CYCLOMETALLATED GOLD(III) COMPLEXES FOR CATALYSIS AND BIOCONJUGATION

KO HOK MING

M.Phil

The Hong Kong Polytechnic University

2015

The Hong Kong Polytechnic University

Department of Applied Biology and Chemical Technology

Cyclometallated Gold(III) Complexes for Catalysis and Bioconjugation

Ko Hok Ming

A thesis submitted in partial fulfilment of

the requirements for the degree of

Master of Philosophy

August, 2014

Certificate of Originality

I hereby declare that this thesis is my own work and that to the best of my knowledge and belief, it reproduces no material previously published or written nor material which has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

_____

Ko Hok Ming

August, 2014

Abstract

Square planar gold(III) complexes have four coordination sites, and hence the diverse ligand design can fine-tune the reactivity of the gold(III) centre. In addition, the four coordination sites allow a distinctive advantage in the design of chiral ligands for asymmetric catalysis that is severely limited in the linear gold(I) catalysts having only two coordination sites. However, poor catalytic activity of the coordinatively saturated gold(III) complexes hindered the development of gold(III) catalysis. We envision that novel strategies of ligand design and substrate activation are the key to open up a new direction for gold(III) catalysis.

We report the development of stable bis-cyclometallated gold(III) complexes [$Au(C\hat{}N)_2BF_4^-$] (HC^N = 2-phenylquinoline and 3-phenylisoquinoline) as efficient catalysts for organic synthesis by employing two novel strategies: (1) distorted square planar complex design and (2) gold-silver dual catalysis for substrate activation. X-ray crystallography study on the bis-cyclometallated gold(III) complex with bulky 2-phenylquinoline ligands revealed the distorted square planar geometry and significant elongation of Au-N bonds (up to 0.141 Å) compared to other cyclometallated gold(III) complexes in literatures. Secondly, the significantly higher catalytic activity (83% vs 8% isolated yields) in propargylamine synthesis could be attributed to this unique distorted complex geometry. The bis-cyclometallated gold(III) complex could also catalyse the

stereoselective propargylamine synthesis (up to 90% isolated yield and dr >99:1) and oligosaccharide modification with high aldehyde conversion. Thirdly, the catalysts were found to be active in indole alkylation by using a novel gold-silver dual catalysis (up to 80% isolated yield). Alkylated indoles with different substituents could also be obtained (up to 94% isolated yield). Finally, recyclability experiments of the catalyst in the propargylamine and dual metal-catalysed alkylated indole synthesis were conducted, demonstrating the exceptionally higher recyclability of bis-cyclometallated gold(III) complexes in catalysis over $KAuCl_4$.

Given the four coordination sites of gold(III) centre, we envisage that the reactivity of gold(III) reductive elimination could be fine-tuned by modular ligand assembly. In this work, we are exploring the novel application of meticulously designed gold(III) complexes for modification of cysteine by C-S bond formation.

A ligand controlled C-S bond formation reaction from gold-peptide adducts for chemoselective cysteine modification has been developed. Cyclometallated gold(III) complexes with bidentate msen as an ancillary ligand exhibited excellent cysteine chemoselectivity to give gold-peptide adducts up to 99% conversion in aqueous medium under mild conditions and various pH values. The structures of gold-peptide adducts and *S*-arylated peptides were supported by model reactions between the gold(III) complexes and *N*-acetyl-L-cysteine benzyl amide. C-S bond formation from gold-peptide adducts

could be controlled by the corresponding arylpyridine ligands to give *S*-arylated peptides up to 99% conversion at 40 ^{o}C. A dansyl functionalized gold(III) complex was synthesized for chemoselective cysteine modification with a biophysical probe under mild reaction conditions.

Acknowledgements

I deeply thank my chief supervisor, Dr. Man Kin Wong for his supervision, support and encouragement as well as suggestions during my research study.

Moreover, I would like to present my heartfelt appreciation to all of the technical and academic staff in the Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, for their sincere help and technical support in my work, especially Dr. Pui Kin So and Mr. Tze Tsun Ng for teaching and assisting in mass spectrometry; Dr. Siu Cheong Yan for his assistance in nuclear magnetic spectroscopy; Prof. Zhong Yuan Zhou for conducting X-ray crystallographic analysis of gold complexes.

Besides, I want to express my sincere thanks to colleagues in Dr. Wong's group from the Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University: Mr. Yat Sing Fung, Mr. King Chi Leung, Mr. Tze Wai Hui, Dr. Jian Fang Cui, especially Dr. Ka Yan Kung for the LC-MS analysis. It is my honour to work with all of you, and you all contributed to the excellent research atmosphere within the group by sharing the findings and experience together.

Table of Contents

Abbreviation

δ	Chemical shift (NMR)
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
MS	Mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
equiv.	Equivalent
h	Hour
rt	Room temperature
ee	Enantiomeric excess
R	Generalized alkyl group
Me	Methyl
Et	Ethyl
n-Bu	n-butyl
i-Pr	isopropyl
t-Bu	t-butyl

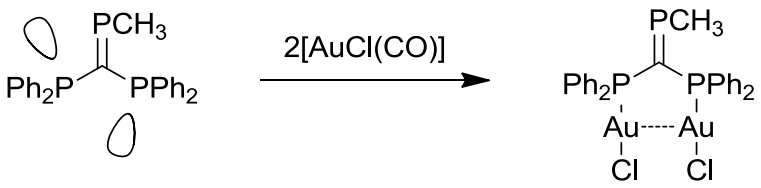
Ar	Aryl
Ph	Phenyl
Bn	Benzyl
Cy	Cyclohex
Tol	Toluoyl
cBRIDP	Di-tert-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)phosphine
Ts	Tosyl
Py	Pyridyl
Piv	Pvaloyl
Ac	Acetyl
Mes	Mesityl
Boc	tert-Butyloxycarbonyl
OTf	Triflyl
THF	Tetrahydrofuran
MeOH	Methanol
EtOH	Ethanol
Et_2O	Diethyl ether
EA	Ethyl acetate

Chapter 1 Introduction

1.1 Gold Chemistry

As a coinage metal, gold is air and moisture stable for thousands of years which the attractive appearance would not be tarnished. Gold has been widely used in jewellery manufacturing or making gold coins for thousands of years because of its tempting colour. Therefore, it was regarded as money due to its inherent value that many of ancient people fought for the treasure over thousands of years. Because of the exceptionally stable properties of gold, the interest of chemists to the catalytic ability of gold was not raised until the discovery gold nanoparticles which show promising catalytic ability.[1],[2]

In fact, there are some special properties in gold chemistry. Firstly, it has lower electrochemical potential than other transition metals. The cationic form of gold tends to accept electrons from reducing agents to form metallic gold. Secondly, gold is the most electronegative metals across the period in periodic table based on Pauling scale. Thirdly, diatomic molecules of Au exist in vapour state which has higher dissociation energy than some non-metal elements such as iodine. Finally, the unusual gold-gold interactions were observed in many organogold compounds which revealed the term aurophilic attraction in gold(I) chemistry. The attraction between the nearby Au(I) ion was discovered in many di-nuclear Au(I) complexes using bidentate phosphine ligands (Scheme 1.1).[3]



Scheme 1.1 The aurophilic attractions in di-nuclear Au(I) complex

1.1.1 Relativistic Effect

Au: [Xe]$4f^{14}5d^{10}6s^{1}$. Based on the theory of relativity, the corrected masses (m) of electrons with speed close to 3 x 10^{8} ms^{-1} (speed of light c) will become larger compared with the rest masses (m_0).

$$m = m_0 \Big/ \sqrt{(1 - (\frac{v}{c})^2)}$$

The relativistic effect leads to a smaller Bohr radius by contraction of the outermost orbitals of the electron. As the outer 6s electrons of Au moved with speed close to light, the corrected mass of the e^- will tend to be infinity resulting in the contraction of the outer 6s orbital. The strong charge density induced by 6s orbital contraction contributes to the superior Lewis acid property of Au(I). Au(I) is even a stronger Lewis acid than neighbouring element such as Ag(I).[4] As the outer 6s orbital contracts, the shielding effect towards 5d orbitals increases. The 5d orbitals are destabilized and more diffused (Figure 1.1).[5] The relativistic effect in gold renders it exceptional soft Lewis acid in nature. This strong Lewis acidity was employed to explain the unique catalytic properties in gold-catalysed organic transformations.

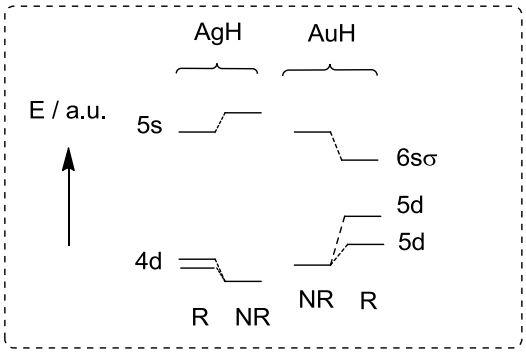


Figure 1.1 Energy levels of outer orbitals of Ag(I) and Au(I) with non-relativistic (NR) or relativistic (R) effects.

1.2 Gold Catalysis

Au(I): $[Xe]4f^{14}5d^{10}$, Au(III): $[Xe]4f^{14}5d^{8}$

The catalytic activity of gold in olefin hydrogenation was discovered by Bond and his co-workers by using a small amount of gold particles. Despite many reports showed that gold has no such catalytic ability and suggested that the reaction might be catalysed by some impurities such as a trace amount of other transition metals leading to bimetallic catalysis.[6],[7] Unlike other transition metals [i.e. rhodium (Rh), iridium (Ir) and silver (Ag)], development of gold catalysis has just started since decades ago. Homogeneous gold catalysis has been rapidly developed in recent years and surprisingly gold(I) or gold(III) catalysts were found to be the best catalysts in some organic transformations.[8] Furthermore, gold nanoparticles were also found to be catalytically active in some fundamental reactions in organic chemistry such as hydrogenation and oxidation.[9] Some notable activities of gold are:

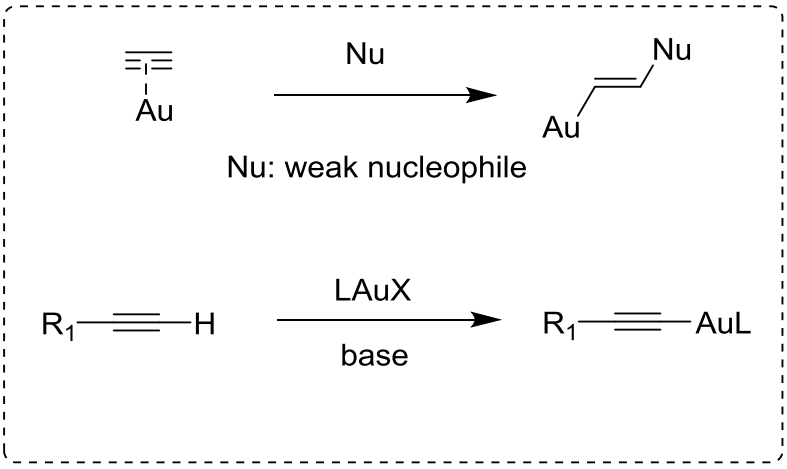
1. Oxidation of CO and H_2 at low temperature.[10]
2. Hydrochlorination of alkynes.[11]
3. Nucleophilic addition of inactivated alkynes.[12]
4. Chemoselective hydrogenation of nitro compounds.[13]
5. Oxidation of alcohols to form carboxylic acids and aldehydes.[14],[15]
6. Hydrogen peroxide formation from hydrogen and oxygen.[16]

The research of gold catalysts increases rapidly due to its alkynophilic nature. Activation of C-C triple bonds can be achieved under mild conditions as a result of alkynophilic nature of soft gold(I) or gold(III) ions rather than oxophillic nature.[17] As one of the coinage metals, exploration of chemistry of gold is much less than silver. In fact, the abundance of gold in our planet is much more than other late transition metals (i.e. rhodium, iridium and platinum). High functional group tolerance and moisture stability are the major advantages of using gold catalysts[1, 8a, 9-10, 17a] As a soft Lewis acid, gold can induce π activation of C-C multiple bonds with exceptional functional tolerance. Besides, gold can also activate carbon-heteroatom bonds such as carbonyls, imines, aziridines, ethers and epoxides through σ-coordination.[18]

In organometallic chemistry, the Au-C bond is more likely to undergo protodeauration rather than β hydride elimination so that the less side reactions with be occurred in the nucleophilic addition of nucleophiles to olefins or alkynes which enhance the product selectivity.[19] This feature reveals that gold is may be useful catalysts in various organic transformations as a π acidic catalyst. However, most of the studies of gold are based on gold(I) catalysed reactions. Only a few of research works focused on the studies of gold(III) catalysts. Unlike soft and Lewis acidic gold(I) with full-filled d^{10} system , gold(III) having unfulfilled d orbitals may give exceptionally different chemistry from gold(I).

1.2.1 Interactions between Gold Catalysts and Alkynes

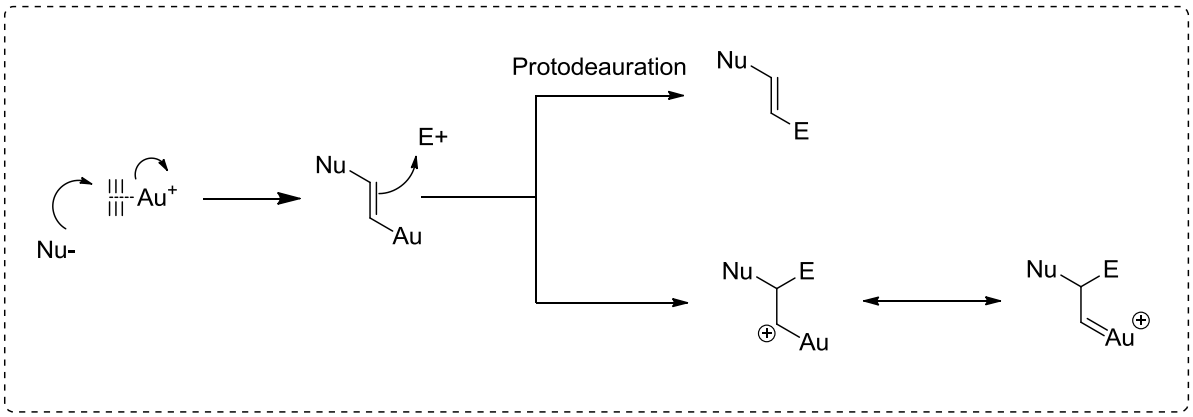
With two π orbitals orthogonal to each other occupied by two pairs of e^-, alkynes are favourable to react via electrophilic addition with halogens or electrophilic metal centres like gold(I) or gold(III).[17b] Alkynes are able to coordinate with electrophilic gold(I) or (III) centres through π electron donation of C-C triple bond to vacant d subshells of the metal centres. Energy of LUMO of alkynes will be lower and hence, the alkynes are more favourable to be attacked by some weak nucleophiles (i.e. H_2O, Cl^-, RNH_2) via nucleophilic addition. By coordinating with gold complexes, the alkyne is activated as a result of contributing electron density to the highly electrophilic metal fragments. The carbon atoms in alkynes are more electropositive and more susceptible to nucleophilic attack (Scheme 1.2, upper). In the case of terminal alkynes, the terminal hydrogen atom will be abstracted by the presence of base. Gold-alkynyl complexes will be formed through σ-coordination. The resulting gold acetylide is more nucleophilic which favours the nucleophilic attack to some electrophiles (Scheme 1.2, lower).



Scheme 1.2 Activation of alkynes by gold.

1.2.2 The Gold Carbenoids

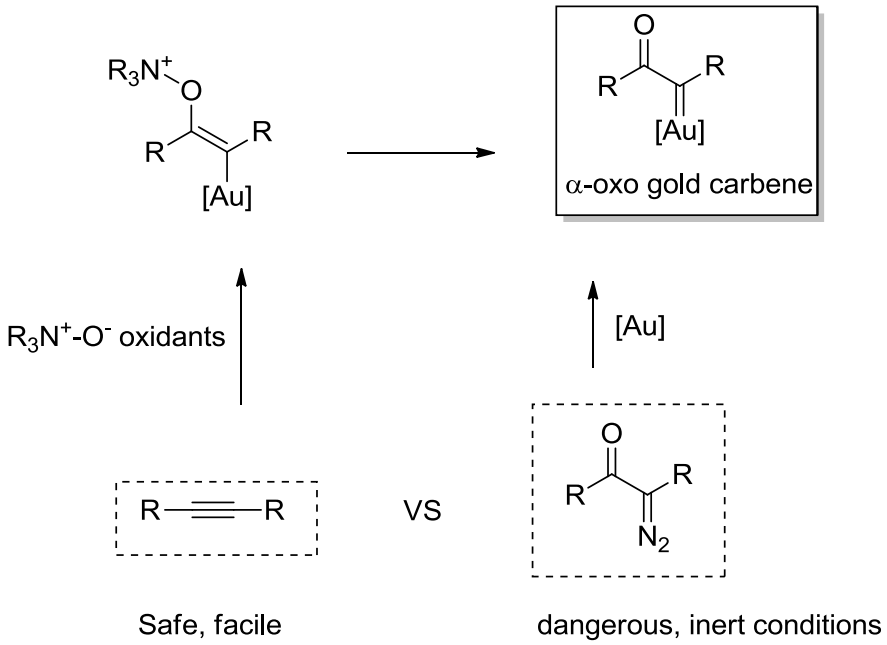
Gold carbenoids refer to carbon species that bear carbocation character and carry a C-Au bond at the same site. Apart from acting as Lewis acidic metal catalysts, thanks to the unusual relativistic effect of gold, experimental results suggested that backbonding from the relativistically expanded 5d orbitals into the LUMO of σ-bonded carbon to give gold carbenoids. The formation of carbenoid was attempted by reacting of Fischer carbenes with Au(I) phosphine complexes by transmetallation. The resulting compounds were studied based on nuclear magnetic resonance spectroscopy at low temperature and theoretical calculation.[20] This data suggested that after the gold activated nucleophilic addition to the alkynes, the trapping of the electrophiles can be accomplished by backdonating of 5d electrons to form a more stabilized gold carbenoid structure (Scheme 1.3).[4, 21]



Scheme 1.3 Formation of the gold carbenoid.

More recently, a resonance stabilized gold carbenoid generated from transmetallation of chromium fisher carbene to gold(I) complexes was obtained in crystalline form. The X-ray crystallography did not support the formation of Au-C double bonds nor a stabilized carbon cation.[22] In fact, the electron density was delocalized through the C-Au bond and the aromatic rings (Scheme 1.4). Although the nature of C-Au bonds in gold carbenoids have

not been ruled out yet, this concept provided an explanation of many novel gold catalysed transformations. The generation of reactive α-oxo gold carbenes was proposed to be achieved by using N-O bond oxidants which is a useful substitute of metal carbenes formation by using dangerous diazo compounds.[23]

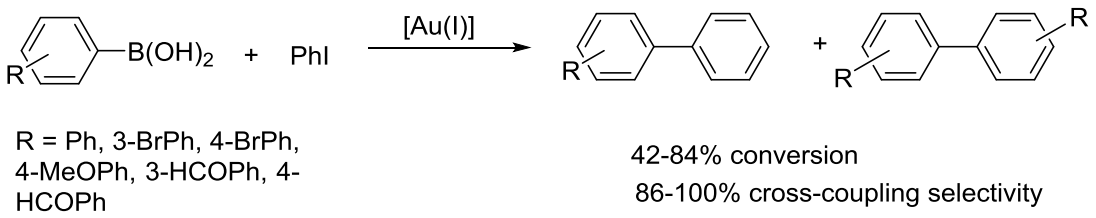


Scheme 1.4 Comparison of generating α-oxo gold carbenes by alkynes and diazo compounds.

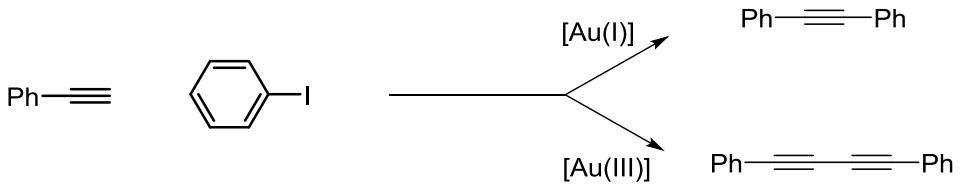
1.2.3 Gold Catalysed C-C Bond Coupling Reactions

As gold usually presented as carbophilic Lewis acid catalysts in organic transformations, the involvement of redox cycle between Au(I) and Au(III) was not drawing much attention because of the high redox potential of Au(I)/Au(III) (E = +1.41 V).[24] Despite of the development of gold catalysis with the distinct mode of reactivity such as gold carbenoids, the reports of organic transformations involving Au(I)/Au(III) redox system are rare.

In 2006, Corma *et. al.* reported of the use of gold(I) catalysts with Schiff base ligands in Suzuki cross-coupling of aryl boronic acid and iodobenzne (Scheme 1.5).[25] Later they have also reported the study of gold(I) and gold(III) catalysts with Schiff base ligands for the Sonogashira reaction.[26] They found that the gold(I) catalyst is active and selective to the reaction without the additional of copper(I) co-catalysts (Scheme 1.6). The homocoupling compounds was formed as major products when gold(III) catalysts was used (Scheme 1.6).



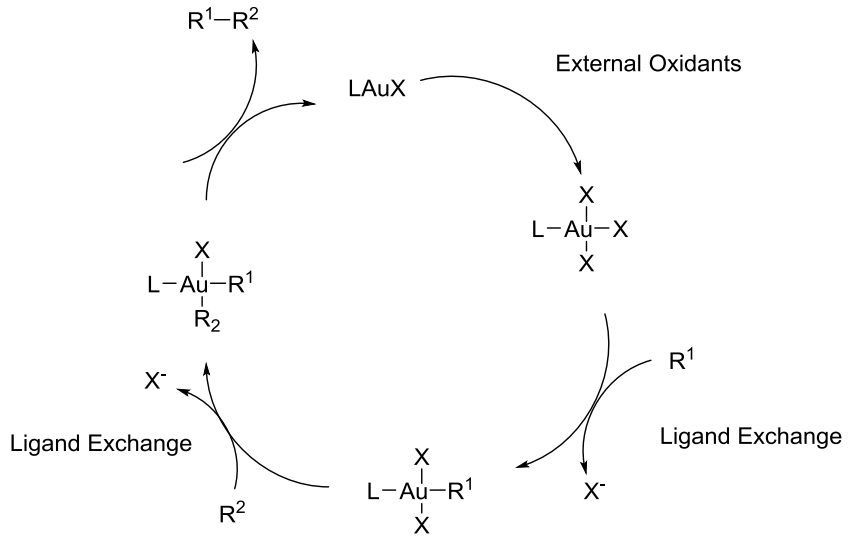
Scheme 1.5 Gold(I) catalysed Suzuki cross-coupling reactions.



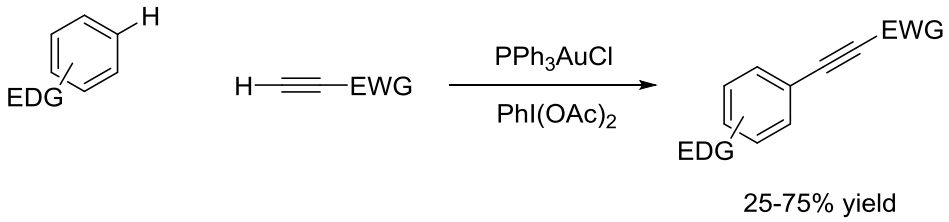
Scheme 1.6 Different reactivities of gold(I) and gold(III) in coupling reactions.

As mentioned, the high redox potential of Au(I)/Au(III) couple leads to generally poor reactivity of gold catalysts in coupling reactions. An alternative approach to pass through the

Au(I)/Au(III) redox barrier for homogeneous catalysis is addition of external oxidants to promote oxidation of Au(I) to Au(III) (Scheme 1.7).[27]

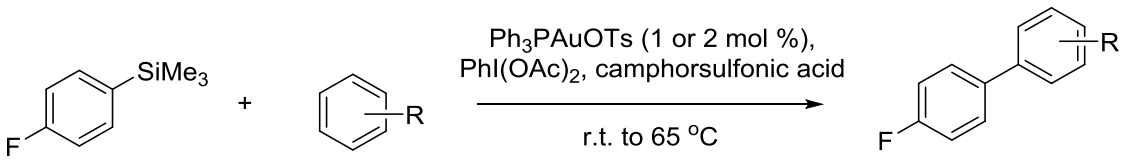


Scheme 1.7 Gold-catalysed oxidative coupling using external oxidants.



Scheme 1.8 Gold(I) catalysed ethynylation of arenes.

One of the most representative examples is the gold(I) catalysed ethynylation of arenes by addition of $PhI(OAc)_2$ as an external oxidant (Scheme 1.8).[28] The use of external oxidizing agent for the gold-catalyzed oxidative coupling is now being further studied. More recently, Russel *et. al.* have reported the direct arylation of arenes by arysilanes at room temperature with high functional group tolerance (Scheme 1.9).[29] However, the mechanistic studies of the key steps in the coupling reactions are relatively unexplored such as the intermediates formed from reactions between gold species and oxidants[30] as well as the reductive elimination for C-C bond formation.[31]



Scheme 1.9 Gold-catalysed direct arylation of arenes with arylsilanes.

1.3 Synthesis of Cyclometallated Gold(III) Complexes

Cyclometalated metal complexes were synthesized and studied extensively for different transition metals (i.e. Pd, Ir, Pt, Rh) in view of synthesizing various metallocyclics for fine-tuning of electronic and steric properties, as well as improving the solubility in organic solvents. Besides, the stability of the complexes can be improved in large extent towards oxidation, reduction or decomposition which is also important to stabilize the reaction intermediates in catalytic cycles affording higher product turnover or extraordinary product selectivity. Constable and Leese first reported the synthesis of cyclometallated gold(III) complexes by direct cycloauration using a bidentate 2-phenyl pyridine ligand.[32] More cyclometallated gold(III) complexes were synthesized by using other bidentate C,N ligands or tridentate C,N,N and C,N,N ligands (Figure 1.2).[33]

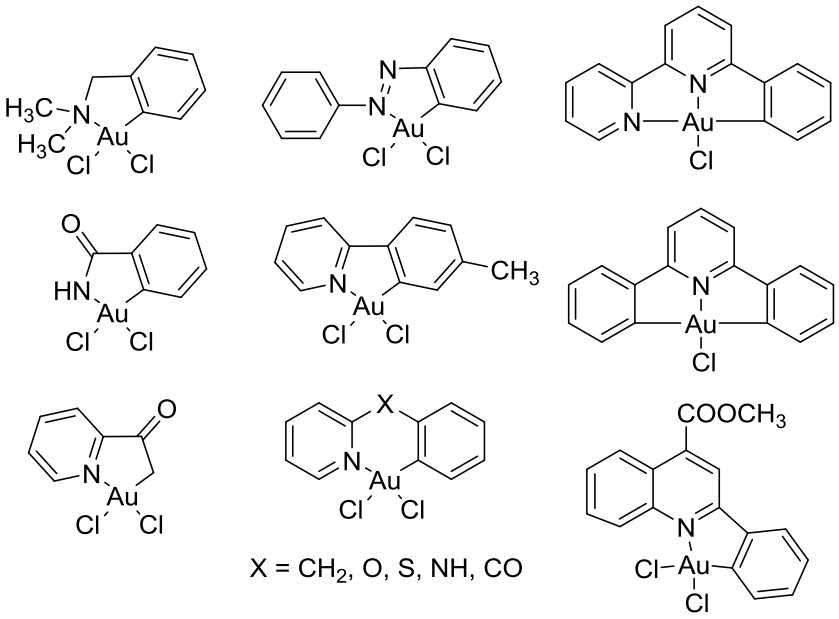


Figure 1.2 Examples of cyclometallated gold(III) complexes with C,N donors.

