further extending the nucleophile scope and the applicability of the system.



Scheme 6.6: C-heteroatom coupling reactions with different *p*-substituted 2-(2-bromophenyl)pyridines.

t (h)	Yield (%) [*]		
	R = H (4d)	R = CF ₃ (4da)	R = OMe (4db)
1	35	78	41
2	61	>99	73
4	>99	>99	93

Table 6.4: Yields obtained during the early stages of the *p*-chlorophenolate coupling to aryl bromide **2d** and its *p*-substituted derivatives.

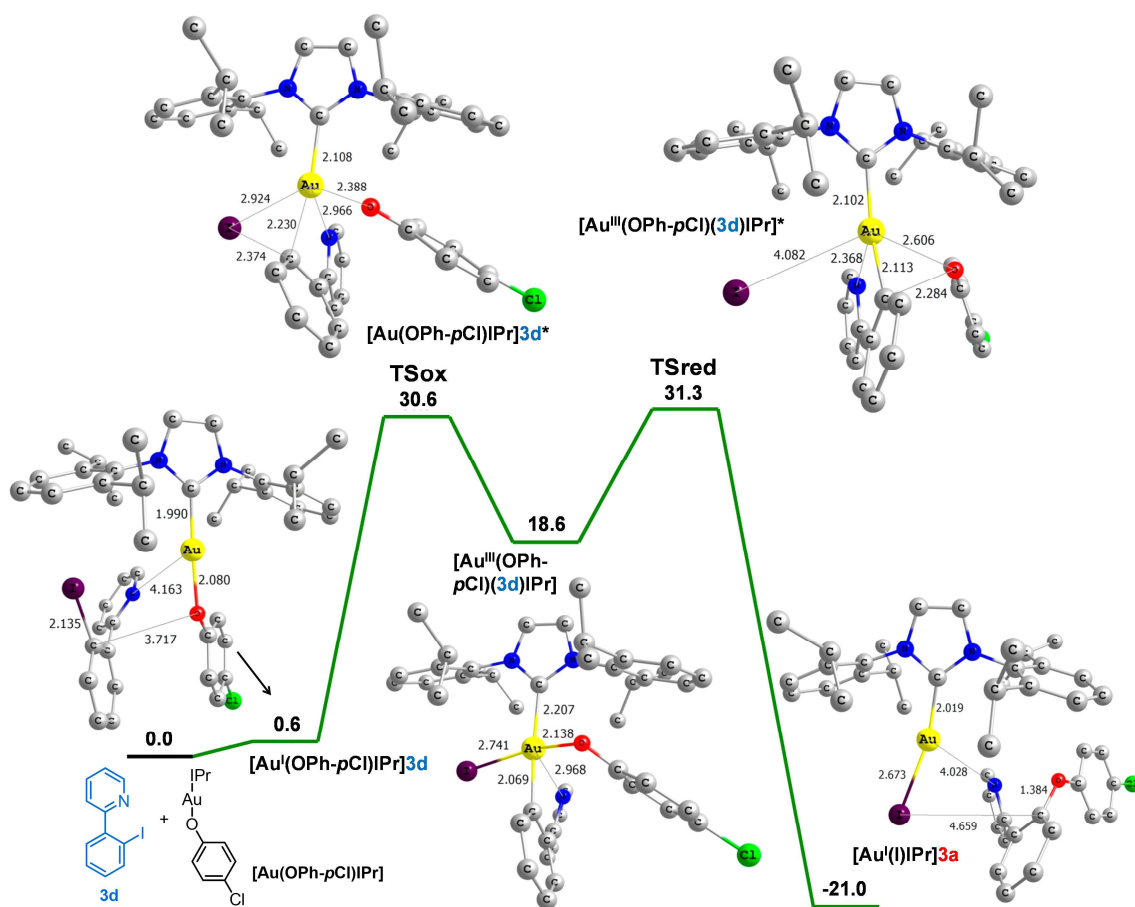
From a mechanistic point of view, the above-described transformations are likely to occur through an Au(I)/Au(III) catalytic cycle, although the key aryl-Au(III) intermediate species analogous to the aryl-Cu(III) and aryl-Ag(III) complexes could not be detected. In this regard, we hypothesize that the coordination environment of the model macrocyclic substrates is not appropriate to stabilize the square-planar geometry of putative Au(III) species. Indeed, when equimolar amounts of **L₁-I** and [Au(NCCH₃)IPr]SbF₆ are heated at 60°C in acetonitrile exclusive formation of **L₁-N-intra** is observed, suggesting very rapid intramolecular C-N reductive elimination after C-I bond activation by Au(I) takes place. On the other hand, the observation of **L₁-N-intra** and **L₁-H** byproducts in C-F and C-O coupling reactions, which is reminiscent of Cu(I)/Cu(III) and Ag(I)/Ag(III) catalysis, also supports the occurrence of a two-electron Au(I)/Au(III) redox cycle.

The off-cycle resting states of the Au(I) catalyst could be identified by ¹H-NMR monitoring. We chose the C-O coupling of *p*-chlorophenol and **2d**, and under catalytic conditions (i.e., in the presence of an excess of phenolate) the immediate conversion of [Au(NCCH₃)IPr]SbF₆ into neutral [Au(OPh-*p*Cl)IPr] was observed. Upon heating, nucleophile exchange occurs at the gold center after C-Br bond activation, resulting in the liberation of [Au(Br)IPr]. Both neutral Au(I) species were isolated and employed as catalysts in the halide exchange and C-O bond forming reactions with macrocyclic and non-macrocyclic substrates, obtaining the same results as with [Au(NCCH₃)IPr]SbF₆. This clearly supports their intermediacy in the reaction mechanism. Albeit the coordination of neutral [Au(OPh-*p*Cl)IPr] or [Au(Br)IPr] to **L₁-Br** or **2d** was not observed by ¹H-NMR, under harsh HRMS conditions we detected the *in situ* formation of [Au(L)IPr]⁺ (L = **L₁-Br** or **2d**) by substitution of the phenolate or bromide, which is the requisite step prior to the activation of the C-Br bond. The latest advances on oxidative addition at Au(I) complexes have demonstrated that ligand dissociation from two-coordinate [L₂Au]⁺ and LAuX complexes is crucial in order to trigger reactivity.^{16,25,26} Since at least one chelating group in the substrate is necessary, we reasoned that this coordination may be responsible for breaking the linearity of the Au(I) resting state upon heating and thus allowing for the reaction to occur. This finds support in the fact that [Au(OPh-*p*Cl)IPr] remains unaltered after 24 h when 2-bromo-1,3-dimethylbenzene, which does not contain any chelating site, is the substrate of choice.

It has been reported that gold nanoparticles formed during Au(I)-catalyzed Sonogashira couplings act as heterogeneous catalysts in these transformations.⁸ In order to assess whether Au(0) colloids are the active species in our coupling reactions, we reproduced the halide exchange and *p*-chlorophenol coupling reactions using both **L₁-Br** and **2d** and in the presence of a large excess of metallic mercury (ca. 500 equivalents with respect to the Au catalyst). Hg(0) acts as a poison towards nanoparticles, and consequently a quenching of reactivity would strongly suggest heterogeneous catalysis.^{27,28} Nonetheless, a minor decrease in the final yields (10-30% lower) was observed at expense of the formation of side-products. Moreover, ¹H-NMR analysis of the reaction crudes revealed that the entire Au(I) catalyst remained in solution in the

form of $[\text{Au}(\text{Br})\text{IPr}]$, ruling out the possibility of detrimental decomposition to $\text{Au}(0)$ colloids.

In order to shed light on the mechanism Density Functional Theory (DFT) calculations were undertaken on the coupling of *p*-chlorophenolate ($p\text{Cl-PhO}^-$) with 2-(2-iodophenyl)pyridine **3d** mediated by $[\text{Au}(\text{NCCH}_3)\text{IPr}]\text{SbF}_6$ catalyst. As expected, the $p\text{Cl-PhO}^-$ binding to $[\text{Au}(\text{NCCH}_3)\text{IPr}]^+$ is an exergonic process ($\Delta G = -11.4 \text{ kcal}\cdot\text{mol}^{-1}$), while the quasi-thermoneutral character of the exchange of the bound $p\text{Cl-PhO}^-$ ($\Delta G = -2.5 \text{ kcal}\cdot\text{mol}^{-1}$) or iodide ($\Delta G = -1.4 \text{ kcal}\cdot\text{mol}^{-1}$) by **3d** suggest that the key formation of $[\text{Au}(\textbf{3d})\text{IPr}]^+$ is feasible under reaction conditions, in accordance with the HRMS experiments. In addition, a complete reaction profile for the C-halide activation was computed at the M06L level (Scheme 6.7), finding a transition state for the oxidative addition step (TS_{ox}) at $30.6 \text{ kcal}\cdot\text{mol}^{-1}$ and for reductive elimination (TS_{red}) at $31.3 \text{ kcal}\cdot\text{mol}^{-1}$. These barriers, located below the kinetic limit, are consistent with rather slow reactions conducted at 110°C . Although DFT calculations indicate that the reductive elimination is the rate-determining step, both transition states are very close in energy and slight changes might induce switching to a rate limiting oxidative addition. The subtle energetic difference between both TS could explain in turn the rather ambiguous trend among the electronically *p*-substituted 2-(2-bromophenyl)pyridine substrates **2da** and **2db**.



Scheme 6.7: DFT reaction profile for the oxidative addition/reductive elimination steps of $[\text{Au}(\text{OPh-}p\text{Cl})]$ over **3d** substrate in CH_3CN . Relative Gibbs energy values in $\text{kcal}\cdot\text{mol}^{-1}$ and selected bond distances in $\text{\AA}$.

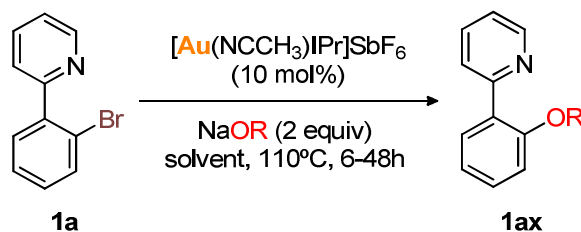
A completely different mechanistic scenario, where the cationic Au(I) center acts as a Lewis acid to increase the reactivity of the C-I bond towards a nucleophilic attack, was also explored. Strikingly, all TS searches for the Au-mediated direct attack of the phenolate to **3d** actually drove the reaction via Au(III) species and converged to TS_{ox}, thus rendering the possibility of a redox neutral functionalization of **3d** improbable.

This Au-assisted nucleophilic aromatic substitution was also evaluated experimentally. In the late 1970s, Meyers and co-workers reported a nucleophilic aromatic displacement of the *o*-methoxy group in similar substrates to **2d** by organolithium and Grignard reagents.²⁹ Having in hand the isolated methoxide insertion product **5d**, we studied if a comparable mechanism mediated by gold was also operative in our system. Thus, **5d** was subjected under the same reaction conditions described for **2d** in the presence of *p*-chlorophenolate and, after enough time to allow any reaction to proceed, the starting material was quantitatively recovered. This observation seems to preclude the involvement of S_NAr as the main operating mechanism.

6.1.2 Au(III)-Aryl Intermediates in Oxidant-Free C-O and C-N Cross-Coupling Catalysis

Compounds referred as **2d**, **3d**, **4d** and **5d** in section 6.1.1, will be labelled as **1a-Br**, **1a-I**, **1aa** and **1ab**, respectively, in this section in agreement with the publication.

The encouraging results obtained in the *p*-chlorophenolate and methoxide couplings with 2-(2-bromophenyl)pyridine substrate **1a-Br** (Scheme 6.8, and Table 6.5, entries 1 and 2) prompted us to study the expansion of the scope to other oxygen-based nucleophiles. In likewise manner, sodium ethoxide inserts to **1a-Br** in 56% yield after 24 h in its conjugate acid (ethanol) as solvent, which could be increased up to 78% after 48 h (Table 6.5, entry 6). The lower reactivity observed compared to sodium ethoxide can be attributed to the larger steric hindrance and basicity of the ethoxide. The preference for more acidic and smaller alkoxides was corroborated by performing the reaction with MeONa in ethanol, whereby the methoxide insertion compound **1ab** was the major product (Table 6.5, entry 5). More sterically encumbered alkoxides such as 2-propoxide (**1ad**) and *tert*-butoxide (**1ae**), with yields of 21% and 4% respectively, further confirmed this trend (Table 6.5, entries 7 and 8).



Scheme 6.8: Au(I)-catalyzed C-O bond formation with a range of alkoxides.

The use of sodium hydroxide as nucleophile, and in water solvent, deserves special mention. To our surprise, the diaryl ether homocoupling product **1ag** was the major

product with 26% yield (52% relative to 1 equivalent of **1a** substrate), instead of the expected 2-(pyridin-2-yl)phenol **1af** (Table 6.5, entry 9). This outcome can be rationalized through the coupling of the early-stage generated phenol to unreacted **1a-Br**, which would act as the preferred nucleophile upon deprotonation in basic media. It is also worth noting that the transformation using NaOH as base was carried out in aqueous media, in the absence of a phase-transfer reagent and without the addition of a co-solvent. The yield of phenol **1ae** increased up to 52% (Table 6.5, entry 10) when NaOH was replaced by NaOMe, which suggests that selectivity and yield of each product might be controlled by proper modification of the reaction conditions. In this sense, combination of sodium hydroxide and methanol led to the complete formation of the methoxide insertion product **1ab** (Table 6.5, entry 2).

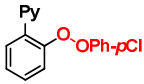
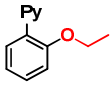
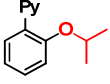
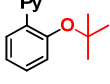
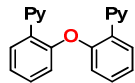
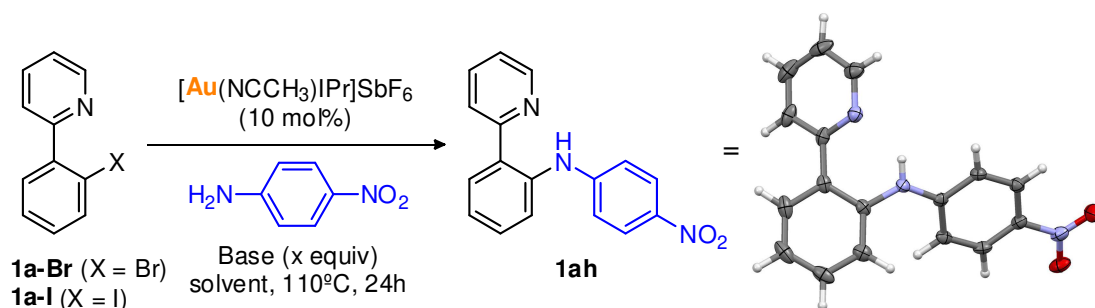
entry	Alkoxide	Solvent	t (h)	Product	Yield (%) [*]
1	<i>p</i> Cl-PhONa	CH ₃ CN	6	 1aa	>99
2	HONa	CH ₃ OH	8		>99
3	MeONa	CH ₃ OH	8	 1ab	>99
4	EtONa	CH ₃ OH	24		>99
5	MeONa	EtOH	24		86 (9) ^a
6	EtONa	EtOH	48	 1ac	78
7	(2-Propoxide)Na ^b	2-Propanol	48	 1ad	21
8	<i>t</i> BuONa	<i>tert</i> -Butanol	48	 1ae	4
9	HONa	H ₂ O	24		34 (1af) + 26 (1ag)
10	MeONa	H ₂ O	24	 1af + 1ag	52 (1af) + 21 (1ag)

Table 6.5: Alkoxide scope of the C-o bond forming reactions. General conditions: [2-(2-bromophenyl)pyridine] = 20 mM, [alkoxide] = 40 mM, 0.5 mL solvent, 110°C. ^{*}Calculated by ¹H-NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. ^aIn parentheses, yield of the ethoxide insertion product (**1ac**). ^bThe alkoxide was generated *in situ* by adding 2 equivalents of sodium *tert*-butoxide as base.

In view of these promising results, we were intrigued to investigate if other nucleophiles were suitable for this methodology. To this end, C_{sp2}-N bond formation through combination of aryl halides and N-based nucleophiles has basically relied on two different approaches: (a) Cu-catalyzed Ullmann-type³⁰ and (b) Pd-catalyzed Buchwald-Hartwig^{31,32} coupling reactions. To the best of our knowledge, this reactivity has only been successfully transferred to nickel.³³ To start with, we selected *p*-

nitroaniline, given its major acidity compared to other amines ($pK_a = 20.9$ in DMSO),³⁴ as the nucleophile to be reacted with **1a-Br** in acetonitrile, using 10 mol% $[\text{Au}(\text{NCMe})\text{IPr}](\text{SbF}_6)$ at 110°C (Scheme 6.9). Regardless of the base used, in all cases the starting material was recovered (Table 6.6). Significantly, solvent optimization led to an encouraging 39% yield of the desired product **1ah** in DMSO and *t*BuOK as base. More reactive 2-(2-iodophenyl)pyridine substrate **1a-I** afforded almost quantitative yields under the same conditions. The solid-state structure of the isolated product confirmed functionalization of the C-halide bond (Scheme 6.9, right). Final optimization set the preferred experimental conditions at 110°C , 24h and an excess of the nucleophile and base of 3 equivalents for further substrate scoping. In addition, a gold-free blank experiment was performed and the reaction did not proceed (0% yield). The sluggishness of the reaction when aryl bromide **1a-Br** is used instead of aryl iodide **1a-I** is in accordance with a rate-limiting oxidative addition step.

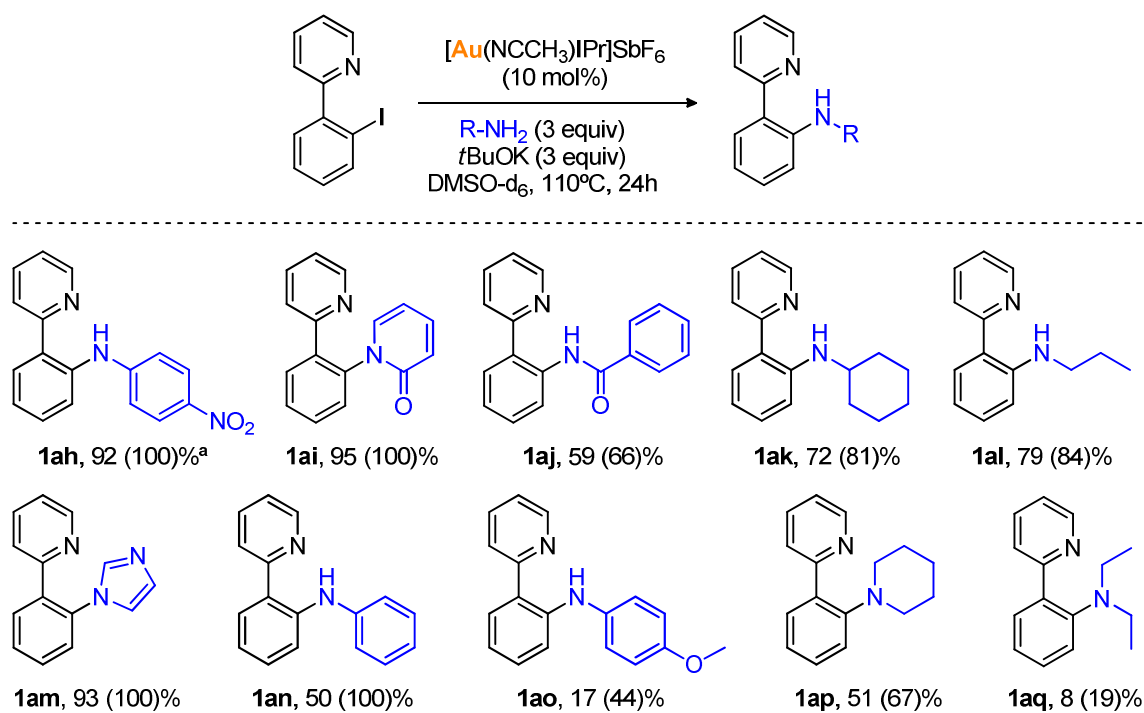


Scheme 6.9: Left: optimization of reaction conditions for the *p*-nitroaniline insertion reaction using 2-(2-bromophenyl)-pyridine (**1a-Br**) or 2-(2-iodophenyl)-pyridine (**1a-I**). Right: X-ray structure of compound **1ah** (ellipsoids set at 50% probability).

entry	X	Solvent	Base	Yield (%) [*]
1	Br	CH ₃ CN	K ₃ PO ₄ (3)	0
2	Br	CH ₃ CN	CsF (3)	0
3	Br	CH ₃ CN	<i>t</i> BuOK(3)	0
4	Br	CH ₃ CN	CsF (5)	0 ^a
5	Br	Toluene	CsF (5)	0 ^a
6	Br	Dioxane	CsF (5)	4 ^{a,b}
7	Br	DMSO	CsF (5)	24 ^a
8	Br	DMSO	<i>t</i> BuOK(5)	39 ^a
9	I	DMSO	CsF (5)	44 ^a
10	I	DMSO	<i>t</i> BuOK(5)	93 ^a
11	I	DMSO	<i>t</i> BuOK(3)	95 (92) ^c

Table 6.6: Conditions: **1a-Br/1a-I** (0.02 mmol), $[\text{Au}(\text{NCMe})\text{IPr}]\text{SbF}_6$ (1.8mg, 0.002 mmol), *p*-nitroaniline and base, and 0.5 mL of solvent. ^{*}Yields as determined by ¹H-NMR using 1,3,5-trimethoxybenzene as an internal standard. ^a[*p*-NO₂aniline] = 100 mM; ^bAfter the required reaction time, solvent was removed under vacuum and CDCl₃ (0.6 mL) was added for ¹H-NMR analysis. ^cT = 100°C.

Afterwards the scope of the optimized protocol was examined using different amines and amides. The best results were obtained with cyclic aromatic and aliphatic amines and amides (2-hydroxypyridine and imidazole products **1ai** and **1am**, respectively, Scheme 6.10), most likely owing to their superior acidity ($pK_a = 18.6$ and 17.0 in DMSO, respectively).³⁴ On the other hand, primary aliphatic amines (products **1ak** and **1al**, Scheme 6.10) afforded good yields, whereas secondary amines were less prone to arylation, with moderate 51% yield for piperidine (**1ap**) and low 8% yield diethylamine (**1aq**). Similarly, benzamide (product **1aj**) exhibited moderate outcomes. Interestingly, and in contrast to the excellent results observed for *p*-nitroaniline, simple aniline did not exceed 50% yield, while electron-rich *p*-methoxyaniline was poorly arylated (17%, **1ao**). This reactivity trend, with sensitivity to less acidic and sterically hindered substrates, suggests a rate-limiting deprotonation step and might also indicate that the destabilization of a high oxidation state gold center (as a putative aryl-Au(III)-nucleophile intermediate) is mandatory for the reaction to proceed.

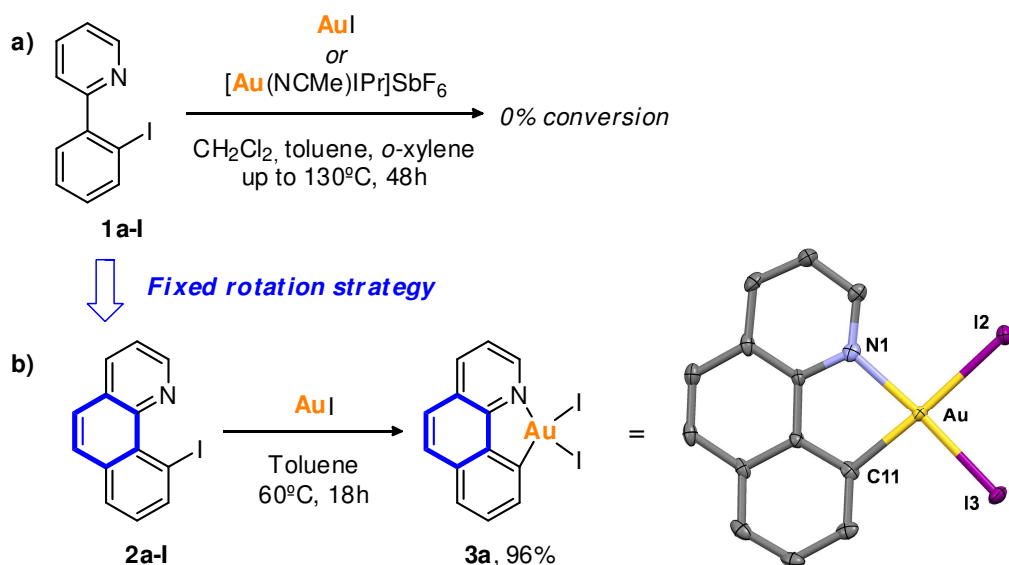


Scheme 6.10: Substrate scope of the C-N coupling reactions. Average GC and ^1H -NMR yields (and, in parentheses, conversions) using 1,3,5-trimethoxybenzene as an internal standard. ^aYield at $100^\circ C$.

In what refers to mechanistic considerations, clearly the access to (C,N)-cyclometalated Au(III) complexes from 2-phenylpyridine scaffolds would be cornerstone to support our previous Au(I)/Au(III) redox cycle proposal. As illustrated in the first chapter (section 1.3), typical strategies to prepare them rely on either transmetalation from unattractive organomercury derivatives,^{35,36} or formal C_{sp^2} -H auration with gold(III) tri or tetrahalide salts under conventional or microwave heating.^{23,37} Only very recently an alternative approach using aryldiazonium salts and Au(I) complexes under visible light photoredox conditions has been devised.³⁸

Therefore, we deemed it worthy to investigate the oxidative addition of C_{sp^2} -X bonds using the 2-(2-halophenyl)-pyridines substrates, since so far this route has not been successfully applied in the synthesis of (C,N)-cyclometalated Au(III) complexes.

Taking inspiration from the pioneering work of Bourissou and co-workers,²⁵ we chose gold(I) iodide to be reacted with 2-(2-iodophenyl)pyridine (**1a-I**) in dichloromethane at room temperature. However, the starting material was quantitatively recovered, even after solvent replacement to toluene and *o*-xylene and strong heating (Scheme 6.11, a). The gold(I) source $[Au(NCMe)IPr]SbF_6$ employed in catalysis led to identical results, regardless of the reaction conditions. In order to rationalize this observation, we argued that, although the oxidative addition has an accessible barrier as expected from the feasible C-O and C-N coupling reactions, the ensuing complex $[Au(\mathbf{1a})I_2]$ is thermodynamically disfavored, pulling the equilibrium back towards the reagents. Aiming at supporting this hypothesis, we performed the same reaction in the presence of a base (*t*BuOK and K_3PO_4) or a nucleophile (sodium *p*-chlorophenolate). In the first case, starting material **1a-I** was fully recovered, which suggests that *t*BuOK and K_3PO_4 cannot displace the iodides and initiate fast reductive elimination in a putative $[Au(\mathbf{1a})I_2]$ complex. Contrastingly, the nucleophilic character of *p*-chlorophenolate leads to the formation of **1aa** in a 90% yield.



Scheme 6.11: Synthetic approach to Au(III) complex **3a**, and molecular structure at the solid state. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Au-C(11) 2.055(7), Au-N(1) 2.113(8), Au-I(2) 2.6402(6), Au-I(3) 2.5755(7); C(11)-Au-I(3) 94.5(2), C(11)-Au-N(1) 81.5(3), I(2)-Au-I(3) 89.3(2), N(1)-Au-I(2) 94.8(2). (Ellipsoids are set at 50% probability; hydrogen atoms have been omitted for clarity).

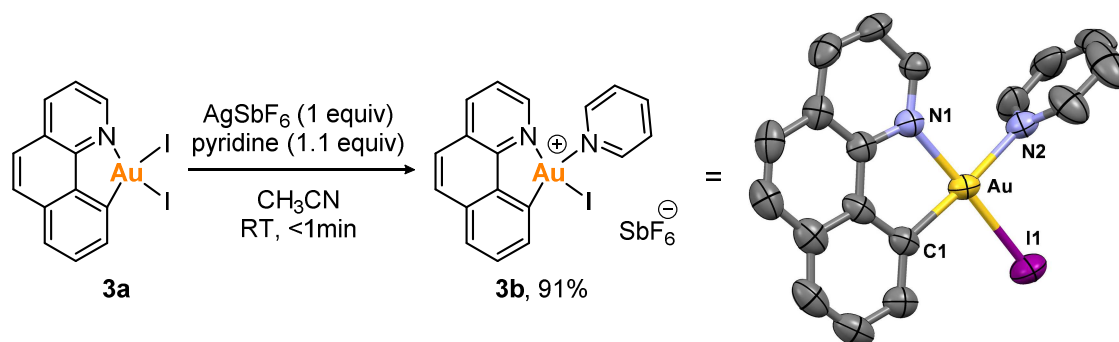
To prevent equilibrium displacement towards reagents and enhance the stability of the desired complex, we envisaged to block the rotation of the pyridine chelating group by incorporating an extra ring into the substrate. Accordingly, 10-iodobenzo[*h*]quinoline **2a-I** was prepared following a two-step procedure starting from benzo[*h*]quinoline. To our delight, oxidative addition of the C_{sp^2} -I bond proceeded readily with AuI at 60°C for 18h to give the cyclometalated Au(III) complex **3a** as a red

powder (Scheme 6.11, b). This complex withstands air and water indefinitely, is insoluble in protic solvents and in CH₃CN and displays poor solubility in CH₂Cl₂, CHCl₃ and DMSO. X-ray-quality crystals were obtained by gently stirring **2a-I** and AuI in CH₂Cl₂ at room temperature for 4 days, followed by slow evaporation of the solvent. The solid-state structure of the complex displays a Au-C bond length of 2.055(7) Å, indicative of a Au(III) center, and a distorted square-planar environment owing to the constraints of the five-membered (N,C) chelate ligand, with a C11-Au-N1 angle of 81.5(3) and an associated N1-Au-I2 angle of 94.8(2).

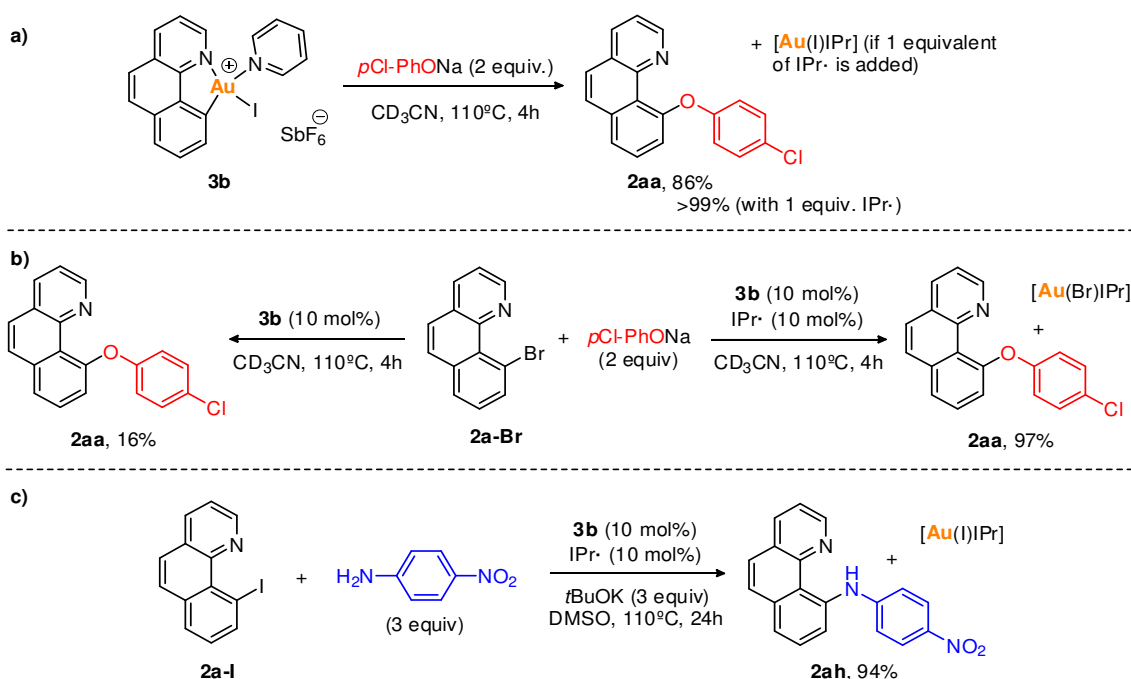
Compared to similar reported (C,N)-cyclometalated [Au(ppy)Cl₂]³⁹ and [Au(tpy)Br₂]²³ complexes (tpy = 2-(*o*-tolyl)pyridine), the Au-I distances are longer in complex **3a** than the analogous Au-Cl and Au-Br ones, consistent with bigger and more labile iodine atoms. The Au-I3 distance (2.5755(7) Å) *trans* to the pyridyl nitrogen is shorter than the Au-I2 distance (2.6402(6) Å), as should be expected from a greater *trans* influence of the aryl group. Most diagnostic of the formation of a C-Au(III) bond is the low-field shift of the ¹H-NMR signal corresponding to the α-proton in the pyridine moiety from δ 9.11 in **2a-I** to 10.35 ppm. Also, in the ¹³C-NMR spectrum the quaternary carbon bound to the Au(III) center moves from δ 88.9 ppm to δ 153.6 ppm due to strong deshielding.

The superior stability and insolubility of **3a** prompted us to abstract an iodide using 1 equivalent of AgSbF₆ (Scheme 6.12) in order to investigate further reactivity. Notably, after vigorously stirring for 3 hours at room temperature in CH₃CN no changes were observed, suggesting that the medium-strength Lewis base character of acetonitrile is not sufficient to stabilize three-coordinate gold(III) species. Consequently, upon addition of pyridine (1.1 equivalents), a stronger Lewis base, **3a** was instantaneously consumed and the solution became bright yellow with formation of abundant grey precipitate (AgI). Complex **3b** was isolated as an orange powder after filtration and solvent removal (91% yield). It also displays air- and moisture-stability and can be kept on the benchtop without noticeable decomposition. It is soluble in polar solvents (acetonitrile, methanol, DMSO, acetone) and partially soluble in dichloromethane and chloroform. The ESI-HRMS spectrum shows one major peak at *m/z* 580.9782 corresponding to the mass of the cationic fragment [Au(bhq)I(py)]⁺ (bhq = benzo[*h*]quinoline). Low-temperature ¹H-NMR (248K) improved the resolution of the peaks, especially that of the γ-proton of the freely rotating pyridine molecule. Crystals of this complex, grown from slow diffusion of diethyl ether in a CH₃CN solution of the compound, confirmed the removal of the iodide *trans* to the Au-C bond, as expected from a larger *trans* effect (Scheme 6.12, right).

With complex **3b** in hand, we reasoned that it might be helpful in trying to unveil the involvement of aryl-Au(III) species in gold(I)-catalyzed halogen exchange and C-O bond formation, as it stands on the threshold of the envisioned intermediates. First, 1 equivalent of complex **3b** was subjected to the same conditions as used for the *p*-chlorophenolate insertion with 2-(2-bromophenyl)-pyridine **1a-Br** and the desired 10-(4-chlorophenoxy)benzo[*h*]quinoline **2aa** was obtained in 86% yield (Scheme 6.13, a).



Scheme 6.12: Synthesis of cationic Au(III) complex **3b** and molecular structure in the solid state. Selected bond lengths [Å] and angles [°]: Au-C(1) 2.023, Au-N(1) 2.068(7), Au-N(2) 2.119(8), Au-I(1) 2.556(2); C(1)-Au-I(1) 95.1(3), C(1)-Au-N(1) 82.8(3), N(2)-Au-I(1) 89.2(2), N(1)-Au-N(2) 93.0(3). (Ellipsoids are set at 50% probability; hydrogen atoms and SbF_6^- counteranion have been omitted for clarity).

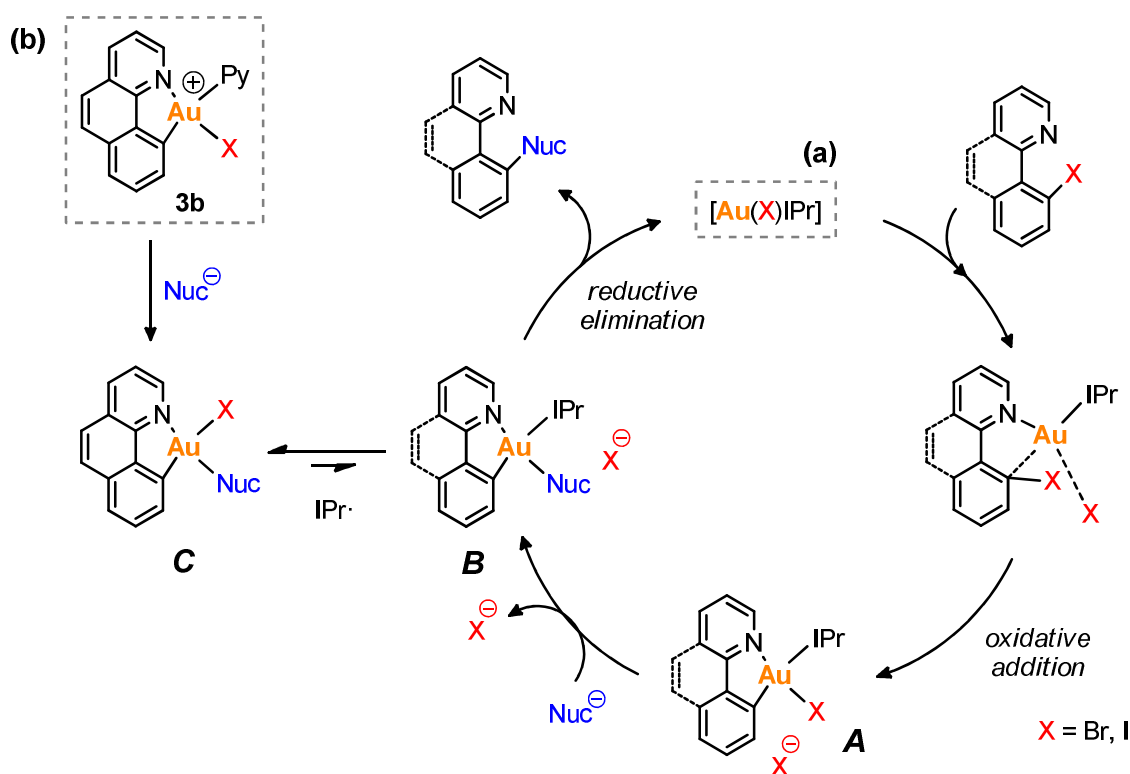


Scheme 6.13: Stoichiometric reactions of complex **3b** with sodium *p*-chlorophenolate in the absence and in the presence of IPr⁺ donor ligand (a). Catalytic version, with and without IPr⁺, starting from **2a-Br** (b), and analogous coupling of *p*-nitroaniline to **2a-I** with IPr⁺.

However, an analogous experiment starting from 10-bromobenzo[*h*]quinoline **2a-Br** and catalytic amounts of **3b** (10 mol%) hardly provided more than 1 catalytic turnover (16% yield of product **2aa**, Scheme 6.13, b). To further stabilize the reductively eliminated Au(I) cations in solution and re-engage them in the catalytic cycle, 10 mol% of the *N*-heterocyclic carbene donor ligand IPr⁺ employed in the catalytic transformations was also added, and we were pleased to find that virtual quantitative yields of **2aa** were achieved (Scheme 6.13, b). Remarkably, ¹H-NMR inspection of the reaction crude revealed that the entire Au(I) remained in solution in the form of [Au(Br)IPr]. Equal behavior was found with the *p*-nitroaniline insertion to **2a-I**

(Scheme 6.13, c), overall unequivocally substantiating the implication of aryl-Au(III) species as competent catalytic intermediates.

Overall, the experimental data collected lends credence to an Au(I)/Au(III) mechanism entailing oxidative addition and reductive elimination steps. The generation of an elusive high-energy $[\text{Au}(\text{ppy})(\text{IPr})\text{X}]$ -type intermediate **A** (Scheme 6.14), predicted by DFT calculations (see Scheme 6.7), constitutes the primary bottleneck in the catalytic cycle. It is accessible through either (a) oxidative addition of $[\text{Au}(\text{X})\text{IPr}]$ salt ($\text{X} = \text{Br}, \text{I}$, nucleophile) to the C_{sp^2} -halide bond or (b) exchange of free IPr $\cdot$ for one of the anionic ligands in $[\text{Au}(\text{L})\text{X}(\text{Nuc})]$ **C** ($\text{L} = \text{ppy}, \text{bhq}$). In both cases heating is required, and the ensuing unstable $[\text{Au}(\text{L})(\text{IPr})\text{X}(\text{Nuc})]$ **B** undergoes fast reductive elimination to yield the cross-coupling product and recover gold(I) as $[\text{Au}(\text{X})\text{IPr}]$.



Scheme 6.14: General proposed mechanism of oxidant-free Au(I)-catalyzed cross-coupling reactions through the intermediacy of aryl-Au(III) species.

6.2 MIGRATORY *SYN* INSERTIONS AT Au(III) COMPLEXES

Insertion reactions of C-C multiple bonds in metal-element bonds are ubiquitous in transition metal chemistry and are encountered as fundamental elementary steps in many catalytic cycles. However, and analogously to oxidative addition, the reactivity of gold complexes with regard to migratory *syn* insertions lags behind.

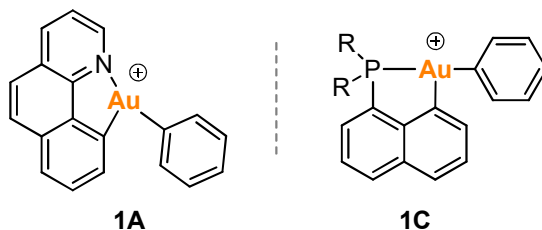
Gold complexes otherwise react with unsaturated substrates such as alkenes or alkynes to form π -complexes, which are activated for subsequent nucleophilic attack. Generally, the outcome of nucleophilic additions at C-C multiple bonds catalyzed by

gold complexes are *trans* configured products, indicating that nucleophilic attack proceeds via an outer-sphere mechanism and in an *anti* fashion (see section 1.2.5).

Nevertheless, the last lustrum has witnessed the development of the first insertion reactions of alkynes at Au(I)-Si bonds⁴⁰ and alkenes at Au(III)-C bonds^{41,42} occurring on the *exo* face and in a *syn* manner, consistent with hitherto unprecedented coordination-insertion mechanisms. In particular, the latter exploits the coordination environment conferred by a (C,P) chelate ligand to generate a cationic Au(III) complex with the requisite free coordination site. In spite of these pioneering works, our understanding on how the ancillary ligands influence the properties and reactivity of gold(III) complexes is poor and much still remains to be done in this area.

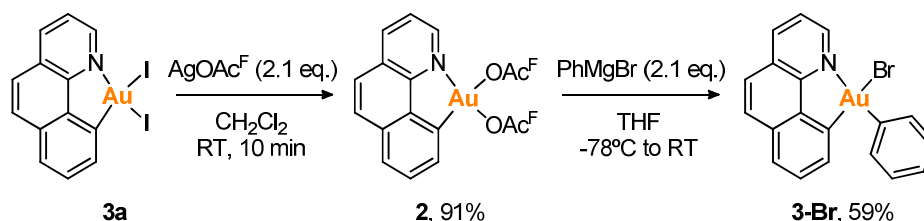
6.2.1 (C,N) *versus* (C,P) Ligands in Cyclometalated Gold(III) Complexes: Noticeable Differences in Migratory Insertion

To tackle this objective, we foresaw that the (C,N)-cyclometalated Au(III) complexes previously disclosed could be good candidates. Given the weaker donor character of nitrogen *versus* phosphorus one might expect different behavior on the two reaction sites *trans* to N and C, eventually altering the thermodynamics and the outcomes of the reaction paths. The key aspect in the quest for olefin insertion at gold lies in the design and access of low coordinated Au(III) complexes. Thus, in likewise manner to the family of (C,P) gold(III) complexes, the entry point to explore whether (C,N) gold(III) complexes are also prone to migratory insertion was the formation of the cationic [(C,N)AuPh]⁺ compound **1A**, which features an Au-Ph bond necessary for the insertion event to take place (Scheme 6.15).



Scheme 6.15: Structures of the (C,N) and (C,P) cationic Au(III) complexes compared in this section.

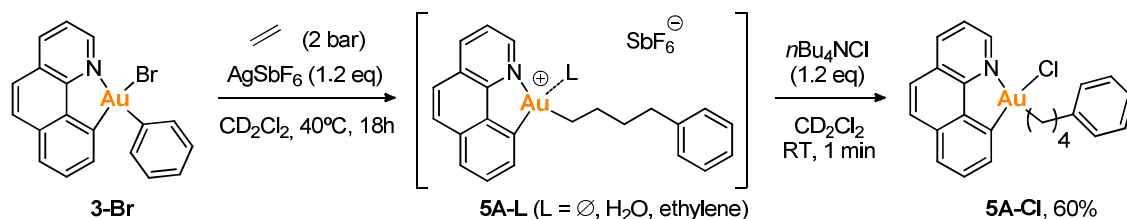
In order to incorporate this new Au(III)-C_{sp2} bond, the selective mono-arylation of the [(C,N)AuI₂] complex **3a** (previously prepared *via* chelation-assisted oxidative addition) was attempted following the same synthetic procedure than that reported for the analogous [(C,P)AuI₂] complex with Grignard reagents.⁴² However, treatment of **3a** with PhMgBr led to an intractable mixture of products. Exchange of the iodines at gold for more labile trifluoroacetate ligands (complex **2**) applying the conditions reported by Tilset and co-workers⁴³ allowed for the synthesis of the desired [(C,N)AuBrPh] complex **3-Br** (Scheme 6.16). Complex **3-Br** was isolated as a white powder in a 59% yield after column chromatography and characterized by NMR spectroscopy and high-resolution mass spectrometry.



Scheme 6.16: Synthetic approaches to novel complexes **2** and **3-Br**.

Afterwards, a CD_2Cl_2 solution the cationic phenyl complex **1A** was reacted with AgSbF_6 under ethylene pressure (2 bar) at room temperature in a J. Young NMR tube. ^1H -NMR spectroscopy revealed no changes within 72 h. Remarkably, upon heating at 40°C virtually complete conversion into a new species with aliphatic signals above δ 1.8 ppm was achieved after 18 h (Scheme 6.17). Furthermore, needle-like crystals formed spontaneously in small amounts inside the NMR tube, and to our surprise X-ray diffraction analysis showed double insertion of ethylene plus coordination to one molecule of adventitious water (**5A-H₂O**, Figure 6.1). With the aim of facilitating the handling and characterization of this product, we quenched the reaction crude with $n\text{Bu}_4\text{NCl}$ in order to generate a neutral four-coordinate gold(III) chloride complex. Gratifyingly, a white solid was isolated in 60% yield and characterized by multinuclear NMR spectroscopy and high-resolution mass spectrometry (HRMS). The relative integration of the aromatic and aliphatic signals in the ^1H NMR spectrum (13H *versus* 8H), and the peak at m/z 508.1346 attributed to the mass of $[(\text{C},\text{N})\text{AuPh}]^+$ augmented by two ethylene molecules, corroborated the double insertion into the Au-Ph bond. The solid-state structure of the complex **5A-Cl** was also determined by X-ray crystallography, displaying the gold atom in a square-planar environment formed by the (C,N) chelate ligand, the chlorine atom and the ethylenyl-phenyl chain located *trans* to the nitrogen atom (Figure 6.2).

It is interesting to note that the stability of the 3-coordinated complex **1A** is notably enhanced in the presence of ethylene. Indeed, without olefins it decomposes after 6h in solution at room temperature into several side-products and metallic gold, while no degradation is observed within at least 72h under ethylene atmosphere, albeit no sign of coordination to the vacant site was detected by ^1H -NMR.



Scheme 6.17: Reaction of Au(III) complex **1A** with ethylene and subsequent trapping with chloride.

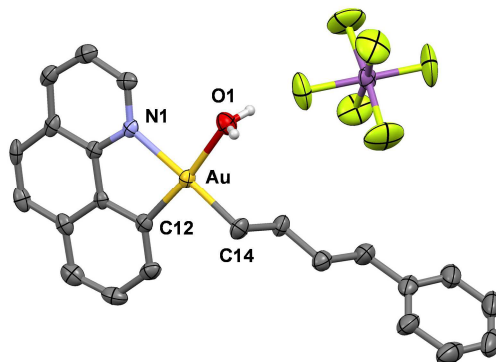


Figure 6.1: Molecular structure of complex **5A-H₂O**. Selected bond lengths [Å] and angles [°]: Au-C(14) 2.057(5), Au-N(1) 2.141(4), Au-C(12) 2.001(5), Au-O(1) 2.150(4); N(1)-Au-O(1) 91.10(17), C(12)-Au-N(1) 82.35(8), C(12)-Au-C(14) 95.0(2), C(14)-Au-O(1) 91.6(2). (Ellipsoids are set at 50% probability; hydrogen atoms, except for water molecule, have been omitted for clarity).

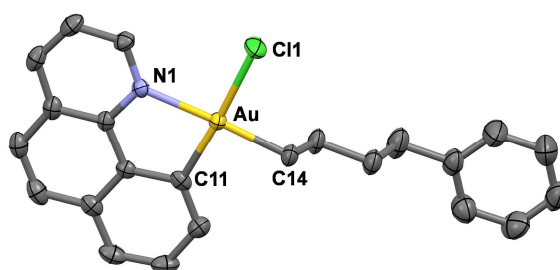
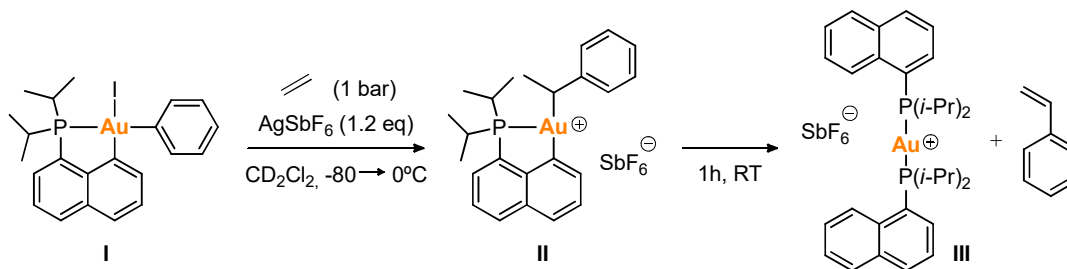


Figure 6.2: Molecular structure of complex **5A-Cl**. Selected bond lengths [Å] and angles [°]: Au-C(14) 2.044(3), Au-N(1) 2.141(2), Au-C(11) 2.024(3), Au-Cl(1) 2.3520(8); N(1)-Au-Cl(1) 94.05(7), C(14)-Au-N(1) 82.44(11), C(11)-Au-C(14) 93.35(13), C(14)-Au-Cl(1) 90.15(10). (Ellipsoids are set at 50% probability; hydrogen atoms have been omitted for clarity).

The double addition of ethylene to complex **1A** is reminiscent of the insertion of two norbornene molecules into the Au-Me bond of the (C,P)-ligated gold(III) dimethyl complex (related to complex **1C**, Scheme 6.15).^{41,52} In this process, the insertion of a second NB into the Au-C_{norbornyl} bond gives access to a more thermodynamically stable complex, with the Au-C_{norbornyl} group in the *trans* position relative to phosphorus. In a similar manner, the strong *trans* influence of the benzoquinolinic carbon in **1A** triggers the migration of the alkyl group by insertion of a second ethylene molecule to the *trans* position relative to nitrogen (weaker *trans* influence, see DFT calculations below).

In spite of the presence of hydrogen atoms in β position, complex **5A-L** shows unusual thermal stability and no formation of styrene or higher olefins was detected during the reaction course. Although it is also possible that labile coordination of the SbF₆ counter anion, the pendant Ph ring and a molecule of water or ethylene contributes to stabilize **5A-L** in solution, the electronic features of the (C,N) chelate ligand are likely to account for its rare stabilization. This is again in stark contrast to behaviour observed in the [(C,P)AuPh]⁺ complex **1C**, where, after ethylene insertion, a β -H elimination and re-insertion sequence takes place leading to the gold(III)-arene complex **II** (Scheme 6.18). This compound eventually evolves into the cationic gold(I) complex

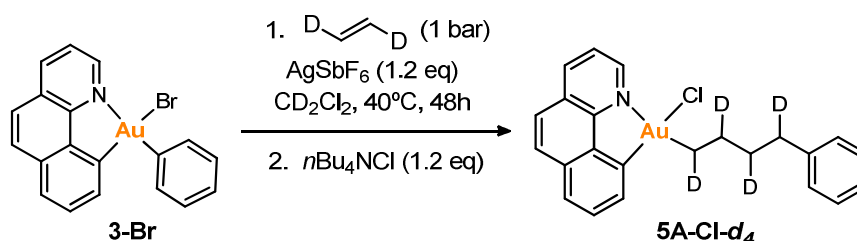
III *via* reductive elimination, styrene release and ligand redistribution after 1 h at room temperature.



Scheme 6.18: Reaction of the (C,P)-ligated complex **I** with ethylene and fate of **II**.

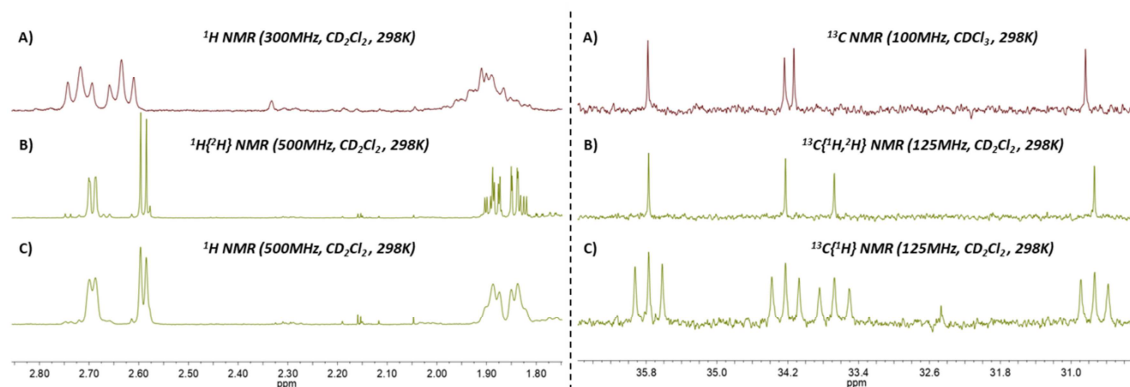
D-labelling experiments:

To probe the possible occurrence of β -H elimination in competition with ethylene insertion, a D-labeling experiment was performed using *trans*-ethylene- d_2 (Scheme 6.19). Using an atmospheric pressure of ethylene, complete conversion was accomplished after two ethylene refillings and 2 x 24 hours heating at 40°C . The reaction was then repeated with *trans*-ethylene- d_2 95.2% D following the same experimental conditions. The reaction mixture was then quenched with 1.2 equivalents of $n\text{Bu}_4\text{NCl}$ and analysed by NMR spectroscopy.



Scheme 6.19: D-Labeling experiment using *trans*-ethylene- d_2 affording selectively the **5A-Cl- d_4** product.

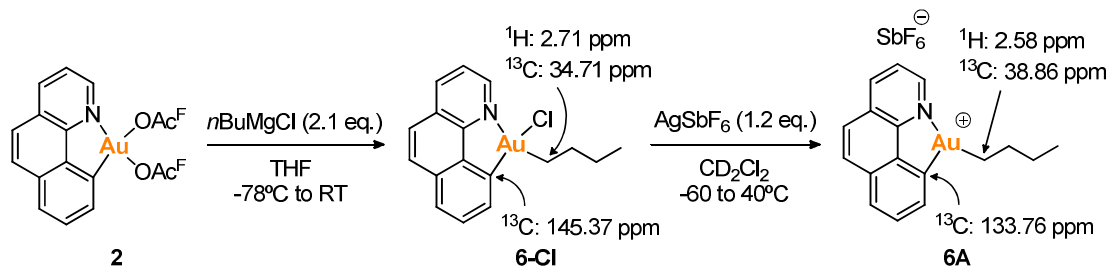
^1H and ^{13}C NMR spectra showed the formation of the expected $\text{Au}(\text{CHD})_4\text{Ph}$ enchainment (**5A-Cl- d_4** , scheme 6.20): the two terminal CHD moieties resonate as doublets compared to triplets for the non-deuterated complex (**5A-Cl**). Accordingly, the corresponding ^{13}C NMR signals all appear as 1:1:1:1 triplets in the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum. The virtual absence of H/D scrambling confirms that β -H elimination does not occur to a significant extent under these conditions and that ethylene insertion prevails.



Scheme 6.20: Aliphatic ^1H and ^{13}C NMR signals of **5A-Cl** (A) and **5A-Cl- d_4** (B, C), as obtained by analysis of the reaction crudes. In case of the complex derived from *trans*-ethylene- d_2 , deuterium-decoupled (B) and deuterium-coupled (C) NMR analyses are shown.

To further probe the reluctance of complex **5A** to undergo β -hydride elimination, the gold(III) *n*-butyl complex **6-Cl** was prepared and its behaviour upon cationization was analysed. The selective mono-alkylation of [(C,N)Au(OAcF)₂] complex **2** was successfully accomplished using 2.1 equivalents of Grignard reagent BuMgCl under identical conditions to those applied for the preparation of [(C,N)AuBrPh] complex **3-Br** (Scheme 6.21). After purification by column chromatography, the targeted [(N,C)AuCl(*n*-Bu)] complex **6-Cl** was isolated as a white powder in 73% yield and characterized by multinuclear NMR spectroscopy and high-resolution mass spectrometry. **6-Cl** is stable under air and can be stored and handled without particular precautions.

With **6-Cl** in hand, we then proceeded with the generation of the corresponding cationic Au(III) complex by chloride abstraction with AgSbF₆ in CD₂Cl₂. According to ^1H -NMR monitoring, the silver salt instantaneously abstracts the chloride from gold at -60°C to form the corresponding [(C,N)Au(*n*-butyl)][SbF₆] complex **6A** (Scheme 6.20). Alike **5A**, no signs of degradation or β -hydride elimination (formation of 2-butenes and butane) were observed by ^1H and ^{13}C -NMR after warming up to room temperature or even upon heating at 40°C for 24h. In consequence, complex could be **6A** fully characterized by NMR spectroscopy and ESI-HRMS at room temperature and under air. ^{13}C -NMR data reveals a significant shift to high field of the aromatic carbon directly bound to gold upon cationization (from δ 145.37 ppm in neutral complex **6-Cl** to δ 133.76 ppm in **6A**). On the other hand, the alkylic carbon of the *n*-butyl chain attached to gold shifts to low field with $\Delta\delta = 4.6$ ppm. Conclusively, the remarkable thermal stability of the *n*-butyl cationic complex goes in line with the lack of β -H elimination in the ethylene insertion reaction of [(N,C)AuPh]⁺ complex **5A**.



Scheme 6.21: Preparation of mono-alkylated n -butyl complex **6-Cl** and subsequent chloride abstraction to generate **6A**. Most diagnostic NMR shifts of the two complexes.

Computational studies on ethylene insertion and β -hydride elimination:

To gain more insight into the mechanism and energetic parameters of the ethylene insertion and β -hydride elimination processes, exhaustive DFT calculations were carried out on the real complex **1A** in its ground-state *cis* geometry. The π -coordination of ethylene to render **2A** is slightly downhill in energy by $-3.4 \text{ kcal}\cdot\text{mol}^{-1}$ (Figure 6.3). Detailed examination of the optimized geometry of **2A** indicates that ethylene is coordinated in a symmetric fashion (two short $\text{Au}\cdots\text{C}$ contacts at $2.40 \text{ \AA}$) and is positioned perpendicular to the metal coordination plane (the CH_2 groups remain quasi-planar). This bonding situation is in accordance with the NBO analysis, which predicted a strong $\pi(\text{CC})\rightarrow\text{Au}$ donation and weak $\text{Au}\rightarrow\pi^*(\text{CC})$ backdonation (corresponding delocalization energies of 45.7 and $14.1 \text{ kcal}\cdot\text{mol}^{-1}$, respectively).

The activation barrier for the migratory insertion of ethylene is $20.7 \text{ kcal}\cdot\text{mol}^{-1}$, in good agreement with a process that requires mild heating (40°C) to proceed. The ensuing complex **3A** is $5.6 \text{ kcal}\cdot\text{mol}^{-1}$ uphill in energy, and the disfavored alkyl chain *trans* to C is somewhat compensated by π -arene coordination to the Au(III) center ($\text{Au}\cdots\text{C}_{\text{ortho}}$ and $\text{Au}\cdots\text{C}_{\text{ipso}}$ contacts of 2.21 and $2.71 \text{ \AA}$, respectively). Donation from the $\pi(\text{C}_{\text{ipso}}\text{C}_{\text{ortho}})$ orbital to $\sigma^*(\text{AuN})$ orbital was found with a NBO delocalization energy of $31.0 \text{ kcal}\cdot\text{mol}^{-1}$, which is lower than in the case of NB ($34.7 \text{ kcal}\cdot\text{mol}^{-1}$), presumably due to a more flexible CH_2CH_2 spacer. The involvement of the *trans* isomer **t-1A** was dismissed because it lies very high in energy ($36.2 \text{ kcal}\cdot\text{mol}^{-1}$ above the *cis* isomer **1A**) as a consequence of the very high electronic dissymmetry of the (C,N) ligand. Interestingly, this very unfavorable *trans* arrangement of the two organic fragments makes the coordination-insertion of ethylene from **t-1A** very facile and strongly exergonic, affording a *cis* product **c-3A** $22.0 \text{ kcal}\cdot\text{mol}^{-1}$ lower in energy than **3A**. Nevertheless, the participation of **c-3A** is improbable because the barrier for *trans* $\rightarrow$ *cis* isomerization is also very high ($28.2 \text{ kcal}\cdot\text{mol}^{-1}$) due to the necessity to break the strong π -arene interaction.

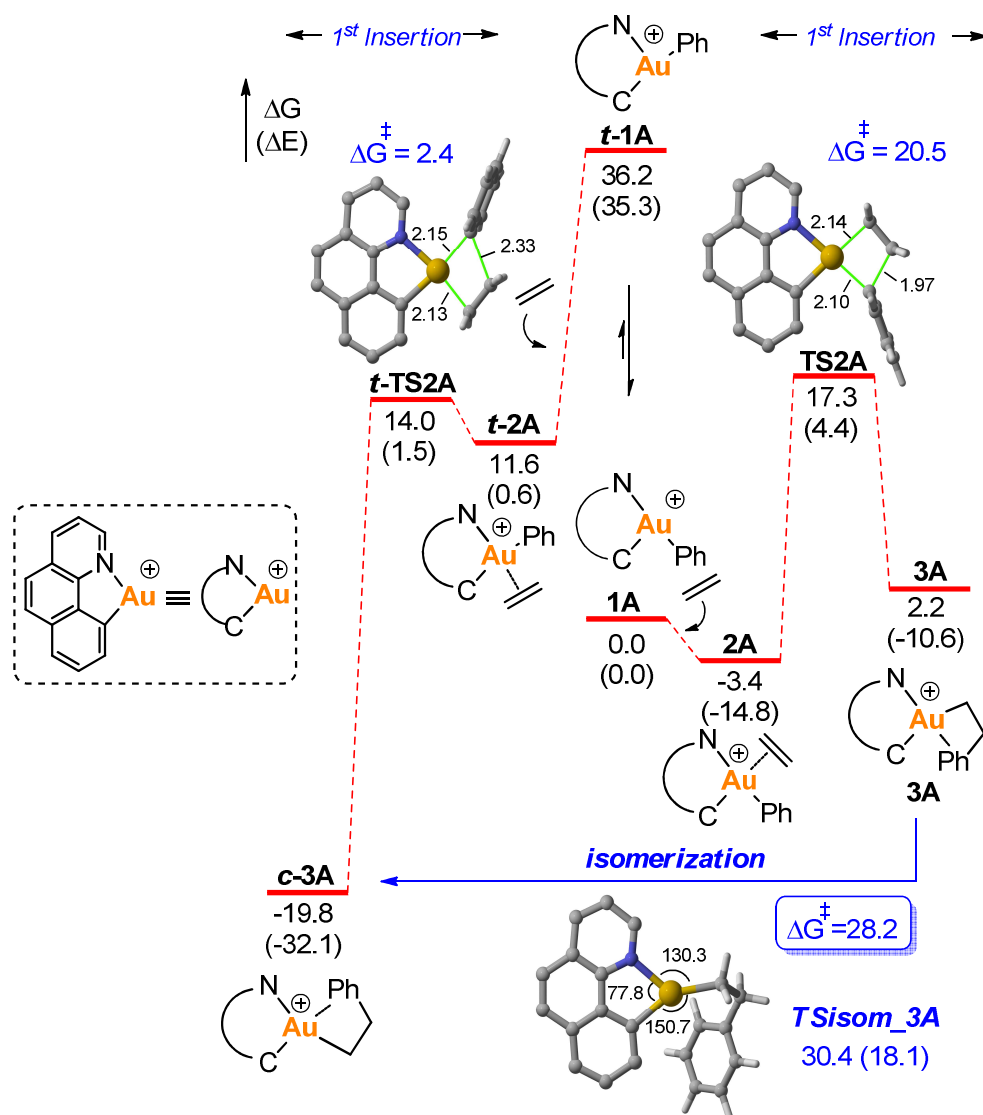


Figure 6.3: Energy profile (ΔG and ΔE values, into brackets in $\text{kcal}\cdot\text{mol}^{-1}$) computed at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory for the insertion of ethylene into the Au-Ph bond of **1A**. Both *cis* and *trans* isomers are considered.

However, the more energetically favorable isomer with the alkyl chain *trans* to weak N donor can be attained through a second insertion event. Indeed, starting from **3A**, the addition of another ethylene molecule is predicted to be very facile, in line with experimental observations. Displacement of the π -arene coordination at **3A** by ethylene is about thermoneutral and migratory insertion then takes place with a very low energy barrier ($6.6 \text{ kcal}\cdot\text{mol}^{-1}$ from **3A**) to give the $[(C,N)Au(CH_2)_4Ph]^+$ complex **5A** (Figure 6.4). Note that the extended linear form of **5A** is slightly more stable than the γ -CH agostic stabilized one **5A- γ** (a $7.1 \text{ kcal}\cdot\text{mol}^{-1}$ $\sigma(CH) \rightarrow \sigma^*(AuC)$ donor-acceptor interaction is found at the second-order perturbation level in NBO analysis). In parallel, β -Hydride elimination from **3A** was also considered (Figure 6.4, pale red profile). Comparably to what observed for the $[(C,P)Au(n\text{-alkyl})]^+$ complexes, it proves facile with an activation barrier of only $2.8 \text{ kcal}\cdot\text{mol}^{-1}$. Given the detrimental *trans*

arrangement of **3A**, the formation of the gold hydride styrene complex **7A** is thermodynamically favored by $\Delta G = 14.4 \text{ kcal}\cdot\text{mol}^{-1}$. After β -hydride elimination, rotation of styrene and re-insertion into the Au-H bond can happen to give the branched complex **8A** as in the case of the (C,P) complex, albeit the corresponding energy barrier is significantly higher ($20.9 \text{ kcal}\cdot\text{mol}^{-1}$). Kinetically, the second ethylene insertion and β -H elimination might compete from **3A**, but the high exergonic character of the second ethylene insertion from **3A** pushes the reaction to the formation of **5A**, enabling its experimental observation.

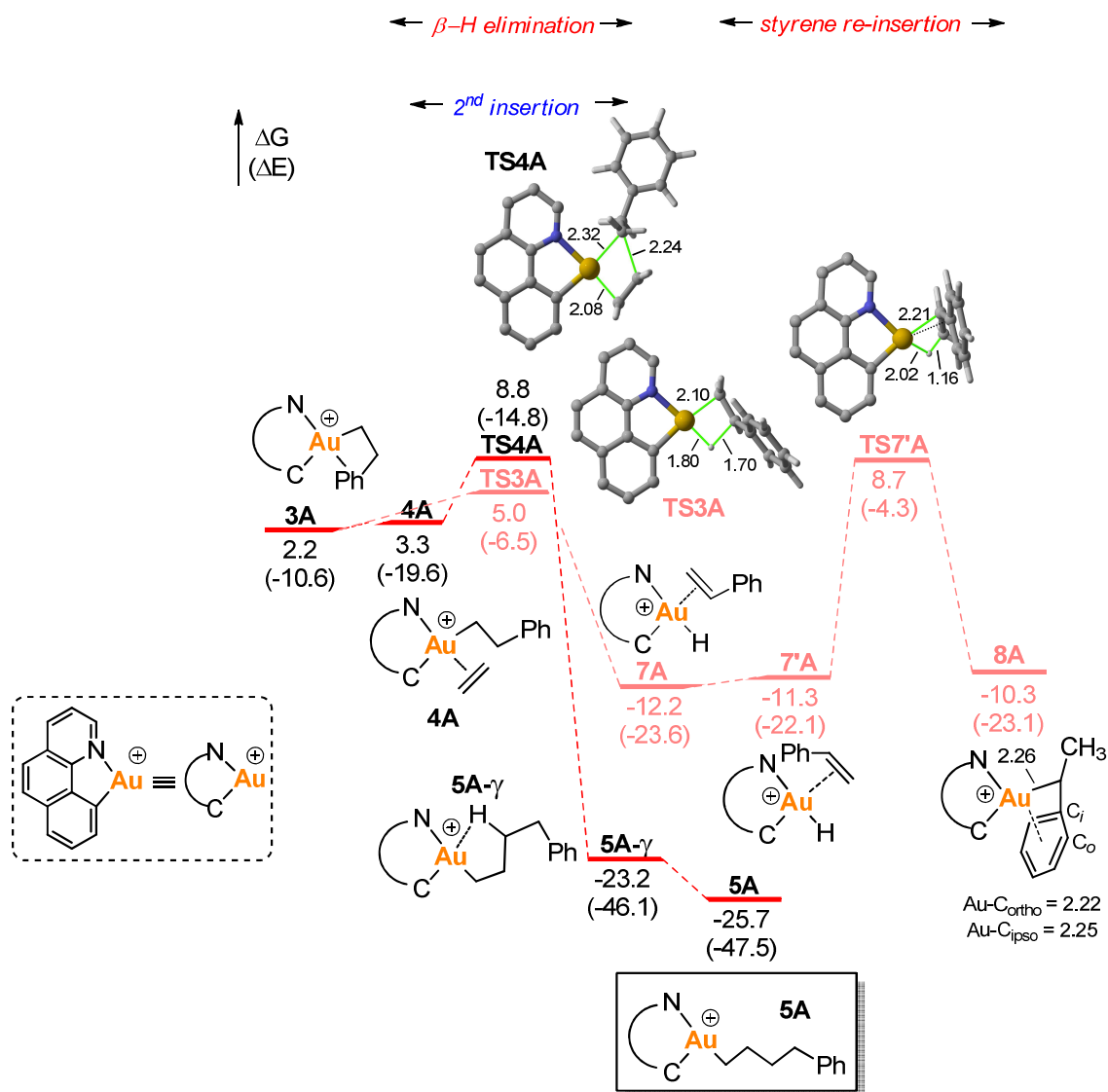


Figure 6.4: Energy profile (ΔG and ΔE values, into brackets in $\text{kcal}\cdot\text{mol}^{-1}$) computed at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G** (other atoms) level of theory for the second ethylene insertion (red profile) and β -hydride elimination (pale red profile) from **3A**.

For the sake of completeness, a third ethylene insertion from **5A** (Figure 6.5, red profile), as well as a second ethylene insertion from **8A** (Figure 6.5, blue profile) were computed, but they were both found to be kinetically or thermodynamically

disfavoured. The same applies to the second ethylene insertion and β -H elimination from **c-3A**, the more stable isomer of the first ethylene addition. Besides, β -H elimination and γ -H elimination from **5A** were also deemed highly improbable, the first owing to its strong exergonic character (ΔG 18.5 kcal·mol⁻¹) and the second due to a prohibitively high activation barrier ($\Delta G^\ddagger$ 41.0 kcal·mol⁻¹). In the case of β -H elimination, the resulting gold hydride olefin complex lies very high in energy again due to the unfavourable *trans* arrangement. This may well explain the stability of the [(C,N)Au(*n*-butyl)]⁺ complex **6A** noticed experimentally.

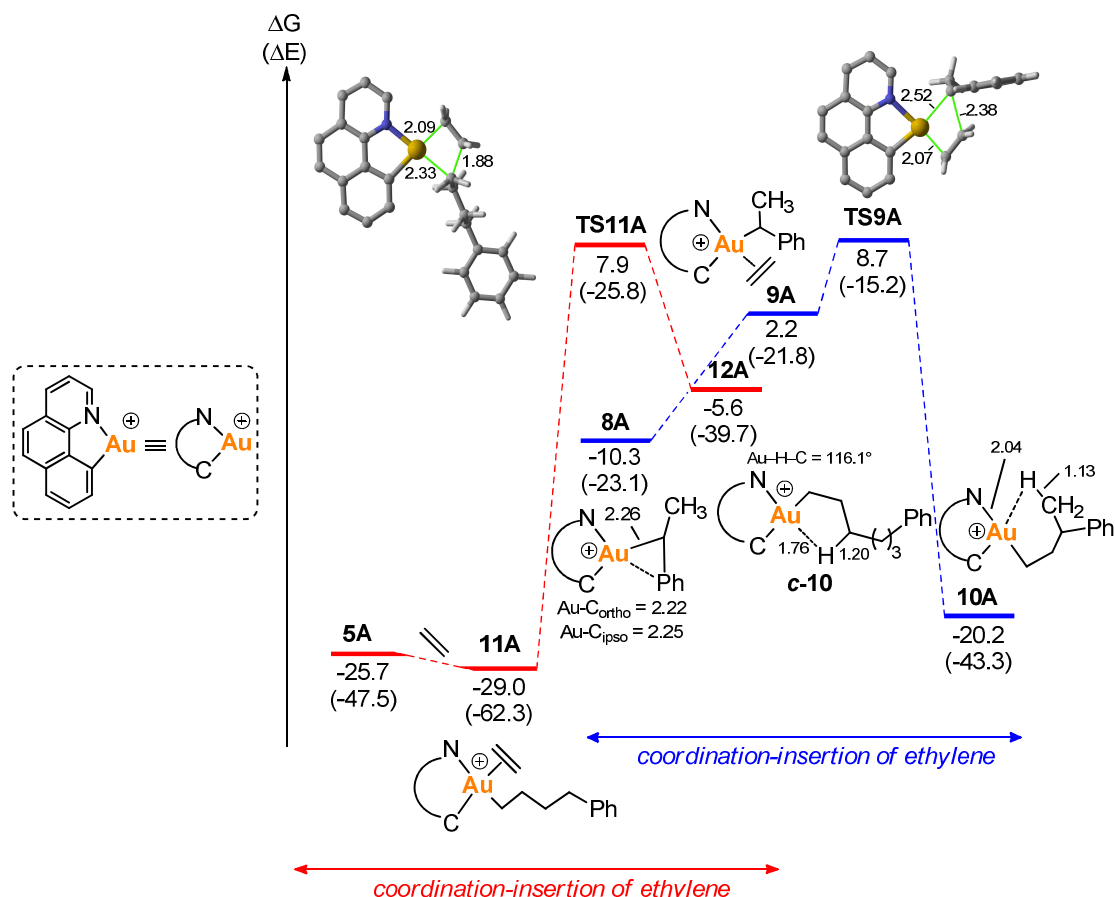


Figure 6.5: Energy profiles (ΔG and ΔE values into brackets, in kcal·mol⁻¹) computed at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G** (other atoms) level of theory for the third ethylene insertion from **5A** (in red) and second ethylene insertion from **8A** (in blue).

Summary of the most noticeable differences between the (C,N) and (C,P) complexes:

- I. The energy gap between the *cis* and *trans* isomers of [(C,N)AuPh]⁺ **1A** and [(C,P)AuPh]⁺ **1C** (as well as of related species) is extraordinarily large. As above-mentioned, the *cis* form of **1A** is more stable than the *trans* isomer by ΔG 36.2 kcal·mol⁻¹. However, the energy gap falls down to 7.1 kcal·mol⁻¹ for **1C**.
- II. The first ethylene insertion with the (C,N) chelate ligand is slightly uphill in energy (ΔG +5.6 kcal·mol⁻¹), while the second insertion is strongly exergonic (ΔG -27.9 kcal·mol⁻¹) and preferred over β -H elimination. Indeed, the absence of noticeable H/D scrambling upon reacting ethylene-*d*₂ (Scheme 6.20) indicates

minimal occurrence, if any, of β -H elimination. In contrast, ethylene insertion from the (C,P) complex **1C** is downhill in energy (ΔG -10.0 kcal·mol⁻¹) but the second ethylene insertion involves a high activation barrier (21.6 kcal·mol⁻¹ *versus* 15.1 kcal·mol⁻¹ for the first insertion) and does not compete with β -H elimination / re-insertion leading to the branched product **II**.

- III. The activation barrier for the third ethylene insertion is *ca* 17 kcal·mol⁻¹ higher than that of the first insertion, in line with the higher reactivity of Au-C_{sp2} vs Au-C_{sp3} bond, as previously observed with the [(P,C)Ph]⁺ and [(P,C)AuMe]⁺ complexes.^{42,51}

These differences essentially arise from the weaker donor character of N *versus* P. In consequence, the (C,N) ligand induces significant electronic dissymmetry on gold compared to the (C,P) ligand, and the two reaction sites *trans* to N or C behave quite distinctly, as previously noticed by Tilset and co-workers for the tolylpyridine (tpy) ligand.^{53,54}

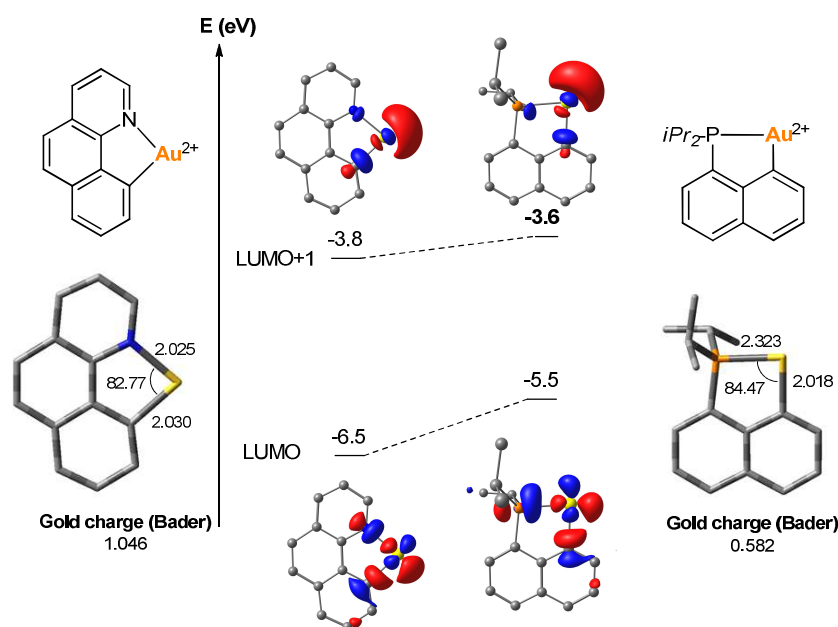


Figure 6.6: Optimized structures (with selected geometrical data) and lowest energy molecular orbitals of the [(N,C)Au]²⁺ and [(P,C)Au]²⁺ fragments computed at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory.

To further highlight the difference in the electronic properties of the (C,N) and (C,P) ligands, calculations were carried out on the naked [(C,N)Au]²⁺ and [(C,P)Au]²⁺ fragments (Figure 6.6). In both cases, the LUMO corresponds to the vacant orbital at Au in *trans* position to the N or P (main contribution of the $\sigma^*(\text{Au-N})/(\text{Au-P})$ orbitals), and it is significantly lower in energy (by 1 eV) in the (C,N) ligand. Contrastingly, the LUMO+1 orbitals of the two fragments, which correspond to the vacant orbitals at Au in *trans* position to the aryl moiety, lie close in energy. Therefore, the (C,N) ligand induces a significantly larger LUMO-LUMO+1 gap than the (C,P) ligand and hence a stronger electronic dissymmetry of the coordination sphere at gold. The lower-lying

LUMO in the (C,N) ligand is a direct consequence of its weaker tunicity, which translates into a significantly more electrophilic gold center than in the (C,P) ligand (1.05 *versus* 0.58 atomic charge at gold, respectively).

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CHAPTER VII

GENERAL CONCLUSIONS

The main objectives of the initially envisioned research project that evolved in the course of this thesis were focused on the deeper understanding of the fundamental organometallic steps of gold. Taking as a starting point the relevant findings in terms of reactivity and mechanistic insights regarding the two-electron redox chemistry of copper and silver in cross-coupling reactions, we wanted to complete the picture of the coinage metals by incorporating gold into this framework. At the beginning we also used as a platform the coordinating opportunities that a family of aryl-halide macrocyclic substrates provide in order to study these transformations. In the course of our investigations unexpected findings were disclosed, pinpointing some analogies but also noticeable differences between gold and the other coinage metals. Our work evolved then to systems featuring more suitable conditions to study high-valent species and explore challenging reactivities, with special attention to the oxidative addition and migratory insertion processes. The results presented herein contribute to the understanding of the organometallic chemistry of gold complexes and hopefully might influence further fundamental and application-oriented research in these fields.

In **Chapter III** we describe the first oxidant-free gold(I)-catalyzed halide exchange, including challenging fluorination, and C_{sp^2} -O bond forming reactions with phenols. The highly coordinating environment of the model triazamacrocyclic substrates $L_n\text{-X}$ was initially envisioned to favor the oxidative addition of Au(I) salts to aryl halides and the following reactivity towards nucleophiles. In fact, this strategy had proved extremely beneficial in the stabilization of square pyramidal aryl-Cu(III) and aryl-Ag(III) complexes. Although in this case the proposed aryl-Au(III) intermediates could not be detected, indirect experimental data (mercury poisoning tests for nanoparticles, by-products reminiscent of cycles involving M^{3+} intermediates,...) and DFT calculations validated the idea of an operative Au(I)/Au(III) redox cycle. This reactivity was afterwards transferred from the model macrocyclic aryl halide substrates to more readily available 2-(2-halophenyl)pyridine compounds, in C_{sp^2} -O bond formation using *p*-chlorophenolate and methoxide. All the data collected points towards the intermediacy of aryl-Au(III) species in the coupling reactions, demonstrating the feasibility of such transformations without the requirement of sacrificial oxidants.

In **Chapter IV** we expand the nucleophile scope from halides and phenols to other alkoxides, including hydroxide, as well as amines and amides within the 2-(2-halophenyl)pyridine compounds. In the first case the system shows preference for small and acidic alkoxides, whereas the acidity and steric hindrance of the *N*-nucleophiles govern the reactivity trend in the C_{sp^2} -N coupling reactions. Furthermore, the intermediacy of Au(III) complexes in such transformations could be confirmed with the synthesis of new (C,N)-cyclometalated Au(III) complexes through mild oxidative addition of a C_{sp^2} -I bond. Incorporation of a third aromatic ring to 2-(2-iodophenyl)pyridine in the form of 10-iodobenzo[*h*]quinoline to prevent rotation of the pyridyl group was crucial to stabilize the targeted cycloaurated complex. This stands as the first example of five-membered [(C,N)AuX₂] complexes generation without

applying the classical procedures, namely (a) transmetalation with organomercury compounds or (b) direct C-H auration upon strong heating or microwave conditions.

In **Chapter V** we turned our attention to migratory *syn* insertion reactions. The reactivity of a well-defined cationic (C,N)-cyclometalated gold(III) complex towards ethylene addition into its Au-Ph bond was thoroughly studied and compared with that of a related (C,P)-cyclometalated complex. Evidence of double insertion of ethylene was obtained by different techniques, including X-ray diffraction. This indicates that the addition of a second molecule of ethylene is preferential over β -hydride elimination, which is in stark contrast to what observed with the (C,P) system. The notable differences between the two sets of ligands arise in large part from the weaker donor character of nitrogen compared with phosphorus, which renders the (C,N) ligand electronically very dissymmetric. The experimental work was closely accompanied by DFT calculations carried out by the group of Dr. Karinne Miqueu (Pau, France). These computational analyses provided a large contribution to the mechanistic investigations of the studied reactions and proved invaluable for the understanding of the electronic properties of the species involved.