The direction C-H bond activation of arenes by gold(III) is rather difficult compared with other transition metals. In some cases, the C,N cyclometallated gold(III) complexes cannot

be synthesized by direct cycloauration. Some gold(III) complexes were reported to be synthesized by silver-assisted cycloauration or transmetallation from organomercury precursors.

Direct C-H Bond Activation

Most gold(III) complexes can be directly synthesized by mixing of ligands with simple gold(III) salts such as $KAuCl_4$ or $HAuCl_4$ in CH_3CN/H_2O and the resulting mixture is refluxed for 12 h to 24 h. Figure 1.3 shows the examples of cyclometallated gold(III) complexes that can be directly obtained by thermal C-H activation.[33]

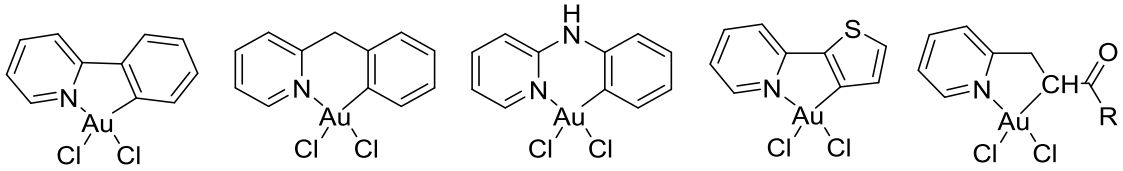
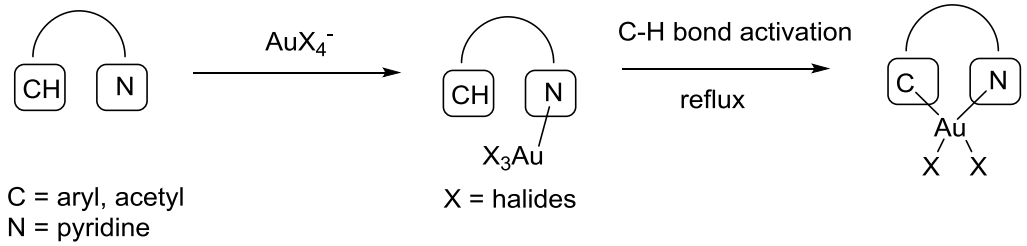


Figure 1.3 Cyclometallated gold(III) complexes synthesized by direct cycloauration.

The coordination of the pyridine N to the Au(III) centre is facile to form monodentate gold(III) complexes. The subsequent C-H bond activation can be achieved by refluxing the mixture in CH_3CN/H_2O for a period of time (Scheme 1.10). This is the direct method to synthesize cyclometallated gold(III) complexes via thermal C-H bond activation. However, it is not suitable for thermally unstable ligands such as oxazoline-type ligands.



Scheme 1.10 Direct C-H bond activation for cycloauration.

More recently, Tilset and Heyn have reported the synthesis of cyclometallated gold(III) complexes by microwave assisted C-H bond activation. This method provides sufficient energy for activation of the aromatic C-H bond in a much shorter time than the thermal method which is useful in production of novel gold(III) complexes in a more convenient way.[34]

Silver Ion Assisted Cycloauration

In a number of cases, silver salts are added with the gold salts as halide ions scavengers by forming insoluble AgCl.[35] A reactive vacant site on the metal fragment are generated which is more favourable to cycloauration under heating (Scheme 1.11).

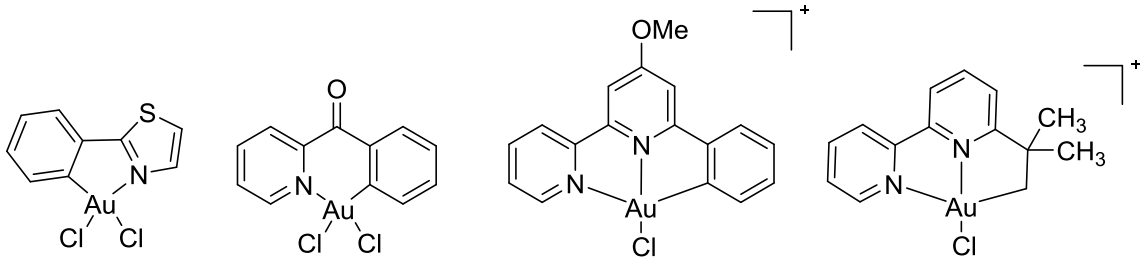
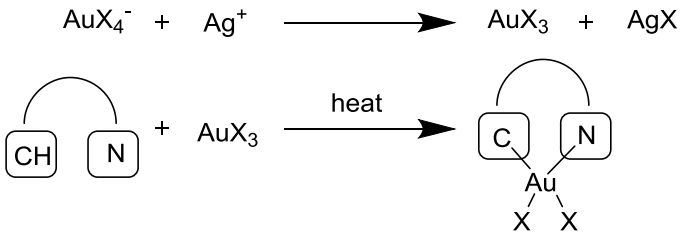


Figure 1.4 Cyclometallated gold(III) complexes synthesized by silver ion assisted cycloauration.



Scheme 1.11 Silver ion assisted cycloauration.

Synthesis of Gold(III) Complexes by Transmetallation

The principle of this method is transmetalation reaction of gold(III) precursors such as $KAuCl_4$ or $HAuCl_4$ with organomercury ligands to synthesize cyclometallated gold(III) compounds that cannot be synthesized by the previous two methods. This is the versatile method for transferring the ligands from Hg(II) to Au(III).[36] Furthermore, the organogold(III) compounds can also be the precursors for transmetallation with the organomercury complexes to form bis-cyclometallated gold(III) complexes. The organomercury precursors are generally formed by reaction of ligands with nBuLi at 0 ^oC to give organolithium compounds which subsequently react with $HgCl_2$ to afford the organomercury compounds (Scheme 1.12). Parish and co-workers have reported the synthesis of a wide range of organomercury precursors which were used to synthesize cyclometallated gold(III) complexes.[36b]

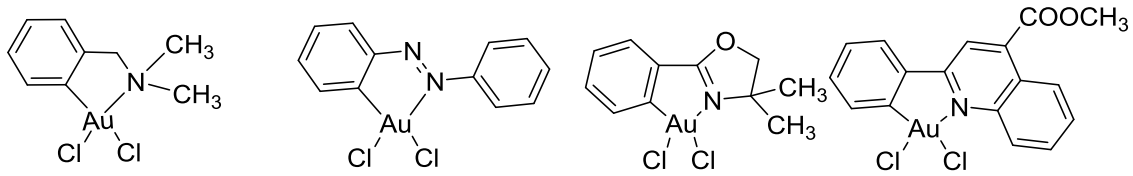
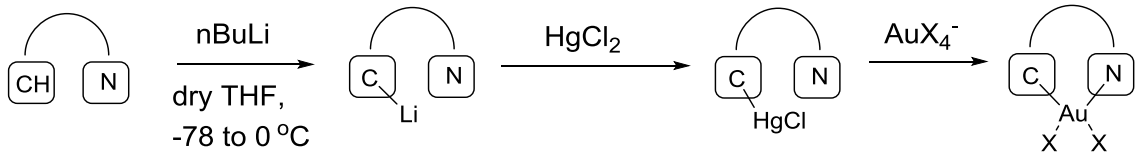


Figure 1.5 Cyclometallated gold(III) complexes synthesized by transmetallation.



Scheme 1.12 Transmetallation reaction of organomercury to gold(III) salts.

1.4 Chemical Modification of Biomolecules

Biomolecules (i.e. proteins, nucleic acids, glycans and lipids) are essential components in cells (Figure 1.6). Besides, there are presence of small molecules such as organic or inorganic metabolites within the biological systems.[37]

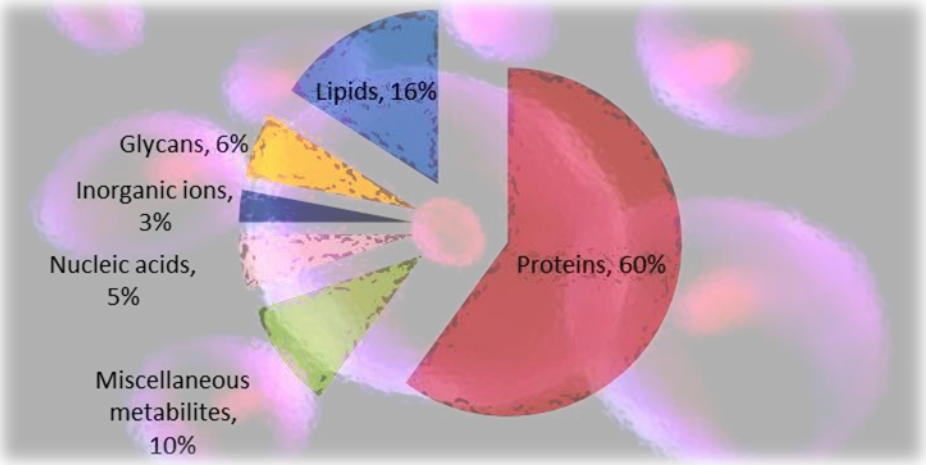


Figure 1.6 Components of biomolecules in a mammal cell.

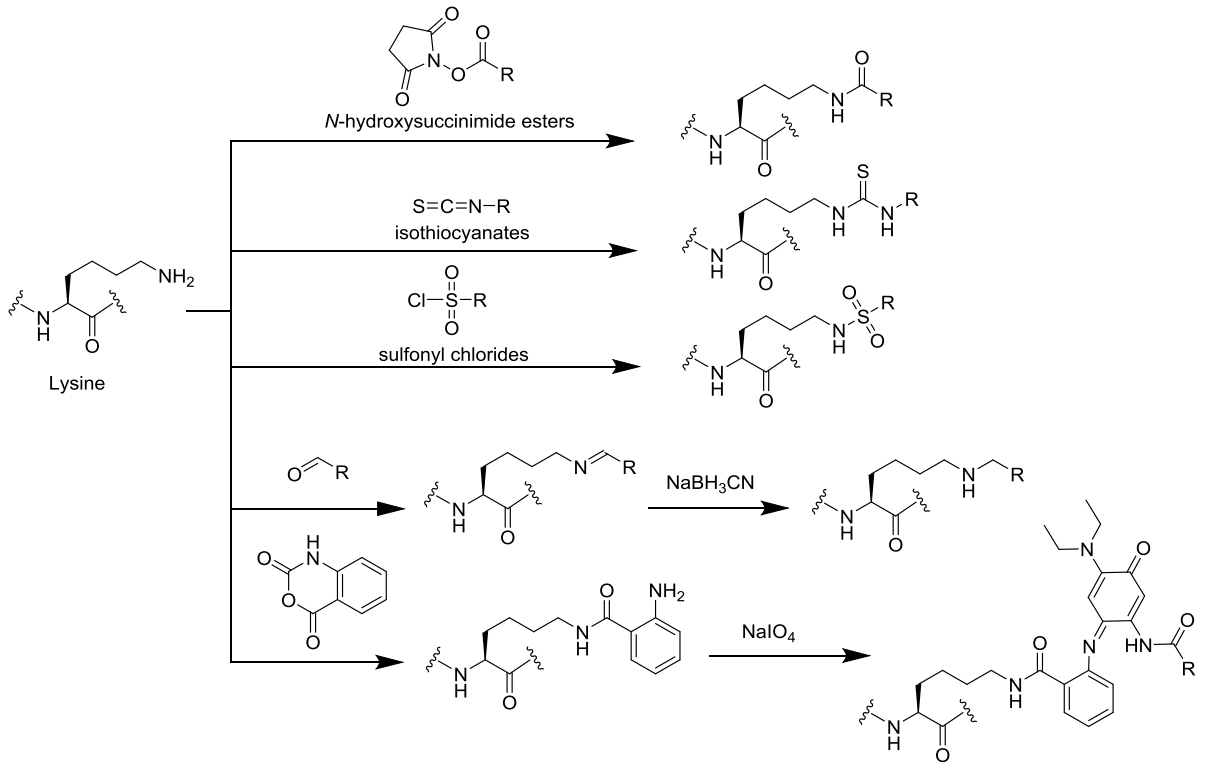
These biomolecules are critical components to maintain the functions of cells which control the whole living organisms. By studying the role of biomolecules in biological activities, scientists are able to have insight into the causes of some diseases as well as the ways to cure. However, very few of them containing distinct features can be detected or identified directly in the complicated milieus. Biomolecule modification in chemical ways allows manufacturing of covalently-bonded synthetic functional probes to biomolecules of interest by biocompatible chemical reactions. The resulting products are regarded as bioconjugates which provide useful information for biological studies.[37-38] Green fluorescent proteins (GFP) or others variants are combination of fluorescent probes with targeting proteins by chemical methods which are used for cell imaging.[39]

Protein Modification

Proteins are the main target of interest for early development for biomolecule modification, which are composed of peptides linked by amide bonds through the assembly of 20 natural occurring amino acids. Every amino acid has a unique side chain containing various functional groups (i.e. amines, thiols, carboxylic acids, phenols, alcohols, guanidines, indoles and imidazoles). The selective modification is based on the reactivities of different amino acids side chains within the target proteins. Through reacting with the functional groups of these residues, other biomolecules (i.e. glycans and lipids) can be incorporated into the target proteins. These chemical modifications are also referred as post-translational modifications (PTM) as these steps occurred after protein biosynthesis steps. After PTM, the biological properties and functions of the modified proteins are changed which lead to different biological outcomes (i.e. phosphorylation of hydroxyl groups of serine, tyrosine residue leading to conformational changes of the proteins).

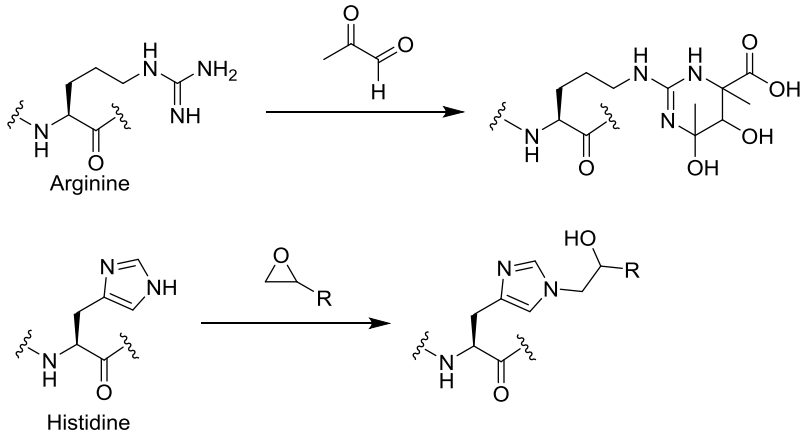
In the 20 natural occurring amino acids, lysine and cysteine are mostly used as the target residues for protein modification because of their inherent nucleophilicity.[40] Lysine is the most accessible residue on the surface of proteins but the least site specific. Cysteine is the strongest nucleophile when compared with other amino acids. Free cysteine residue is rare (~1.7%) as most of them exist as disulfide form, allowing site specific modification.

Lysine bearing ε-amino moiety can react as a nucleophile even the side chain is protonated. The primary amine group in lysine is reactive to common electrophiles such as *N*-hydroxysuccinimide esters, isothiocyanates, sulfonyl chlorides, aldehydes or other reagents affording the corresponding amides, thioureas, sulfonamides or imines respectively (Scheme 1.13).[40b, 41]



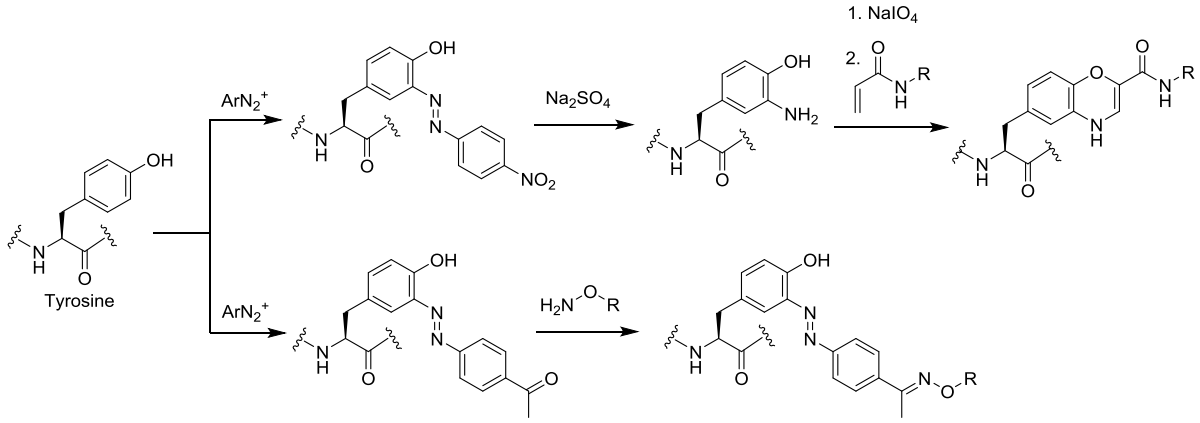
Scheme 1.13 Current chemical modification methods for lysine.

For arginine residues, the nitrogen atoms of the guanine can react with methylglyoxal to afford a pyrimidine derivative (Scheme 1.14, upper). However, the long reaction time (~14 d) makes in inefficient and inapplicable in cell labelling.[42] Modification of histidine residue can be achieved by reacting with epoxide derivatives and the method was shown to be selective to histidine (Scheme 1.14, lower).[43]



Scheme 1.14 Modification of arginine and histidine residues.

Furthermore, the phenol group on tyrosine can react as a nucleophile to diazonium salts affording diazo compounds which can be further transformed into stable benzoxazine derivatives (Scheme 1.15, upper).[44] By using ketone-derived aryldiazonium salts, ketone-derived diazo compounds can be formed which can further react with hydroxylamines to give oxime ethers (Scheme 1.15, lower).[45]



Scheme 1.15 Modification of tyrosine residues.

Cysteine contains nucleophilic thiol group (-SH) as the side chain residue. Because of stronger nucleophilicity of -SH group among other nucleophilic residues such as R-NH_2 and –OH groups, the site selective modification of cysteine over other amino acids is possible by choosing suitable chemical reagents. Moreover, the low natural abundance (~1.7 %) of cysteine in protein sequences makes it as a useful handle for modification of target protein containing cysteine residues. The modification of cysteine will be discussed in chapter 3.

1.5 Objectives

There is an increasing trend in exploration of gold catalysis in organic chemistry. The attraction of gold catalysis is due to its unique chemical properties over other transition metals commonly employed in catalysis. For instance, gold catalysts are chemically stable in the presence of air and moisture, and carbophilic gold(I)/(III) catalysts render a wide range of catalytic organic transformations based on activation of C-C multiple bonds. Due to the advance in development of novel organic transformations, gold catalysis will be a promising tool for efficient organic transformation reactions as well as selective modification of biomolecules.

In chapter 2, the bis-cyclometallated gold(III) complexes would be synthesized and their catalytic activity would be examined in propargylamine synthesis and indole alkylation. The geometry of the resulting gold(III) complexes would be studied by X-ray crystallography. By understanding the geometry of the bis-cyclometallated gold(III) complexes, strategies for activating the gold(III) catalysts would be developed for organic transformations.

In chapter 3, cyclometallated gold(III) complexes with different ancillary ligands would be synthesized and the chemoselectivity towards cysteine modification would be studied by conducting control experiments. The interaction between the cyclometallated gold(III) complexes and cysteine would be studied by conducting model reactions. The ease of formation of *S*-arylated peptides from reactions between cysteine-containing peptides and different cyclometallated gold(III) complexes would be studied under various conditions.

1.6 References

[1] Haruta, M., *Nature* **2005**, *437*, 1098–1099.

[2] Hutchings, G. J.; Haruta, M., *Appl. Catal., A.* **2005**, *291*, 2–5.

[3] Bardají, M.; Laguna, A., *J. Chem. Educ.* **1999**, *76*, 201–203.

[4] Gorin, D. J.; Toste, F. D., *Nature* **2007**, *446*, 395–403.

[5] Pyykkö, P., *Angew. Chem. Int. Ed.* **2004**, *43*, 4412–4456.

[6] Hutchings, G. J.; Brust, M.; Schmidbaur, H., *Chem. Soc. Rev.* **2008**, *37*, 1759–1765.

[7] Schwank, J., *Gold Bull.* **1985**, *18*, 2–10.

[8] (a) Gorin, D. J.; Toste, F. D., *Nature* **2007**, *446*, 395–403; (b) Li, Z.; Brouwer, C.; He, C., *Chem. Rev.* **2008**, *108*, 3239–3265; (c) Corma, A.; Leyva-Pérez, A.; Sabater, M. J., *Chem. Rev.* **2011**, *111*, 1657–1712.

[9] Bond, G. C.; Thompson, D. T., *Catal. Rev. Sci. Eng.* **1999**, *41*, 319–388.

[10] Haruta, M.; Yamada, N.; Kobayashi, T.; Iijima, S., *J. Catal.* **1989**, *115*, 301–309.

[11] Hutchings, G. J., *J. Catal.* **1985**, *96*, 292–295.

[12] Teles, J. H.; Brode, S.; Chabanas, M., *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.

[13] Corma, A.; Serna, P., *Science* **2006**, *313*, 332–334.

[14] Prati, L.; Rossi, M., *J. Catal.* **1998**, *176*, 552–560.

[15] Abad, A.; Concepción, P.; Corma, A.; García, H., *Angew. Chem. Int. Ed.* **2005**, *44*, 4066–4069.

[16] (a) Landon, P.; Ferguson, J.; Solsona, B. E.; Garcia, T.; Carley, A. F.; Herzing, A. A.; Kiely, C. J.; Golunski, S. E.; Hutchings, G. J., *Chem. Commun.* **2005**, 3385–3387; (b) Landon, P.; Collier, P. J.; Papworth, A. J.; Kiely, C. J.; Hutchings, G. J., *Chem. Commun.* **2002**, 2058–2059.

[17] (a) Stephen, A.; Hashmi, K., *Gold Bull.* **2004**, *37*, 51–65; (b) Hashmi, A. S. K., *Gold Bull.* **2003**, *36*, 3–9; (c) Fürstner, A.; Davies, P., *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449.

[18] (a) Yamamoto, Y., *J. Org. Chem.* **2007**, *72*, 7817–7831; (b) Ramón, R. S.; Marion, N.; Nolan, S. P., *Chem. Eur. J.* **2009**, *15*, 8695–8697.

[19] Chiarucci, M.; Bandini, M., *Beilstein J. Org. Chem.* **2013**, *9*, 2586–2614.

[20] Raubenheimer, H. G.; Esterhuysen, M. W.; Timoshkin, A.; Chen, Y.; Frenking, G., *Organometallics* **2002**, *21*, 3173–3181.

[21] Echavarren, A. M., *Nat. Chem.* **2009**, *1*, 431–433.

[22] (a) Seidel, G.; Fürstner, A., *Angew. Chem. Int. Ed.* **2014**, *53*, 4807–4811; (b) Seidel, G.; Gabor, B.; Goddard, R.; Heggen, B.; Thiel, W.; Fürstner, A., *Angew. Chem. Int. Ed.* **2014**, *53*, 879–882.

[23] (a) Xiao, J.; Li, X., *Angew. Chem. Int. Ed.* **2011**, *50*, 7226–7236; (b) Yeom, H. S.; Shin, S., *Acc. Chem. Res.* **2014**, *47*, 966–977; (c) Zhang, L., *Acc. Chem. Res.* **2014**, *47*, 877–888.

[24] Bratsch, S. G., *J. Phys. Chem. Ref. Data* **1989**, *18*, 1–21.

[25] González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F., *J. Catal.* **2006**, *238*, 497–501.

[26] González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F., *Angew. Chem. Int. Ed.* **2007**, *46*, 1536–1538.

[27] Hopkinson, M. N.; Gee, A. D.; Gouverneur, V., *Chem. Eur. J.* **2011**, *17*, 8248–8262.

[28] Haro, T.; Nevado, C., *J. Am. Chem. Soc* **2010**, *132*, 1512–1513.

[29] Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A., *Science* **2012**, *337*, 1644–1648.

[30] Mankad, N. P.; Toste, F. D., *J. Am. Chem. Soc* **2010**, *132*, 12859–12861.

[31] (a) Scott, V. J.; Labinger, J. A.; Bercaw, J. E., *Organometallics* **2010**, *29*, 4090–4096; (b)

Wolf, W. J.; Winston, M. S.; Toste, F. D., *Nature Chem.* **2014**, *6*, 159–164.

[32] Constable, E. C.; Leese, T. A., *J. Organomet. Chem.* **1989**, *363*, 419–424.

[33] Henderson, W., *Advances in Organometallic Chemistry* **2006**, *54*, 207–266.

[34] (a) Shaw, A. P.; Tilset, M.; Heyn, R. H.; Jakobsen, S., *J. Coord. Chem.* **2010**, *64*, 38-47; (b) Venugopal, A.; Shaw, A. P.; Törnroos, K. W.; Heyn, R. H.; Tilset, M., *Organometallics* **2011**, *30*, 3250–3253; (c) Langseth, E.; Görbitz, C. H.; Heyn, R. H.; Tilset, M., *Organometallics* **2012**, *31*, 6567–6571.

[35] (a) Fuchita, Y.; Ieda, H.; Tsunemune, Y.; Kinoshita-Nagaoka, J.; Kawano, H., *J. Chem. Soc., Dalton Trans.* **1998**, 791–796; (b) Ieda, H.; Fujiwara, H.; Fuchita, Y., *Inorg. Chim. Acta* **2001**, *319*, 203–206.

[36] (a) Bonnardel, P. A.; Parish, R. V., *J. Organomet. Chem.* **1996**, *515*, 221–232; (b) Bonnardel, P. A.; Parish, R. V.; Pritchard, R. G., *J. Chem. Soc., Dalton Trans.* **1996**, 3185–3193.

[37] Prescher, J. A.; Bertozzi, C. R., *Nat. Chem. Biol.* **2005**, *1*, 13–21.

[38] Hackenberger, C. P. R.; Schwarzer, D., *Angew. Chem. Int. Ed.* **2008**, *47*, 10030–10074.

[39] (a) Tsien, R. Y., *Annu. Rev. Biochem.* **1998**, *67*, 509–544; (b) Lippincott-Schwartz, J.; Patterson, G. H., *Science* **2003**, *300*, 87–91.