ANNEXES

Supplementary Material Chapter III

Oxidant-Free Au(I)-Catalyzed Halide Exchange and Csp²-O Bond Forming Reactions

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1. Materials and methods

1.1. Materials and Instrumentation

Reagents and solvents used were commercially available reagent quality unless indicated otherwise. Solvents were purchased from SDS-Carlo Erba and Scharlab and were purified and dried by passing through an activated alumina purification system (MBraun SPS-800). Preparation and handling of air-sensitive materials was carried out in a N₂ drybox (JACOMEX) with O₂ and H₂O concentrations < 1.0 ppm. NMR data were collected on a BRUKER 400 or 300 AVANCE spectrometer in the corresponding deuterated solvent (CDCl₃ or CD₃CN) and ¹H and ¹⁹F{¹H} experiments were recorded under routine conditions. ESI-MS experiments were collected and analyzed on a Bruker Daltonics Esquire 6000 spectrometer with acetonitrile or acetonitrile/water (80:20) as solvent. High resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOF-Q II TM instrument using ESI or Cryospray ionization sources with acetonitrile as solvent by Dr. Laura Gómez of Serveis Tècnics of the University of Girona.

1.2. Synthesis of ligands, substrates and catalysts

Ligands **L₁-X** (X = F, Cl, Br, I) and **L₅-X** (X = F, Cl, Br) were synthesized following the procedures previously described.^[1,2] 2-Bromo-1,3-dimethylbenzene (**2a**) and 2-bromo-*N*-methylbenzylamine (**2b**) were purchased from Sigma Aldrich and used without further purification. 2-bromo-*N,N*-dimethylbenzylamine (**2c**) was prepared according to the literature procedure.^[3] 2-(2-bromophenyl)-pyridine (**2d**) was synthesized as previously described by Pd-catalyzed cross-coupling of 2-bromopyridine and 2-bromophenylboronic acid.^[4] Two derivatives, 2-(2-bromo-5-(trifluoromethyl)phenyl)pyridine (**2da**) and 2-(2-bromo-5-methoxyphenyl)pyridine (**2db**) were prepared similarly by using 2-bromo-5-(trifluoromethyl)phenylboronic acid and (2-bromo-5-methoxyphenyl)boronic acid, respectively.

2d: ¹H-NMR (CDCl₃, 400 MHz) δ, ppm: 8.71 (dq, *J* = 4.8, 2.0, 0.8 Hz, 1H, H^a), 7.76 (td, *J* = 7.6, 1.6 Hz, 1H, H^c), 7.67 (dd, *J* = 8.0, 1.2 Hz, 1H, H^b), 7.60 (dt, *J* = 8.0, 1.2 Hz, 1H, H^d), 7.54 (dd, *J* = 8.0, 1.6 Hz, 1H, H^e), 7.41 (td, *J* = 7.6, 1.2 Hz, 1H, H^g), 7.27 (m, 2H, H^b, H^f); ¹³C-NMR (CDCl₃, 70 MHz) δ, ppm: 158.57 (C5), 149.65 (C1), 141.46 (C6), 136.07 (C3), 133.51 (C10), 131.65 (C7), 129.96 (C8), 127.77 (C9), 124.98 (C4), 122.66 (C2), 122.00 (C11); **HRMS (ESI)** (CH₃CN, *m/z*): calcd for C₁₁H₈BrN [M + H⁺] 233.9913, found: 233.9918.

(1) A. Casitas, M. Canta, M. Solà, M. Costas, X. Ribas, *J. Am. Chem. Soc.* **2011**, *133*, 19386.

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2da: Product was purified by column chromatography on silica gel (hexane-diethyl ether 70:30) affording a colorless oil in a 64 % isolated yield. **¹H-NMR** (CDCl₃, 400 MHz) δ, ppm: 8.74 (dq, *J* = 4.8, 2.0, 1.2 Hz, 1H, H^a), 7.80 (m, 3H, H^c, H^e, H^g), 7.63 (dt, *J* = 8.0, 1.2 Hz, 1H, H^d), 7.51 (m, 1H, H^f), 7.35 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H^b); **¹³C-NMR** (CDCl₃, 100 MHz) δ, ppm: 156.99 (C5), 149.72 (C1), 141.96 (C6), 136.10 (C3), 133.97 (C11), 130.18 (q, ²*J*_{CF} = 32.9 Hz, C8), 128.38 (q, ³*J*_{CF} = 3.7 Hz, C7), 126.24 (q, ³*J*_{CF} = 3.6 Hz, C10), 125.73 (C12), 124.68 (C4), 123.72 (q, ¹*J*_{CF} = 270.9 Hz, C9), 123.02 (C2); **¹⁹F-NMR** (CDCl₃, 376.5 MHz) δ, ppm: -62.70; **HRMS (ESI)** (CH₃CN, *m/z*): calcd for C₁₂H₇BrF₃N [M + H⁺] 301.9787, found: 301.9774.

2db: Product purified by column chromatography on silica gel (hexane-diethyl ether 50:50) affording a pale yellow oil in a 53 % isolated yield. **¹H-NMR** (CDCl₃, 400 MHz) δ, ppm: 8.71 (dq, *J* = 4.8, 2.0, 0.8 Hz, 1H, H^a), 7.76 (ddd, *J* = 8.0, 7.6, 2 Hz, 1H, H^c), 7.61 (dt, *J* = 8.0, 1.2 Hz, 1H, H^d), 7.54 (d, *J* = 8.8 Hz, 1H, H^b), 7.30 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H^b), 7.09 (d, *J* = 3.2 Hz, 1H, H^e), 6.83 (dd, *J* = 8.8, 3.2 Hz, 1H, H^g), 3.83 (s, 3H, H^f); **¹³C-NMR** (CDCl₃, 100 MHz) δ, ppm: 159.00 (C8), 148.29 (C5), 149.40 (C1), 141.97 (C6), 135.83 (C3), 133.98 (C11), 124.77 (C4), 122.50 (C2), 116.35 (C10), 116.30 (C7), 112.18 (C12), 55.59 (C9); **HRMS (ESI)** (CH₃CN, *m/z*): calcd for C₁₂H₁₀BrNO [M + H⁺] 264.0024, found: 264.0008.

The cationic NHC-Au(I) catalyst [Au(NCMe)IPr]SbF₆ was prepared following a literature procedure.^[5]

[Au(OPh-*p*Cl)IPr]: In a vial, [Au(NCMe)IPr]SbF₆ (25 mg, 0.029 mmol) was dissolved in 1 mL of acetonitrile and sodium *p*-chlorophenolate (4.4 mg, 0.029 mmol) was added. The reaction was stirred at room temperature for 10-15 minutes, solvent was reduced under vacuum and dichloromethane (1 mL) was added. The resulting mixture was filtered through a pad of Celite® and the filtrate dried under vacuum to yield [Au(OPh-*p*Cl)IPr] as a white powder (20.6 mg, quantitative). **¹H-NMR** (CD₃CN, 400 MHz) δ, ppm: 7.63 (t, *J* = 8.0 Hz, 2H, H^a), 7.57 (s, 2H, H^f), 7.44 (d, *J* = 8.0 Hz, 4H, H^b), 6.76 (d, *J* = 8.8 Hz, 2H, H^g), 6.13 (d, *J* = 8.8 Hz, 2H, H^b), 2.61 (sept, *J* = 6.8 Hz, 4H, H^c), 1.33 (d, *J* = 6.8 Hz, 12H, H^d or H^e), 1.26 (d, *J* = 6.8 Hz, 12H, H^d or H^e).

[Au(Br)IPr]: A vial was charged with [Au(NCMe)IPr]SbF₆ (25 mg, 0.029 mmol) and tetrabutylammonium bromide (9.4 mg, 0.029 mmol) and dissolved in acetonitrile (1 mL). After stirring at room temperature for 5 minutes, recrystallization by diethyl ether diffusion yielded the desired complex as a white solid (14.3 mg, 74 %). **¹H-NMR** (CD₃CN, 400 MHz) δ, ppm: 7.59 (t, *J* = 8.0 Hz, 2H, H^a), 7.51 (s, 2H, H^f), 7.41 (d, *J* = 8.0 Hz, 4H, H^b), 2.57 (sept, *J* = 6.8 Hz, 4H, H^c), 1.31 (d, *J* = 6.8 Hz, 12H, H^d or H^e), 1.24 (d, *J* = 6.8 Hz, 12H, H^d or H^e).

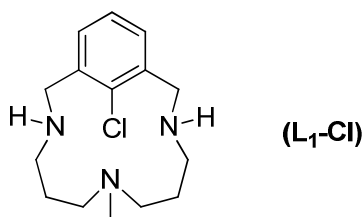
(5) P. de Frémont, N. Marion, S. P. Nolan, *J. Organomet. Chem.* **2009**, 694, 551.

1.3. Catalytic halide exchange reactions

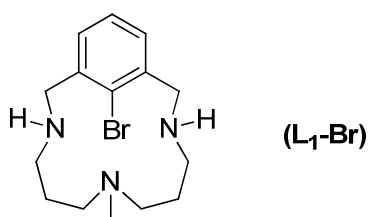
A typical experiment for the catalytic halide exchange reaction using the macrocyclic ligands, L_Y-X ($X = Cl, Br, I$; $Y = 1$ or 5) is herein described:

Ligand (ca. 5 mg), $[Au(X)PPh_3]$ ($X = Cl, NTf_2$; 10 mol%) or $[Au(NCMe)IPr]SbF_6$ (10 mol%) and halide source were weighed using a precision balance (accuracy: ± 0.01 mg) into a glass vial. The vial was then entered into an inert-atmosphere glove box (N_2) and a solution of 1,3,5-trimethoxybenzene (100 μL , 10 mM in CD_3CN) as internal standard,) and 400 μL of CD_3CN were added. The solution was stirred, transferred to a sealed NMR tube (covered in aluminum foil when AgF was used). The reaction mixture was heated at the required temperature in an oil bath and at the end of the reaction the yield was calculated from the ^1H NMR spectrum using the 1,3,5-trimethoxybenzene as internal standard. The identity of the products was also confirmed by ESI-MS analysis and in the case of fluorinated compounds, ^{19}F NMR spectroscopy ($NaCF_3SO_3$ was used to additionally confirm the product yields).

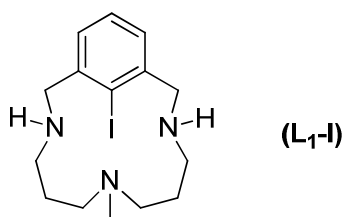
1.4. Characterization data for L_1-X ($X = Cl, Br, I$ and F) and L_5-F



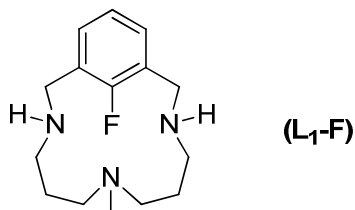
L_1-Cl : ^1H -NMR (CD_3CN , 400MHz) δ , ppm: 7.09 (m, 3H), 4.36 (d, $^2J_{HH} = 14.4$ Hz, 2H), 3.46 (d, $^2J_{HH} = 14.0$ Hz, 2H), 2.30 (m, 8H), 1.93 (m, 2H), 1.77 (s, 3H), 1.45 (m, 4H); **ESI-MS** (CH_3CN , m/z): 282.2 (100) $[C_{15}H_{25}ClN_3]^+$.



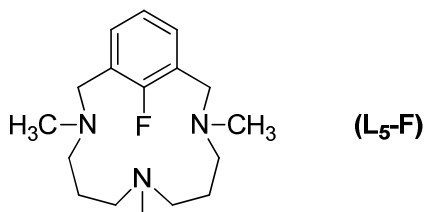
L_1-Br : ^1H -NMR (CD_3CN , 400 Mhz) δ , ppm: 7.15 (t, $^3J_{HH} = 7.6$ Hz, 2H), 7.06 (d, $^3J_{HH} = 7.6$ Hz, 1H), 4.25 (d, $^2J_{HH} = 14.0$ Hz, 2H), 3.52 (d, $^2J_{HH} = 14.0$ Hz, 2H), 2.28 (m, 8H), 1.94 (m, 2H), 1.80 (s, 3H), 1.40 (m, 4H); **ESI-MS** (CH_3CN , m/z): 326.1 (100) $[C_{15}H_{25}BrN_3]^+$.



L_I-I: ¹H-NMR (CD₃CN, 400MHz) δ, ppm: 7.15 (t, ³J_{HH} = 6.4 Hz, 1H), 7.05 (d, ³J_{HH} = 7.2 Hz, 2H), 4.28 (d, ²J_{HH} = 14.4 Hz, 2H), 3.64 (d, ²J_{HH} = 14 Hz, 2H), 2.44 (m, 2H), 2.35 (m, 2H), 2.21 (m, 2H), 1.97 (m, 2H), 1.82 (s, 3H), 1.42 (m, 4H); **ESI-MS** (CH₃CN, m/z): 374.1 (100) [C₁₅H₂₅IN₃]⁺.



L_I-F: ¹H-NMR: (CD₃CN, 400 MHz) δ, ppm: 7.17 (t, ³J_{HH} = 7.2 Hz, 2H), 6.99 (t, ²J_{HH} = 7.2 Hz, 1H), 3.97 (s, 4H), 2.55 (m, 4H), 2.30 (m, 4H), 2.12 (s, 2H), 1.95 (s, 3H), 1.51 (m, 4H); ¹⁹F-NMR: (CD₃CN, 282.4 MHz) δ, ppm: -124.5 ppm; **ESI-MS** (CH₃CN, m/z): 266.2 [C₁₅H₂₅N₃F]⁺.



L₅-F: ¹H-NMR: (CD₃CN, 400 MHz) δ, ppm: 7.20 (t, ³J_{HH} = 7.2 Hz, 2H), 7.07 (t, ³J_{HH} = 7.6 Hz, 1H), 3.49 (s, 4H), 2.32 (s, 6H), 2.20 (m, 8H), 1.90 (s, 3H), 1.29 (m, 4H); ¹⁹F-NMR: (CD₃CN, 282.4 MHz) δ, ppm: -122.12 ppm; **ESI-MS** (CH₃CN, m/z): 294.2 (100) [C₁₇H₂₈N₃F]⁺.

1.5. General procedure for the screening of reaction conditions in the iodination of *ortho*-substituted aryl bromides.

A vial was charged with aryl bromide **2a-d**, **2da** and **2db** (0.05 mmol), Au(I) source (0.005 mmol, 10.0 mol%) and NaI (74.5 mg, 10.00 mmol). *N,N'*-dimethylethylenediamine (when required, 1.10 μL, 0.01 mmol, 20.0 mol%) and solvent (0.5 mL) were added under N₂. The vial was sealed and the reaction mixture was stirred at 110°C for 24 h. The resulting suspension was allowed to reach room temperature and 1,3,5-trimethoxybenzene (200 μL, 0.165M in MeCN) was added. Subsequently, the reaction was quenched by adding AcOEt (2.5 mL). Work-up consisted of filtering 400 μL of the reaction mixture through silica gel using AcOEt as eluent. Yields and conversions were determined by GC relative peak areas using the internal standard (1,3,5-trimethoxybenzene) and a calibration curve prepared from authentic product samples.

Table S1. Screening of reaction conditions for the iodination reaction using 2-(2-bromophenyl)-pyridine (**2d**, entries 1-11) and derivatives (**2da** and **2db**, entries 12-13)

Entry	Au(I)	DMEDA (mol%)	Solvent	Conversion [%] ^a	Yield [%] ^a
1	[Au(Cl)PPh ₃]	-	MeCN	0	0
2	[Au(Cl)P ^t Bu ₃]	-	MeCN	0	0
3	[Au(NTf ₂)PPh ₃]	-	MeCN	0	0
4 ^b	AuI	-	MeCN	4	4
5	[Au(Cl)S(Me) ₂]	(10 mol%)	MeCN	2.5	2
6	[Au(Cl)S(Me) ₂]	(20 mol%)	MeCN	23	21
7	[Au(Cl)S(Me) ₂]	(10 mol%)	DMSO	28	27
8	-	(20 mol%)	DMSO	24	21
9	[Au(Cl)S(Me) ₂]	(20 mol%)	DMSO	58	41
10	[Au(NCMe)IPr]SbF ₆	-	MeCN	48	46
11	[Au(NCMe)IPr]SbF₆	-	DMSO	69	65
12 ^c	[Au(NCMe)IPr]SbF ₆	-	DMSO	48	51
13 ^d	[Au(NCMe)IPr]SbF ₆	-	DMSO	45	53

^aYields and conversions as determined by GC using 1,3,5-trimethoxybenzene as an internal standard. ^bWith 10 mol% of *n*Bu₄N-I as solubilizing additive. ^c2-(2-bromo-5-(trifluoromethyl)phenyl)pyridine (**2da**) as substrate. ^d2-(2-bromo-5-methoxyphenyl)pyridine (**2db**) as substrate.

1.5.1. Synthesis of **3d**, **3da** and **3db** by Au(I)-catalyzed iodination of substrate **2d**, **2da** and **2db**, respectively

Following the optimized procedure previously described (Table S1, entries 11, 12 and 13), 2-(2-iodophenyl)-pyridine (**3d**) was synthesized and purified by flash chromatography on silica gel (hexane-diethyl ether 3:1) to provide the desired product. ¹H-NMR (CDCl₃, 400 MHz) δ, ppm: 8.71 (dq, *J* = 4.8, 2.0, 1.2 Hz, 1H, H^a), 7.97 (ddd, *J* = 8.0, 0.8, 0.4 Hz, 1H, H^c), 7.77 (td, *J* = 7.6, 1.6 Hz, 1H, H^c), 7.51 (dt, *J* = 8.0, 0.8 Hz, 1H, H^d), 7.44 (m, 2H, H^e and H^b), 7.31 (ddd, *J* = 4.8, 2.8, 1.2 Hz, 1H, H^b), 7.09 (ddd, *J* = 8.0, 2.4, 1.2 Hz, 1H, H^f); ¹³C-NMR (CDCl₃, 100 MHz) δ, ppm: 160.96 (C5), 149.39 (C1), 145.22 (C6), 139.91 (C7), 136.12 (C3), 130.41 (C9), 129.84 (C8), 128.39 (C10), 124.54 (C4), 122.65 (C2), 96.82 (C11); HRMS (ESI) (CH₃CN, *m/z*): calcd for C₁₁H₈NI [M + H⁺] 281.9774, found: 281.9784.

3da: The final reaction mixture was purified by column chromatography on silica using a solvent mixture of hexane-diethyl ether 70:30. The desired product was obtained as a colorless oil in a 29% isolated yield. ¹H-NMR (CDCl₃, 400 MHz) δ, ppm: 8.73 (dq, *J* = 4.8, 2.0, 1.2 Hz, 1H, H^a), 8.10 (dd, *J* = 8.4, 0.4 Hz, 1H, H^e), 7.81 (td, *J* = 8.0, 2.0 Hz, 1H, H^c), 7.71 (d, *J* = 2.4 Hz, 1H, H^c), 7.53 (dt, *J* = 8.0, 1.2 Hz, 1H, H^d), 7.34 (m, 2H, H^b, H^f); ¹³C-NMR (CDCl₃, 100 MHz) δ, ppm:

159.55 (C5), 149.54 (C1), 145.82 (C6), 140.47 (C11), 136.28 (C3), 130.94 (q, $^2J_{\text{CF}} = 32.8$ Hz, C8), 126.88 (q, $^3J_{\text{CF}} = 3.7$ Hz, C7), 126.09 (q, $^3J_{\text{CF}} = 3.6$ Hz, C10), 124.33 (C2), 123.82 (q, $^1J_{\text{CF}} = 270.7$ Hz, C9), 123.09 (C4), 101.03 (C12); $^{19}\text{F-NMR}$ (CDCl_3 , 376.5 MHz) δ , ppm: -63.16; **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{12}\text{H}_7\text{IF}_3\text{N}$ [$\text{M} + \text{H}^+$] 349.9648, found: 349.9566.

3db: The final reaction mixture was purified by column chromatography on silica using a solvent mixture of hexane-diethyl ether 50:50. The iodination product was obtained as a colorless oil in a 24% isolated yield. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ , ppm: 8.71 (dq, $J = 4.8, 2.0, 0.8$ Hz, 1H, H^{a}), 7.81 (d, $J = 8.4$ Hz, 1H, H^{b}), 7.77 (td, $J = 7.6, 2.0$ Hz, 1H, H^{c}), 7.51 (dt, $J = 7.6, 1.2$ Hz, 1H, H^{d}), 7.31 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H, H^{b}), 7.03 (d, $J = 3.2$ Hz, 1H, H^{c}), 6.70 (dd, $J = 8.8, 3.2$ Hz, 1H, H^{e}), 3.82 (s, 3H, H^{f}); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ , ppm: 160.70 (C5), 159.93 (C8), 149.24 (C1), 145.91 (C6), 140.34 (C11), 135.98 (C3), 124.44 (C4), 122.58 (C2), 116.54 (C10), 115.81 (C7), 85.18 (C12), 55.48 (C9); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{12}\text{H}_{10}\text{INO}$ [$\text{M} + \text{H}^+$] 311.9880, found: 311.9866.

1.6. General procedure for the coupling of phenolic substrates to $\text{L}_1\text{-Br}$

To a vial containing $\text{L}_1\text{-Br}$ (5.0 mg, 15.31 μmol) was added $[\text{Au}(\text{X})\text{PPh}_3]$ ($\text{X} = \text{Cl}$, NTf_2 ; 10 mol %) or $[\text{Au}(\text{NCMe})\text{IPr}]\text{SbF}_6$ (1.53 μmol , 10 mol%), substituted phenol (20 equivalents, 0.31 mmol), trimethoxybenzene (internal standard, 2.6 mg, 15.31 μmol) and 0.5 mL of CD_3CN under a nitrogen atmosphere. The mixture was stirred and then loaded into a sealed NMR tube. The NMR tube was heated in an oil bath. After the required reaction time, the NMR tube was removed from the oil bath, cooled to room temperature and the products in the crude reaction mixture were identified by ^1H NMR and ESI-MS (see Supplementary Figures) by comparison with the spectra previously reported in the literature.^[6]

1.7. General procedure for the coupling of *p*-chlorophenolate to substrates

2d and 3d

A vial was charged with substrates **2d** or **3d** (0.05 mmol), $[\text{Au}(\text{NCMe})\text{IPr}]\text{SbF}_6$ (4.3 mg, 0.005 mmol), sodium *p*-chlorophenolate (15.1 mg, 0.1 mmol) and 0.5 mL of MeCN were added. The vial was capped and the reaction mixture was stirred at 90°C or 110°C for 4h. The reaction crude was allowed to reach room temperature and a standard solution of 1,3,5-trimethoxybenzene (0.165M, 20 μL , 0.0033 mmol) was added. The resulting suspension was dried under vacuum, redissolved in CDCl_3 and further analyzed by $^1\text{H-NMR}$. The presence of the final C-O coupling

(6) L. M. Huffman, A. Casitas, M. Font, M. Canta, M. Costas, X. Ribas, S. S. Stahl, *Chem. Eur. J.* **2011**, *17*, 10643.

product **4d** was also confirmed by HRMS (see Supplementary Figure S30). The same procedure was followed for aryl bromides **2da** and **2db**.

Product isolation: A larger scale reaction was also performed: (0.2 mmol **2d** –or **2da** or **2db**–; 0.02 mmol [Au(NCMe)IPr]SbF₆; 0.4 mmol sodium *p*-chlorophenolate) in 0.8 mL of MeCN. After cooling down to room temperature the solvent was evaporated under vacuum and the residue subjected to column chromatography on silica gel (hexane-ethyl acetate 70:30). The desired product, **4d**, was obtained as a colorless oil (34.8 mg, 62% isolated yield). ¹H-NMR (CDCl₃, 400 MHz) δ, ppm: 8.67 (dq, *J* = 4.8, 2.0, 0.8 Hz, 1H, H^a), 7.90 (dd, *J* = 7.6, 1.6 Hz, 1H, H^e), 7.77 (dt, *J* = 8.0, 1.2 Hz, 1H, H^d), 7.65 (ddd, *J* = 8.0, 7.6, 2.0 Hz, 1H, H^c), 7.38 (ddd, *J* = 7.6, 7.4, 1.6 Hz, 1H, H^e), 7.29 (td, *J* = 8., 7.6, 1.2 Hz, 1H, H^f), 7.20 (m, 2H, H^b and Hⁱ), 7.01 (dd, *J* = 7.4, 1.2 Hz, 1H, H^h), 6.86 (d, *J* = 8.8 Hz, 2H, H^j); ¹³C-NMR (CDCl₃, 100 MHz) δ, ppm: 156.33 (C12), 155.10 (C5), 153.63 (C11), 149.75 (C1), 136.13 (C3), 132.44 (C6), 131.76 (C7), 130.34 (C9), 129.77 (C13), 127.89 (C15), 124.92 (C8), 124.81 (C4), 122.29 (C2), 120.44 (C10), 119.26 (C14); **HRMS (ESI)** (CH₃CN, *m/z*): calcd for C₁₇H₁₂NCIO [M + H⁺] 282.0680, found: 282.0683.

4da: Column chromatography on silica gel (hexane-diethyl ether 70:30) provided a colorless oil (45.5 mg, 65% isolated yield). ¹H-NMR (CDCl₃, 400 MHz) δ, ppm: 8.65 (dq, *J* = 4.8, 2.0, 1.2 Hz, 1H, H^a), 8.17 (d, *J* = 2.0 Hz, 1H, H^e), 7.77 (dt, *J* = 8.0, 1.2 Hz, 1H, H^d), 7.62 (ddd, *J* = 8.0, 7.6, 2.0 Hz, 1H, H^c), 7.51 (m, 1H, H^f), 7.19 (m, 3H, H^b, H^h), 6.95 (d, *J* = 8.8 Hz, 1H, H^e), 6.86 (d, *J* = 9.2 Hz, 1H, Hⁱ); ¹³C-NMR (CDCl₃, 100 MHz) δ, ppm: 156.73 (C12), 154.81 (C13), 153.56 (C5), 149.84 (C1), 136.15 (C3), 131.94 (C16), 130.02 (C14), 129.20 (C6), 129.15 (q, ³*J*_{CF} = 3.8 Hz, C7), 126.97 (q, ³*J*_{CF} = 3.6 Hz, C10), 126.40 (q, ²*J*_{CF} = 32.8 Hz, C8), 125.34 (C4), 124.27 (q, ¹*J*_{CF} = 270.3 Hz, C9), 122.73 (C2), 120.278 (C15), 119.164 (C11); ¹⁹F-NMR (CDCl₃, 376.5 MHz) δ, ppm: -62.22; **HRMS (ESI)** (CH₃CN, *m/z*): calcd for C₁₈H₁₁ClF₃NO [M + H⁺] 350.0554, found: 350.0542.

4db: Column chromatography on silica gel (hexane-diethyl ether 50:50) provided a pale yellow oil (29.9 mg, 48% isolated yield). ¹H-NMR (CDCl₃, 400 MHz) δ, ppm: 8.67 (dq, *J* = 4.8, 2.0, 1.2 Hz, 1H, H^a), 7.75 (dt, *J* = 8.0, 0.8 Hz, 1H, H^d), 7.62 (ddd, *J* = 8.0, 7.6, 2.0 Hz, 1H, H^c), 7.46 (d, *J* = 3.2 Hz, 1H, H^e), 7.17 (m, 3H, H^b and Hⁱ), 6.99 (dd, *J* = 8.8, 0.8 Hz, 1H, H^h), 6.94 (dd, *J* = 8.8, 2.8 Hz, 1H, H^e), 6.78 (d, *J* = 9.2 Hz, 2H, H^j), 3.88 (s, 3H, H^f); ¹³C-NMR (CDCl₃, 100 MHz) δ, ppm: 157.12 (C13), 156.78 (C8), 154.73 (C5), 149.59 (C1), 146.51 (C12), 136.03 (C3), 133.54 (C6), 129.48 (C14), 127.04 (C16), 124.53 (C4), 122.59 (C11), 122.27 (C2), 118.02 (C15), 116.76 (C10), 115.14 (C7), 55.80 (C9); **HRMS (ESI)** (CH₃CN, *m/z*): calcd for C₁₈H₁₄NCIO₂ [M + H⁺] 312.0786, found: 312.0769.

1.8. Catalytic C-Heteroatom bond forming reactions in the presence of Hg(0)

The same synthetic procedure was followed as described at **1.3**, **1.5.1**, **1.6** and **1.7**, additionally adding approximately 500 eq. of mercury (with respect to [Au(NCMe)IPr]SbF₆ catalyst).

Table S2. Halide exchange and phenol insertion reactions with and without a large excess of Hg(0)

Starting material	MY	Additive	T (°C)	t (h)	Yield [%]	Conversion [%]
L₁-Br	Bu ₄ N-Cl	-	40	12	>99	>99
		Hg(0)			74	92
	<i>p</i> -chlorophenol	-		24	61	62
		Hg(0)			63	>99
	NaI	-	70	4	94	96
		Hg(0)			53	>99
2d	Sodium <i>p</i> -chlorophenolate	-	110	4	>99	>99
		Hg(0)			71	74
	NaI	-		24	65	69
		Hg(0)			48	62

1.9. C-Heteroatom bond forming reactions catalyzed by other NHC-based Au(I) complexes

The previously used cationic Au(I) source ([Au(NCMe)IPr]SbF₆) was replaced in the transformations described above by derivatives, following identical experimental protocols.

Table S3. Halide exchange and C-O coupling reaction catalyzed by different NHC-Au(I) complexes.

Starting material	[AuIPr] cat. (10 mol%)	MY (eq.)	T (°C)	t (h)	Yield [%]	Conversion [%]
L₁-I	[Au(NCMe)IPr]SbF ₆	Bu ₄ N-Cl (2)	40	6	>99	>99
	[Au(Cl)IPr]				>99	>99
L₁-Br	[Au(NCMe)IPr]SbF ₆	Bu ₄ N-Cl (2)		12	99	>99
	[Au(Cl)IPr]				>99	>99
L₁-Cl	[Au(NCMe)IPr]SbF ₆	NaI (10)	70	48	67	75
	[Au(Cl)IPr]				64	71
2d	[Au(NCMe)IPr]SbF ₆	NaI (10)	110	24	65	69
	[Au(Br)IPr]				59	61
	[Au(Cl)IPr]				62	71

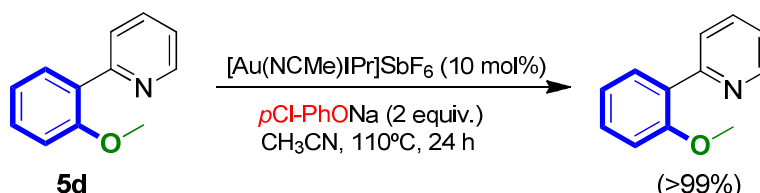
[Au(NCMe)IPr]SbF ₆			>99	>99
[Au(Br)IPr]	Sodium <i>p</i> -chlorophenolate	4	97	>99
[Au(OPh- <i>p</i> Cl)IPr]	(2)		98	>99

1.10. General procedure for the coupling of sodium methoxide to substrate 2d

The same synthetic protocol as described in **1.7** was followed, in this case using sodium methoxide as nucleophile and methanol as solvent. A vial was charged with **2d** (23.4 mg, 0.1 mmol), [Au(NCMe)IPr]SbF₆ (8.6 mg, 0.01 mmol), sodium methoxide (16.2 mg, 0.3 mmol) and 0.5 mL of MeOH were added. The vial was capped and the reaction mixture was stirred at 110°C for 8h. The reaction crude was allowed to reach room temperature and the solvent evaporated under vacuum. The resulting grey oil was purified by column chromatography on silica gel using a solvent mixture of hexane-ethyl acetate 50:50. Product **5d** was obtained as a colorless oil in a 78% isolated yield (14.5 mg). ¹H-NMR (CDCl₃, 400 MHz) δ, ppm: 8.70 (dq, *J* = 4.8, 2.0, 1.2 Hz, 1H, H^a), 7.81 (dt, *J* = 8.0, 1.2 Hz, 1H, H^d), 7.76 (dd, *J* = 7.6, 2.0 Hz, 1H, H^e), 7.70 (td, *J* = 7.6, 2.0 Hz, 1H, H^c), 7.37 (ddd, *J* = 8.8, 7.6, 2.0 Hz, 1H, H^e), 7.20 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H^b), 7.08 (td, *J* = 7.6, 1.2 Hz, 1H, H^f), 7.01 (dd, *J* = 8.4, 1.2 Hz, 1H, H^h), 3.86 (s, 3H, Hⁱ); HRMS (ESI) (CH₃CN, *m/z*): calcd for C₁₂H₁₁NO [M + H⁺] 186.0913, found: 186.0915.

1.11. Attempt to couple sodium *p*-chlorophenolate to substrate 5d (Meyers-type reaction)

The same synthetic protocol as described in **1.7** was followed, replacing substrate **2d** by **5d**.



2. Computational Details

DFT calculations on gold systems were carried out with the Gaussian09 software package,^[7] with the M06-L local functional.^[8] The geometries have been edited with the Chemcraft program.^[9] Geometry optimizations of gold intermediates were performed without any symmetry restrictions, where I and Au atoms were treated with the Stuttgart-Dresden relativistic effective core potential (SDD) and its associated basis set.^[10] The SDD basis set has been augmented with a *f* polarization function for gold (orbital exponent of $\alpha_f(\text{Au}) = 1.05$).^[11] For iodine, *d* and *f* functions were also added ($\alpha_d(\text{I}) = 0.73$ and $\alpha_f(\text{I}) = 0.55$).^[12] Cl has been described with the 6-31+G* basis set, while the 6-31G* basis set was used for all other atoms (C, N, H, O). The solvating effect of acetonitrile was included in geometry optimizations through the SMD polarizable continuum model.^[13]

Analytical frequency calculations were performed at the same level of theory to evaluate enthalpy and entropy corrections at 298.15 K and establish the nature of stationary points in solvent-phase.

Single point calculations on the equilibrium geometries, including the solvent effects (E_{sp}), with the cc-pVTZ dunning basis set for the C, N and H atoms, the aug-cc-pvtz for O and Cl and the inclusion of *spdf* diffuse functions extracted from the aug-SDB-cc-pVTZ basis set for the

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iodine,^[14] were used to refine the Gibbs energy values (G):

$$G = E_{\text{sp}} + G_{\text{corr.}} \quad (1)$$

where the Gibbs correction ($G_{\text{corr.}}$) was obtained from a thermo-statistical analysis at the M06-L/SMD level. In the ligand exchange reactions, the free energy change associated with moving from a standard-state gas phase pressure of 1 atm to a standard state gas phase concentration of 1 M for solutes and 19.1 M for acetonitrile solvent ($\Delta G^{o/*}$) was also included in the final free energies. The value of $\Delta G^{o/*}$ at 298.15 K is 1.9 kcal·mol⁻¹ for 1 M standard state solutes and 3.6 kcal·mol⁻¹ for 19.1 M standard state acetonitrile.

(14) J. M. L. Martin, A. Sunderman, *J. Chem. Phys.* **2001**, *114*, 3408.

3. Supplementary Figures

Figure S1. ^1H -NMR spectrum of $[\text{Au}(\text{Br})\text{IPr}]$ in CD_3CN , 400 MHz, at 298 K.

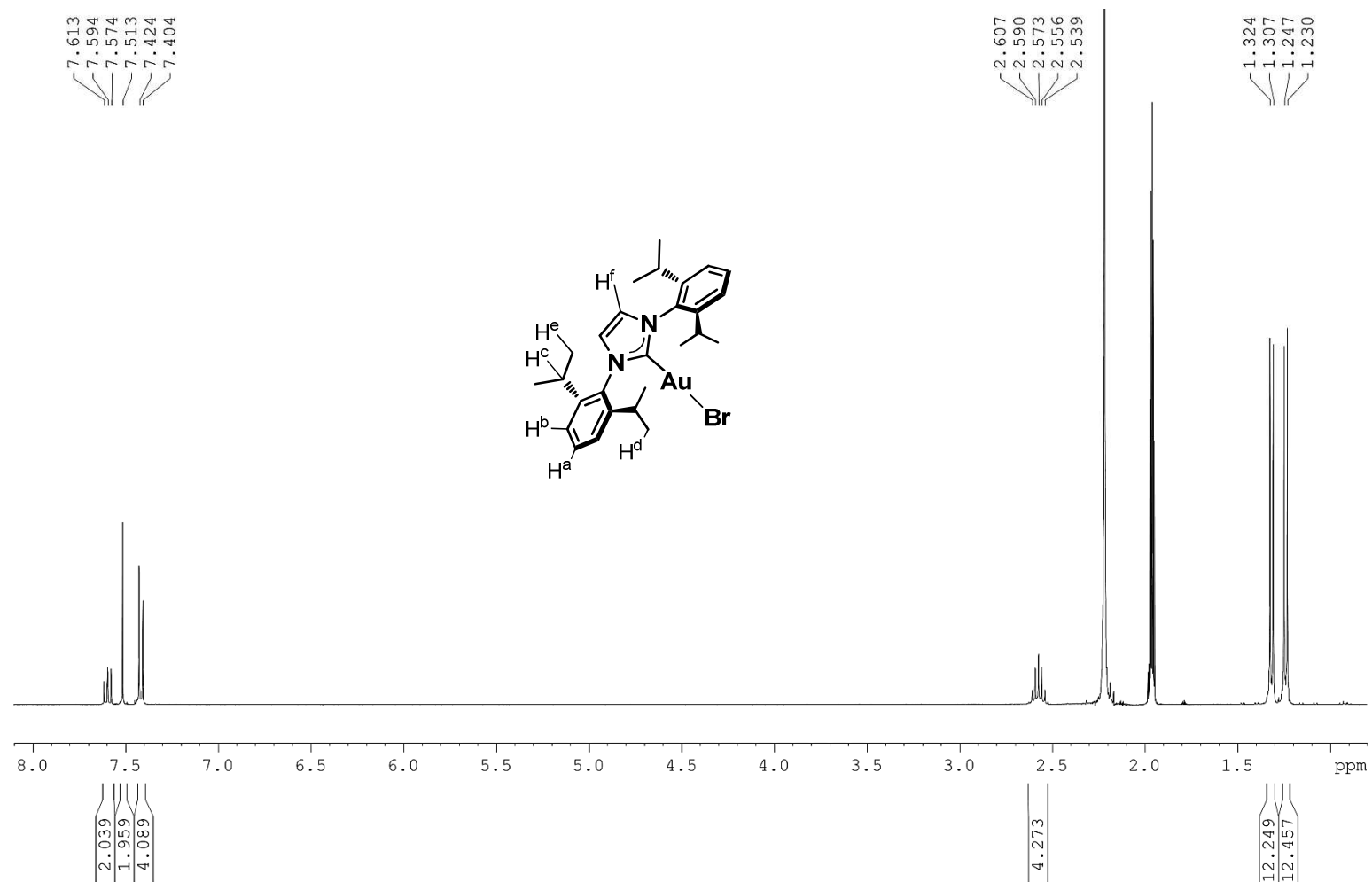


Figure S2. ^1H -NMR spectrum of $[\text{Au}(\text{OPh-}i{p}\text{Cl})\text{IPr}]$ in CD_3CN , 400 MHz, at 298 K.

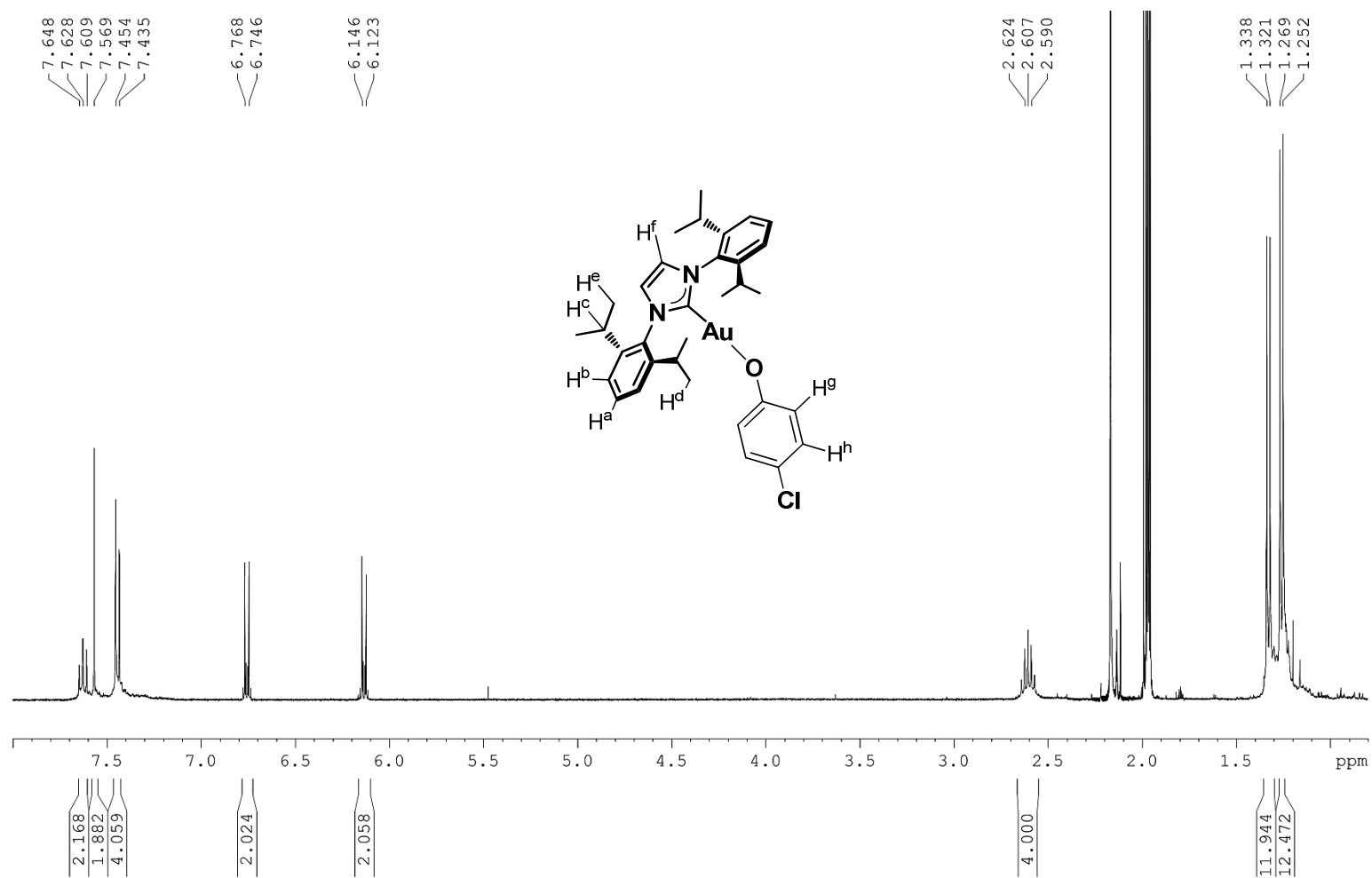


Figure S3. ^1H -NMR spectrum of **L₁-Cl** in CD_3CN , 400 MHz, at 298 K.

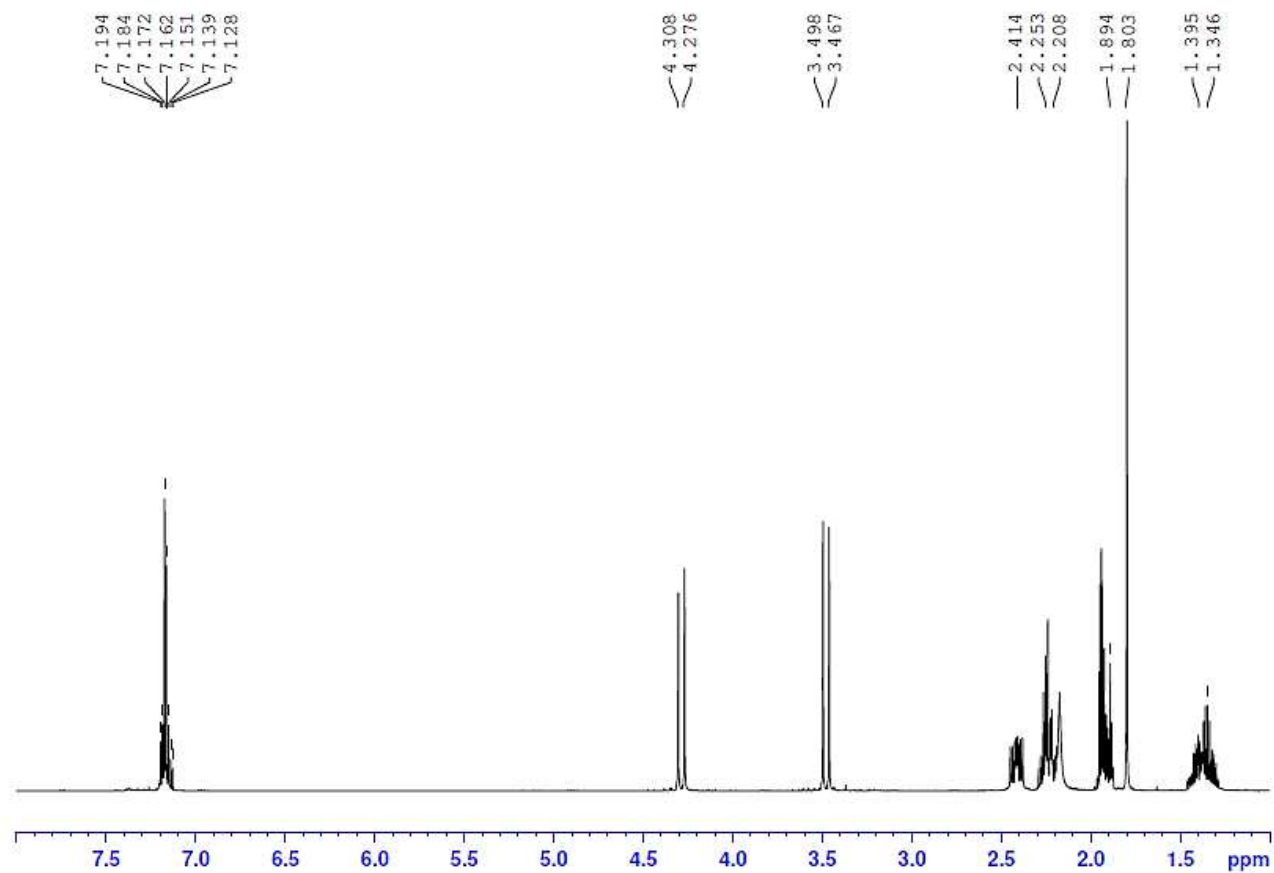


Figure S4. ^1H -NMR spectrum of **L₁-Br** in CD_3CN , 400 MHz, at 298 K.

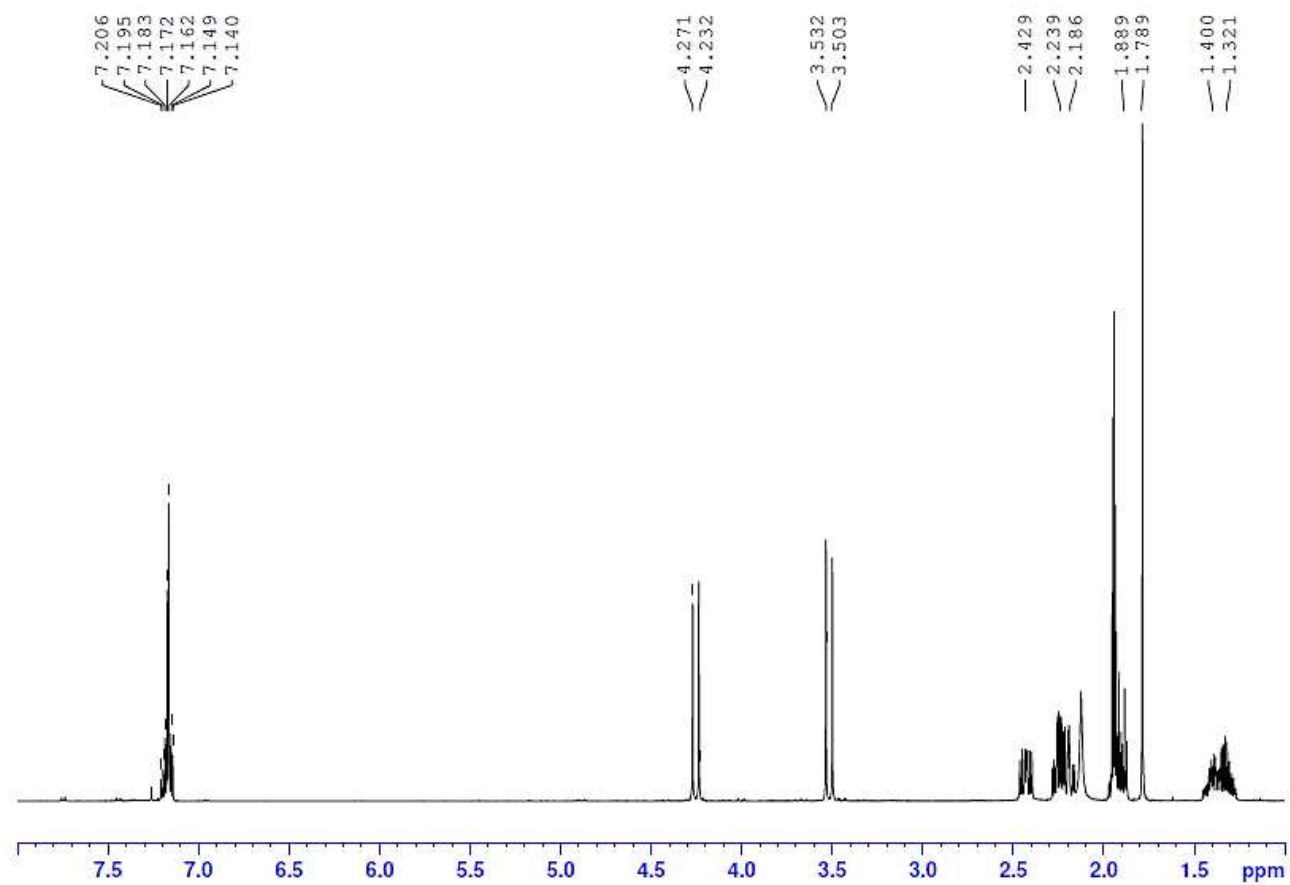


Figure S5. ^1H -NMR spectrum of **L₁-I** in CD_3CN , 400 MHz, at 298 K.

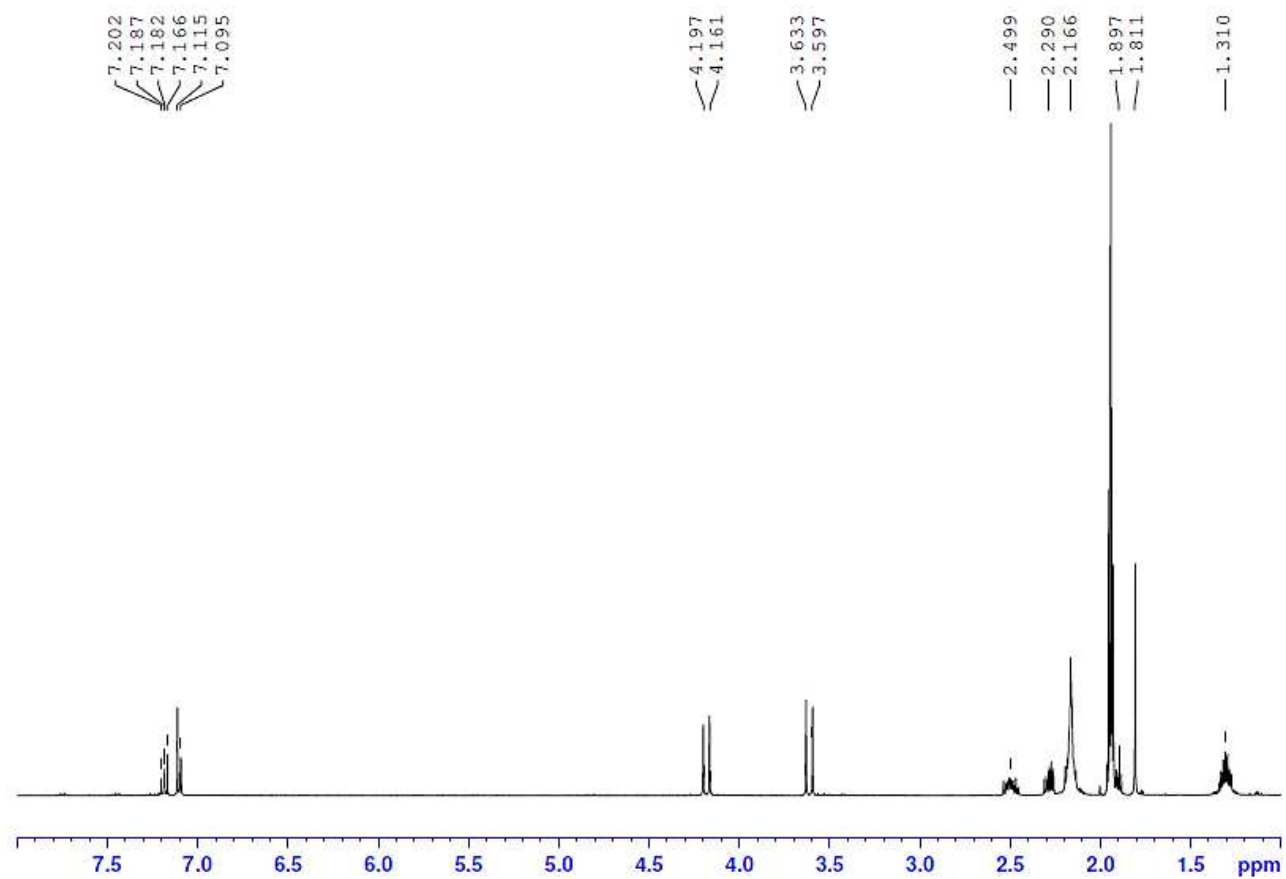


Figure S6. ^1H -NMR spectrum of **L₁-F** in CD_3CN , 400 MHz, at 298 K.

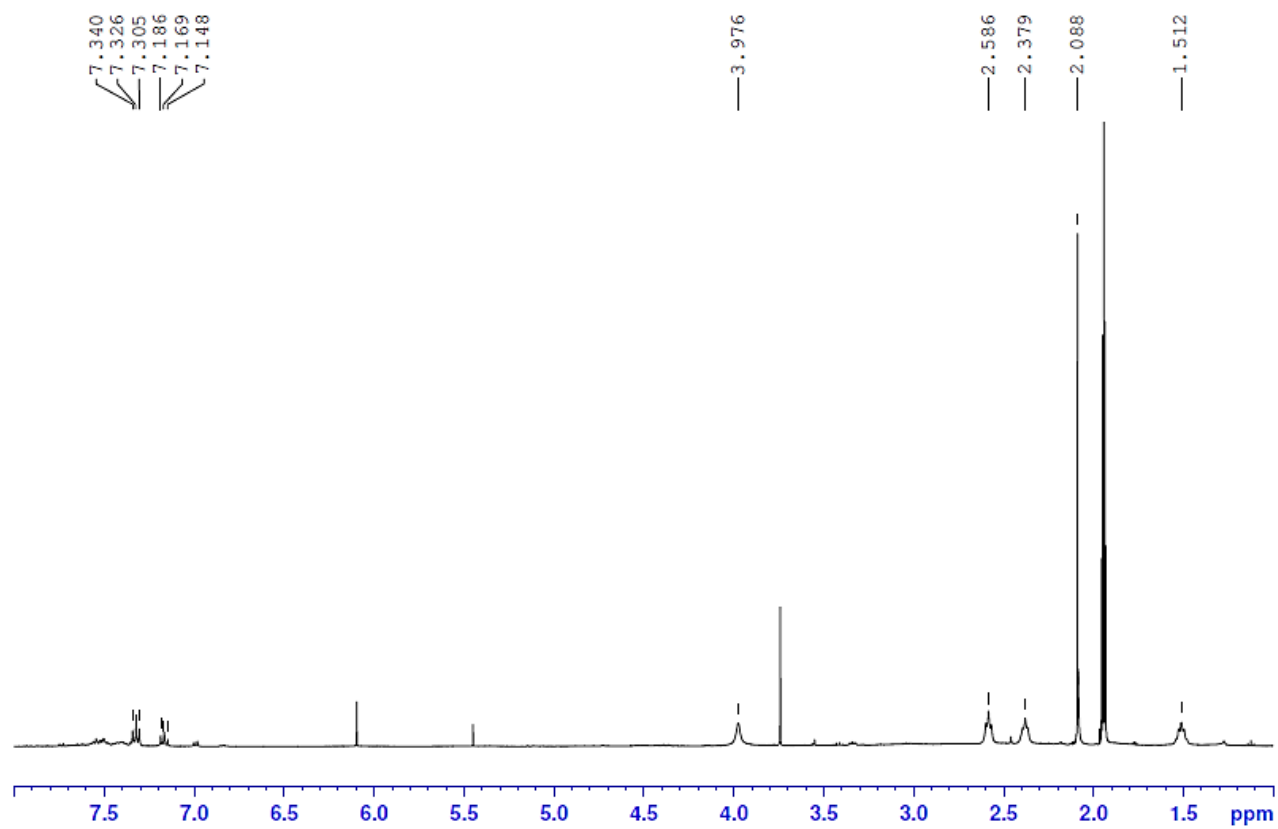


Figure S7. ^{19}F -NMR spectrum of **L₁-F** in CD_3CN , 282.4 MHz, at 298 K, using NaCF_3SO_3 as internal standard (-79.0 ppm).

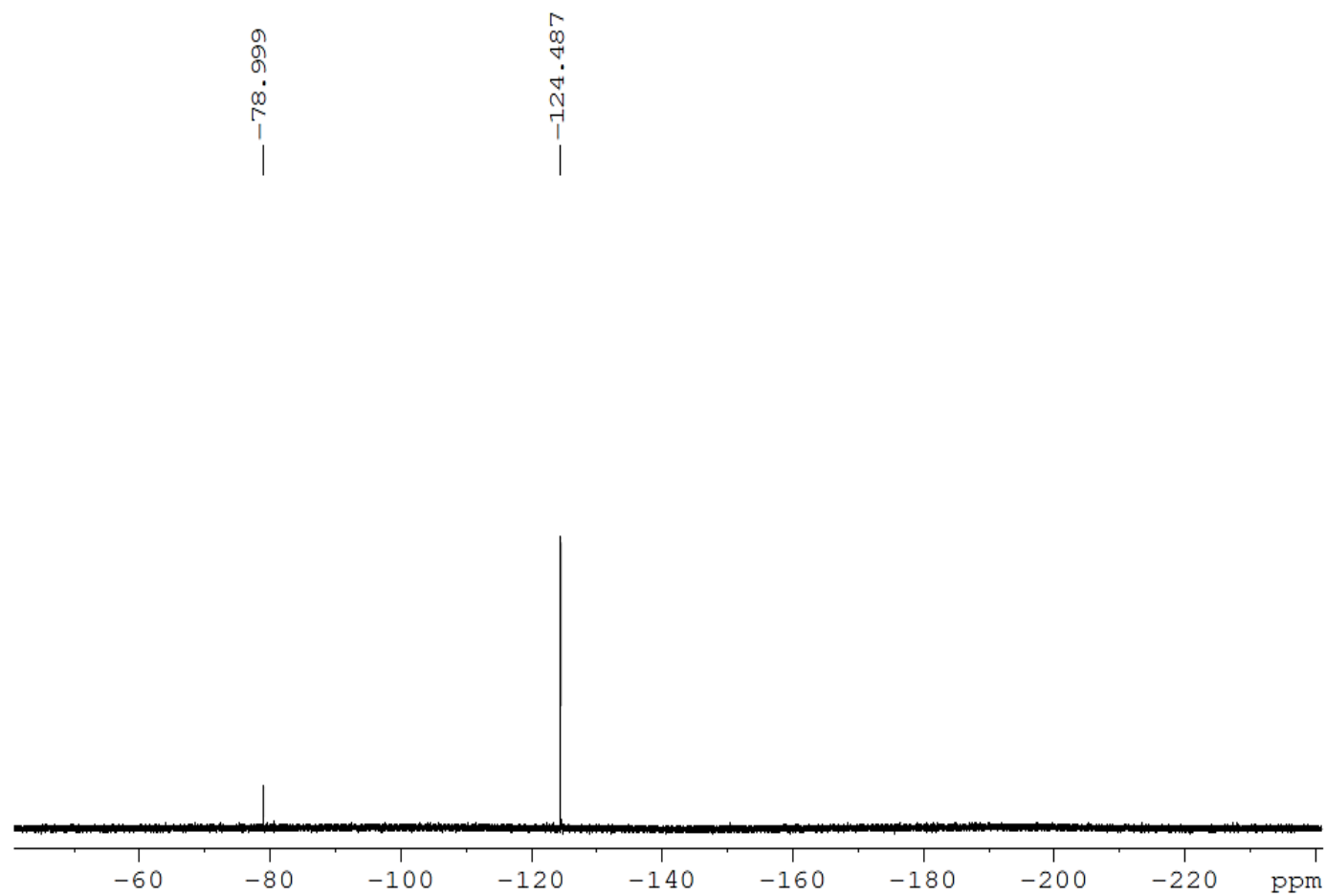


Figure S8. ^1H -NMR spectrum of **L₅-F** in CD_3CN , 400 MHz, at 298 K (reaction corresponding to entry 6 of Table 6.2, section 6.1.1).

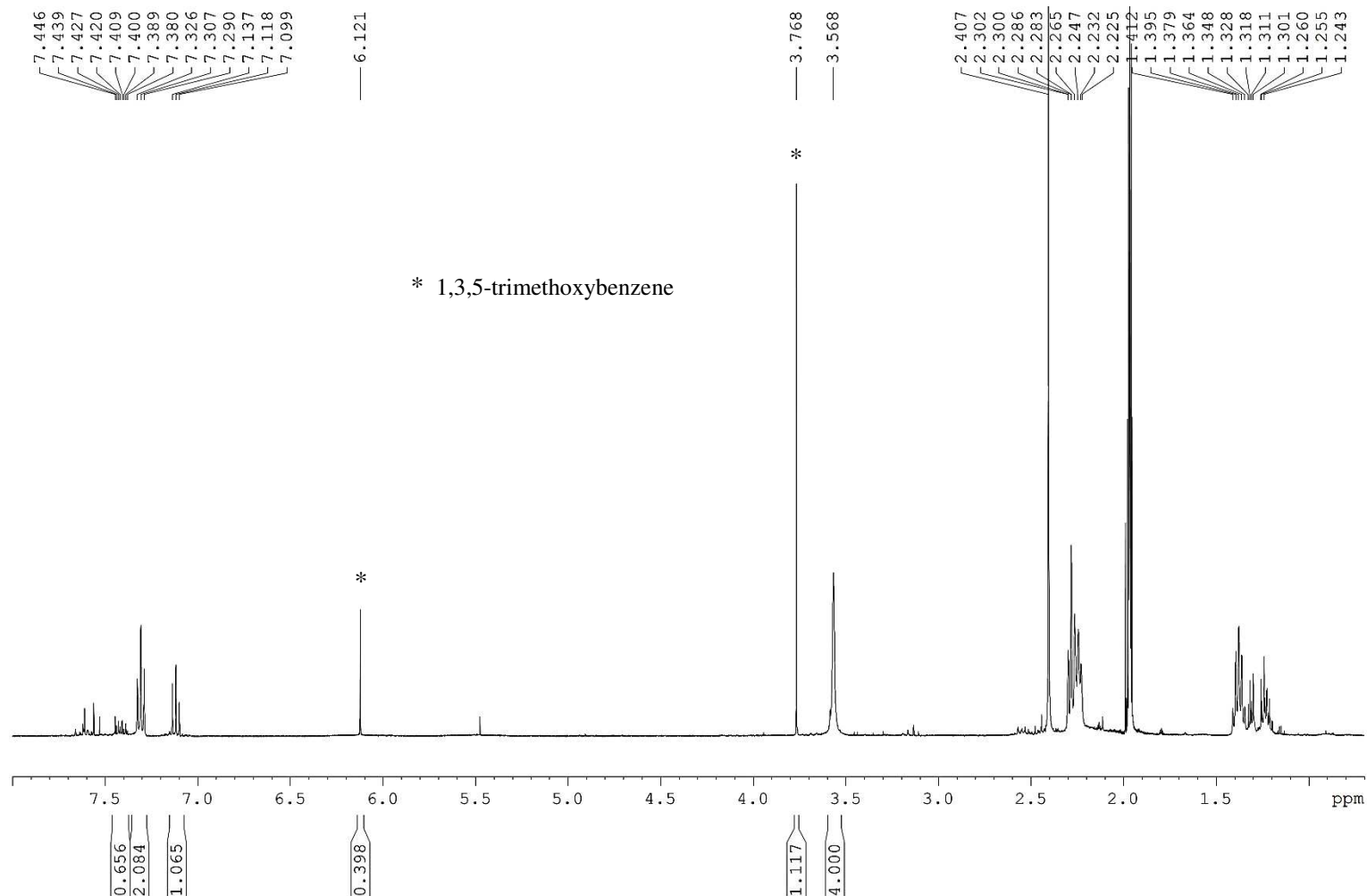


Figure S9. ^{19}F -NMR spectrum of **L₅-F** in CD_3CN , 282.4 MHz, at 298 K, using NaCF_3SO_3 as internal standard (-79.0 ppm).

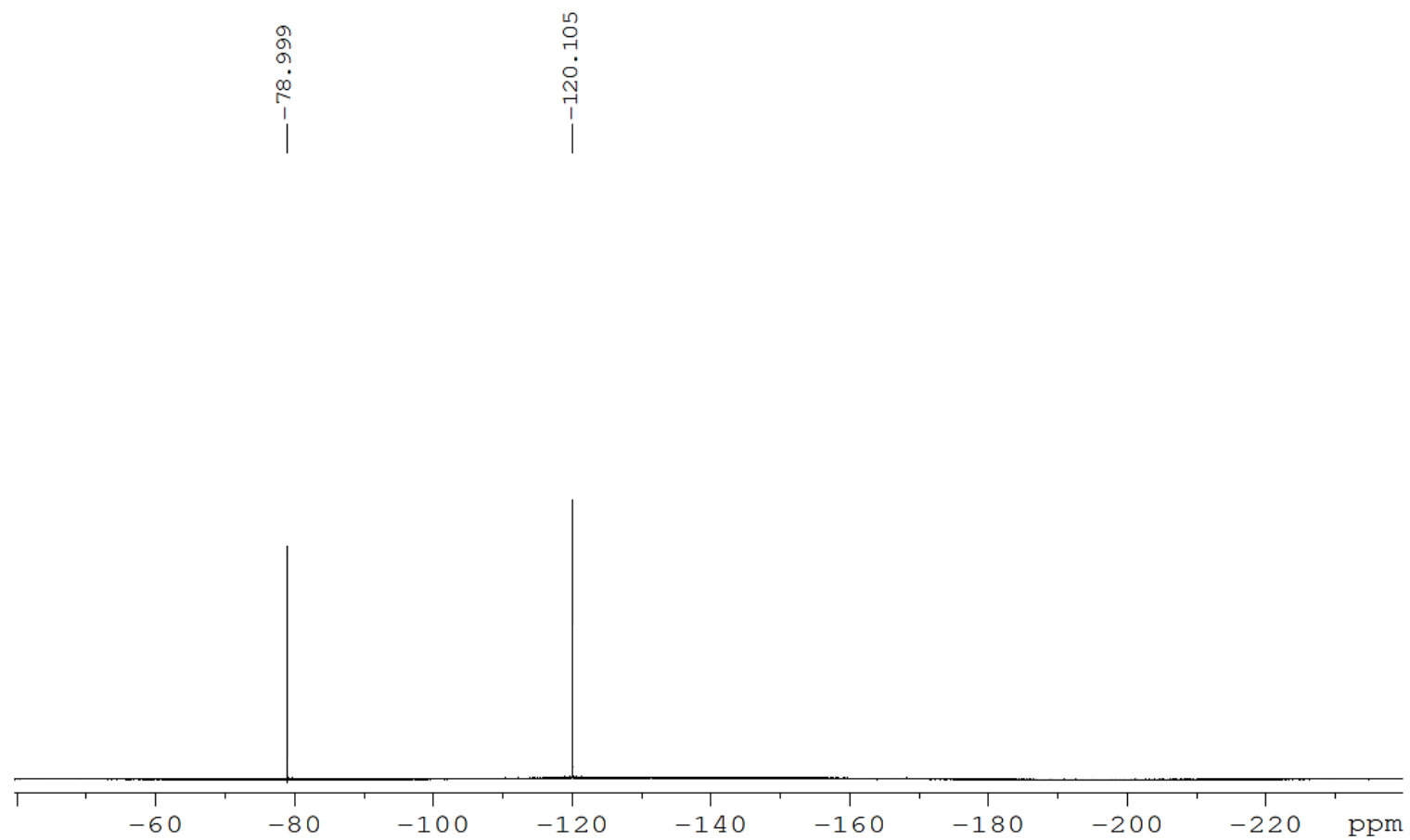
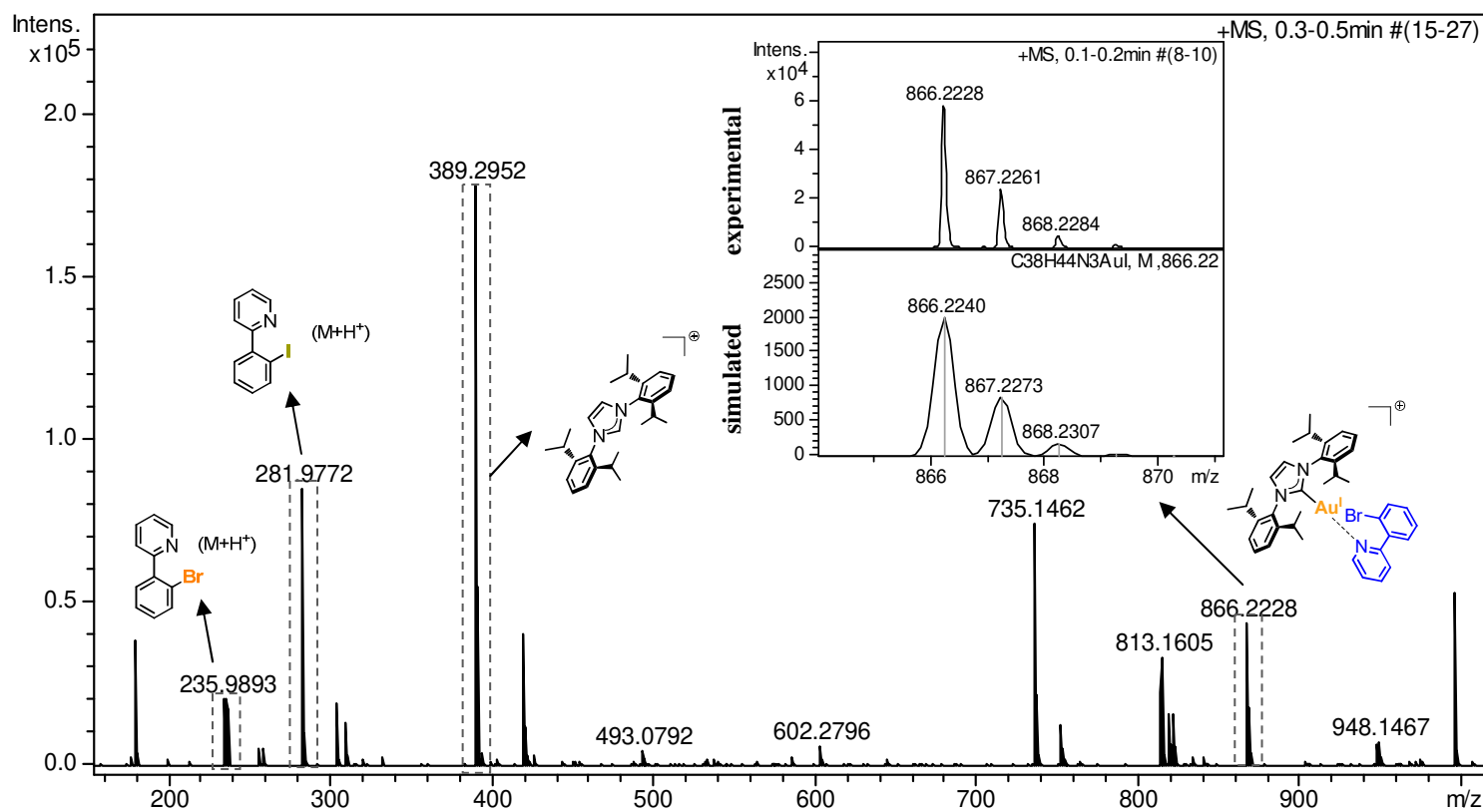
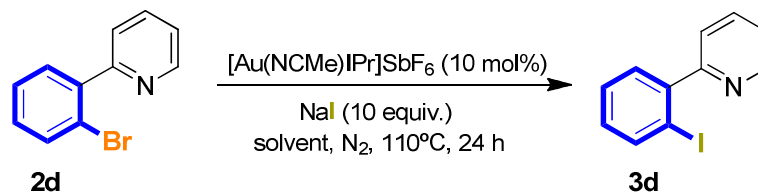


Figure S10. a) HRMS (CH_3CN) of the final reaction crude corresponding to the conversion of **2d** to **3d** (Table S1, entry 11). IPr^+ peaks correspond to the in situ decomposition of $[\text{Au}(\text{Br})\text{IPr}]$ in the gas phase. b) HRMS (CH_3CN) of independently synthesized $[\text{Au}(\text{Br})\text{IPr}]$.

a)



b)

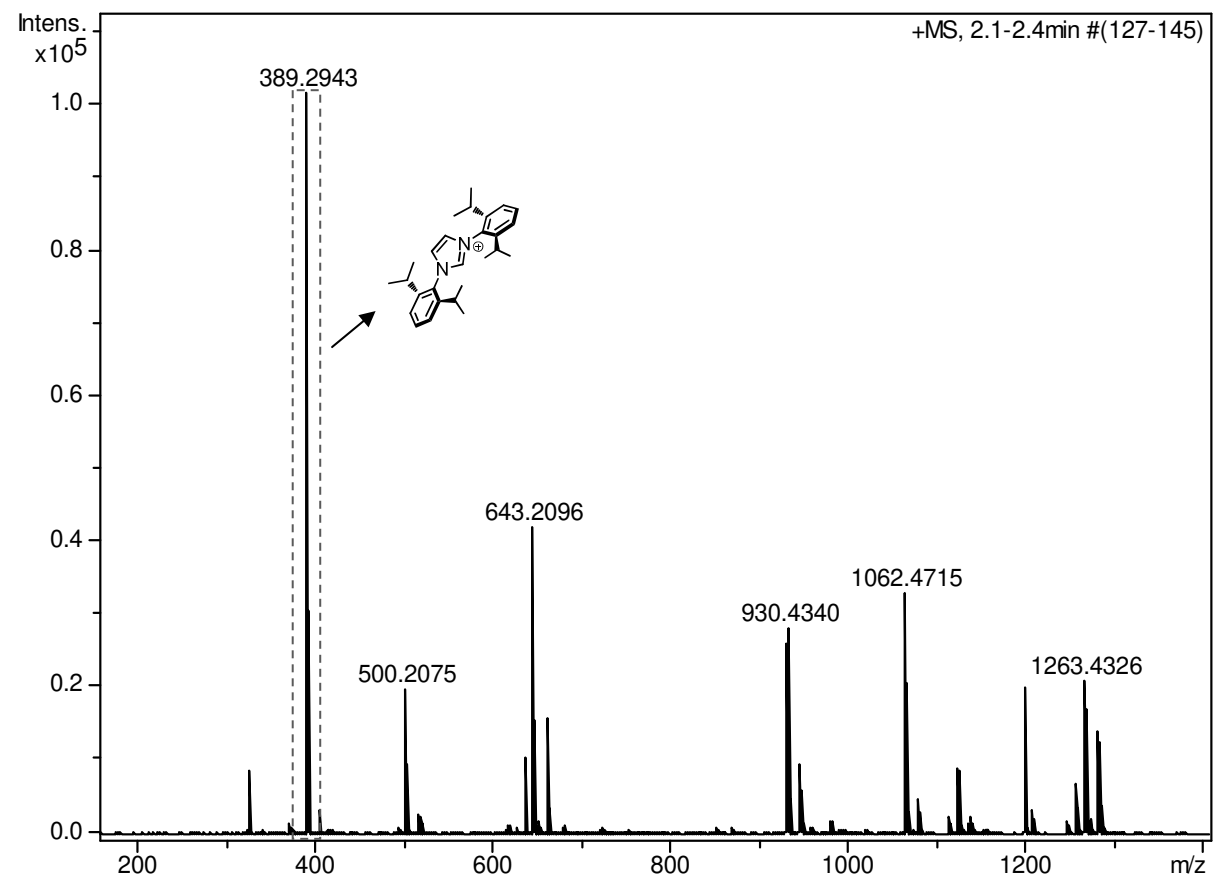


Figure S11. Spectra obtained after reaction of **L₁-Br** and phenol (Conditions: entry 2, Table 6.3, section 6.1.1). *Left:* ¹H-NMR spectrum of crude reaction mixture CD₃CN, 300 MHz, 298 K. *Right:* HRMS (ESI-MS) spectrum of crude reaction mixture in CH₃CN (Top: Full spectrum. Bottom: Zoom with simulated spectra for peaks of **L₁-Br** and product).^[5]

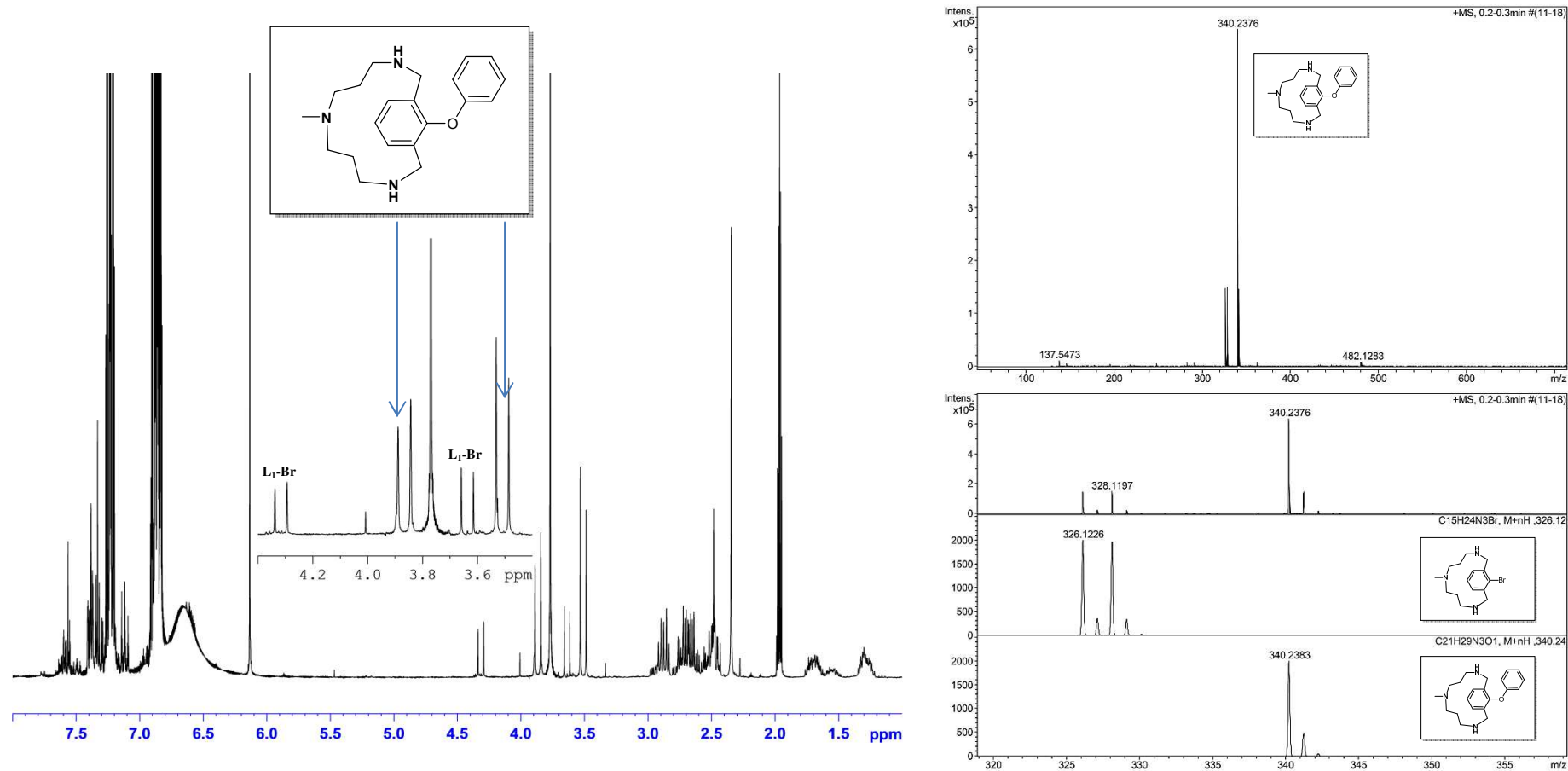


Figure S12. Spectra obtained after reaction of **L₁-Br** and 4-methylphenol (Conditions: entry 3, Table 6.3, section 6.1.1). *Left:* ¹H-NMR spectrum of crude reaction mixture CD₃CN, 300 MHz, 298 K. *Right:* HRMS (ESI-MS)spectrum of crude reaction mixture in CH₃CN (Top: Full spectrum. Bottom: Zoom with simulated spectra for peaks of **L₁-Br** and product).^[5]

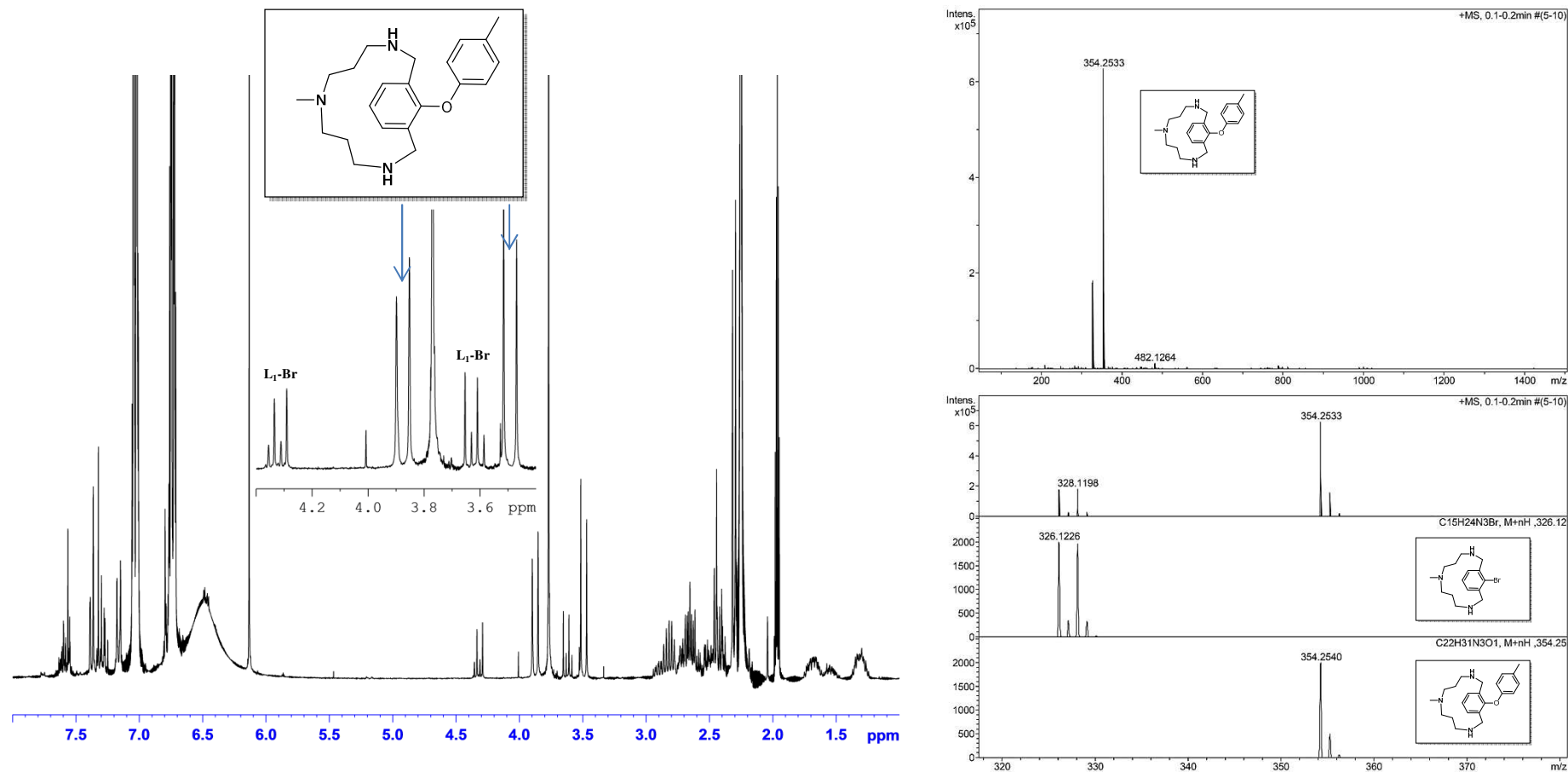


Figure S13. Spectra obtained after reaction of **L₁-Br** and 4-methoxyphenol (Conditions: entry 4, Table 6.3, section 6.1.1). *Left:* ¹H-NMR spectrum of crude reaction mixture CD₃CN, 300 MHz, 298 K. *Right:* HRMS (ESI-MS) spectrum of crude reaction mixture in CH₃CN (Top: Full spectrum. Bottom: Zoom with simulated spectra for peaks of **L₁-Br** and product).^[5]