[40] (a) Sletten, E. M.; Bertozzi, C. R., *Angew. Chem. Int. Ed.* **2009**, *48*, 6974–6998; (b) Gauthier, M. A.; Klok, H. A., *Chem. Commun.* **2008**, 2591–2611.

[41] Baslé, E.; Joubert, N.; Pucheault, M., *Chem. Biol.* **2010**, *17*, 213−227.

[42] Oya, T.; Hattori, N.; Mizuno, Y.; Miyata, S.; Maeda, S.; Osawa, T.; Uchida, K., *J. Biol. Chem.* **1999**, *274*, 18492–18502.

[43] Chen, G.; Heim, A.; Riether, D.; Yee, D.; Milgrom, Y.; Gawinowicz, M. A.; Sames, D., *J.*

Am. Chem. Soc **2003**, *125*, 8130–8133.

[44] Hooker, J. M.; Kovacs, E. W.; Francis, M. B., *J. Am. Chem. Soc* **2004**, *126*, 3718–3719.

[45] Schlick, T. L.; Ding, Z.; Kovacs, E. W.; Francis, M. B., *J. Am. Chem. Soc.* **2005**, *127*, 3718–3723.

Chapter 2

Bis-cyclometallated Gold(III) Complexes as Efficient Catalysts for Synthesis of Propargylamines and Alkylated Indoles

2.1 Introduction

Gold catalysis has drawn significant interest in recent years because of its superior soft Lewis acid character. This character leads to extraordinary selectivity and functional tolerance in reactions when compared with other late transition metals. Applications of gold in organic synthesis were reported for decades.[1] However, most examples of gold catalysed organic synthesis were based on simple gold(I) or gold(III) salts. In general, it is not favourable for catalysis research because of lacking in tunable and stable catalysts for affording catalysts with better reactivity and chemoselectivity. Gold(I) or gold(III) catalyst development has been started in recent years aiming to improve the reactivity, selectivity or enantioselectivity in organic reactions.

2.1.1 Development of Gold Catalysis

The works on simple gold salts (e.g. AuCl and $AuCl_3$) employed as catalysts for organic synthesis have been reported widely.[2] Indeed, simple gold salts can provide a new approach for catalytic organic transformations that were usually catalysed by other noble metals such as palladium,[3] rhodium[4] or platinum[5] where the abundance of gold was the highest among them. Nevertheless, the instability of simple gold salts without appropriate ligands presence in catalytic cycles leads to poor product turnovers in reactions.[6] In this manner, development of gold(I) catalysts (Figure 2.1) have been largely expanded by using different types of ligands as effective catalysts[7] to perform novel synthetic transformations or as substitutes for existing reactions catalysed by other catalysts in the view of better reactivity, selectivity and functional group tolerance (Scheme 2.1).

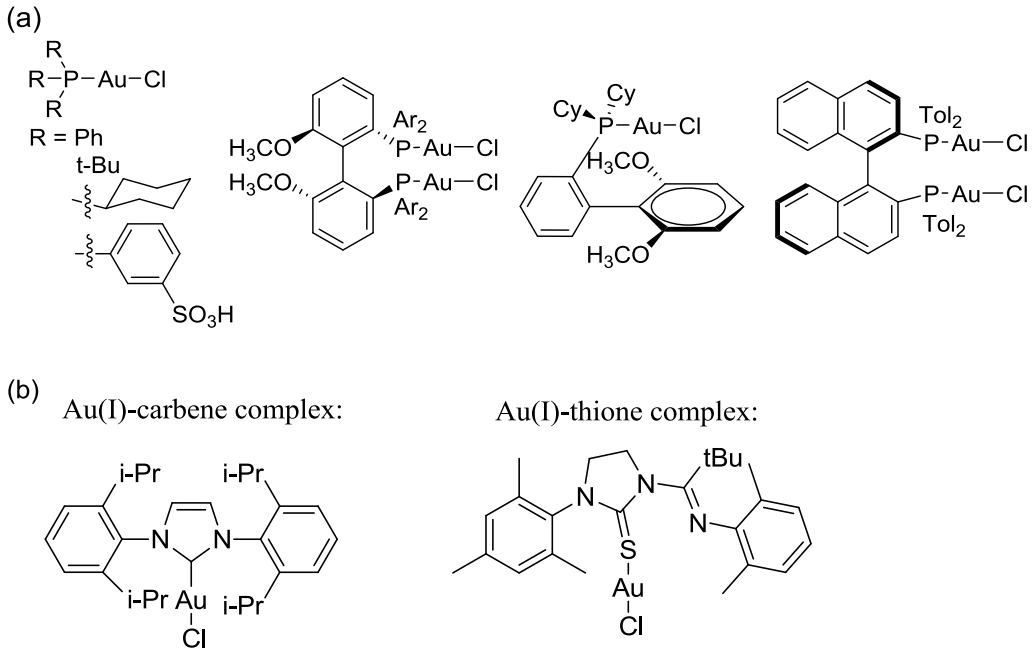
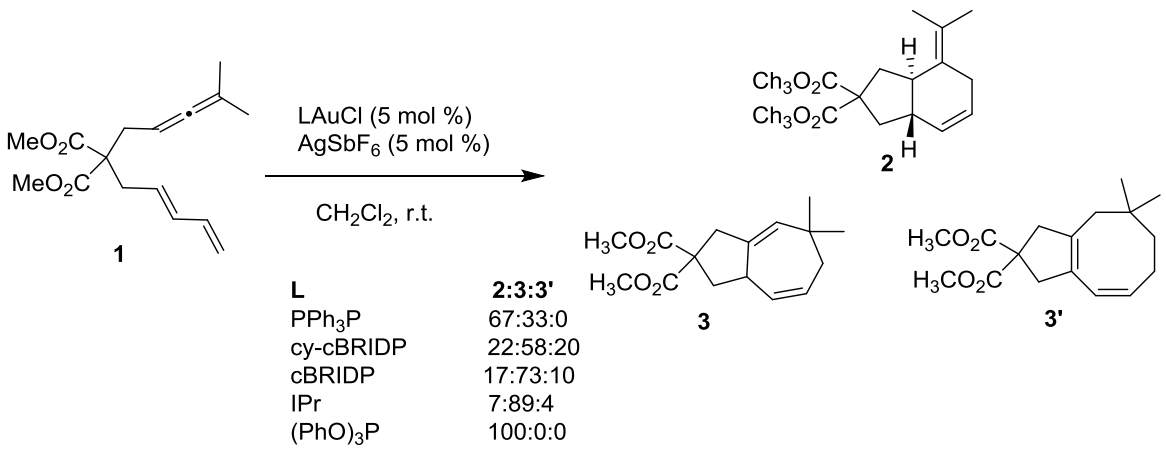


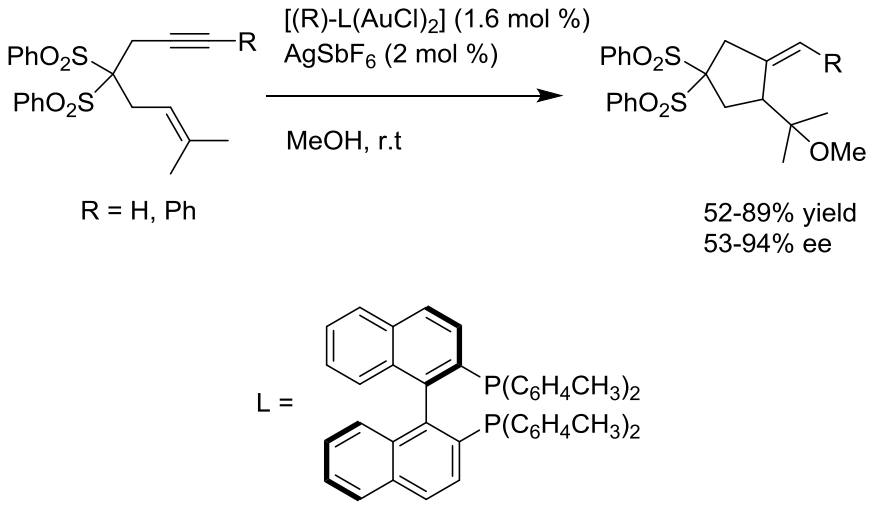
Figure 2.1(a) Au(I)-phosphine complexes.[6c] **(b)** Au(I)-carbene[8] and Au(I)-thione complexes.[9]



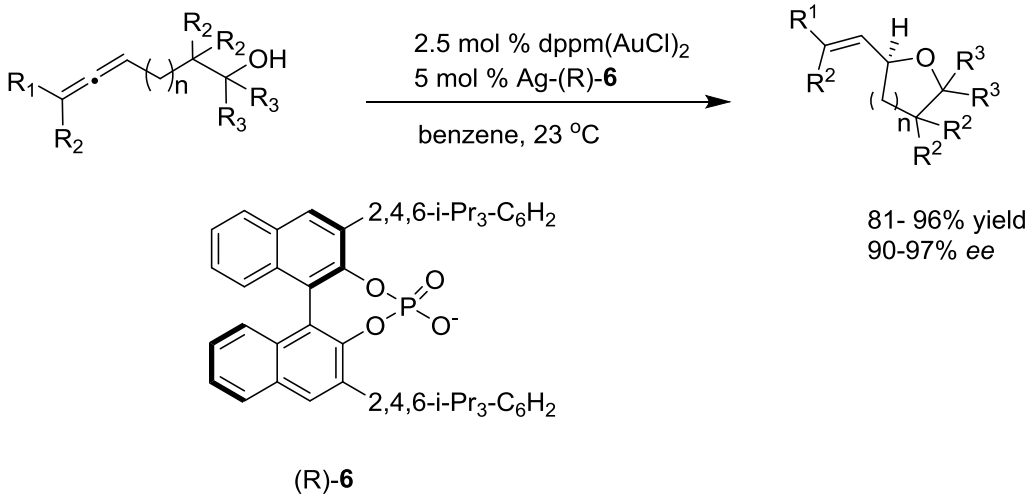
L	2:3:3'
PPh_3P	67:33:0
cy-cBRIDP	22:58:20
cBRIDP	17:73:10
IPr	7:89:4
$(PhO)_3P$	100:0:0

Scheme 2.1 Ligand effect in gold complexes affecting the product distribution.[7a]

One of the major reasons of the rapid development in gold(I) catalysis is similar ligand design strategies to palladium(II) catalysis[10] which have been well developed in different areas of catalysis. For instance, chiral phosphine ligands used in palladium catalysed asymmetric synthesis were found to be useful in developing chiral gold(I) catalysis. Asymmetric cyclization of 1,6-diynes by BINAP gold(I) catalyst has been reported (scheme 2.2).[11] With the presence of a wide range of chiral ligands in hands, gold(I) asymmetric synthesis has been progressively explored because of readily coordination of the chiral phosphine ligands to Au(I) centre.[12] Furthermore, it was reported that chiral anion strategies could be applied in asymmetric gold(I) catalysis (scheme 2.3).[13] On the contrary, evolution of gold(III) complexes for catalysis and asymmetric gold(III) catalysis remains unexplored.



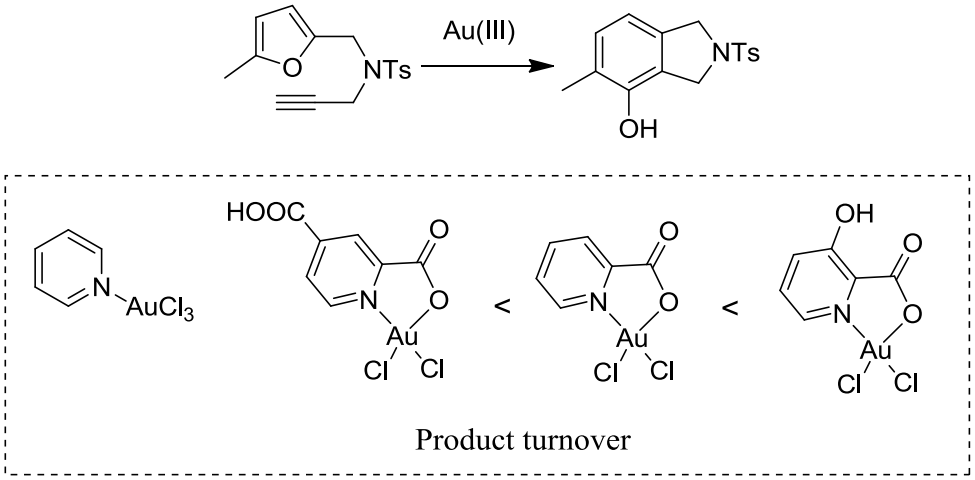
Scheme 2.2 Asymmetric cyclization of enynes via chiral gold(I) catalysts.



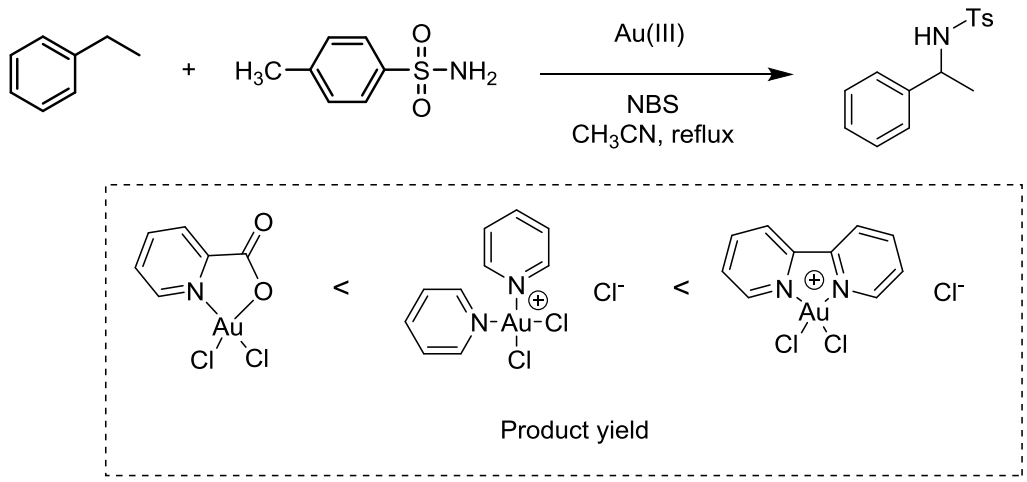
Scheme 2.3 The chiral anion strategy for asymmetric alkoxylation.

2.1.2 Gold(III) Catalysts for Organic Synthesis

Although gold(I) catalysts showed profound applications in organic synthesis, the linear gold(I) centre with only two coordination sites confined the design of ligands. It is generally difficult to improve product selectivity by the design of monodentate ligands. Besides, relatively long distance of substrates from the chiral centre leads to inefficient chirality transfer from ligands to substrates. Unlike linear gold(I) geometry, square planar gold(III) complexes are four-coordinated. The stability of gold(III) centre can be enhanced by using various bidentate ligands. Furthermore, the reactivity of the gold(III) centre can be controlled easily by choosing suitable ligands in a modular approach similar as other transition metal complexes. Cyclization reaction of furan alkynes for phenol synthesis by using cyclometallated gold(III) complexes with N,O donors has been reported (Scheme 2.4) and the cationic bipyridine gold(III) complex was found to effectively catalyse the amidation of benzylic C-H bond (Scheme 2.5).[14]



Scheme 2.4 Gold(III) catalysed phenol synthesis.[14a]



Scheme 2.5 Gold(III) catalysed amidation of benzylic C-H bond.[14g]

2.1.3 Previous Works on Cyclometallated Gold(III) Catalysts

Cyclometallated gold(III) complexes with 5 or 6-membered rings metallocycles containing both soft sp^2 carbon and hard nitrogen ligands are extraordinary stable in air and moisture as a resulted of strong Au-C bonds. Similar to *cis*-platin, these complexes could be regarded as potential anticancer drugs due to its stability *in vitro* and showing promising activity and selectivity.[15] However, seldom do researchers utilize these air and moisture stable complexes in organic synthesis in which gold(I) catalysis were scrutinized much more. Synthesis of cyclometallated gold(III) complexes with C,N donor ligands via direct cycloauration was reported by Constable *et al.*[16] since 1989. The studies of these cyclometallated gold(III) complexes were only based on biological properties,[17] and electrochemical properties.[18] More recently, the application of cyclometallated (C^N) gold(III) complexes has been extended to photochemical studies because of interesting luminescent properties with different auxiliary ligands (Figure 2.2).[19]

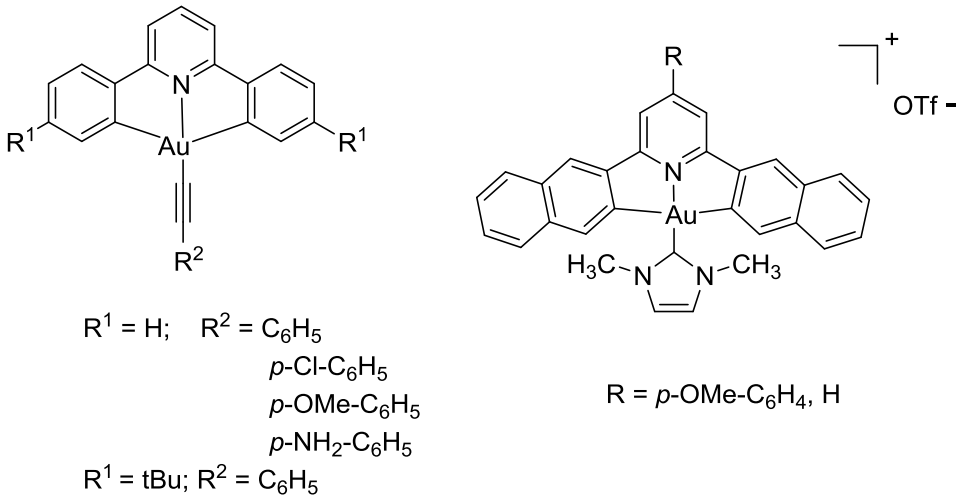


Figure 2.2 Luminescent cyclometallated gold(III) complexes.[19b, 20]

Professor Hashimi's group pioneered the use of gold(III) complexes in organic transformations. They strived to overcome the instability of simple gold salts and controlling the reactivity and selectivity of gold(III) catalysts by ligand design. Over the years, Wong and Che had been developing cyclometallated (C^N) gold(III) complexes catalysed organic reactions. In 2006, they found that gold(III) salen complexes (Figure 2.3) performed excellent catalytic ability towards three-component coupling reactions of propargylamine synthesis in aqueous medium.[21] It was noted that the gold(III) salen complex was unstable under reaction conditions in air and hence nitrogen atmosphere was necessary to ensure high substrate conversion.

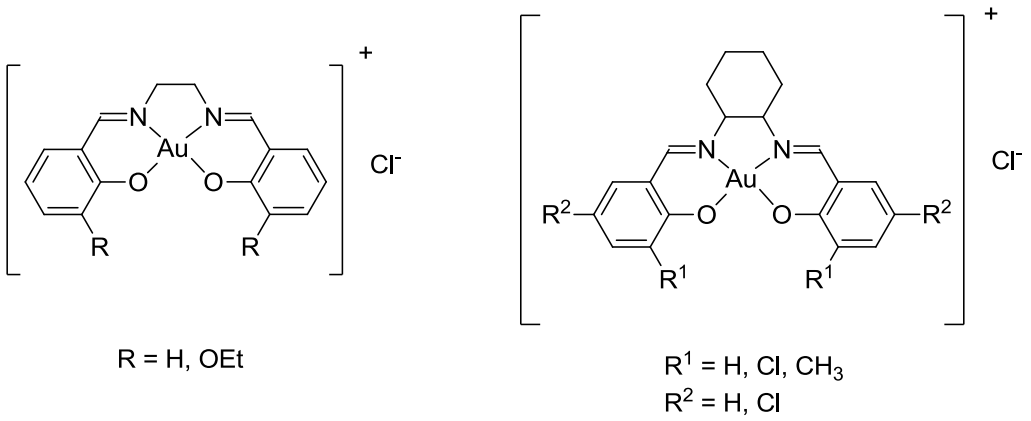


Figure 2.3 Structures of gold(III) salen complexes.

Later they found that cyclometallated (C^N) gold(III) complex (C^N = 2-phenylpyridine) could also catalyse the three-component coupling reactions in normal atmosphere.[22] Moreover, recycling experiment showed that the catalyst was stable in the reaction conditions and able to perform ten cycles without significant loss of catalytic activity. More recently, various cyclometallated (C,N) gold(III) complexes were designed and synthesized to be the catalysts in the synthesis of propargylamines, allenes and isoxazoles (Figure 2.4).[23]

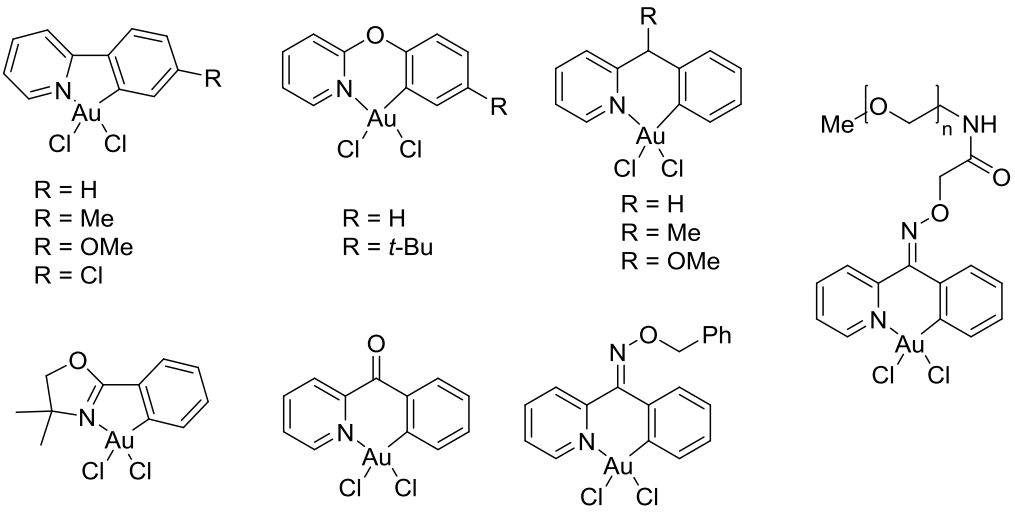
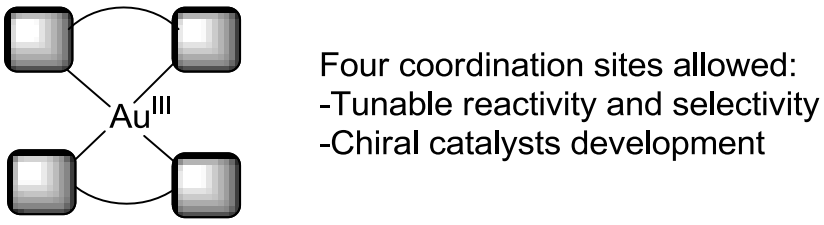


Figure 2.4 Catalytic active cyclometallated gold(III) complexes for organic transformations.

In addition, cyclometallated gold(III) complex with 2-benzylpyridine was found to catalyse the bifunctional modification of oligosaccharides via three-component coupling reactions.[24] These findings motivated us in the development of more efficient gold(III) catalysts in organic synthesis or bioconjugation. Apart from developing new gold(III) catalysts, we are also interested in searching for strategies to make these gold(III) catalysts more reactive in catalysis.

As a matter of fact, a significant challenge in the pursuing of efficient gold(III) catalysts is to make a balance between the stability and reactivity. Same as other transition metals, the stability of gold(III) centres increases significantly by coordination with ligands. However, a stable gold(III) complex generally lose its catalytic ability in the reactions compared with simple gold (III) salts. Novel strategies in ligand design and substrate activation are imperative in the future development in effective gold(III) catalysts for organic transformations.



2.1.4 Helical Metal Complexes

Square planar metal complexes with d^8 system (e.g. Rh(I), Ir(I), Pd(II), Ni(II), Pt(II) and Au(III)) lead to diverse metal complexes by modular ligand design (i.e. ligands with σ donating or π accepting properties for fine-tuning of reactivity, and chiral ligands for asymmetric catalysis). However, examples of ligand designs for altering the geometry of metal complexes are rare.

Pt(II) as a d^8 metal centre is the most typical representative of square planar complexes. Although other d^8 transition metal such as Pd(II), Rh(I) and Ir(I) frequently showed distortion of square planar by increasing the ligand size and decreasing the local symmetry.[25] Distortion of square planar Pt(II) complexes towards tetrahedral geometry has not been discovered until Stoeckli-Evans and Zelewsky *et. al.* reported the synthesis of Pt(II) complexes with helical chirality by using 2,6-diphenylpyridine ligands (Figure 2.5).[26] X-ray crystallography revealed that the distortion geometry may be arisen due to the ligand interaction (i.e. π–π stacking of aromatic rings) instead of a coplanar geometry by forming a *trans* square planar complex. The similar helical complexes were synthesized by using more bulky ligands.

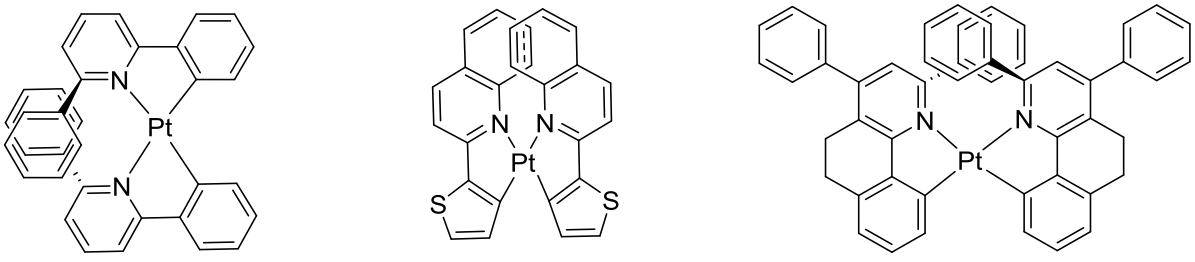


Figure 2.5 Structures of helical Pt(II) complexes.

It is envisioned that by using pyridine ligands with chiral moieties[27] is a potential strategy to prepare helically chiral metal complexes with distorted square planar geometry. Later, they successfully synthesized Pt(II) complexes with predetermined chirality by using chiral pyridine ligands.[28] The crystal structures of these complexes confirmed the helical chirality induced by the bulky chiral pyridine ligands *cis* to each other. They attempted to synthesize the Pd(II) complexes with helical chirality. However, the resulting compound is highly unstable towards reductive elimination to give Pd(0). Only using the less sterically hindered chiral pyridine as ligand can afford a square planar Pd(II) complex.

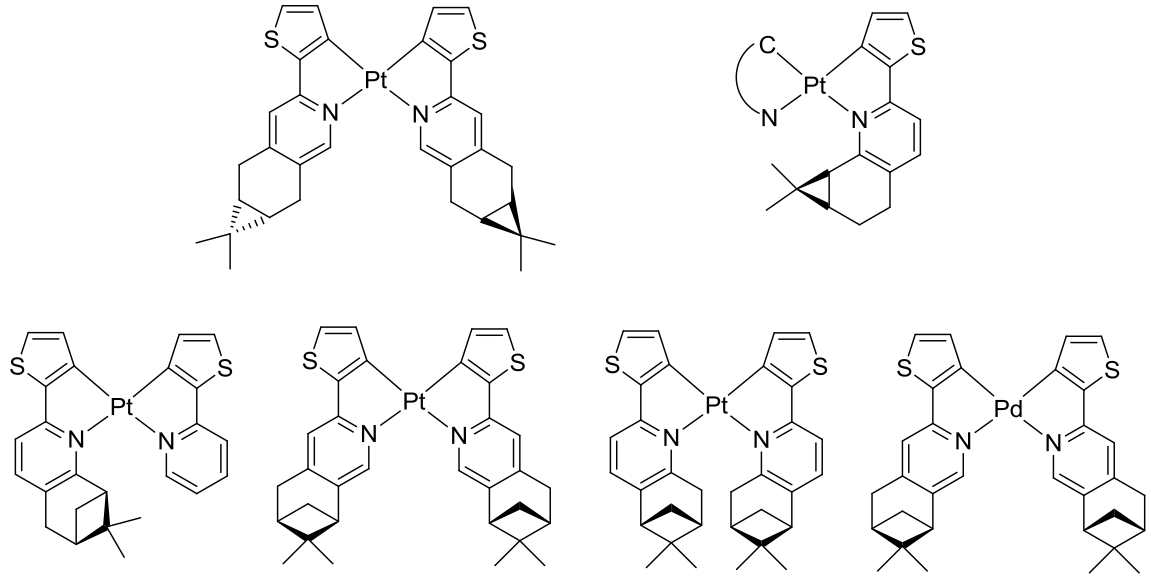
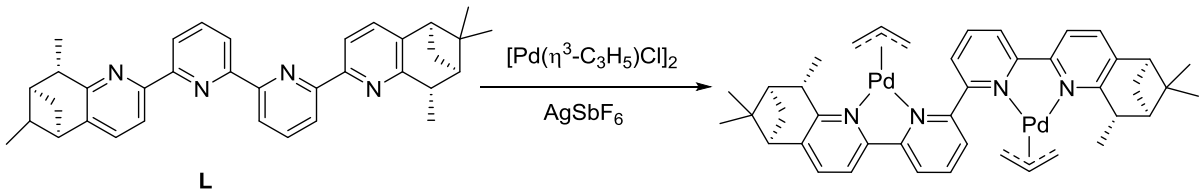


Figure 2.6 Structures of Pt(II) and Pd(II) complexes with predetermined chirality.

The distorted square planar ligand design can also be used in the construction of metal helicates.[29] Kwong *et. al.* developed a helical bimetallic palladium complex by using a chiral quaterpyridine ligand. The X-ray crystallography of the crystal structure revealed a single stranded helical structure with each Pd(II) centre adopted a distorted square planar structure (Scheme 6).[30] The complex was found to catalyse allylic substitution of 1,3-diphenylprop-2-enyl acetate by malonate with up to 85% *ee*.



Scheme 2.6 Synthesis of a single stranded Pd(II) complex.

Furthermore, Kwong and Yeung reported the synthesis of chiral double stranded Cu(I) helicates by using chiral oligopyridines (Figure 2.7).[31] The resulting double helical complexes were found to catalyse the asymmetric cyclopropanation of alkenes efficiently. More recently, they have successfully produced more examples of double stranded metal helicates by using Mn(II)[32] and Re(I)[33] metal centres.

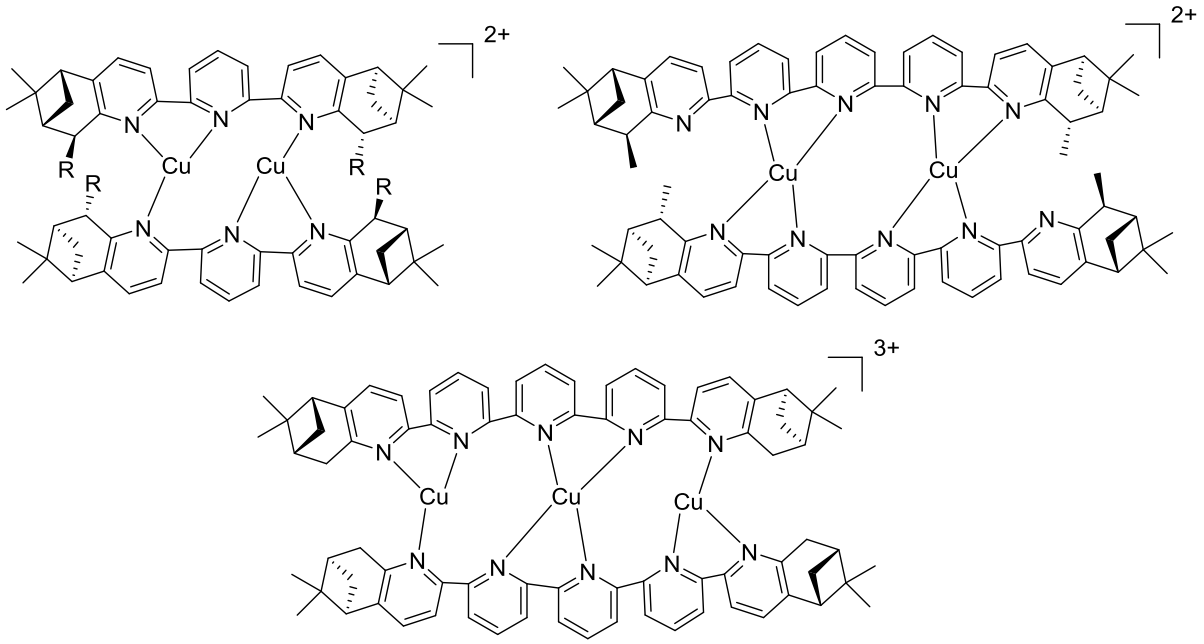


Figure 2.7 Chiral double stranded Cu(I) helicates.

2.1.5 Propargylamines

Propargylamines are commonly found structural elements in natural products which showed significant biological activities. For instance, Uncialamycin, a new antibiotic containing two carbon-carbon triple bonds and propargylamine moiety was isolated from the surface of British Columbia lichen (Figure 2.8a). This natural compound was found to show antibacterial properties against some human pathogens causing death of patients with cystic fibrosis. Another example is Dynemicin A isolated from ethyl acetate extract of Micromonospora chersina which has similar structure to Uncialamycin and showed anti-cancer properties (Figure 2.8b).

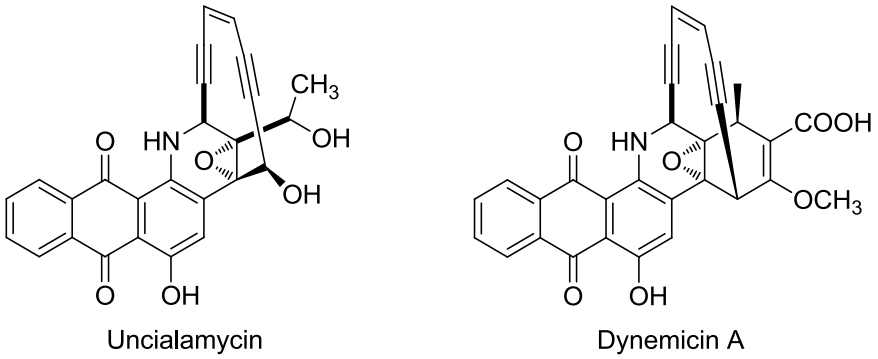
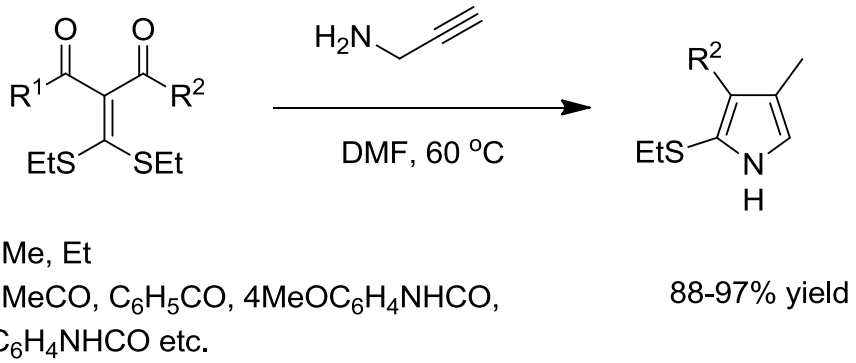
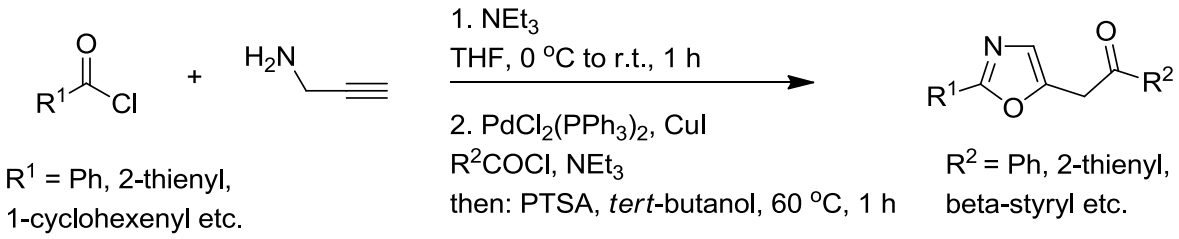


Figure 2.8 Structures of (a) Uncialamycin: an antibiotic from lichen Cladonia uncialis.[34] (b) Dynemicin A: a metabolite derivative from bacterium Micromonospora chersina.[35]

In organic synthesis, most of *N*-heterocyclic compounds such as pyrrolidines,[36] pyrroles,[37] oxazoles[38] and allenes[39] can be synthesized based on propargylamine intermediates. Propargylamines are also utilized for the total synthesis of natural products containing pyrroles groups. [40]



Scheme 2.7 Synthesis of 2, 3, 4 tri-substituted pyrroles from propargylamines and α,α-diacetylketene dithioacetal.[37b]



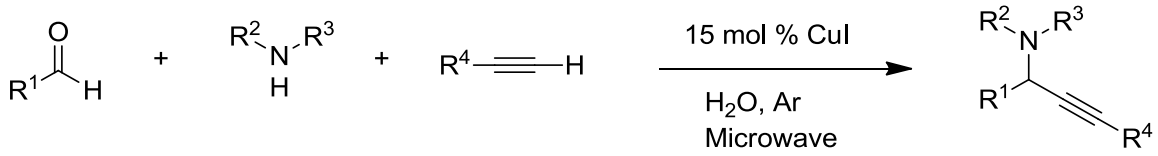
Scheme 2.8 A three-component oxazole synthesis via amidation–coupling–cycloisomerization.[38]

Since propargylaimnes showed biological activities and were versatile structural motifs in organic synthesis, chiral propargylamine-containing compounds are of importance potential drugs for various diseases. For instance, L-Deprenyl and rasagiline are early developed propargylamine-type drugs for inhibiting monoamine oxidase B in human brains in the treatment for Parkinson's and Alzheimer's diseases. The researches based on propargylamine-type drugs have been undergoing.[41]

Traditional approaches for propargylamine synthesis were mainly based on the nucleophilic attack of highly unstable iminium ions by lithium acetylides or Grignard reagents. This usually required extreme conditions such as high temperature, inert

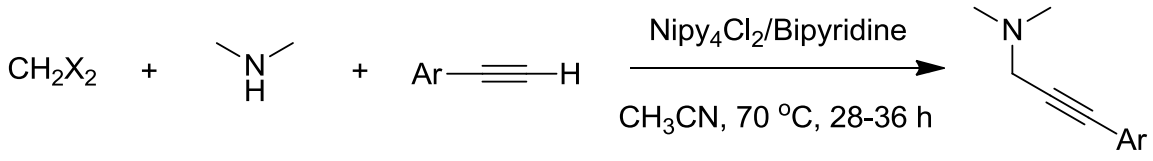
atmosphere and dry solvents. Use of highly reactive reagents resulted in poor functional groups tolerance and hence functional group protection was required before the synthesis. However, regioselectivities and yields of propargylamines were generally poor by using these methods.

Later, transition metal catalysed[42] propargylamine synthesis were developed by using silver,[43] copper[44] and other transition metals[45] via generating the metal acetylides for the nucleophilic attack to the iminium ions, which provided more efficient and regioselective approaches in the synthesis of diverse propargylamines. Scheme 2.9 shows microwave assisted Cu(I) catalysed propargylamine synthesis in water[44b] and scheme 2.10 shows Ni(II) catalysed propargylamine synthesis by using dihalomethanes.[45f] Besides, unlike using lithium acetylides or Grignard reagents, the reactions can be catalysed under mild conditions with relatively high functional tolerance.



R^1, R^2, R^3, R^4 = aryl, alkyl, H

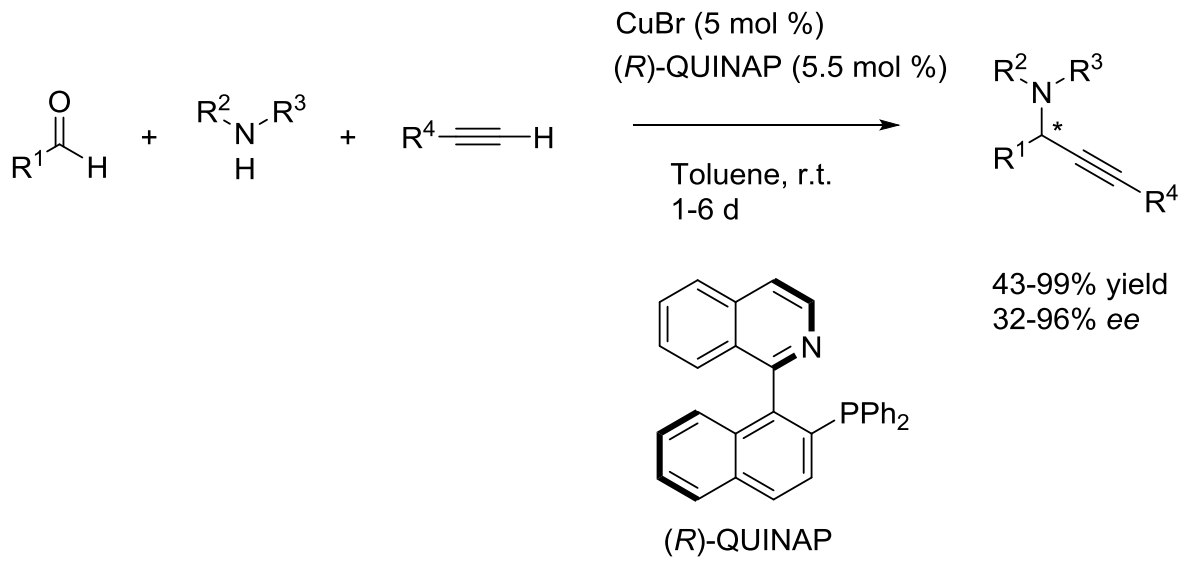
Scheme 2.9 A three-component coupling reaction of propargylamine synthesis.[44b]



Ar = aryl, heteroaryl
X= Cl, Br, I

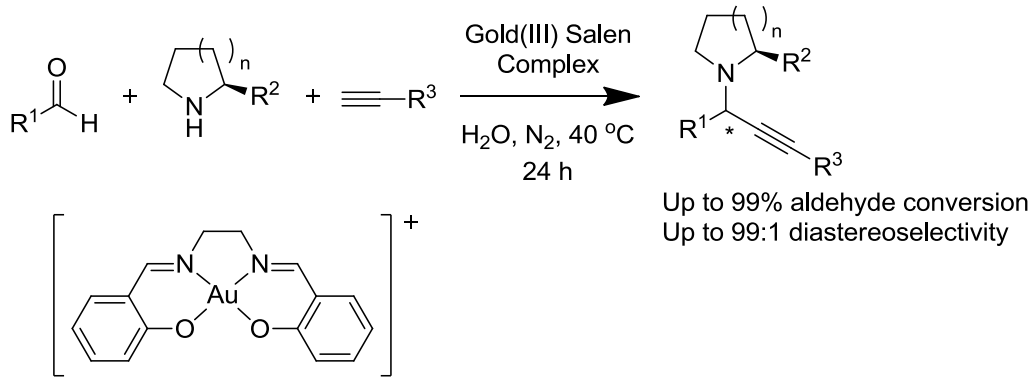
Scheme 2.10 Propargylamine synthesis via three-component coupling reaction of dihalomethanes, amines and alkynes.

Furthermore, enantioselective synthesis of propagylamines have been developed by using chiral ligands[46] which is fundamental to future drug development. Copper catalysed asymmetric synthesis of propargylamines has been achieved by adding (*R*)-QUINAP as a ligand (Scheme 2.11).



Scheme 2.11 A chiral copper(I) catalyst for asymmetric propargylamine synthesis.[46c]

Notably, Che and Wong successfully developed gold(III) salen complex catalysed diasteroselective propargylamine synthesis by using chiral 2^{o} amines with up to 99:1 diastereomeric ratios (Scheme 2.12). The gold(III) catalysed three-component coupling reaction was also applied in synthesizing propargylamine-modified artemisinin derivatives with excellent yields and diastereoselectivity (Figure 2.9).[21]



Scheme 2.12 Gold(III) salen complex catalysed three-component coupling reactions.

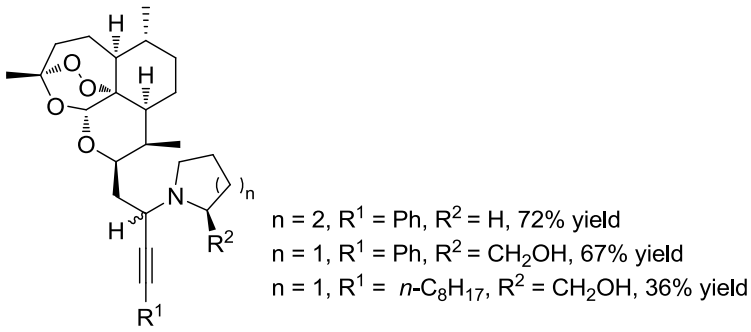
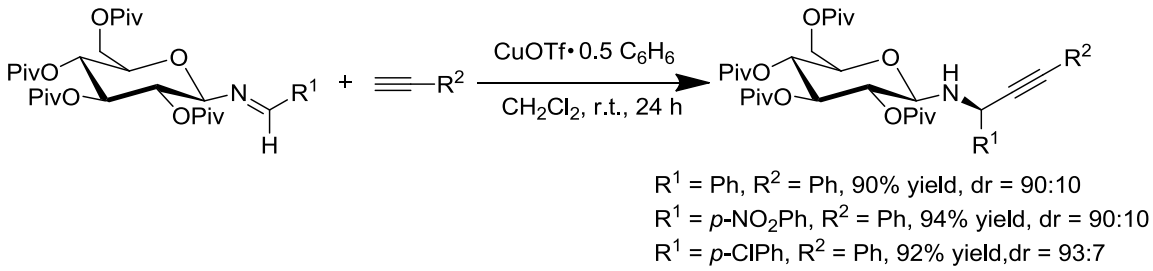


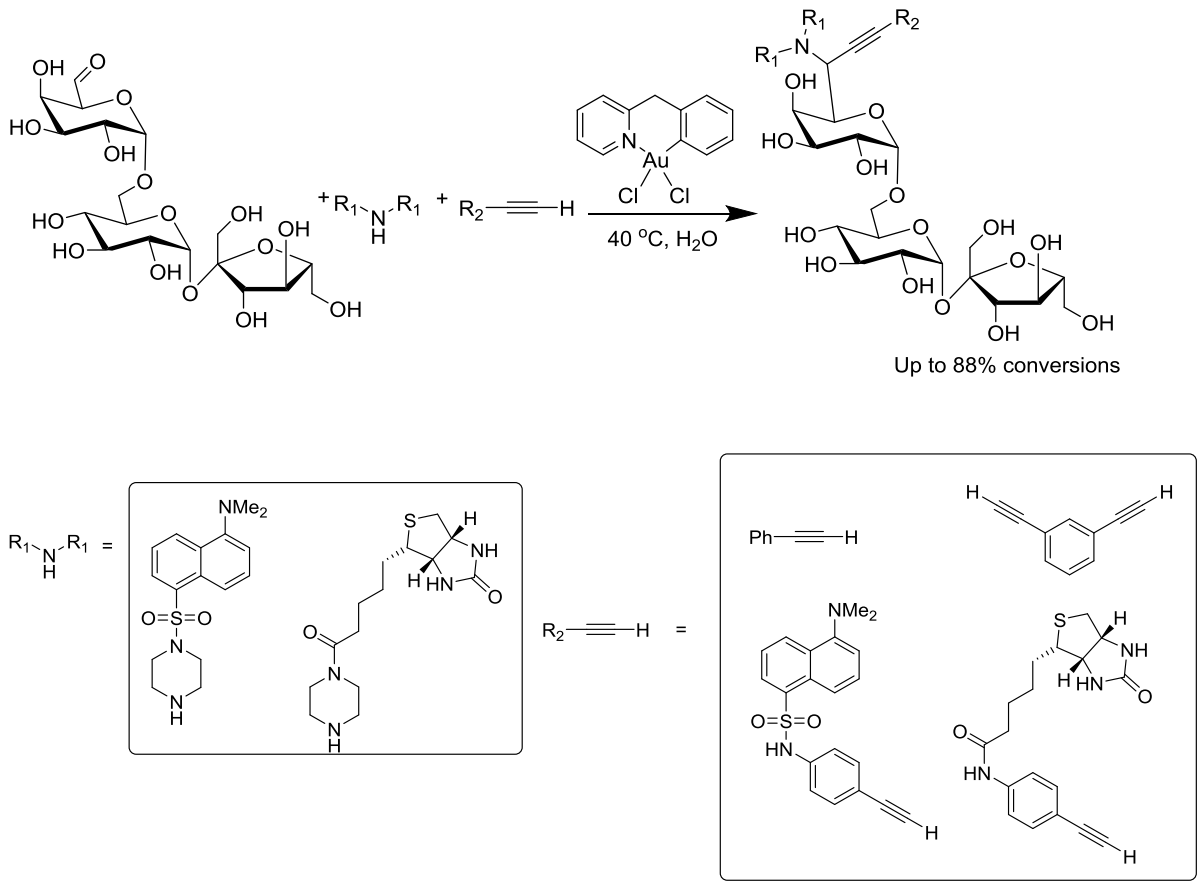
Figure 2.9 Modification of artemisinin via three-component coupling reactions.

Propargylamine synthesis, combining different functional groups together in a single compound provides excellent pathway for modification of natural compounds with various functional groups.[47] Scheme 2.13 shows the Cu(I) catalysed alkynylation of glucose-modified imines by alkynes.[47a] However, those reactions developed were required to be carried out in high temperature or organic solvent. An aqueous compatible and mild reaction for modification of natural compounds or biomolecules was still highly demanding.



Scheme 2.13 Diasteroselective alkynylation of glucose-modified imines with terminal alkynes.

As Wong and Che continually spent their effort into gold(III) catalysed propargylamine synthesis under mild conditions and aqueous medium.[21-23] The reaction was further applied in bifunctional modification of oligosaccharides with remarkably high conversions under aqueous medium leading to highly efficient modification of oligosaccharides via three-component coupling reactions by using biophysical probes. It was reported that the modification of D-raffinose aldehyde by gold(III) mediated three-component coupling reaction resulting in up to 88% substrate conversion and implied the feasibility in modification of more complicated biomolecules (Scheme 2.14).[24]



Scheme 2.14 Gold(III) mediated bifunctional modification of oligosaccharides.

Three-component coupling reactions of propargylamine synthesis are one of the important reactions in development of gold catalysis[48] based on highly reliable substrate conversions resulted by superior affinity of gold with carbon-carbon multiple bonds. The reaction became one of the reactions used for the screening of catalytic abilities of new gold(III) complexes.

2.1.6 Indole Alkylation

Indole, a heterocyclic aromatic compound containing N-H, is a good hydrogen bond donor with pKa about 21 in DMSO.[49] Amino acid tryptophan is an indole derivative which mostly acts as anion binding through hydrogen bond in proteins. For instance, sulphate binding protein, Salmonella typhimirium, binding the sulphate via amide N-H bonds and one of them coming from tryptophan.[50] Indole structure is a common feature among natural molecules (Figure 2.10). Serotonin, in tryptamine family, is a neurotransmitter in the human body. Besides, melatonin, a hormone found in participating in the circadian rhythms regulation, belongs to the same family.

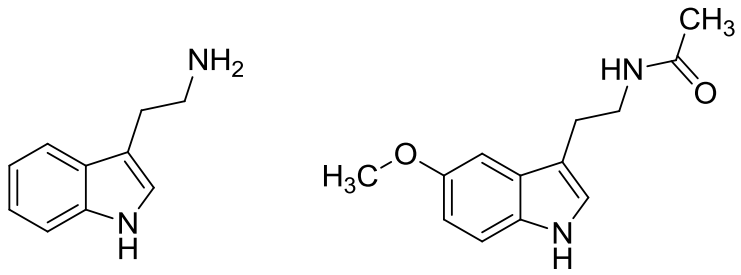
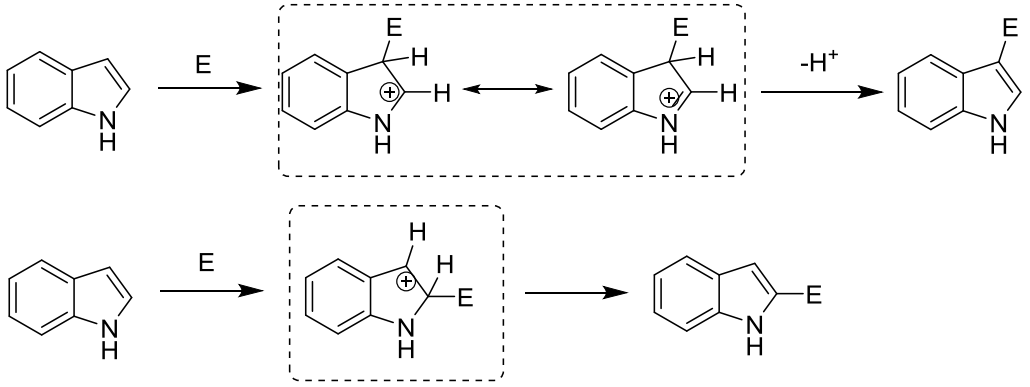


Figure 2.10 Structures of Serotonin (left) and melatonin (right).