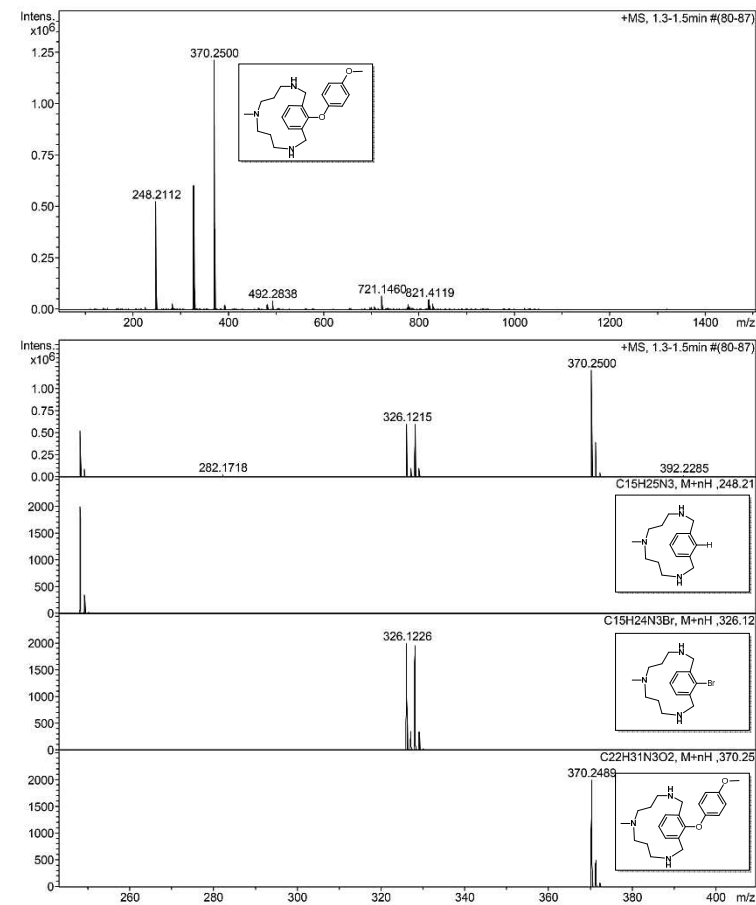
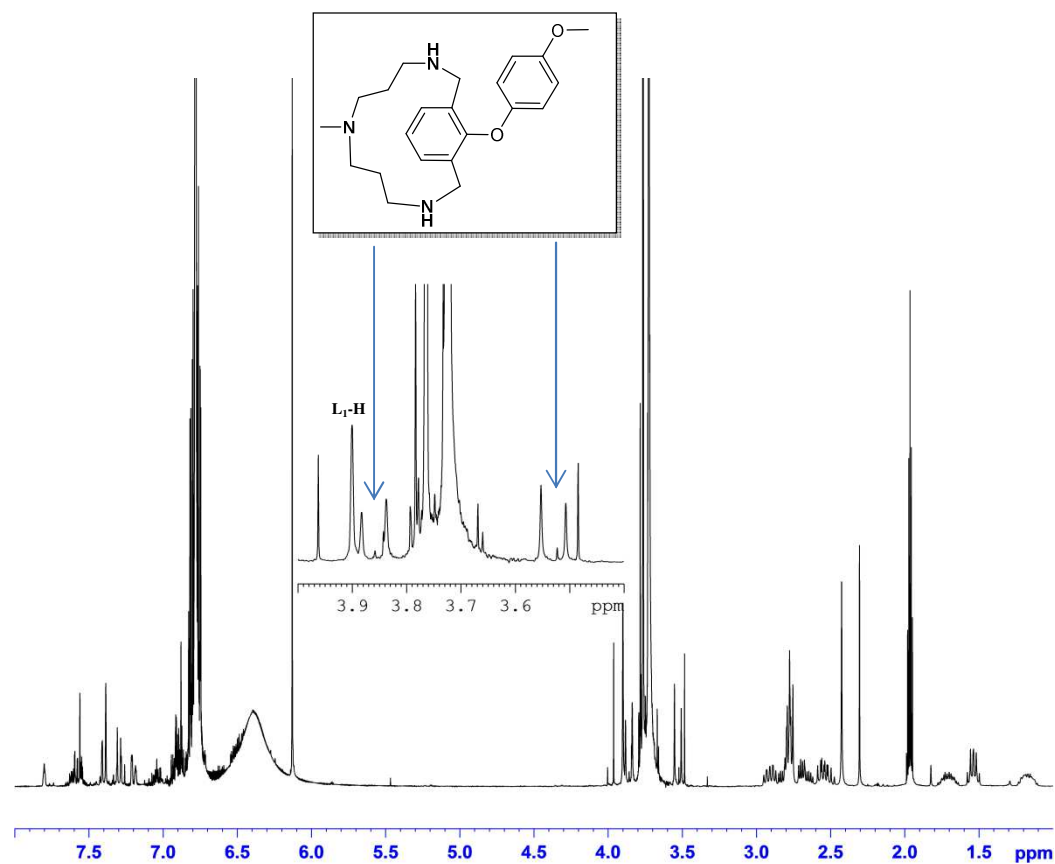


Figure S14. Spectra obtained after reaction of **L₁-Br** and 4-nitrophenol (Conditions: entry 6, Table 6.3, section 6.1.1). *Left:* ¹H-NMR spectrum of crude reaction mixture CD₃CN, 300 MHz, 298 K. *Right:* HRMS (ESI-MS) spectrum of crude reaction mixture in CH₃CN (Top: Full spectrum. Bottom: Zoom with simulated spectra for peaks of **L₁-Br** and product).^[5]

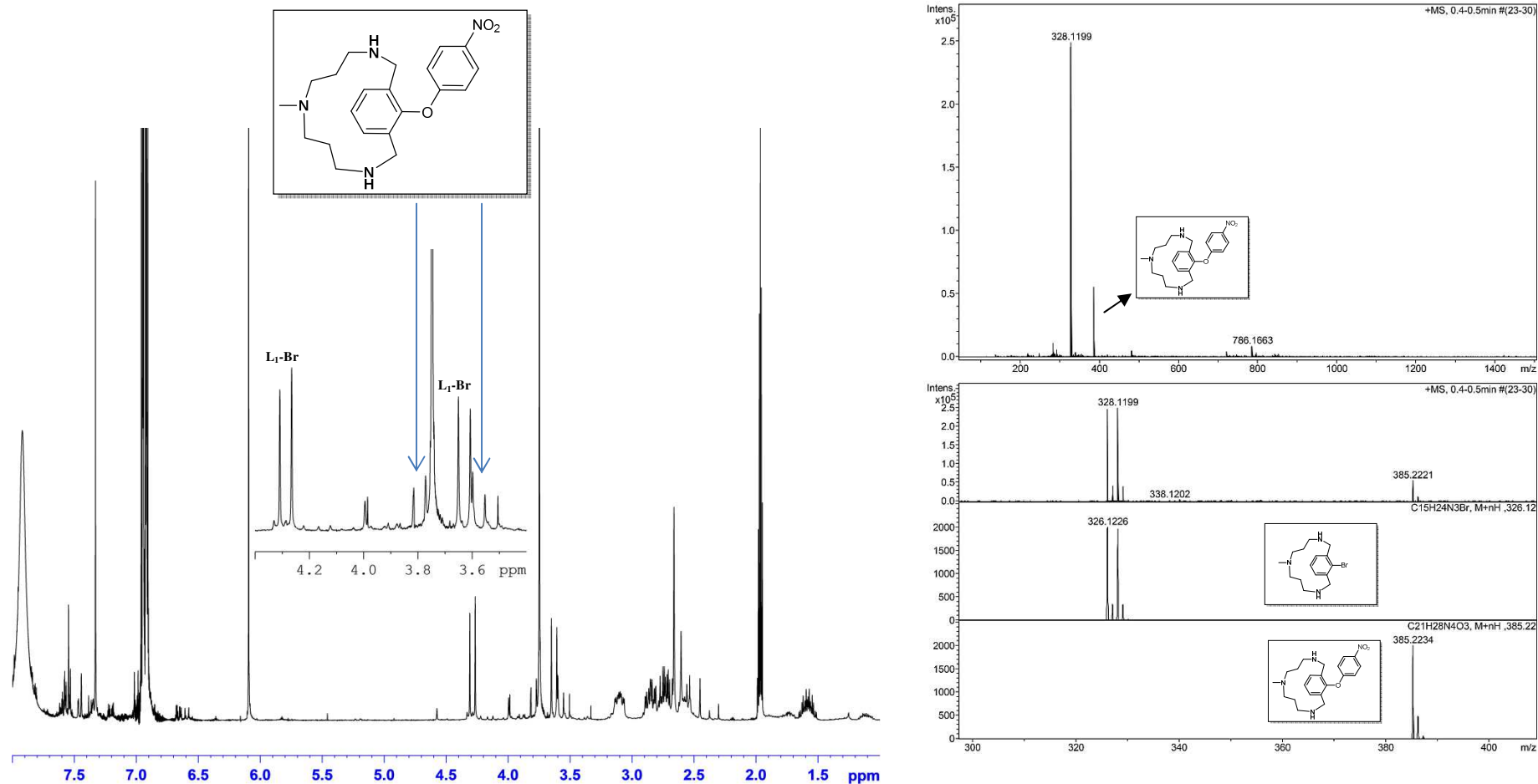
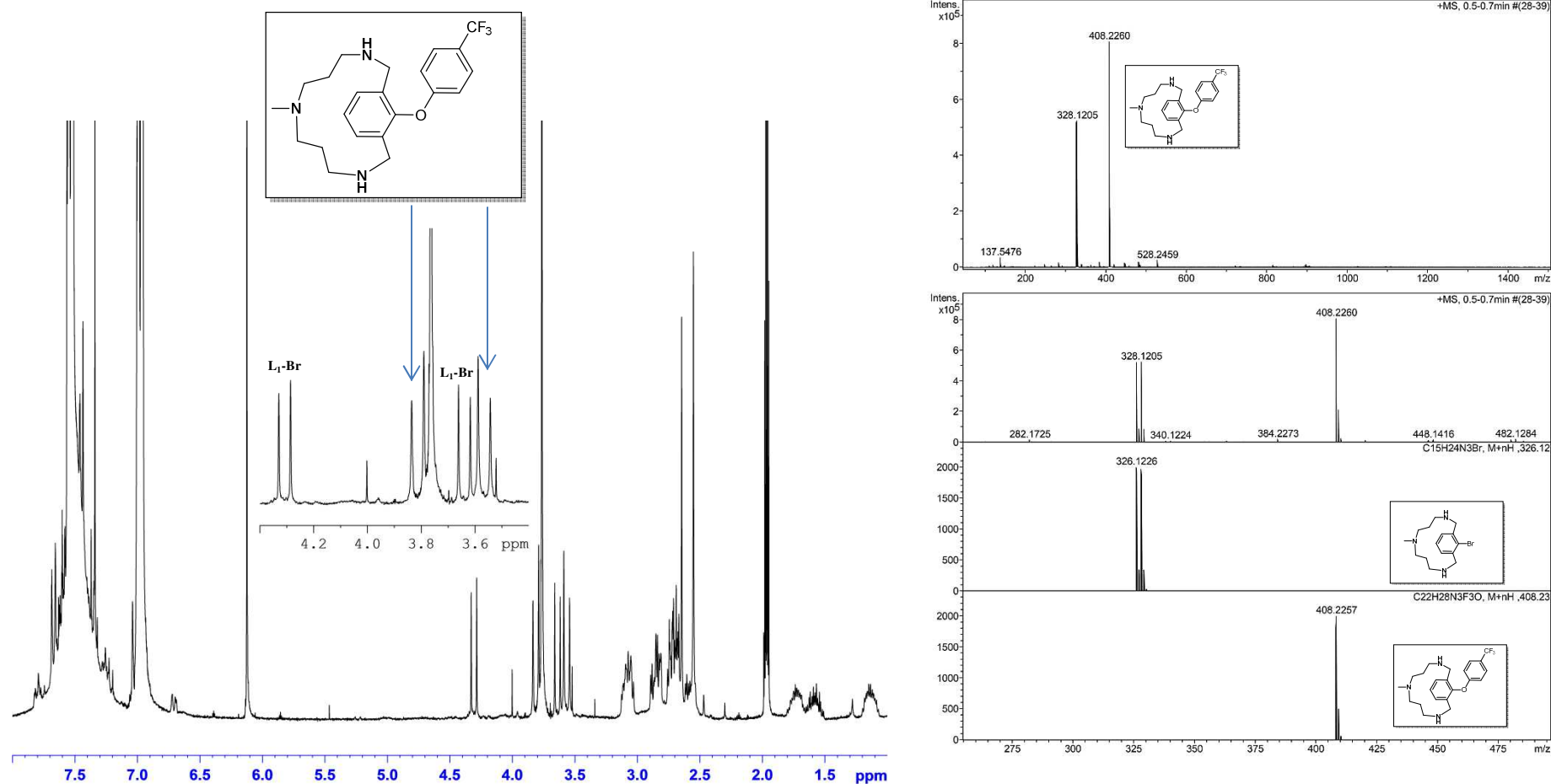


Figure S15. Spectra obtained after reaction of **L₁-Br** and 4-trifluoromethylphenol (Conditions: entry 7, Table 6.3, section 6.1.1). *Left:* ¹H-NMR spectrum of crude reaction mixture CD₃CN, 300 MHz, 298 K. *Right:* HRMS (ESI-MS) spectrum of crude reaction mixture in CH₃CN (Top: Full spectrum. Bottom: Zoom with simulated spectra for peaks of **L₁-Br** and product).^[5]



The figure displays the ^1H NMR spectrum of L1-Br in CDCl_3 . The main spectrum shows peaks from 0 to 8 ppm. An inset zooms in on the 3.6-4.3 ppm region, showing two sets of peaks labeled L1-Br . Blue arrows point from the chemical structure of L1-Br to these peaks. The chemical structure is a macrocyclic ligand with two secondary amine groups and a 4-chlorophenyl ether substituent.

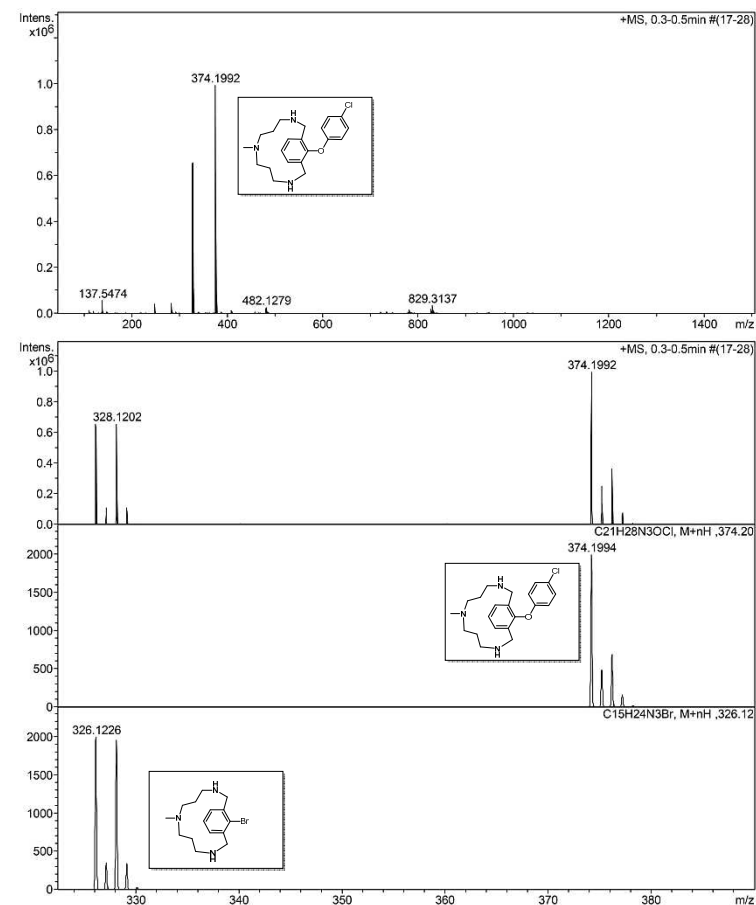


Figure S17. ^1H NMR Spectra obtained during the initial stages of the coupling of 4-methylphenol to **L₁-Br** using $[\text{AuCl}(\text{PPh}_3)]$ as catalyst.

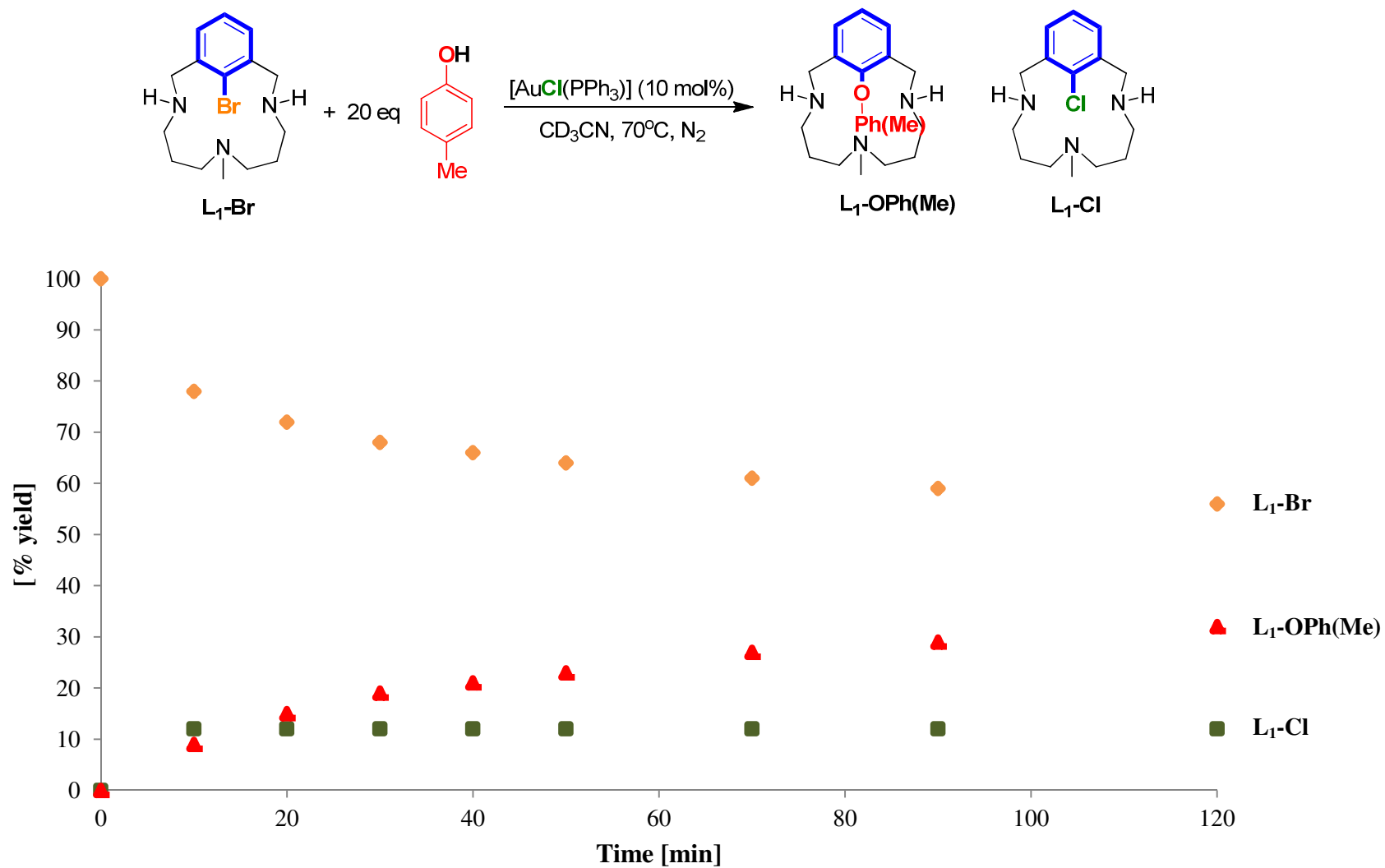
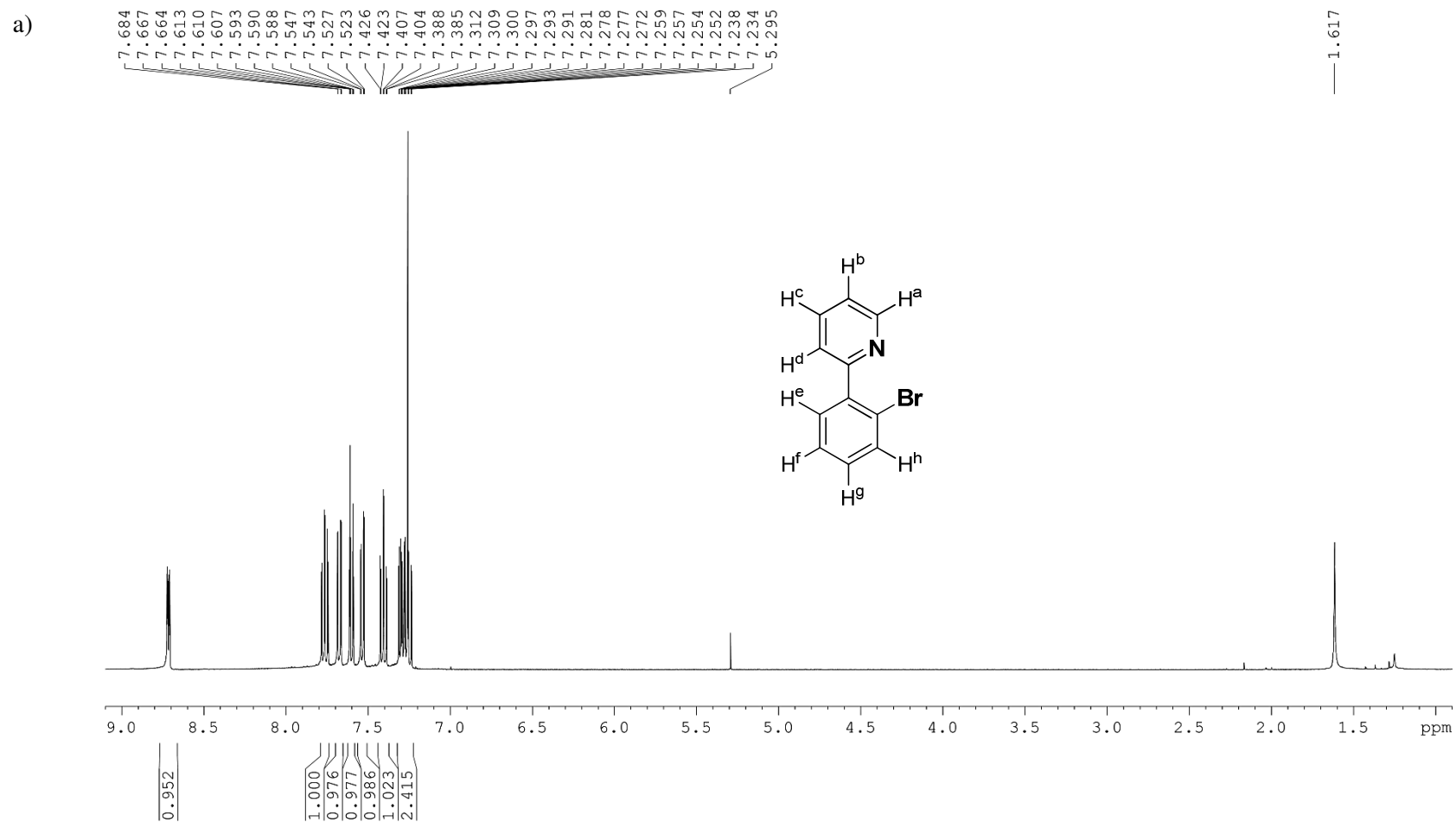
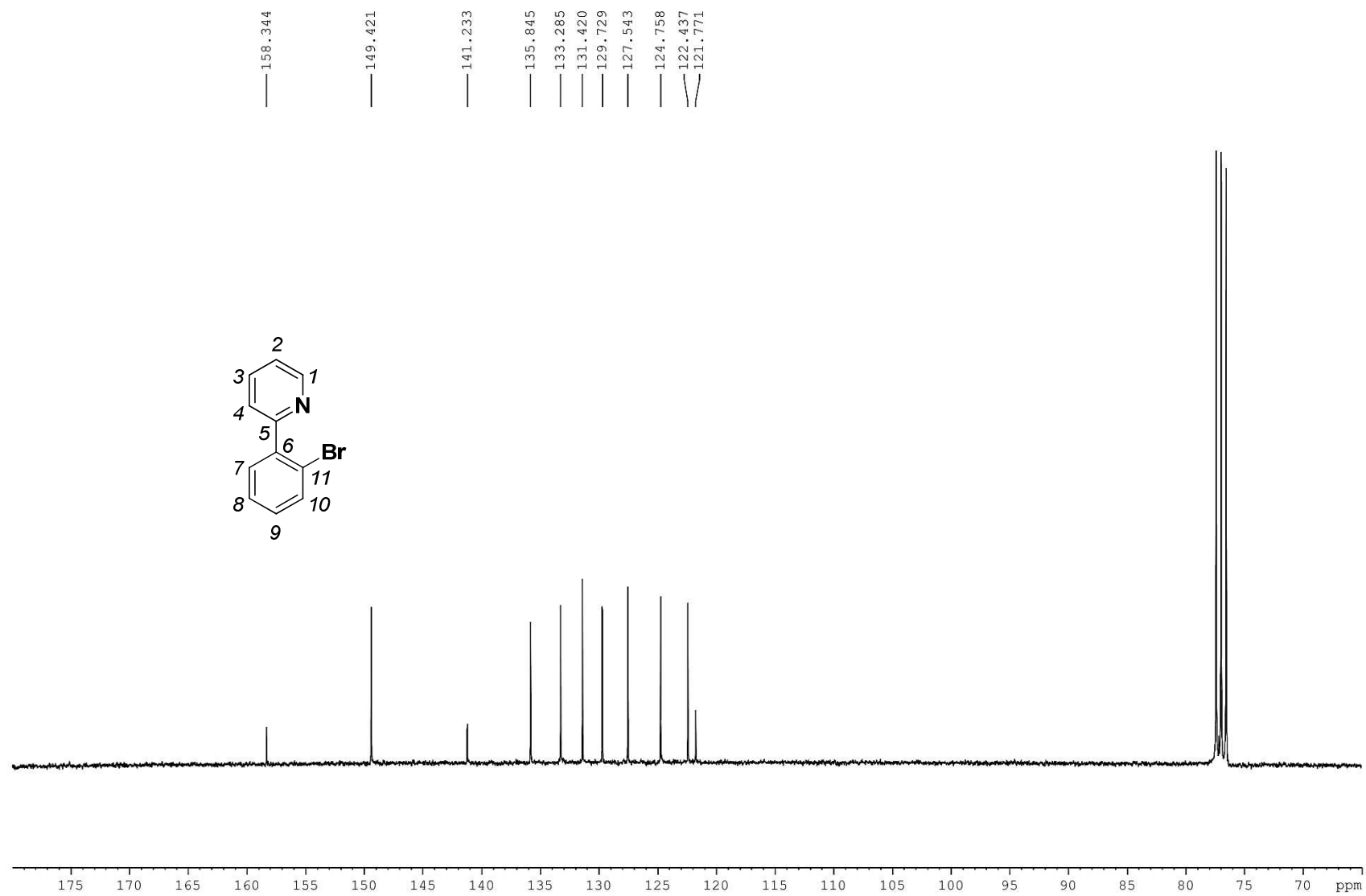


Figure S18. a) ^1H -NMR spectrum of compound **2d** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 70 MHz, 298 K); c) Observed HRMS with the theoretical isotope prediction (inset).



b)



c)

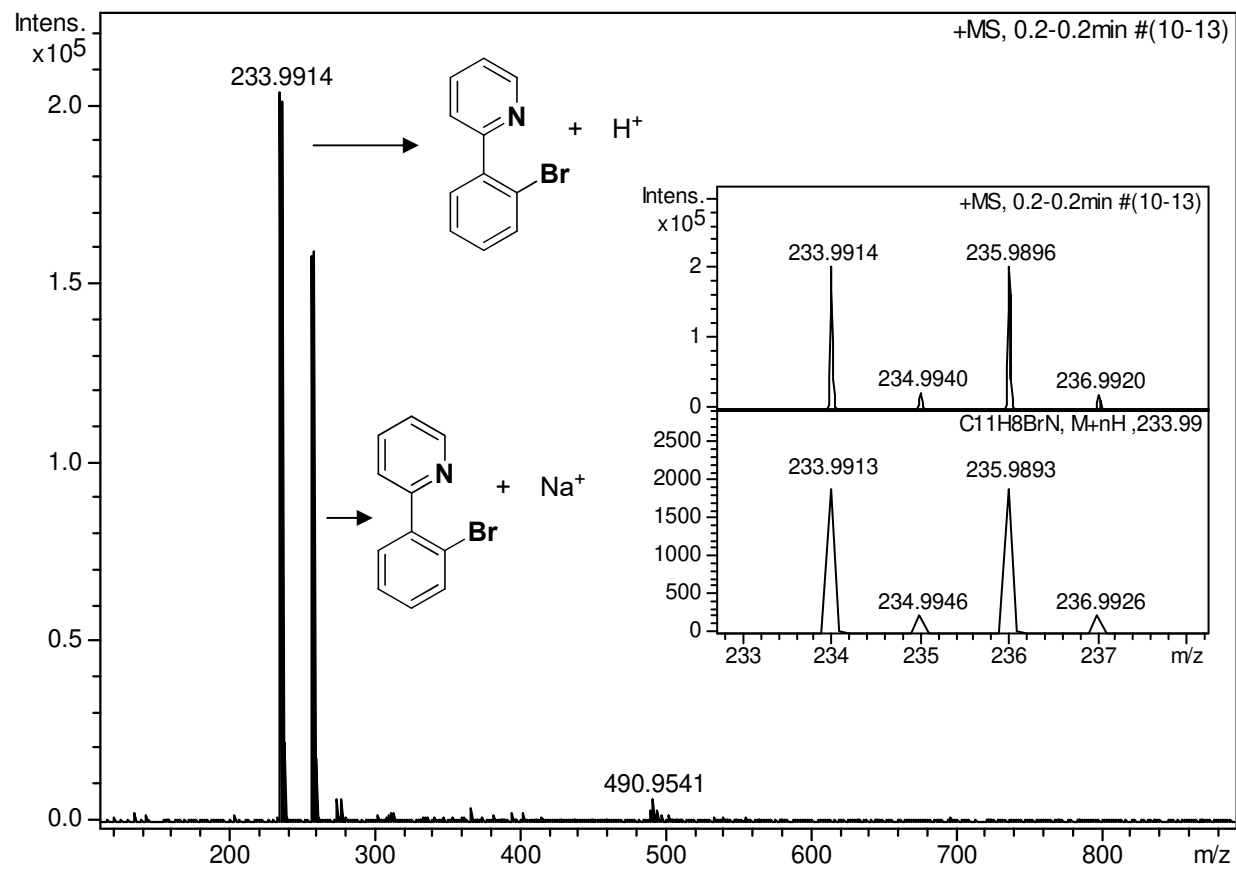
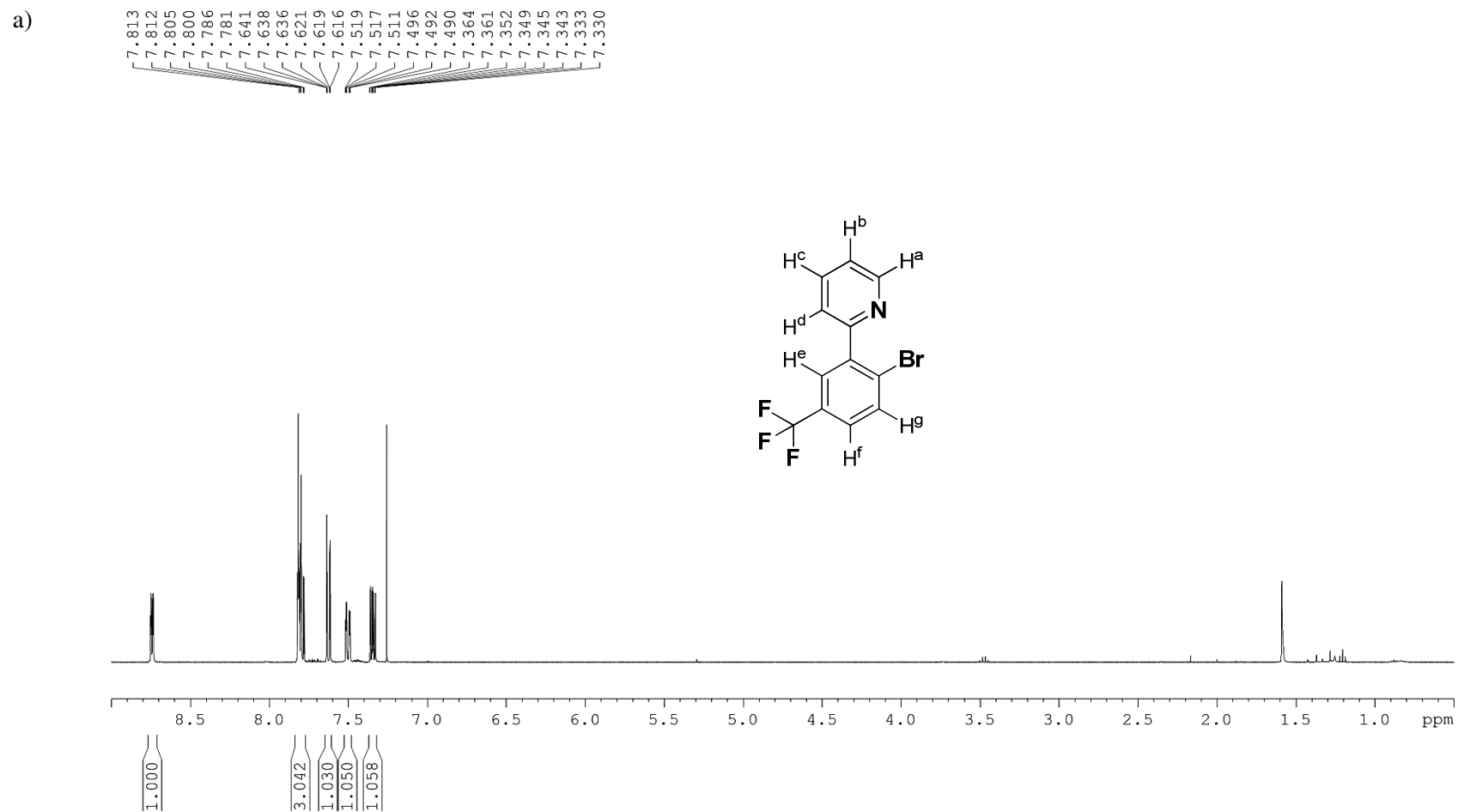
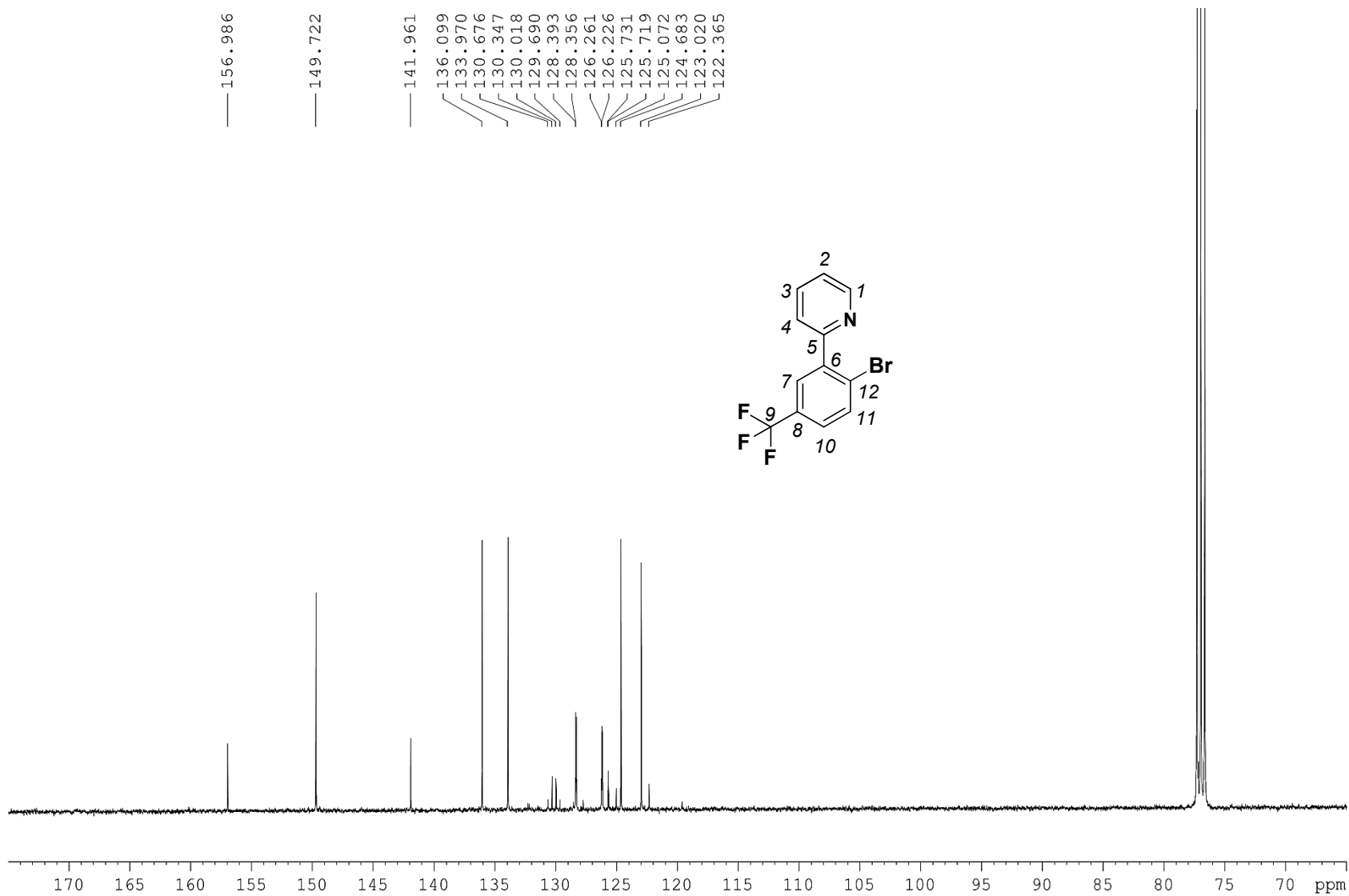


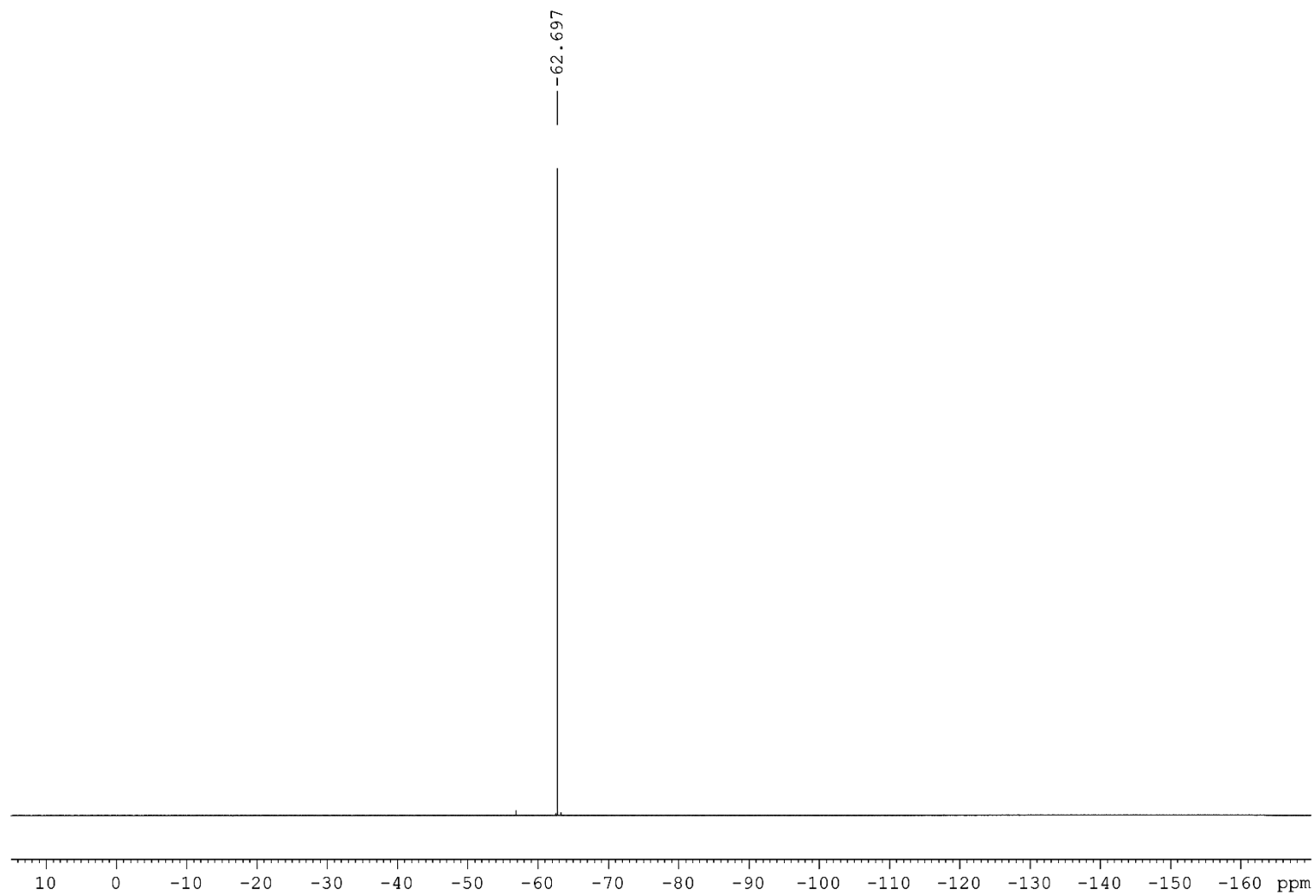
Figure S19. a) ^1H -NMR spectrum of compound **2da** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) ^{19}F -NMR spectrum in CDCl_3 , 376.5 MHz, at 298 K, using NaCF_3SO_3 as internal standard (-78.8 ppm); d) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)



c)



d)

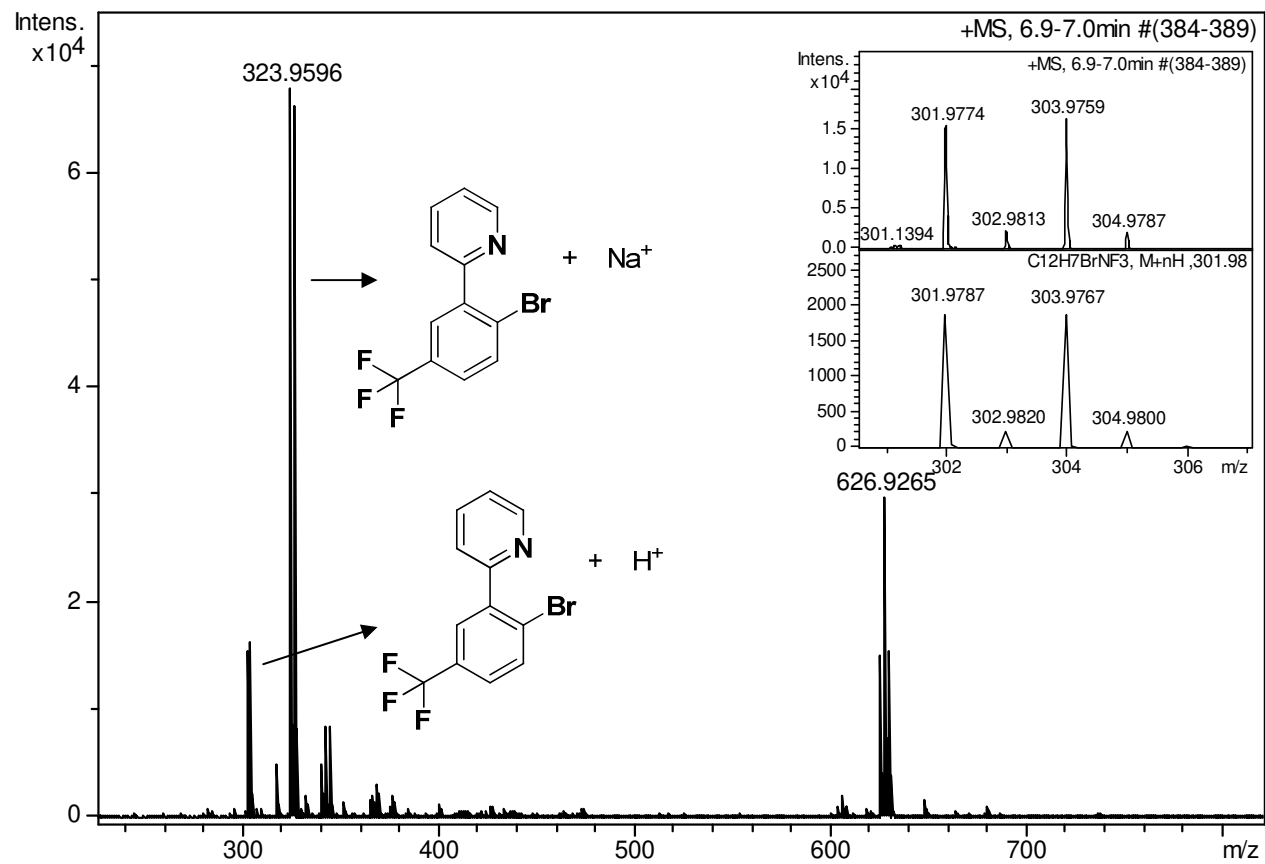
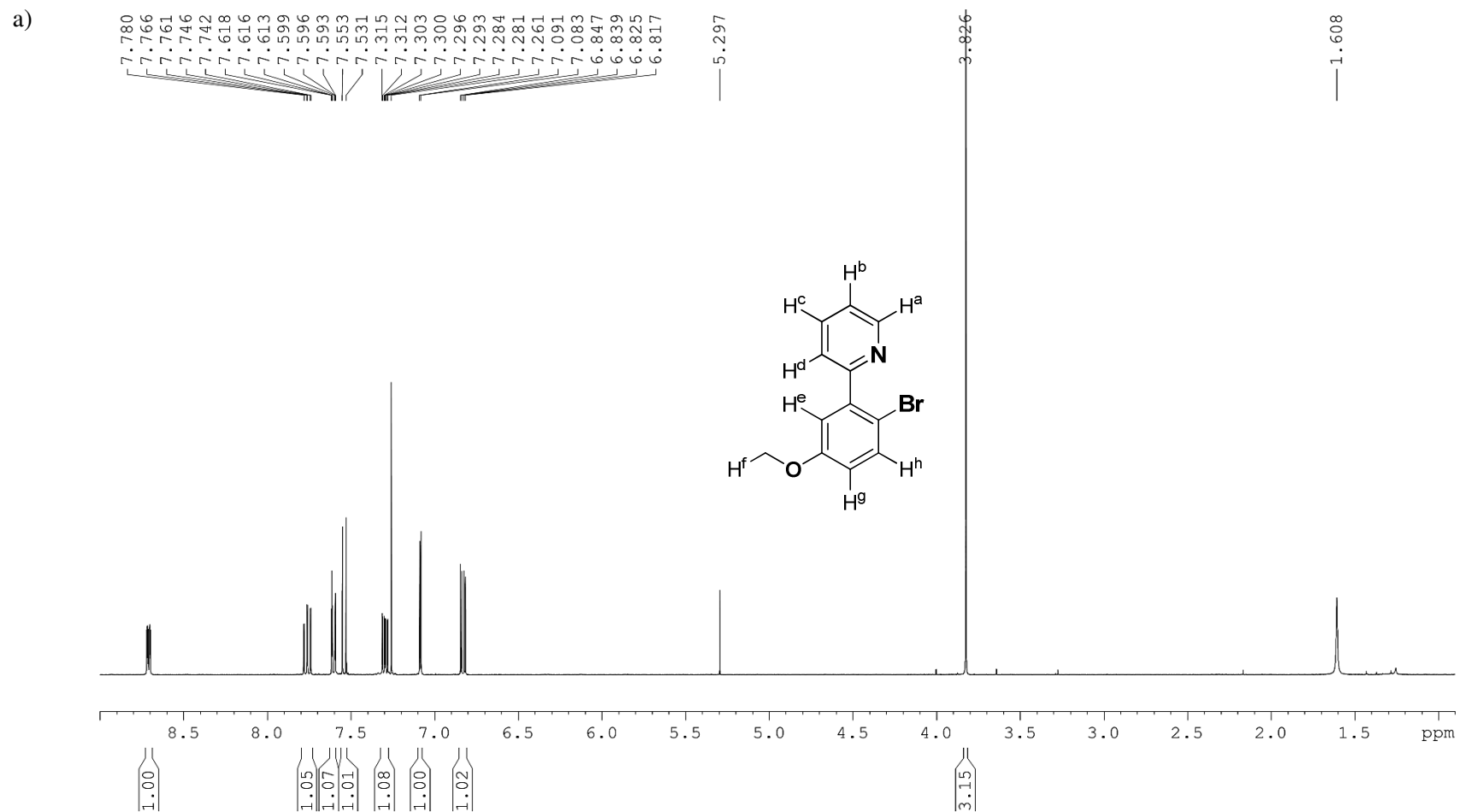
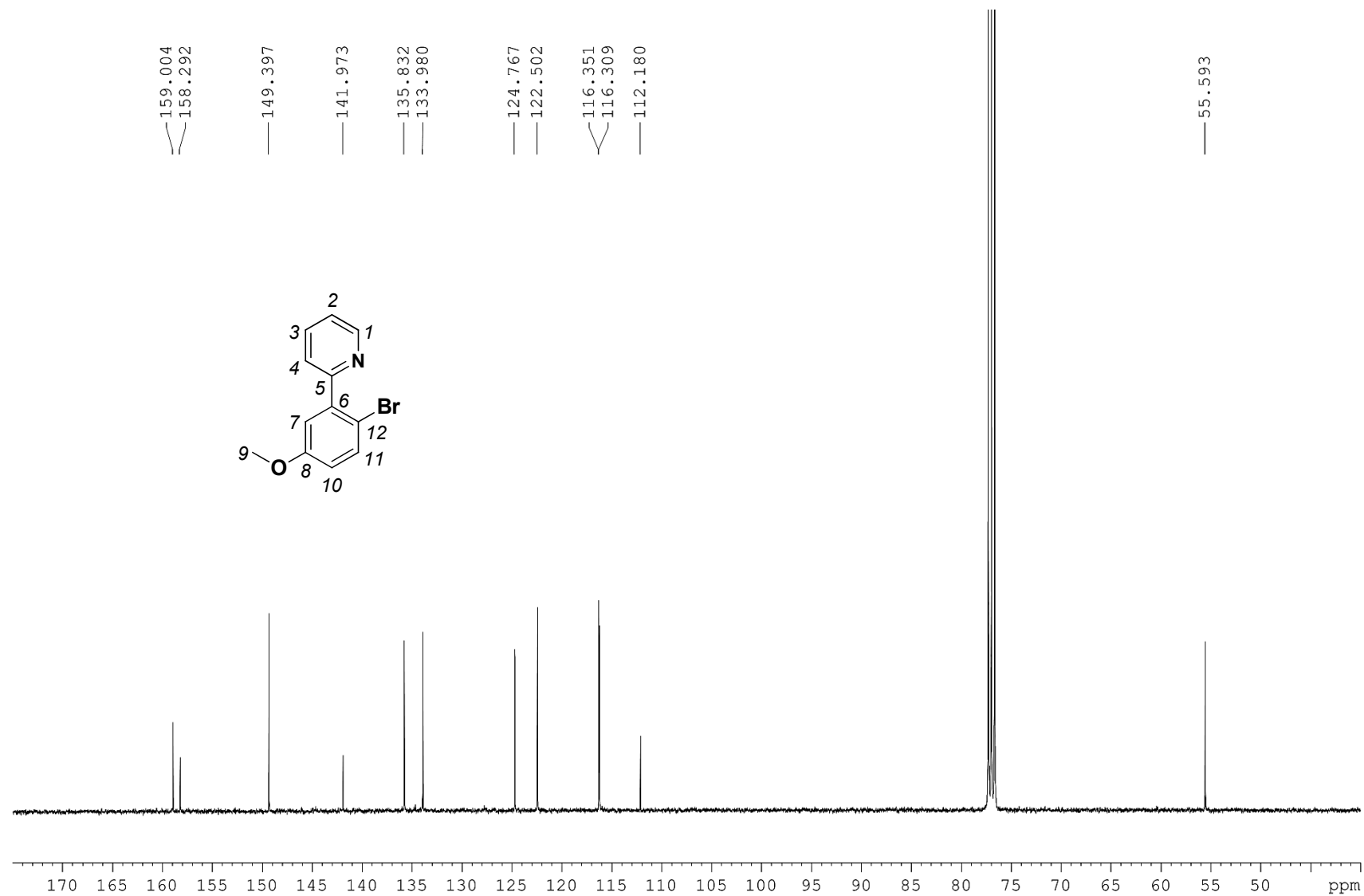


Figure S20. a) ^1H -NMR spectrum of compound **2db** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)



c)

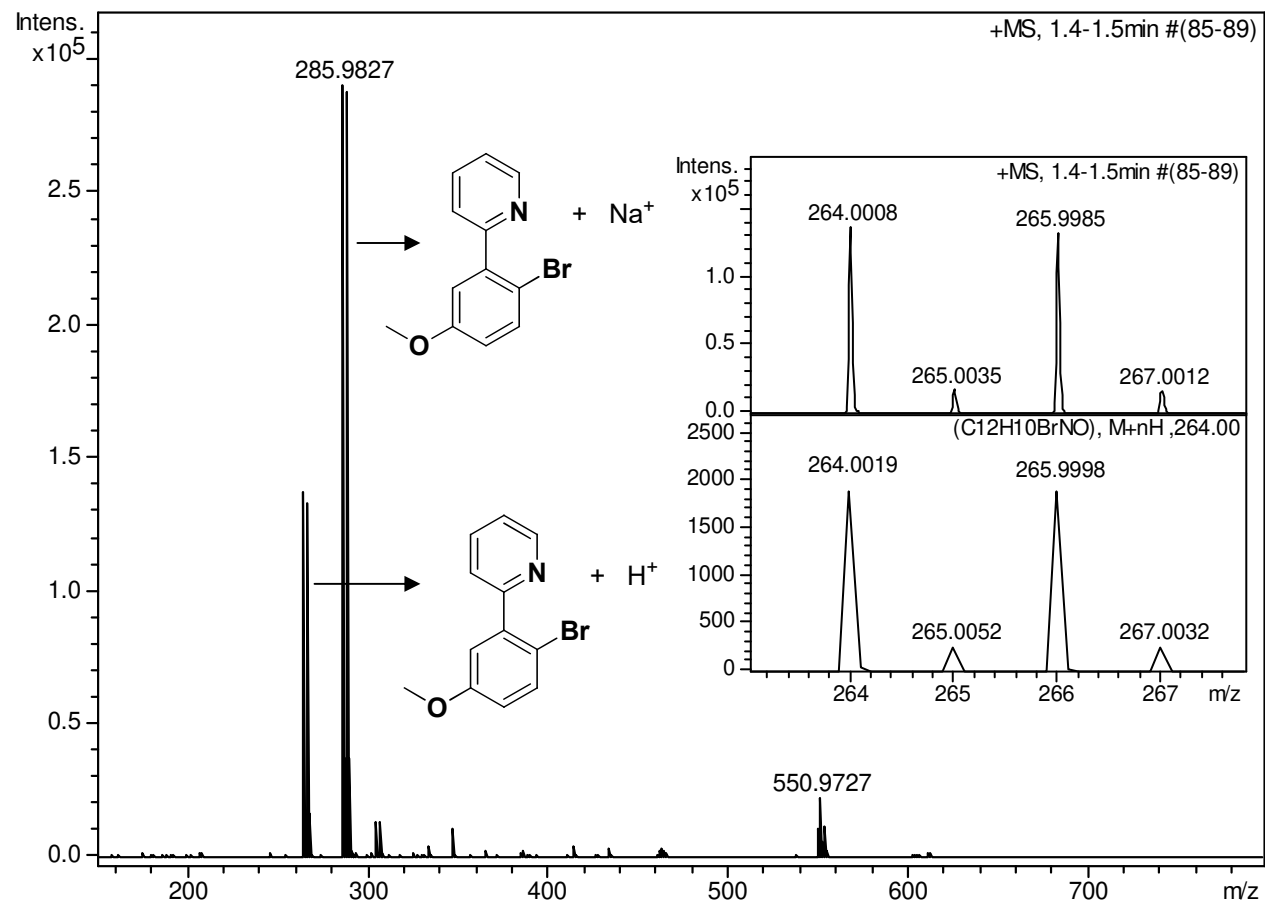
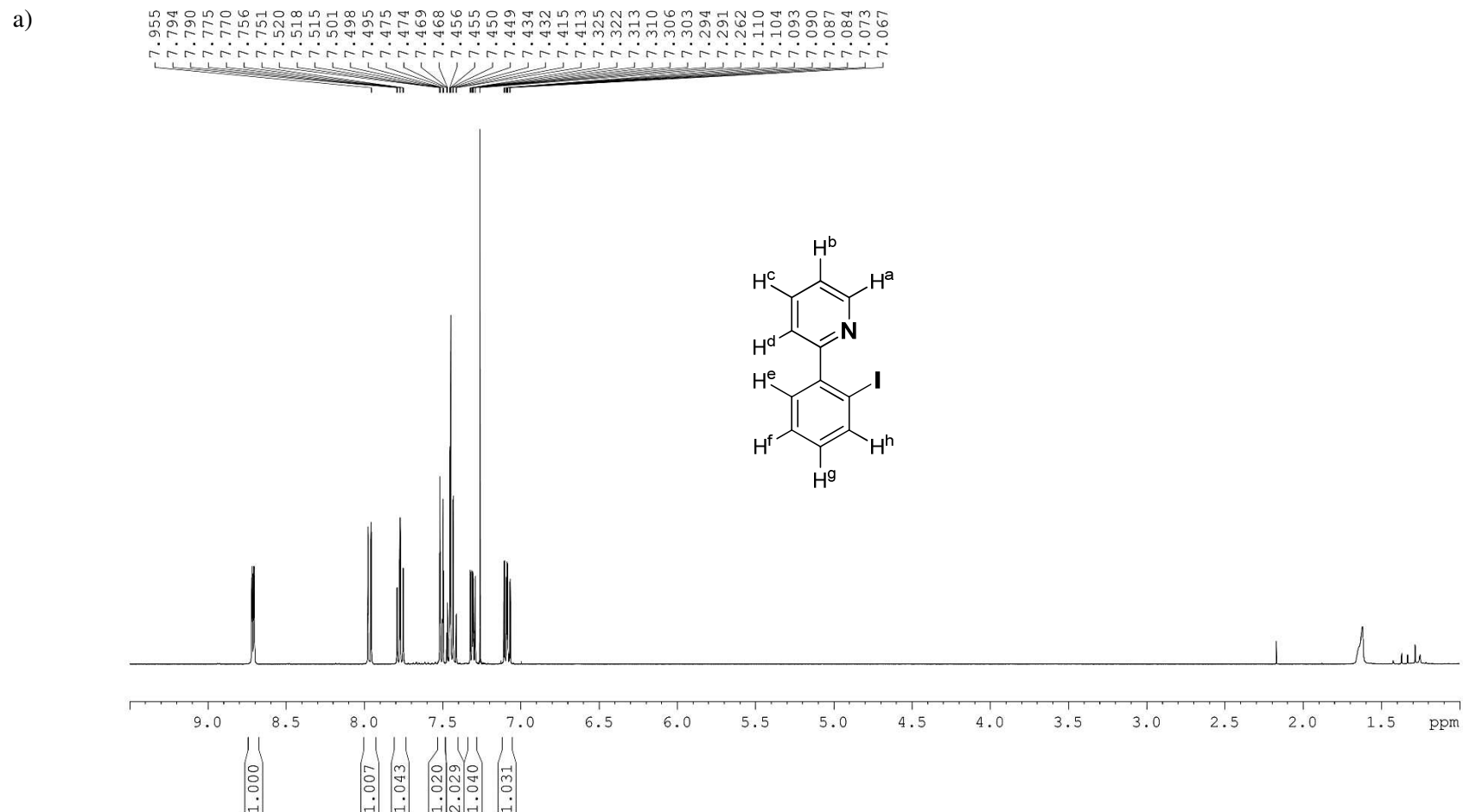
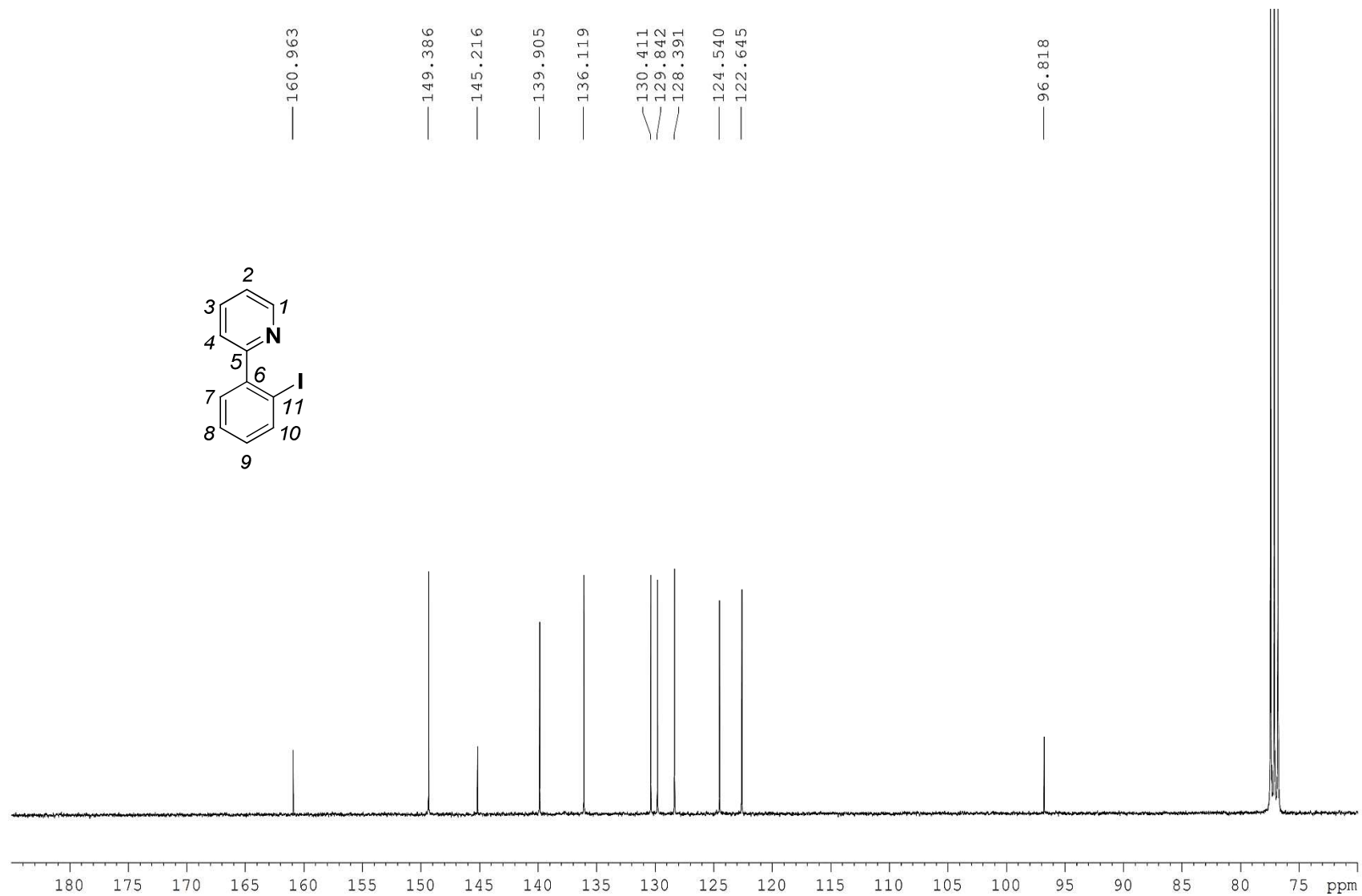


Figure S21. a) ^1H -NMR spectrum of compound **3d** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)



c)

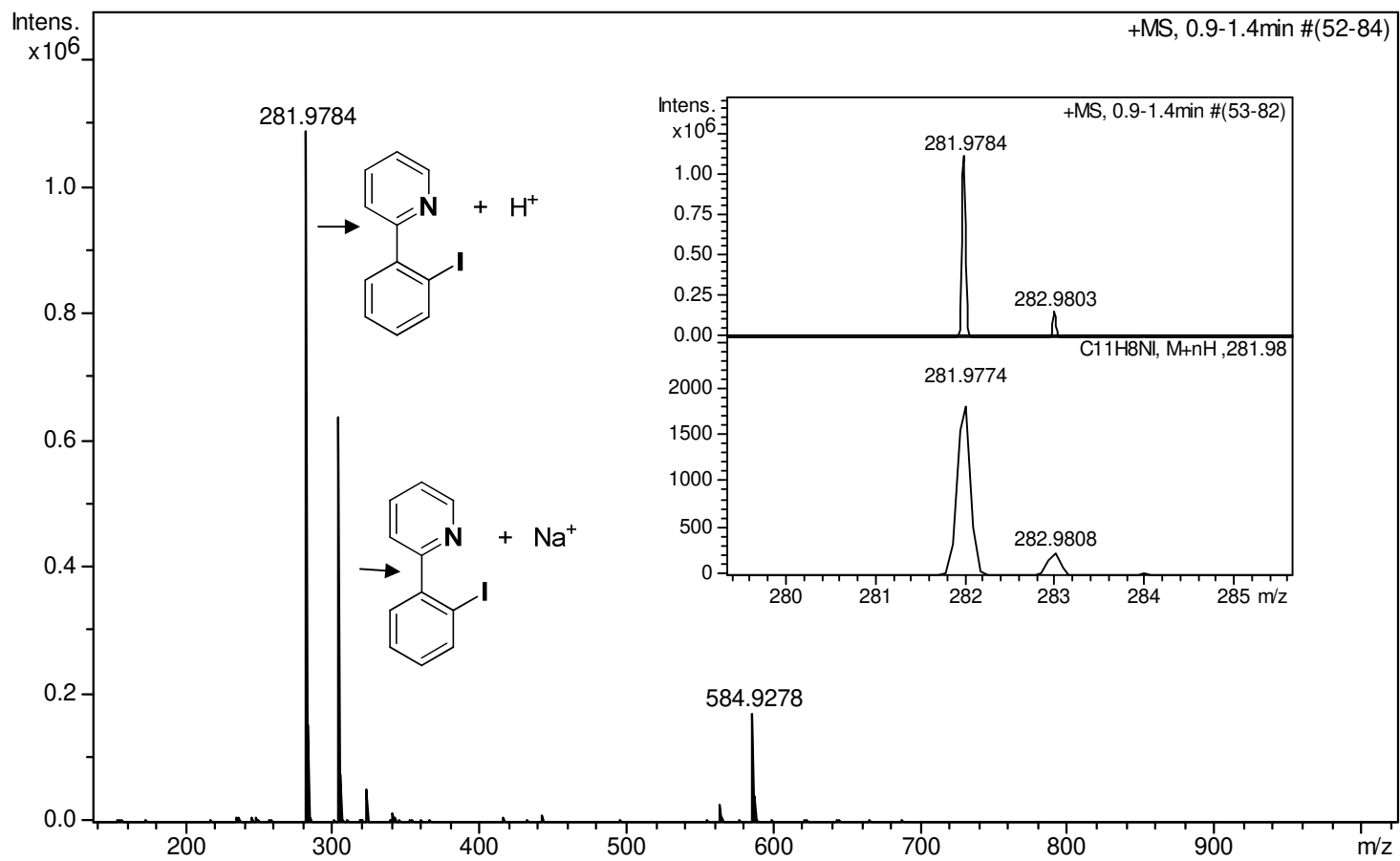
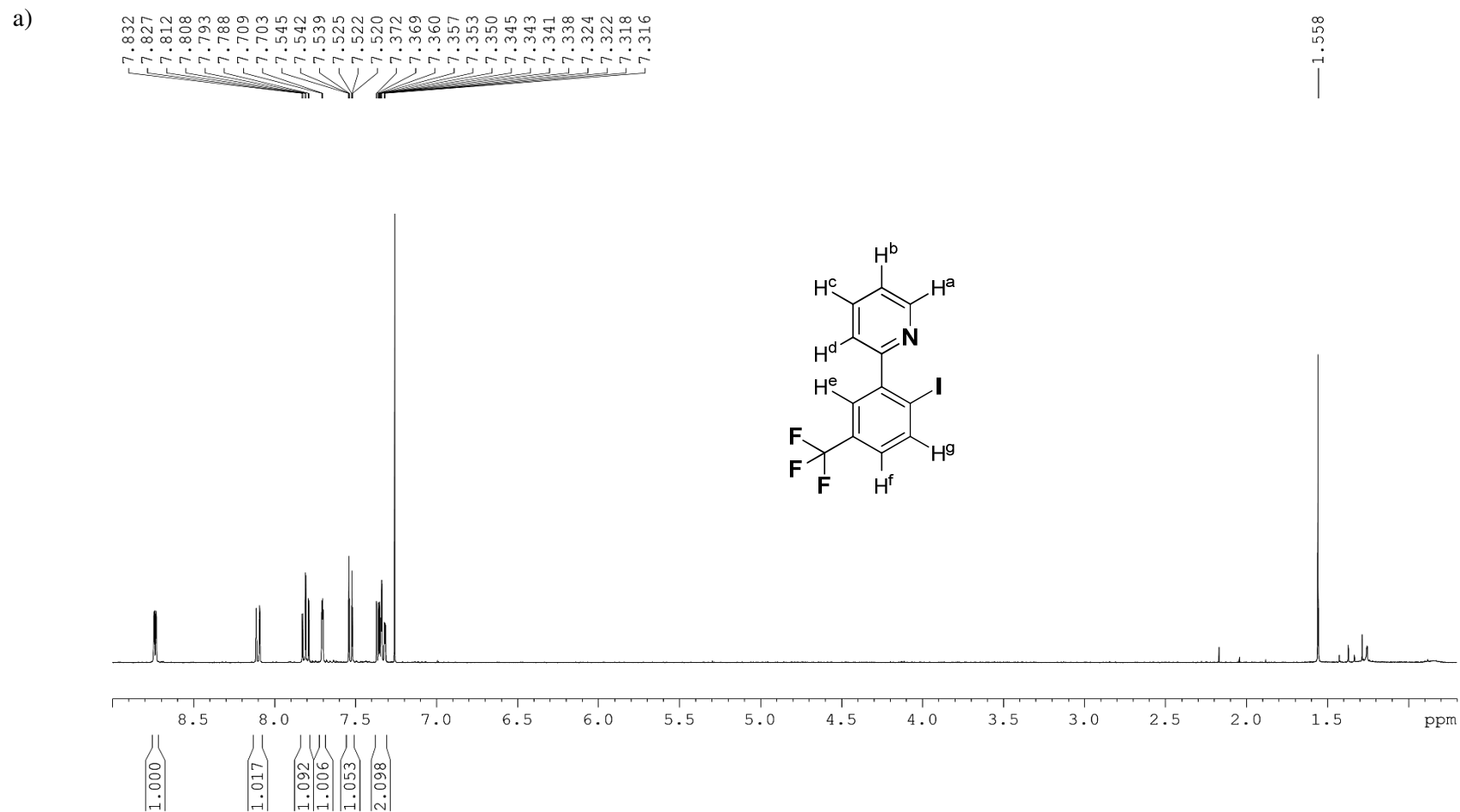
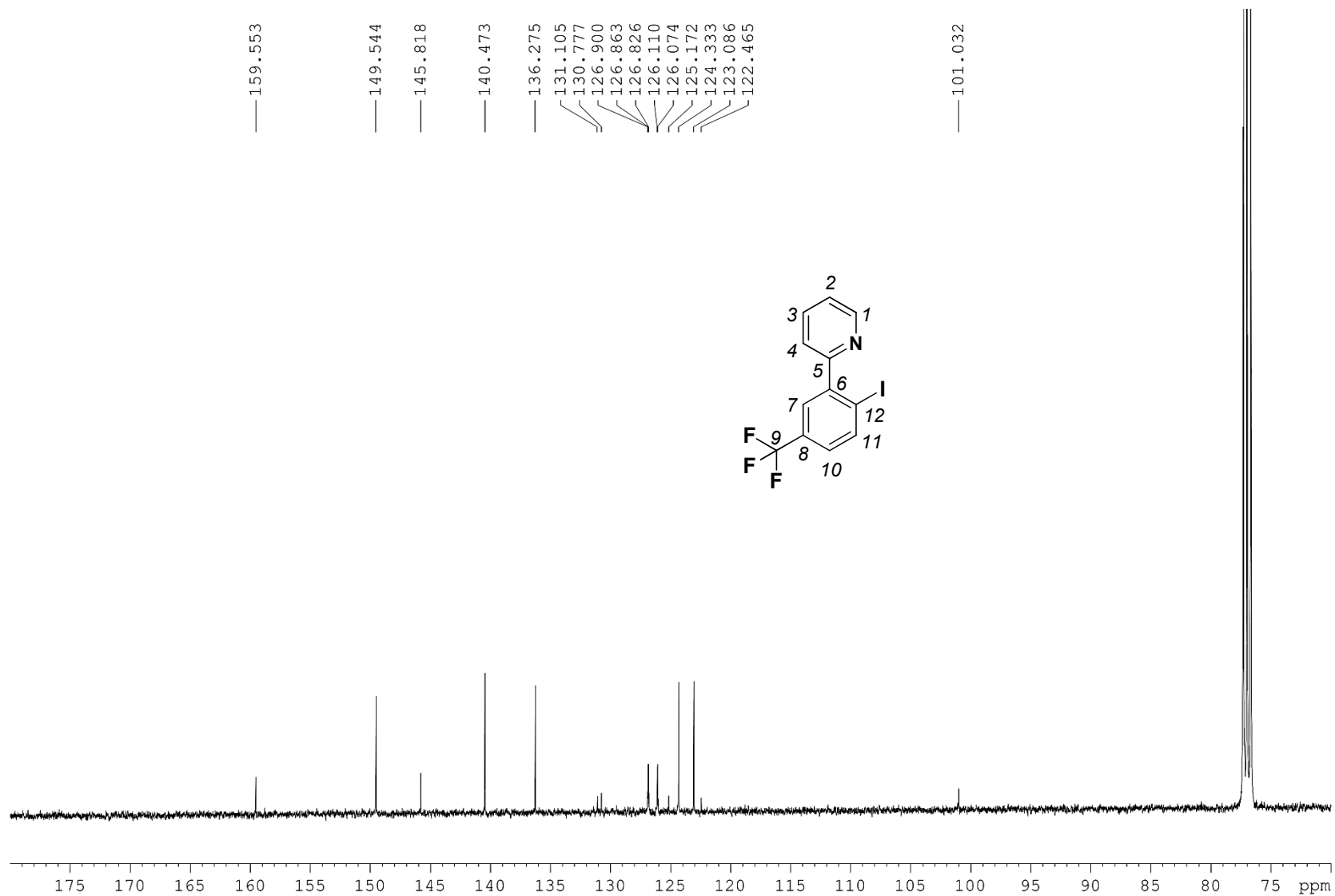


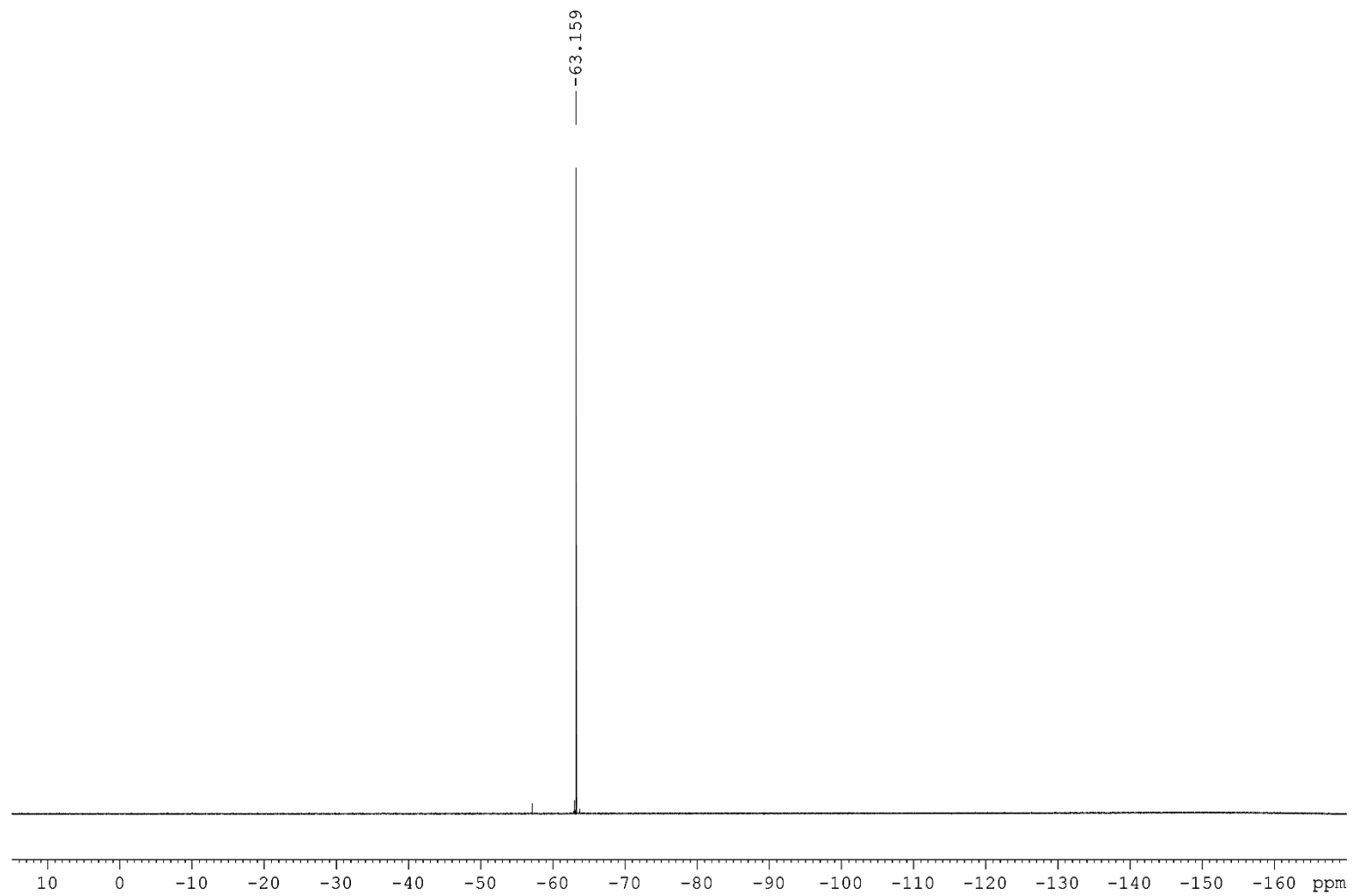
Figure S22. a) ^1H -NMR spectrum of compound **3da** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) ^{19}F -NMR spectrum in CDCl_3 , 376.5 MHz, at 298 K, using NaCF_3SO_3 as internal standard (-78.8 ppm); d) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)



c)



d)

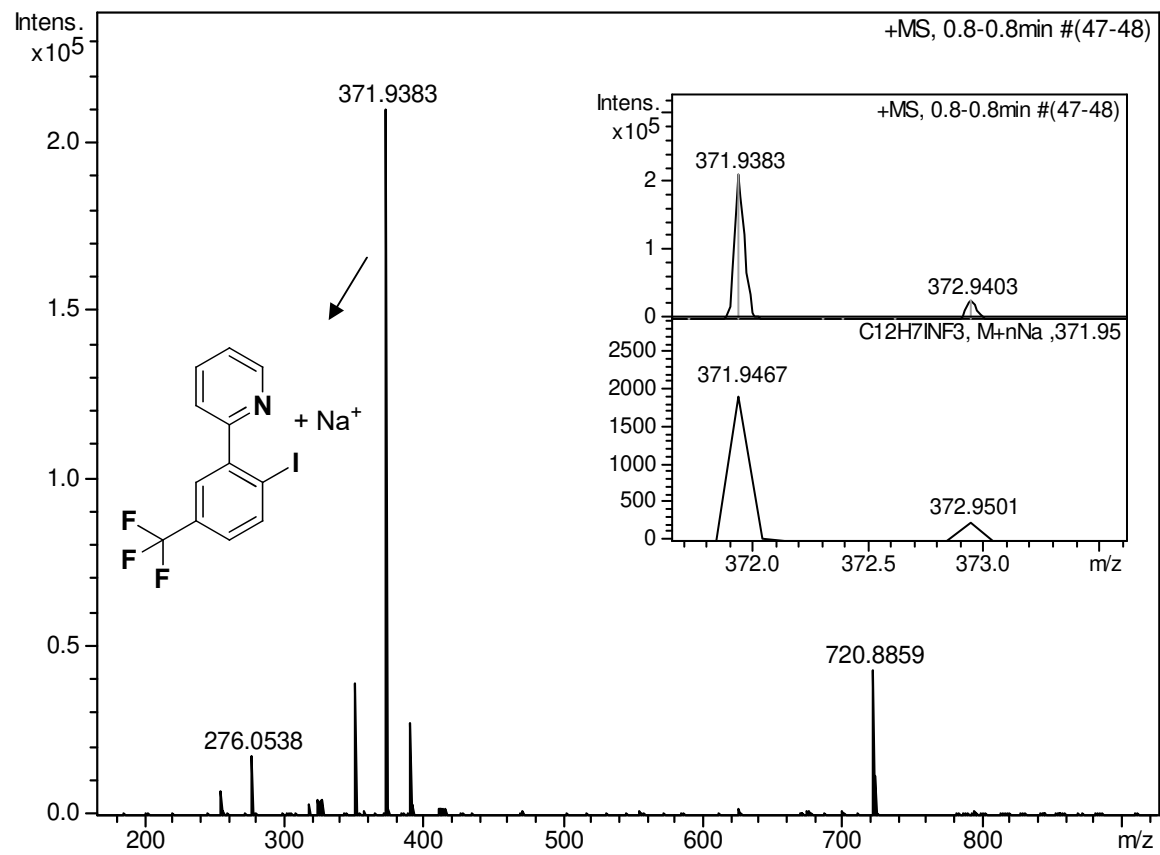
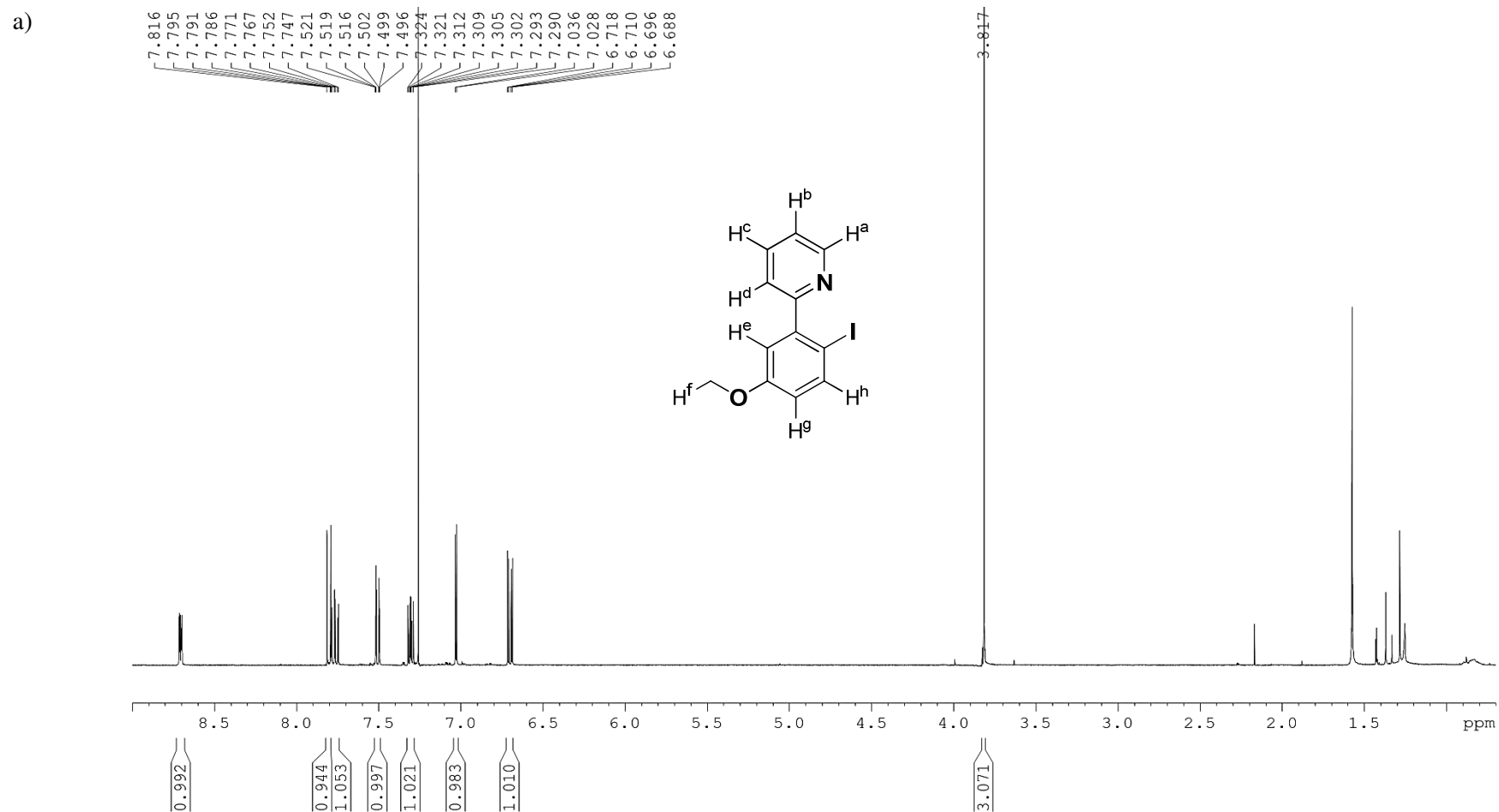
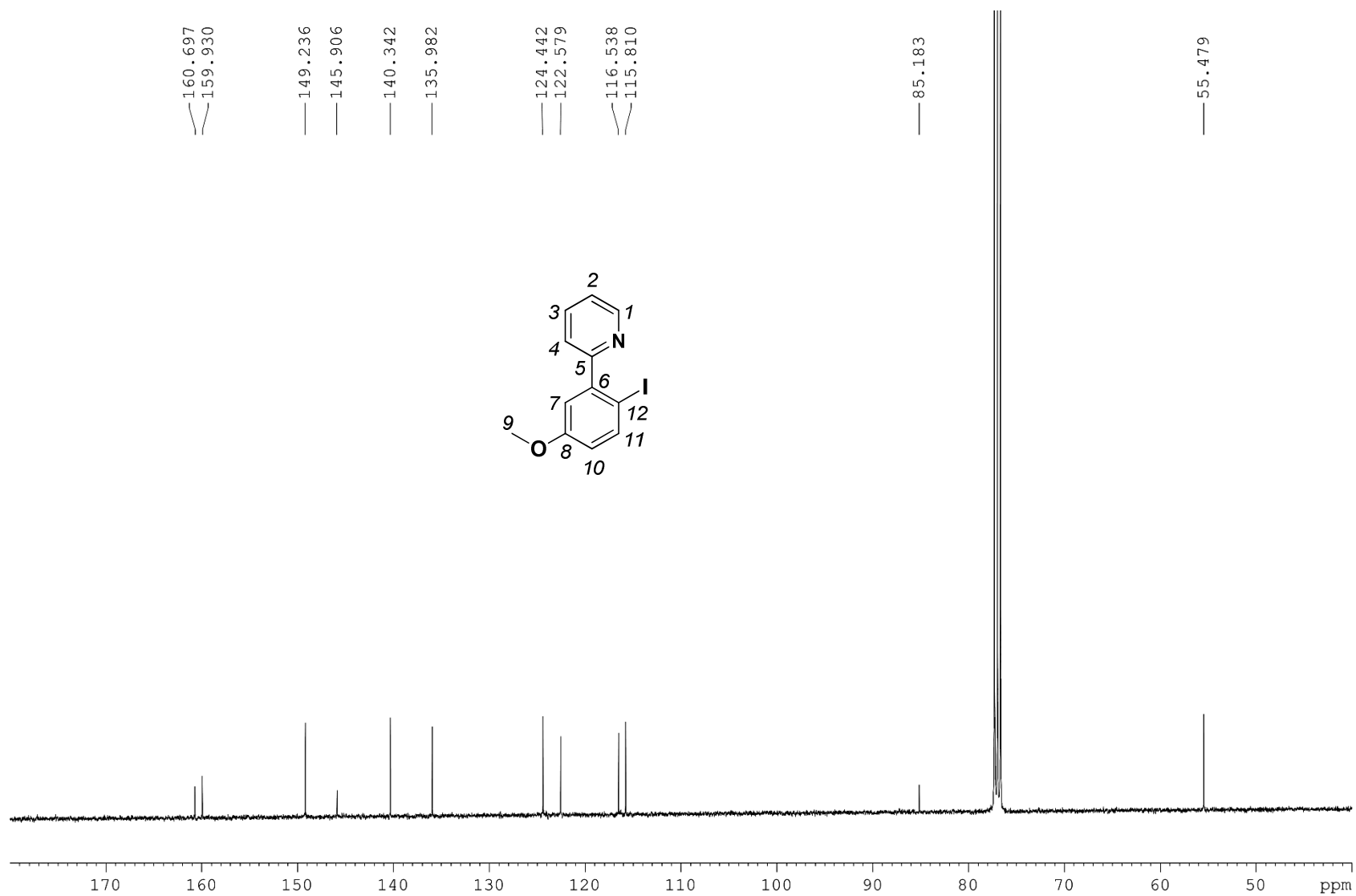


Figure S23. a) ^1H -NMR spectrum of compound **3db** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)



c)

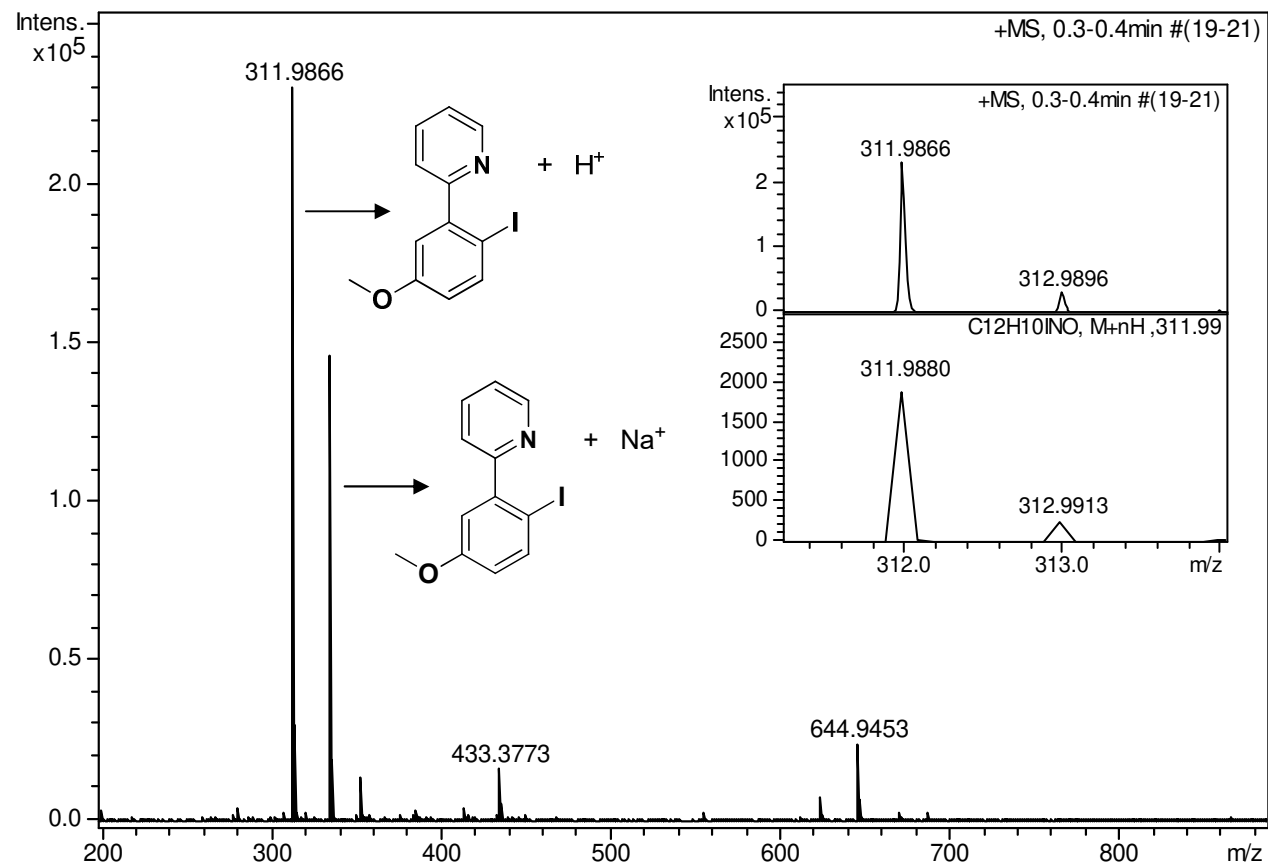
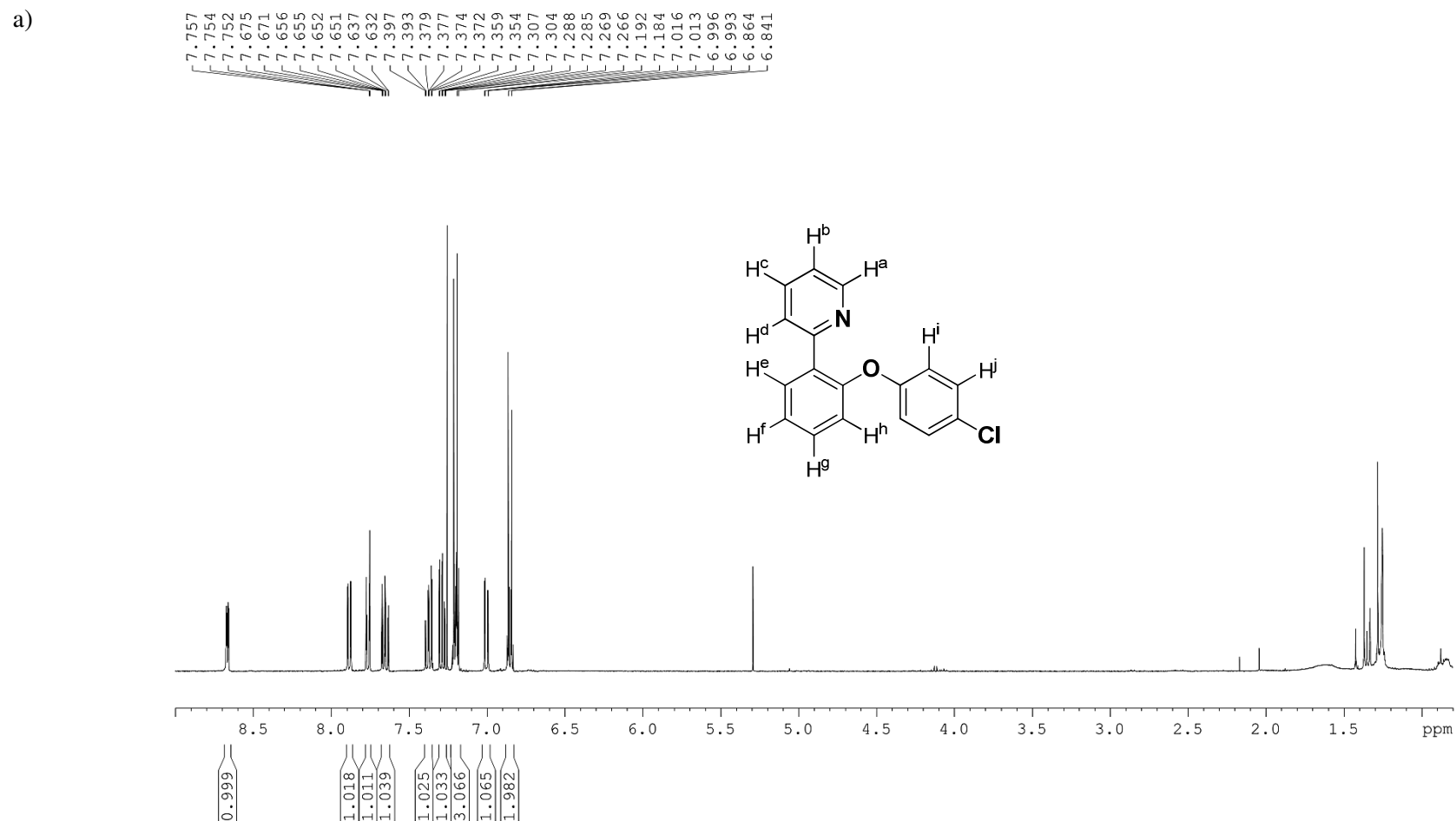
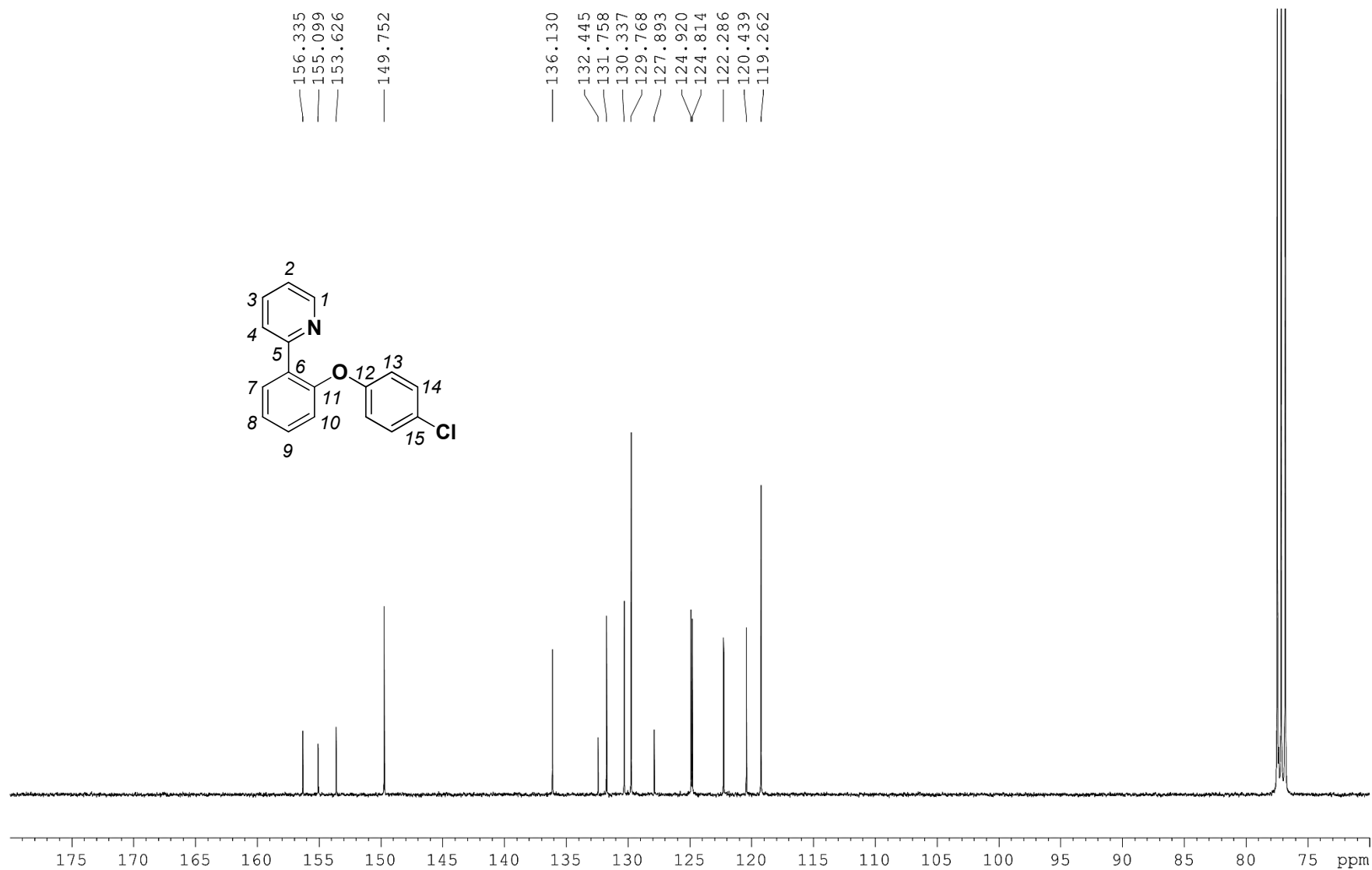


Figure S24. a) ^1H -NMR spectrum of compound **4d** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)



c)

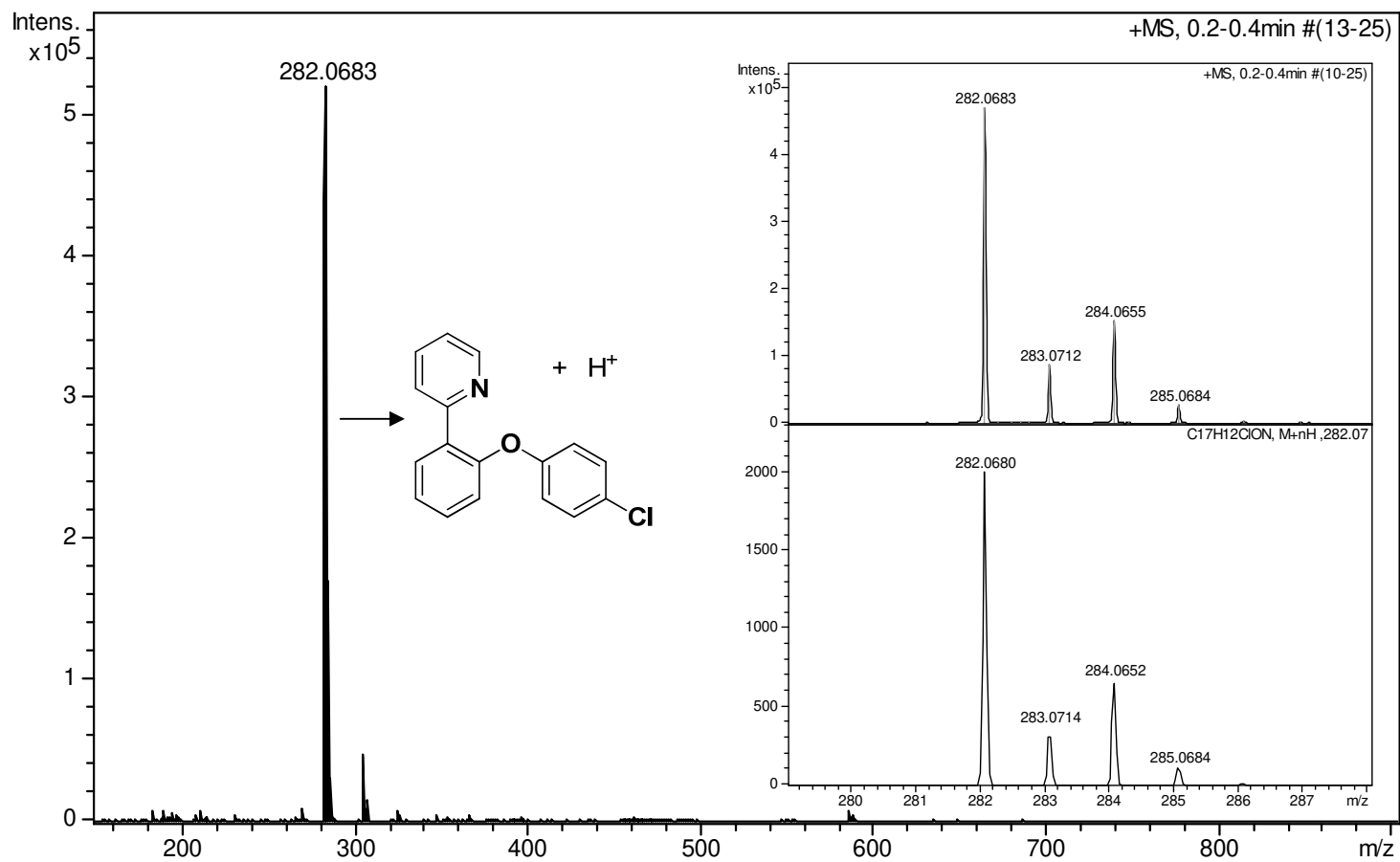
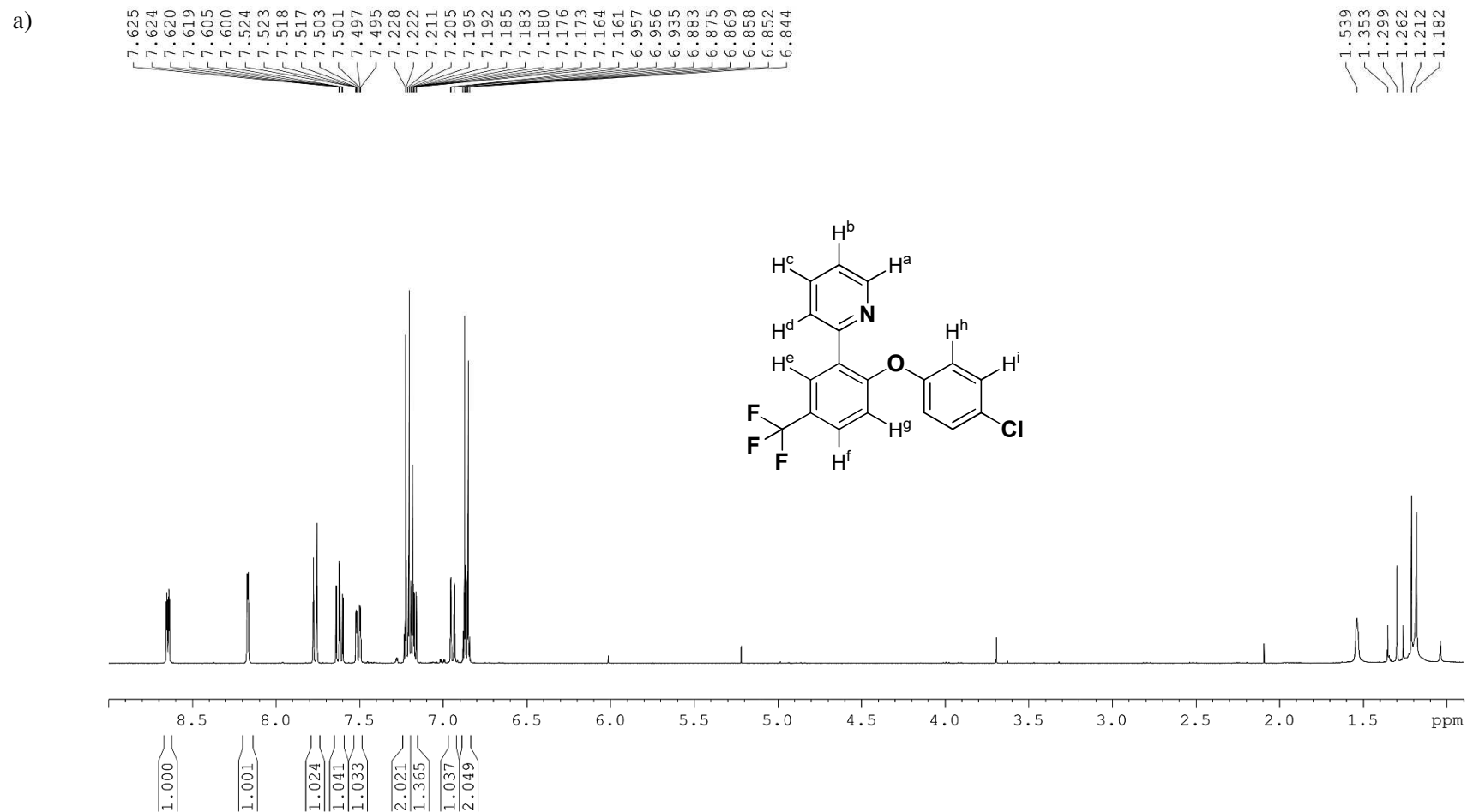
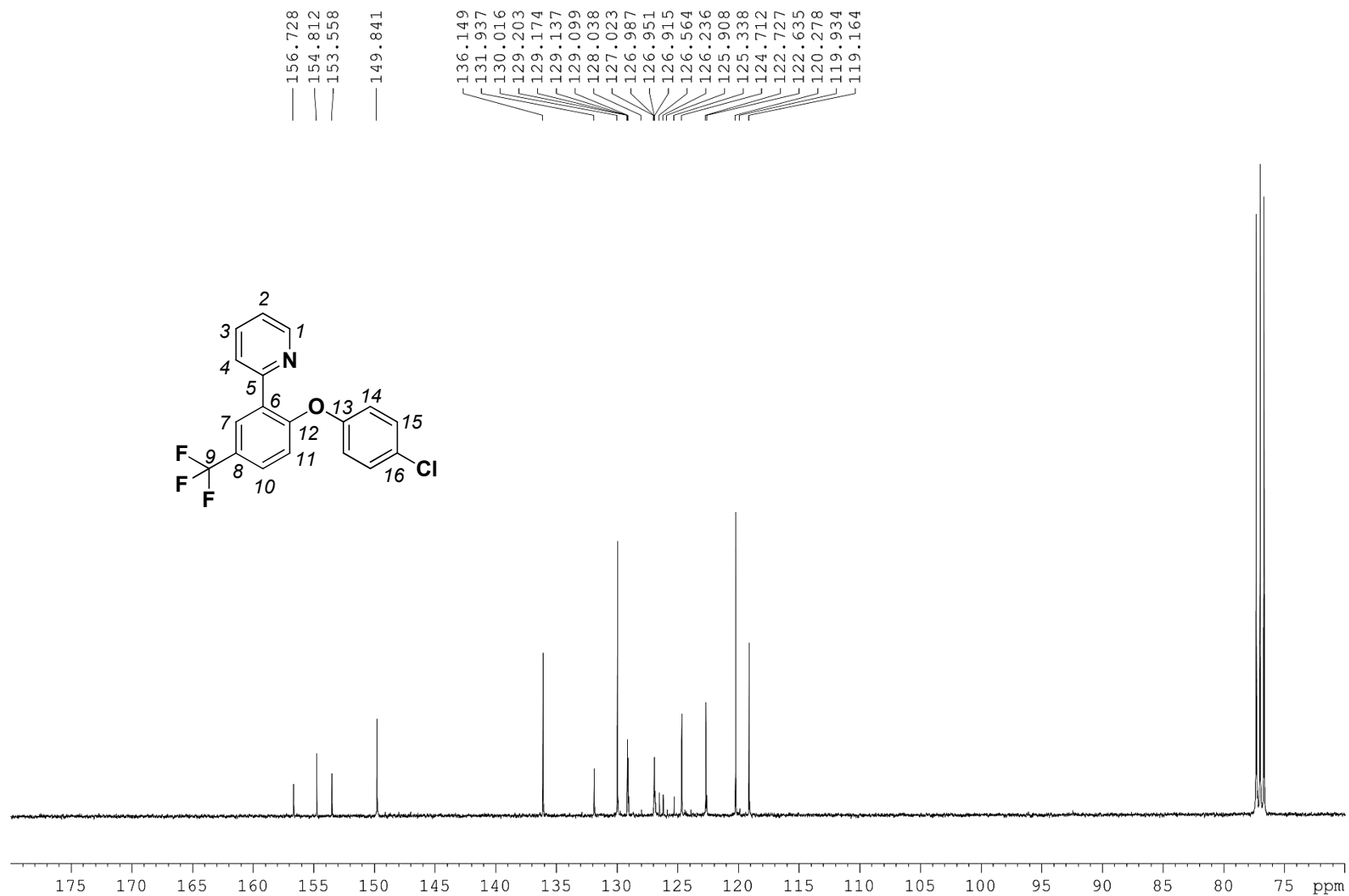


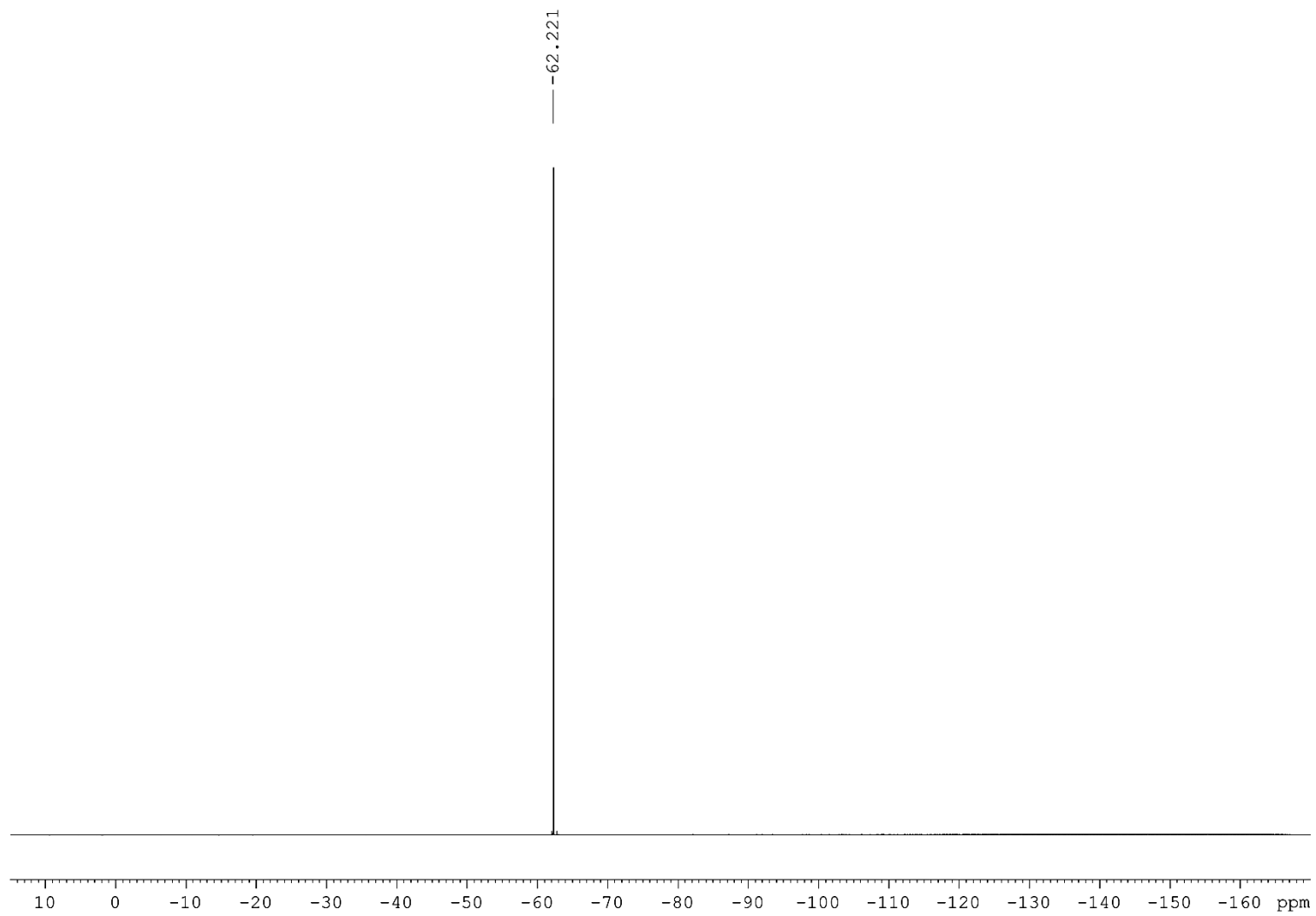
Figure S25. a) ^1H -NMR spectrum of compound **4da** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) ^{19}F -NMR spectrum in CDCl_3 , 376.5 MHz, at 298 K, using NaCF_3SO_3 as internal standard (-78.8 ppm); d) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)



c)



d)

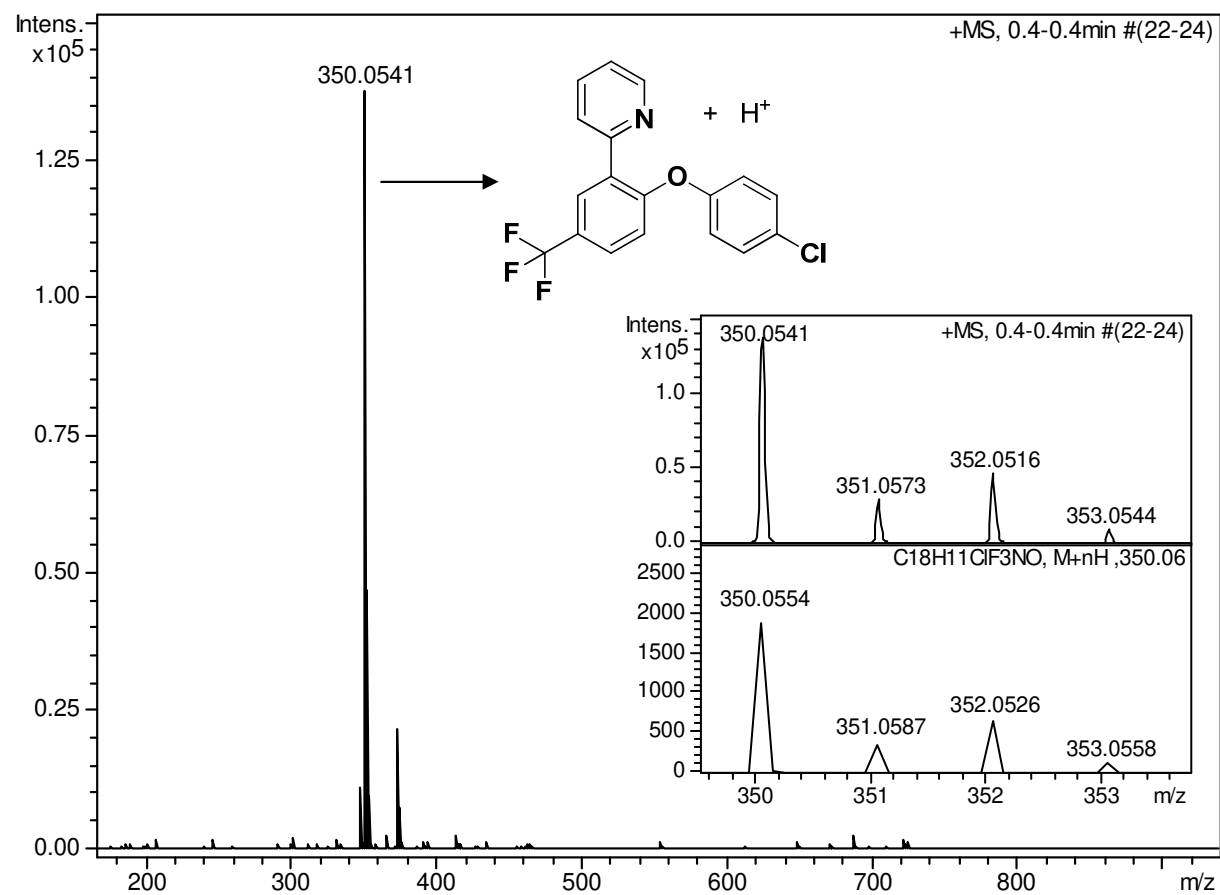
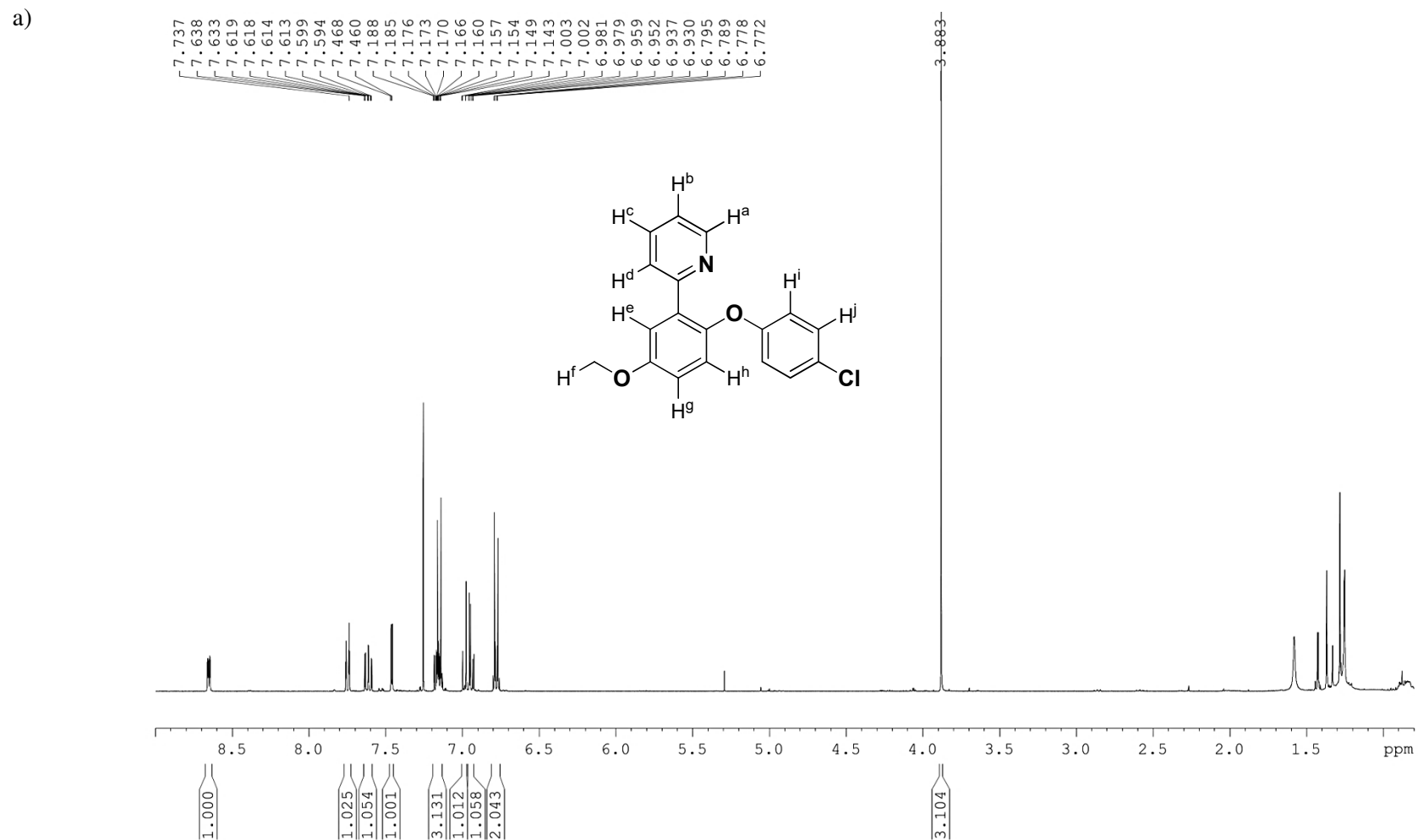
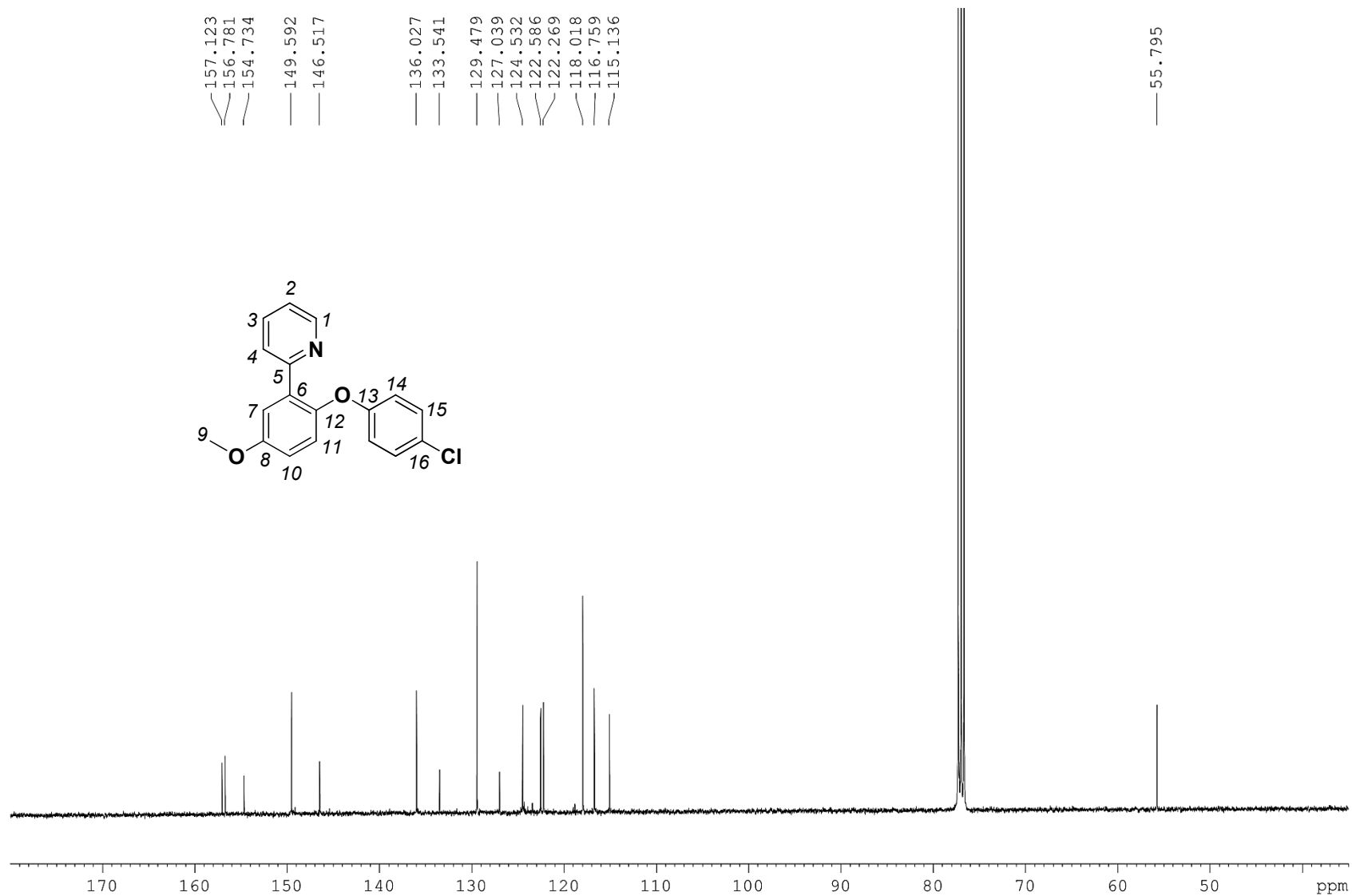


Figure S26. a) ^1H -NMR spectrum of compound **4db** in CDCl_3 , 400 MHz, at 298 K; b) ^{13}C -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)



c)

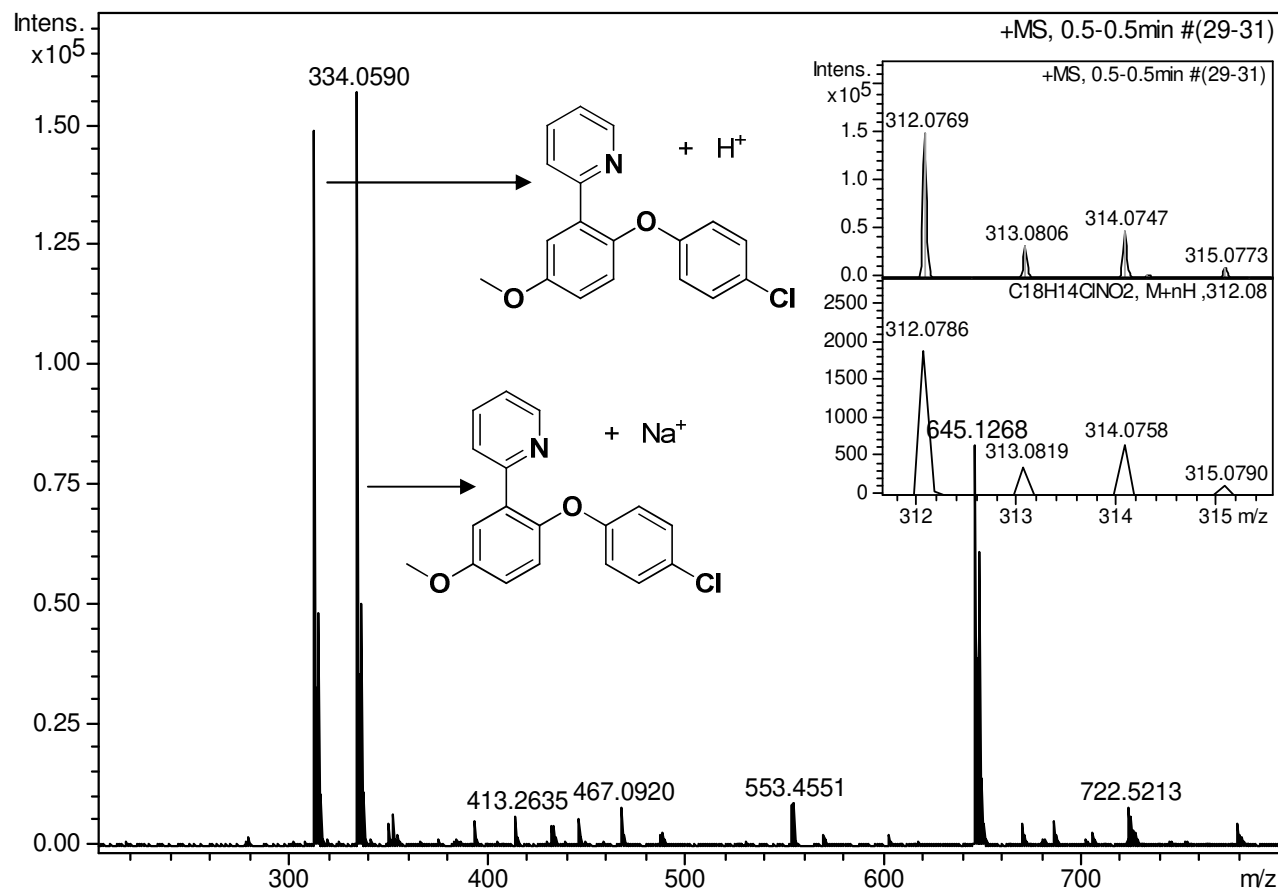
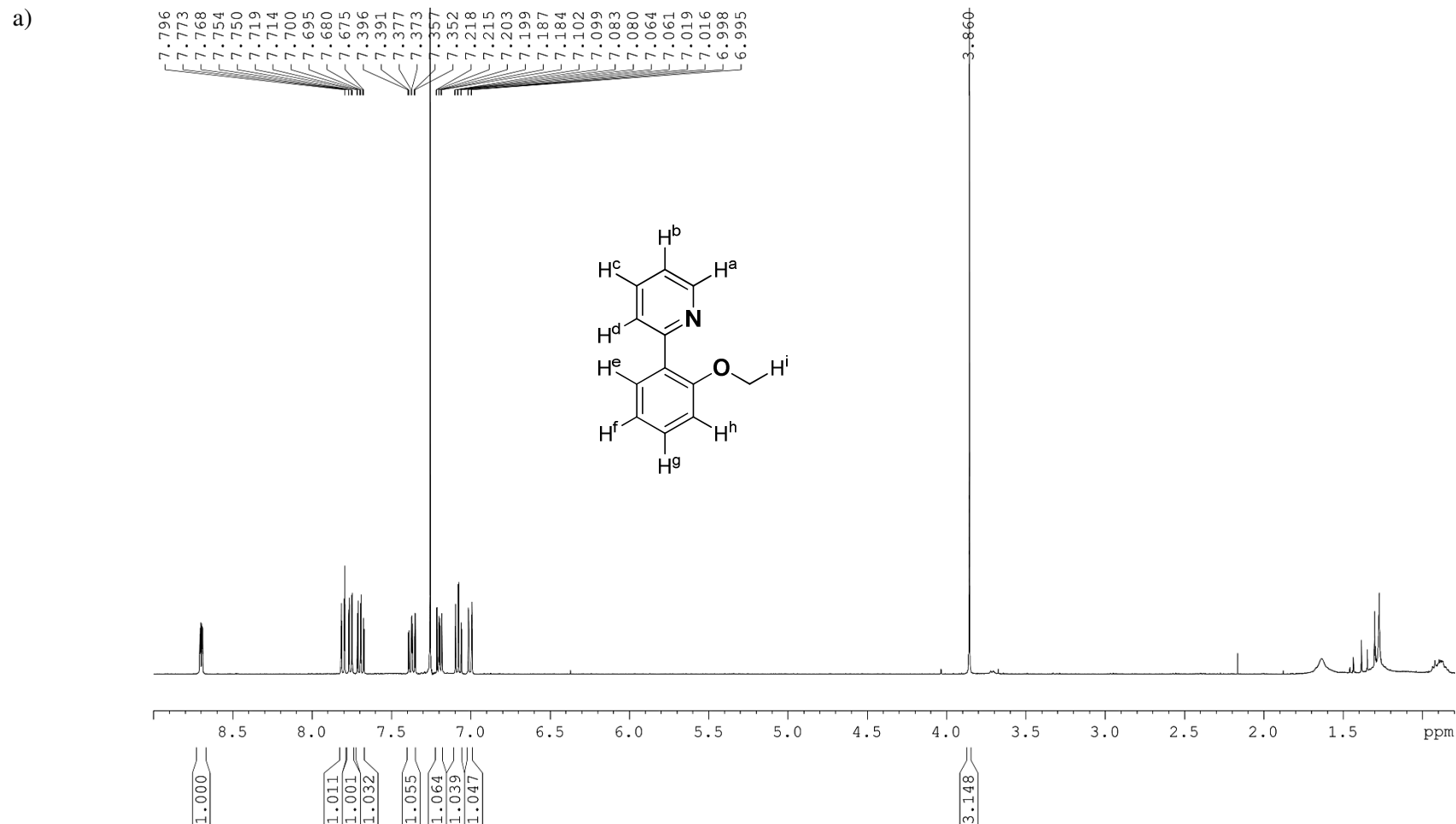


Figure S27. a) ^1H -NMR spectrum of compound **5d** in CDCl_3 , 400 MHz, at 298 K; b) HRMS (ESI-MS) spectrum (m/z). Observed HRMS with the theoretical isotope prediction (inset).



b)

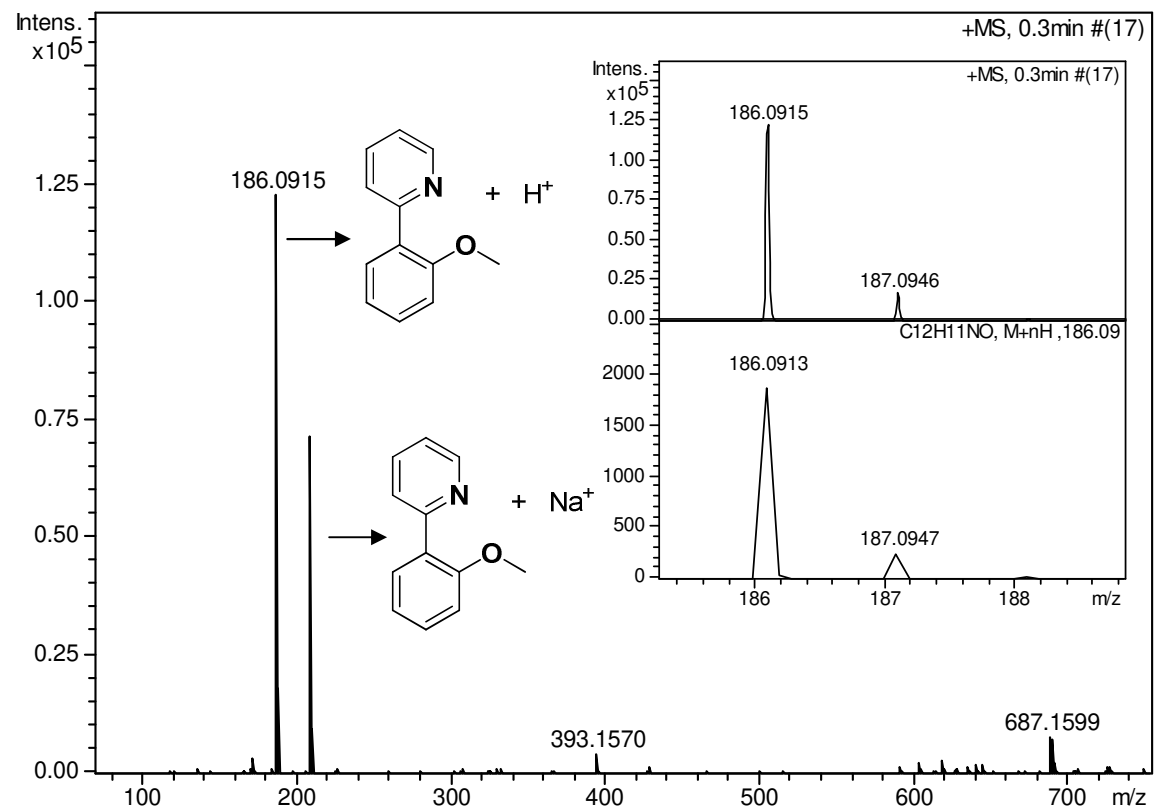


Figure S28. HRMS (25°C, CH₃CN) of **L₁-Br** (1 eq) coordination to [Au(NCCH₃)IPr]SbF₆ (1 eq)

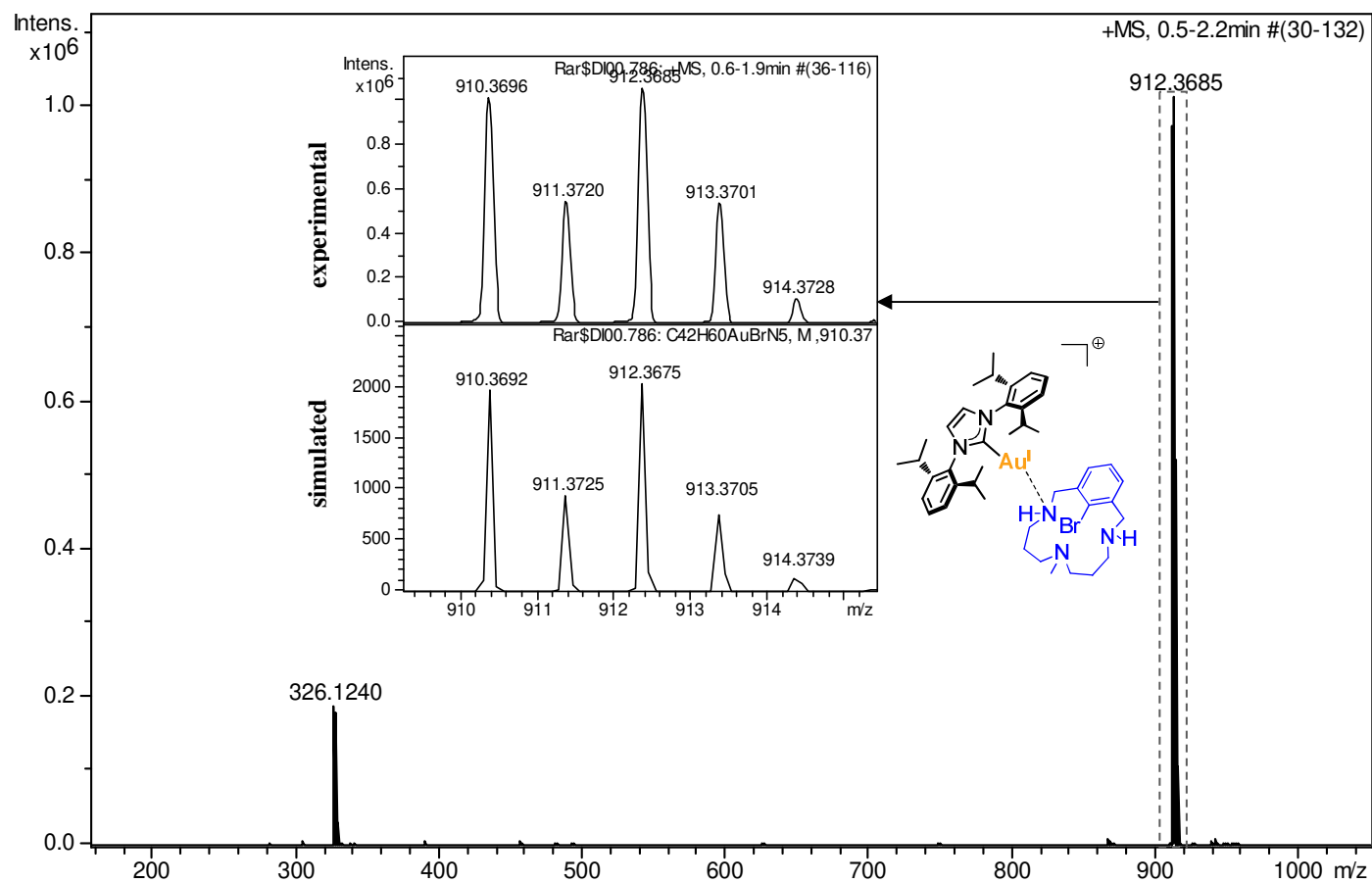
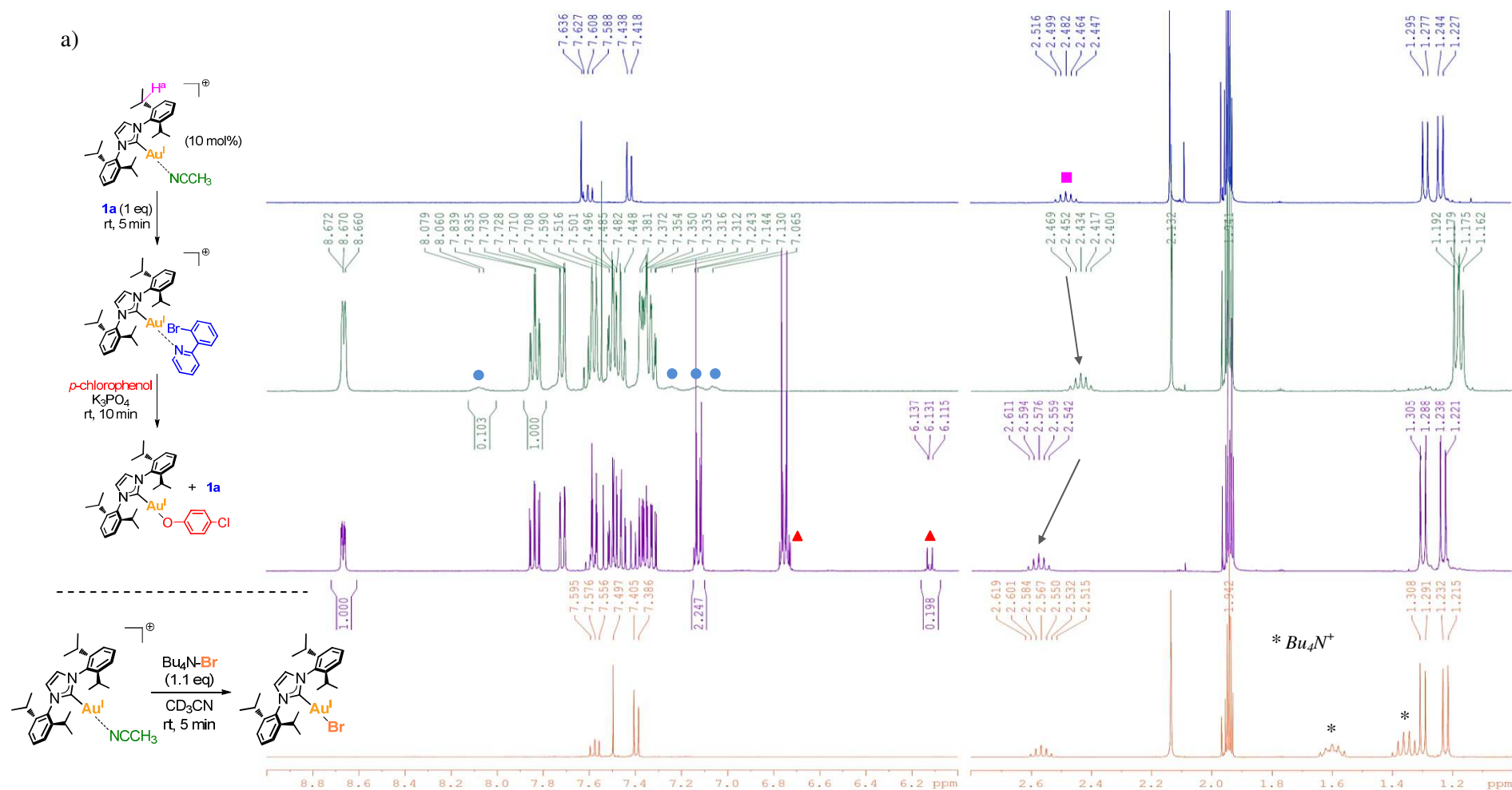


Figure S29. a) ^1H -NMR sequence (CD_3CN) of **2d** coordination (●) to 10 mol% $[\text{Au}(\text{NCCH}_3)\text{IPr}]\text{SbF}_6$, and subsequent formation of $[\text{Au}(\text{OPh})\text{IPr}]$ (▲) upon addition of *p*-chlorophenol (1.1 eq) and K_3PO_4 (1.1 eq) at rt. Isopropyl proton H^a (■) reveals the formation of different Au(I) species. Last spectrum corresponds to independently prepared $[\text{AuBr}(\text{IPr})]$. b) HRMS (25°C , CH_3CN) of **2d** (1 eq) coordination to 10 mol% $[\text{Au}(\text{NCCH}_3)\text{IPr}]\text{SbF}_6$.



b)

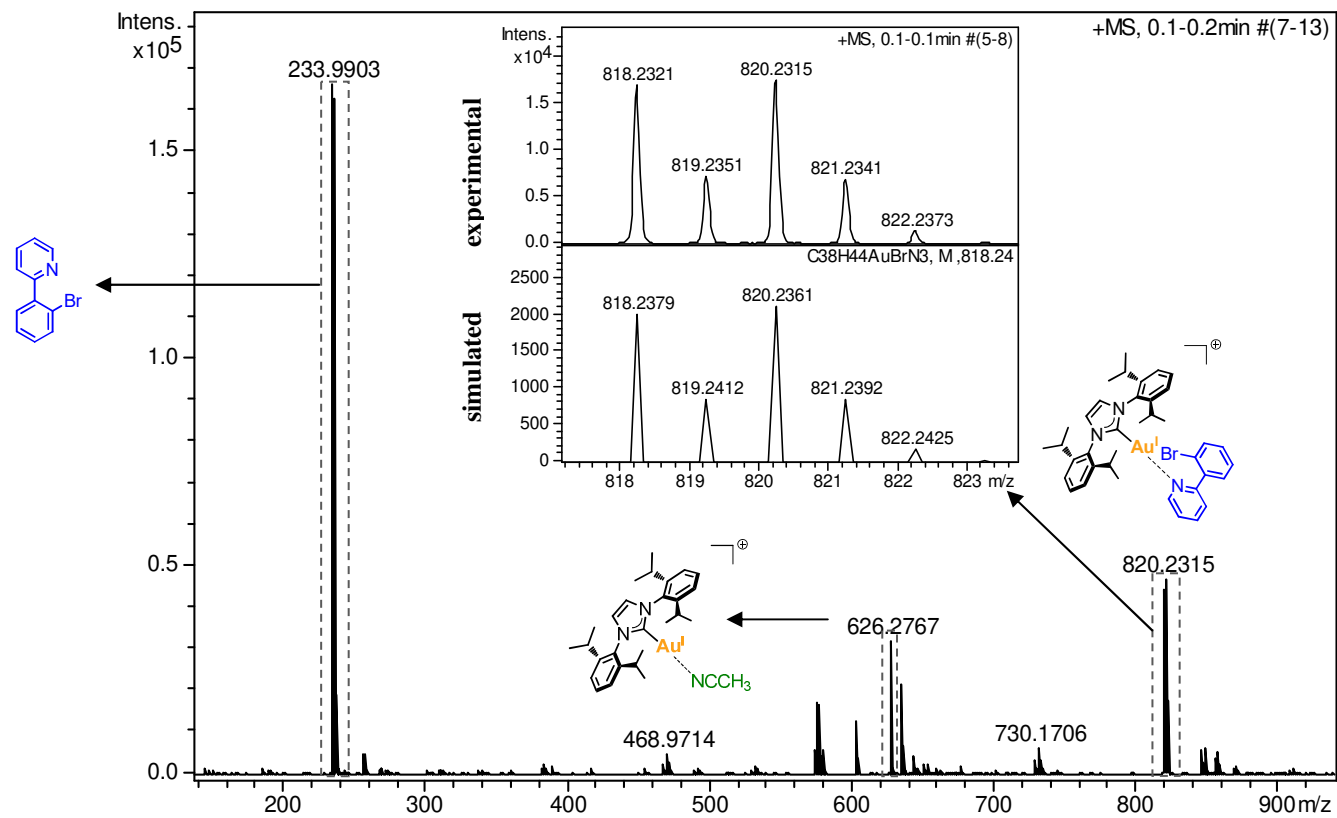
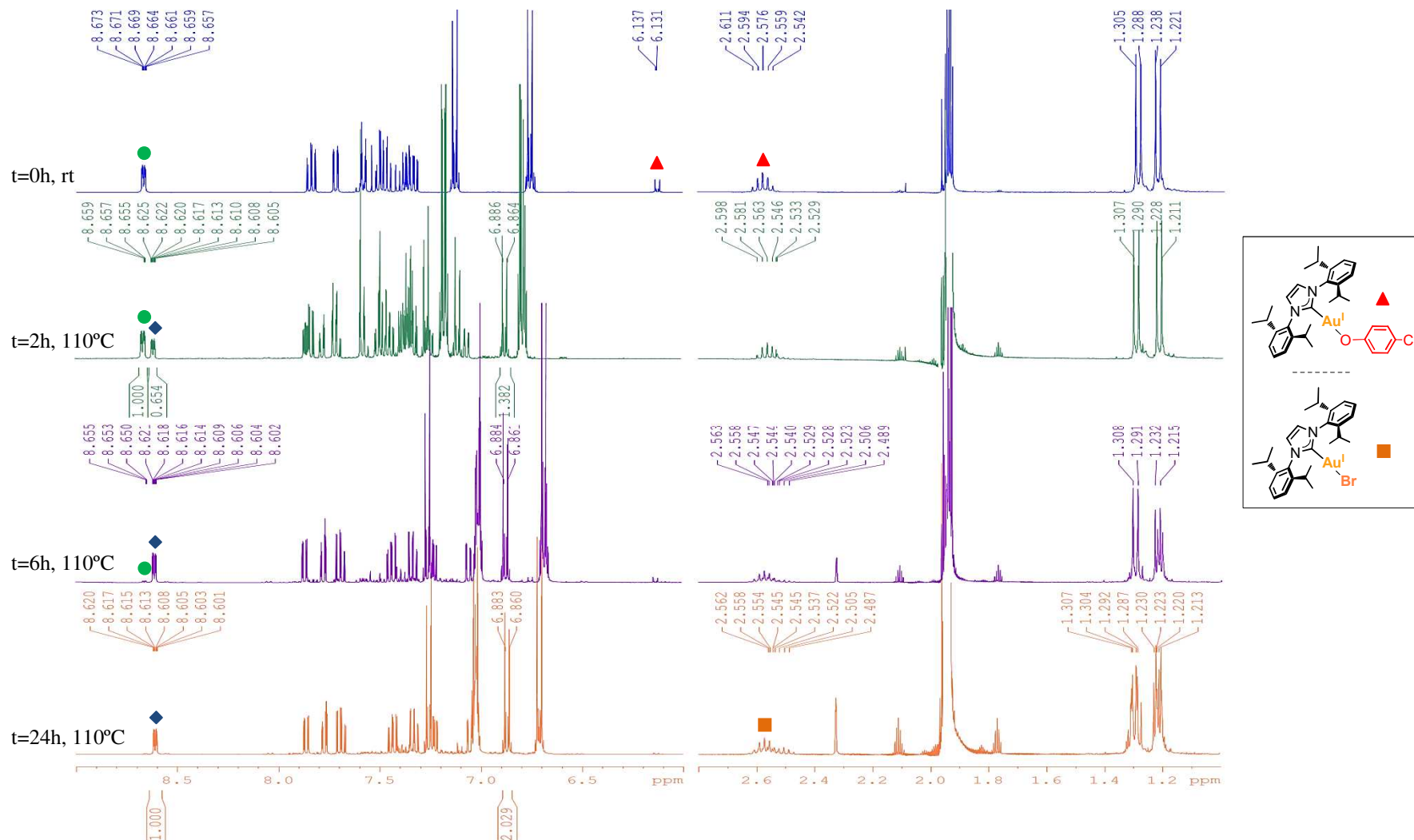


Figure S30. a) ^1H -NMR spectra (CD_3CN) acquired during the catalytic course of the $[\text{Au}(\text{CNMe})\text{IPr}]\text{SbF}_6$ catalysed (10 mol%) coupling of *p*-chlorophenol with substrate **2d** (●) at room temperature, to form **3d** (◆) at 110°C . b) HRMS (ESI, CH_3CN) of the final reaction crude (t=24h).



b)

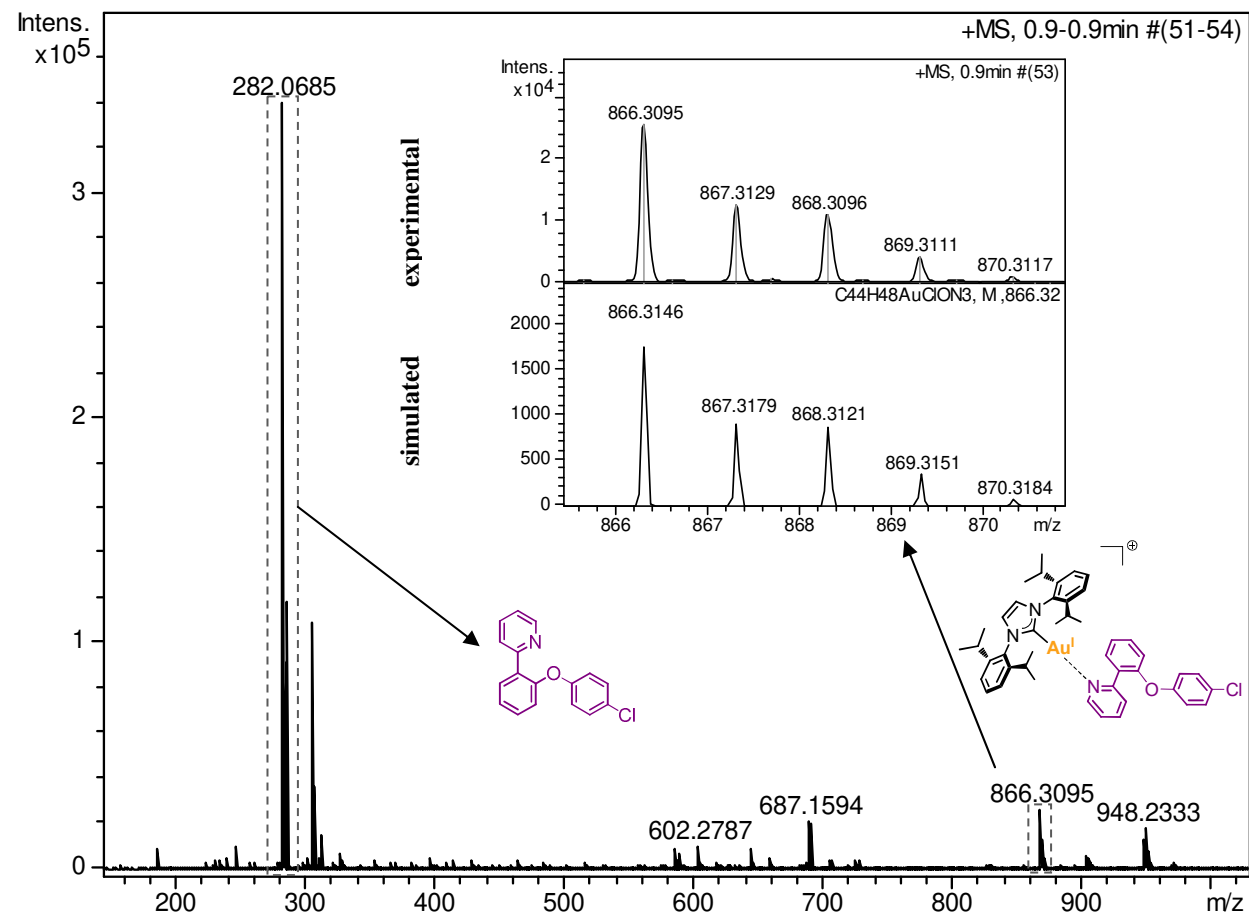


Figure S31. a) HRMS (CryoSpray®, CH₃CN) of a mixture of [AuBr(IPr)] and substrate **2d** at 25°C and b) HRMS at standard ionization temp. (ca. 150°C). Peaks of IPr⁺ correspond to in situ degradation of [Au(Br)IPr], see Figure S10b.

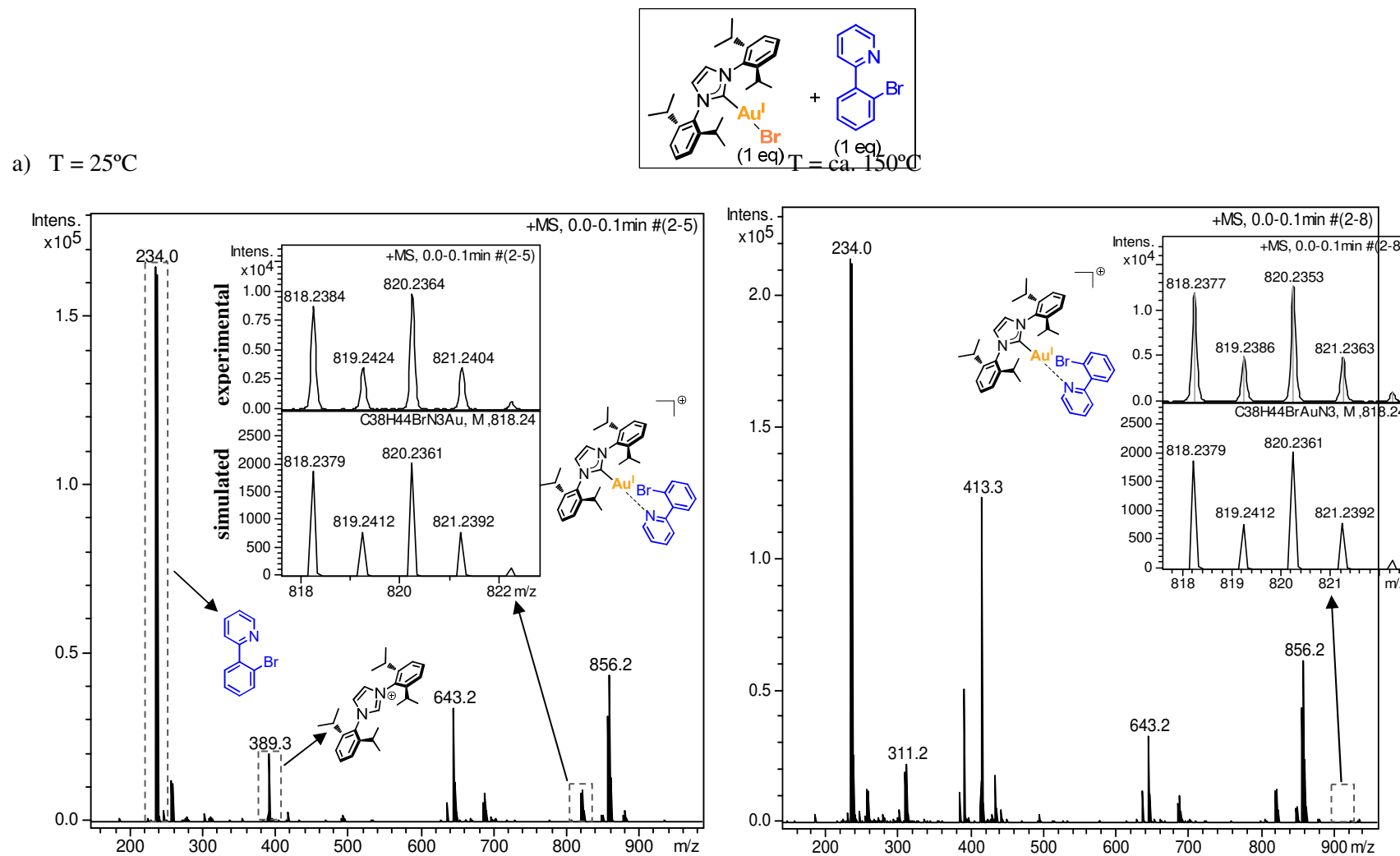


Figure S32.HRMS (ESI, CH₃CN) of a mixture of [Au(OPh)IPr] and substrate **2d** at room temperature.

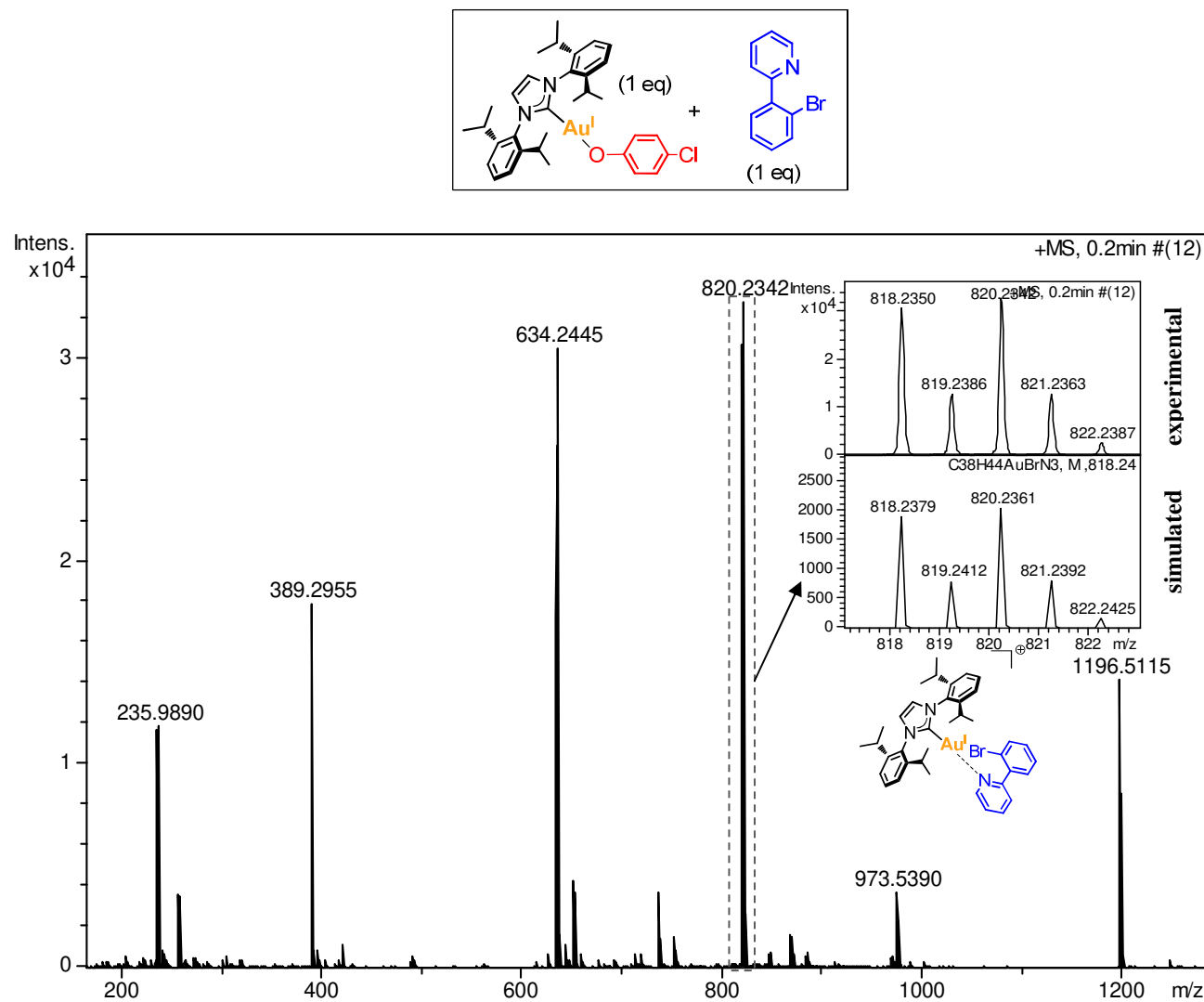


Figure S33. ^1H -NMR comparison of different NHC species, together with a catalytic reaction outcome (entry 9 of Table 6.1, section 6.1.1).