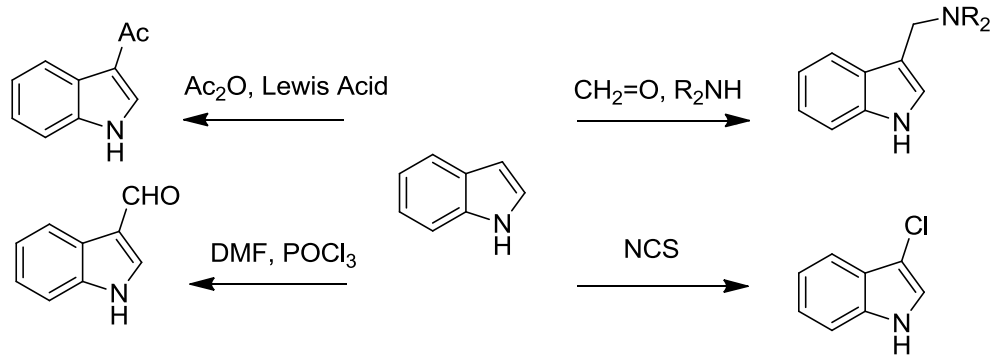
Because of the inherent nucleophilicity of indoles as a result of π-excessive aromatic properties, the major reactions related to indoles are electrophilic substitutions. There are two carbons C2 and C3 on indoles that can undergo electrophilic substitution reactions. Different from pyrroles, the electrophilic substitution usually takes place at the C3 rather than C2. In organic synthesis, most indole related reactions are found at the C3 position on the five-member heterocyclic rings. The phenomenon can be explained by drawing resonance structures of indole being attacked at C2 or C3. It shows that extra stability is gained resulted

from the delocalization of positive charge to the aromatic ring in the intermediate while C3 is attacked by electrophiles (E) (Scheme 2.15).



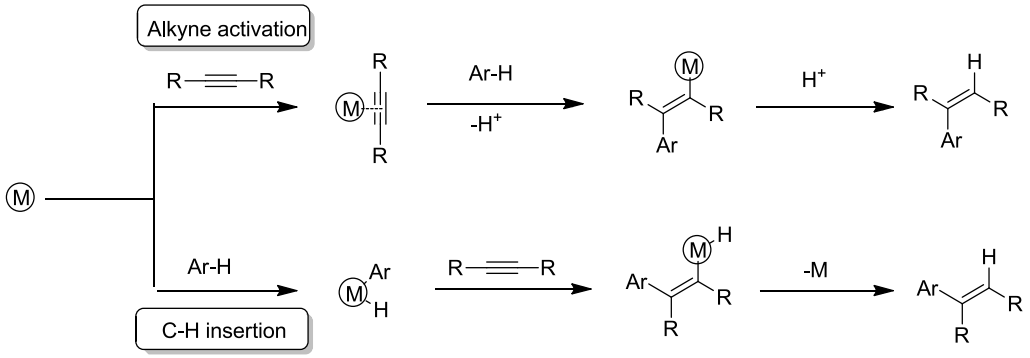
Scheme 2.15 Possible resonance structures formed by electrophilic attack on the indole ring.

The development of a highly effective, selective and green synthetic method for functionalization of indole at C3 position has attracted much attention because of potential building blocks for the synthesis of therapeutic and biologically active compounds, medicines, and natural products. Traditionally, Friedel–Crafts acylations, Mannich type alkylations, Vilsmeier–Haack reaction and halogenations are common electrophilic aromatic substitution reactions allowed for functionalization of indoles at C3 position (Scheme 2.16).[51] Alkylation of indoles is the most attractive reaction because of the formation of strong carbon-carbon bonds. In the past, indole alkylation has been performed by alkyl halides via electrophilic substitution. However, the regioselectivity is generally poor.[52] Although regioselective alkylation of indoles can been achieved in reactions with aldehydes,[53] α,β-unsaturated ketones,[54] or other reagents,[55] these reactions required additions of large amounts of acids with moderate to low yields.



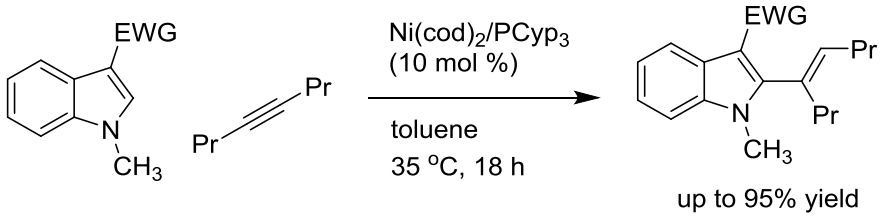
Scheme 2.16 Electrophilic substitution reactions of indoles.

In addition, further functionalization of indoles can be achieved through C-C multiple bonds activation by transition metal catalysis. Addition of arenes to unactivated multiple bonds such as alkene, alkynes or allenes through transition metal catalysis is a highly effective and regioselective method for preparation of functionalized aromatic compounds. Late transition metals (i.e., Cu, Pd, Pt, Au and Rh) are known as π acidic catalysts in various C-C multiple bond activation reactions (Scheme 2.17). This allowed the C-H addition of indoles to those unactivated C-C multiple bonds taking the advantage of excellent functional group compatibility.

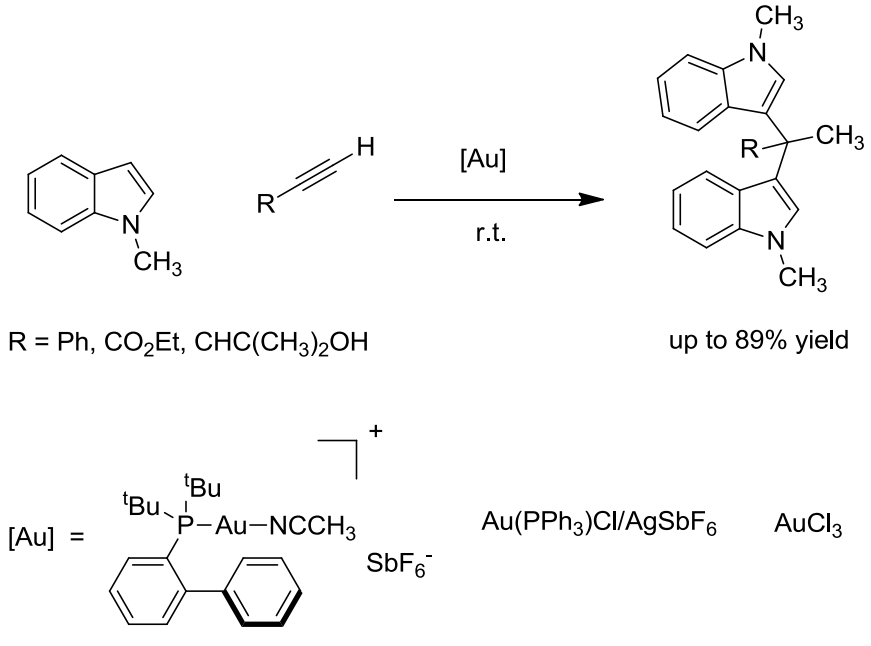


Scheme 2.17 Hydroarylation of C-C multiple bonds by transition metal catalysis.[56]

Nakao and Hiyama *et al.* reported the nickel(0) catalysed regioselective C2 addition of indoles to internal alkynes (Scheme 2.18).[57] The regioselectivity was found to be controlled by the presence of electron-withdrawing groups (EWG) (i.e., CN, COOR). Application of gold catalysis in the intermolecular hydroarylation of alkynes at C3 is also a useful approach in the synthesis of bis-indolyl alkanes (Scheme 2.19).[58] Furthermore, the intramolecular addition of indoles to alkynes was developed by C3 alkyne functionalized indoles to afford six, seven or eight-membered rings.[59]

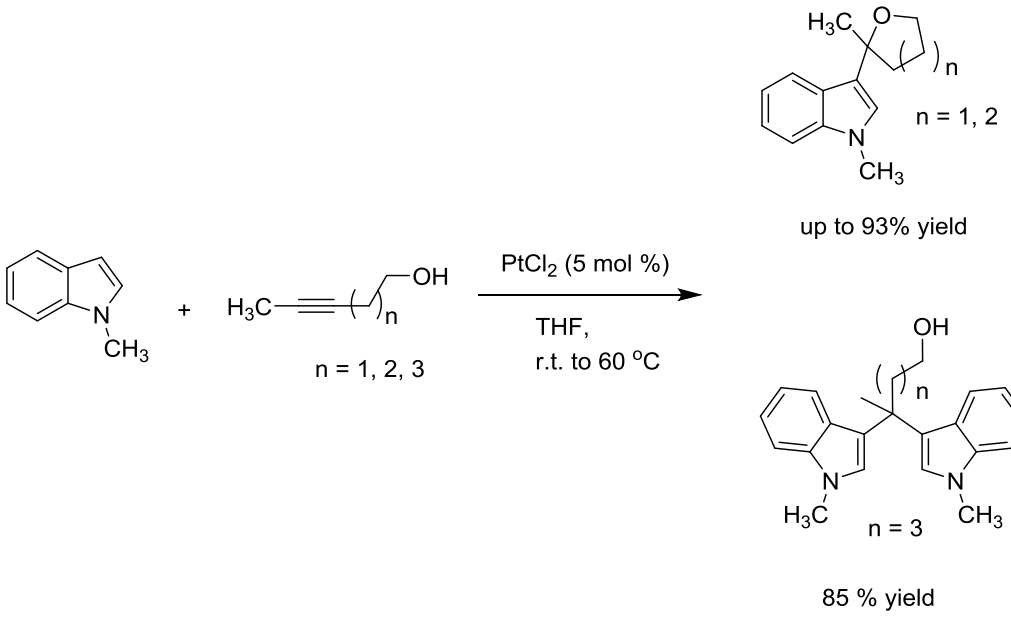


Scheme 2.18 Nickel-catalysed hydroarylation of indole.

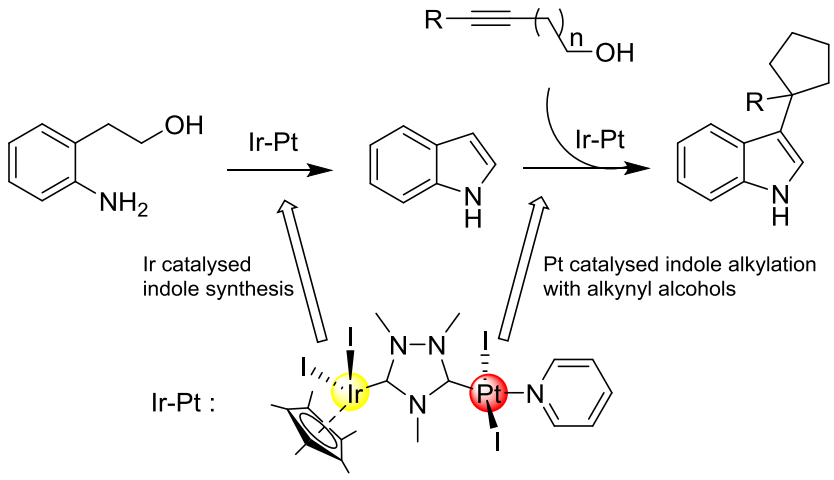


Scheme 2.19 Gold catalysed addition of indoles to alkynes.

Alkylation of indoles with internal and terminal alkynyl alcohols catalysed by $PtCl_2$ was also reported by Cheng *et al.* (Scheme 2.20).[60] More recently, Zanardi and Peris *et al.* reported the synthesis of alkylated indoles from multistep reactions of amino alcohols and alkynyl alcohols by using a heterodimetallic Ir-Pt complex (Scheme 2.21).[61]



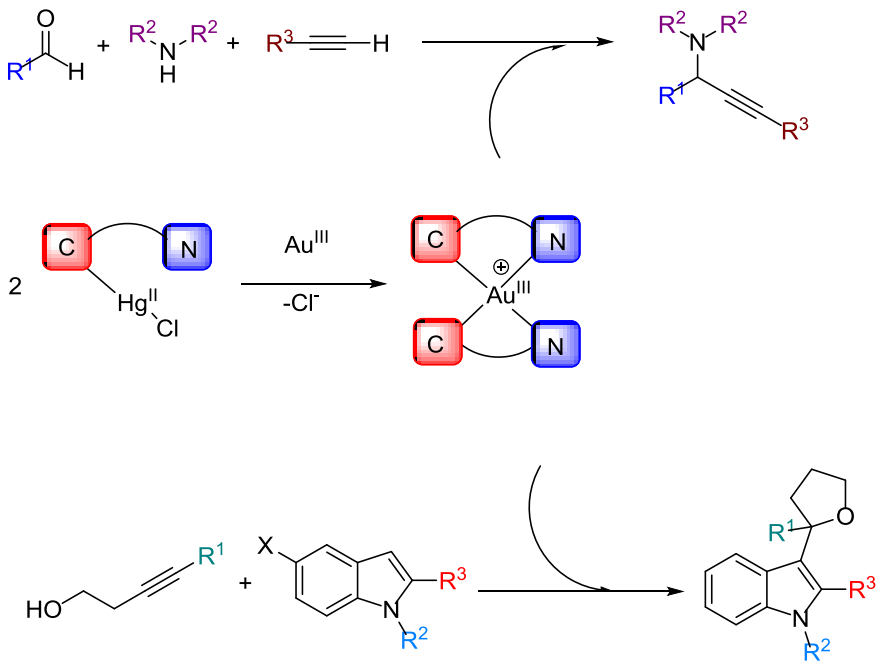
Scheme 2.20 Pt(II) catalysed multi-step reaction of indoles with alkynyl alcohols.



Scheme 2.21 Synthesis of alkylated indoles from amino alcohols and alkynyl alcohols by a Ir-Pt catalyst.

2.2 Objectives

The bis-cyclometallated (C^N) gold(III) complexes would be synthesized and their catalytic activity would be examined in propargylamine synthesis and indoles alkylation. The geometry of the resulting gold(III) complexes would be studied by X-ray crystallography. By understanding the geometry of the bis-cyclometallated (C^N) gold(III) complexes, strategies for activating the gold(III) catalysts would be developed for organic transformations.



2.3 Results and Discussion

2.3.1 Synthesis of Bis-cyclometallated Gold(III) Complexes with C,N Donor Ligands

Transmetallation reactions of organomercury complexes with other transition metal salts were reported to be highly efficient for synthesizing new organo metal complexes under mild conditions.[62] However, there was limited examples for the study of transmetallation between organomercury complexes with cyclometallated gold(III) complexes. Pritchard *et.al.* reported that adding one more equivalent of Hg(pqcm)Cl (where Hpqcm = 2-Phenyl-4-(methylcarboxylate)quinoline) with $Au(pqcm)Cl_2$ resulted in formation of $Au(pqcm)_2Cl$ (Figure 2.11).[63]

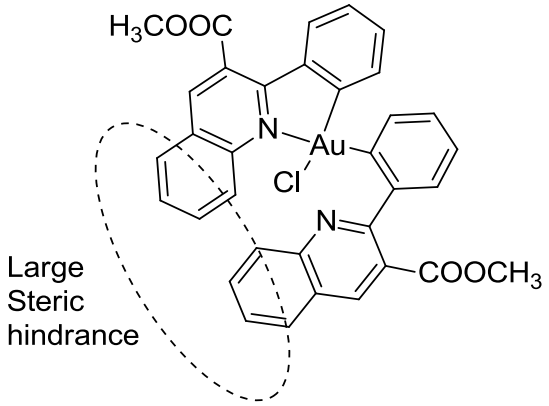
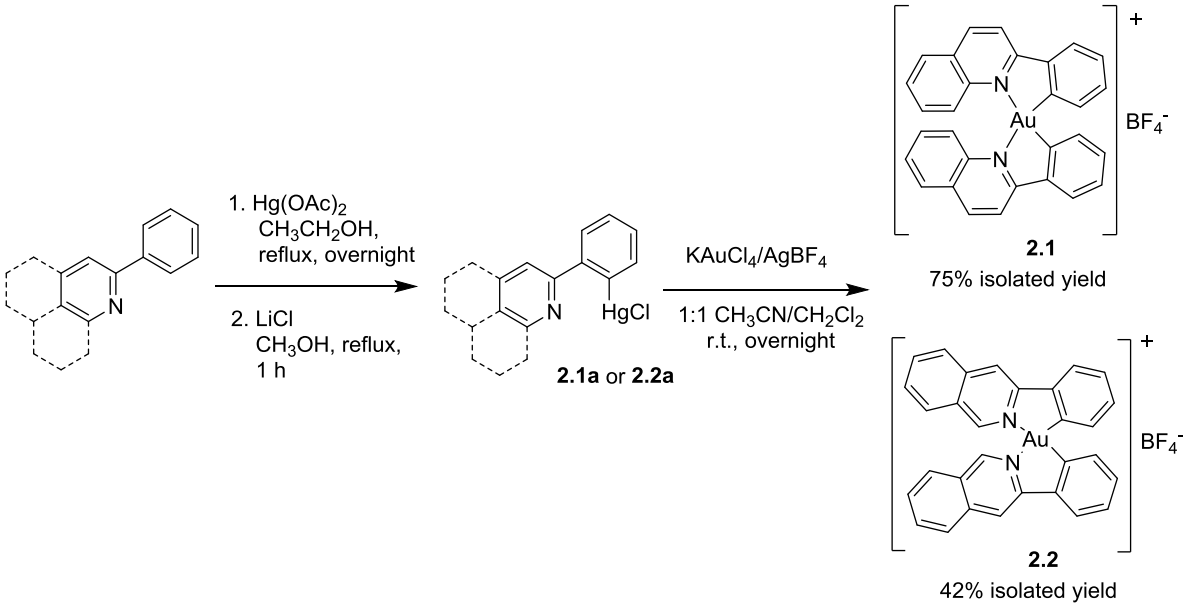


Figure 2.11 Structure of $Au(pqcm)_2Cl$.

Their findings suggested that formation of square planar bis-cyclometallated gold(III) complexes are not favorable because of trans effect of sp^2 carbon ligand and strong steric effect of ligands encountered. *Herein, we reported the first example to produce bis-*

cyclometallated gold(III) complexes via silver salts promoted transmetallation reaction by using bulky 2-phenylquinoline ligand.

Bis-cyclometallated gold(III) complexes $[Au(C\text{^}N)_2BF_4]$ **2.1** and **2.2** (HC^N = 2-phenylquinoline and 3-phenylisoquinoline respectively) were synthesized by transmetallation reaction from organomercury complexes Hg(C^N)Cl [**2.1a** or **2.2a**] and $KAuCl_4$ based on the modified method.[63] Complexes **2.1** and **2.2** were synthesized from their organomercury precursors with 75% and 42% yields (Scheme 2.22). After purification by flash column chromatography, pale yellow or white solids were collected and ^1H NMR suggested the symmetrical ligand coordination where mass spectrometry (ESI-MS) provided the formula of $Au(C\text{^}N)_2^+$. The characterization data provide that two identical ligands chelated to the gold(III) centre to form a symmetric gold(III) complex. Addition of silver salts (6 equiv.) ensured the removal of Cl^- by precipitation of AgCl leading to improvement of product yields.



Scheme 2.22 Synthesis of bis-cyclometallated gold(III) complexes **2.1** and **2.2**.

2.3.2 The Distorted Square Planar Geometry of Complex 2.1

Formation of bis-cyclometallated gold(III) complexes using bulky ligands should be unfavourable due to strong steric repulsion between the ligands. Although ^{1}H NMR spectra and mass spectrometry suggested this structure, the actual geometry of complex **2.1** was revealed only when crystal structure of **2.1** was elucidated by X-ray crystallography (Figure 2.12).

(a) (b)

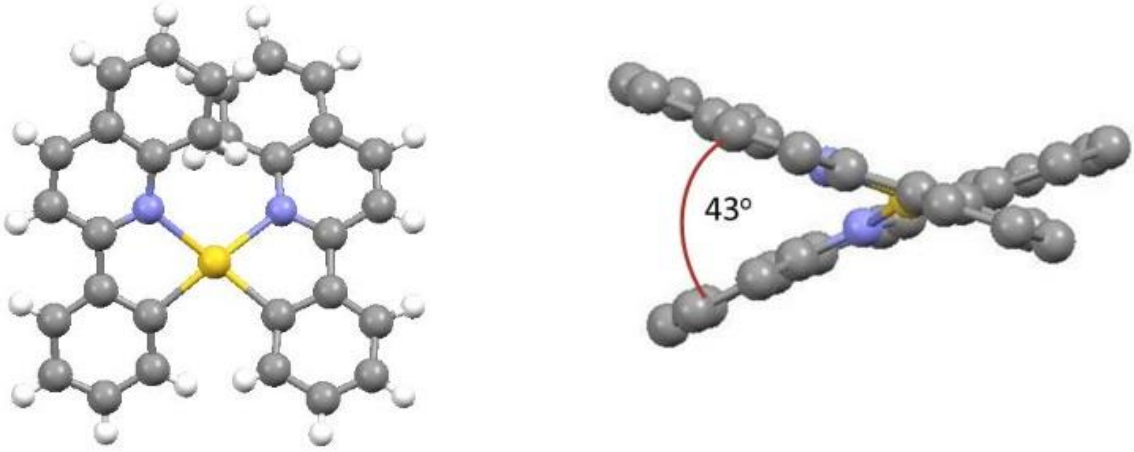
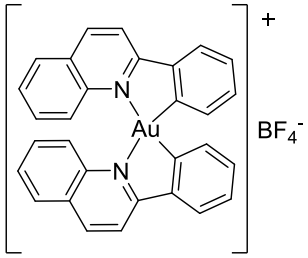
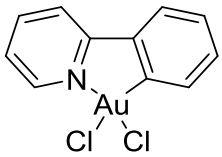
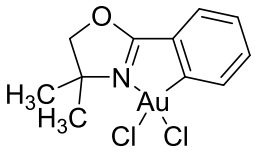
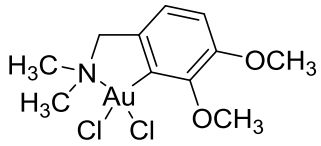


Figure 2.12 Crystal structure of **2.1**; (a) top view and (b) side view with anion omitted.[64]

X-ray crystallography revealed a distorted square planar geometry of **2.1** instead of a square planar structure. Notably, because of steric repulsion between the quinoline rings, two C^N ligands were tilted and a dihedral angle (43^{o}) was formed. Crystal structure of **2.1** also revealed significant elongation of Au-N bonds when compared with other square planar cyclometallated gold(III) complexes in literature (Table 2.1).[65] The Au-N bond lengths in **2.1** were found to be longer than typical Au-N bonds up to 0.141 Å. To minimize steric repulsion between two ligands, the complex adopted an non-planar geometry in order to keep the chelation of 2-phenylquinoline to the gold(III) centre (Figure 2.13).

Table 2.1 Comparisons of selected bond lengths between **2.1** and gold(III) complexes in literatures.[65]

Complex	Au-N (Å)	Au-C (Å)
	2.175 (3)	2.046 (4)
Complex **2.1**		
$[Au(C\hat{}N)_2][BF_4]$ (HC^N = 2-phenylquinoline)		
	2.034 (1)	1.950 (2)
$[Au(ppy)Cl_2]$ (Hppy = 2-phenylpyridine)		
	2.051 (8)	2.040 (8)
$[Au(C\hat{}N)Cl_2]$		
(HC^N = 4,4-dimethyl-2-phenyl-2-oxazoline)		

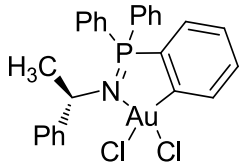


2.050 (3) 2.080 (2)

[Au(C^N)Cl_2]

(HC^N = 1-(3,4-dimethoxyphenyl)-N,N-

dimethylmethanamine)



2.072 (10) 2.045 (8)

[(2-$Cl_2AuC_6H_4$)Ph_2P=N-(*S*)-CHMePh]

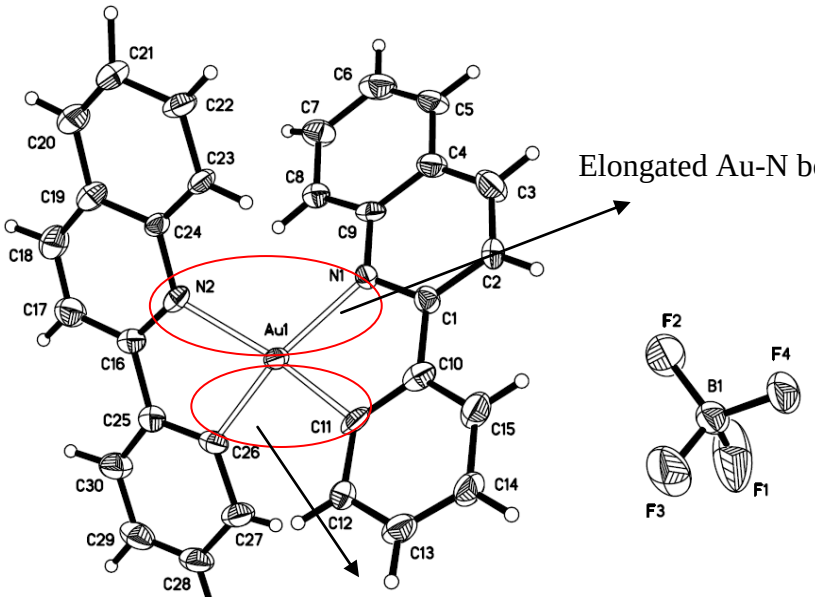
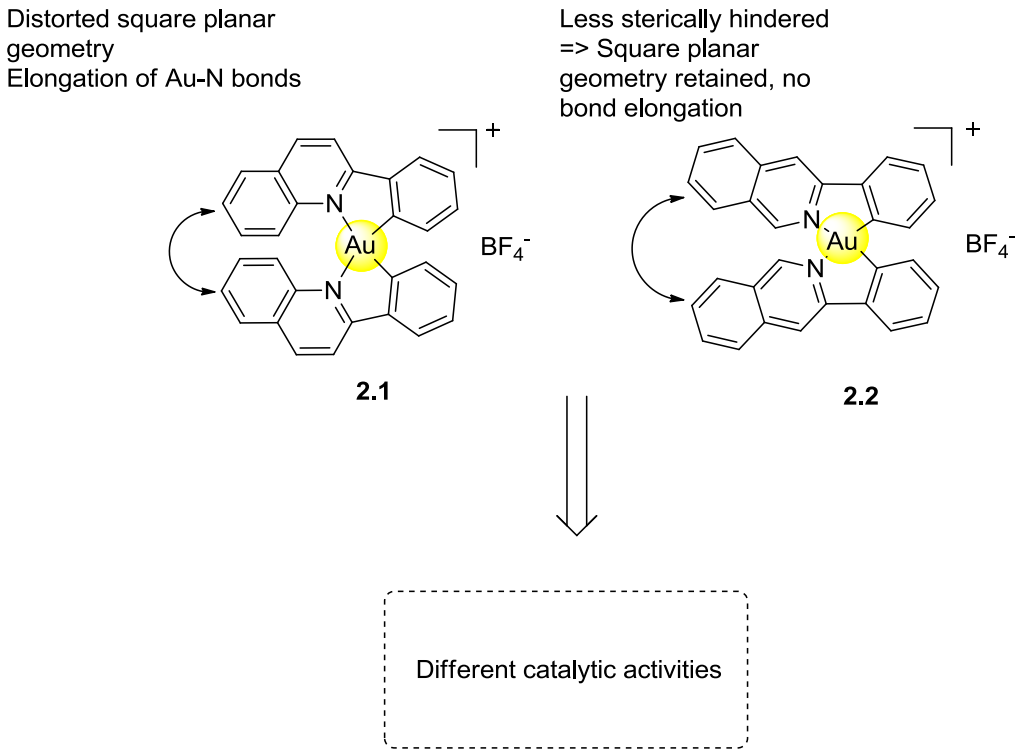


Figure 2.13 X-ray crystal structure of bis-cyclometallated gold(III) complex **2.1** with anion BF_4^-.