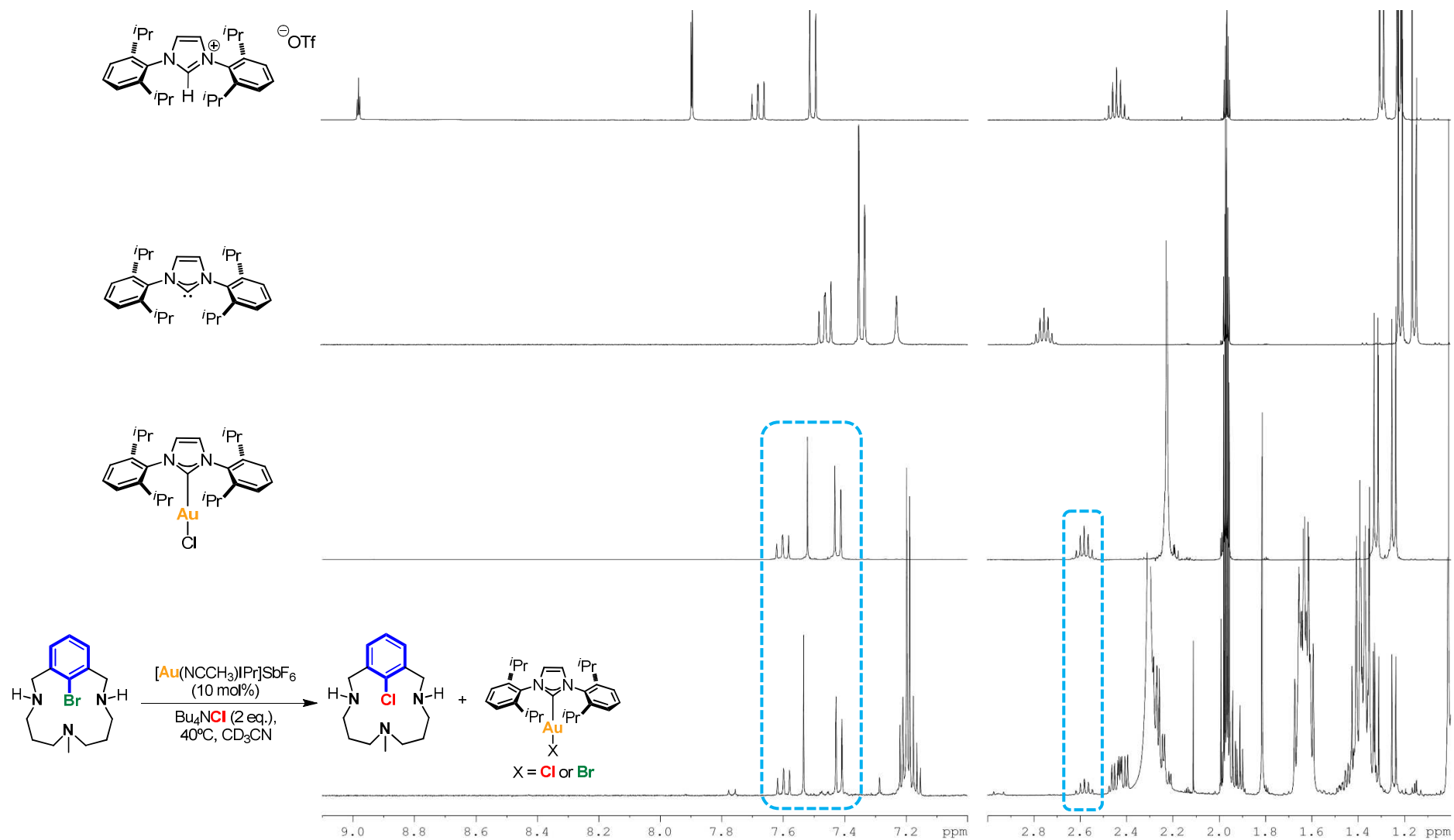
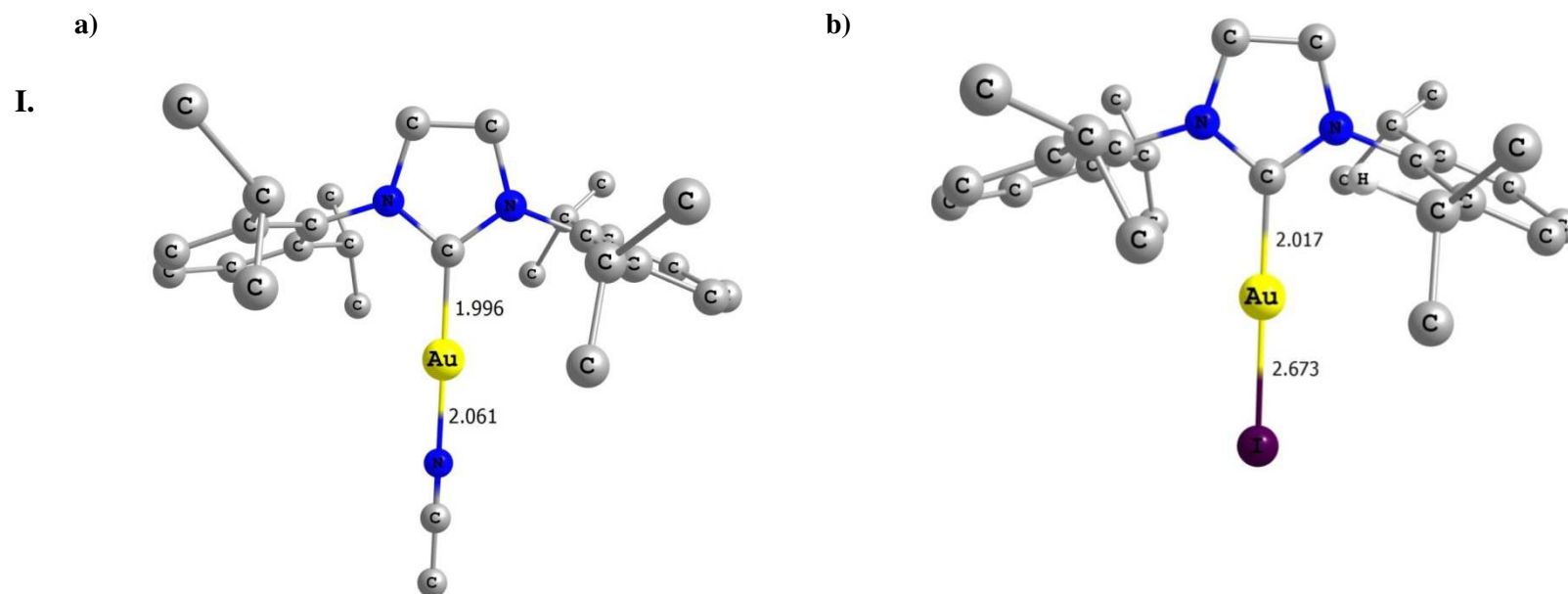
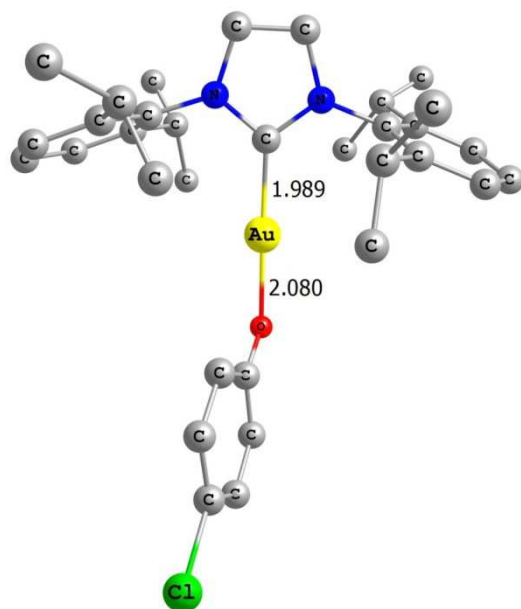


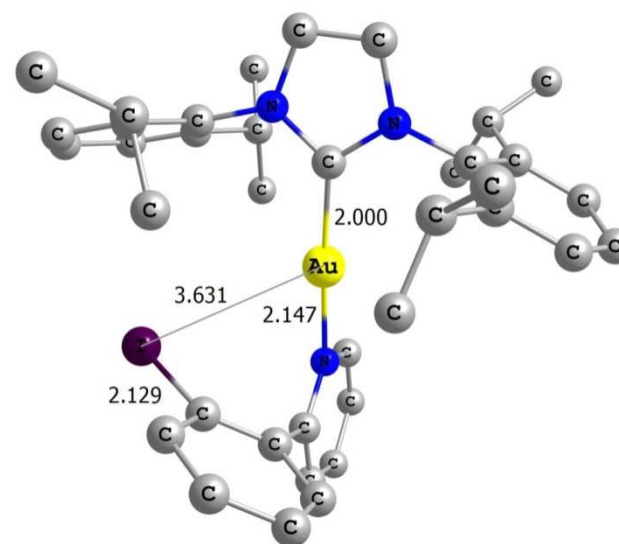
Figure S34. DFT optimized gold(I) species detected experimentally (see Scheme 5 in the main text). a) $[\text{Au}(\text{NCMe})\text{IPr}]^+$; b) $[\text{Au}(\text{I})\text{IPr}]$; c) $[\text{Au}(\text{OPh-}p\text{Cl})\text{IPr}]$; d) $[\text{Au}(\mathbf{3d})\text{IPr}]^+$; e) $[\text{Au}(\mathbf{3d})\text{IPr}](\text{OPh-}p\text{Cl})$; f) thermodynamics of the exchange of the coordinated iodide in $[\text{Au}(\text{I})\text{IPr}]$ by $\mathbf{3d}$ (at 25°C); g) thermodynamics of the exchange of the coordinated $p\text{Cl-PhO}^-$ in $[\text{Au}(\text{OPh-}p\text{Cl})\text{IPr}]$ by $\mathbf{3d}$ (at 25°C). Relative Gibbs energy values in acetonitrile solution are given in $\text{kcal}\cdot\text{mol}^{-1}$ and selected bond distances in Å (H atoms are omitted for clarity).



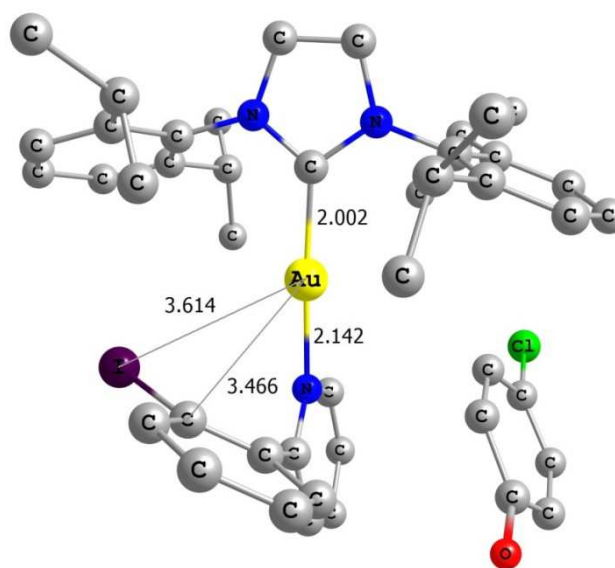
c)



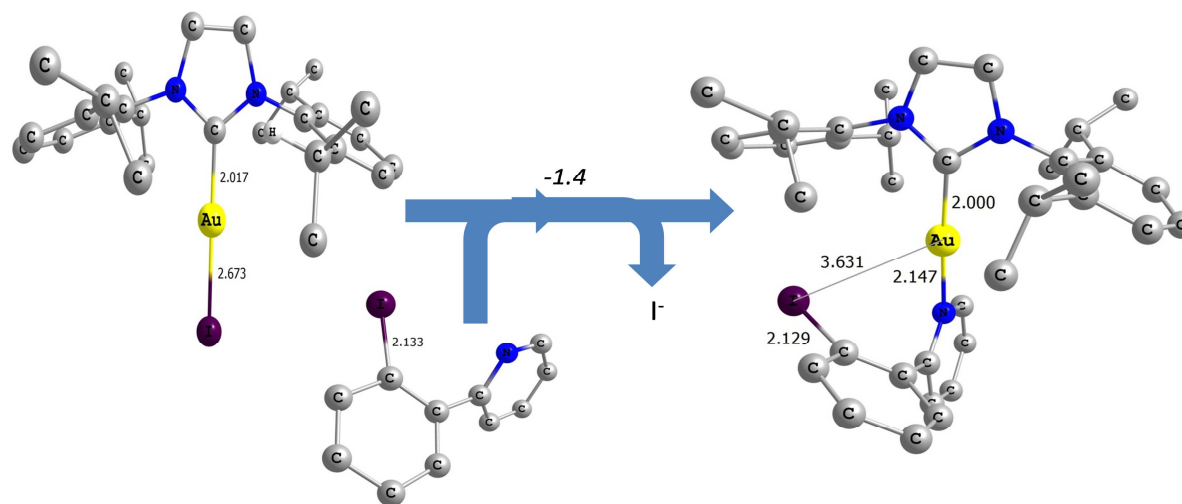
d)



e)



f)



g)

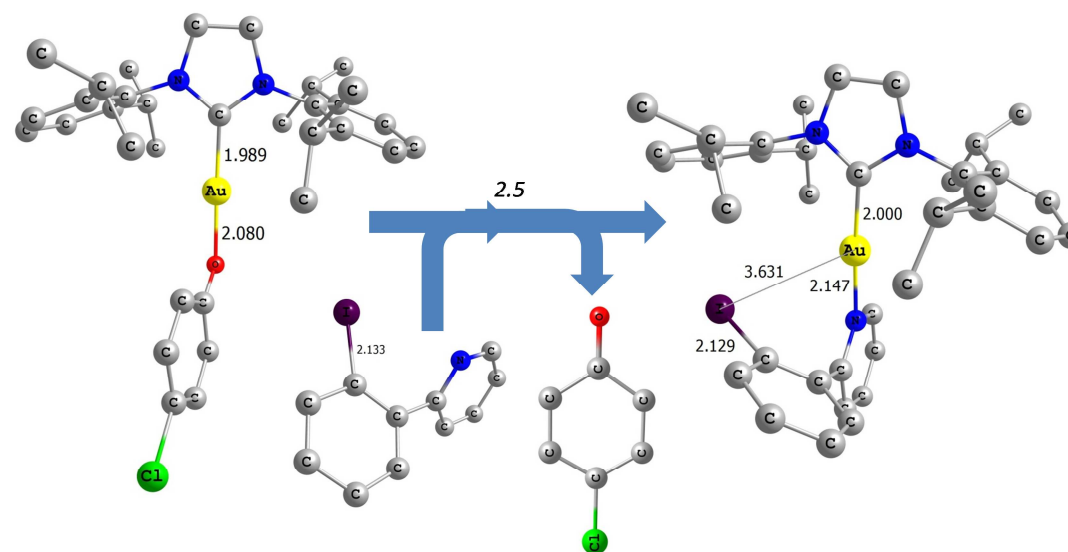
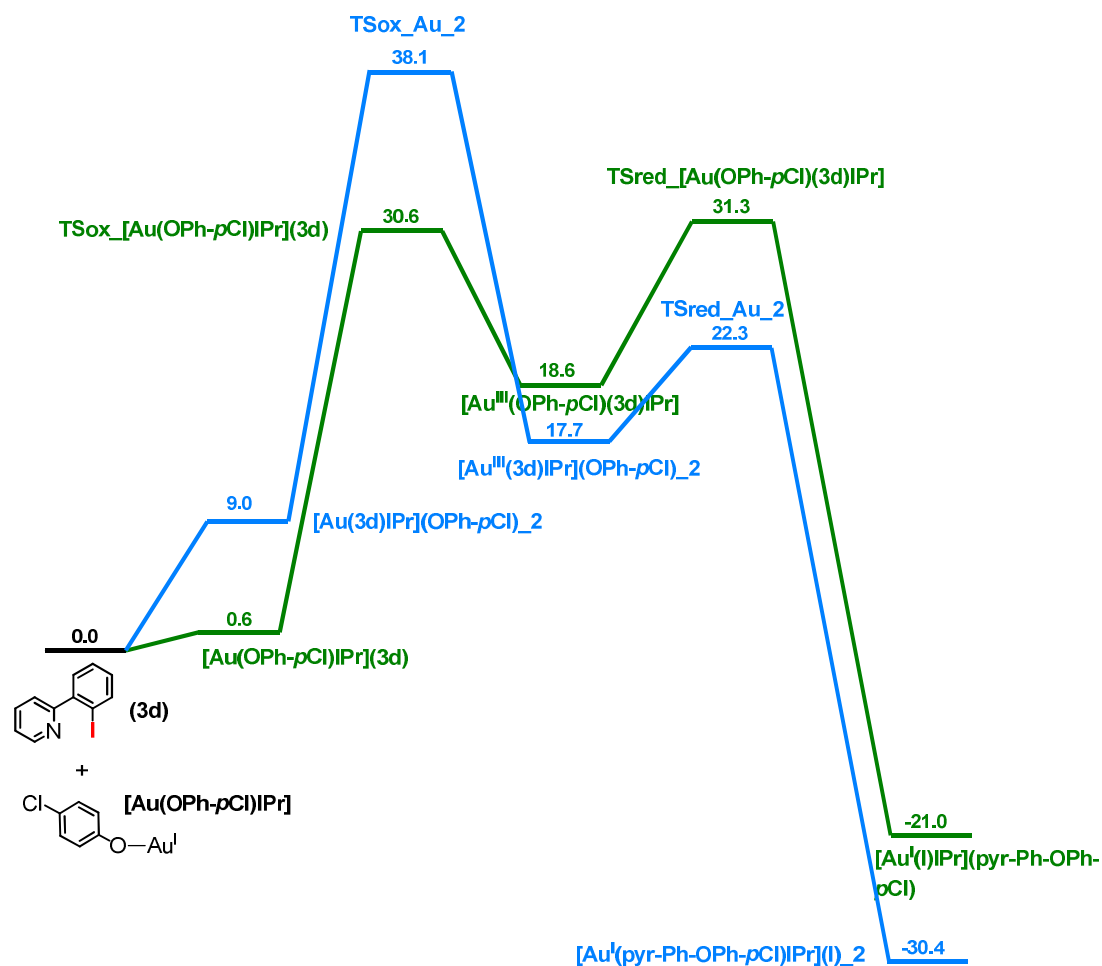
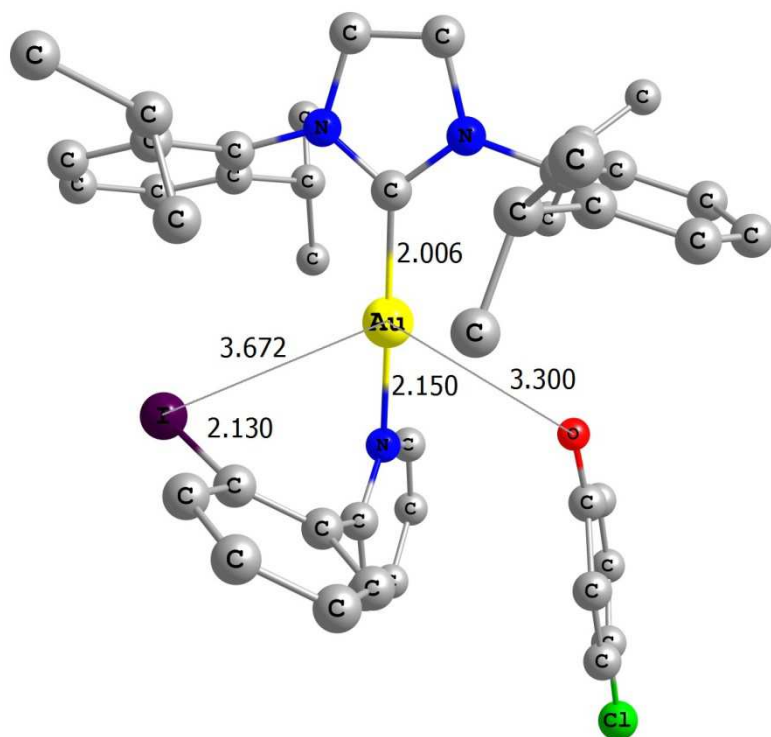
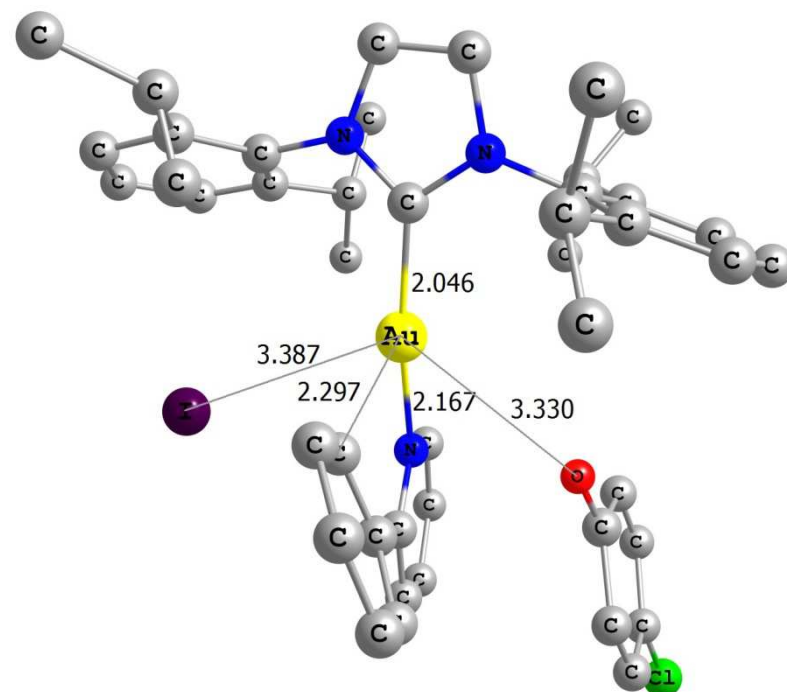


Figure S35. DFT computed free energy reaction profile for the oxidative addition and reductive elimination steps of the $[\text{Au}(\mathbf{3d})\text{IPr}](\text{OPh-}p\text{Cl})_2$ isomer (in **blue**), where the pyridine moiety is coordinated in *trans* to the IPr carbene ligand. The pathway depicted in Scheme 6 (main text) is also overlapped for comparison (in **green**). Relative Gibbs energy values are given in $\text{kcal}\cdot\text{mol}^{-1}$.

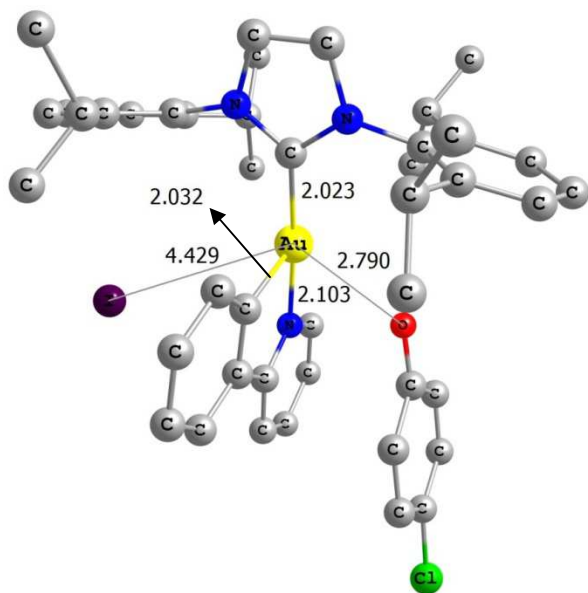




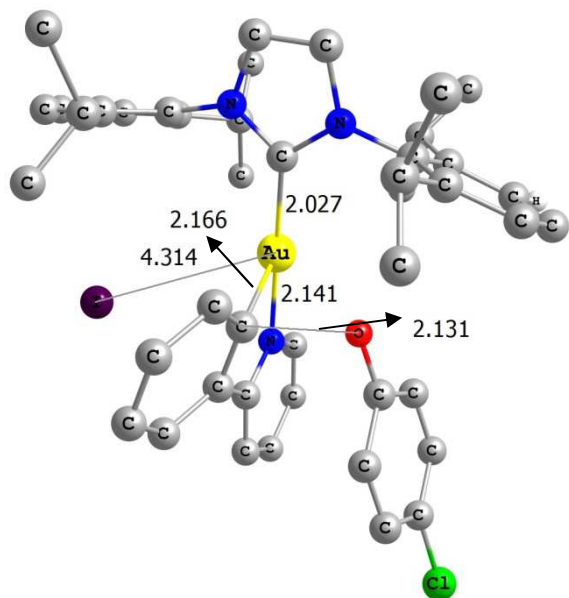
[Au(3d)IPr](OPh-*p*Cl)_2 (9.0 kcal·mol⁻¹)



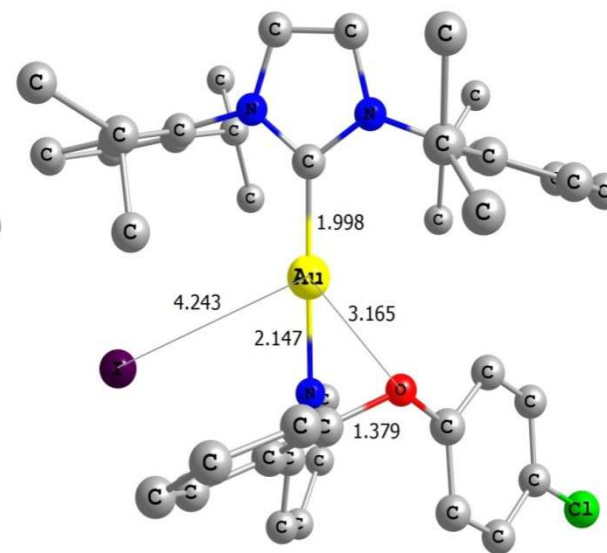
TSox_Au_2 (38.1 kcal·mol⁻¹)



$[\text{Au}^{\text{III}}(3\text{d})\text{IPr}](\text{OPh-}p\text{Cl})_2$ (17.7 kcal·mol⁻¹)



TSred_Au_2 (22.3 kcal·mol⁻¹)



$[\text{Au}^{\text{I}}(\text{pyr-Ph-OPh-}p\text{Cl})\text{IPr}](\text{I})_2$ (30.4 kcal·mol⁻¹)

Supplementary Information Chapter IV

Au(III)-Aryl Intermediates in Oxidant-Free C-N and C-O Cross-Coupling Catalysis

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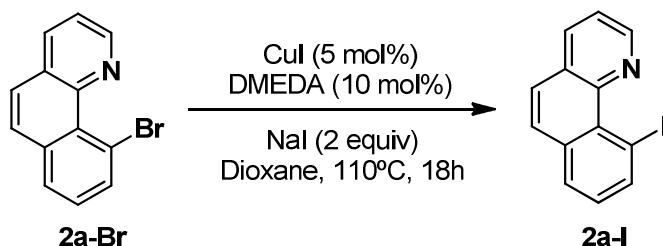
1. Materials and methods

1.1. Materials and Instrumentation

Reagents and solvents used were commercially available reagent quality unless indicated otherwise. Solvents were purchased from SDS-Carlo Erba and Scharlab and were purified and dried by passing through an activated alumina purification system (MBraun SPS-800). Preparation and handling of air-sensitive materials was carried out in a N₂ drybox (JACOMEX) with O₂ and H₂O concentrations < 1.0 ppm. NMR data were collected on a BRUKER 400 or 300 AVANCE spectrometer in the corresponding deuterated solvent, and ¹H and ¹³C{¹H} experiments were recorded under routine conditions. ESI-MS experiments were collected and analyzed on a Bruker Daltonics Esquire 6000 spectrometer with acetonitrile or acetonitrile/water (80:20) as solvent. High resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF-Q II TM instrument using ESI or Cryospray ionization sources with acetonitrile as solvent by Dr. Laura Gómez of Serveis Tècnics of the University of Girona.

1.2. Synthesis of substrates and catalysts

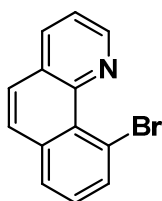
The cationic NHC-Au(I) catalyst [Au(NCMe)IPr]SbF₆ was prepared following a literature procedure.^[1] 2-(2-bromophenyl)-pyridine (**1a-Br**) was synthesized as previously described by Pd-catalyzed cross-coupling of 2-bromopyridine and 2-bromophenylboronic acid.^[2] Derivative 2-(2-iodophenyl)-pyridine (**1a-I**) was prepared following a procedure found in the literature.^[3] 10-Bromobenzo[*h*]quinolone (**2a-Br**) was prepared according to the literature procedure starting from benzo[*h*]quinolone.^[4] Derivative 10-Iodobenzo[*h*]quinolone (**2d**) was synthesized from **2a-Br** following Buchwald's copper-catalyzed iodination of aryl bromides.^[2]



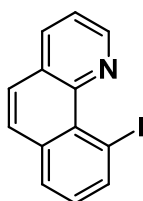
A vial was charged with **2a-Br** (516 mg, 2 mmol) and NaI (600 mg, 4 mmol) and entered in an inert-atmosphere glovebox. There CuI (19.0 mg, 0.1 mmol, 5 mol%), *N,N'*-Dimethylethylenediamine (22 μL, 0.2 mmol) and dry dioxane (1 mL) were added. The vial was

-
- (1) P. de Frémont, N. Marion, S. P. Nolan, *J. Organomet. Chem.*, **2009**, 694, 551.
(2) X. Mu, H. Zhang, P. Chen, G. Liu, *Chem. Sci.*, **2014**, 5, 275.
(3) A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.*, **2002**, 124, 14844.
(4) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.*, **2004**, 126, 2300.

capped and the reaction mixture was stirred at 110 °C for 18h. The resulting mixture was purified by column chromatography on silica using a solvent mixture of hexane-ethyl acetate 9:1. The desired product was obtained as a white solid (407 mg, 67% isolated yield).

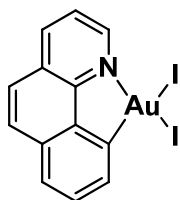


2a-Br: Spectral data are in accordance with those reported in the literature.¹**H-NMR** (CDCl₃, 400 MHz) δ , ppm: 9.11 (dd, J = 4.4, 2.0 Hz, 1H, H^a), 8.18 (dd, J = 8.0, 2.0 Hz, 1H, H^c), 8.10 (dd, J = 7.6, 1.2 Hz, 1H, H^b), 7.88 (dd, J = 8.0, 0.8 Hz, 1H, H^f), 7.75 (dd, J = 8.8 Hz, 2H, H^d+H^e), 7.57 (dd, J = 8.0, 4.4 Hz, 1H, H^b), 7.47 (t, J = 8.0 Hz, 1H, H^g); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₃H₈BrN [M + H⁺] 257.9913, found: 257.9910.

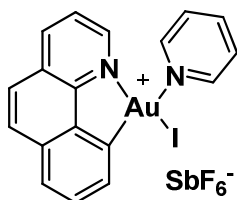


2a-I: ¹**H-NMR** (CDCl₃, 400 MHz) δ , ppm: 9.11 (dd, J = 4.4, 2.0 Hz, 1H, H^a), 8.55 (dd, J = 7.6, 1.2 Hz, 1H, H^b), 8.17 (dd, J = 8.0, 2.0 Hz, 1H, H^c), 7.92 (dd, J = 8.0, 1.2 Hz, 1H, H^f), 7.74 (dd, J = 8.8 Hz, 2H, H^d+H^e), 7.58 (dd, J = 8.0, 4.4 Hz, 1H, H^b), 7.28 (t, J = 8.0 Hz, 1H, H^g); ¹³**C{1H}-NMR** (CDCl₃, 100 MHz) δ , ppm: 145.85 (C1), 144.52 (C13), 143.41 (C10), 135.58 (C3), 135.20 (C7), 129.22 (C8), 129.14 (C12), 128.45 (C9), 128.15 (C6), 126.80 (C4), 126.18 (C5), 122.17 (C2), 88.85 (C11); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₃H₈IN [M + H⁺] 305.9774, found: 305.9771.

1.3. Synthesis of the Gold(III) complexes 3a and 3b



To a mixture of gold iodide (65.2 mg, 0.2 mmol) and 10-Iodobenzo[*h*]quinolone (**2a-I**) was added toluene (1 mL) at room temperature and stirred at 60°C for 18h. The resulting suspension was then dried under vacuum and washed with cold DCM to yield **3a** as a red powder (120.8 mg, 96%). ¹**H-NMR** (CDCl₃, 400 MHz, 323K) δ , ppm: 10.36 (dd, J = 5.6, 1.2 Hz, 1H, H^a), 8.93 (dd, J = 8.0, 0.8 Hz, 1H, H^b), 8.55 (dd, J = 8.0, 0.4 Hz, 1H, H^c), 7.88 (d, J = 8.8 Hz, 1H, H^e), 7.87 (d, J = 8.0 Hz, 1H, H^f), 7.79 (dd, J = 8.0, 5.6 Hz, 1H, H^b), 7.71 (d, J = 8.7 Hz, 1H, H^d), 7.59 (t, J = 8.0 Hz, 1H, H^g); ¹³**C{1H}-NMR** (CDCl₃, 100 MHz, 323K) δ , ppm: 154.81 (C13), 153.63 (C11), 150.00 (C1), 140.64 (C12), 140.26 (C3), 135.88 (C7), 134.52 (C10), 131.44 (C9), 130.38 (C6), 129.22 (C4), 126.33 (C8), 124.06 (C5), 122.60 (C2).



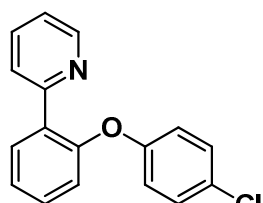
3b: Complex **3a** (25.2 mg, 0.04 mmol) and AgSbF₆ (13.9 mg, 0.04 mmol) were suspended in acetonitrile (1 mL) and pyridine (3.5 mg, 0.044 mmol) was added at room temperature. After stirring for <1 min at room temperature, the resulting orange mixture was filtered through Celite®, dried under vacuum and washed with hexanes (3 x 2 mL) to give the desired complex as a yellow solid (29.7 mg, 91%). ¹**H-NMR** (CD₃CN, 400 MHz, 248K) δ , ppm: 8.89 (m, 3H, H^b+Hⁱ), 8.82 (m, 1H, H^c), 8.33 (tt, J = 8.0, 1.6 Hz, 1H, H^k), 7.98 (m, 4H, H^f+H^e+H^j), 7.91 (d, J = 8.8 Hz, 1H, H^d), 7.75 (m, 2H, H^a+H^b), 7.49 (t, J = 8.0 Hz, 1H, H^g); ¹³**C{1H}-**

NMR(CD₃CN, 100 MHz, 248K) δ , ppm: 152.23 (C13), 150.55 (C14), 145.66 (C1), 142.74 (C3), 142.62 (C16), 139.50 (C11), 139.33 (C12), 138.56 (C10), 136.21 (C7), 131.88 (C9), 130.32 (C6), 129.32 (C4), 128.80 (C15), 127.74 (C8), 125.29 (C5), 123.59 (C2); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₈H₁₃AuIN₂ [M⁺] 580.9783, found: 580.9782.

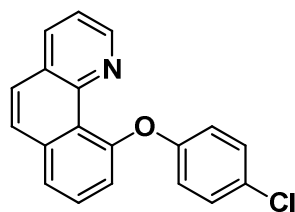
1.4. General procedure for the coupling of *p*-chlorophenolate and sodium alkoxides to substrates **1a-Br** and **2a-Br**

Substrates **1a-Br** or **2a-Br** (0.02 mmol), [Au(NCMe)IPr]SbF₆ (2 μ mol, 10 mol%) and *p*-chlorophenolate or sodium alkoxide (2 equivalents, 0.04 mmol) were weighed using a precision balance (accuracy: +/-0.01 mg) into a glass vial, and dissolved in CD₃CN for *p*-chlorophenolate or the protic solvent of choice for the other alkoxides. The vial was sealed and the mixture stirred at 110°C. After the required reaction time, the crude was allowed to reach room temperature and, if needed, solvent evaporated under vacuum. The residue was re-dissolved in CDCl₃ and a standard solution of 1,3,5-trimethoxybenzene (20mM, 40 μ L) was added. The products in the crude reaction mixture were identified by ¹H-NMR and ESI-HRMS.

Product isolation: The same synthetic protocol was followed, in this case employing 0.2 mmol substrate **1a-Br** or **2a-Br**, 0.02 mmol [Au(NCMe)IPr]SbF₆ and 0.4 mmol alkoxide in 0.8 mL of solvent. After solvent evaporation the residue was subjected to column chromatography on silica gel (eluent: hexanes/EtOAc).

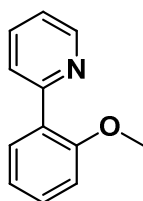


1aa: Column chromatography on silica gel (hexane-ethyl acetate 7:3) provided a colorless oil (41.0 mg, 73% isolated yield). Spectroscopic data are consistent with literature reports.^[41] **¹H-NMR** (CDCl₃, 400 MHz) δ , ppm: 8.67 (dq, J = 4.8, 2.0, 0.8 Hz, 1H, H^a), 7.90 (dd, J = 7.6, 1.6 Hz, 1H, H^e), 7.77 (dt, J = 8.0, 1.2 Hz, 1H, H^d), 7.65 (ddd, J = 8.0, 7.6, 2.0 Hz, 1H, H^c), 7.38 (ddd, J = 7.6, 7.4, 1.6 Hz, 1H, H^e), 7.29 (td, J = 8., 7.6, 1.2 Hz, 1H, H^f), 7.20 (m, 2H, H^b+Hⁱ), 7.01 (dd, J = 7.4, 1.2 Hz, 1H, H^h), 6.86 (d, J = 8.8 Hz, 2H, H^j); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₇H₁₂NCIO [M + H⁺] 282.0680, found: 282.0682.

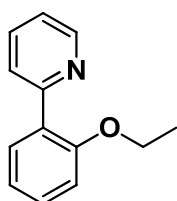


2aa: Column chromatography on silica gel (hexane-ethyl acetate 4:1) provided a pale yellow solid (47.6 mg, 78% isolated yield). **¹H-NMR** (CDCl₃, 400 MHz) δ , ppm: 8.80 (dd, J = 4.4, 2.0 Hz, 1H, H^a), 8.11 (dd, J = 8.0, 2.0 Hz, 1H, H^e), 7.84 (d, J = 8.8 Hz, 1H, H^c), 7.83 (dd, J = 8.0, 1.2 Hz, 1H, H^h), 7.70 (d, J = 8.8 Hz, 1H, H^d), 7.69 (t, J = 8.0 Hz, 1H, H^e), 7.43 (dd, J = 8.0, 1.6 Hz, 1H, H^f), 7.41 (dd, J = 8.0, 4.4 Hz, 1H, H^b), 7.15 (d, J = 9.2, 1.6 Hz, 2H, H^j), 6.82 (d, J = 9.2 Hz, 2H, Hⁱ); **¹³C{¹H}-NMR** (CDCl₃, 100 MHz) δ , ppm: 158.49 (C14), 153.21 (C11), 148.84 (C1), 145.79 (C13), 136.60 (C7), 135.38 (C3), 129.09 (C16), 128.51

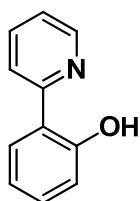
(C5), 127.94 (C6), 127.12 (C4), 126.67 (C9), 126.03 (C17), 125.80 (C10), 124.40 (C12), 122.31 (C8), 121.43 (C2), 117.65 (C15); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{19}\text{H}_{12}\text{NOCl}$ [$\text{M} + \text{H}^+$] 306.0680, found: 306.0677.



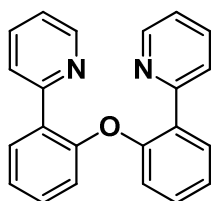
1ab: Column chromatography on silica gel (hexane-ethyl acetate 1:1) afforded a colorless oil (30.7 mg, 83% isolated yield). Spectral data match literature reports. ⁵¹**H-NMR** (CDCl_3 , 400 MHz) δ , ppm: 8.70 (ddd, $J = 4.8, 2.0, 1.2$ Hz, 1H, H^a), 7.81 (dt, $J = 8.0, 1.2$ Hz, 1H, H^d), 7.76 (dd, $J = 7.6, 2.0$ Hz, 1H, H^c), 7.70 (td, $J = 7.6, 2.0$ Hz, 1H, H^c), 7.37 (ddd, $J = 8.8, 7.6, 2.0$ Hz, 1H, H^e), 7.20 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H, H^b), 7.08 (td, $J = 7.6, 1.2$ Hz, 1H, H^f), 7.01 (dd, $J = 8.4, 1.2$ Hz, 1H, H^h), 3.86 (s, 3H, H^i); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{12}\text{H}_{11}\text{NO}$ [$\text{M} + \text{H}^+$] 186.0913, found: 186.0914.



1ac: Column chromatography on silica gel (hexane-ethyl acetate 3:1) gave a yellow oil (24.3 mg, 61% isolated yield). Spectral data match previously reported data. ⁶¹**H-NMR** (CDCl_3 , 400 MHz) δ , ppm: 8.70 (ddd, $J = 4.8, 2.0, 1.2$ Hz, 1H, H^a), 7.90 (dt, $J = 8.0, 1.2$ Hz, 1H, H^c), 7.81 (dd, $J = 7.6, 2.0$ Hz, 1H, H^c), 7.69 (td, $J = 8.0, 2.0$ Hz, 1H, H^c), 7.34 (ddd, $J = 8.4, 7.2, 1.6$ Hz, 1H, H^e), 7.19 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H, H^b), 7.07 (td, $J = 7.6, 1.2$ Hz, 1H, H^f), 7.01 (dd, $J = 8.4, 1.2$ Hz, 1H, H^h), 4.09 (q, $J = 7.2$ Hz, 2H, H^i), 1.39 (t, $J = 7.2$ Hz, 3H, H^j); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{13}\text{H}_{13}\text{NO}$ [$\text{M} + \text{H}^+$] 200.1064, found: 200.1070.



1af: Column chromatography on silica gel (hexane-ethyl acetate 9:1) afforded a yellow oil (14.4 mg, 42% isolated yield). Spectral data match literature reports. ⁷¹**H-NMR** (CDCl_3 , 400 MHz) δ , ppm: 14.36 (s, br, 1H, O-H), 8.52 (ddd, $J = 4.8, 1.6, 0.8$ Hz, 1H, H^a), 7.92 (d, $J = 8.4$ Hz, 1H, H^d), 7.84 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H, H^c), 7.81 (dd, $J = 8.0, 1.6$ Hz, 1H, H^c), 7.31 (ddd, $J = 8.4, 7.2, 1.6$ Hz, 1H, H^e), 7.25 (ddd, $J = 7.6, 4.8, 0.8$ Hz, 1H, H^b), 7.03 (dd, $J = 8.4, 1.2$ Hz, 1H, H^h), 6.91 (ddd, $J = 8.0, 7.2, 1.2$ Hz, 1H, H^f); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{11}\text{H}_9\text{NO}$ [$\text{M} + \text{H}^+$] 172.0757, found: 172.0763.



1ag: Column chromatography on silica gel (hexane-ethyl acetate 3:2) provided a white solid (13.0 mg, 20% isolated yield). ¹**H-NMR** (CDCl_3 , 400 MHz) δ , ppm: 8.67 (ddd, $J = 4.8, 2.0, 0.8$ Hz, 2H, H^a), 7.86 (dd, $J = 7.6, 2.0$ Hz, 2H, H^c), 7.72 (dt, $J = 8.0, 2.0$ Hz, 2H, H^d), 7.58 (td, $J = 7.6, 2.0$ Hz, 2H, H^c), 7.30 (ddd, $J = 8.0, 7.2, 2.0$ Hz, 2H, H^e), 7.21 (td, $J = 7.6, 1.2$ Hz, 2H, H^f), 7.17 (ddd, $J = 7.2, 4.8, 1.2$ Hz, 2H, H^b), 6.95 (dd, $J = 8.0, 1.2$ Hz, 2H, H^h); ¹³**C{1H}**-

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(6) T. Vogler, A. Studer, *Org. Lett.*, **2008**, 10, 129.

(7) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem.*, **2006**, 128, 6790.

NMR(CDCl₃, 100 MHz) δ , ppm: 155.15 (C5), 154.22 (C11), 149.52 (C1), 135.84 (C3), 131.56 (C6), 131.42 (C7), 130.03 (C9), 124.74 (C4), 123.89 (C8), 122.02 (C2), 119.05 (10); **HRMS** (**ESI**) (CH₃CN, *m/z*): calcd for C₂₂H₁₆N₂O [M + H⁺] 325.1335, found: 325.1318.

1.5. General procedure for the C-N bond formation with **1a-I** and **2d**

For the optimization of the reaction conditions with *p*-nitroaniline, a vial was charged with **1a-I** (0.02 mmol), [Au(NCMe)IPr]SbF₆ (1.8mg, 0.002 mmol), *p*-nitroaniline and base, and 0.5 mL of deuterated solvent were added. The vial was capped and the mixture stirred at 110°C for 24h. The reaction crude was then allowed to reach room temperature and a standard solution of 1,3,5-trimethoxybenzene (20mM, 40 μ L) was added. The resulting suspension was analyzed by ¹H-NMR. The presence of the final C-N coupling product **1ah** was also confirmed by ESI-MS.

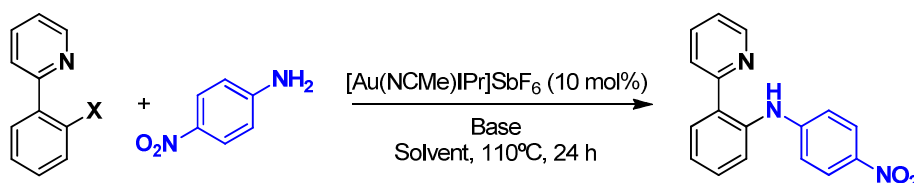


Table S1. Optimization of reaction conditions for the *p*-nitroaniline insertion reaction using 2-(2-bromophenyl)-pyridine (**1a-Br**) or 2-(2-iodophenyl)-pyridine (**1a-I**)

Entry	X	Solvent	Base	Yield 1ah (%) ^a
1	Br	CH ₃ CN	K ₃ PO ₄ (3)	0
2	Br	CH ₃ CN	CsF (3)	0
3	Br	CH ₃ CN	KOt-Bu (3)	0
4	Br	CH ₃ CN	CsF (5)	0^b
5	Br	Toluene	CsF (5)	0^b
6	Br	Dioxane	CsF (5)	4^{b,c}
7	Br	DMSO	CsF (5)	24^b
8	Br	DMSO	KOt-Bu (5)	39^b
9	I	DMSO	CsF (5)	44^b
10	I	DMSO	KOt-Bu (5)	93^b
11	I	DMSO	KOt-Bu (3)	95 (92)^d

^aYields as determined by ¹H-NMR using 1,3,5-trimethoxybenzene as an internal standard. ^b[*p*-NO₂aniline] = 100 mM;

^cAfter the required reaction time, solvent was removed under vacuum and CDCl₃ (0.6 mL) was added for ¹H-NMR analysis. ^dT = 100°C.

Following the optimized procedure described above (Table S1), different amines and amides were screened. General conditions: [**2-(2-iodophenyl)pyridine**] = 20 mM, [Au(I)] = 2 mM, [nucleophile] = 60 mM, [KOt-Bu] = 60 mM, 0.5 mL DMSO-d₆, 110°C, 24h.

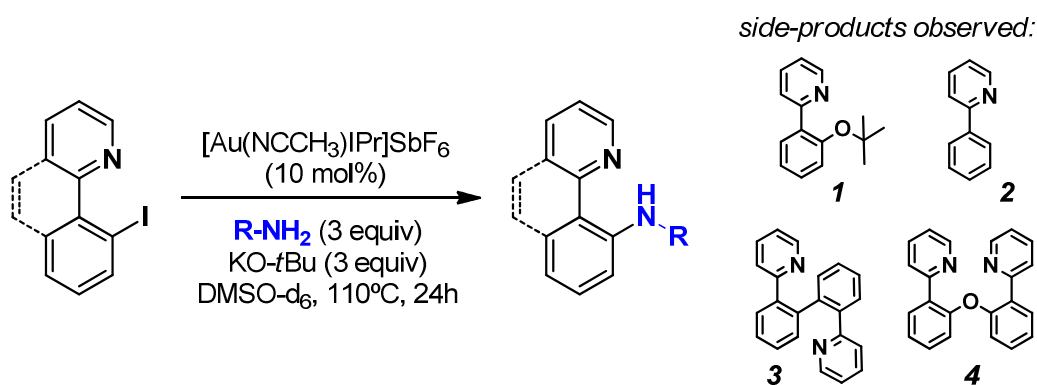
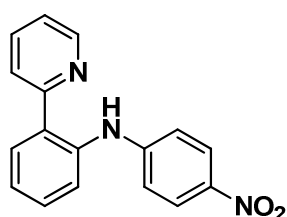


Table S2. Outcomes of the C-N cross-coupling reactions using **1a-I** and **2a-I**.

Entry	Nucleophile	T (°C)	Yield [%] ^a	Conversion [%] ^a	Side-products (% yield) ^a
1	<i>p</i> -Nitroaniline	100	92	100	1 (trace)
2 ^b	<i>p</i> -Nitroaniline	100	93	100	-
3	2-Hydroxypyridine	100	95	100	-
4	Imidazole	100	93	100	-
5	Benzamide	110	59	66	4 (trace)
6 ^c	Cyclohexylamine	110	72	81	3 (5)
7 ^c	Propylamine	110	79	84	4 (trace)
8 ^c	Piperidine	110	51	67	2 (4); 3 (6)
9	Aniline	110	50	100	2 (8); 3 (15); 4 (9)
10	<i>p</i> -Anisidine	110	17	44	1 (12); 3 (7)
11	Diethylamine	110	8	19	-

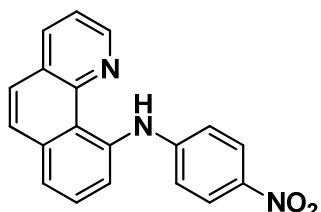
^aAverage yields and conversions of at least two experiments as determined by ¹H-NMR using 1,3,5-trimethoxybenzene as internal standard. ^b10-Iodobenzo[*h*]quinolone (**2a-I**) as substrate. ^cAverage GC and ¹H-NMR yields and conversions using 1,3,5-trimethoxybenzene as an internal standard.

Product isolation: A larger scale reaction was also performed: (0.2 mmol substrate **1a-I** or **2a-I**; 0.02 mmol [Au(NCMe)IPr]SbF₆; 0.6 mmol nucleophile; 0.6 mmol KO-*t*Bu) in 0.8 mL of DMSO. After cooling down to room temperature the residue was subjected to column chromatography on silica gel (eluent: hexanes/EtOAc).

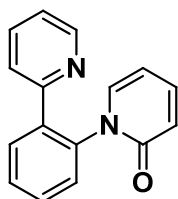


1ah: Column chromatography on silica gel (hexanes-ethyl acetate 3:2) provided a yellow solid (43.8 mg, 79% isolated yield). ¹H-NMR (CDCl₃, 400 MHz) δ, ppm: 10.89 (s, 1H, Hⁱ), 8.66 (dq, *J* = 4.8, 2.0, 0.8 Hz, 1H, H^a), 8.11 (d, *J* = 8.8 Hz, 2H, H^k), 7.83 (ddd, *J* = 8.0, 7.6, 2.0 Hz, 1H, H^c), 7.72 (dt, *J* = 8.0, 1.2 Hz, 1H, H^d), 7.67 (dd, *J* = 7.6, 1.2

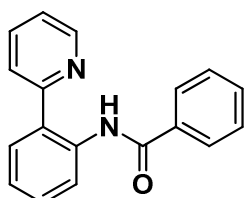
Hz, 1H, H^b), 7.60 (dd, $J = 8.0, 0.8$ Hz, 1H, H^c), 7.39 (td, $J = 7.6, 1.6$ Hz, 1H, H^g), 7.28 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H, H^b), 7.15 (td, $J = 7.6, 1.2$ Hz, 1H, H^f), 7.11 (d, $J = 8.8$ Hz, 2H, H^j); **¹³C{¹H}-NMR** (CDCl₃, 100 MHz) δ , ppm: 158.21 (C5), 149.41 (C12), 147.66 (C1), 139.76 (C15), 139.42 (C11), 137.56 (C3), 130.21 (C10), 129.69 (C9), 127.85 (C6), 126.10 (C14), 123.03 (C4), 122.82 (C8), 121.95 (C2), 119.97 (C17), 115.10 (C13); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₇H₁₃N₃O₂ [M + H⁺] 291.1075, found: 291.1081.



2ah: Column chromatography on silica gel (hexane-ethyl acetate 3:2) afforded an orange solid (52.9 mg, 84% isolated yield). **¹H-NMR** (CDCl₃, 400 MHz) δ , ppm: 13.65 (s, br, 1H, Hⁱ), 8.95 (dd, $J = 4.4, 2.0$ Hz, 1H, H^a), 8.26 (dd, $J = 8.0, 2.0$ Hz, 1H, H^c), 8.21 (d, $J = 9.2$ Hz, 2H, H^k), 7.84 (dd, $J = 8.0, 1.2$ Hz, 1H, H^b), 7.83 (d, $J = 8.8$ Hz, 1H, H^e), 7.69 (d, $J = 8.8$ Hz, 1H, H^d), 7.65 (t, $J = 8.0$ Hz, 1H, H^g), 7.57 (dd, $J = 8.0, 4.4$ Hz, 1H, H^b), 7.54 (dd, $J = 8.0, 0.8$ Hz, 1H, H^f), 7.45 (d, $J = 9.2$ Hz, 2H, H^j); **¹³C{¹H}-NMR** (CDCl₃, 100 MHz) δ , ppm: 149.44 (C14), 148.18 (C13), 146.11 (C1), 141.88 (C11), 140.41 (C17), 136.35 (C3), 136.02 (C7), 129.29 (C6), 128.33 (C9), 127.47 (C4), 126.05 (C16), 125.64 (C5), 121.13 (C8), 120.79 (C2), 118.00 (C12), 116.72 (C15), 114.35 (C10); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₉H₁₃N₃O₂ [M + H⁺] 316.1081, found: 316.1074

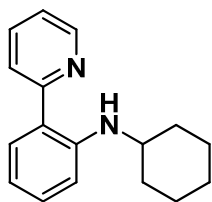


1ai: Column chromatography on silica gel (hexane-ethyl acetate 2:3) provided a colorless oil (37.2 mg, 75% isolated yield). **¹H-NMR** (CDCl₃, 400 MHz) δ , ppm: 8.63 (dq, $J = 4.8, 2.0, 1.2$ Hz, 1H, H^a), 8.14 (dq, $J = 5.2, 2.0, 0.8$ Hz, 1H, H^l), 7.89 (dd, $J = 8.0, 1.6$ Hz, 1H, H^e), 7.72 (dt, $J = 8.0, 1.2$ Hz, 1H, H^d), 7.59 (m, 2H, H^c+H^j), 7.44 (ddd, $J = 8.0, 7.6, 1.6$ Hz, 1H, H^g), 7.35 (td, $J = 7.6, 1.2$ Hz, 1H, H^f), 7.16 (dd, $J = 8.0, 1.2$ Hz, 1H, H^b), 7.13 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H, H^b), 6.91 (ddd, $J = 7.2, 5.2, 1.2$ Hz, 1H, H^k), 6.77 (dt, $J = 8.4, 1.2$ Hz, 1H, Hⁱ); **¹³C{¹H}-NMR** (CDCl₃, 100 MHz) δ , ppm: 163.68 (C12), 155.35 (C5), 153.56 (C6), 149.54 (C1), 147.87 (C16), 139.33 (C3), 135.89 (C14), 133.19 (C11), 131.39 (C7), 129.96 (C9), 125.49 (C8), 124.48 (C4), 122.50 (C10), 121.95 (C2), 118.31 (C15), 111.10 (C13); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₆H₁₂N₂O [M + H⁺] 249.1022, found: 249.1022.

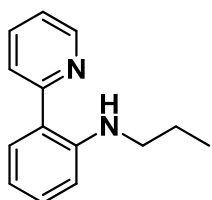


1aj: Column chromatography on silica gel (hexane-diethyl ether 50:50) afforded a white solid (24.7 mg, 45% isolated yield). **¹H-NMR** (CDCl₃, 400 MHz) δ , ppm: 8.79 (dd, $J = 8.4, 1.2$ Hz, 1H, H^b), 8.69 (dq, $J = 4.8, 1.6, 0.8$ Hz, 1H, H^a), 8.04 (m, 2H, H^j), 7.87 (ddd, $J = 8.0, 7.2, 2.0$ Hz, 1H, H^c), 7.81 (dt, $J = 8.0, 1.2$ Hz, 1H, H^d), 7.74 (dd, $J = 8.0, 1.6$ Hz, 1H, H^e), 7.50 (m, 4H, H^k+H^l+H^g), 7.30 (ddd, $J = 7.2, 4.8, 1.2$ Hz, 1H, H^b), 7.21 (ddd, $J = 8.0, 7.2, 1.2$ Hz, 1H, H^f); **¹³C{¹H}-NMR** (CDCl₃, 100 MHz) δ , ppm: 165.58 (C12), 158.40 (C5), 147.33 (C1), 138.13 (C11), 137.87 (C3), 135.79 (C13), 131.50 (C16), 130.28 (C7), 128.77 (C9), 128.60 (C15), 127.39

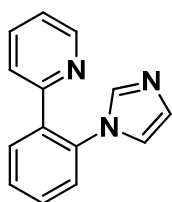
(C14), 125.64 (C6), 123.56 (C8), 123.02 (C4), 121.98 (C10), 121.96 (C2); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}$ [$\text{M} + \text{Na}^+$] 297.0998, found: 297.1008.



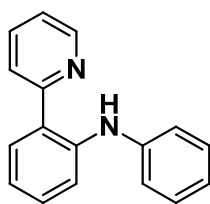
1ak: Column chromatography on silica gel (hexane-ethyl acetate 3:2) afforded a yellow oil (34.4 mg, 70% isolated yield). **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz) δ , ppm: 8.57 (dq, $J = 4.8, 2.0, 0.8$ Hz, 1H, H^a), 8.18 (s, 1H, H^i), 7.73 (ddd, $J = 8.0, 7.2, 2.0$ Hz, 1H, H^c), 7.66 (dt, $J = 8.0, 1.2$ Hz, 1H, H^d), 7.52 (dd, $J = 7.6, 1.6$ Hz, 1H, H^e), 7.23 (ddd, $J = 8.4, 7.2, 1.6$ Hz, 1H, H^g), 7.14 (ddd, $J = 7.2, 4.8, 1.2$ Hz, 1H, H^b), 6.77 (d, $J = 8.4$ Hz, 1H, H^h), 6.66 (ddd, $J = 7.6, 7.2, 0.4$ Hz, 1H, H^f), 3.41 (m, 1H, H^j), 2.04 (m, 2H, H^k), 1.76 (m, 2H, H^m), 1.60 (m, 1H, H^o), 1.36 (m, 5H, $\text{H}^l + \text{H}^n + \text{H}^p$); **$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$** (CDCl_3 , 100 MHz) δ , ppm: 159.91 (C5), 147.32 (C1), 146.90 (C11), 136.73 (C3), 130.20 (C9), 129.69 (C7), 122.35 (C4), 121.04 (C6), 120.54 (C2), 115.03 (C8), 111.94 (C10), 50.80 (C12), 32.95 (C13), 26.11 (C15), 24.70 (C14); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2$ [$\text{M} + \text{H}^+$] 253.1699, found: 253.1696.



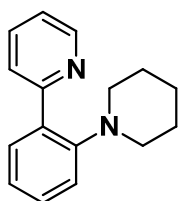
1al: Column chromatography on silica gel (hexane-ethyl acetate 3:2) gave a pale yellow oil (30.1 mg, 71% isolated yield). **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz) δ , ppm: 8.58 (dq, $J = 4.8, 2.0, 1.2$ Hz, 1H, H^a), 8.12 (s, br, 1H, H^i), 7.74 (ddd, $J = 8.4, 7.2, 2.0$ Hz, 1H, H^c), 7.67 (dt, $J = 8.4, 1.2$ Hz, 1H, H^d), 7.53 (dd, $J = 8.0, 1.6$ Hz, 1H, H^e), 7.26 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H, H^g), 7.15 (ddd, $J = 7.2, 4.8, 1.2$ Hz, 1H, H^b), 6.75 (dd, $J = 8.4, 1.2$ Hz, 1H, H^h), 6.70 (ddd, $J = 8.0, 7.6, 1.2$ Hz, 1H, H^f), 3.17 (t, $J = 7.2$ Hz, 2H, H^j), 1.71 (sext., $J = 7.2$ Hz, 2H, H^k), 1.03 (t, $J = 7.2$ Hz, 3H, H^l); **$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$** (CDCl_3 , 100 MHz) δ , ppm: 159.86 (C5), 147.90 (C11), 147.38 (C1), 136.81 (C3), 130.32 (C9), 129.44 (C7), 122.34 (C4), 121.15 (C6), 120.65 (C2), 115.39 (C8), 111.35 (C10), 45.19 (C12), 22.53 (C13), 11.86 (C14); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2$ [$\text{M} + \text{H}^+$] 213.1386, found: 213.1381



1am: Column chromatography on silica gel (hexane-ethyl acetate 1:4) provided a colorless liquid, which was subsequently washed with brine (5 x 3mL) in order to remove residual DMSO. A white solid was obtained (33.6 mg, 76% isolated yield). **$^1\text{H-NMR}$** (CDCl_3 , 400 MHz) δ , ppm: 8.65 (dq, $J = 4.8, 2.0, 0.8$ Hz, 1H, H^a), 7.79 (dd, $J = 7.2, 2.0$ Hz, 1H, H^e), 7.54 (m, 3H, $\text{H}^c + \text{H}^g + \text{H}^f$), 7.44 (s, br, 1H, H^k), 7.39 (dd, $J = 7.2, 2.0$ Hz, 1H, H^b), 7.20 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H, H^h), 7.06 (s, br, 1H, H^i), 6.89 (s, br, 1H, H^j), 6.83 (dt, $J = 8.0, 0.8$ Hz, 1H, H^d); **$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$** (CDCl_3 , 100 MHz) δ , ppm: 155.69 (C5), 149.93 (C1), 137.53 (C14), 136.52 (C6), 136.42 (C3), 135.20 (C11), 131.45 (C7), 129.65 (C13), 129.59 (C8), 128.92 (C9), 126.36 (C10), 123.13 (C4), 122.51 (C2), 120.61 (C12); **HRMS (ESI)** (CH_3CN , m/z): calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3$ [$\text{M} + \text{H}^+$] 222.1026, found: 222.1020.



1an: Column chromatography on silica gel (hexane-ethyl acetate 9:1) provided a yellow oil (20.2 mg, 41% isolated yield). Spectroscopic data are consistent with literature reports.^[8] **¹H-NMR** (CDCl₃, 400 MHz) δ , ppm: 10.22 (s, 1H, Hⁱ), 8.63 (dq, J = 4.8, 1.6, 0.8 Hz, 1H, H^a), 7.78 (ddd, J = 8.0, 7.2, 2.0 Hz, 1H, H^c), 7.70 (dt, J = 8.0, 1.2 Hz, 1H, H^d), 7.61 (dd, J = 8.0, 1.6 Hz, 1H, H^e or H^h), 7.47 (dd, J = 8.4, 1.2 Hz, 1H, H^e or H^h), 7.23 (m, 6H, H^j+H^k+H^g+H^b or H^f), 6.92 (m, 2H, H^l+H^b or H^f); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₇H₁₄N₂ [M + H⁺] 247.1230, found: 247.1231.



1ap: Column chromatography on silica gel (hexane-ethyl acetate 2:3) gave a colorless oil (19.0 mg, 40% isolated yield). Spectral data match literature reports.^[9] **¹H-NMR** (CDCl₃, 400 MHz) δ , ppm: 8.69 (dq, J = 4.8, 2.0, 0.8 Hz, 1H, H^a), 8.08 (dt, J = 8.0, 1.2 Hz, 1H, H^d), 7.65 (ddd, J = 8.0, 7.6, 2.0 Hz, 1H, H^g), 7.58 (dd, J = 7.6, 2.0 Hz, 1H, H^e), 7.31 (ddd, J = 8.0, 7.6, 2.0 Hz, 1H, H^c), 7.17 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H, H^b), 7.09 (td, J = 7.6, 1.2 Hz, 1H, H^f), 7.05 (dd, J = 8.0, 1.2 Hz, 1H, H^h), 2.79 (m, 4H, CH₂), 1.49 (m, 6H, CH₂); **HRMS (ESI)** (CH₃CN, m/z): calcd for C₁₆H₁₈N₂ [M + H⁺] 239.1543, found: 239.1541.

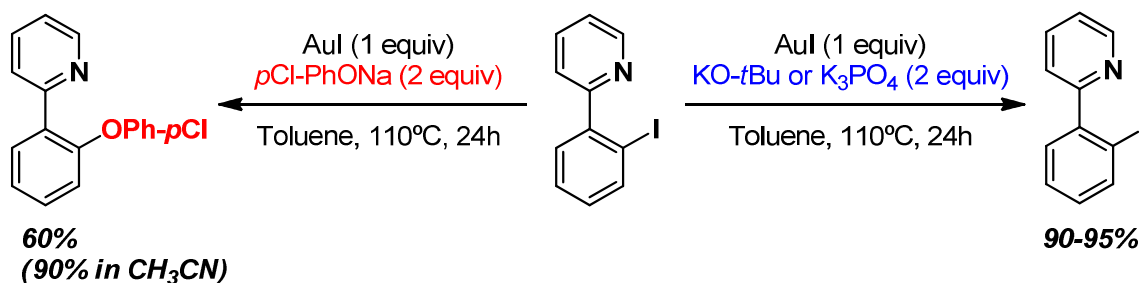
1.6. Reactivity of 1a-I and AuI in the presence of bases and *p*-chlorophenolate

Attempts to isolate a C-N cyclometalated gold(III) complex by reacting **1a-I** and AuI led in all cases to quantitative recovery of the starting substrate. We rationalize that, although the oxidative addition has an accessible barrier, as expected from the C-O and C-N coupling reactions, the ensuing complex [Au(**1a**)I₂] is thermodynamically disfavored, pulling the equilibrium back towards the reagents. Aiming at supporting this proposal, we performed the reaction in the presence of a base or sodium *p*-chlorophenolate. Thus, **1a-I** (5.6 mg, 0.02 mmol), AuI (6.5, 0.02 mmol) and KO-*t*Bu (4.5 mg, 0.04 mmol) or K₃PO₄ (8.5 mg, 0.04 mmol) or sodium *p*-chlorophenolate (6.0 mg, 0.04 mmol) were weighed into a glass vial, and dissolved in toluene. The vial was capped and the mixture stirred at 110°C for 24h. ¹H-NMR analyses of the crude revealed presence of **1a-I** (90-95%) for potassium *tert*-butoxide and potassium phosphate, while in the presence of sodium *p*-chlorophenolate 60% of the **1aa** coupling product was observed. This yield could be increased up to 90% upon toluene replacement for acetonitrile (see Scheme S1).

(8) M. A. Ali, X. Yao, G. Li, H. Lu, *Org. Lett.*, **2016**, *18*, 1386.

(9) S. Thapa, A. Kafle, S. K. Gurung, A. Montoya, P. Riedel, R. Giri, *Angew. Chem. Int. Ed.*, **2015**, *54*, 8236.

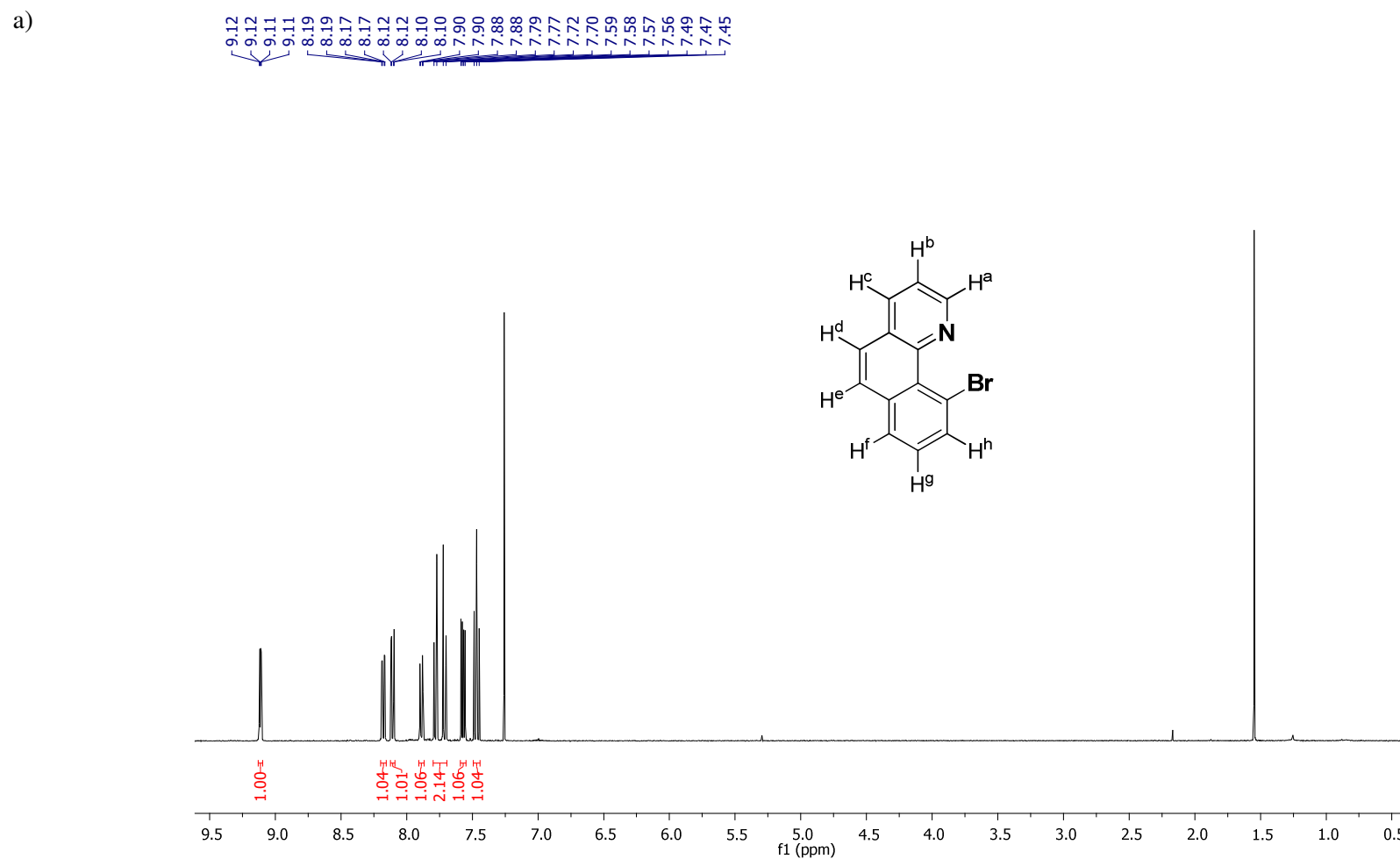
KO-*t*Bu and K₃PO₄ cannot displace the iodides in a putative [Au(**1a**)I₂] complex, which would immediately lead to the reductive elimination and consumption of **1a-I**. On the other hand, however, the nucleophilic character of sodium *p*-chlorophenolate allows for this process occur. A catalytic performance can be likewise attained by adding IPr· carbene in the reaction mixture. Overall, this strongly suggests C_{sp2}-I bond activation by Au(I).



Scheme S1: Outcomes observed in the reaction between **1a-I** and AuI, when potassium *tert*-butoxide, potassium phosphate or sodium *p*-chlorophenolate are added.

2. Supplementary Figures

Figure S1. a) ^1H -NMR spectrum of compound **2a-Br** in CDCl_3 , 400 MHz, at 298 K; b) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).



b)

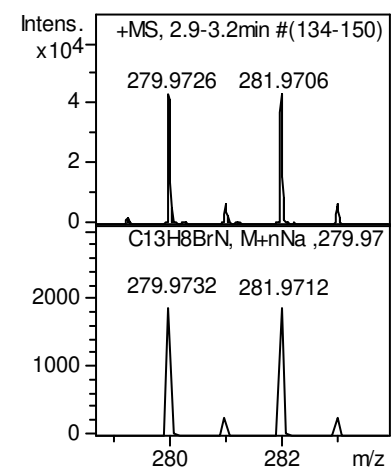
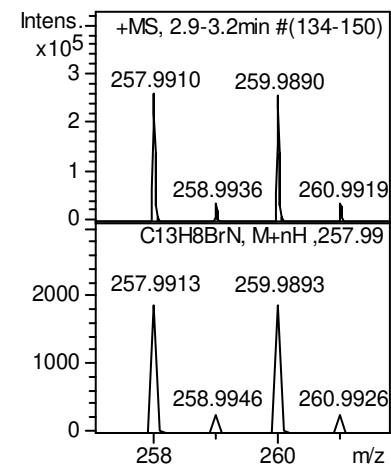
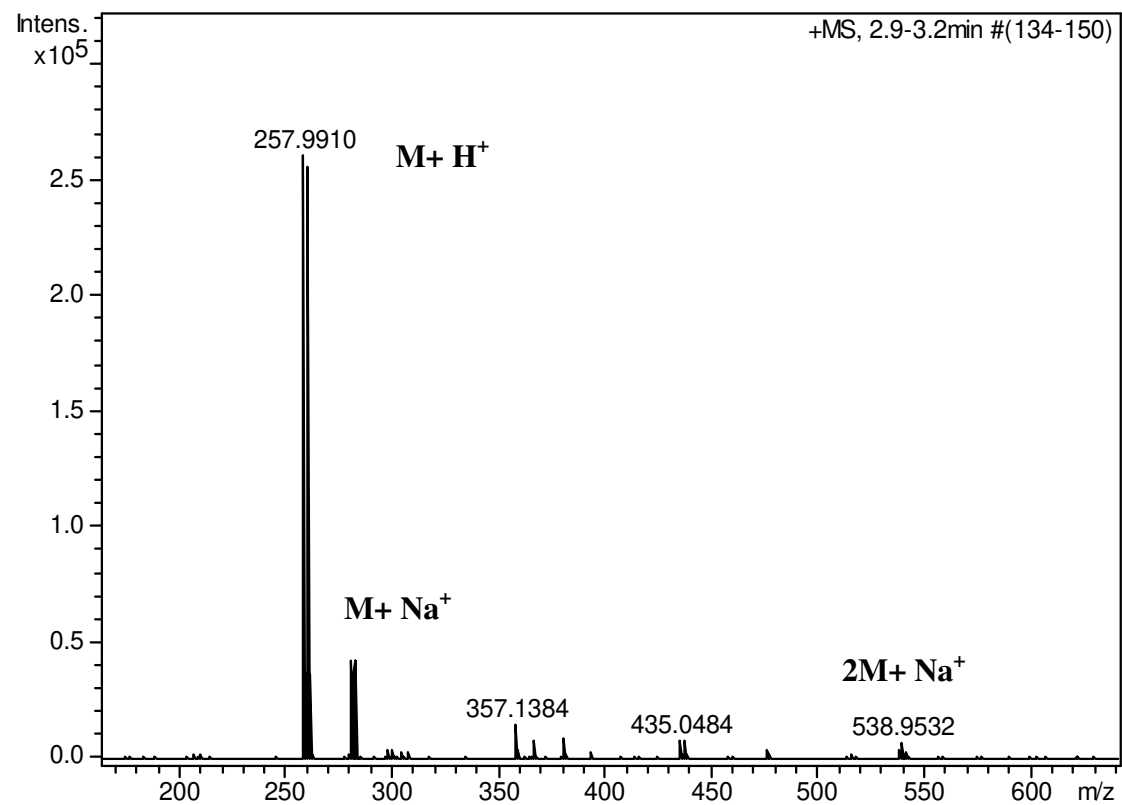
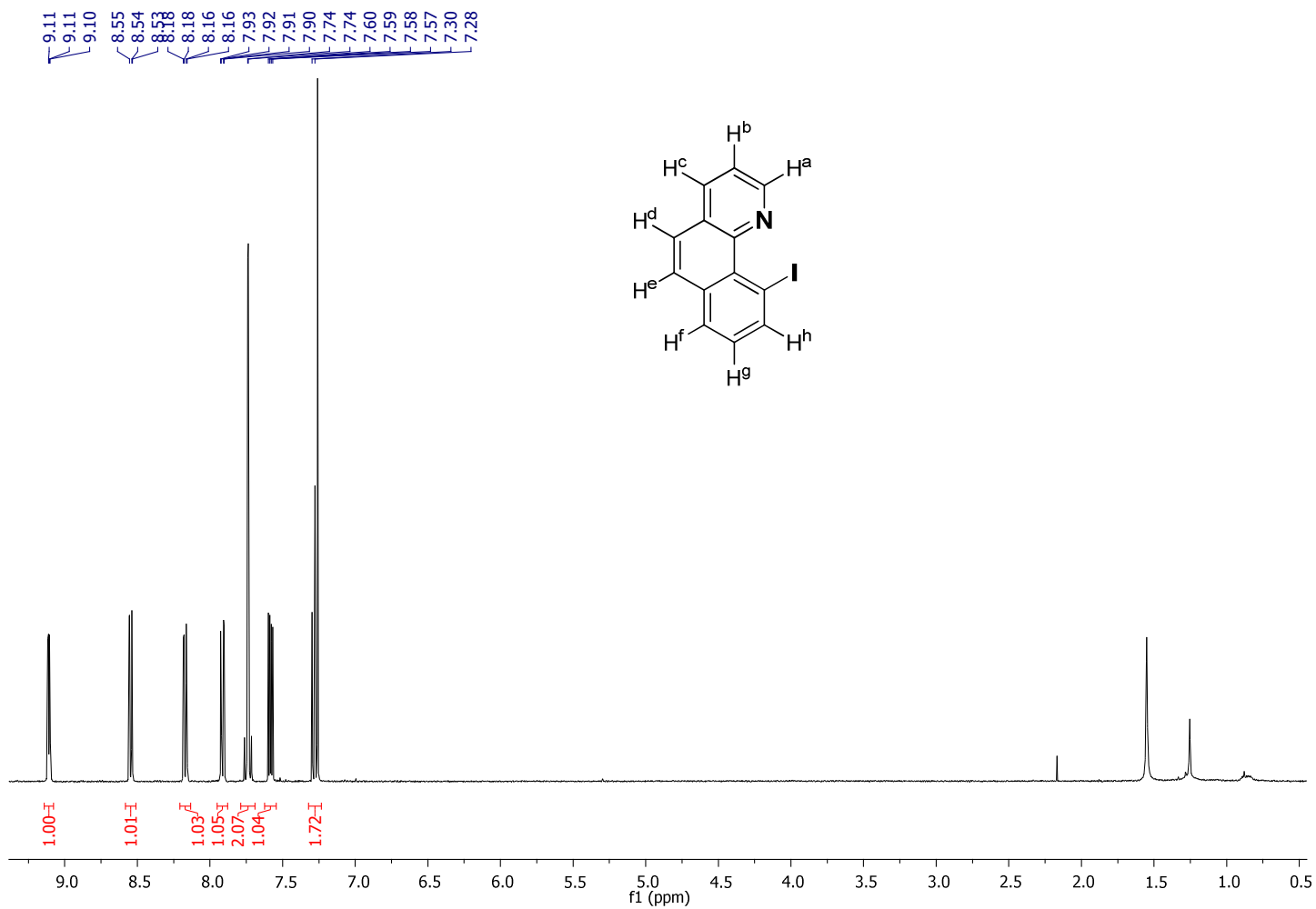
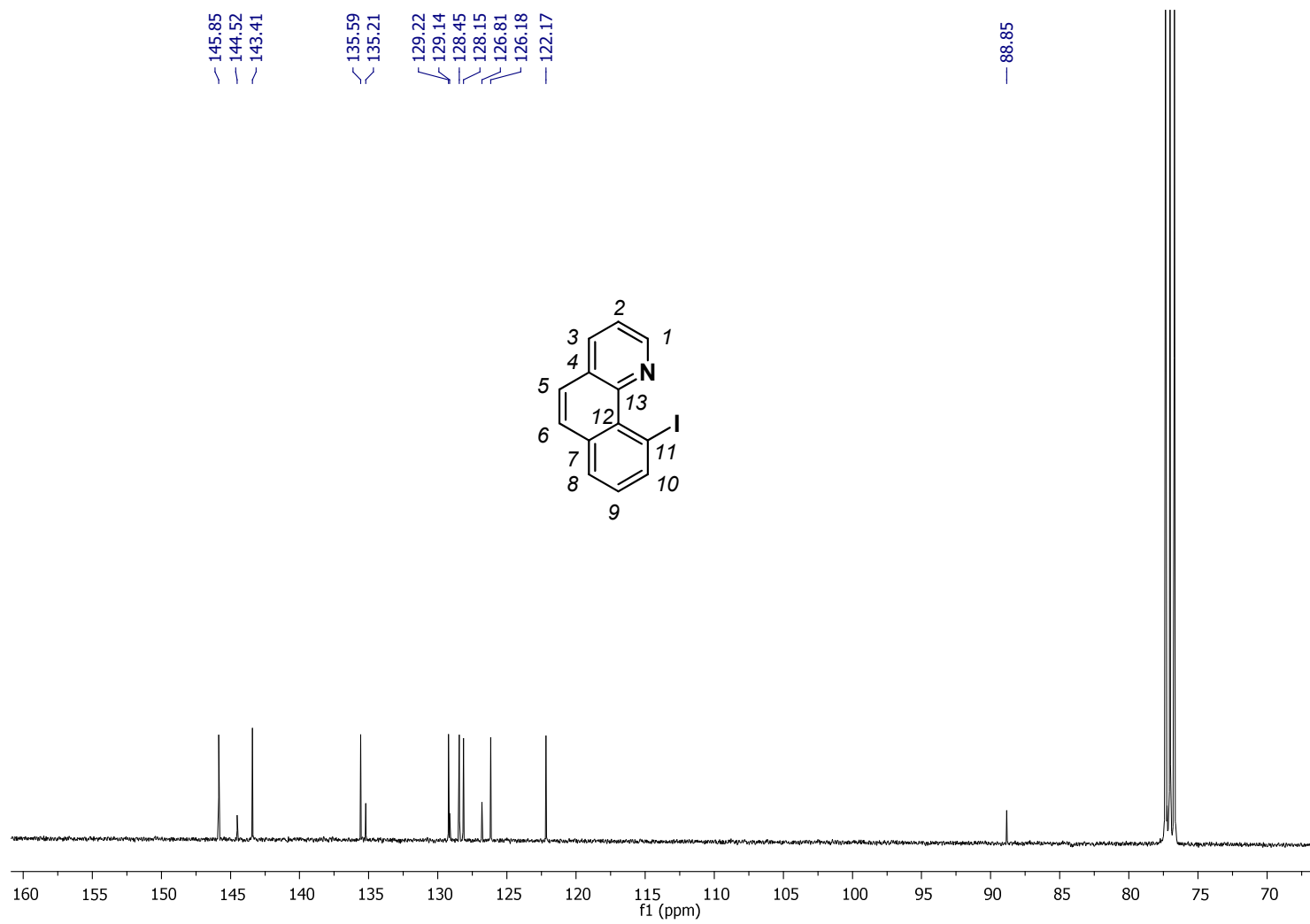


Figure S2. a) ^1H -NMR spectrum of compound **2a-I** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

a)



b)



c)

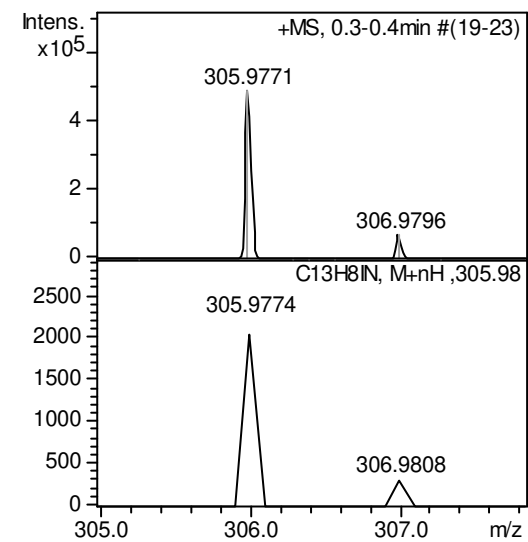
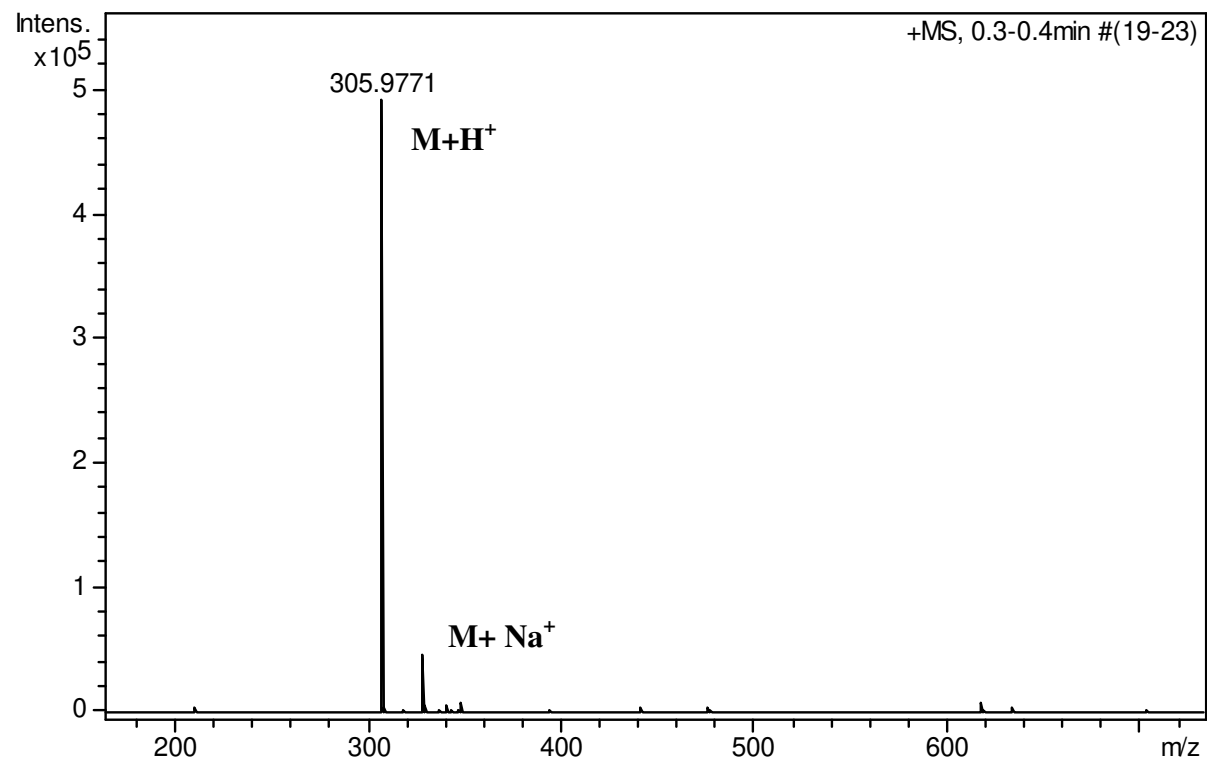
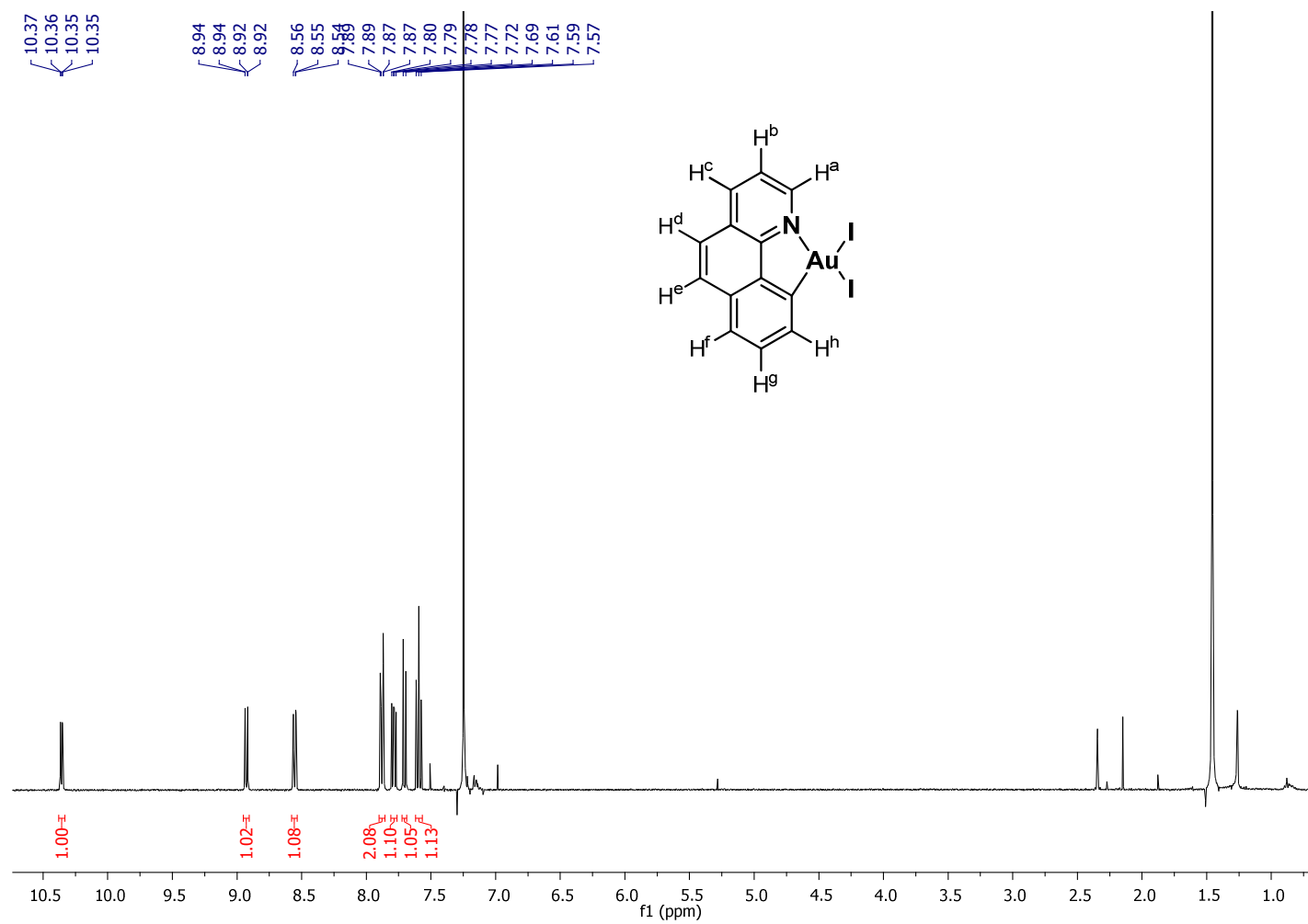


Figure S3. a) ^1H -NMR spectrum of complex **3a** in CDCl_3 , 400 MHz, at 323 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 323 K).

a)



b)

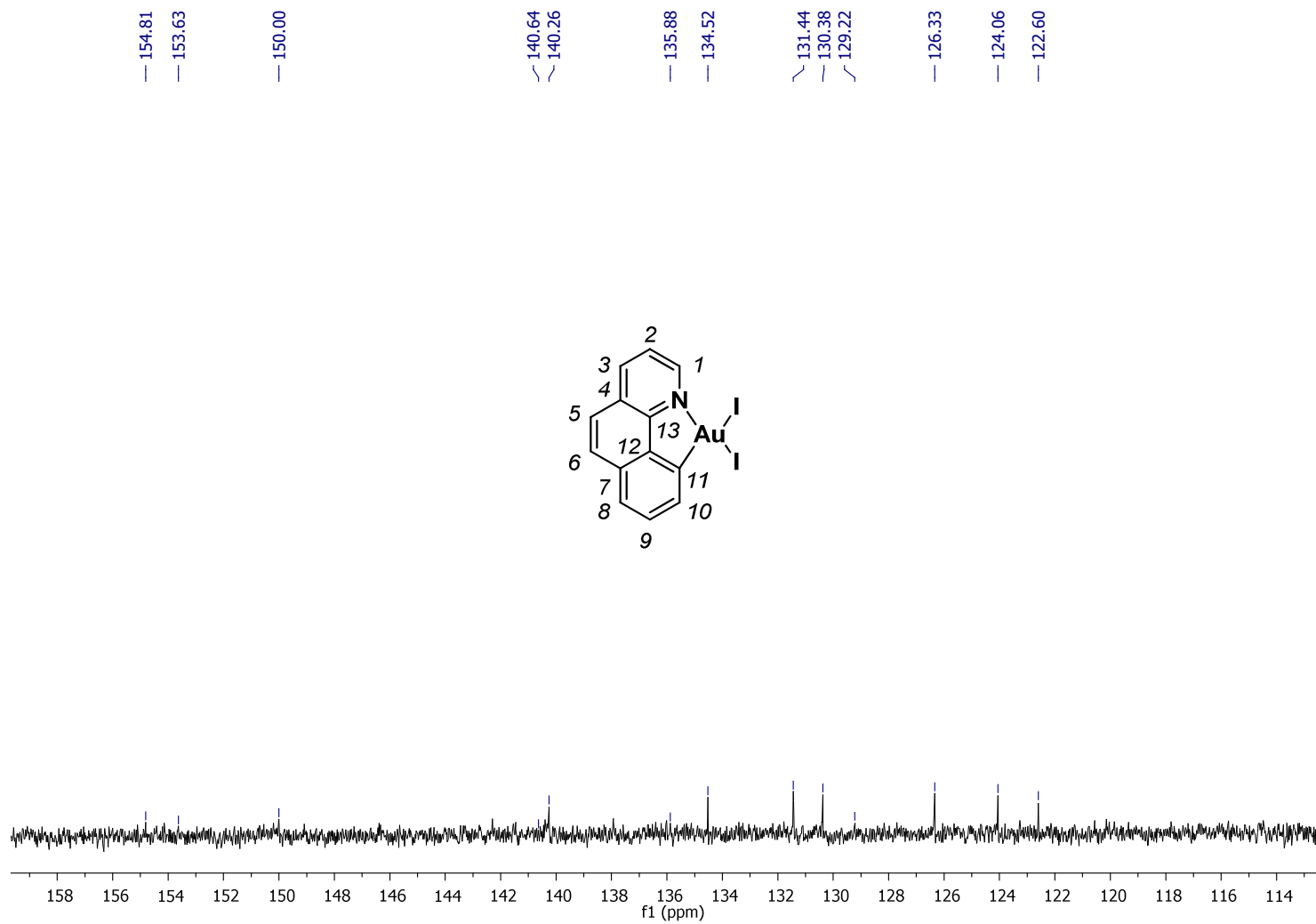
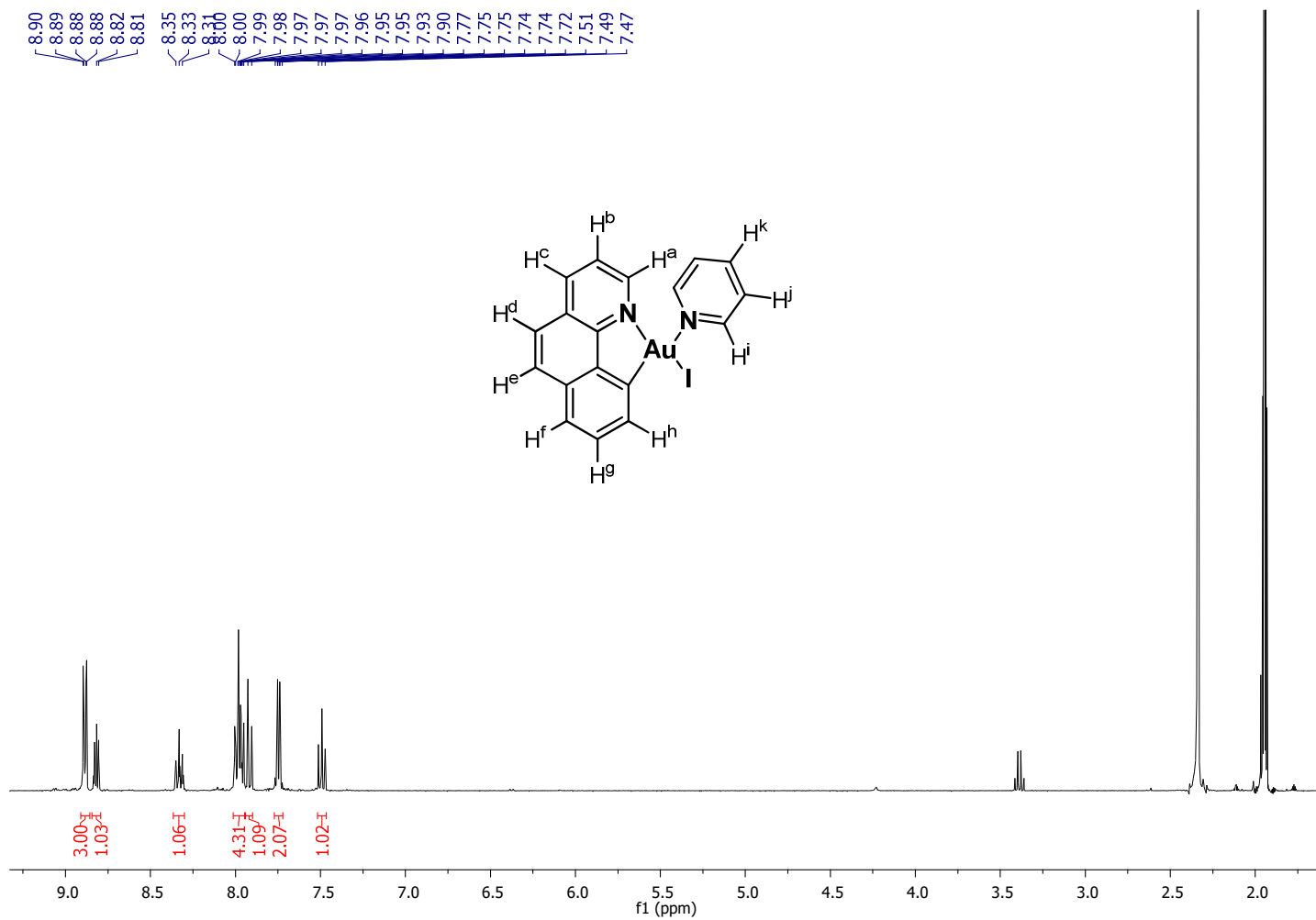
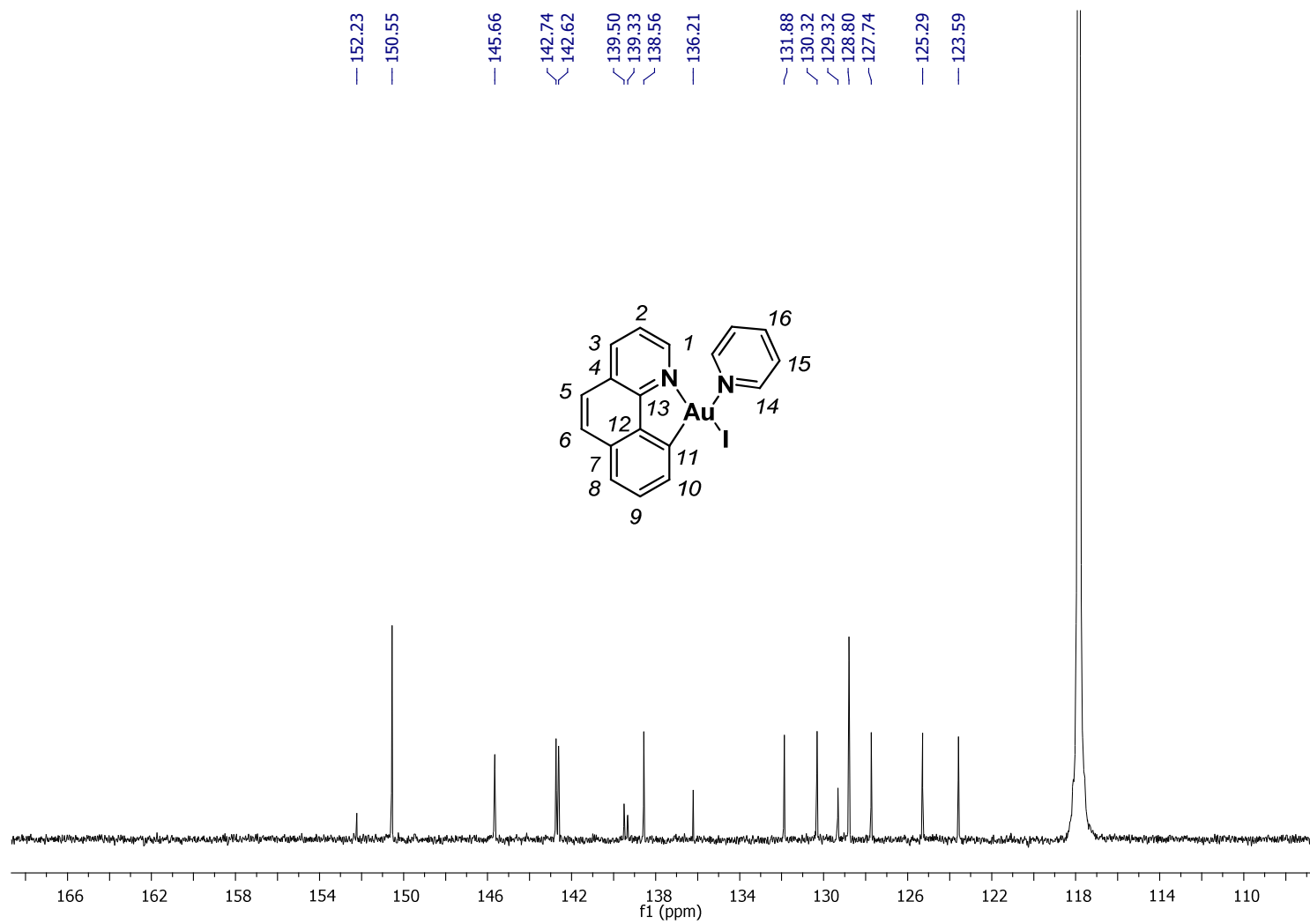


Figure S4. a) ^1H -NMR spectrum of complex **3b** in CDCl_3 , 400 MHz, at 248 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 248 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (top) with the theoretical isotope prediction (bottom).

a)



b)



c)

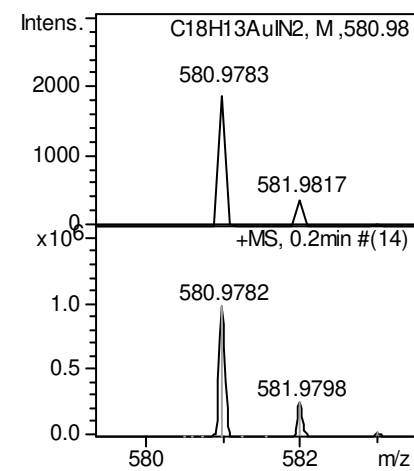
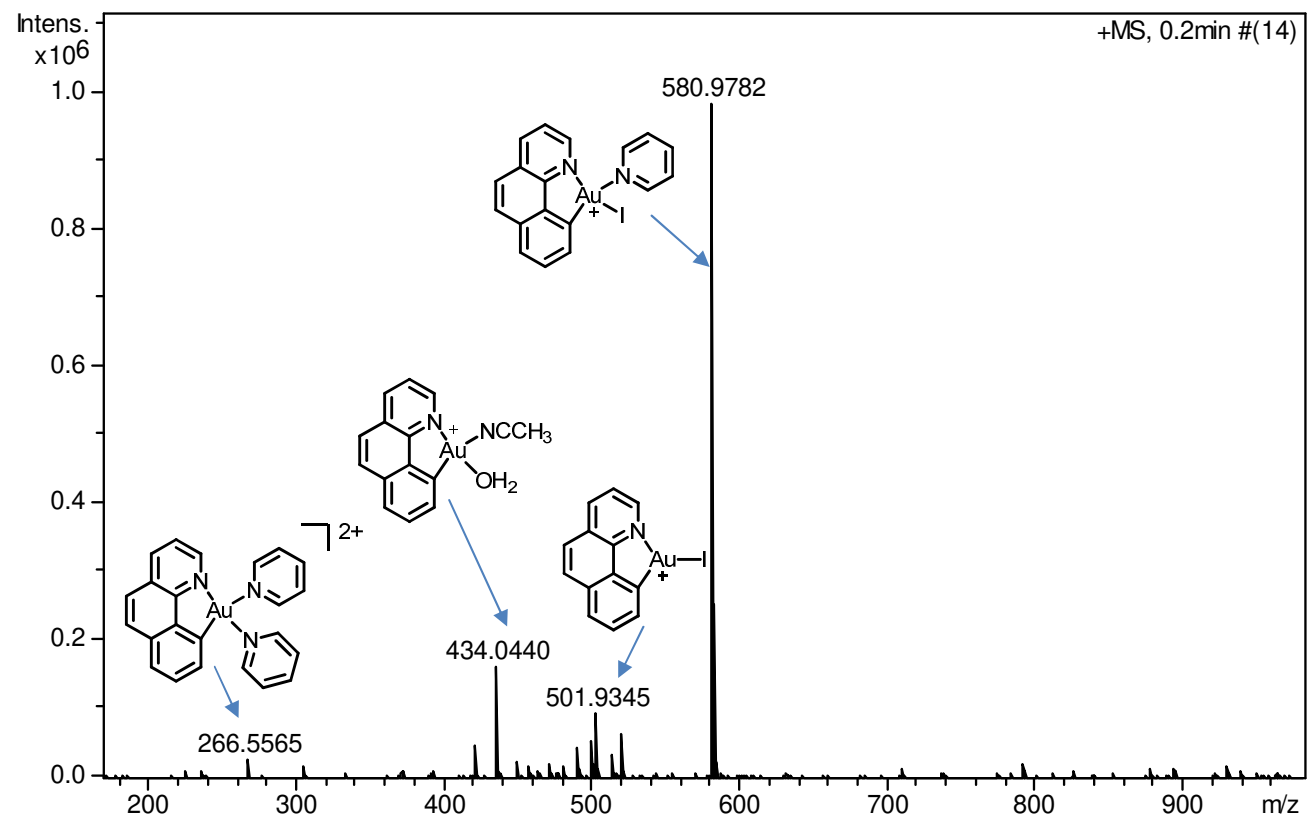
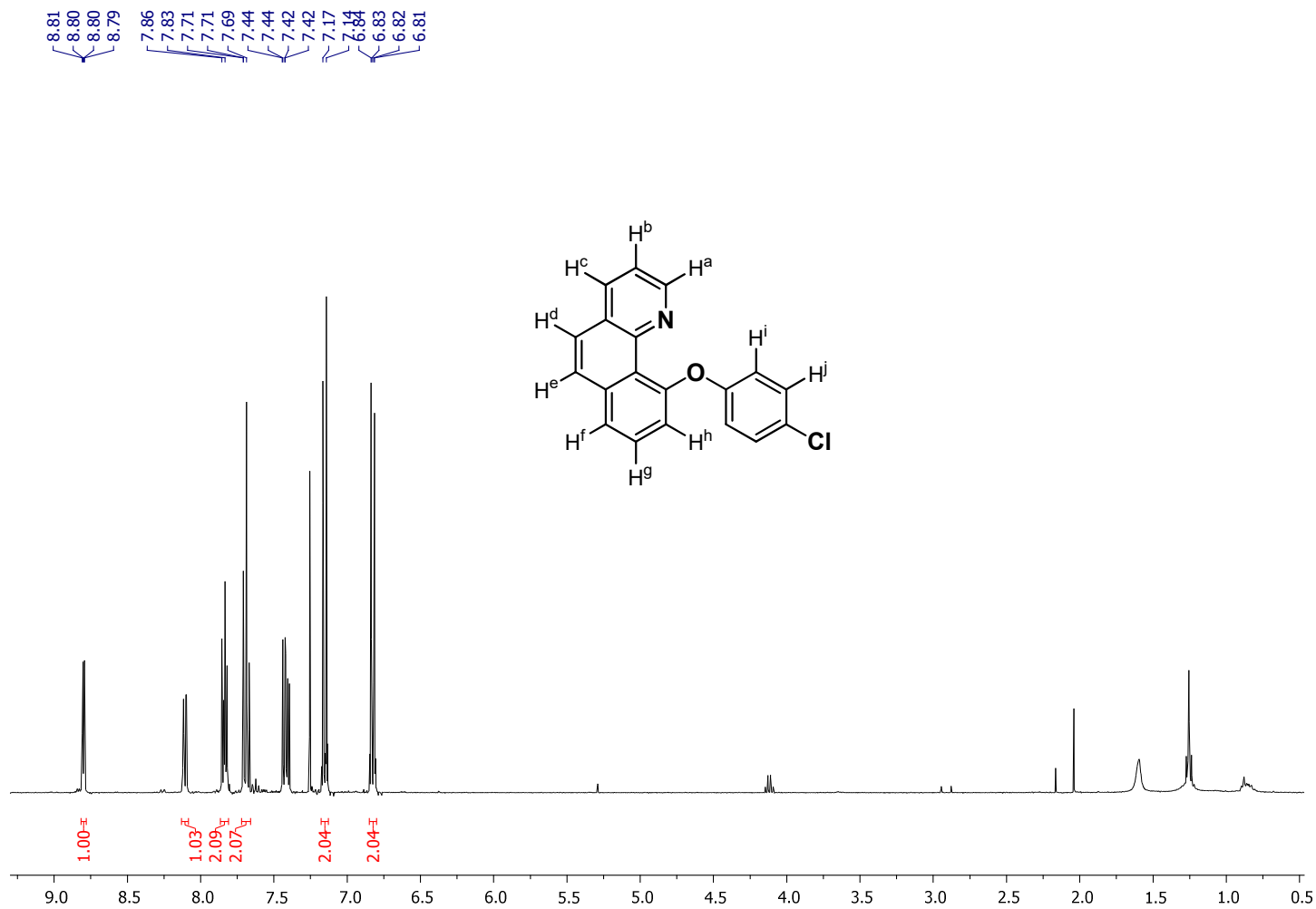
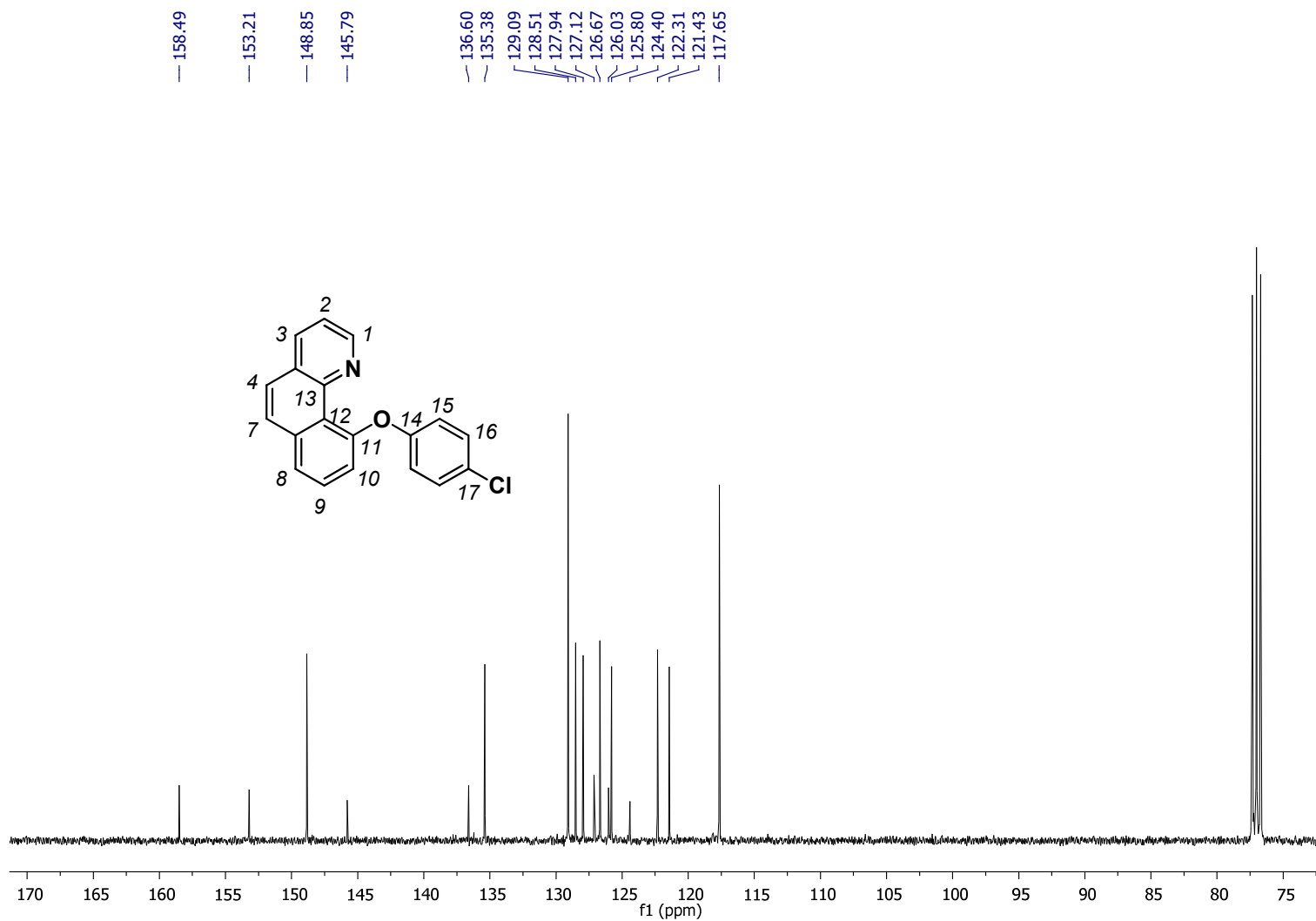


Figure S5. a) ^1H -NMR spectrum of compound **2aa** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

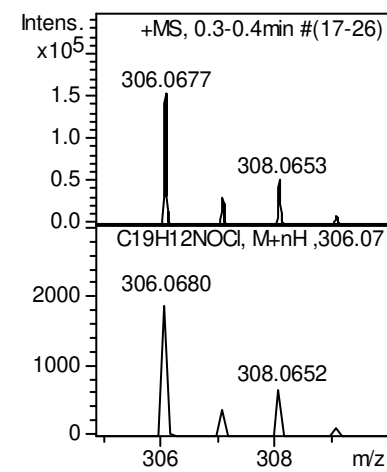
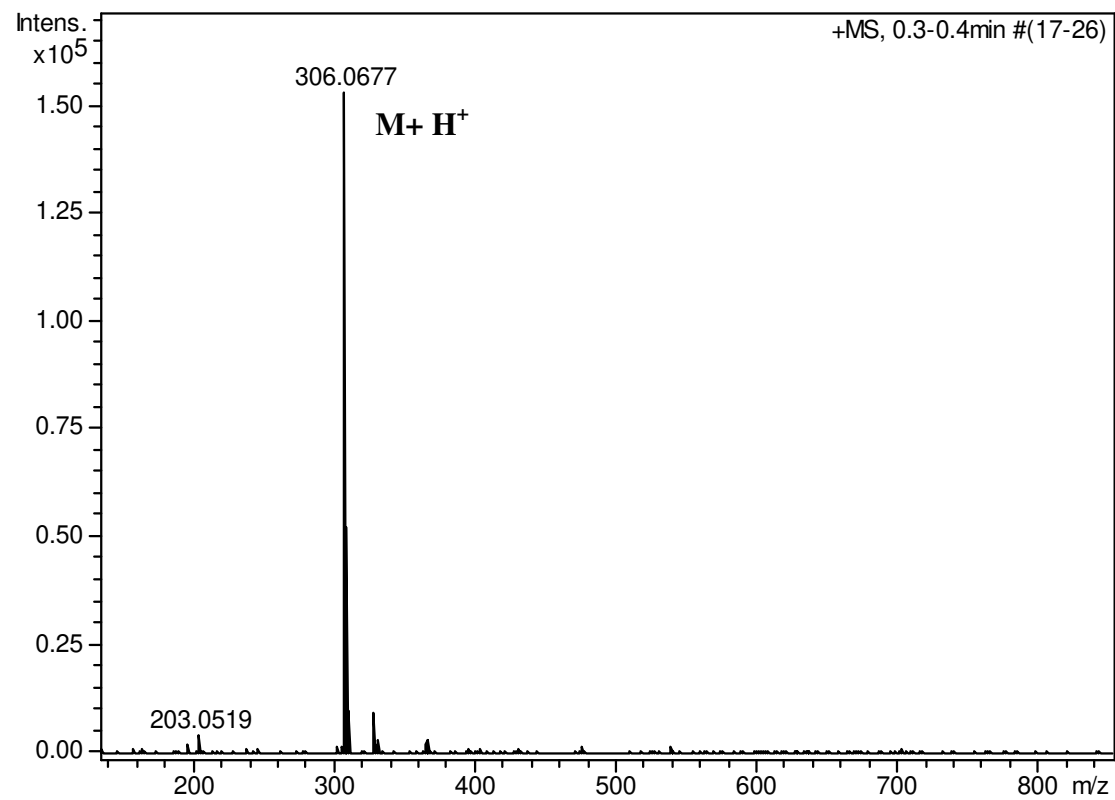
a)



b)



c)



a)



b)

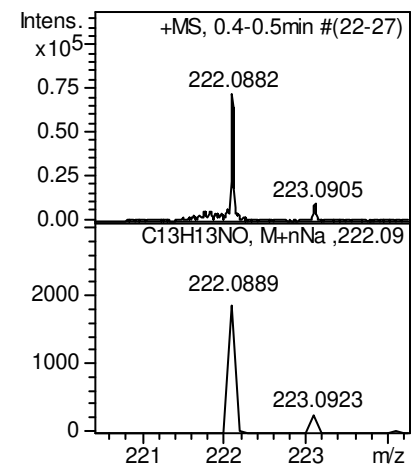
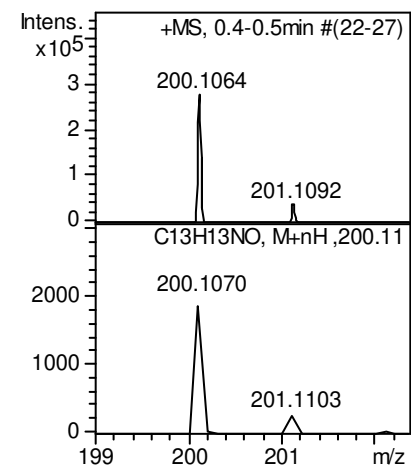
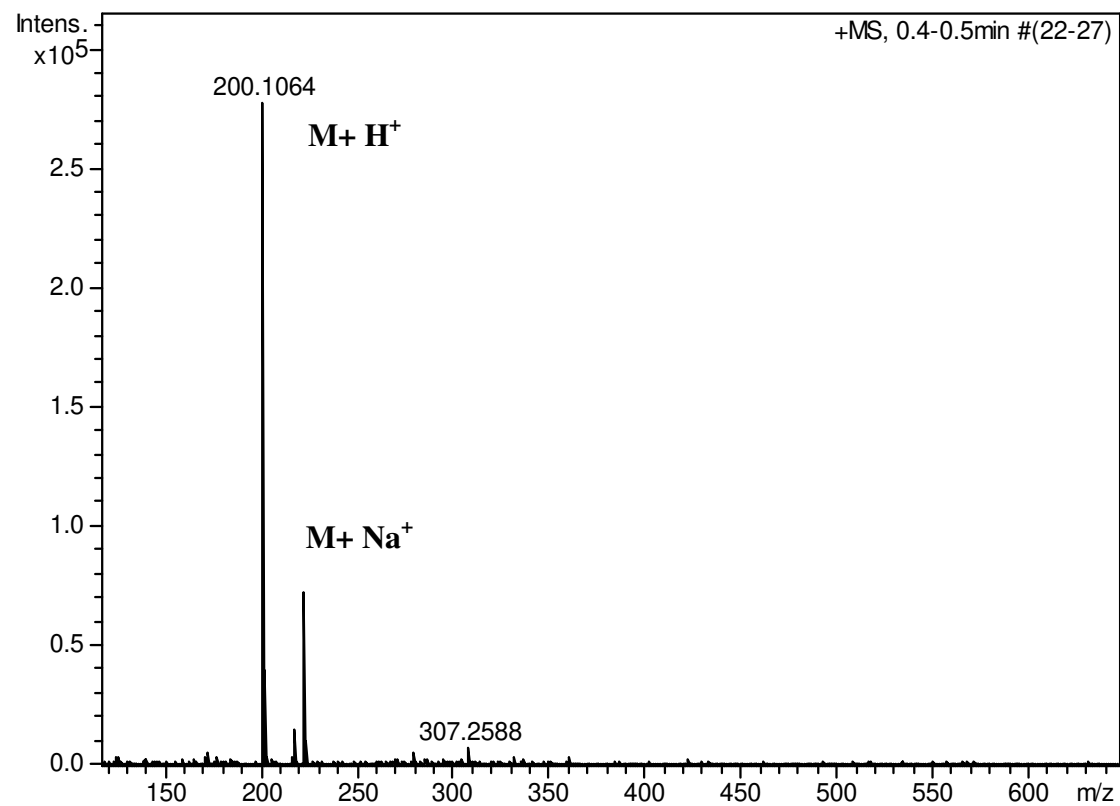
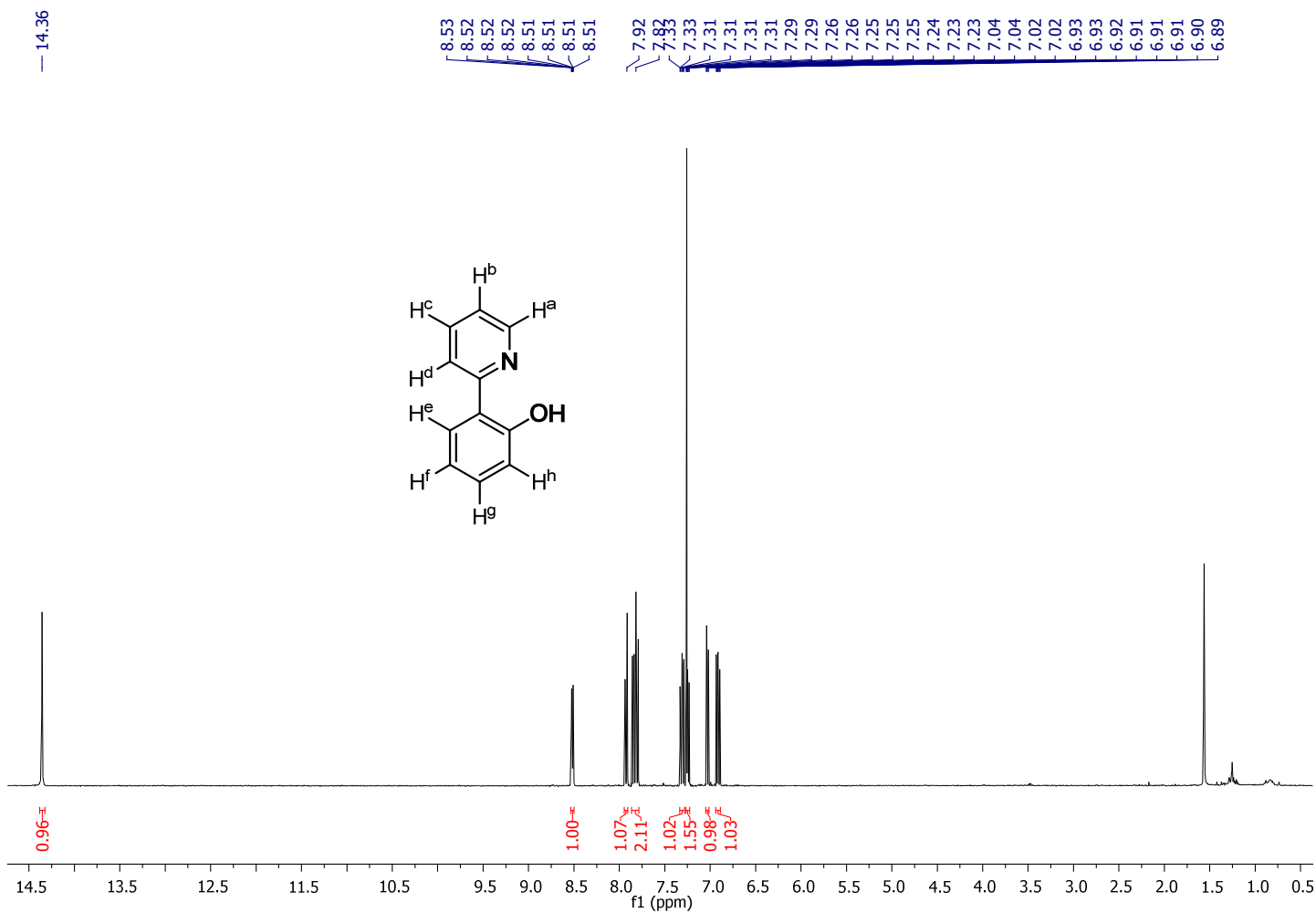


Figure S7. a) ^1H -NMR spectrum of compound **1af** in CDCl_3 , 400 MHz, at 298 K; b) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

a)



b)

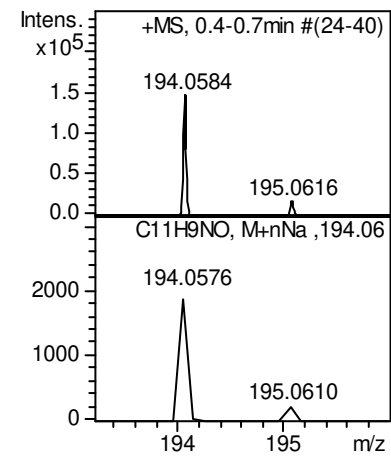
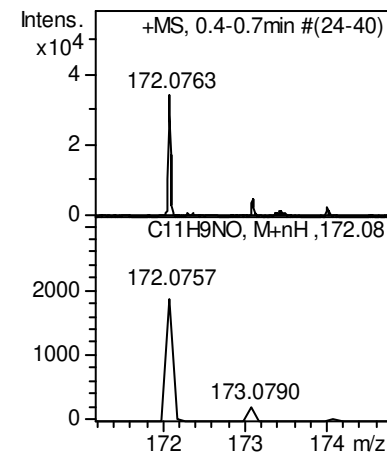
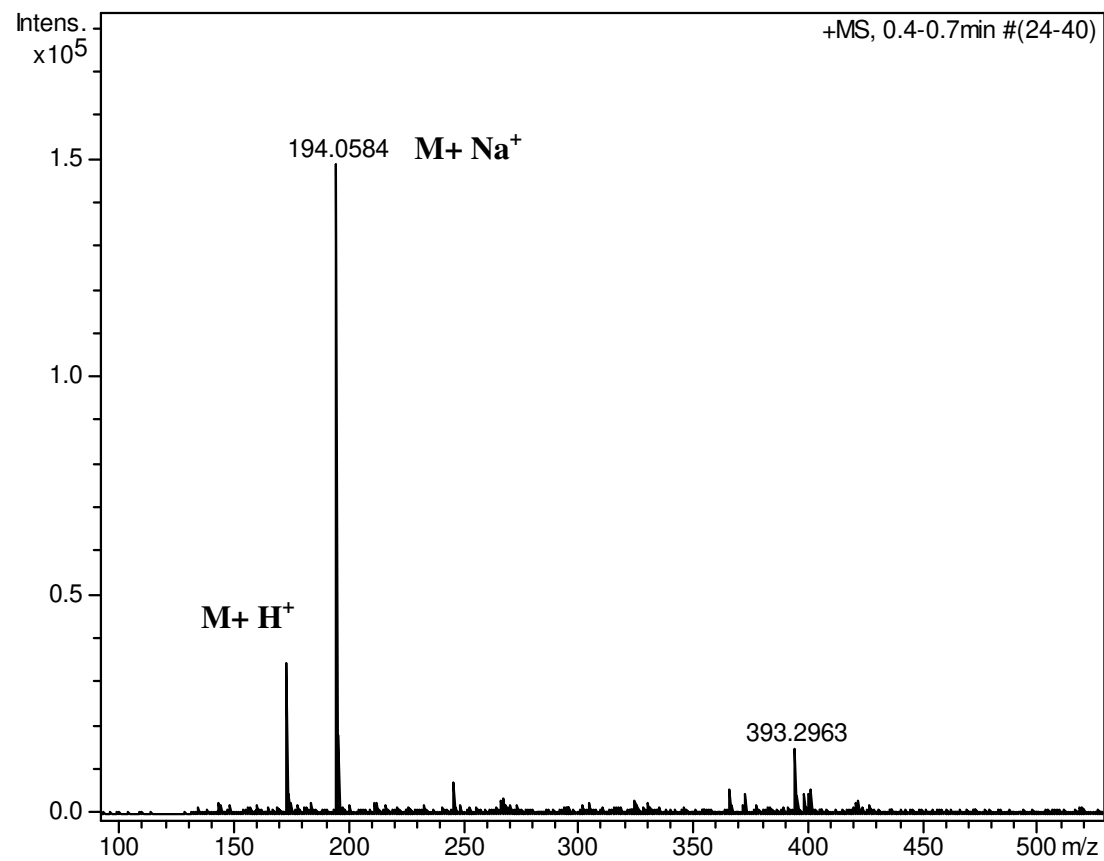
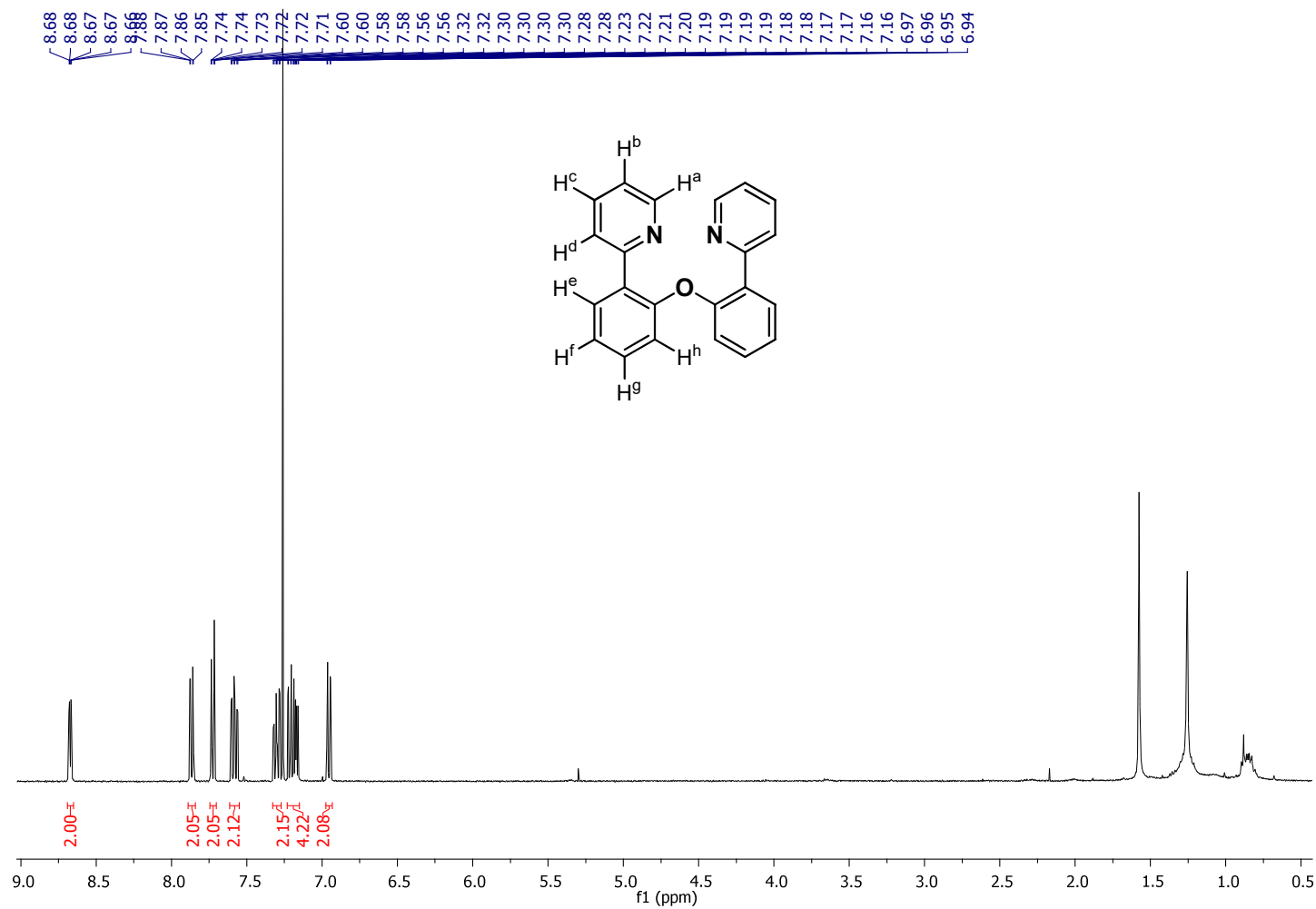
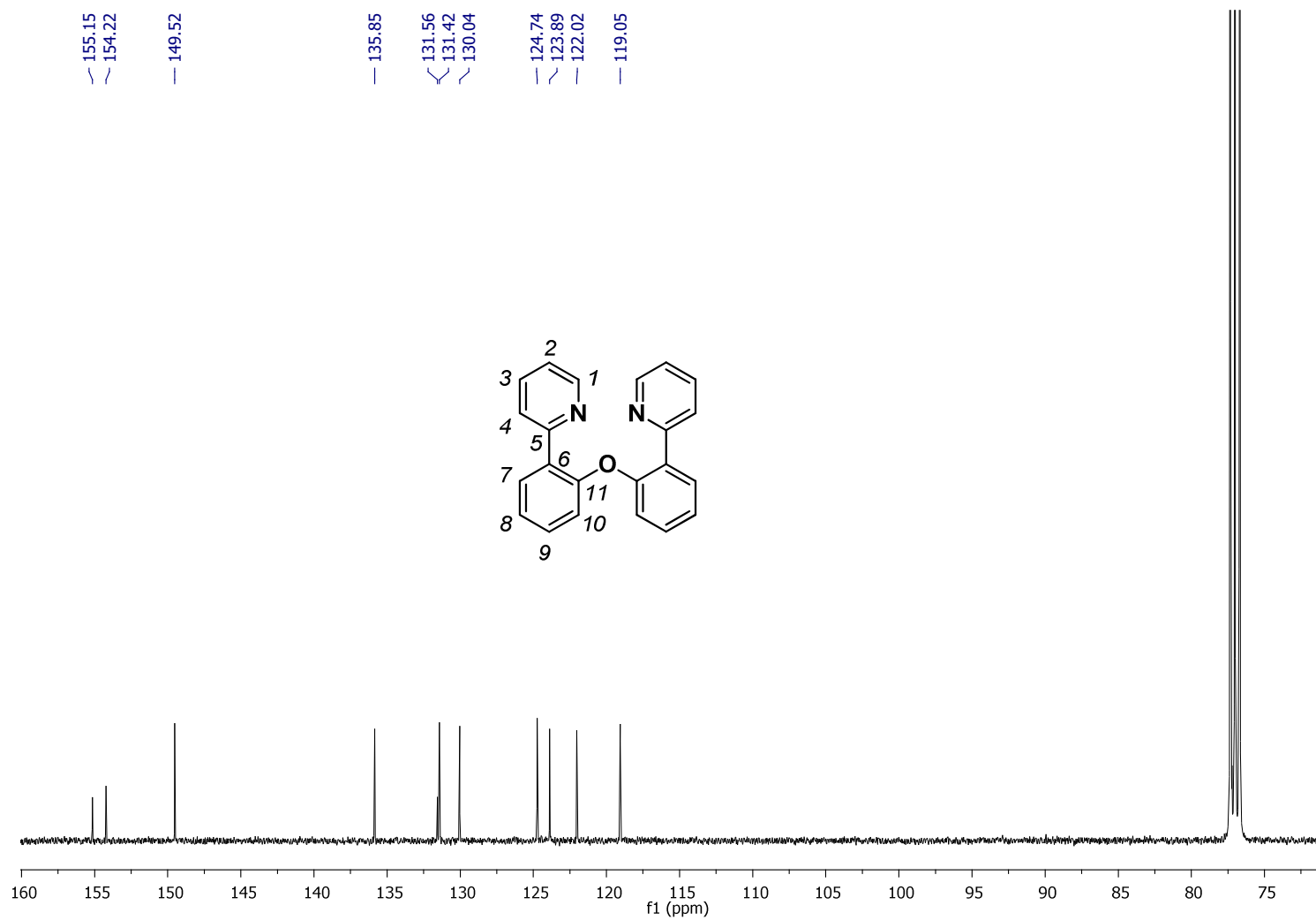


Figure S8. a) ^1H -NMR spectrum of compound **1ag** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

a)



b)



c)

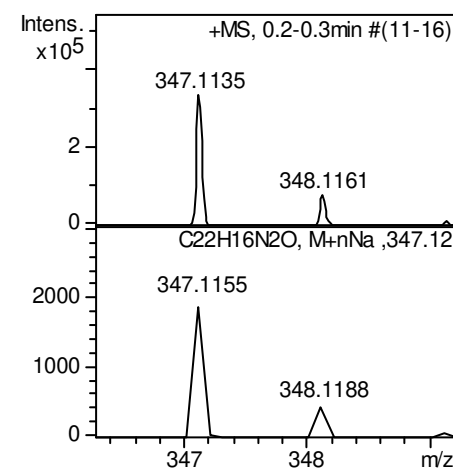
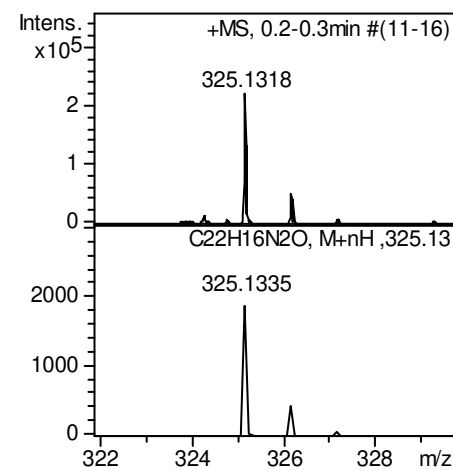
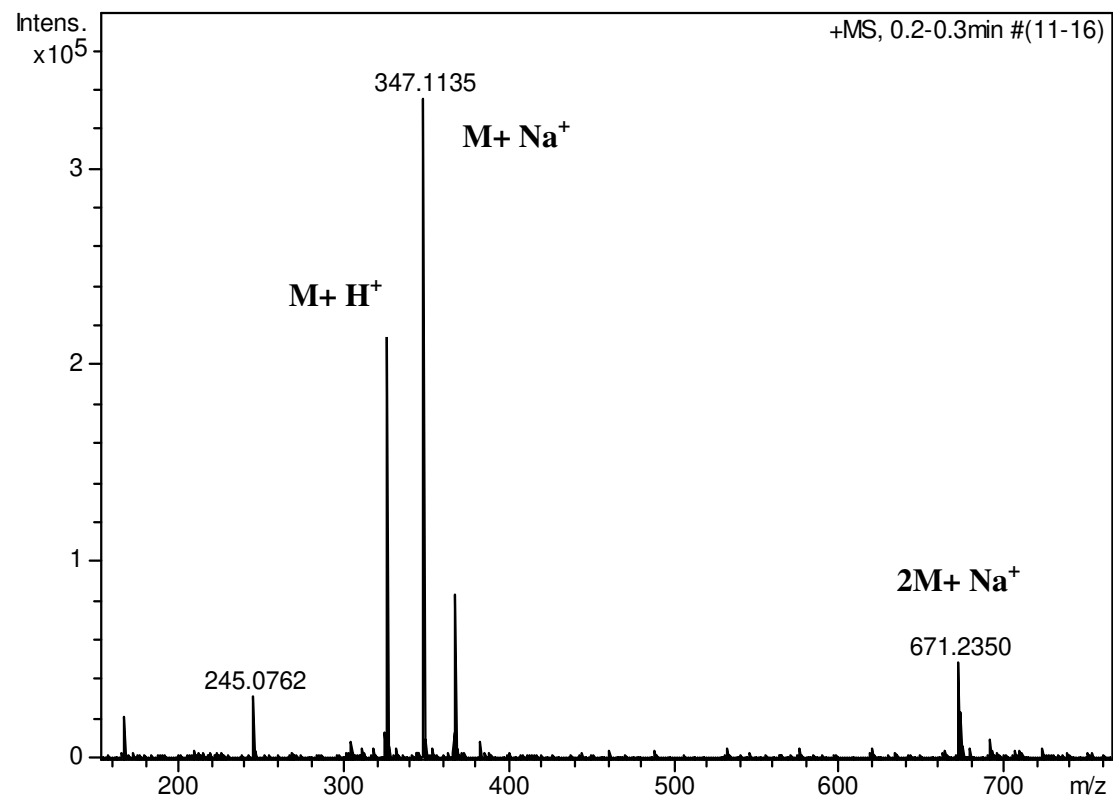
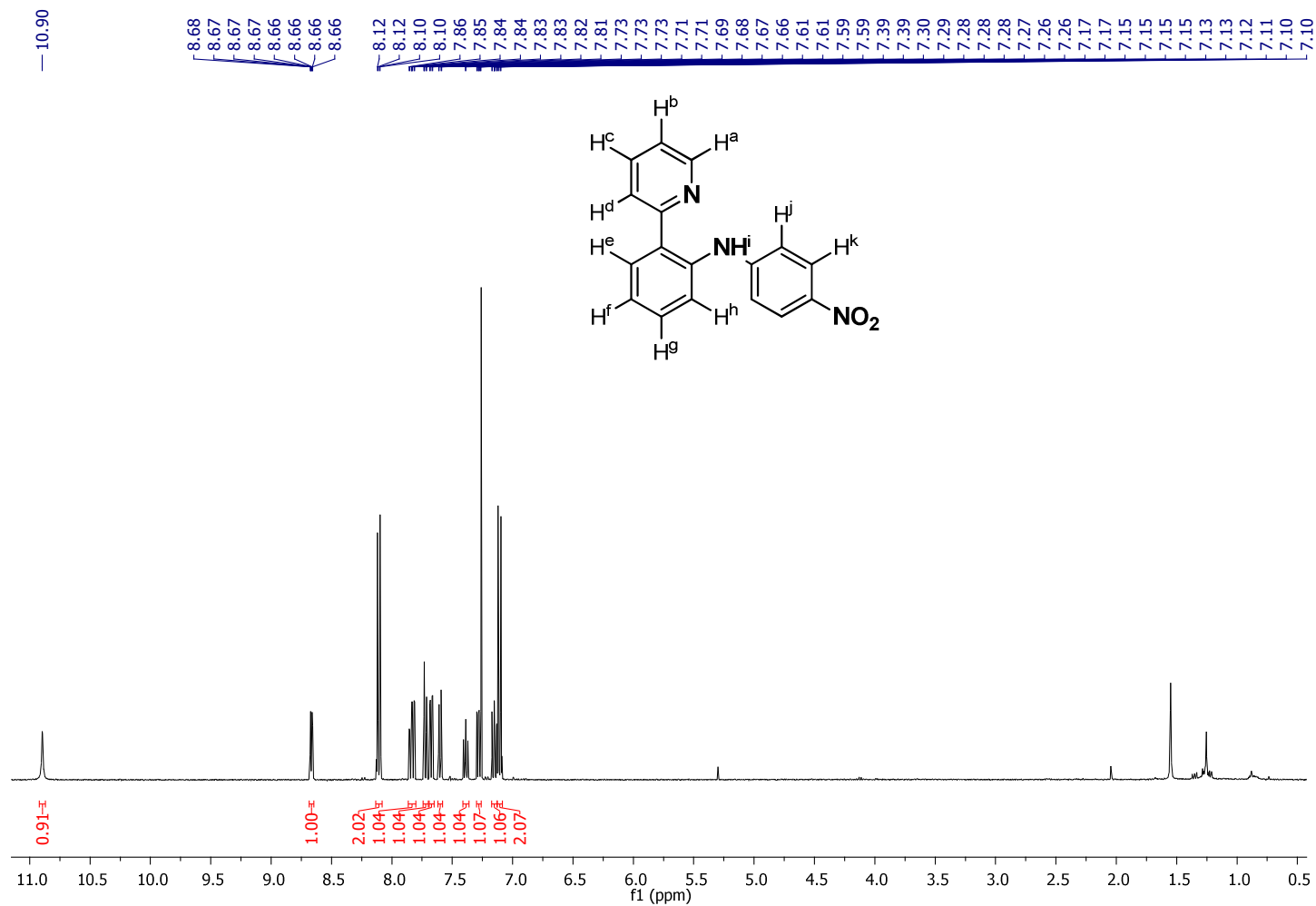
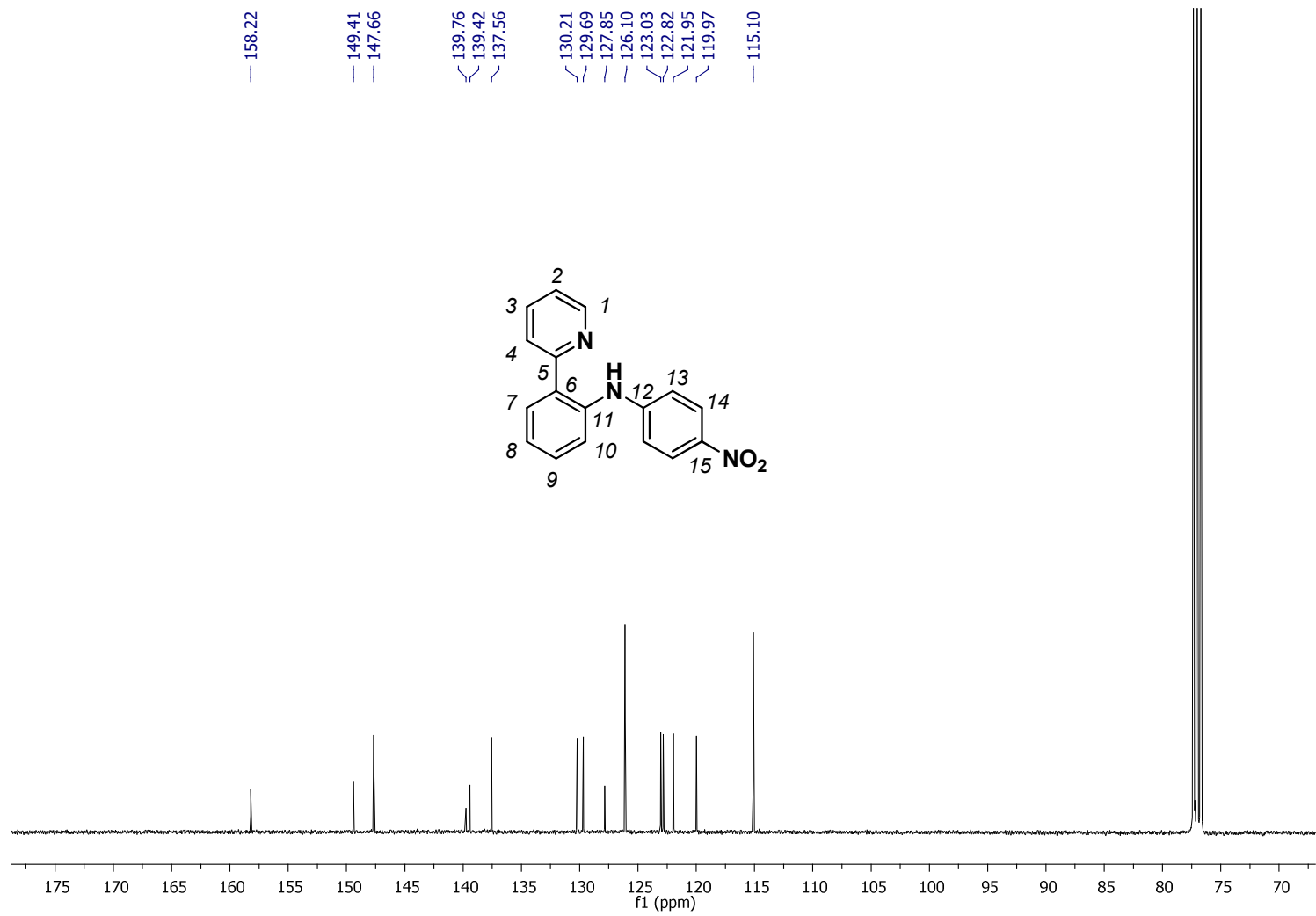


Figure S9. a) ^1H -NMR spectrum of compound **1ah** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

a)



b)



c)

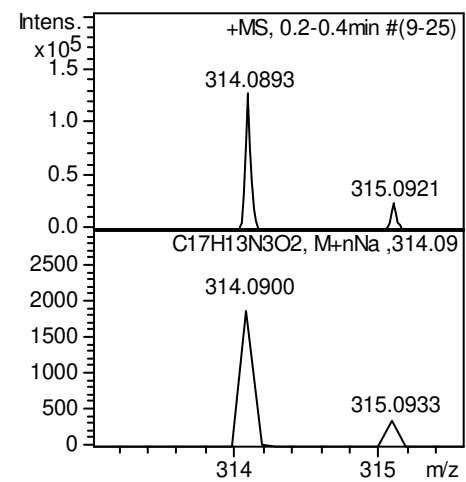
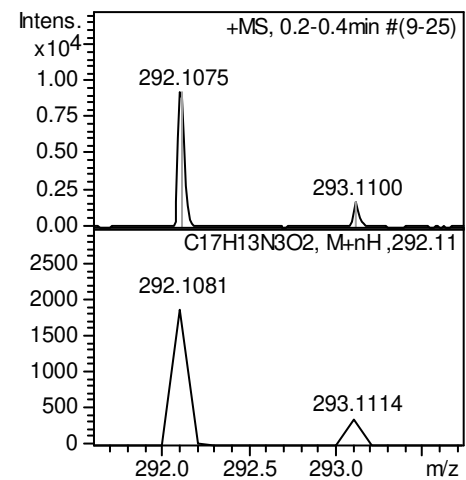
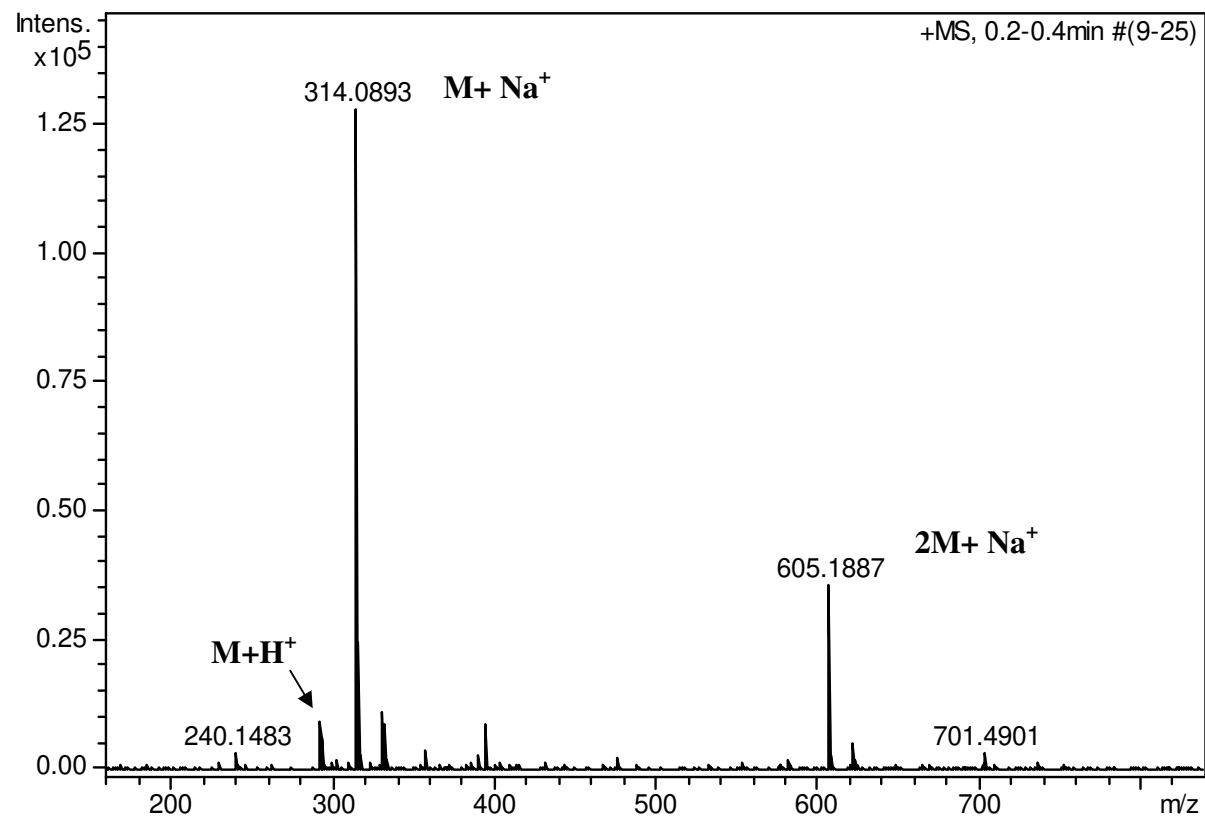
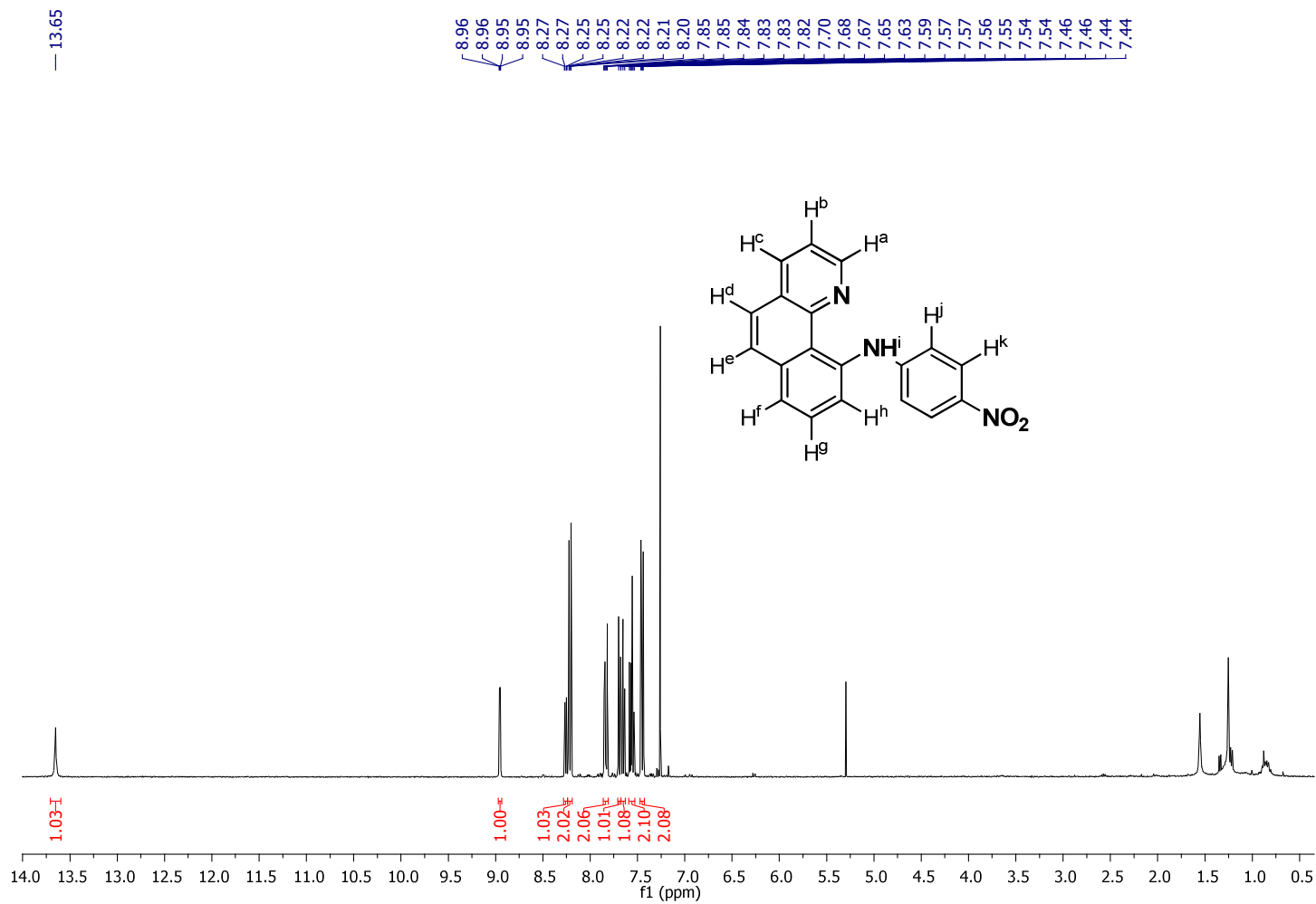
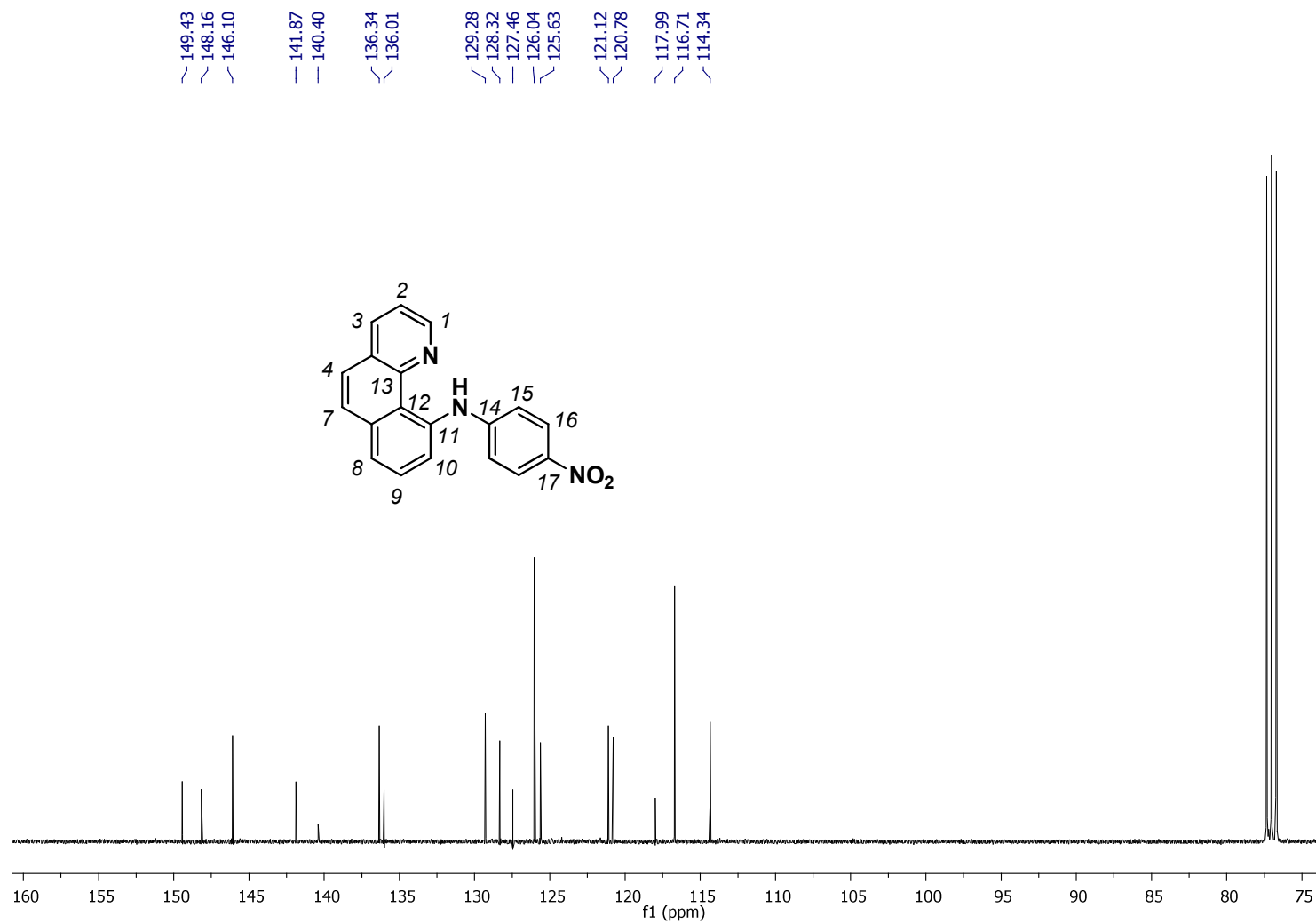


Figure S10. a) ^1H -NMR spectrum of compound **2ah** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

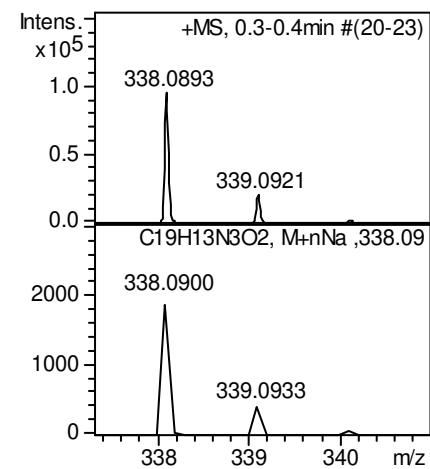
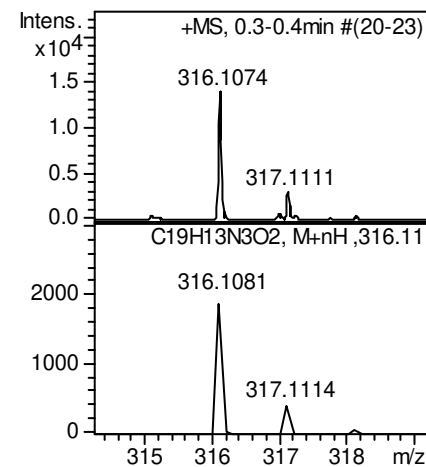
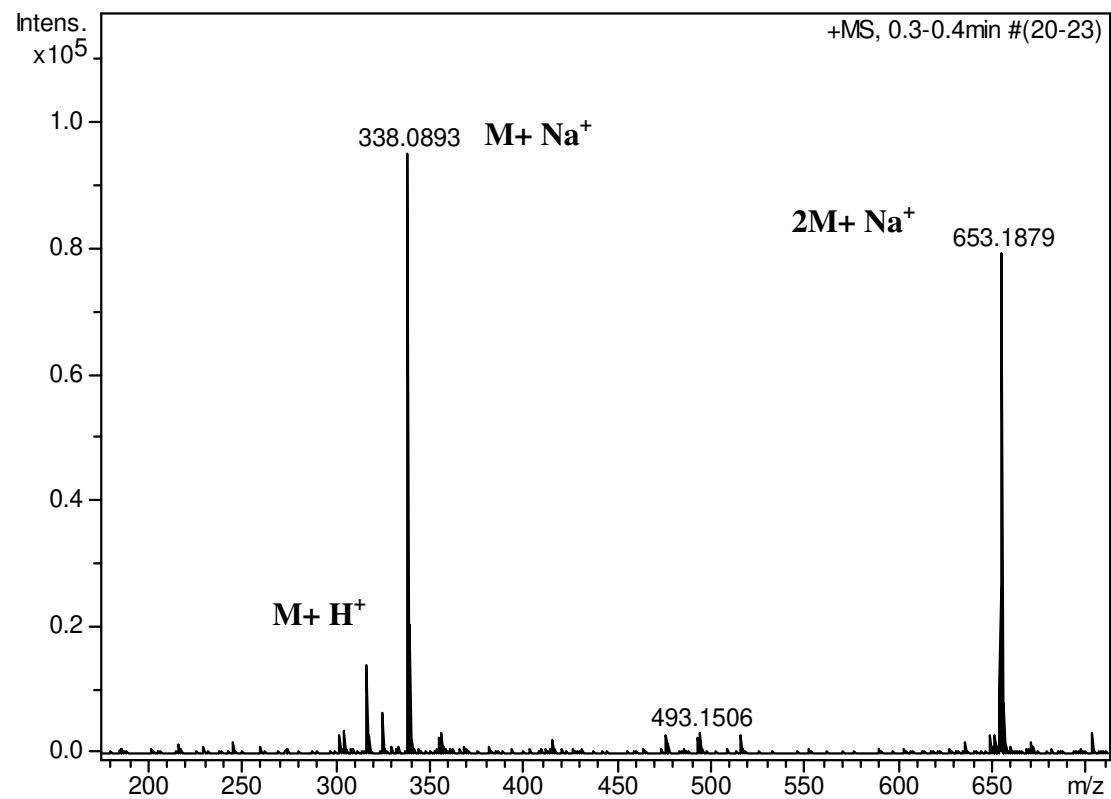
a)



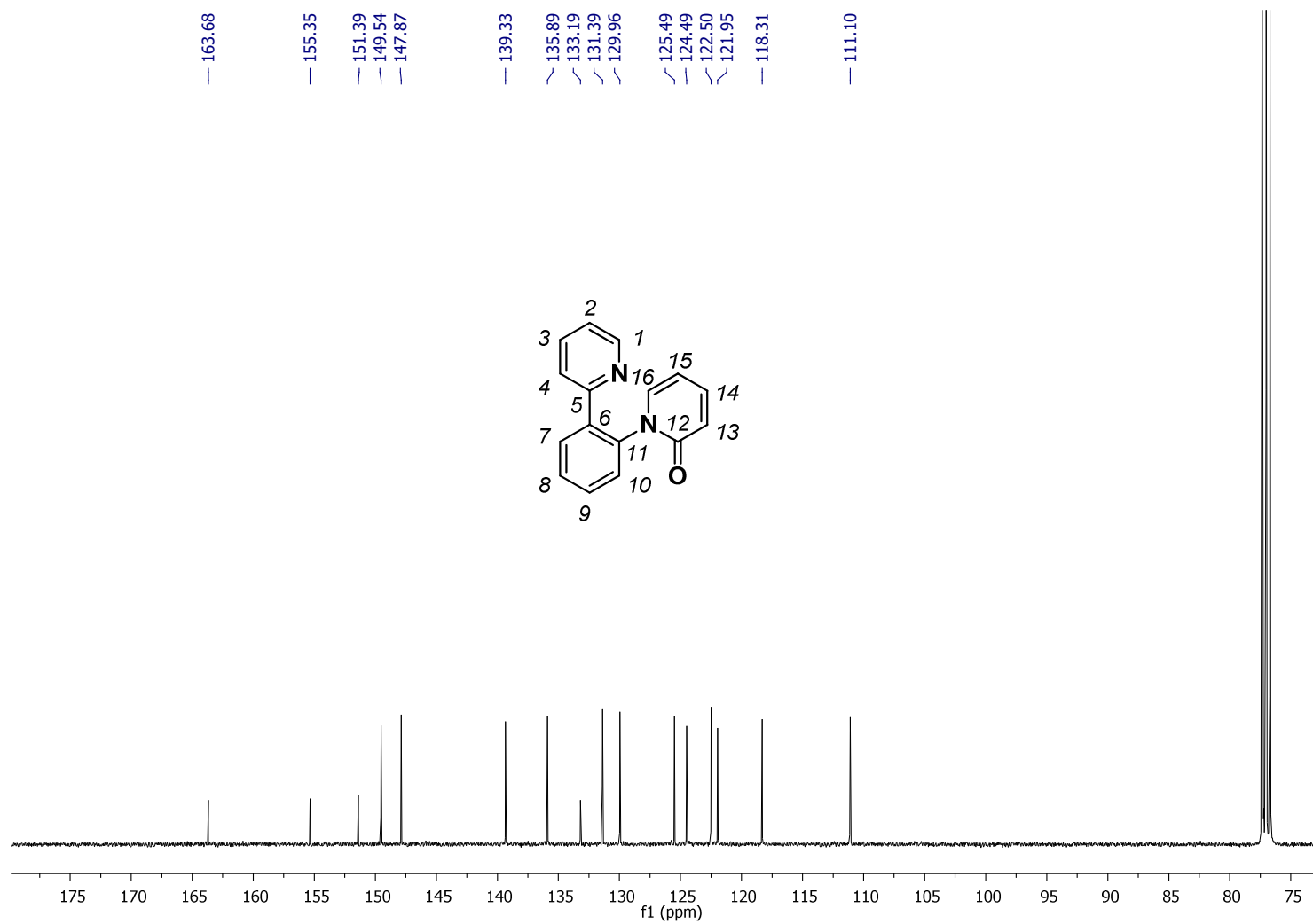
b)