Less bulky 3-phenylisoquinoline mercury precursor reacted with $KAuCl_4$ to form gold(III) complex **2.2** with expected square planar geometry according to literature reports and NMR spectroscopy. Notably, the yield of complex **2.2** was lower than complex **2.1** which supposed to encounter less steric hindrance between the ligands and be more favourable to give a bis-cyclometallated complex. In theory, complex **2.2** without distorted square planar geometry should have comparable Au-N bonds with other square planar cyclometallated gold(III) complexes. This revealed that bis-cyclometallated gold(III) complexes **2.1** having weakened Au-N may have different catalytic activities compared to complex **2.2**.



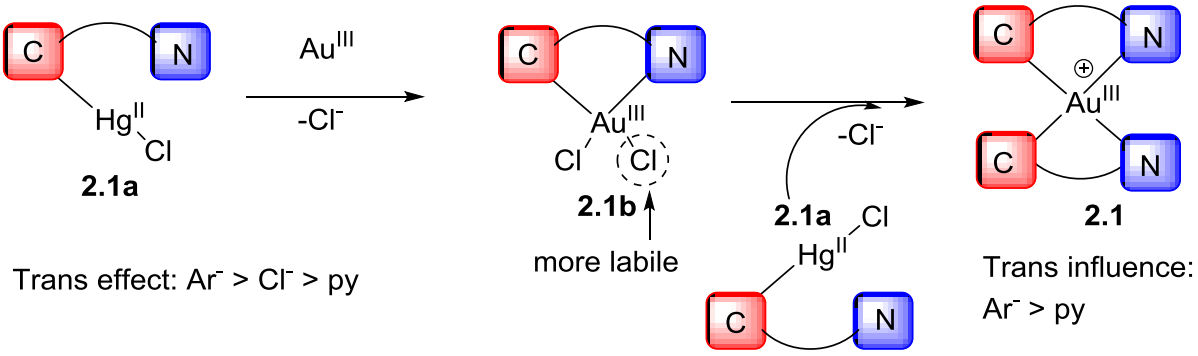
Trans Effect

As sterically bulky 2-phenyl quinolines were used as ligands in the synthesis of the bis-cyclometallated gold(III) complex, there is a competition between trans effect and steric effect resulted by the coordination of ligands. Briefly, the trans effect is defined as the effect of a coordinated ligand upon the rate of substitution of opposite ligands by incoming ligands and the steric effect is defined as the bulkiness of a coordinated ligand affecting the coordination of another ligand. Later, the crystal structure of **2.1** revealed that the Au-C bonds were *cis* to each other. As carbon has stronger trans effect than nitrogen, the rate of substitution of the opposite ligand of carbon is higher than the nitrogen in square gold(III) complexes.

During the formation of complex **2.1**, the transmetallation reaction between another equivalent of organomercury precursor and the gold(III) dichloride complex **2.1b** was controlled by the relative strength of trans effect of the sp^2 carbon (Ar^-) and the quinoline nitrogen (py). The substitution of more labile chloride ligand opposite to the sp^2 carbon was faster by quinoline nitrogen to give *cis* Au-N bonds. The subsequent transmetallation led to substitution of less labile chloride ligand opposite to the quinoline nitrogen with the sp^2 carbon resulting in *cis* Au-C bonds (Scheme 2.23). Although the bulky quinoline rings in complex **2.1** were on the same side which resulted in strong steric hindrance in the square planar gold(III) complex, there was no trans isomer of **2.1** observed. The stability of **2.1** towards isomerization can be explained by using trans influence.

Trans Influence

Trans influence is referred to the impact of a ligand on the strength of the metal-ligand bond opposite to it. As the sp^2 carbons having stronger *trans* influence than quinoline nitrogen, the Au-ligand bond *trans* to the carbon ligand will be weakened in the greater extent. More stable *cis* configuration was preferred in order to form stronger Au-C bonds. To minimize the strong steric repulsion between the ligands, a new geometry should be adopted.

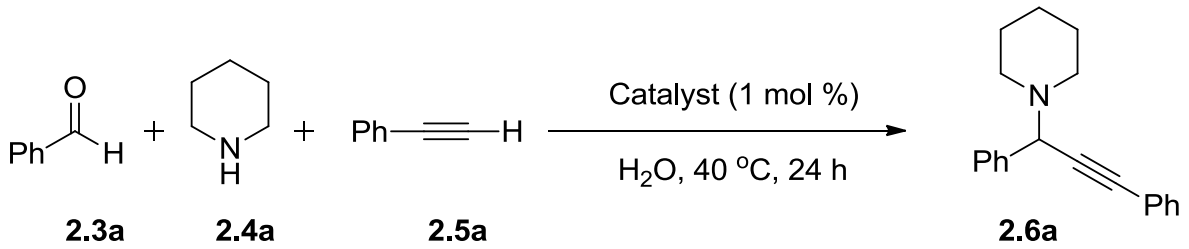


Scheme 2.23 Transmetallation between **2.1a** and **2.1b** controlled by trans effect of the coordinated ligand.

2.3.3 The Distorted Square Planar Design in Bis-cyclometallated Gold(III) Complexes for Gold-catalysed Three-component Coupling Reactions

Next, the catalytic activities of well characterized bis-cyclometallated gold(III) complexes **2.1** and **2.2** with different geometry were examined based on three-component coupling reaction of propargylamine synthesis. Since the complex **2.1** has weakened Au-N bonds, the difference in catalytic activities would be examined by gold-catalysed propargylamine synthesis.

Catalytic activities of **2.1** and **2.2** in propargylamine synthesis by three-component reaction were studied and the results are given in Table 2.2. It was found that distorted square planar complex **2.1** (1 mol %) catalysed the reaction efficiently and propargylamine **2.6a** was obtained in 83% isolated yield after stirred for 24h at 40 ^{o}C in H_2O (Entry 1). Entry 2 showed that **2.6a** was obtained in 60% isolated yield when only 0.1 mol % of **2.1** was used. The catalytic activity of gold(III) complex **2.1** was similar to that of cyclometallated (C^N) gold(III) complexes studied previously.[23] it was noted that complex **2.1** (1 mol %) was found to catalyse the reaction even at room temperature (Entry 3). However, 5 mol % of **2.2** gave 8% isolated yield only (Entry 4) while no product formation with 1 mol % of **2.2** (Entry 5). The results showed that complex **2.2** exhibited poorer catalytic activity than complex **2.1** in three-component coupling reactions.



2.3a **2.4a** **2.5a** **2.6a**

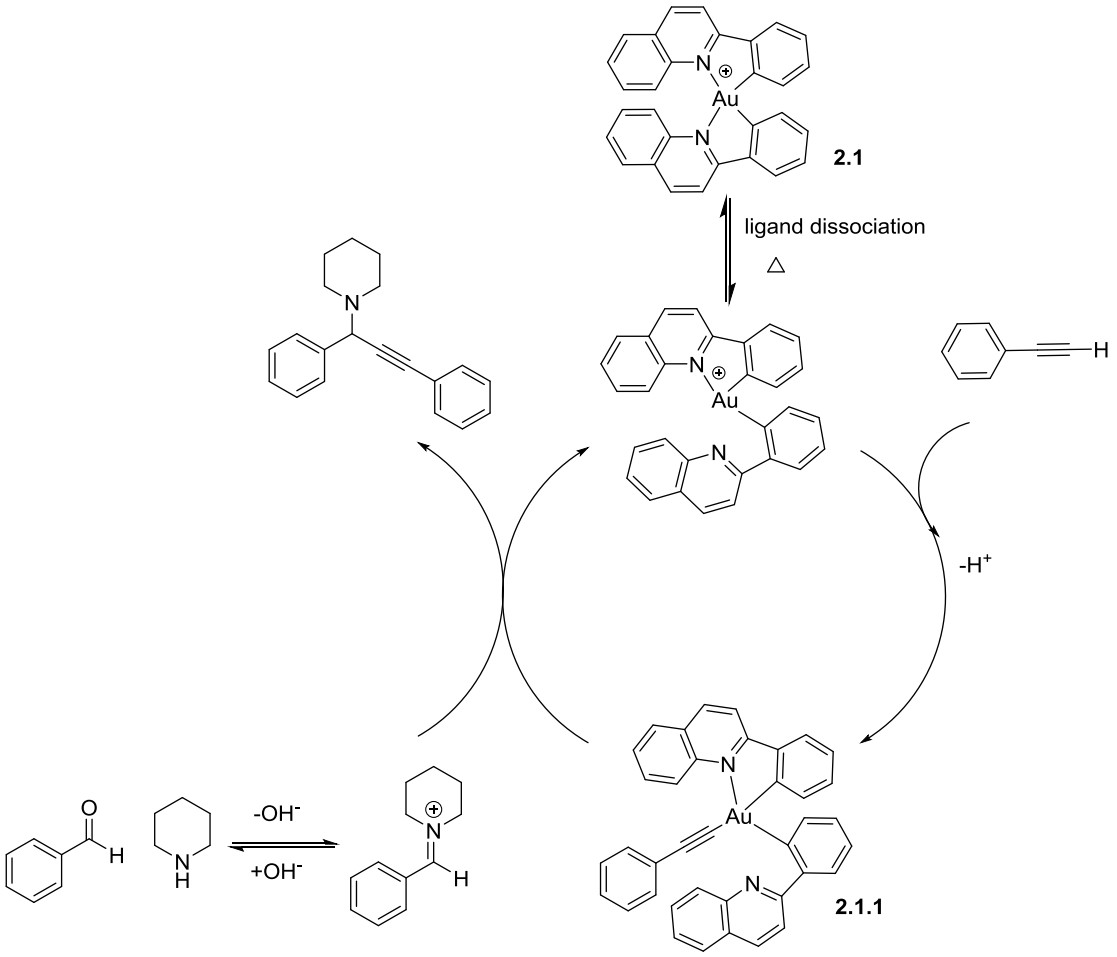
Table 2.2 Bis-cyclometallated gold(III) complex-catalysed three-component coupling reaction for propargylamine synthesis[a]

Entry	Catalyst (mol %)	Isolated Yield (%)
1	**2.1** (1)	83
2	**2.1** (0.1)	60
3[b]	**2.1** (1)	25
4	**2.2** (5)	8
5	**2.2** (1)	0

[a] Reaction conditions: **2.3a** (0.5 mmol), **2.4a** (0.55 mmol) and **2.5a** (0.75 mmol) in H_2O (1 mL) at 40 °C. [b] r.t.

The remarkably higher catalytic activity of **2.1** than **2.2** can be explained based on their difference in geometry. Complex **2.1** with distorted square planar geometry has elongated bond lengths. The elongated Au-N bonds are supposed to be weakened as a result of poorer overlapping of orbitals between metal and the ligand. Dissociation of Au-N bonds by heating is more readily in complex **2.1** than complex **2.2**. Hence, ligand dissociation of **2.1** in 40 °C

would form a highly reactive gold specie for terminal alkyne activation where dissociation of Au-N bonds in square planar complexes **2.2** is rather difficult in 40 ^{o}C which catalyse the reaction slowly. The design of distorted geometry of gold(III) complexes with enhancement of the reactivity is potentially applicable in metal catalysed organic transformations. Scheme 2.24 showed the possible mechanism based on the previous proposed by Wong and Che *et al.*[22] The catalytic cycle was proposed to start from the dissociation of one of Au-N bonds to give an unstable 14 e^{-} specie which provided vacant orbitals for the coordination of C-C triple bonds of phenylacetylene to give a gold acetylide **2.1.1**. Subsequent nucleophilic attack of the gold acetylide **2.1.1** to iminium ions generated from condensation reaction of benzaldehyde and piperidine afford the propargylamine product and release the catalysts will be regenerated which can be stabilized by forming back the bis-cyclometallated gold(III) complex. According to the proposed catalytic cycle, the distorted square planar bis-cyclometallated gold(III) complexes gain advantage in stability and maintain the catalytic ability by having labile Au-N bonds for generation of coordination sites.



Scheme 2.24 Proposed reaction mechanism of three-component coupling reactions

To further investigate the interaction between phenylacetylene **2.3a** and complex **2.1**, a mixture containing **2.3a** and complex **2.1** in CH_3CN/H_2O was heated at 40 ^oC for 2 h. The resulting mixture was subjected ESI-MS analysis. The mass spectrum revealed the formation of compound **2.1.2** which is possibly formed by the ligand substitution of 2-phenylquinoline ligand in **2.1.1** with phenylacetylene **2.3a** (Figure 2.14).

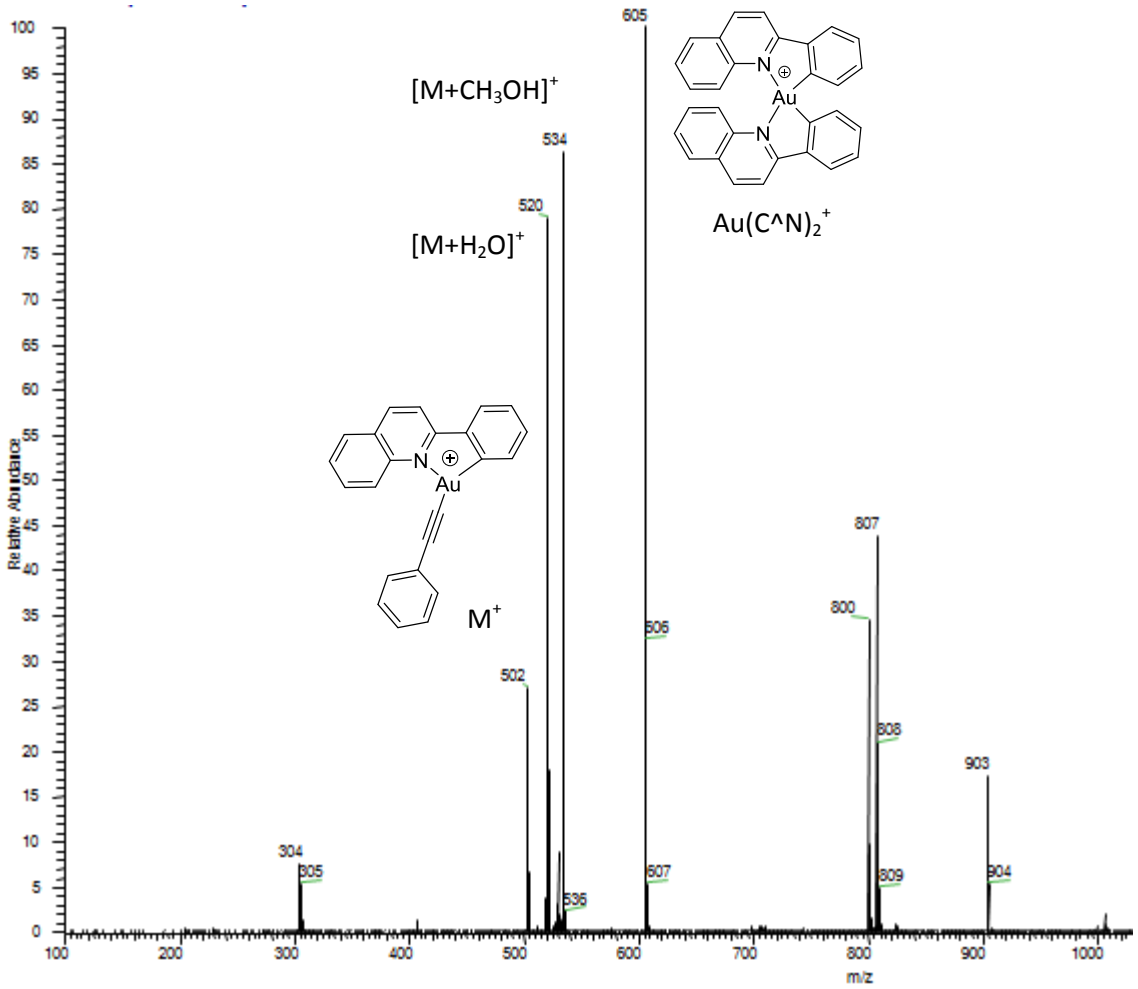
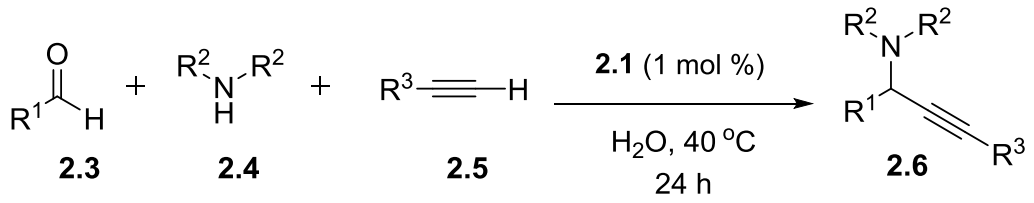
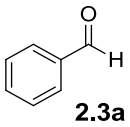
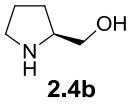
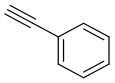
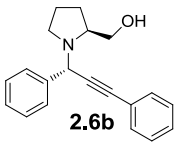
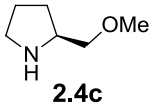
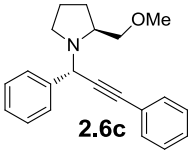
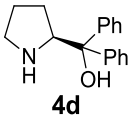
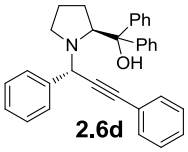
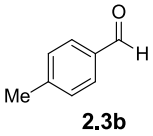
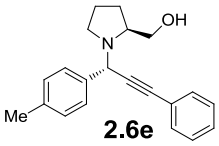
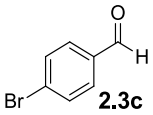
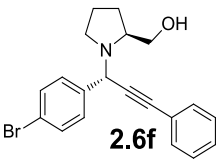
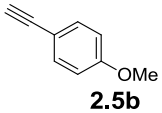
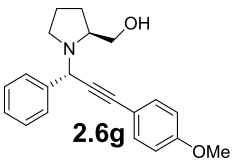


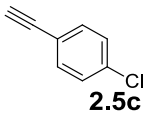
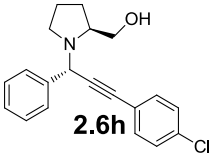
Figure 2.14 Mass spectrum of the crude mixture containing **2.1.2** (M^+).

According to our previous studies,[21-23] cyclometallated (C^N) gold(III) complexes were effective catalysts for propargylamine synthesis by using chiral secondary amines. A pair of diastereomers of propargylamine was formed in the reaction and ^{1}H NMR studies showed that one of the diastereomers was dominant (up to 99:1). The distorted square planar ligand design strategy was also applied in the diastereoselective synthesis of propargylamines. Propargylamines **2.6b-h** were synthesized with 70-90% isolated yield and diasteromeric ratio up to 99:1 by using complex **2.1** (Table 2.3).

Table 2.3 Diasteroselective synthesis of propargylamines.

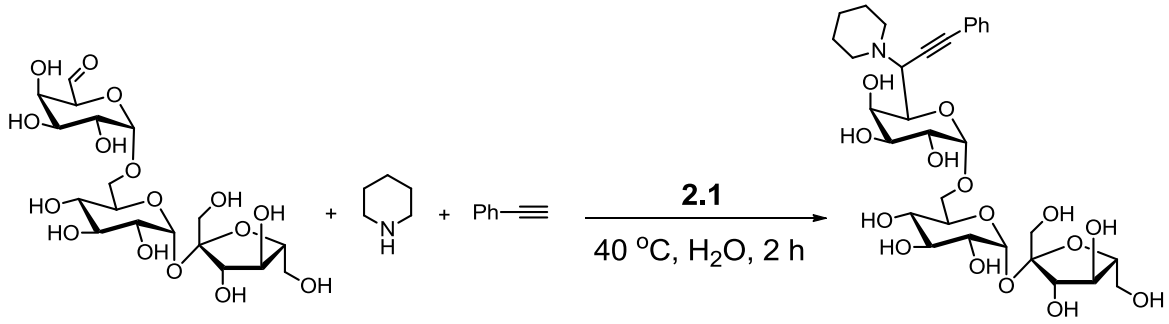


Entry	Aldehyde	Amine	Alkyne	Product[b]	Yield (%)[c]	dr[d]
1	 2.3a	 2.4b	 2.5a	 2.6b	75	95:5
2	**2.3a**	 2.4c	**2.5a**	 2.6c	71	96:4
5	**2.3a**	 4d	**2.5a**	 2.6d	81	>99:1
6	 2.3b	**2.4b**	**2.5a**	 2.6e	90	95:5
7	 2.3c	**2.4b**	**2.5a**	 2.6f	70	95:5
8	**2.3a**	**2.4b**	 2.5b	 2.6g	86	92:8

9	**2.3a**	**2.4b**	 **2.5c**  **2.6h**	73	94:6

[a]Unless otherwise specified, all reactions were carried out with aldehyde **2.3** (0.5 mmol), amine **2.4** (0.55 mmol, 1.1 equiv.), alkyne **2.5** (0.75 mmol, 1.5 equiv.) and **2.1** (5 μmol, 1 mol %) in H_2O (1 mL) at 40 °C for 24 h. [b]The absolute configuration of the major product is shown. [c]Isolated yield. [d]Determined by ^1H NMR analysis of crude reaction mixture.

Furthermore, complex **2.1** was capable of achieve selective modification of D-raffinose aldehyde based on our previous in the selective modification of oligosaccharides via Au(C^N)Cl_2 catalysed three-component coupling reaction of propargylamine synthesis.[24] Stirring of complex **2.1** with D-raffinose aldehyde, piperdine **2.4a** and phenylacetylene **2.5a** in water at 40 °C for 2 h, the reaction mixture was then analyzed by LC-MS for determining the conversion of D-raffinose aldehyde to propargylamine modified D-raffinose **2.6i** (Scheme 2.25).



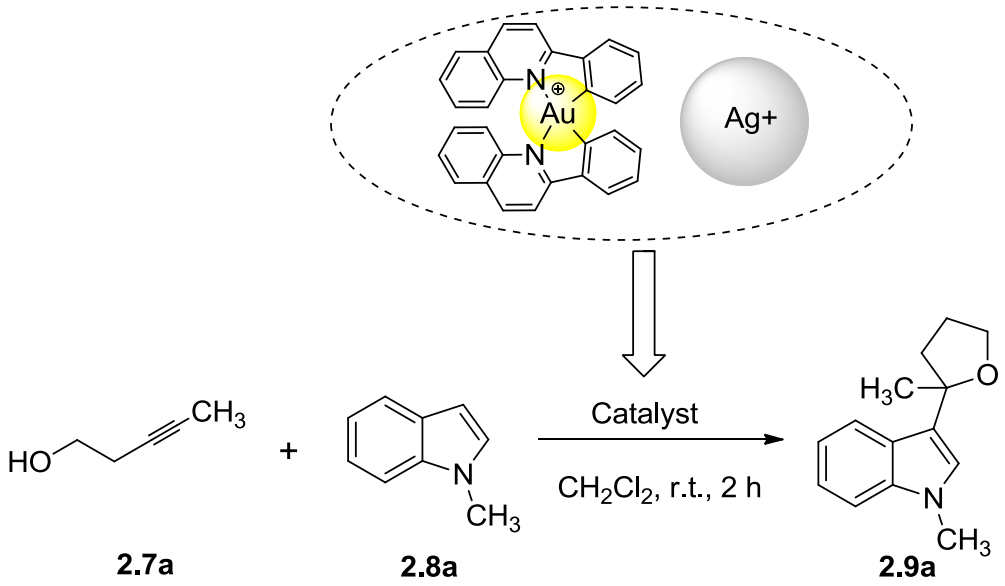
D-raffinose aldehyde **2.4a** **2.5a** **2.6i**

85% Aldehyde conversion

Scheme 2.25 Bifunctional modification of oligosaccharides.

2.3.4 Indole Alkylation by Gold and Silver Dual Catalysis

In this section, we developed a gold-silver dual catalysis[64] which was employed in indole alkylation by using bis-cyclometallated gold(III) complexes and silver salts as a catalytic system (Scheme 2.26).



Scheme 2.26 Au(III)-Ag catalysed cyclization-addition of alkynyl alcohols and indoles.

Based on literatures, the alkylated indole **2.9a** was proposed to be formed by cyclization of alkynyl alcohol **2.7a** to give enol ether and subsequent C-H addition of indole **2.8a** to the enol ether.[60-61]

Complex **2.1** was used as catalyst for indole alkylation based on literature procedures to examine its catalytic activity. However, there was no reaction for either **2.1** or **2.2** when the reaction mixture was stirred under room temperature. Product **2.9a** was only formed when the reaction mixture containing complex **2.1** was heated at 70 ^{o}C in 1, 2-dichloroethane with 74% isolated yield. The low in reactivity of the bis-cyclometallated gold(III) complexes at room temperature can be explained by coordinative saturation in the d^8 system. As we

proposed previously in three-component coupling reaction, heat induced ligand dissociation provided vacant sites of metal centre and hence increase the reactivity. By systematic screening of different metal salts additives (Table 2.4), it was found that silver salts are capable of working with the bis-cyclometallated gold(III) complexes synergistically to catalyse the reaction in room temperature.

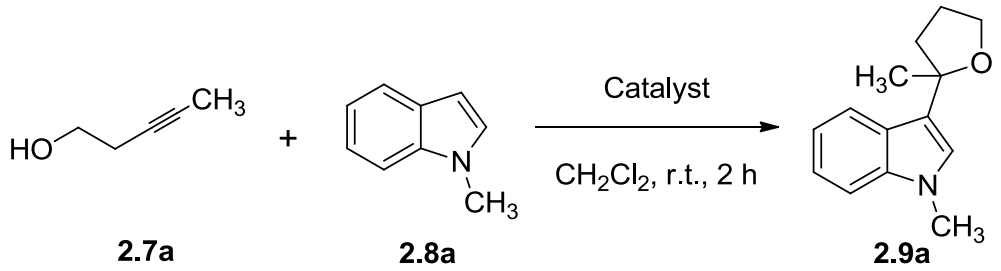
The optimized condition was using 2.5 mol % of **2.1** with 5 mol % of $AgBF_4$ to be the catalytic system. Under this condition, alkynyl alcohol **2.7a** reacted with indole **2.8a** to afford alkylated indole **2.9a** in 80% isolated yield at room temperature for 2 h (Entry 2). Complex **2.1** was also applied with different silver salts (Entries 3-6) where only AgOTf could have similar catalytic activity with $AgBF_4$.

This strategy could also be applied to square planar bis-cyclometallated gold(III) complex **2.2**. By using complex **2.2** (2.5 mol %) with $AgBF_4$ (5 mol %), the reaction gave 47% isolated yield of **2.9a** at room temperature for 2 h (Entry 9). Moreover, adding of other metal salts such as $Zn(OTf)_2$ or $Yb(OTf)_3$ could catalyse the reaction but with lower isolated yields (76% and 39% isolated yields respectively) (Entries 7-8).