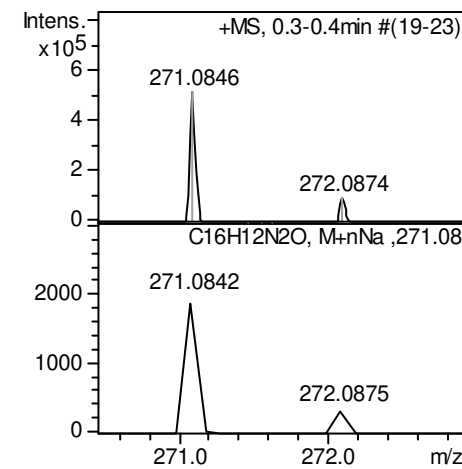
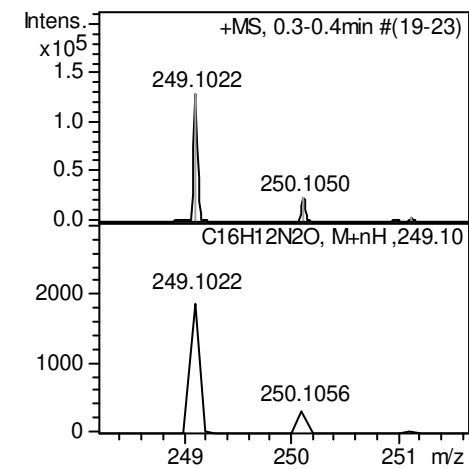
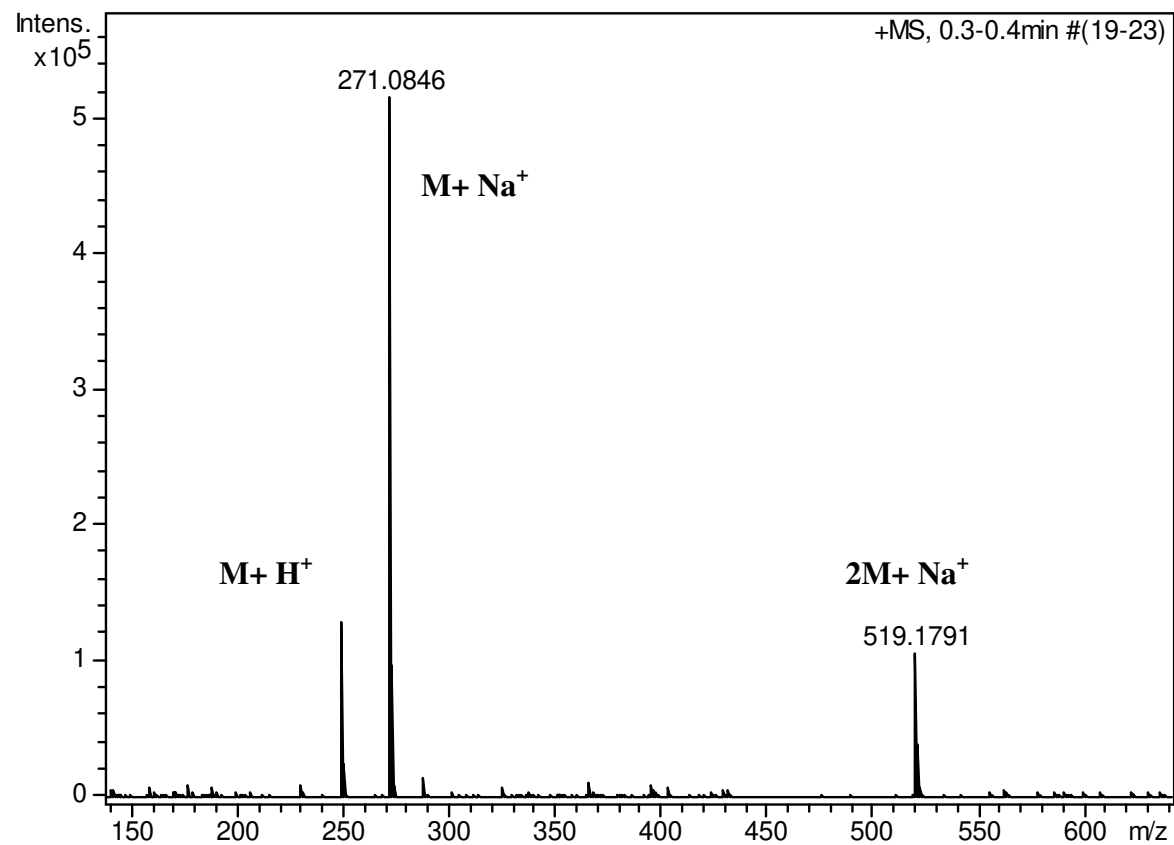
c)



b)



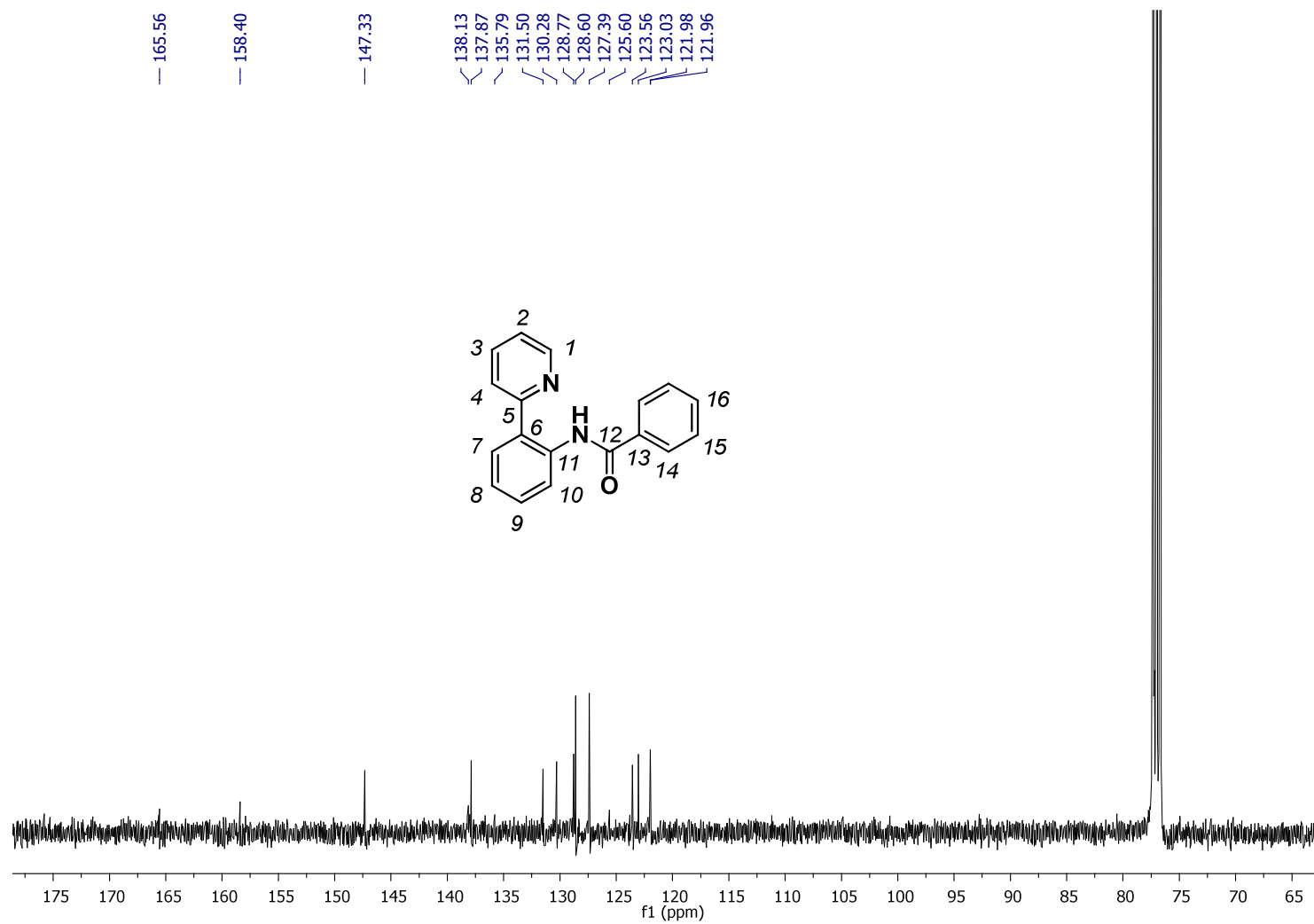
c)



a)



b)



c)

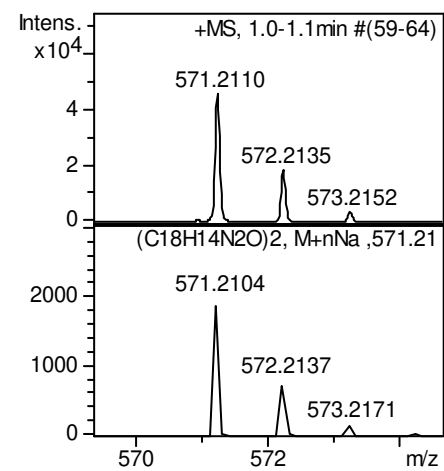
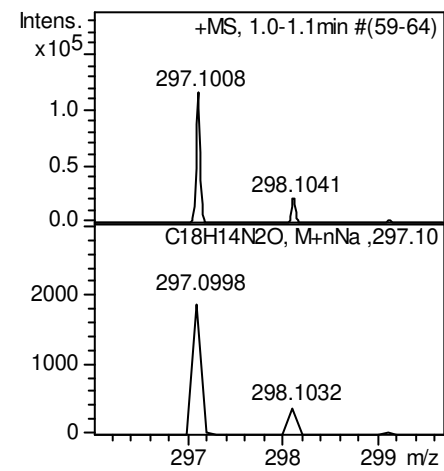
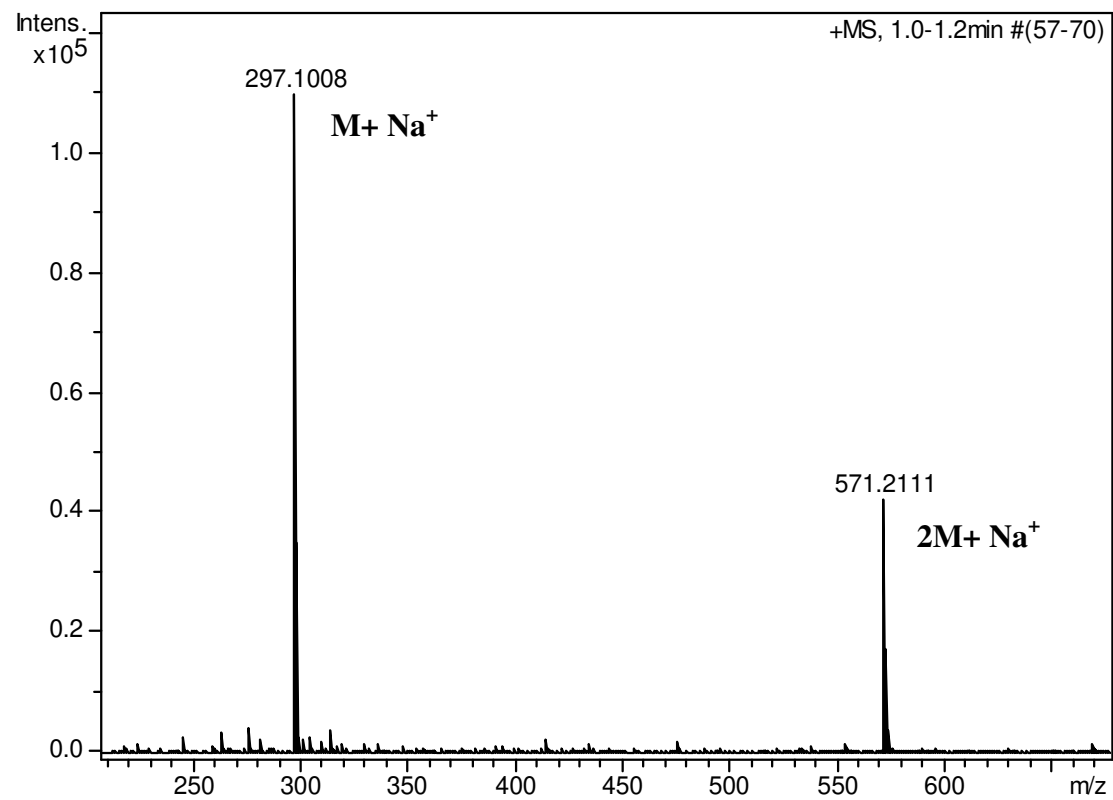
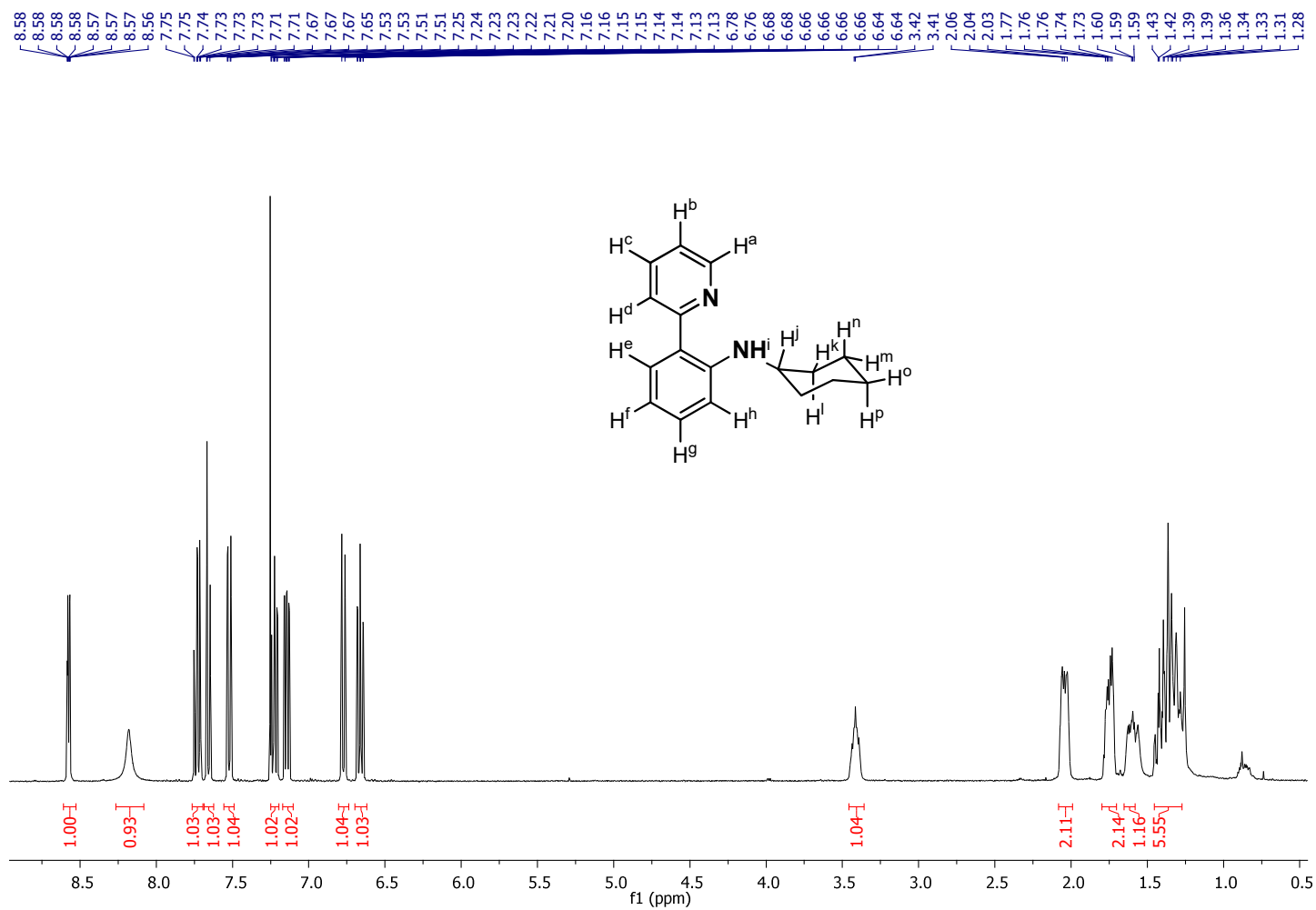
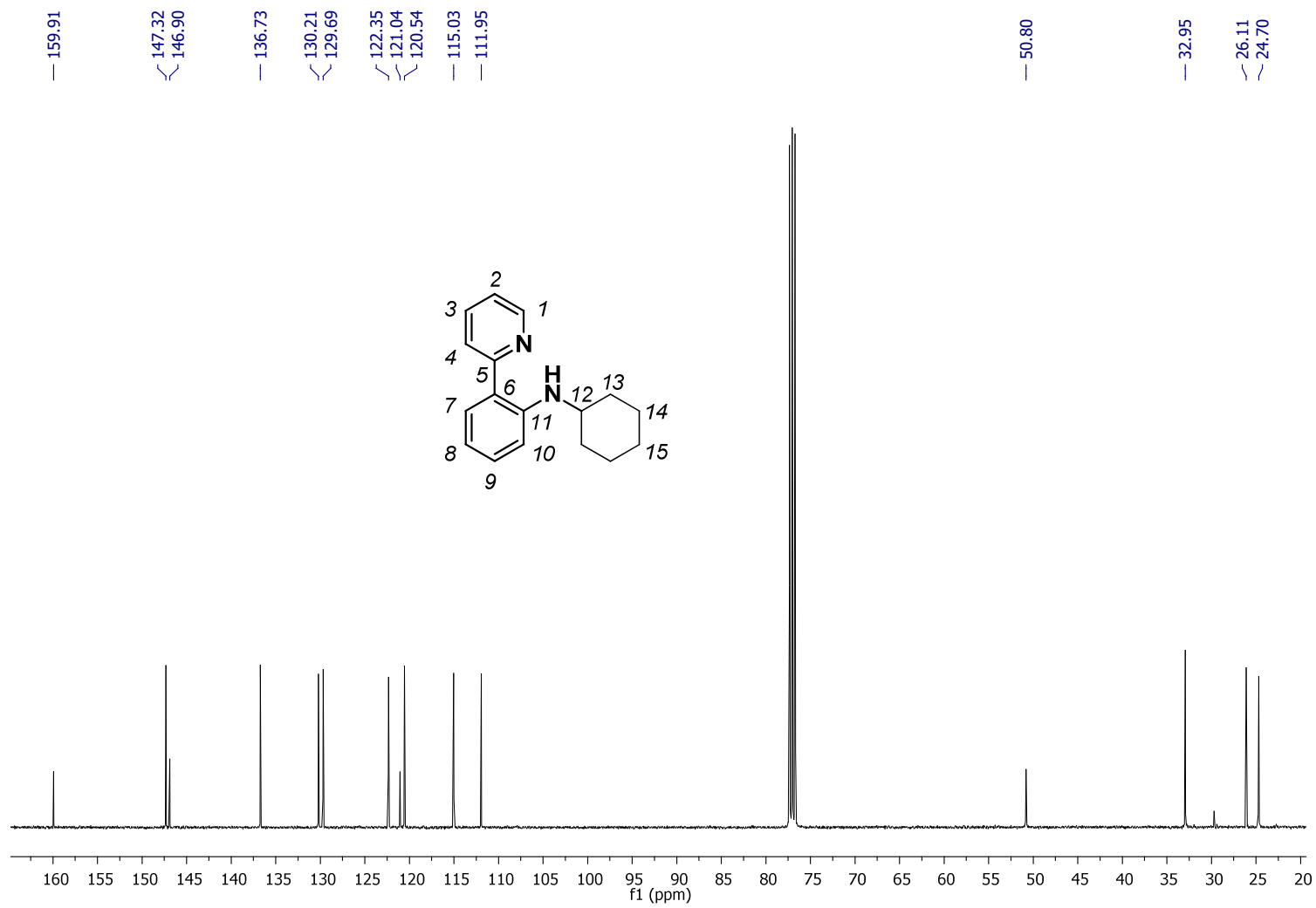


Figure S13. a) ^1H -NMR spectrum of compound **1ak** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

a)



b)



c)

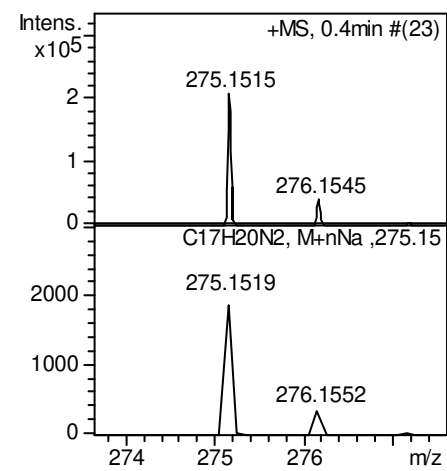
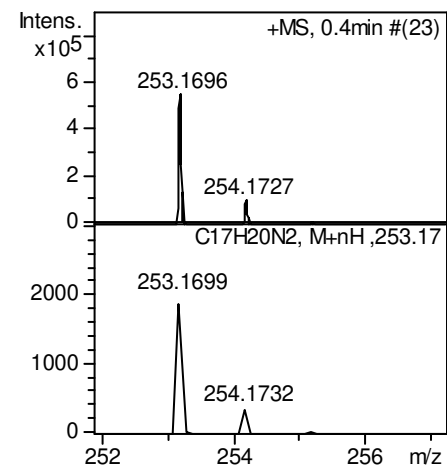
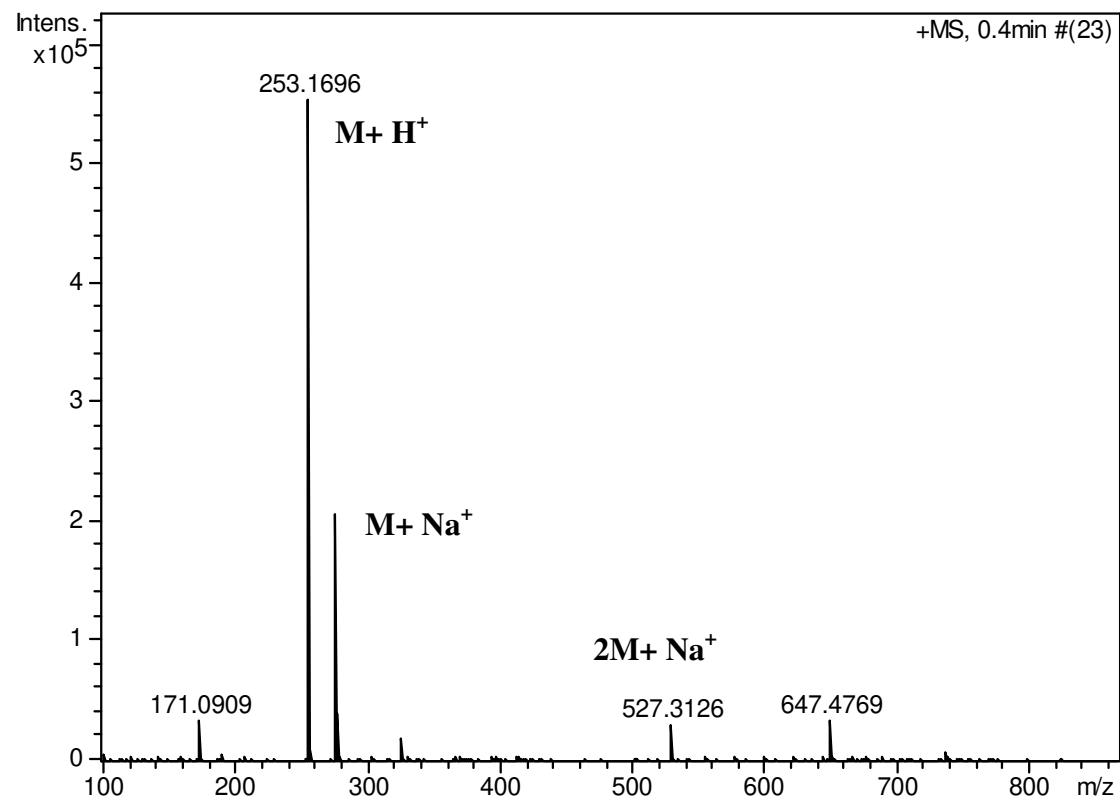
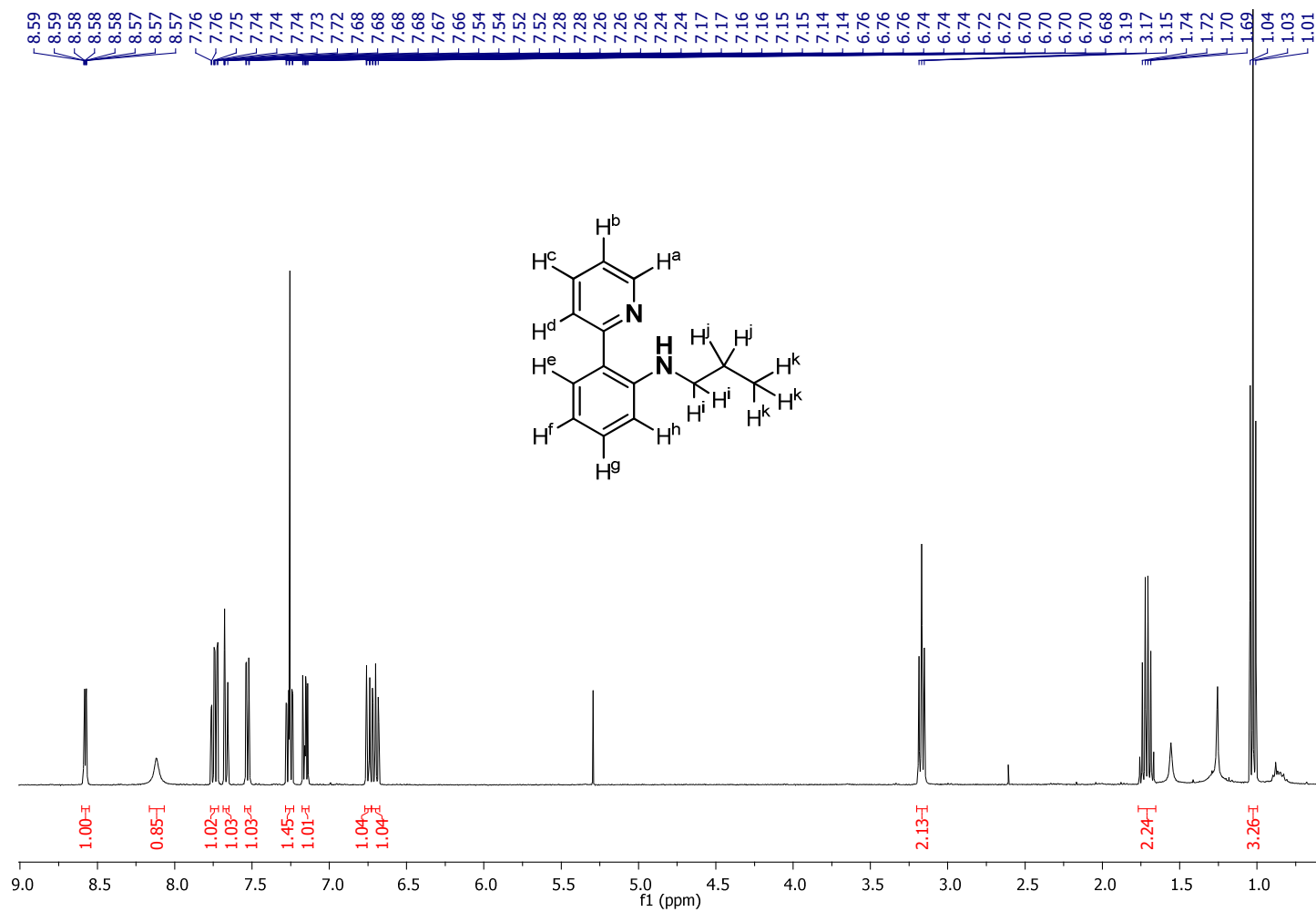
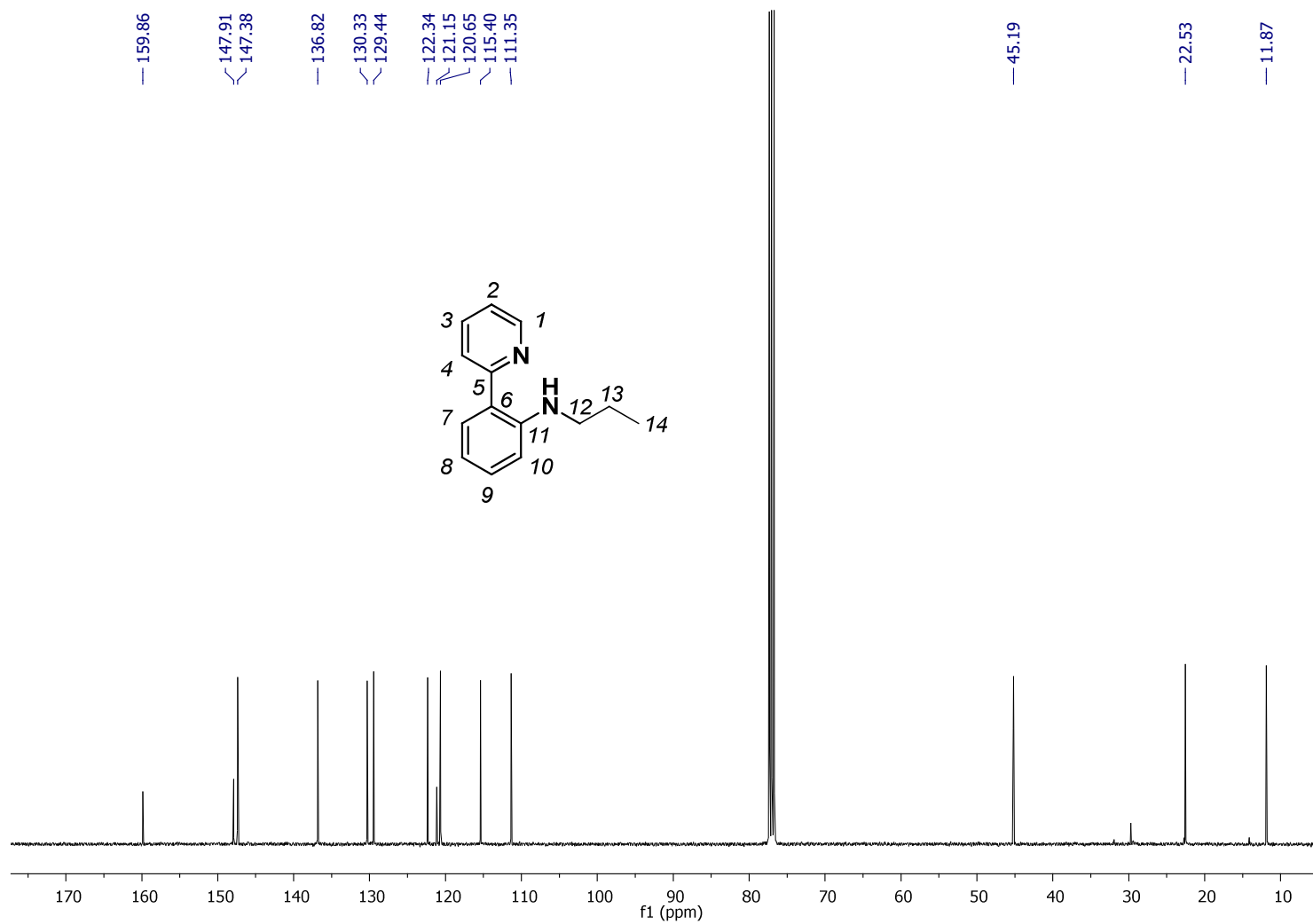


Figure S14. a) ^1H -NMR spectrum of compound **1al** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K); c) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

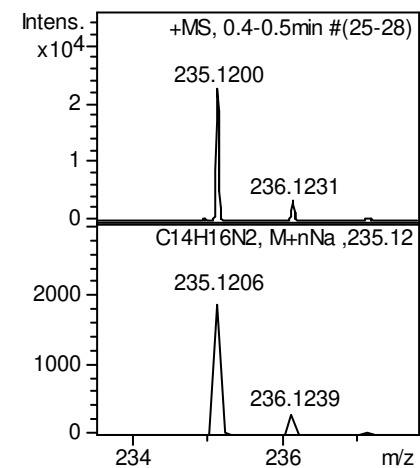
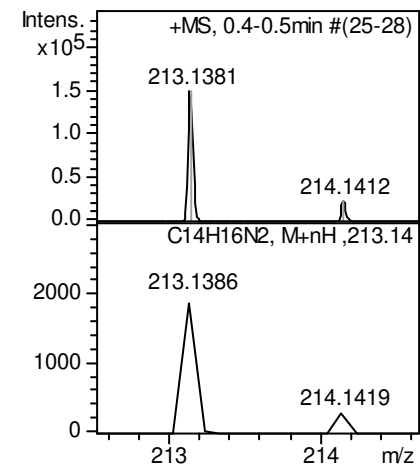
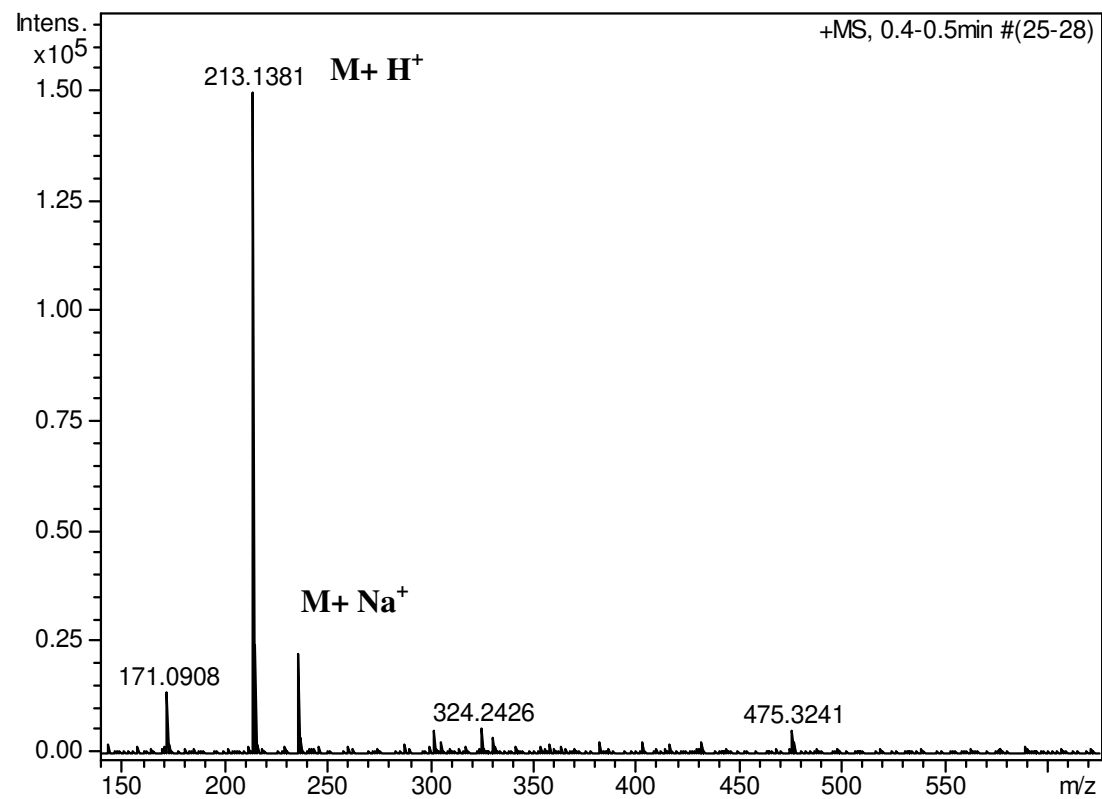
a)



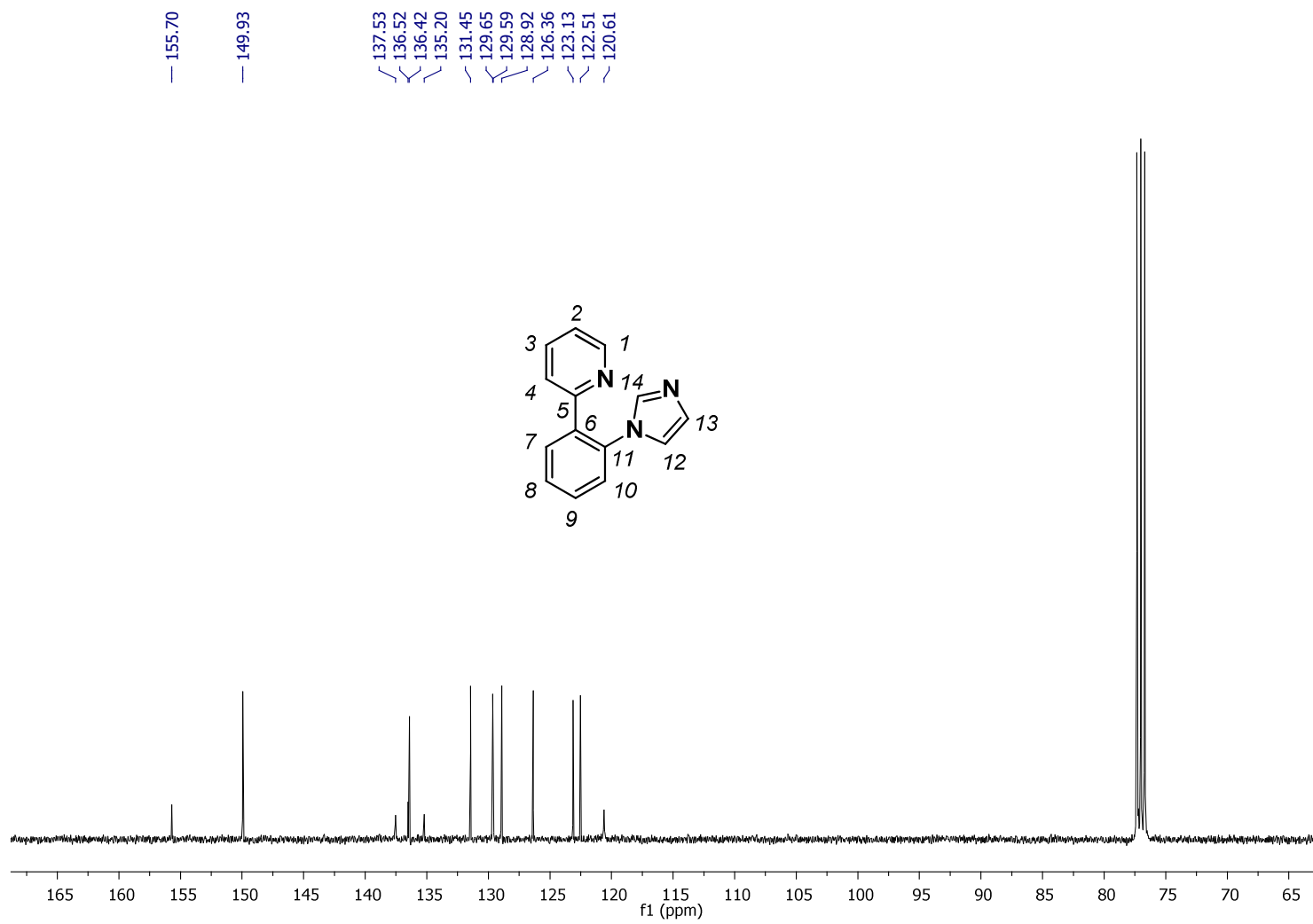
b)



c)



b)



c)

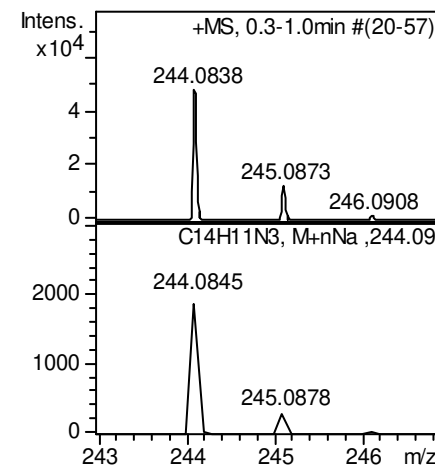
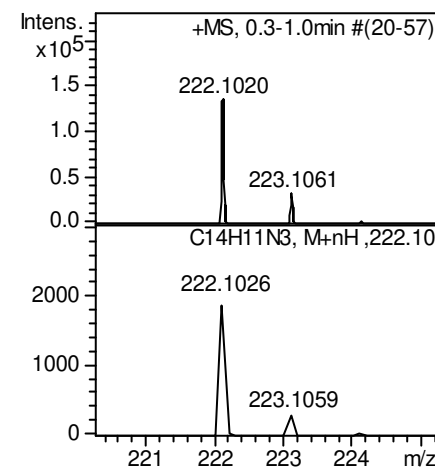
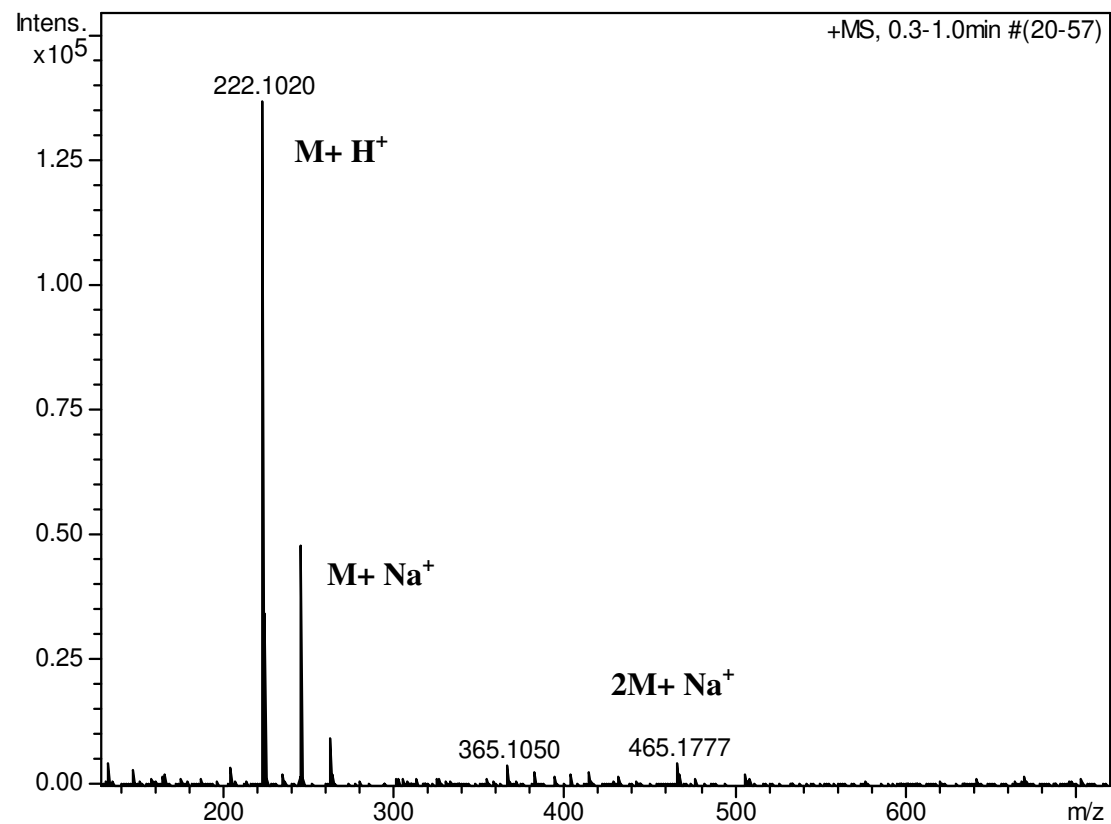
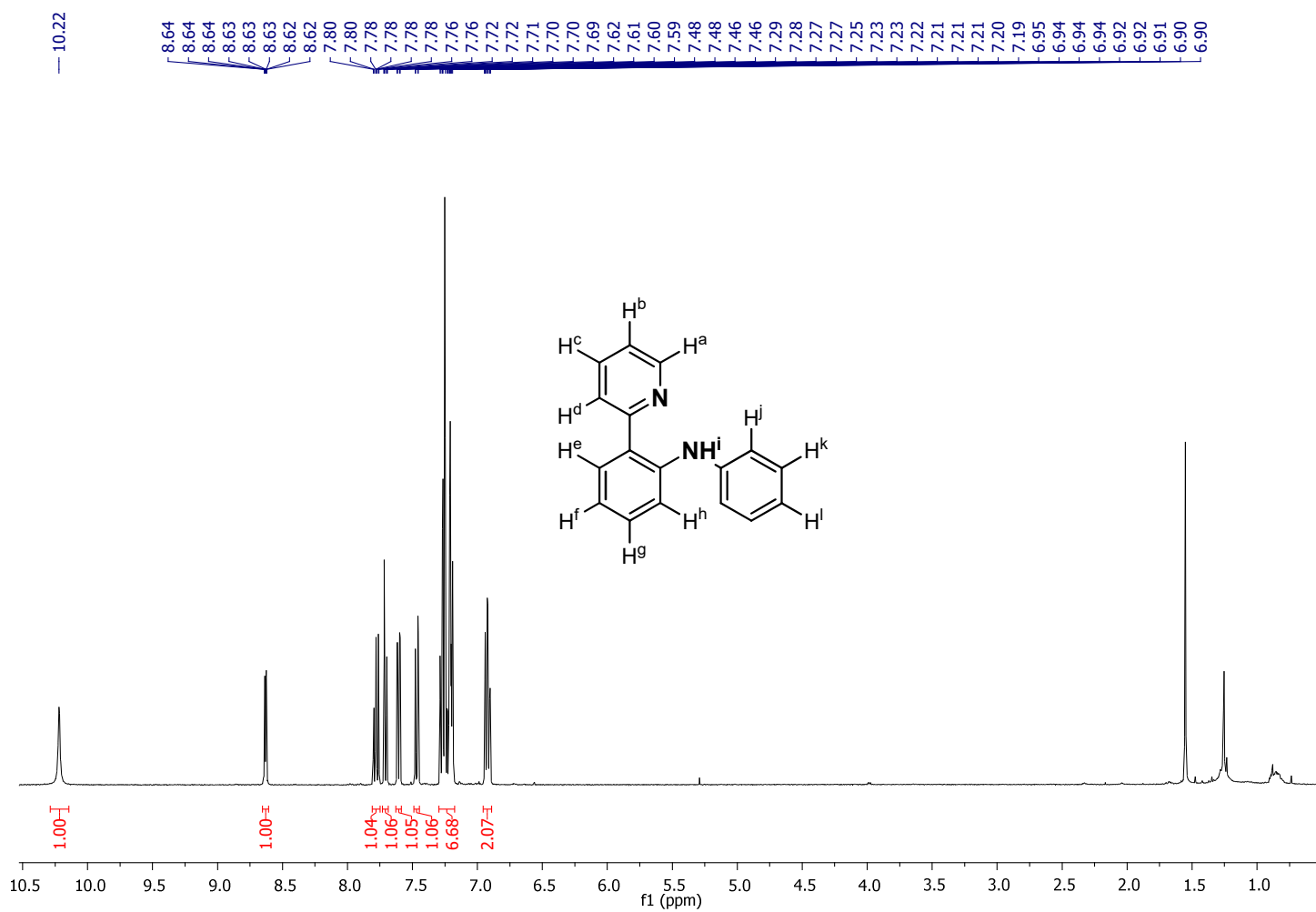
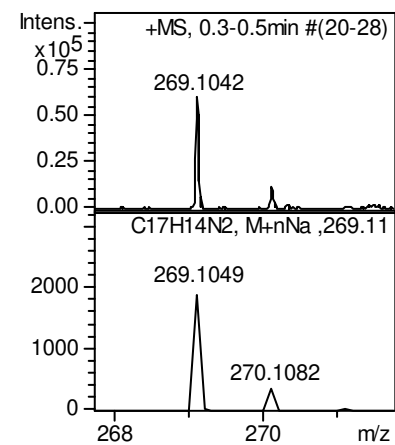
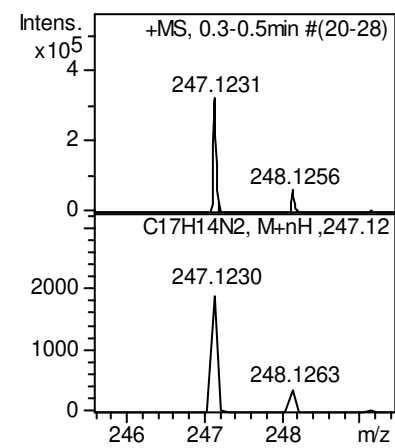
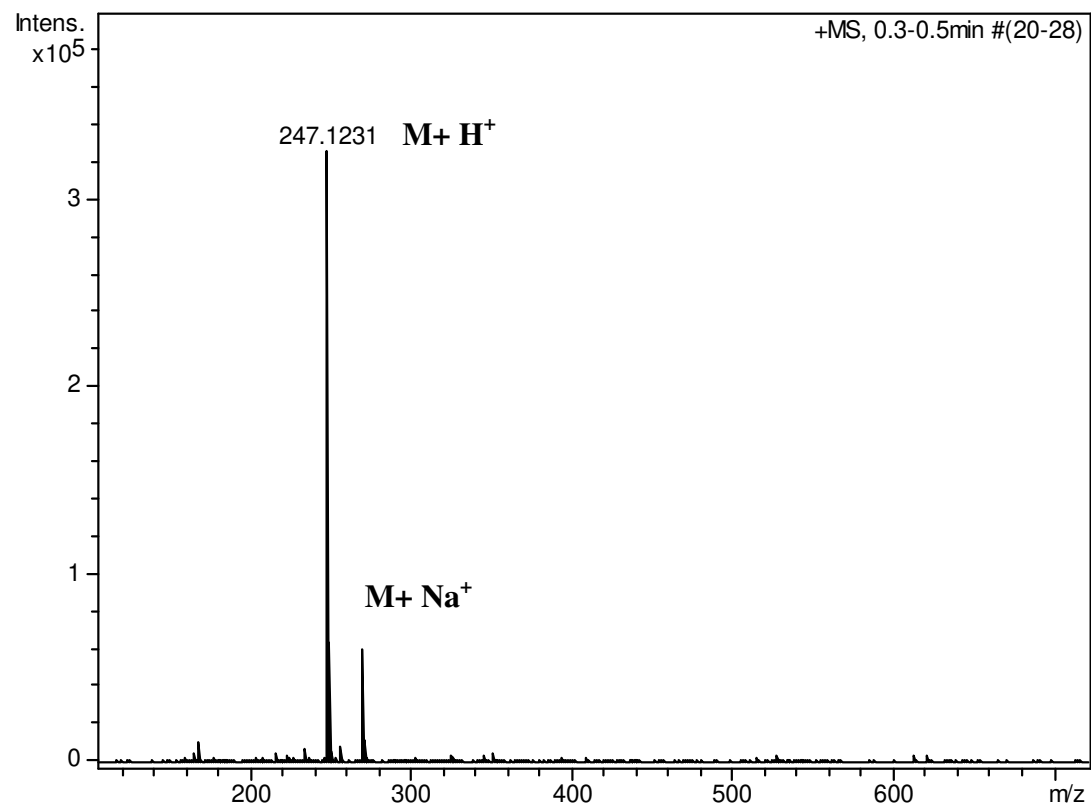


Figure S16. a) ^1H -NMR spectrum of compound **1an** in CDCl_3 , 400 MHz, at 298 K; b) HRMS (ESI-MS) spectrum (m/z). Observed HRMS (left) with the theoretical isotope prediction (right).

a)



b)



a)



b)

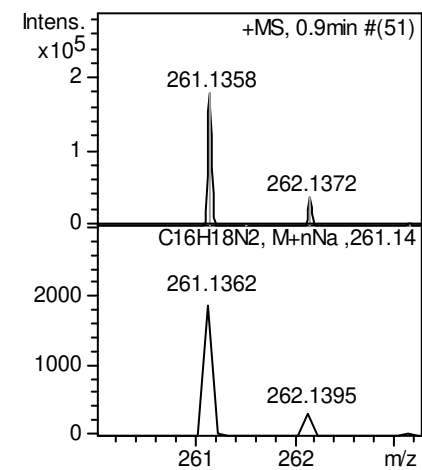
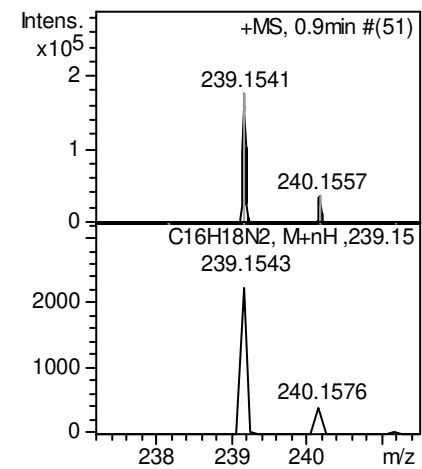
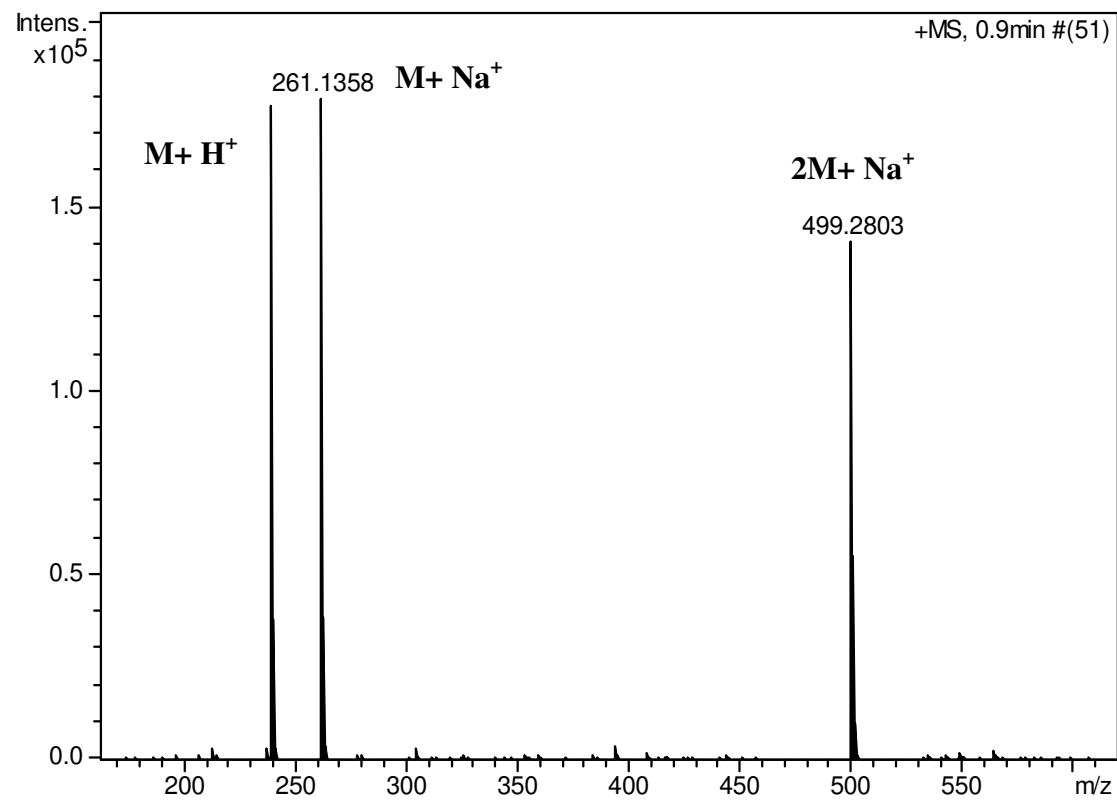
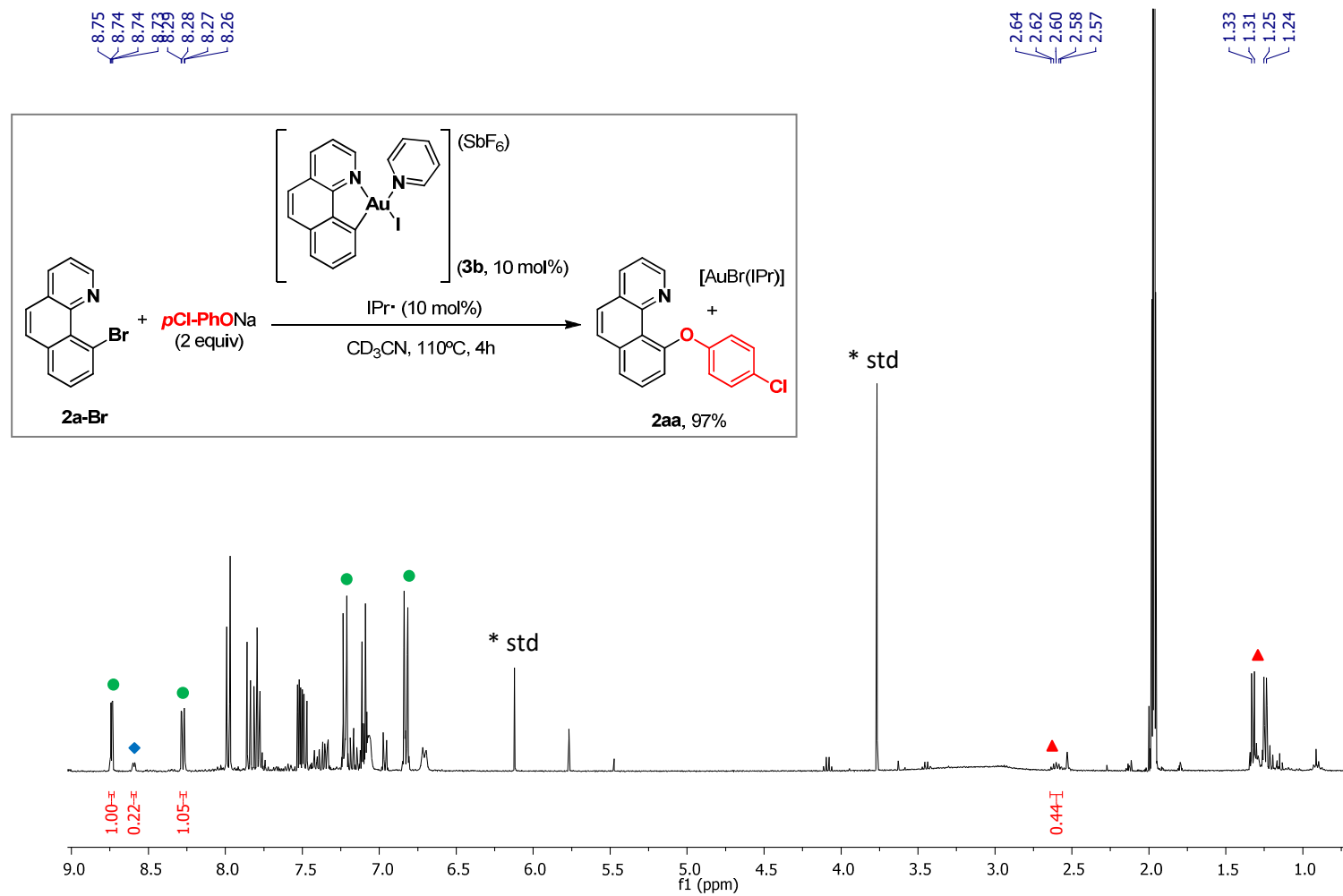


Figure S18. a) ^1H -NMR spectrum (CD_3CN , 298K) of the reaction crude of quantitative *p*-chlorophenolate insertion to **2a-Br** to form **2aa**(●) catalyzed by **3b**, followed by formation of $[\text{Au}(\text{Br})\text{IPr}]$ (▲) and liberation of the pyridine moiety (◆).



3. X-ray crystallography data

Crystallographic data for compound **1ah** (CCDC-1489676) and complexes **3a** (CCDC-1489681) and **3b** (CCDC-1489682) can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif.

X-Ray structure of **1ah**:

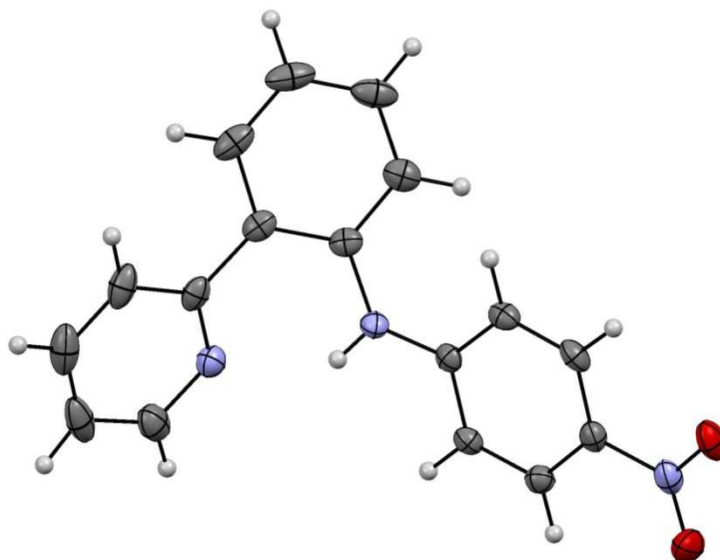


Figure S19. X-Ray structure of compound **1ah** obtained by crystallization from CHCl_3 . Ellipsoids are set at 50% probability.

Yellow crystals were grown from slow evaporation of a CHCl_3 solution of the compound, and used for low temperature (100(2) K) X-ray structure determination. The measurement was carried out on a *BRUKER SMART APEX CCD* diffractometer using graphite-monochromated $\text{Mo } K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) from an x-Ray Tube. The measurements were made in the range 2.144 to 28.317° for θ . Full-sphere data collection was carried out with ω and ϕ scans. A total of 20282 reflections were collected of which 3428 [$R(\text{int}) = 0.0312$] were unique. Programs used: data collection, *Smart*^[10]; data reduction, *Saint+*^[11]; absorption correction, *SADABS*^[12]. Structure solution and refinement was done using *SHELXTL*.^[13]

The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 . The non-hydrogen atoms were refined anisotropically. The H-atoms were placed in geometrically optimized positions and refined without constraints or restraints.

Chemical formula	C ₁₇ H ₁₃ N ₃ O ₂
fw (g mol⁻¹)	291.30
T (K)	100(2)
Space group	Orthorhombic, P 21/c
<i>a</i> (Å)	13.283(2)
<i>b</i> (Å)	13.585(2)
<i>c</i> (Å)	7.6811(13)
<i>α</i> (deg.)	90
<i>β</i> (deg.)	90
<i>γ</i> (deg.)	90
<i>V</i> (Å³)	1386.0(4)
<i>ρ</i>_{calcd.} (g cm⁻³)	1.396
<i>λ</i> (Å)	0.71073
<i>R</i>₁ [<i>I</i> > 2σ(<i>I</i>)]	0.0380
<i>wR</i>₂ [<i>I</i> > 2σ(<i>I</i>)]	0.0873

X-Ray structure of 3a:

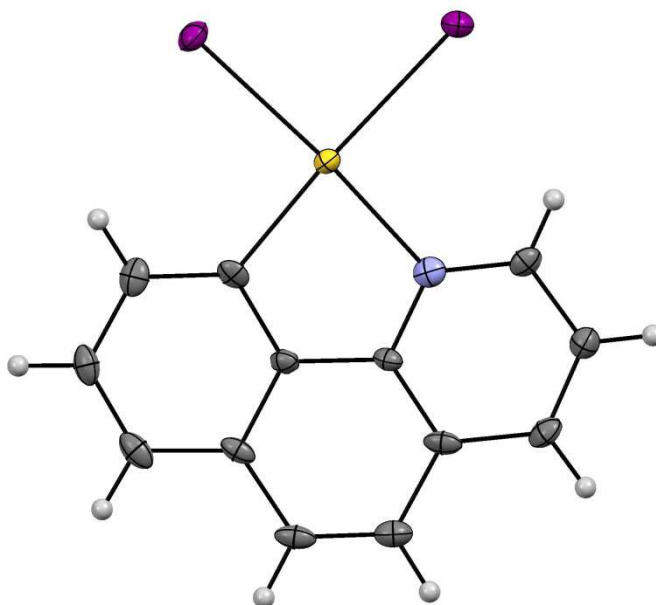


Figure S20. X-Ray structure of compound **3a** obtained by crystallization from CH₂Cl₂. Ellipsoids are set at 50% probability.

Red crystals were grown from CH₂Cl₂, and used for low temperature (100(2) K) X-ray structure determination. The measurement was carried out on a *BRUKER SMART APEX CCD* diffractometer using graphite-monochromated Mo *Kα* radiation ($\lambda = 0.71073$ Å) from an x-Ray Tube. The measurements were made in the range 2.171 to 28.295° for θ . Full-sphere data collection was carried out with ω and ϕ scans. A total of 19253 reflections were collected of which 3202 [*R*(int) = 0.0647] were unique. Programs used: data collection, Smart^[10]; data

reduction, Saint+^[11]; absorption correction, SADABS^[12]. Structure solution and refinement was done using SHELXTL^[13].

The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 . The non-hydrogen atoms were refined anisotropically. The H-atoms were placed in geometrically optimized positions and forced to ride on the atom to which they are attached.

Chemical formula	C ₁₃ H ₈ AuI ₂ N
fw (g mol⁻¹)	628.97
T (K)	100(2)
Space group	Monoclinic, P 21/c
a (Å)	10.4599(18)
b (Å)	13.687(2)
c (Å)	10.1110(17)
α (deg.)	90
β (deg.)	116.270(3)
γ (deg.)	90
V (Å³)	1298.1(4)
ρ_{calcd.} (g cm⁻³)	3.218
λ (Å)	0.71073
R₁ [I > 2σ(I)]	0.0341
wR₂ [I > 2σ(I)]	0.0849

X-Ray structure of 3b:

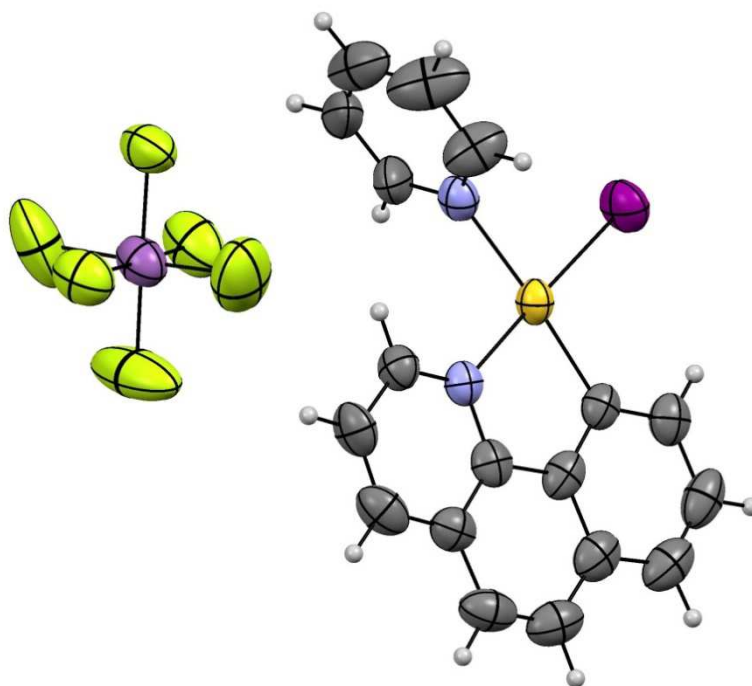


Figure S21. X-Ray structure of compound **3b** obtained by crystallization from CH₃CN and diethyl ether. Ellipsoids are set at 50% probability.

Orange crystals were grown from slow diffusion of diethyl ether in a CH₃CN solution of the compound, and used for low temperature (100(2) K) X-ray structure determination. The measurement was carried out on a *BRUKER SMART APEX CCD* diffractometer using graphite-monochromated Mo *K*α radiation ($\lambda = 0.71073 \text{ \AA}$) from an x-Ray Tube. The measurements were made in the range 2.07 to 28.58° for θ . Full-sphere data collection was carried out with ω and ϕ scans. A total of 62991 reflections were collected of which 10037 [R(int) = 0.0686] were unique. Programs used: data collection, Smart^[10]; data reduction, Saint+^[11]; absorption correction, SADABS^[12]. Structure solution and refinement was done using SHELXTL^[13].

The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 . The non-hydrogen atoms were refined anisotropically. The H-atoms were placed in geometrically optimized positions and forced to ride on the atom to which they are attached.

Chemical formula	C ₁₈ H ₁₃ AuIN ₂ F ₆ Sb
fw (g mol⁻¹)	816.92
T (K)	100(2)
Space group	Monoclinic, P 21/c
<i>a</i> (Å)	14.260(9)
<i>b</i> (Å)	20.667(13)
<i>c</i> (Å)	14.033(9)
α (deg.)	90
β (deg.)	104.38(1)
γ (deg.)	90
<i>V</i> (Å³)	4006(4)
$\rho_{\text{calcd.}}$ (g cm⁻³)	2.709
λ (Å)	0.71073
R₁ [I > 2σ(I)]	0.0598
wR₂ [I > 2σ(I)]	0.1587

(10) Bruker Advanced X-ray Solutions. SMART: Version 5.631, **1997-2002**.

(11) Bruker Advanced X-ray Solutions. SAINT+: Version 6.36A, **2001**.

(12) G. M. Sheldrick, *Emperical Absorption Correction Program*, Universität Göttingen, **1996**, Bruker Advanced X-ray Solutions. SADABS Version 2.10, **2001**.

(13) G. M. Sheldrick, *Program for Crystal Structure Refinement*, Universität Göttingen, **1997**, Bruker Advanced X-ray Solutions. SHELXTL Version 6.14, **2000-2003**. SHELXL-2013 (Sheldrick, **2013**).

Supplementary Information Chapter V

Cyclometalated Gold(III) Complexes: Noticeable Differences between (N,C) and (P,C) Ligands in Migratory Insertion

Jordi Serra, Pau Font, Eric-Daiann Sosa-Carrizo, Sonia Mallet-Ladeira, Stéphane Massou, Teodor Parella, Karinne Miqueu, Abderrahmane Amgoune, Xavi Ribas*, and Didier Bourissou*

CONTENTS

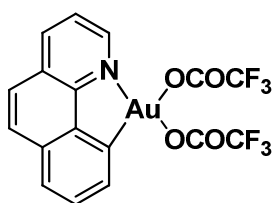
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1. Materials and Methods

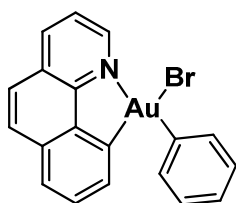
1.1. Materials and instrumentation

Reagents and solvents used were commercially available reagent quality unless indicated otherwise. All reactions and manipulations were carried out under an atmosphere of dry argon using standard Schlenk techniques or in a glovebox under inert atmosphere with O₂ and H₂O concentrations < 1.0 ppm. Dry, oxygen-free solvents were employed. Solution ¹H, ¹³C and ¹⁹F NMR spectra were recorded on Bruker AVANCE 300, 400 or 500 spectrometers under routine conditions at 298 K unless otherwise specified. The following abbreviations and their combinations are used: br, broad; s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet. The ¹H and ¹³C resonance signals were attributed by means of 2D COSY, HSQC and HMBC experiments. High resolution mass spectra (HRMS) were recorded on a Waters LCT apparatus and/or a Bruker MicrOTOF-Q II TM instrument using ESI or Cryospray ionization sources.

1.2. Synthesis and characterization of the Au(III) complexes

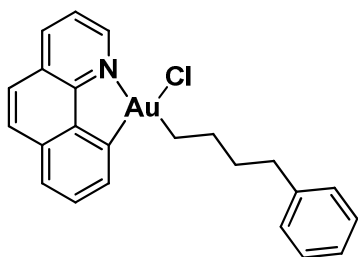


2: Complex **1** (248.1 mg, 0.39 mmol) and AgOAc^F (183.3 mg, 0.83 mmol) were suspended in CH₂Cl₂ (8 mL). After stirring for 10 min at room temperature, solvent was removed under vacuum and acetone (8 mL) was added. The resulting light yellow mixture was filtered through *Celite*®, dried under vacuum and washed with hexanes (3 x 3 mL) to give the desired complex as a pale yellow solid (213.4 mg, 91%). **¹H-NMR** (acetone-d₆, 400 MHz, 298K) δ, ppm: 9.08 (dd, *J* = 8.0, 1.2 Hz, 1H, H^c), 8.95 (dd, *J* = 5.6, 1.2 Hz, 1H, H^a), 8.16 (dd, *J* = 8.0, 5.6 Hz, 1H, H^b), 8.10 (m, 3H, H^d+H^e+H^f), 7.72 (t, *J* = 8.0 Hz, 1H, H^g), 7.25 (d, *J* = 7.6 Hz, 1H, H^h); **¹³C{¹H}-NMR** (acetone-d₆, 100 MHz, 298K) δ, ppm: 153.32 (C13), 148.15 (C1), 143.44 (C3), 140.54 (C11), 137.18 (C12), 135.52 (C7), 130.22 (C9), 129.60 (C5), 129.35 (C4), 128.29 (C8), 126.22 (C10), 125.50 (C6), 124.08 (C4); **¹⁹F{¹H}-NMR** (acetone-d₆, 282 MHz, 298K) δ, ppm: -74.85 (s, CF₃*trans* to N, 3F), -73.99 (s, br, CF₃*cis* to N, 3F); **HRMS (ESI)** (Acetone/CH₃CN, *m/z*): calcd for C₁₇H₈AuF₆NO₄ [M+Na]⁺ 623.9915, found: 623.9962.

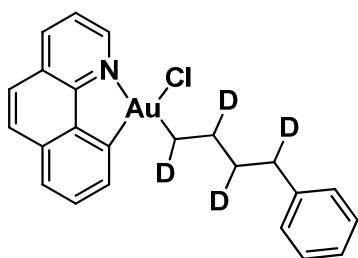


3-Br: To a solution of complex **2** (210.5 mg, 0.35 mmol) in THF (10 mL) was added dropwise PhMgBr (2.1 equiv, 2M in diethyl ether) at -78°C. The reaction mixture was stirred at -78°C for 1 h and then at room temperature for 1 h. The solvent was removed in vacuo and the resulting solid was dissolved in CH₂Cl₂ (8 mL) and washed with distilled water (2 x 2 mL). The organic phase was dried over Na₂SO₄, filtered through *Celite*® and all volatiles were then removed under vacuum to give a pale yellow solid, which was finally purified by column chromatography on silica gel (CH₂Cl₂:hexane 3:2) to yield **3-Br** as a white solid (110.0 mg,

59%). **¹H-NMR** (CDCl₃, 500 MHz, 298K) δ, ppm: 9.89 (dd, *J* = 5.0, 1.5 Hz, 1H, H^a), 8.53 (dd, *J* = 8.0, 1.5 Hz, 1H, H^c), 7.93 (d, *J* = 8.5 Hz, 1H, H^e), 7.85 (dd, *J* = 8.0, 5.0 Hz, 1H, H^b), 7.83 (dd, *J* = 7.5, 0.5 Hz, 1H, H^f), 7.78 (d, *J* = 8.5 Hz, 1H, H^d), 7.61 (dd, *J* = 8.0, 1.0 Hz, 2H, Hⁱ), 7.54 (t, *J* = 7.5 Hz, 1H, H^g), 7.31 (t, *J* = 7.5 Hz, 2H, H^j), 7.25 (tt, *J* = 7.5, 1.5 Hz, 1H, H^k), 7.06 (dd, *J* = 7.5, 1.0 Hz, 1H, H^h); **¹³C{¹H}-NMR** (CDCl₃, 125 MHz, 298K) δ, ppm: 151.97 (C13), 149.41 (C11), 148.68 (C1), 141.18 (C14), 139.56 (C3), 138.60 (C7), 134.50 (C12), 133.08 (C15), 131.66 (C10), 130.44 (C9), 129.70 (C6), 129.44 (C16), 127.77 (C4), 126.21 (C8), 125.97 (C17), 124.11 (C5), 122.91 (C2); **HRMS (ESI)** (CHCl₃, *m/z*): calcd for C₁₉H₁₃AuN [M⁺] 452.0714, found: 452.0722. **Anal. Calcd for C₁₉H₁₃AuBrN**: C, 42.88; H, 2.46; N, 2.63. Found: C, 42.91; H, 2.34; N, 2.98.

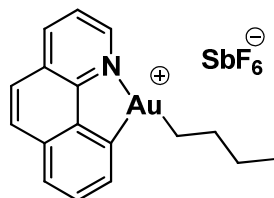


5A-Cl: In an inert-atmosphere glovebox, a pressure screw-cap NMR tube was charged with **3-Br** (16.0 mg, 0.03 mmol) in CD₂Cl₂ (0.35 mL). AgSbF₆ (12.4 mg, 0.036 mmol) was placed into a small glass vial and solubilized in CD₂Cl₂ (0.35 mL). The solution was loaded into a plastic syringe equipped with a stainless steel needle, and the syringe was closed by blocking the needle with a septum. Outside the glovebox, the NMR tube was pressurized under argon atmosphere and cooled down to –60 °C (Acetone/N₂ coldbath). At this temperature, the solution of AgSbF₆ was added. The overall mixture was degassed 3 times using the Freeze-Pump-Thaw degassing technique and 2 bar of ethylene were added. The reaction was monitored by ¹H-NMR. After heating overnight at 40°C the ethylene pressure was released and the reaction crude was filtered through *Celite*® on a vial-containing *n*Bu₄N-Cl (10.0 mg, 0.036 mmol). The resulting solution was purified by column chromatography on silica gel (CH₂Cl₂:hexane 2:1) to give **5A-Cl** as a white solid (9.6 mg, 60%). **¹H-NMR** (CDCl₃, 400 MHz, 298K) δ, ppm: 9.58 (dd, *J* = 5.2, 1.6 Hz, 1H, H^a), 8.46 (dd, *J* = 8.0, 1.6 Hz, 1H, H^c), 7.92 (d, *J* = 8.8 Hz, 1H, H^d), 7.86 (dd, *J* = 7.6, 0.8 Hz, 1H, H^f), 7.82 (m, 2H, H^b + H^h), 7.75 (d, *J* = 8.8 Hz, 1H, H^e), 7.74 (t, *J* = 7.6 Hz, 1H, H^g), 7.26 (m, 4H, H^m + Hⁿ), 7.18 (tt, *J* = 7.2, 1.6 Hz, 1H, H^o), 2.76 (t, *J* = 8.0 Hz, 2H, Hⁱ), 2.72 (t, *J* = 8.0 Hz, 2H, H^j), 1.97 (m, 4H, H^k + H^l); **¹³C{¹H}-NMR** (CDCl₃, 100 MHz, 298K) δ, ppm: 150.81 (C13), 147.00 (C1), 145.37 (C11), 142.70 (C18), 139.20 (C7), 139.08 (C3), 134.71 (C12), 130.22 (C9), 129.56 (C5), 128.51 (C19), 128.23 (C20), 128.13 (C10), 127.41 (C4), 126.22 (C8), 125.57 (C21), 124.07 (C6), 122.73 (C2), 35.78 (C17), 34.24 (C14), 34.13 (C15), 30.84 (C16); **HRMS (ESI)** (CHCl₃, *m/z*): calcd for C₂₃H₂₁AuN [M⁺] 508.1340, found: 508.1346; **Anal. Calcd for C₂₃H₂₁AuNCl**: C, 50.80; H, 3.89; N, 2.58. Found: C, 50.45; H, 3.48; N, 2.89.



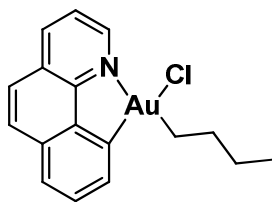
5A-Cl-d₄: In an inert-atmosphere glovebox, a pressure screw-cap NMR tube was charged with **3-Br** (14.6 mg, 0.027 mmol) in CD₂Cl₂ (0.3mL). AgSbF₆ (12.0mg, 0.035 mmol) was placed into a small glass vial and solubilized in CD₂Cl₂ (0.3 mL). The

solution was loaded into a plastic syringe equipped with a stainless steel needle, and the syringe was closed by blocking the needle with a septum. Outside the glovebox, the NMR tube was filled with argon and cooled down to $-60\text{ }^{\circ}\text{C}$ (Acetone/ N_2 coldbath). At this temperature, the solution of AgSbF_6 was added. The overall mixture was degassed 3 times using the Freeze-Pump-Thaw degassing technique and 1 bar of *trans*-ethylene- d_2 was added. After heating for 24 h at $40\text{ }^{\circ}\text{C}$, the NMR tube was refilled with 1 bar of *trans*-ethylene- d_2 and the mixture was heated for 24 h more at $40\text{ }^{\circ}\text{C}$. Then, in an inert-atmosphere glovebox, the reaction crude was filtered through *Celite*® on a vial-containing $n\text{Bu}_4\text{NCl}$ (9.2 mg, 0.033 mmol). The resulting solution was analyzed by NMR without further purification. **5A-Cl- d_4** was isolated as a white solid (5.0 mg, 33%) by column chromatography on silica gel (CH_2Cl_2 :hexane 2:1). **^1H -NMR** (CD_2Cl_2 , 500 MHz, 298K) δ , ppm: 9.43 (dd, $J = 5.1, 1.5\text{ Hz}$, 1H, H^a), 8.45 (dd, $J = 8.0, 1.5\text{ Hz}$, 1H, H^c), 7.88 (d, $J = 8.8\text{ Hz}$, 1H, H^d), 7.83 (dd, $J = 7.9, 0.8\text{ Hz}$, 1H, H^f), 7.80 – 7.67 (m, 4H, $\text{H}^b + \text{H}^h + \text{H}^e + \text{H}^g$), 7.27 – 7.19 (m, 4H, $\text{H}^m + \text{H}^n$), 7.15 (tt, $J = 7.2, 1.6\text{ Hz}$, 1H, H^o), 2.69 (d, $J = 6.1\text{ Hz}$, 1H, H^i), 2.59 (d, $J = 5.7\text{ Hz}$, 1H, H^j), 1.88 (t, $J = 7.0\text{ Hz}$, 1H, H^k or H^l), 1.84 (t, $J = 7.0\text{ Hz}$, 1H, H^j or H^k); **$^{13}\text{C}\{^1\text{H}\}$ -NMR** (CD_2Cl_2 , 125 MHz, 298K) δ , ppm: 151.18 (C13), 147.29 (C1), 145.77 (C11), 143.38 (C18), 139.83 (C3), 139.58 (C7), 135.19 (C12), 130.62 (C9), 129.93 (C5), 128.98 (C19), 128.72 (C20), 128.48 (C10), 127.99 (C4), 126.72 (C8), 126.07 (C21), 124.76 (C6), 123.39 (C2), 35.77 (t, C17), 34.23 (t, C14), 33.67 (t, C15), 30.73 (t, C16); **HRMS (ESI)** (CHCl_3 , m/z): calcd for $\text{C}_{23}\text{H}_{17}\text{D}_4\text{AuN} [\text{M}^+]$ 512.1591, found: 512.1559.



6A: In an inert-atmosphere glovebox, a pressure screw-cap NMR tube was charged with **6-Cl** (9.4 mg, 0.02 mmol) in CD_2Cl_2 (0.35 mL). AgSbF_6 (8.2 mg, 0.024 mmol) was placed into a small glass vial and solubilized also in CD_2Cl_2 (0.35 mL). The solution was loaded into a plastic syringe equipped with a stainless steel needle, and the syringe was closed by blocking the needle with a septum. Outside the glovebox, the NMR tube was pressurized under argon atmosphere and cooled down to $-60\text{ }^{\circ}\text{C}$ (Acetone/ N_2 coldbath). At this temperature, the solution of AgSbF_6 was added. The tube was immediately introduced in the NMR machine and the reaction was monitored by ^1H -NMR from $-60\text{ }^{\circ}\text{C}$ to room temperature. Complex **6A** was generated at $-60\text{ }^{\circ}\text{C}$ and no formation of butane or 2-butenes was observed upon warming. The complex was characterized at room temperature: **^1H -NMR** (CD_2Cl_2 , 400 MHz, 298K) δ , ppm: 8.98 (dd, $J = 3.6\text{ Hz}$, 1H, H^a), 8.63 (dd, $J = 8.0\text{ Hz}$, 1H, H^c) 8.00 (m, 3H, $\text{H}^b + \text{H}^e + \text{H}^f$), 7.89 (d, $J = 8.8\text{ Hz}$, 1H, H^d), 7.79 (m, 2H, $\text{H}^h + \text{H}^g$), 2.58 (dd, $J = 7.6\text{ Hz}$, 2H, H^i), 1.88 (dd, $J = 7.6\text{ Hz}$, 2H, H^j), 1.65 (sext, $J = 7.6\text{ Hz}$, 2H, H^k), 1.07 (t, $J = 7.6\text{ Hz}$, 3H, H^l); **$^{13}\text{C}\{^1\text{H}\}$ -NMR** (CD_2Cl_2 , 100 MHz, 298K) δ , ppm: 147.79 (C13), 146.59 (C1), 140.57 (C3), 135.04 (C7), 133.76 (C11), 131.64 (C12), 130.24 (C9), 129.47 (C6), 128.71 (C10), 128.00 (C8), 125.39 (C4), 124.76

(C5), 123.99 (C2), 38.86 (C14), 32.43 (C15), 25.36 (C16), 13.64 (C17); **HRMS (ESI)** (CH_2Cl_2 , m/z): calcd for $\text{C}_{17}\text{H}_{17}\text{AuN}$ [M^+] 432.1021, found: 432.1027.



6-Cl: To a solution of complex **2** (41.9 mg, 0.07 mmol) in THF (4 mL) was added dropwise BuMgCl (2.1 equiv, 2M in diethyl ether) at -78°C . The reaction mixture was stirred at -78°C for 1 h and then at room temperature for 1 h. The solvent was removed in vacuo and the resulting solid was dissolved in CH_2Cl_2 (3 mL) and washed with distilled water (2 x 1 mL). The collected organic phases were dried over Na_2SO_4 , filtered through *Celite*® and all volatiles were then removed under vacuum to give the light yellow solid, which was subsequently purified by column chromatography on silica gel (CH_2Cl_2 :hexane 3:1) to yield **6-Cl** as a white solid (23.9 mg, 73%). **^1H -NMR** (CDCl_3 , 400 MHz, 298K) δ , ppm: 9.58 (dd, $J = 5.2, 1.2$ Hz, 1H, H^a), 8.46 (dd, $J = 8.0, 1.2$ Hz, 1H, H^c), 7.92 (d, $J = 8.8$ Hz, 1H, H^e), 7.88 (m, 2H, $\text{H}^g + \text{H}^f$), 7.81 (dd, $J = 8.0, 5.2$ Hz, 1H, H^b), 7.76 (m, 2H, $\text{H}^h + \text{H}^d$), 2.71 (t, $J = 7.6$ Hz, 2H, H^i), 1.92 (quint, $J = 7.6$ Hz, 2H, H^j), 1.63 (sext, $J = 7.6$ Hz, 2H, H^k), 1.03 (t, $J = 7.6$ Hz, 3H, H^l); **$^{13}\text{C}\{^1\text{H}\}$ -NMR** (CDCl_3 , 100 MHz, 298K) δ , ppm: 150.76 (C13), 146.96 (C1), 145.37 (C11), 139.20 (C7), 139.02 (C3), 134.68 (C4), 130.18 (C10), 129.55 (C6), 128.14 (C9), 127.38 (C12), 126.19 (C8), 124.05 (C5), 122.71 (C2), 34.71 (C14), 33.40 (C15), 25.68 (C16), 14.06 (C17); **HRMS (ESI)** (CHCl_3 , m/z): calcd for $\text{C}_{17}\text{H}_{17}\text{AuN}$ [M^+] 432.1021, found: 432.1018.

2. Computational Details

All calculations were performed using the Gaussian 09 package^[1] and the B3PW91 hybrid^[2] functional on the real cationic experimental systems, taking into account solvent effect

(1) Gaussian 09, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

(2) (a) A. D. Becke *J. Chem. Phys.* **1993**, 98, 5648; (b) J. P. Perdew, in *Electronic Structure of Solids '91*, Ed. P. Ziesche and H. Eschrig, Akademie Verlag, Berlin, **1991**, 11.

(dichloromethane) by means of polarizable continuum model PCM.^[3] The weakly coordinating counter-anion SbF_6^- has not been considered in the calculations since we previously showed that even a more coordinating counter-anion like NTf_2^- has no significant impact on the reaction profile (migratory insertion of norbornene and ethylene, β -hydride elimination) in similar processes than those described in this work.^[4] The gold atom was described with the relativistic electron core potential SDD and associated basis set,^[5] augmented by a set of f-orbital polarization functions.^[6] The 6-31G** basis set were employed for other atoms. All stationary points involved were fully optimized in solvent. Frequency calculations were undertaken to confirm the nature of the stationary points, yielding one imaginary frequency for transition states (TS), corresponding to the expected process, and all of them positive for *minima*. The connectivity of the transition states and their adjacent *minima* was confirmed by intrinsic reaction coordinate (IRC)^[7] calculations.

Natural Bond Orbital^[8] calculations (NBO, 5.9 version)^[9] have been carried to analyze the bonding situation, in particular for the description of gold π -complexes and complexes involving β -H and γ -H interactions. Natural Localized Molecular Orbital (NLMO) were plotted with Molekel 4.3^[10] and all the geometrical structures with Gaussview 5.0 and CYLview.^[11]

^{13}C NMR chemical shifts for complex **4** (*cis* and *trans* isomers) were evaluated by employing the direct implementation of the Gauge Including Atomic Orbitals (GIAO),^[12] with the

-
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IGLOII^[13] basis set on C, H and N atoms, using as reference the corresponding SiMe₄ shielding constant calculated at the same level of theory.

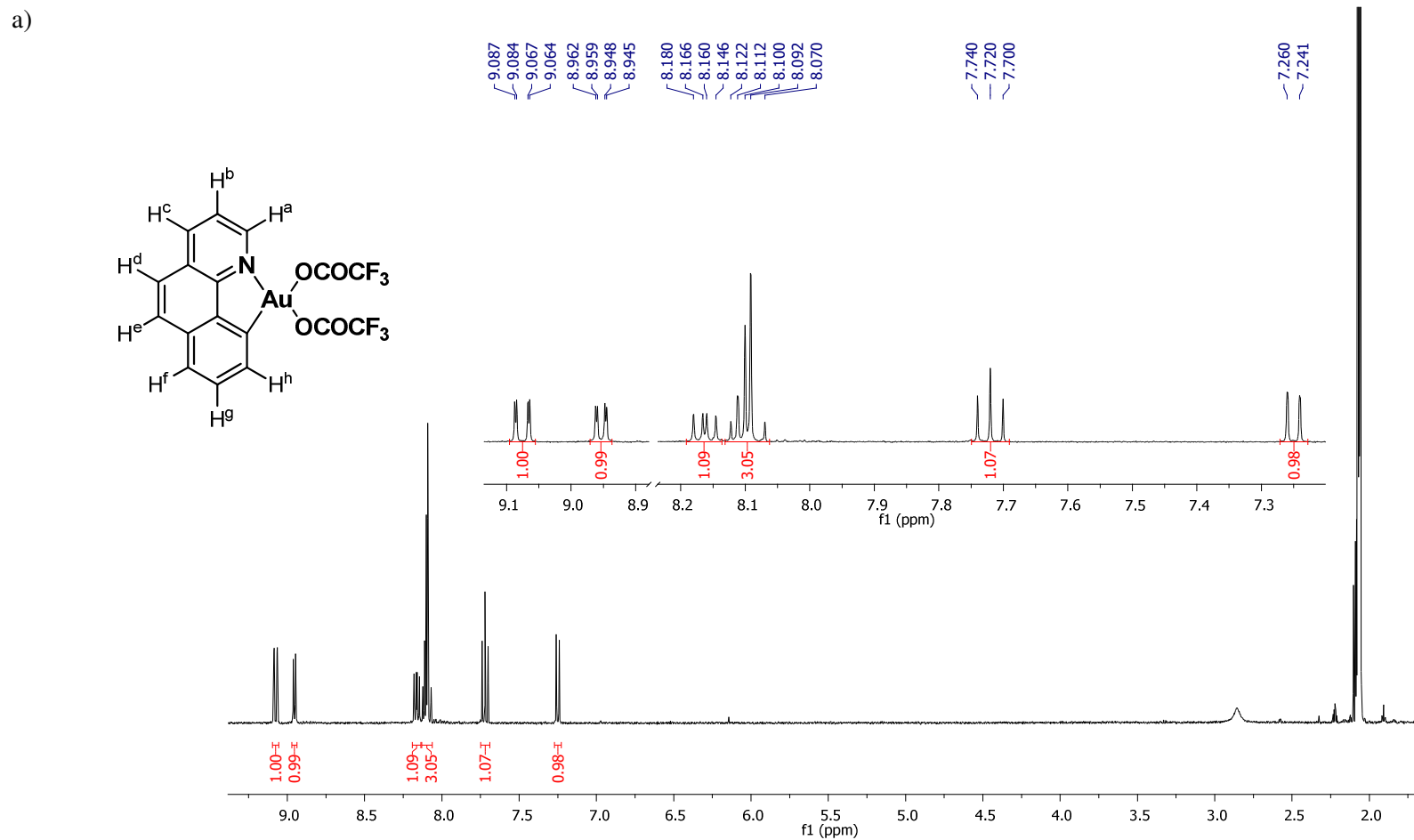
Bader^[14] charges have been computed for the dicationic species [(N,C)Au]²⁺ and [(P,C)Au]²⁺ in order to analyze atomic charge at gold.

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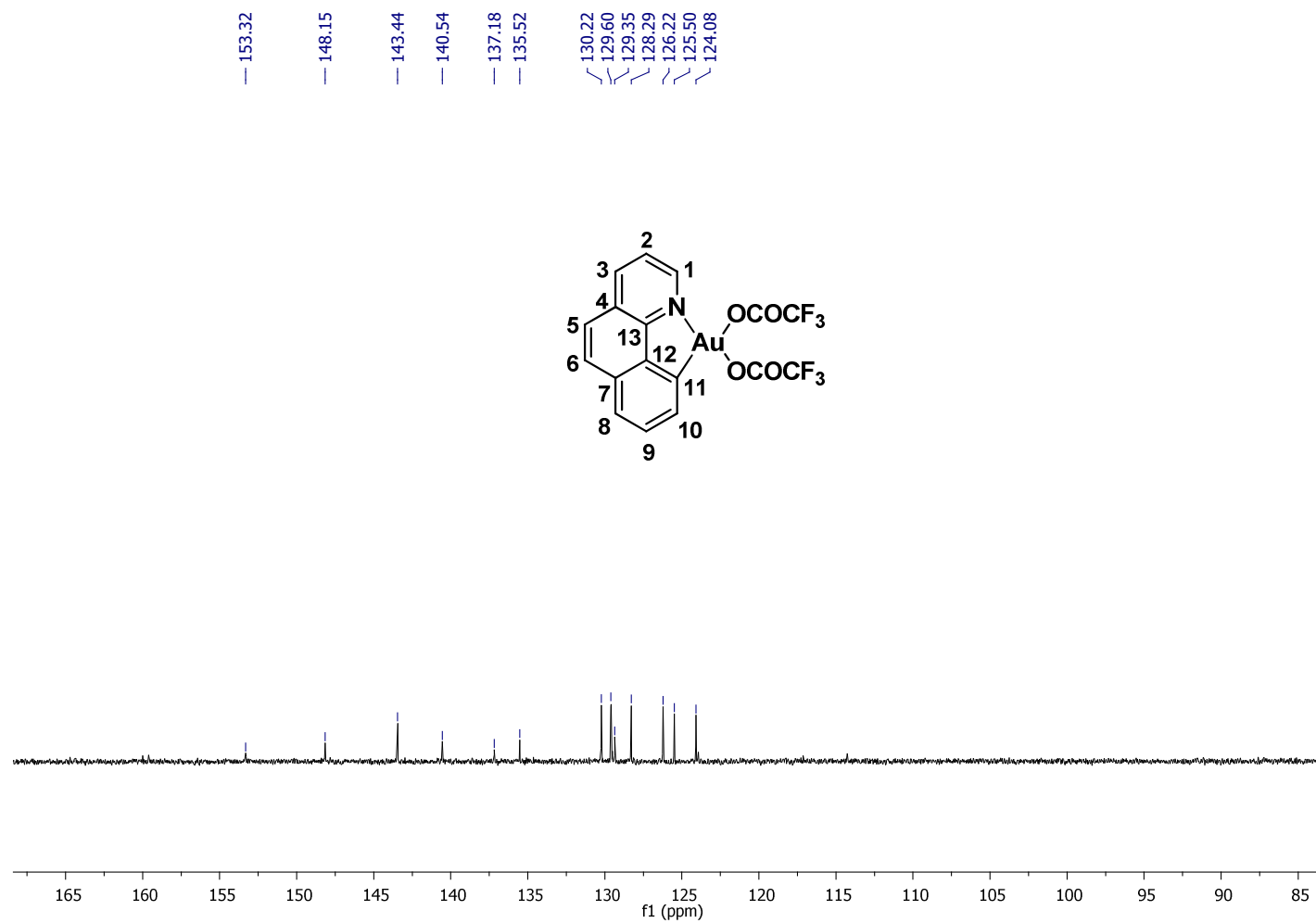
(14) (a) R. F. W. Bader, *Atoms in Molecules: A Quantum Theory*; Oxford University Press: New-York Ed., **1990**; (b) R. F. W. Bader, *Chem. Rev.* **1991**, *91*, 893; (c) AIMAll (Version 10.10.11), Todd A. Keith, **2010**.

3. Figures and Tables

Figure S1. a) ^1H -NMR spectrum of complex **2** in acetone- d_6 , 400 MHz, 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (acetone- d_6 , 100 MHz, 298 K); c) $^{19}\text{F}\{^1\text{H}\}$ -NMR spectrum (acetone- d_6 , 282 MHz, 298 K).



b)



c)

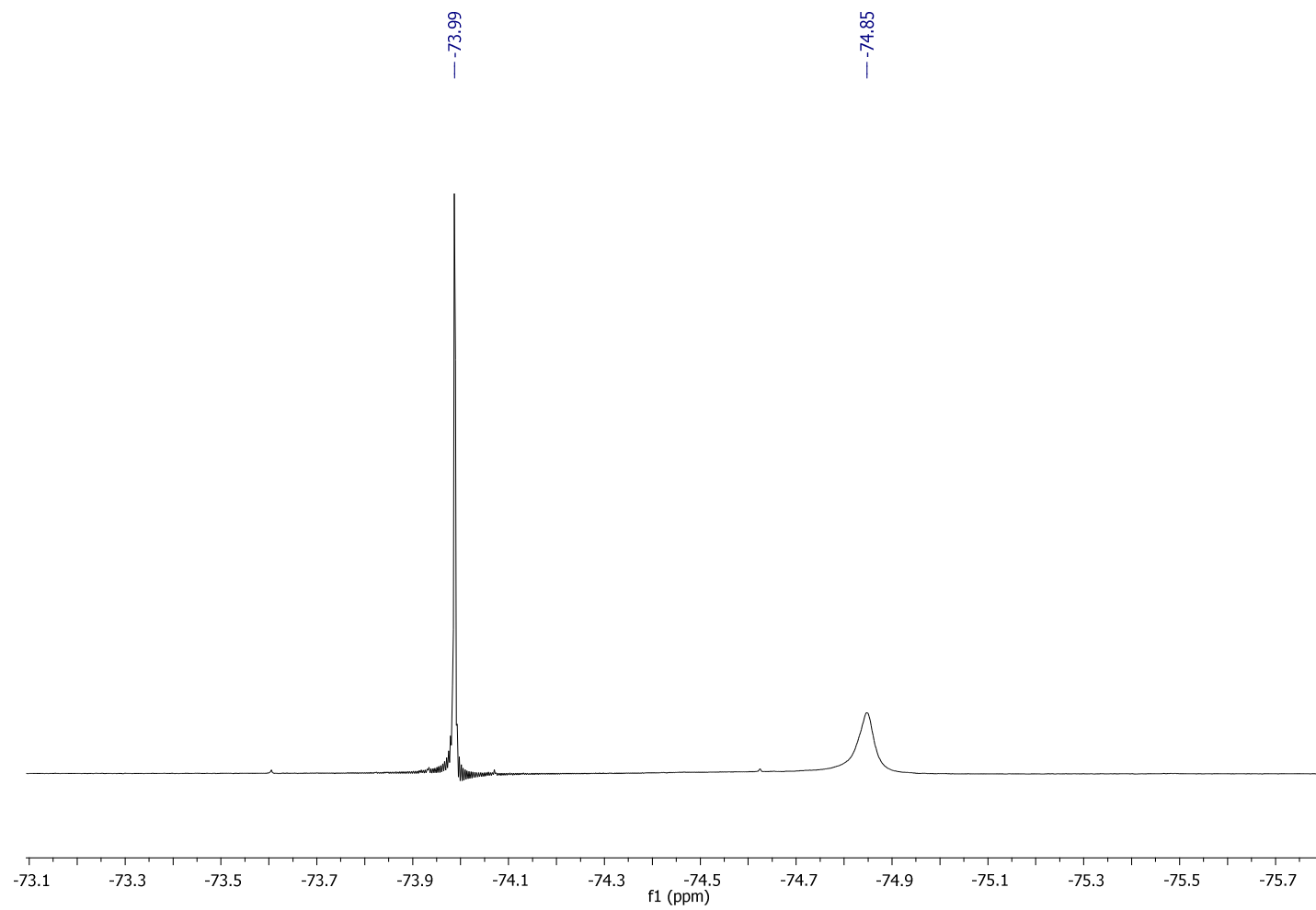
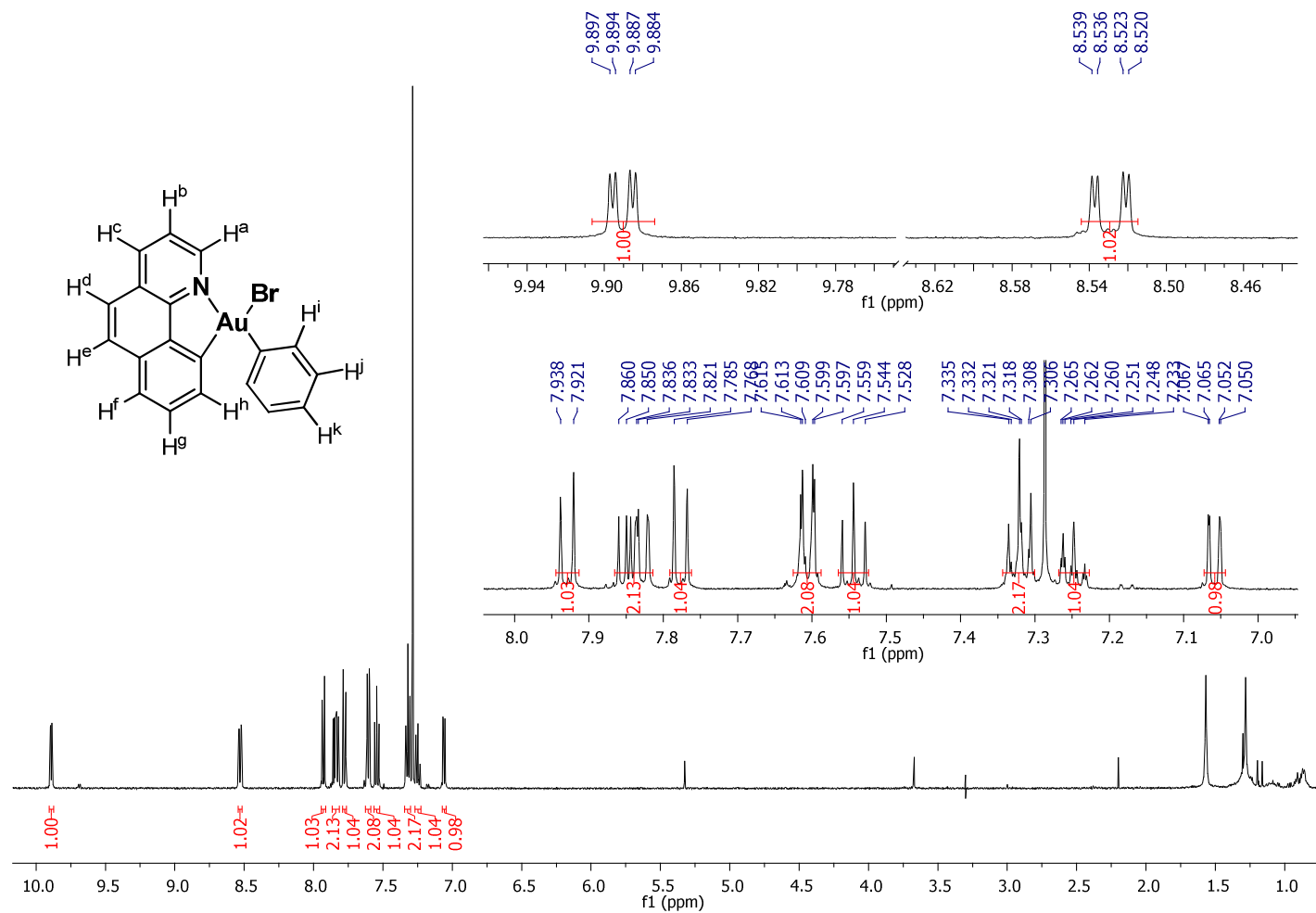


Figure S2. a) ^1H -NMR spectrum of complex **3-Br** in CDCl_3 , 500 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 125 MHz, 298 K).

a)



b)

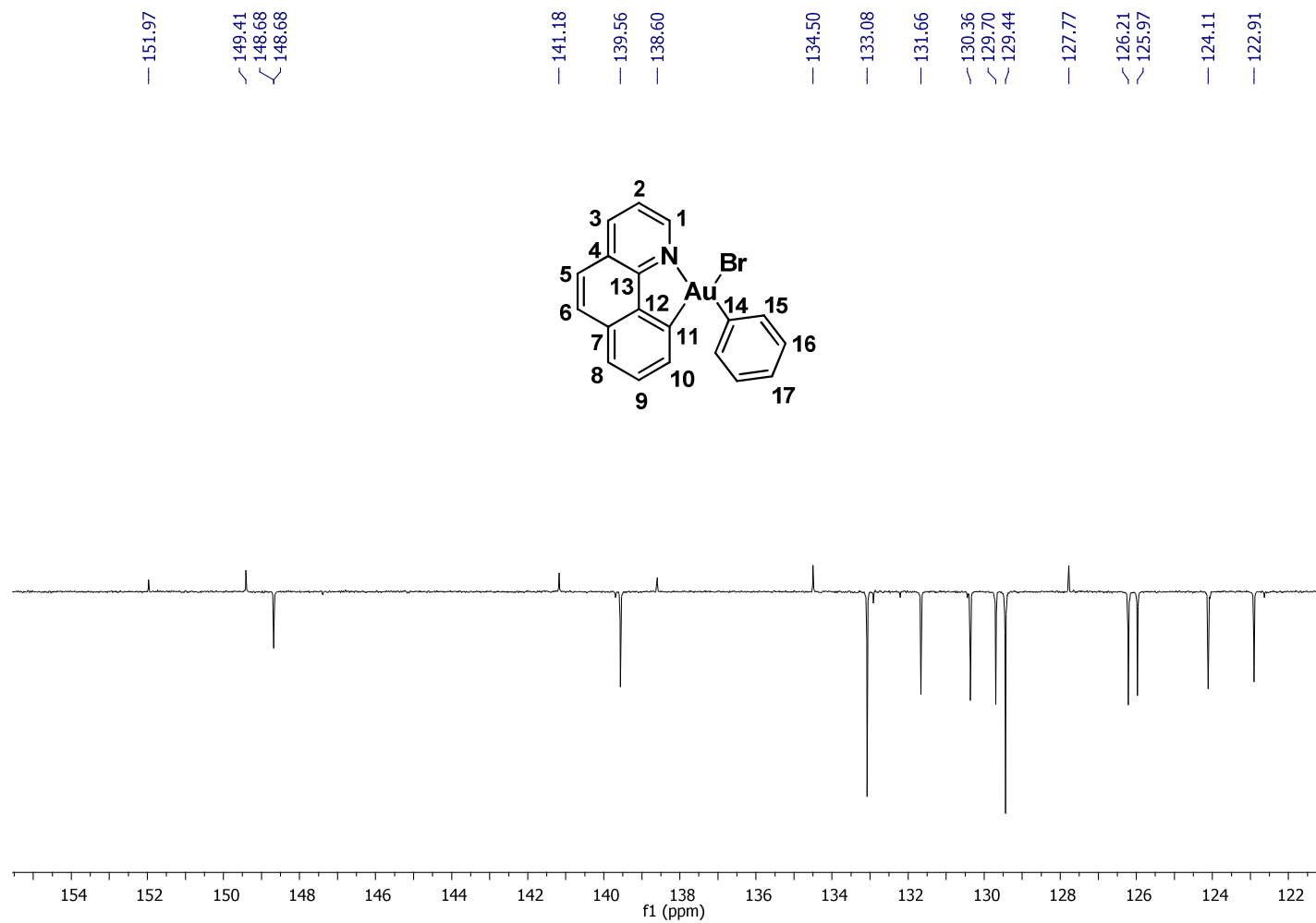
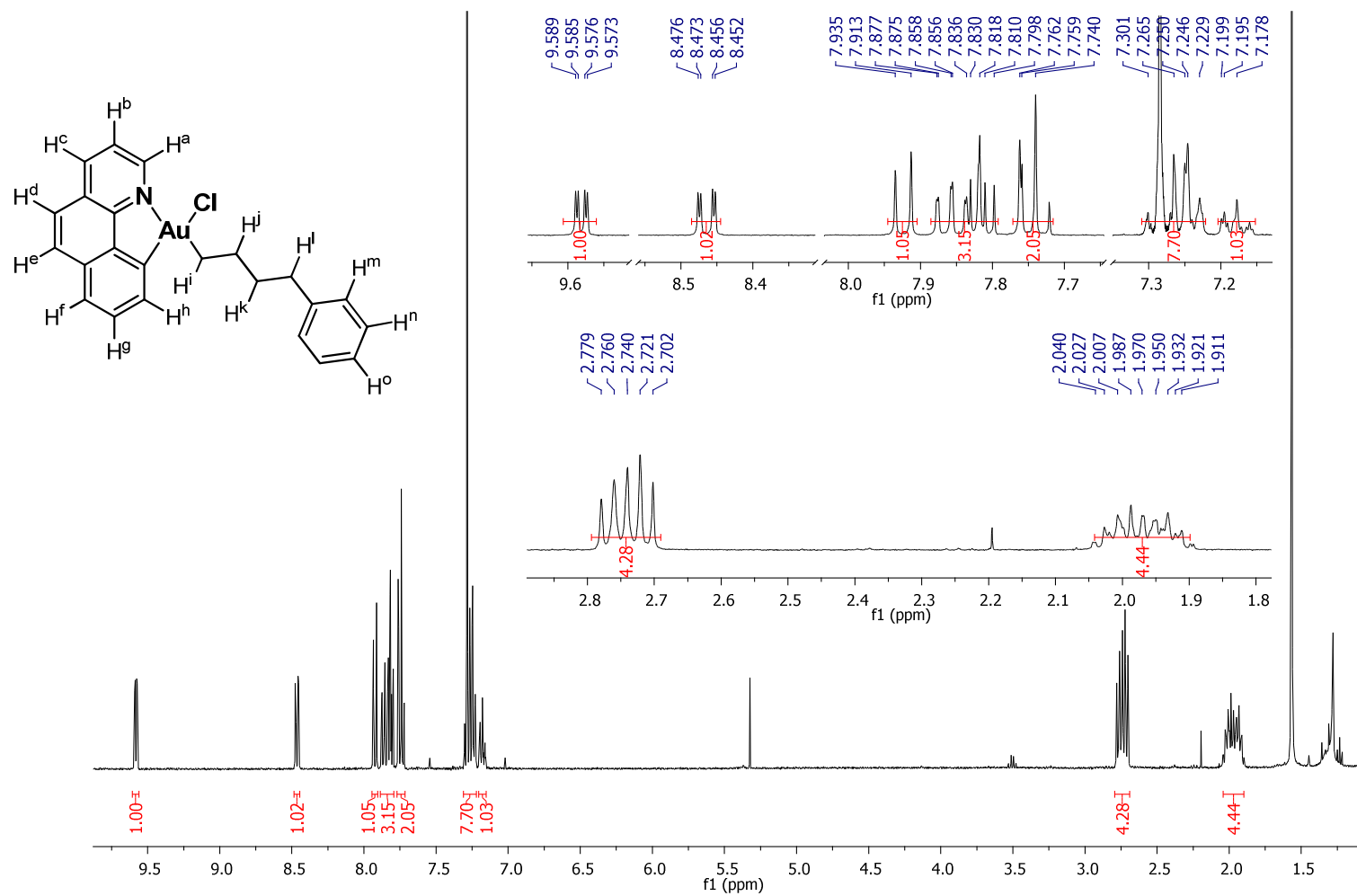


Figure S3. a) ^1H -NMR spectrum of complex **5A-Cl** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K).

a)



b)

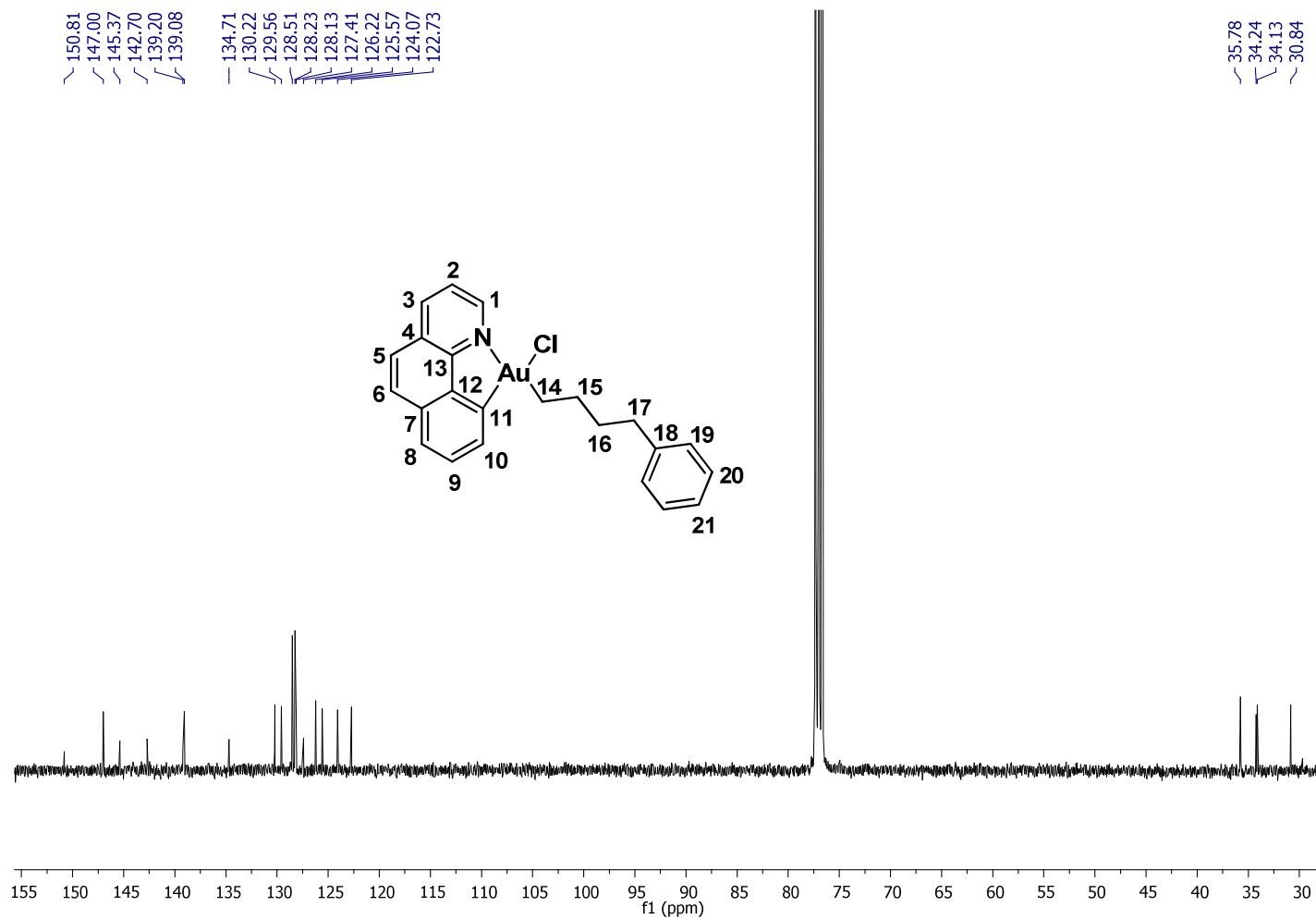
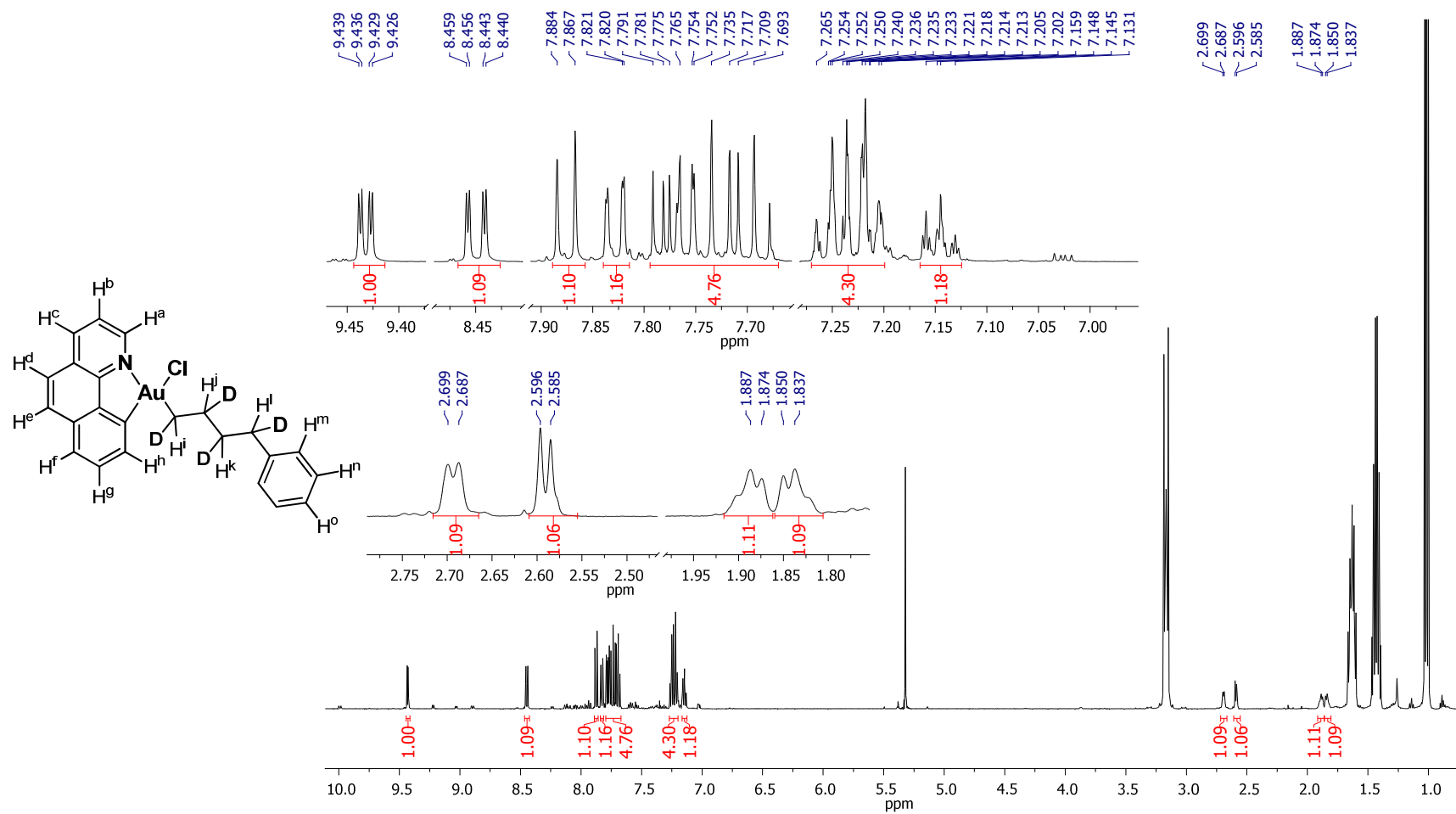


Figure S4. a) ^1H -NMR spectrum of complex **5A-Cl- d_4** in CD_2Cl_2 , 500 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CD_2Cl_2 , 125 MHz, 298 K).

a)



b)

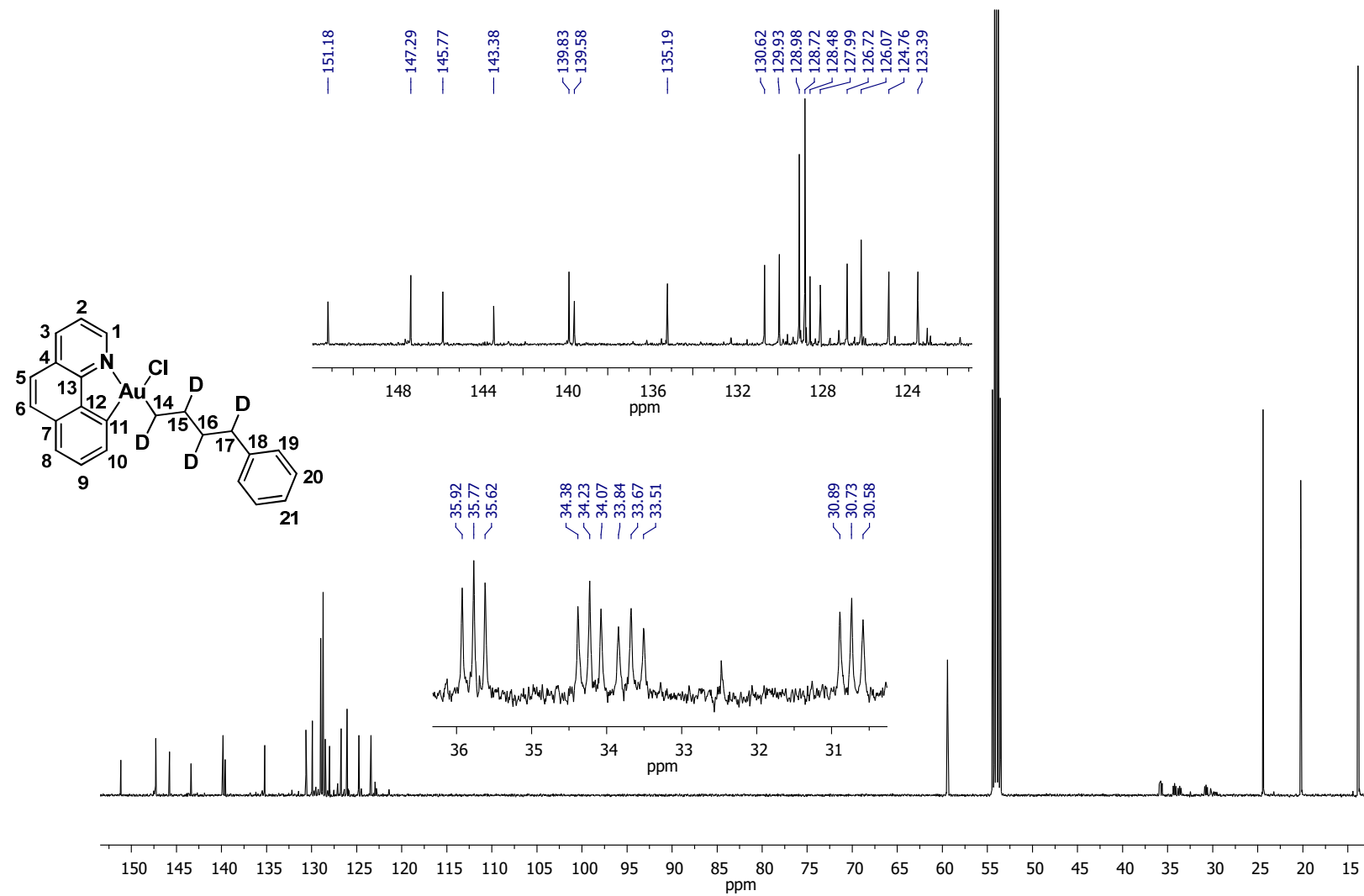
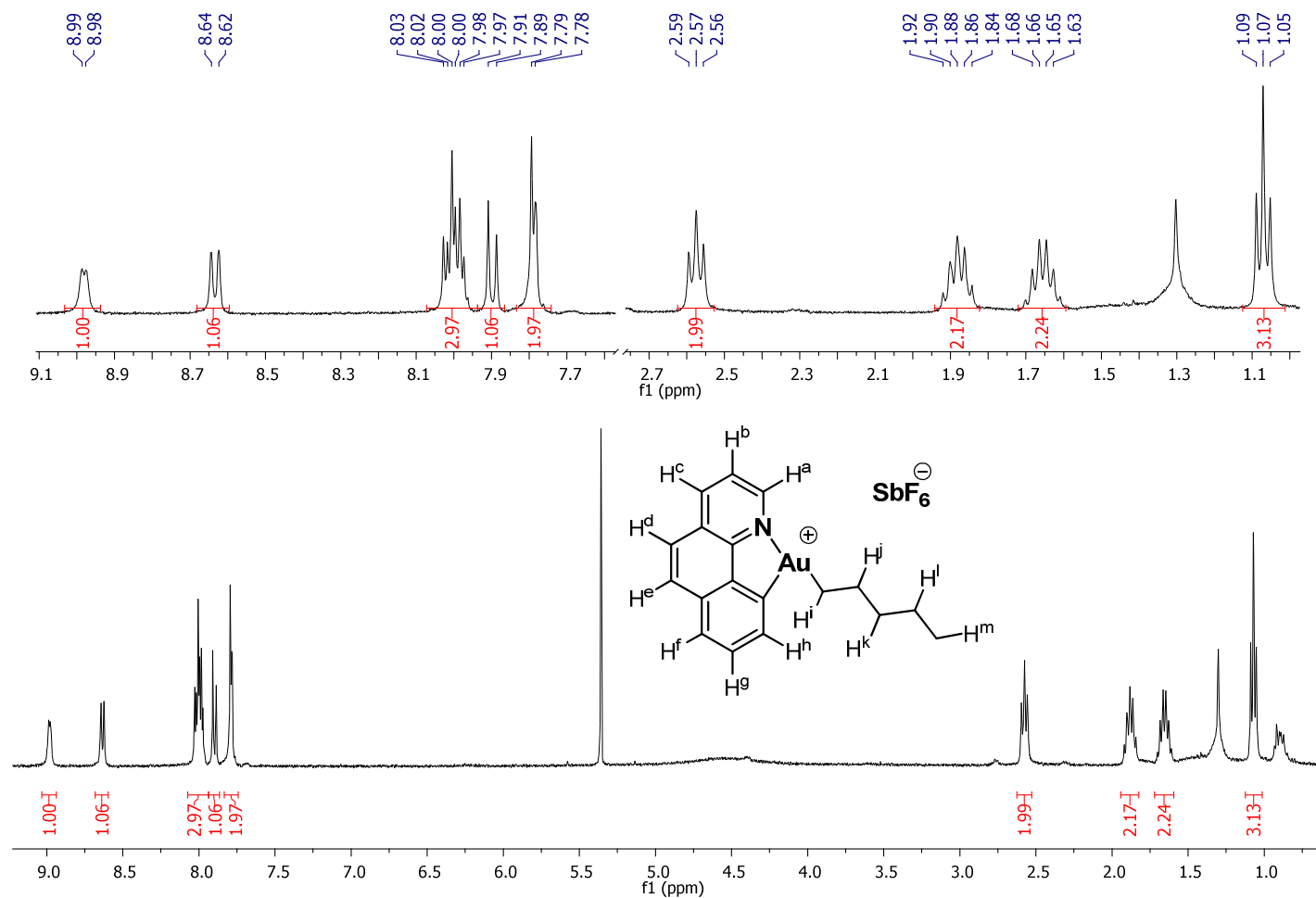


Figure S5. a) ^1H -NMR spectrum of complex **6A** in CD_2Cl_2 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CD_2Cl_2 , 100 MHz, 298 K).

a)



b)

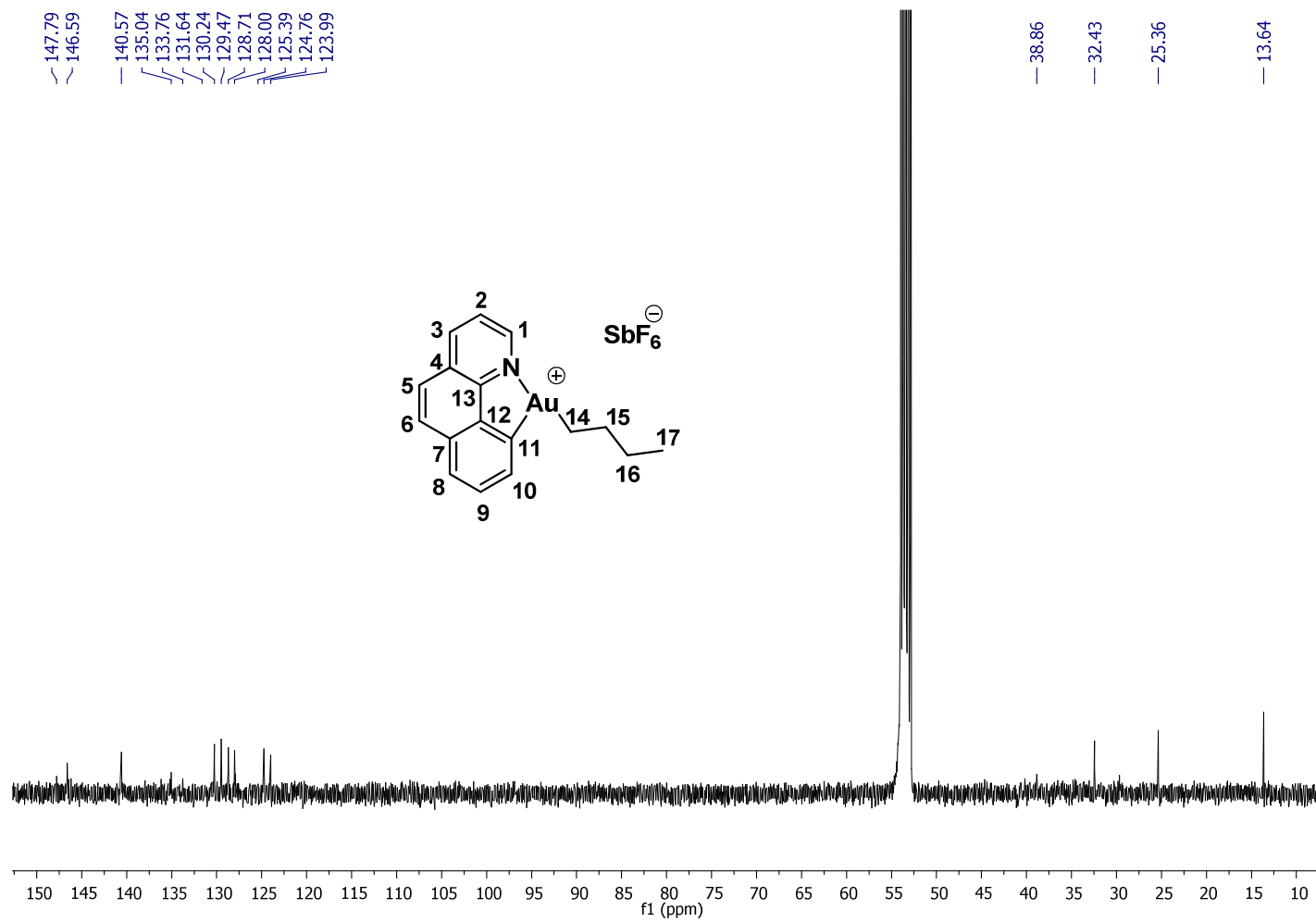
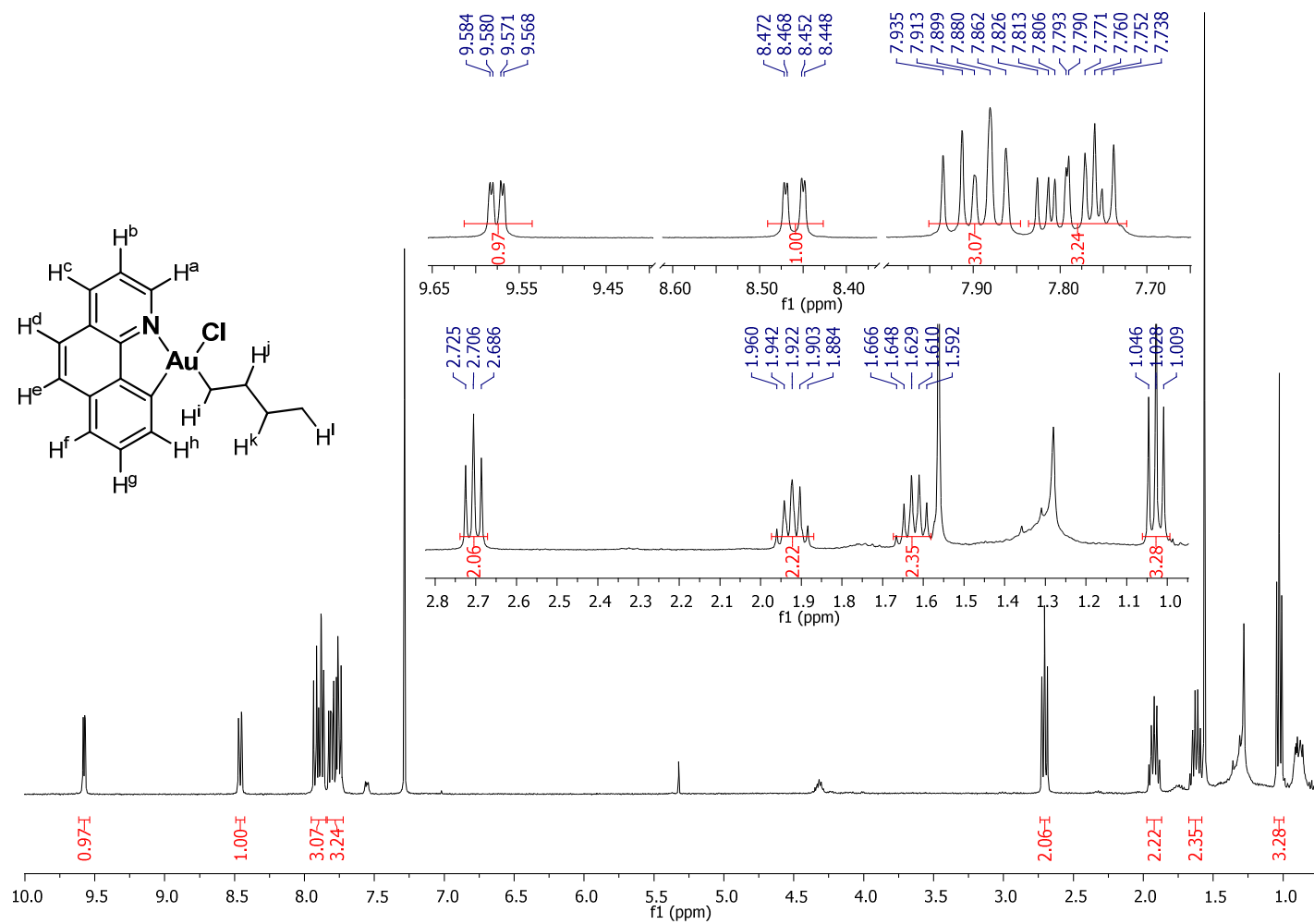


Figure S6. a) ^1H -NMR spectrum of complex **6-Cl** in CDCl_3 , 400 MHz, at 298 K; b) $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum (CDCl_3 , 100 MHz, 298 K).

a)



b)

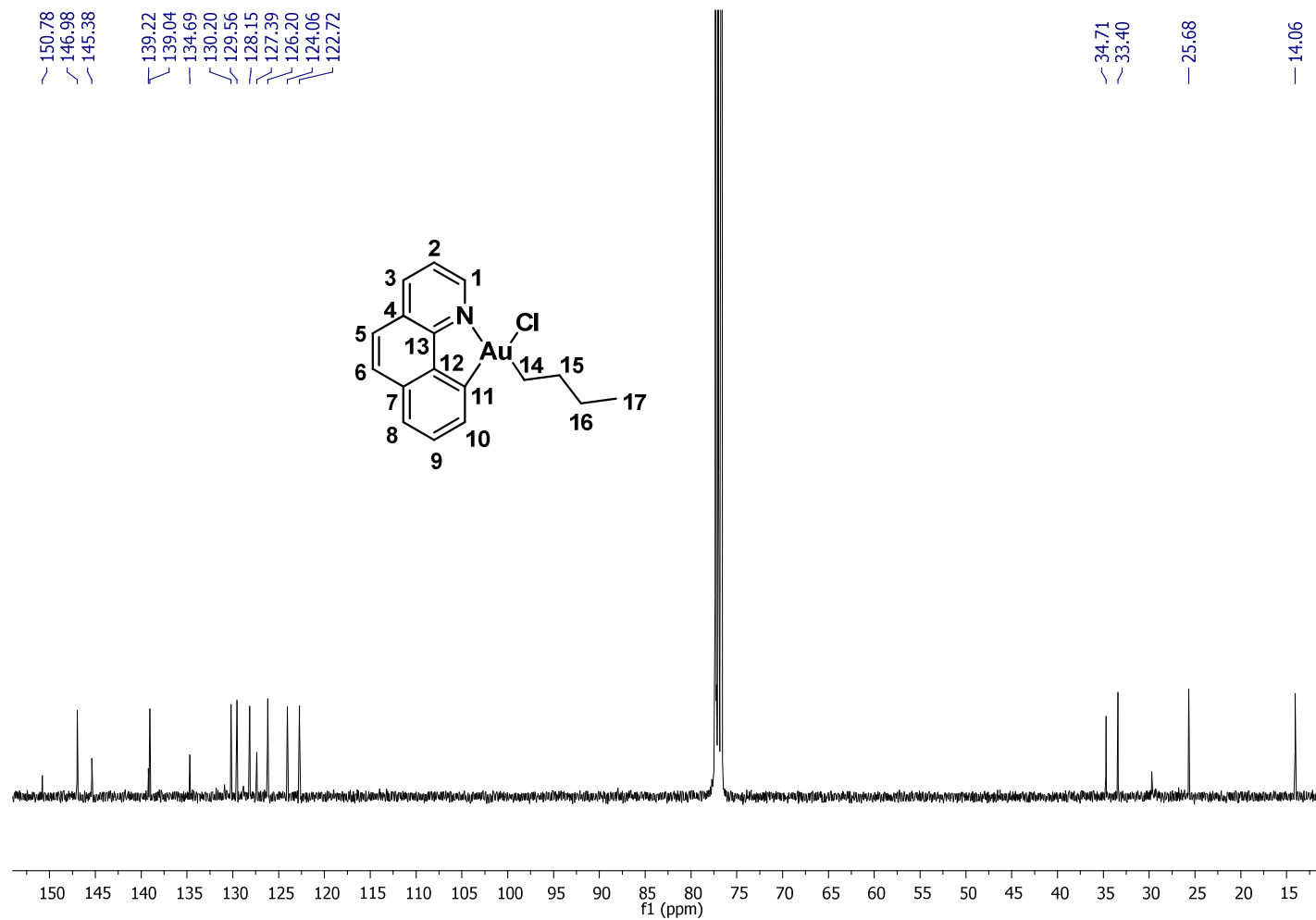


Figure S7. Impact of counter-anion SbF₆⁻: the activation barrier associated with the insertion of NB into the Au–Ph bond is quite similar for the naked cationic (N,C) and (P,C) complexes (14.3 kcal/mol and 14.8 kcal/mol, respectively). But the cationic [(N,C)AuPh]⁺ complex **1A** is more tightly bound to the SbF₆⁻ counter-anion than the corresponding [(P,C)AuPh]⁺ complex **1C** (by 5.2 kcal/mol according to the isodesmic reaction below). This probably explains why the insertion of NB is much slower with the (N,C) complex.

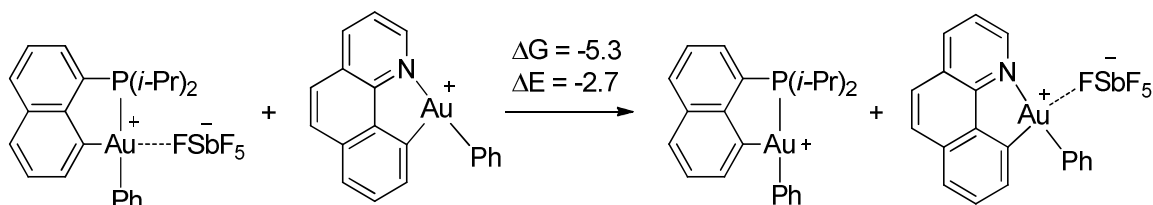


Table S1. (N,C)-ligand. Bonding situation (NBO analysis) for complexes **1A- π** , **4-trans** and **4-cis** at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory, accounting for the π -interaction between phenyl ring and gold atom.

Complex	Donation ^a	Back-Donation ^a	NLMO $\pi_{C=C}$ ^b
1A-π	34.7 ($\pi_{C=C} \rightarrow \sigma^*_{AuC}$)	-- ($d_{Au} \rightarrow \pi^*_{C=C}$)	37.6 % C 48.0 % C 6.5 % Au 5.8 % C _{napht}
4-trans	33.3 ($\pi_{C=C} \rightarrow \sigma^*_{AuN}$)	4.4 ($d_{Au} \rightarrow \pi^*_{C=C}$)	25.6 % C _{ipso} 47.8 % C _{ortho} 13.6 % Au 4.1 % N
4-cis	20.3 ($\pi_{C=C} \rightarrow \sigma^*_{AuC}$)	3.5 ($d_{Au} \rightarrow \pi^*_{C=C}$)	41.1 % C _{ipso} 39.3 % C _{ortho} 3.5 % Au 2.9 % C _{napht}

^a Stabilizing energy $\Delta E(2)$ in kcal/mol. ^b Participation of each atom (%) in the NLMO $\pi_{C=C}$ (donation).

Figure S8. Full energy profile (ΔG and ΔE values into brackets, in kcal/mol) computed at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory for different insertions of ethylene and β -hydride elimination from the [(N,C)AuPh]⁺ complex **1A** (*cis* and *trans* isomers).

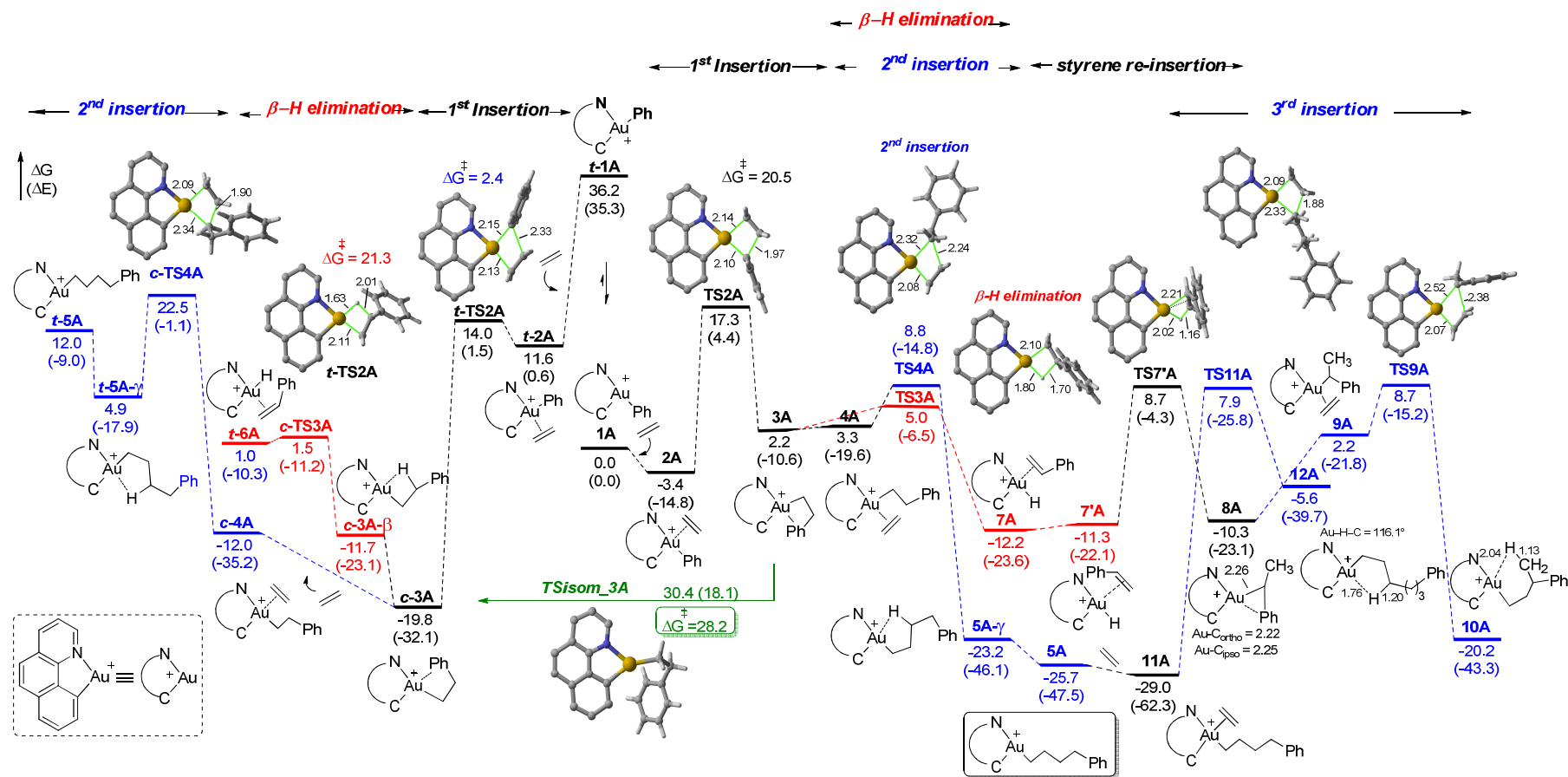


Figure S9. Key structures and selected geometric parameters (distances in Å) for the insertion of ethylene into the Au-Ph bond of complex **1A** at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory.

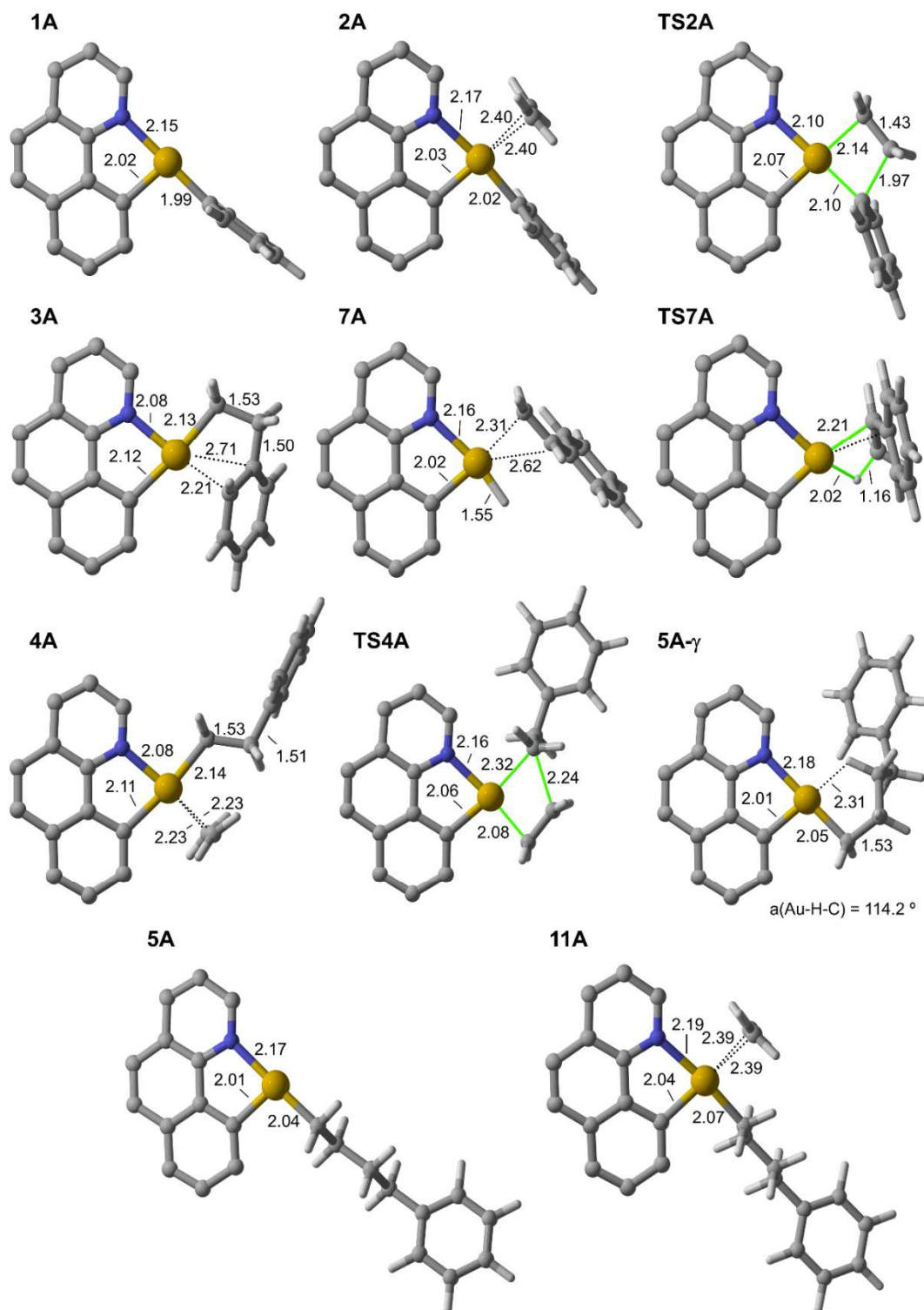
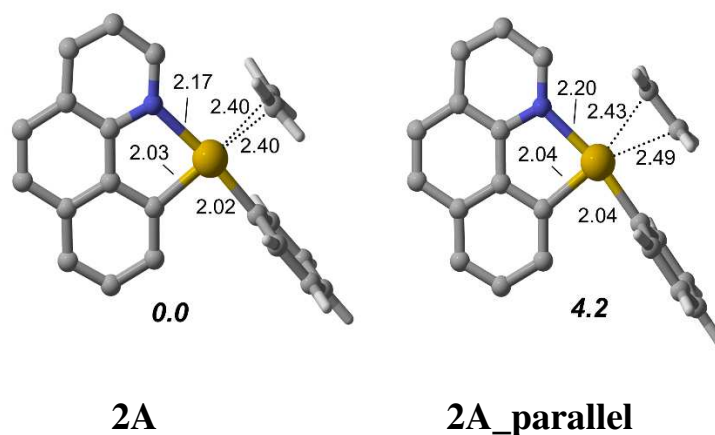


Table S2. NBO analysis of the π -ethylene coordination in complex **2A**, of the π -arene coordination in complex **3A** and of the γ -CH agostic interaction in complex **5A- γ** at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory. Relative stability of complexes **2A** and **2A_parallel** in kcal·mol⁻¹.



Complex	Donation ^a	Back-Donation ^a	NLMO ^b
2A <i>ethylene perpendicular</i>	45.7 ($\pi_{CC} \rightarrow \sigma^*_{AuC}$)	14.1 ($d_{Au} \rightarrow \pi^*_{CC}$)	43.7 % C 43.7 % C 6.5% Au 5.6% C _{naph}
2A_parallel <i>ethylene parallel</i>	50.9 ($\pi_{CC} \rightarrow \sigma^*_{AuC}$)	9.7 ($d_{Au} \rightarrow \pi^*_{CC}$)	40.2 % C 48.1% C 6.0 % Au 5.0 % % C _{naph}
3A	31.0 ($\pi_{CC} \rightarrow \sigma^*_{AuN}$)	-- ($d_{Au} \rightarrow \pi^*_{CC}$)	22.8 % C _{ipso} 50.5 % C _{ortho} 1.5% N 13.0% Au
5A-γ	7.1 ($\sigma_{CH} \rightarrow \sigma^*_{AuC}$)	2.3 ($\sigma_{AuC} \rightarrow \sigma^*_{C-H}$)	57.0 % C 40.2 % H 1.1 % Au

^a Stabilizing energy $\Delta E(2)$ in kcal/mol. ^b Participation of each atom (%) in the NLMO $\pi_{C=C}$ and the NLMO σ_{CH} .

Figure S10. Energy profiles (ΔG and ΔE values into brackets, in kcal/mol) computed at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory for β - and γ -hydride eliminations from complex **5A**.

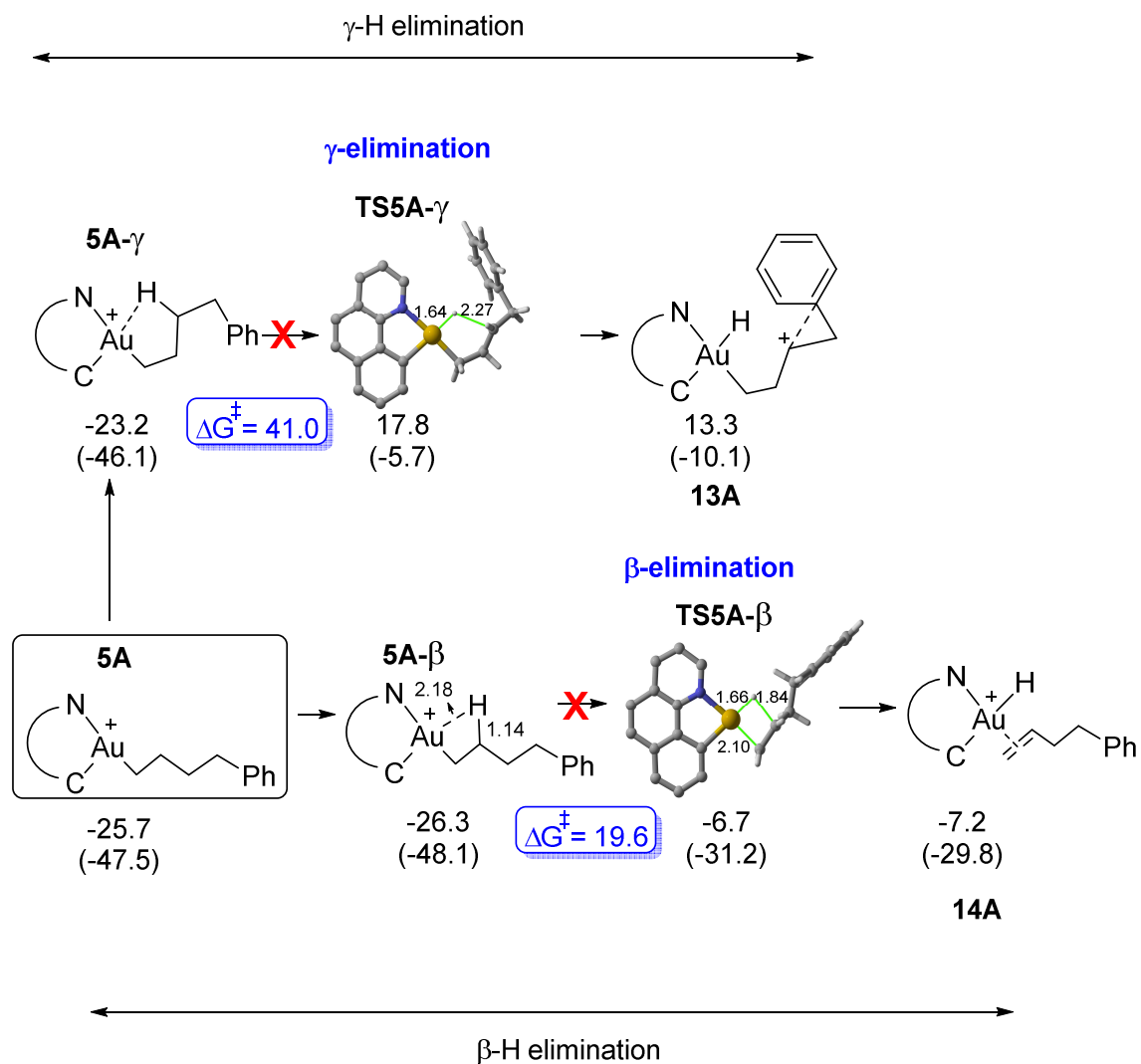


Figure S11. Energy profile (ΔG and ΔE values in kcal/mol) computed at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory for β -hydride and 2nd insertion from **t-3A** (see complete profile in Figure S8).

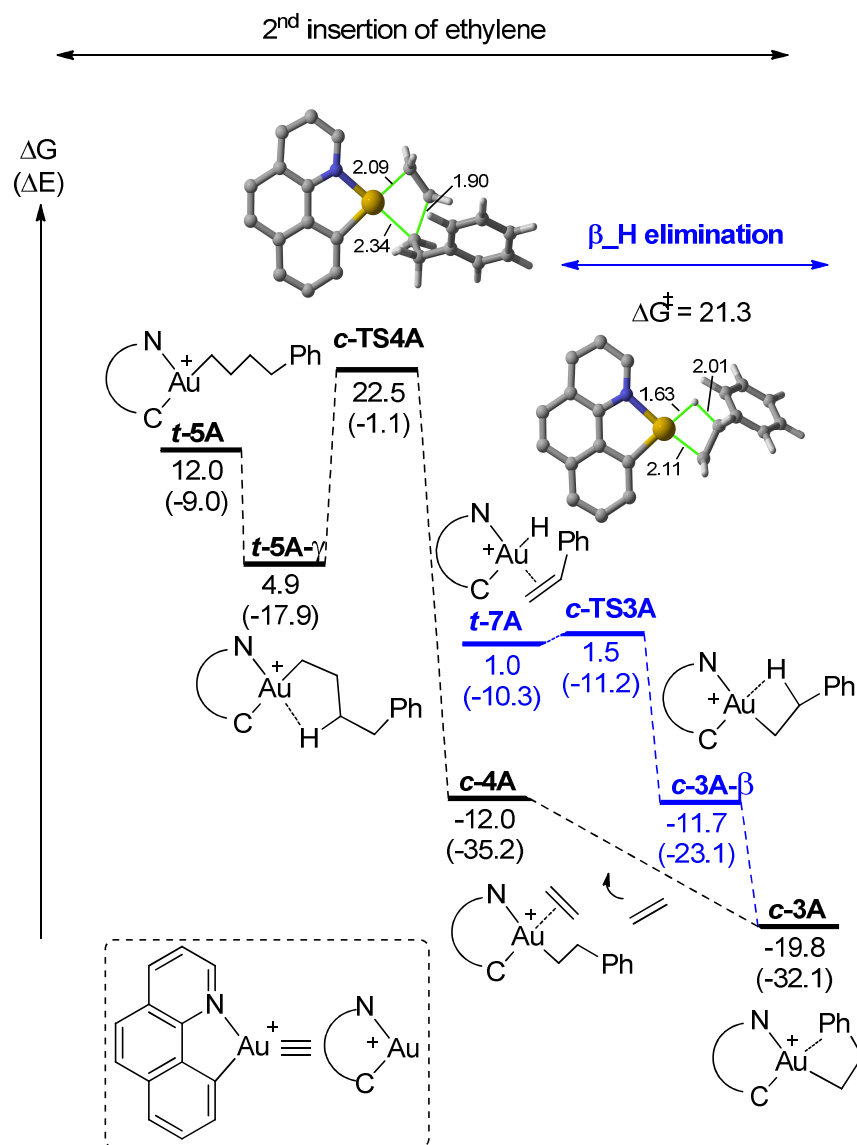
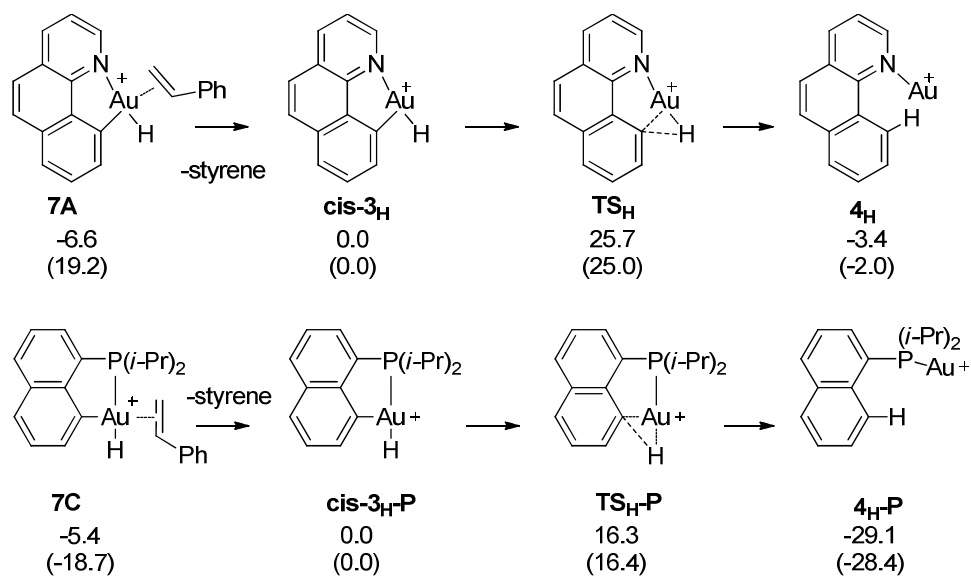


Figure S12. Reaction paths (ΔG and ΔE values, into brackets in kcal/mol) computed at the PCM(Dichloromethane)-B3PW91/SDD+f(Au)/6-31G**(other atoms) level of theory for the reductive elimination (C_{sp^2} -H coupling) of the gold(III) hydride complexes **7A** and **7C**.



4. X-ray Crystallography Data

Crystallographic data for complexes **5A-H₂O** (CCDC-1574199) and **5A-Cl** (CCDC-1574200) can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif.

Colorless crystals were grown from a CD₂Cl₂ solution of the compound for **5A-H₂O**, and from slow diffusion of pentane in a CHCl₃ solution of the **5A-Cl** complex. The data were collected at low temperature (193(2)K) on a Bruker-AXS APEX II QUAZAR diffractometer equipped with a 30W air-cooled microfocus source for **5A-H₂O** and on a Bruker-AXS PHOTON100 D8 VENTURE diffractometer for **5A-Cl**, using MoK α radiation (λ = 0.71073 Å). Phi- and omega-scans were used. An empirical absorption correction with SADABS was applied.^[15] The structures were solved by direct methods (SHELXS-97)^[16] or using Intrinsic phasing method (SHELXT)^[17] and refined by full-matrix least squares on F^2 .^[15] All non-H atoms were refined with anisotropic displacement parameters.

Table S3. Key structural parameters of complex **5A-H₂O**.

Chemical formula	C ₂₃ H ₂₃ Au ₁ N ₁ O ₁ ¹⁺ ,F ₆ Sb ₁ ¹⁻
fw (g mol⁻¹)	762.15
Bond precision	C-C = 0.0083 Å
T (K)	193
a (Å)	6.6287(3)
b (Å)	16.4246(8)
c (Å)	21.5858(11)
α (deg.)	90
β (deg.)	90
γ (deg.)	90
V (Å³)	2350.1(2)
$\rho_{\text{calcd.}}$ (g cm⁻³)	2.154
λ (Å)	0.71073
Mu (mm⁻¹)	7.448
F000	1440.0
F000'	1430.69
h, k, lmax	9,22,29
Nref	6595[3740]
R₁ [I > 2sigma(I)]	0.0262(6022)
wR₂ [I > 2sigma(I)]	0.0466(6582)

(15) SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.

(16) Sheldrick, G. M., *Acta Cryst.* **2008**, A64, 112-122.

(17) Sheldrick, G. M., *Acta Cryst.* **2015**, A71, 3-8.

Figure S13. X-Ray structure of complex **5A-H₂O** obtained by crystallization from CD₂Cl₂. Ellipsoids are set at 50% probability.

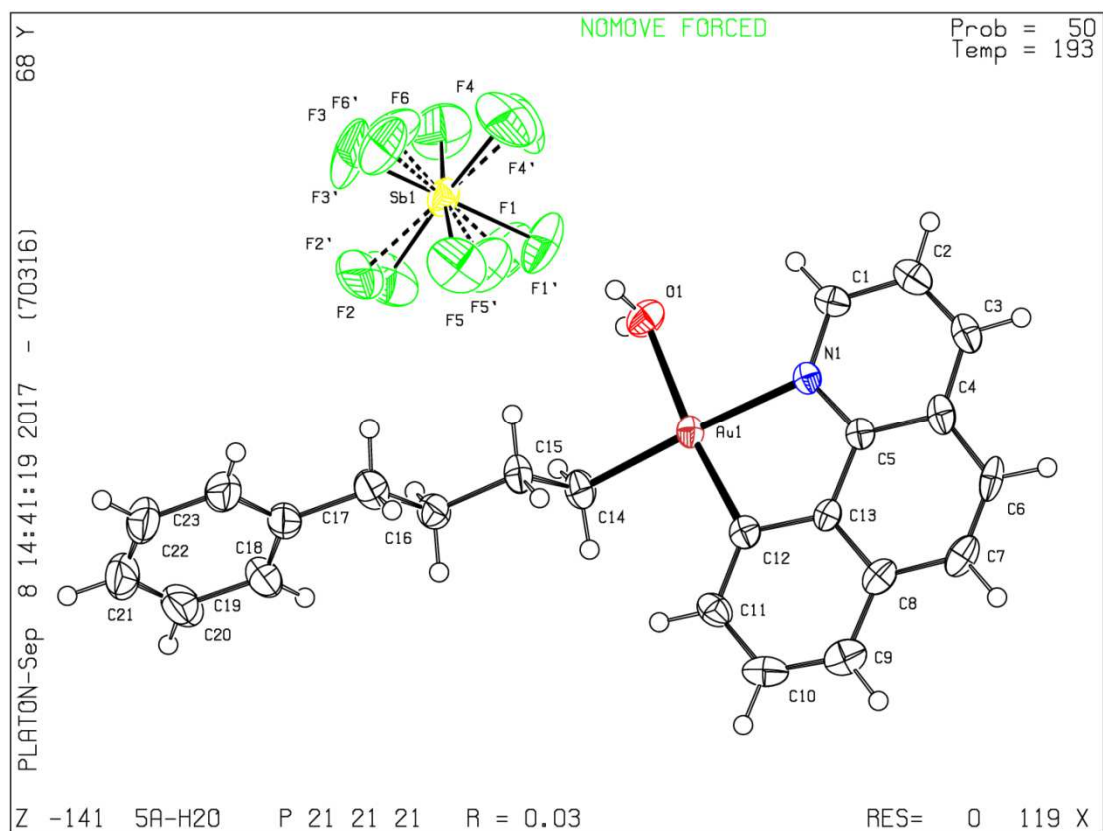


Table S4. Key structural parameters of complex **5A-Cl**.

Chemical formula	C ₂₃ H ₂₁ Au ₁ Cl ₁ N ₁ C ₁ H ₁ Cl ₃
fw (g mol⁻¹)	663.20
Bond precision	C-C = 0.0055 Å
T (K)	193
a (Å)	7.4651(4)
b (Å)	9.8244(5)
c (Å)	16.9630(9)
α (deg.)	98.935(2)
β (deg.)	91.454(2)
γ (deg.)	106.868(2)
V (Å³)	1172.83(11)
ρ_{calcd.} (g cm⁻³)	1.878
λ (Å)	0.71073
Mu (mm⁻¹)	6.739
F000	640.0
F000'	637.48
h, k, lmax	10,13,23
Nref	6872
R₁ [I > 2σ(I)]	0.0247(6265)
wR₂ [I > 2σ(I)]	0.0583(6865)

Figure S14. X-Ray structure of complex **5A-Cl** obtained by crystallization from CHCl_3 . Ellipsoids are set at 50% probability.