In the control experiments (Entries 11, 13-19), there were only up to 13% isolated yields of **2.9a** by using single metal catalyst (either complex **2.1** or metal salts). Notably, simple gold(III) salts $KAuCl_4$ was found to catalyze the reaction to afford 68% isolated yield (Entry 12). However, it was latter shown that catalyst system of "**2.1** + $AgBF_4$" could undergo more than 11 cycles with high substrate conversions in the recyclability experiment where $KAuCl_4$ lose its catalytic activity in the 2^{nd} cycle. (Table 2.6) Screening of catalysts using different metal salts (Entries 20-28) was also performed which indicates that only suitable dual metal catalyst combination is feasible to render stable bis-cyclometallated gold(III) complexes as

effective catalysts in organic transformations.

Table 2.4 Systematic screening of different catalyst combinations.[a]



2.7a **2.8a** **2.9a**

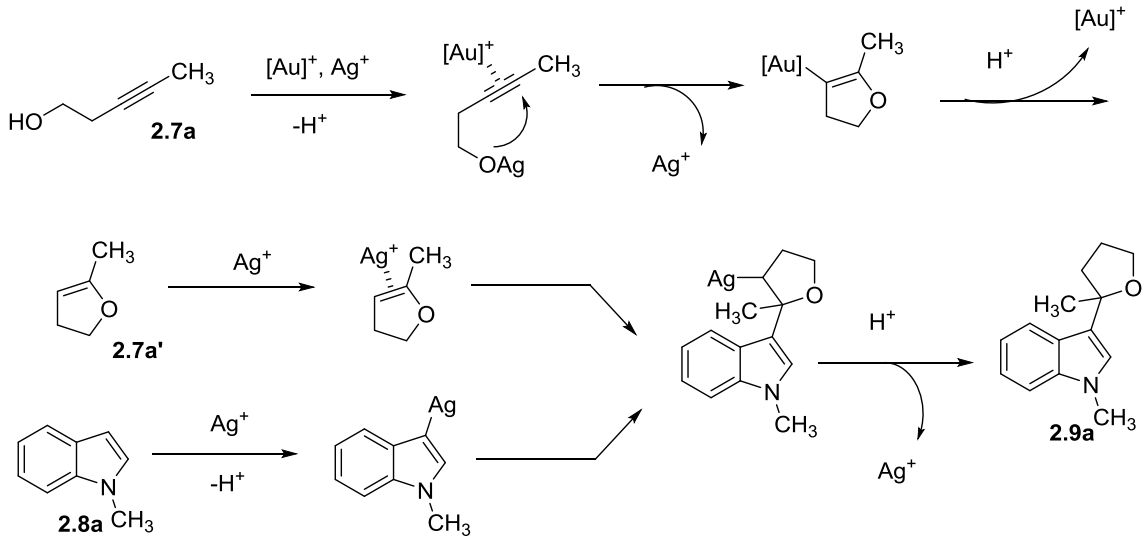
Entry	Catalyst (mol %)	Isolated Yield (%)
1	**2.1** (5) + $AgBF_4$ (5)	81
2	**2.1** (2.5) + $AgBF_4$ (5)	80
3	**2.1** (2.5) + AgOTf (5)	80
4	**2.1** (2.5) + $AgOOCCF_3$ (5)	50
5	**2.1** (2.5) + $AgNO_3$ (5)	12[b]
6	**2.1** (2.5) + Ag_2CO_3 (5)	0[b]
7	**2.1** (2.5) + $Zn(OTf)_2$ (5)	76
8	**2.1** (2.5) + $Yb(OTf)_3$ (5)	39
9	**2.2** (2.5) + $AgBF_4$ (5)	47
10	**2.2** (2.5) + AgOTf (5)	45
11	**2.1** (5)	13[b]
12	$KAuCl_4$ (5)	68
13	AgOTf (5)	10[b]
14	$AgBF_4$ (5)	10[b]
15	Ag_2CO_3 (5)	0[b]

16	$AgOOCCF_3$ (5)	0[b]
17	**2.2** (5)	0[b]
18	$Zn(OTf)_2$ (5)	0[b]
19	$Yb(OTf)_3$ (5)	0[b]
20	**2.1** (2.5) + Ag_2CO_3 (5)	0[b]
21	**2.1** (2.5) + CuI (5)	0[b]
22	**2.1** (2.5) + $PdCl_2$ (5)	0[b]
23	**2.1** (2.5) + $Zn(OAc)_2$ (5)	0[b]
24	**2.1** (2.5) + $NiBr_2$ (5)	0[b]
25	**2.1** (2.5) + LiCl (5)	0[b]
26	**2.1** (2.5) + $Mn(OAc)_2$ (5)	0[b]
27	**2.1** (2.5) + $NaBF_4$ (5)	0[b]
28	**2.1** (2.5) + $LaCl_3$ (5)	0[b]

[a] Reaction conditions: **2.7a** (0.24 mmol) and **2.8a** (0.2 mmol) in CH_2Cl_2 (2 mL). [b] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

There was a recent report about dual catalysis of gold and zinc salts for the synthesis of *N*-protected indoles.[66] The role of zinc salts was proposed to enhance the nucleophilicity of –OH which could attack the gold activated alkynes easier. The possible function of silver salts in this reaction involved in the enhancement of nucleophilicity of –OH of alkynyl alcohol **2.7a** to form **2.7a'** (Scheme 2.27) according to the proposed reaction mechanism by Cheng *et al.*[60] Interestingly, the use of Lewis acidic $Zn(OTf)_2$ instead of silver salts also gave high

yields (Table 2.4, entry 7). This implied that combining of gold(III) with Lewis acidic metal salts could be efficient catalyst system in this reaction. To further verify the proposed role of silver ions, we conducted experiments for investigating the dual metal catalysed-cyclization reaction.

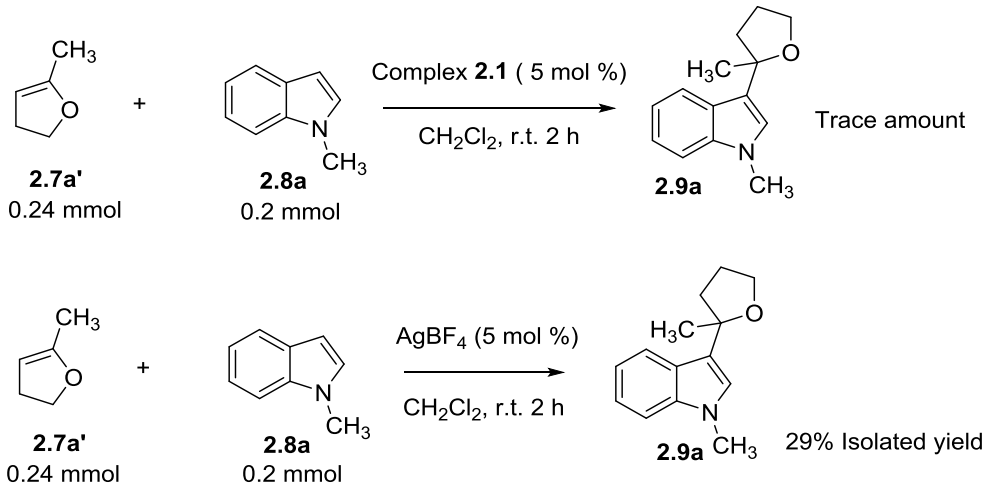


Scheme 2.27 Proposed mechanism of indole alkylation. ($[Au]^+$ = Complex **2.1**).

Firstly, by adding complex **2.1**, $AgBF_4$ or "**2.1** + $AgBF_4$" to the solution of **2.7a**, it was found that only the combination of "**2.1** + $AgBF_4$" gave complete conversion of **2.7a** in 2 h (Table 2.4, entry 2). However, either **2.1** or $AgBF_4$ gave poor consumption of **2.7a** (Table 2.4, entries11, 14).

Secondly, the reaction of commercially available **2.7a'** and **2.8a** in CH_2Cl_2 (Scheme 2.28) by complex **2.1** only gave a trace amount of product **2.9a** while $AgBF_4$ could catalyse the reaction to afford **2.9a** with 29% isolated yield. This suggested that the subsequent addition of indole **2.8a** to **2.7a'** was catalysed by Ag^+. As the reaction involved two metal catalysts,

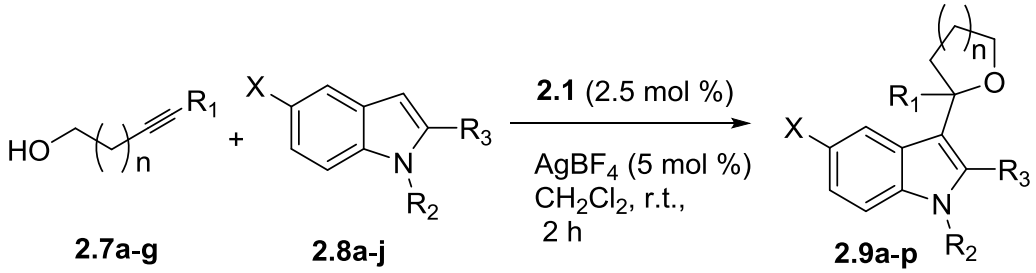
the exact role of each catalyst could not be understood thoughtfully at this moment. Therefore, further detailed mechanistic studies are needed.



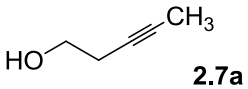
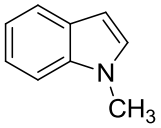
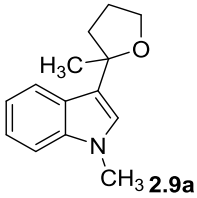
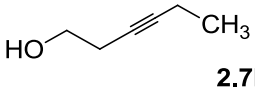
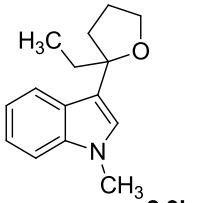
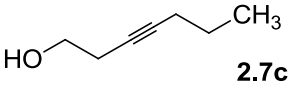
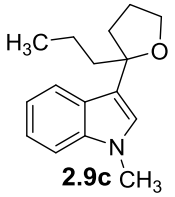
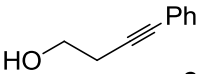
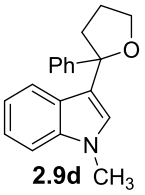
Scheme 2.28 Reaction between **2.7a'** and **2.8a** to give **2.9**.

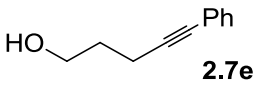
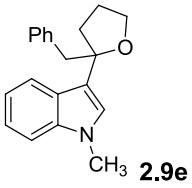
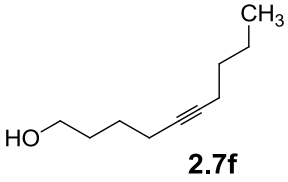
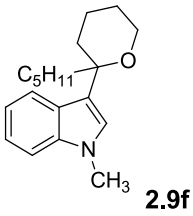
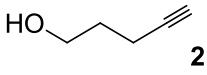
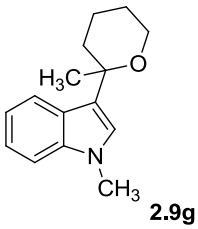
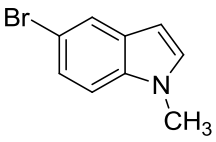
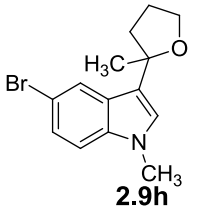
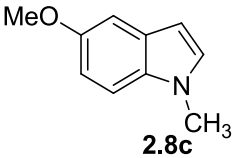
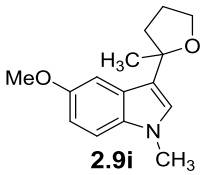
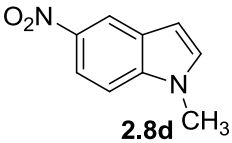
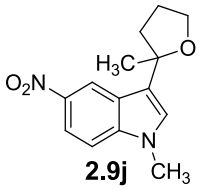
To expand substrate scope of the gold-silver dual catalysis for indole alkylation, a series of alkynyl alcohols with different chain lengths **2.7a-g** and indoles with different substituents (**2.8a**-**j**) were employed in the synthesis of alkylated indoles **2.9a** to **2.9b** (Table 2.5). The isolated yields were found to be up to 94%. The results demonstrated that the reactivity and regioselectivity of the indole alkylation reactions were consistent with literature reports.[60-61]

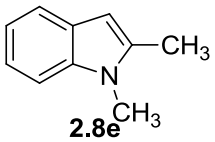
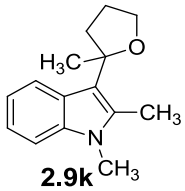
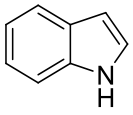
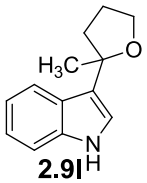
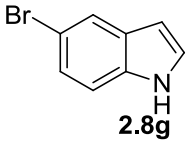
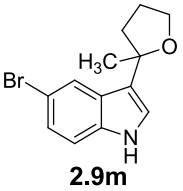
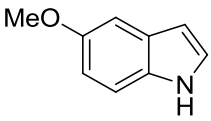
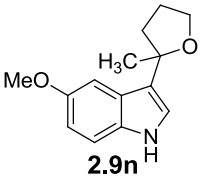
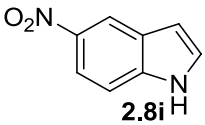
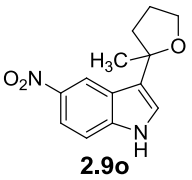
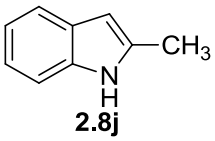
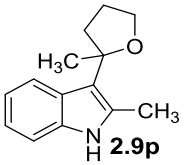
Table 2.5 Gold(III)-silver cyclization-addition of alkynyl alcohols and indoles.



2.7a-g 2.8a-j 2.9a-p

Entry	Alkynyl alcohol	Indole	Product	Isolated Yield (%)
1	 2.7a	 2.8a	 2.9a	80
2	 2.7b	**2.8a**	 2.9b	74
3	 2.7c	**2.8a**	 2.9c	78
4	 2.7d	**2.8a**	 2.9d	75

5	 **2.7e**	**2.8a**	 **2.9e**	74[b]
6	 **2.7f**	**2.8a**	 **2.9f**	84[c]
7	 **2.7g**	**2.8a**	 **2.9g**	94[c]
8	**2.7a**	 **2.8b**	 **2.9h**	80
9	**2.7a**	 **2.8c**	 **2.9i**	80
10	**2.7a**	 **2.8d**	 **2.9j**	67[d]

11	**2.7a**	 **2.8e**	 **2.9k**	40
12	**2.7a**	 **2.8f**	 **2.9l**	75
13	**2.7a**	 **2.8g**	 **2.9m**	71[e]
14	**2.7a**	 **2.8h**	 **2.9n**	53
15	**2.7a**	 **2.8i**	 **2.9o**	70[d]
16	**2.7a**	 **2.8j**	 **2.9p**	58

[a] Reaction conditions: **2.7a-g** (0.24 mmol) and **2.8a-j** (0.2 mmol) in CH_2Cl_2 (2 mL) at room temperature for 2 h. [b] 5-exo-dig cyclized product was formed. [c] 6-exo-dig cyclized products were formed. [d] 16 h. [e] 4 h.

2.3.5 Recyclability Experiments

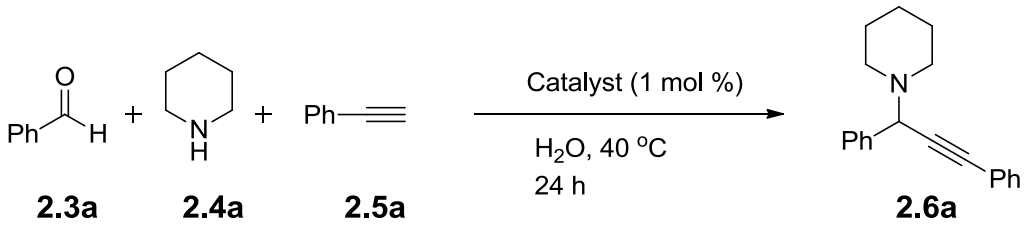
Tunable catalytic activity and coordination stability are important advantages of gold(III) complexes compared with simple gold(III) salts in catalysis. Herein, we demonstrated how stabilities of bis-cyclometallated (C^N) gold(III) complexes and gold(III) salts affect their performances in recyclability expermient in three-component coupling reaction and indole alkylation.

The recyclability experiments of catalyst **2.1** in three-component coupling reaction were conducted (Table 2.6). Complex **2.1** showed excellent catalytic activity in seven cycles leading to 638 product turnovers without significant drop in aldehyde conversion. However, the catalytic activity of $KAuCl_4$ became poor along with 7 cycles. The aldehyde conversion droped to 29% after seven reaction cycles. These findings provide indication of the superior recyclability of catalyst **2.1** over simple gold(III) salts.

Next, recyclability experiment of catalyst **2.1** and $KAuCl_4$ in the dual catalysis of indole alkylation was set out (Table 2.7). Catalyst **2.1** performed high reactivity in repeatedly using for 11 cycles to give 73-88% conversions. It was noticed that the silver salt was found to be deactivated for 5 cycles which affected the substrate conversions. Therefore, addition of $AgBF_4$ at the sixth and eleventh cycles provided fleshy silver ions for dual catalysis such that catalyst **2.1** could be reused with further addition of $AgBF_4$ for reactivating the catalyst. At the end of the tenth cycle, the reaction was subjected to ESI-MS analysis which showed that the complex **2.1** remained intact. The above results suggest that catalyst **2.1** keeps high reactivity along with repeating reactions without significant loss of catalyst or deactivation. However, by using $KAuCl_4$ or "$KAuCl_4$ + $AgBF_4$" as catalysts in the recyclability experiment, the substrate conversion dropped to zero in the second cycle. This implied that simple

gold(III) salts lost its catalytic ability in the reaction completely regarding to its poor stability under such reaction conditions.

Table 2.6 Recyclability experiments of catalysts **2.1** and $KAuCl_4$ in three-component reaction[a]

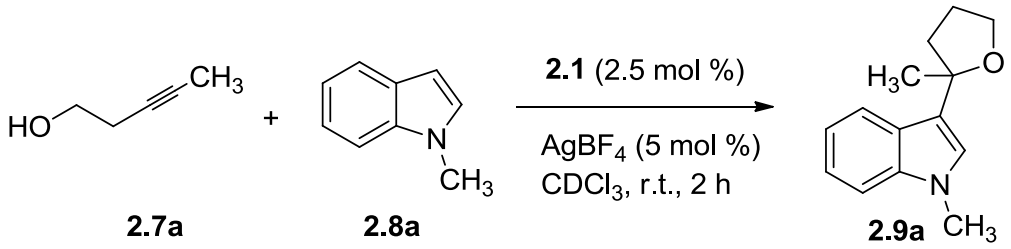


2.3a **2.4a** **2.5a** **2.6a**

Cycle	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Conversion (%)[b] by **2.1**	99	97	93	85	89	86	89
Conversion (%)[b] by $KAuCl_4$	99	94	82	65	51	38	29

[a] Reaction conditions: **2.3a** (1 mmol), **2.4a** (1.1 mmol) and **2.5a** (1.5 mmol) in H_2O (1 mL) at 40 °C. [b] Determined by ^1H NMR.

Table 2.7 Recyclability experiment of catalyst (**2.1** + $AgBF_4$) in the reaction of **2.7a** and **2.8a** at room temperature in $CDCl_3$[a]



2.7a **2.8a** **2.9a**

Cycle	*1*	*2*	*3*	*4*	*5*	*6*[c]	*7*	*8*	*9*	*10*	*11*[c]
Conversion (%)[b]	**85**	**81**	**81**	**78**	**73**	**88**	**87**	**85**	**81**	**74**	**83**

[a] Reaction conditions: **7a** (0.24 mmol) and **8a** (0.2 mmol) in $CDCl_3$ (2 mL) at room temperature. [b] Determined by ^1H NMR. [c] Additional $AgBF_4$ (5 mol %) was added.

This work regarding the use of bis-cyclometallated gold(III) complexes for efficient catalysts of propargylamine synthesis and indole alkylation has been published in *Chem. Commun.* **2013**, *49*, 8869–8871.

2.4 Conclusion

In conclusion, we have developed two different strategies to make stable bis-cyclometallated gold(III) complexes as effective catalysts in organic transformations by (1) distorted square planar geometry ligand design for metal-ligand bond elongation and (2) combining with other metal salt catalysts. Both strategies were successfully applied in three-component coupling reactions for propargylamine synthesis, and indoles alkylation respectively with high reusability when compared with simple gold(III) salts.

2.5 Experimental Section

General Methods

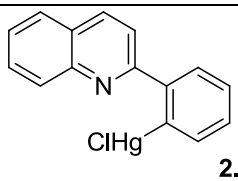
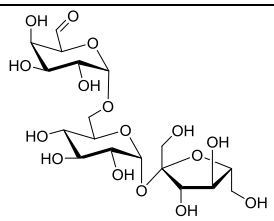
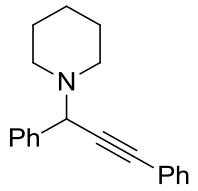
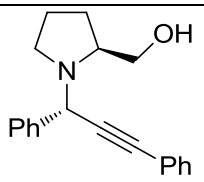
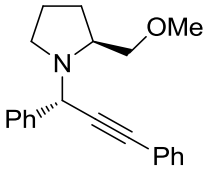
All chemicals were commercially available and used without further purification. Compounds **2.1a, 2.2a, 2.7d-e**, **2.8b-e** and D-raffinose aldehyde were synthesized according to literature procedures. Flash column chromatography was conducted using silica gel 60 (230-400 mesh ASTM) with *n*-hexane/EtOAc or MeOH/CH_2Cl_2 as eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-400 and Varian Unity Inova 400 NB spectrometers. The chemical shifts are expressed in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; br s, broad singlet; d, doublet; dd, double doublet; t, triplet; td, triplet doublet; m, multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Low resolution mass spectra (MS) and high resolution mass spectra (HR-MS) were obtained on Waters Micromass Q-TOF 2^{TM} with a positive ESI source. X-ray crystal structures were obtained by Bruker CCD area detector diffractometer. Milli-Q® water used as reaction solvent in oligosaccharide modification and LC-MS was deionised using a Milli-Q® Gradient A10 system (Millipore, Billerica, USA).

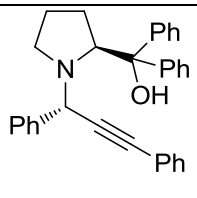
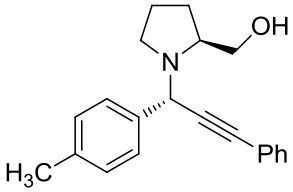
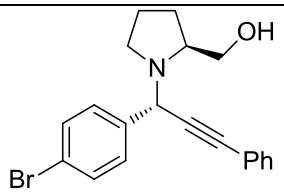
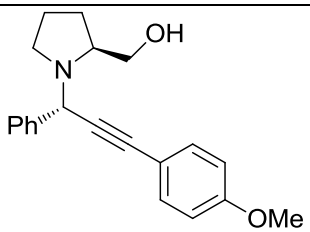
LC–MS Analysis Procedures for Modification of D-raffinose

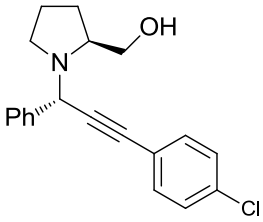
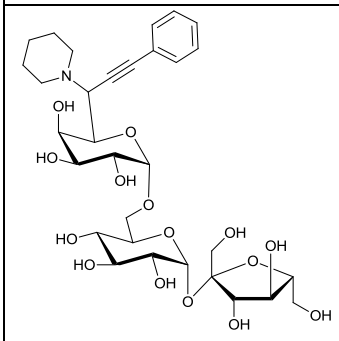
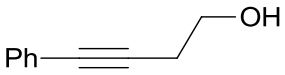
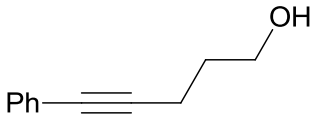
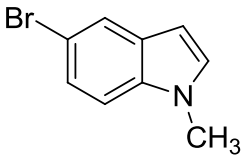
The LC system was based on CapLC® system from Waters (Manchester, UK). The system was equipped with a Poroshell 300SB-C18 column with 1.0 mm ID ×75 mm, 5μm) and ZORBAX Poroshell guard column with 1.0 mm ID ×17 mm, 5 μm (Agilent-Technologies Inc., Wilmington, United States of America). Mass spectrometry analysis was conducted by

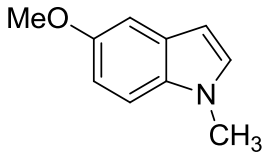
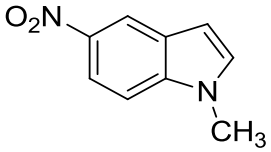
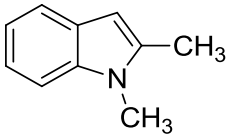
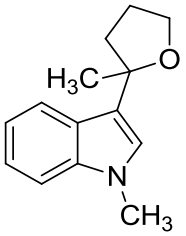
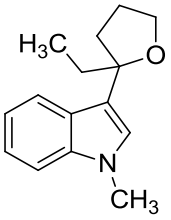
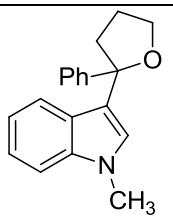
using Q-TOF 2™ (Waters-Micromass, Manchester, UK) as the ESI source in the positive ion mode. Mobile phase A consisted of formic acid (0.5%) in Milli-Q® water and mobile phase B consisted of formic acid (0.5%) in CH_3CN. 2 μL of sample was injected with a flow rate of 40 μL/min at room temperature. The initial conditions for separation were 3% B in 0-3 min, followed by a linear gradient to 70% B in 4-30 min and 3% B in 31-45 min. The mass spectra were scanned over m/z 200-2000, and the raw spectra were deconvoluted by using the MassLynx 4.1 Transform Program (Waters, Manchester, UK). Desolvation and source temperatures were set to be 150 ℃ and 80 ℃ respectively. Operating conditions optimized for the detection of target ions in the reaction mixture were as follows: capillary voltage 3 kV, sample cone voltage 30 V, extraction voltage 4 V and collision cell voltage 10 eV.

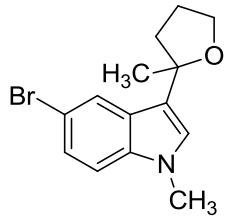
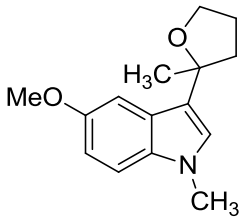
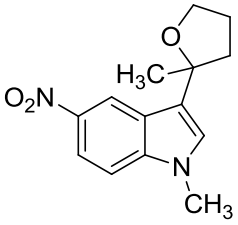
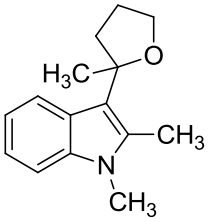
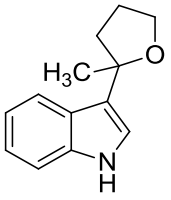
Literature References

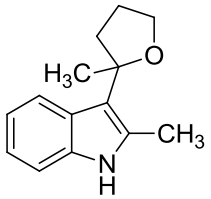
 **2.1a**	Al-Salim, N.; West, A. A.; McWhinnie, W. R. and Hamor, T. A., *J. Chem. Soc., Dalton Trans.* **1988**, 2363.
 D-raffinose aldehyde	Parikka, K. and Tenkanen, M., *Carbohydr. Res.* **2009**, *344*, 14.
 **2.6a**	a) Wei, C. and Li, C. J., *J. Am. Chem. Soc.* **2003**, *125*, 9584; b) Wei, C. Li, C. and Li, C. J., *Org. Lett.*, **2003**, *5*, 4473; c) Shi, L.; Tu, Y. Q.; Wang. M.; Zhang, F. M. and Fan, C. A., *Org. Lett.* **2004**, *6*, 1001.
 **2.6b**	Lo, V. K. Y.; Liu. Y.; Wong, M. K. and Che. C. M., *Org. Lett.* **2006**, *8*, 1529.
 **2.6c**	Gommermann, N.; Koradin, C.; Polborn, K. and Knochel, P., *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

 **2.6d**	Lo, V. K. Y.; Liu. Y.; Wong, M. K. and Che. C. M., *Org. Lett.* **2006**, *8*, 1529.
 **2.6e**	a) Lo, V. K. Y.; Kung, K. K. Y.; Wong, M. K. and Che. C. M., *J. Organomet. Chem*. **2009**, *694*, 583; b) Kung, K. K. Y. L., V. K. Y.; Ko, H. M.; Li, G. L.; Chan, P. Y.; Leung, K. C.; Zhou, Z.; Wang, M. Z.; Che, C. M.; Wong, M. K., *Adv. Synth. Catal.* **2013**, *355*, 2055.
 **2.6f**	a) Lo, V. K. Y.; Liu. Y.; Wong, M. K. and Che. C. M., *Org. Lett.* **2006**, *8*, 1529.; b) Lo, V. K. Y.; Kung, K. K. Y.; Wong, M. K. and Che. C. M., *J. Organomet. Chem*. **2009**, *694*, 583.
 **2.6g**	Kung, K. K. Y. L., V. K. Y.; Ko, H. M.; Li, G. L.; Chan, P. Y.; Leung, K. C.; Zhou, Z.; Wang, M. Z.; Che, C. M.; Wong, M. K., *Adv. Synth. Catal.* **2013**, *355*, 2055.

 **2.6h**	Kung, K. K. Y. L., V. K. Y.; Ko, H. M.; Li, G. L.; Chan, P. Y.; Leung, K. C.; Zhou, Z.; Wang, M. Z.; Che, C. M.; Wong, M. K., *Adv. Synth. Catal.* **2013**, *355*, 2055.
 **2.6i**	Kung, K. K. Y.; Li, G. L.; Zou, L.; Chong, H. C.; Leung, Y. C.; Wong, K. H.; Lo, V. K. Y.; Che, C. M.; Wong, M. K., *Org. Biomol. Chem*. **2012**, *10*, 925.
 **2.7d**	a) Alami, M.; Ferri, F. and Linstrumelle, G., *Tetrahedron Lett.* **1993**, *34*, 6403; b) Wu, H.; He, Y. P. and Gong, L. Z., *Adv. Synth. Catal.* **2012**, *354*, 975.
 **2.7e**	a) Alami, M.; Ferri, F. and Linstrumelle, G., *Tetrahedron Lett.* **1993**, *34*, 6403; b) Wu, H.; He, Y. P. and Gong, L. Z., *Adv. Synth. Catal.* **2012**, *354*, 975.
 **2.8b**	Kikugawa Y. and Miyake, Y. *Synthesis*, **1981**, *6*, 461.

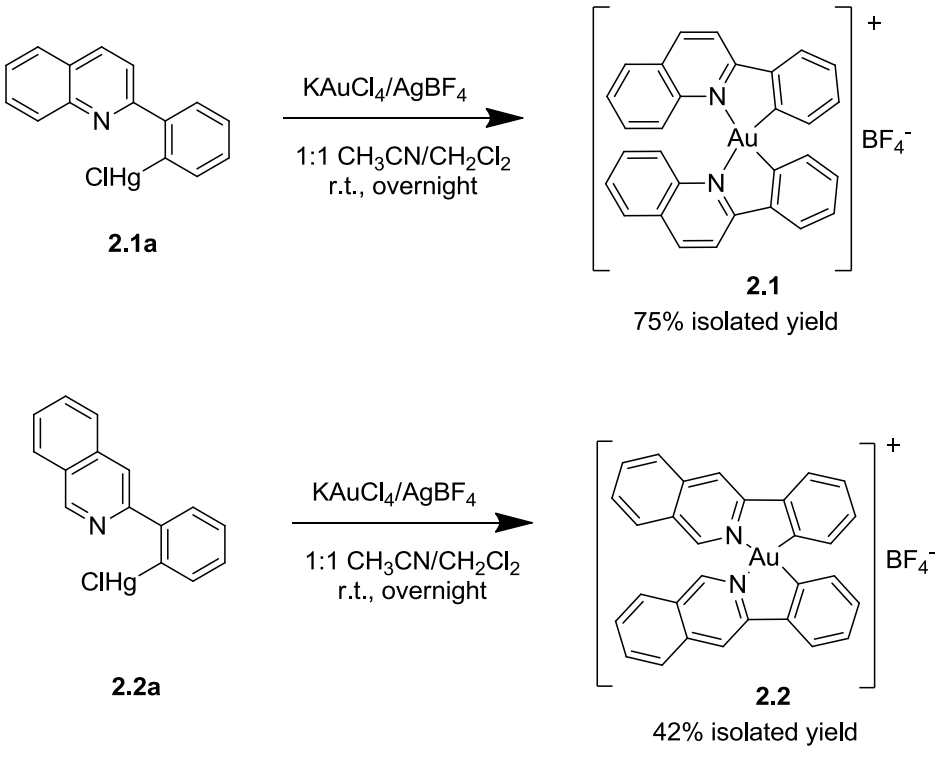
 **2.8c**	Kikugawa Y. and Miyake, Y. *Synthesis*, **1981**, *6*, 461.
 **2.8d**	Kikugawa Y. and Miyake, Y. *Synthesis*, **1981**, *6*, 461.
 **2.8e**	Kikugawa Y. and Miyake, Y. *Synthesis*, **1981**, *6*, 461.
 **2.9a**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.
 **2.9b**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.
 **2.9d**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.

 **2.9h**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.
 **2.9i**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.
 **2.9j**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.
 **2.9k**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.
 **2.9l**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.

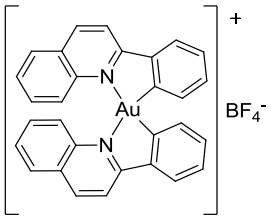
 **2.9p**	Bhuvaneswari, S.; Jeganmohan, M. and Cheng, C. H., *Chem. Eur. J.* **2007**, *13*, 8285.

General Procedure for Synthesis of Bis-cyclometallated Gold(III) Complexes via Transmetallation

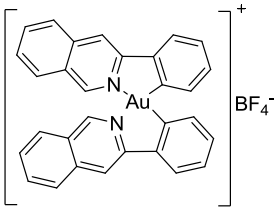
Synthesis of complexes **2.1** and **2.2** were based on modified literature procedures.[62a, 63] The organomercury intermediate **2.1a** or **2.2a** (0.4 mmol, 2 equiv.), $KAuCl_4$ (0.2 mmol, 1 equiv.) and $AgBF_4$ (1.2 mmol, 6 equiv.) were dissolved in CH_3CN/CH_2Cl_2 (1:1, 10 mL) and stirred at room temperature for overnight. After the reaction, precipitates were first removed by filtration. The yellow filtrate was then evaporated to dryness and redissolved in CH_2Cl_2 (10 mL). The solution was extracted with water (3 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to give pale yellow solid. The product was further purified by flash column chromatography using CH_2Cl_2/MeOH as eluent.



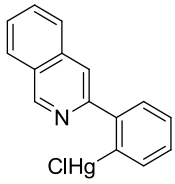
Scheme 2.29 Synthesis of bis-cyclometallated gold(III) complexes **2.1** and **2.2**.

Compound **2.1**: 

Transparent crystal for X-ray crystallography study was obtained by slow diffusion of n-hexane to a solution of **1** in $CHCl_3$; ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.81 (d, J = 8.7 Hz, 1H), 8.53 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.0, 1H), 7.89 (m, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.50–7.54 (t, J = 7.5 Hz, 2H), 7.42–7.45 (t, J = 7.5 Hz, 1H), 7.28–7.31 (t, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 162.5, 146.8, 145.7, 143.6, 142.7, 133.4, 132.9, 131.6, 129.3, 129.1, 128.7, 128.2, 126.1, 119.4; MS (ESI^+): *m/z* 605 $[M]^+$; HR-MS (ESI^+): *m/z* 605.1295 $[M]^+$, calcd. for $C_{30}H_{20}N_2Au$: *m/z* 605.1292.

Compound **2.2**: 

Grey solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.71 (s, 1H), 8.74 (s, 1H), 8.47, (d, J = 8.3 Hz, 1H), 8.15, (d, J = 8.3 Hz, 1H), 8.03–8.07 (t, J = 7.4 Hz, 1H), 7.94, (d, J = 7.1 Hz, 1H), 7.84–7.88, (t, J = 7.4 Hz, 1H), 7.68, (d, J = 7.7 Hz, 1H), 7.23–7.27, (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 154.0, 153.3, 146.4, 144.5, 137.8, 135.6, 134.1, 131.5, 131.2, 129.9, 129.3, 128.2, 127.8, 125.6, 118.9; MS (ESI^+): *m/z* 605 $[M]^+$; HR-MS (ESI^+): *m/z* 605.1268 $[M]^+$, calcd. for $C_{30}H_{20}N_2Au$: *m/z* 605.1292.

Compound **2.2a**: 

White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (s, 1H), 8.27 (s, 1H), 8.19 (d, J = 6.8 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.56–7.59 (m, 1H), 7.44–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 149.3, 148.8, 142.5, 138.2, 137.4, 131.7, 129.4, 129.2, 128.6, 128.2, 128.0, 127.4, 127.1, 117.2; MS (ESI^+): *m/z* 438 $[M+H]^+$; HR-MS (ESI^+): *m/z* 438.0241 $[M+H]^+$, calcd. for $C_{15}H_{11}N_1Hg$: *m/z* 438.0247.

Table 2.8 Crystal data and structure refinement for bis-cyclometallated gold(III) complex **2.1**.

Empirical formula	$Au(C_{30}H_{20}N_2)\ .BF_4$
Formula weight	692.26
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 15.2230(3) Å α = 90°
	b = 7.6173(2) Å β= 93.8440(10)°
	c = 20.9299(4) Å γ = 90°
Volume	2421.53(9) $Å^3$
Z	4
Density (calculated)	1.899 Mg/m^3
Absorption coefficient	6.130 mm^{-1}
F(000)	1336
Crystal size	0.50 x 0.22 x 0.10 mm^3
Theta range for data collection	1.60 to 27.51°.
Index ranges	-19<=h<=19, -9<=k<=9, -26<=l<=27
Reflections collected	28180
Independent reflections	5427 [R(int) = 0.0657]
Completeness to theta = 27.51°	97.7 %

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7456 and 0.3707
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5427 / 0 / 363
Goodness-of-fit on F^2	1.003
Final R indices [I>2sigma(I)]	R1 = 0.0529, wR2 = 0.1556
R indices (all data)	R1 = 0.0628, wR2 = 0.1627
Largest diff. peak and hole	2.458 and -2.017 e.Å $^{-3}$

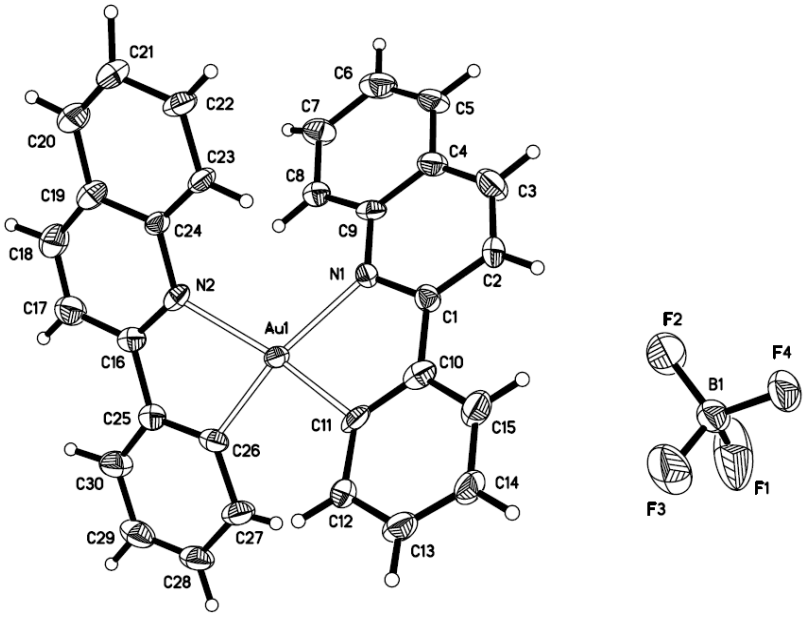


Figure 2.15 X-ray crystal structure of bis-cyclometallated gold(III) complex **2.1**.

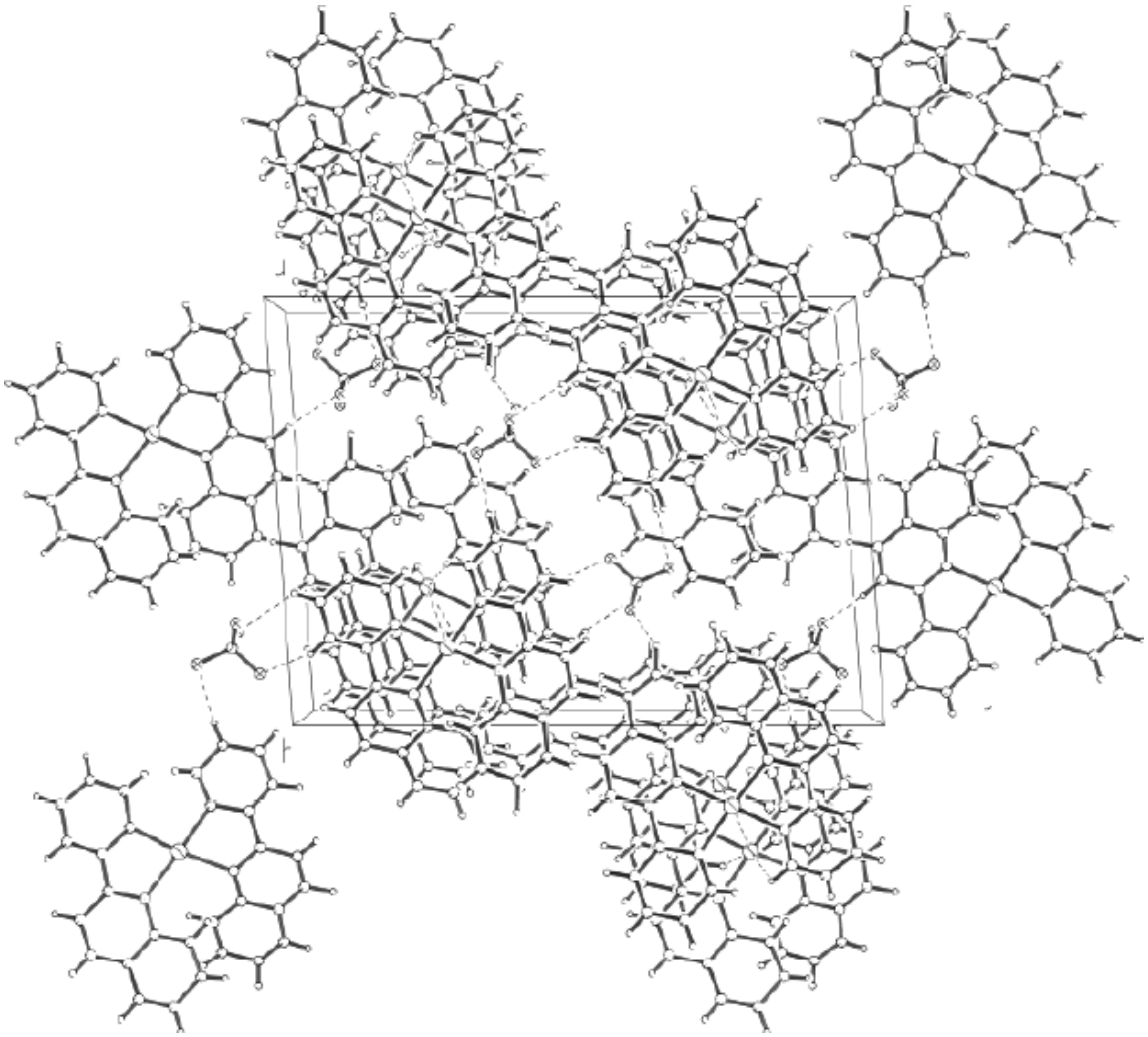


Figure 2.16 A representation (top view) of packing in a single crystal of **2.1**.

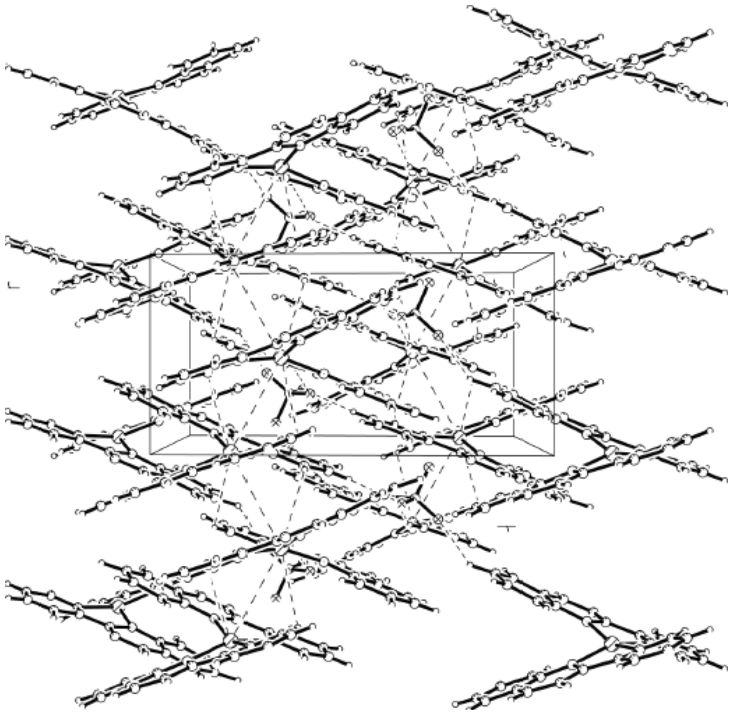


Figure 2.17 A representation (side view) of packing in a single crystal of **2.1**.

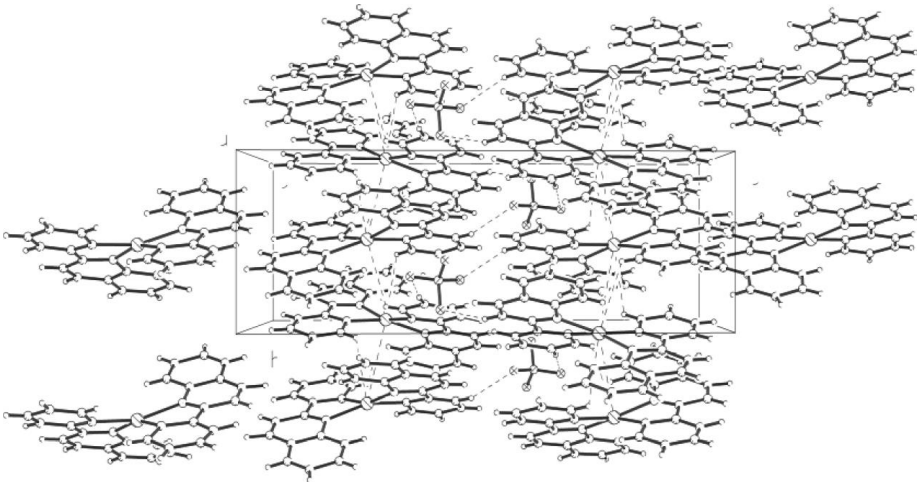
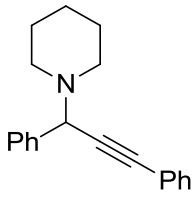


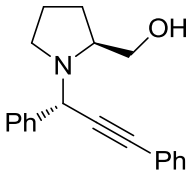
Figure 2.18 A representation (rear view) of packing in a single crystal of **2.1**.

General Procedure for Bis-cyclometallated Gold(III) Complex-Catalysed Synthesis of Propargylamines via Three-component Coupling Reaction

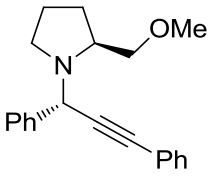
A mixture of bis-cyclometallated gold(III) complex **2.1** or **2.2** (1 mol %), aldehyde **2.3a-c** (0.5 mmol), amine **2.4a-d** (0.55 mmol) and alkyne **2.5a-c** (0.75 mmol) in water (1 mL) was stirred at 40 ^{o}C for 24 h.[22] The reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Propargylamine **2.6a-h** was purified by flash column chromatography using *n*-hexane/EtOAc as eluent.

Compound **2.6a**: 

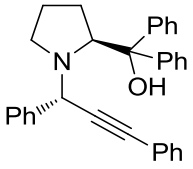
Yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64–7.62 (m, 2H), 7.50–7.53 (m, 2H), 7.24–7.37 (m, 6H), 4.79 (s, 1H), 2.54–2.57 (m, 4H), 1.55–1.61 (m, 4H), 1.42–1.45 (m, 2H); MS (ESI$^+$): *m/z* 276 $[M+H]^+$.

Compound **2.6b**: 

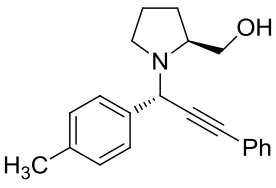
Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.61 (d, *J* = 7.2 Hz, 2H), 7.48–7.53 (m, 2H), 7.30–7.40 (m, 6H), 5.12 (s, 1H), 3.81–3.86 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.51–3.56 (dd, *J* = 10.9, 2.2 Hz, 1H), 3.27–3.31 (m, 1H), 2.77–2.86 (dd, *J* = 9.2, 7.3 Hz, 1H), 2.59–2.66 (td, *J* = 8.0, 3.0 Hz, 1H), 1.92–1.97 (m, 1H), 1.75–1.87 (m, 1H), 1.66–1.73 (m, 2H); MS (ESI$^+$): *m/z* 292 $[M+H]^+$.

Compound **2.6c**: 

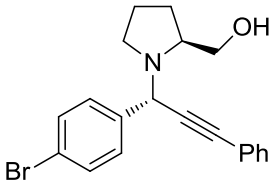
Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.61 (m, 2H), 7.48–7.53 (m, 2H), 7.30–7.40 (m, 6H), 5.12 (s, 1H), 3.84 (dd, J = 10.9, 3.5 Hz, 1H), 3.54 (dd, J = 10.9, 2.2 Hz, 1H), 3.27–3.31 (m, 1H), 2.82 (dd, J = 9.2, 7.3 Hz, 1H), 2.63 (td, J = 8.0, 3.0 Hz, 1H), 1.92–1.97 (m, 1H), 1.75–1.87 (m, 1H), 1.66–1.73 (m, 2H); MS (ESI$^+$): *m/z* 306 $[M+H]^+$.

Compound **2.6d**: 

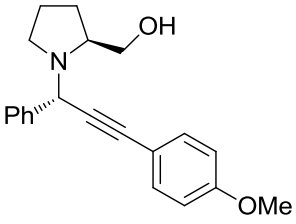
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.86 (m, 2H), 7.61–7.64 (m, 2H), 7.54–7.57 (m, 2H), 7.37–7.40 (m, 3H), 7.29–7.32 (m, 6H), 7.21–7.26 (m, 3H), 7.12–7.20 (m, 2H), 4.69 (s, 1H), 4.51 (q, J = 5.0 Hz, 1H), 4.27 (s, 1H), 2.94 (td, J = 9.1, 7.1 Hz, 1H), 1.82–1.98 (m, 1H), 1.60–1.81 (m, 3H); MS (ESI$^+$): *m/z* 444 $[M+H]^+$.

Compound **2.6e**: 

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.51 (m, 4H), 7.29–7.33 (m, 3H), 7.15–7.17 (d, J = 7.9 Hz, 2H), 5.07 (s, 1H), 3.77–3.82 (dd, J = 10.9, 3.6 Hz, 1H), 3.49–3.54 (dd, J = 10.9, 2.4 Hz, 1H), 3.22–3.29 (m, 1H), 2.76–2.85 (td, J = 9.2, 7.3 Hz, 1H), 2.60–2.66 (m, 1H), 2.34 (s, 3H), 1.65–2.01 (m, 4H); MS (ESI$^+$): *m/z* 306 $[M+H]^+$.

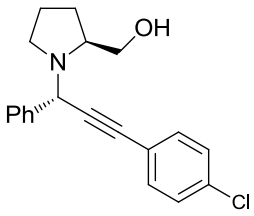
Compound **2.6f**: 

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.52 (m, 6H), 7.33–7.36 (m, 3H), 5.07 (s, 1H), 3.80 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.54 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.16–3.30 (m, 1H), 2.75–2.79 (m, 1H), 1.65–2.02 (m, 4H); MS (ESI$^+$): *m/z* 370 $[M+H]^+$.

Compound **2.6g**: 

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.5 Hz, 2H), 7.41–7.47 (m, 2H), 7.32–7.38 (m, 2H), 7.24–7.30 (m, 1H), 6.82–6.88 (m, 2H), 5.10 (s, 1H), 3.82 (dd, *J* = 3.0 Hz, 1H), 3.79 (s, 3H), 3.55 (dd, *J* = 11.0, 3.0 Hz, 2H), 3.20–3.31 (m, 1H), 2.80 (q, *J* = 16.6, 11.0 Hz, 1H), 2.70 (br s, 1H), 2.56–2.65 (m, 1H), 1.90–2.22 (m, 1H), 1.78–1.89 (m, 1H), 1.58–1.88 (m, 2H); MS (ESI$^+$): *m/z* 322 $[M+H]^+$.

Compound **2.6h**:



Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.61 (m, 2H), 7.40–7.47 (m, 2H), 7.33–7.40 (m, 3H), 5.11 (s, 1H), 3.73 (dd, J = 11.0, 3.0 Hz, 1H), 3.55 (dd, J = 11.0, 3.0 Hz, 1H), 3.22–3.27 (m, 1H), 2.80 (q, J = 16.6, 11.0 Hz, 1H), 2.60–2.66 (m, 1H), 2.55 (br s, 1H), 1.90–2.05 (m, 1H), 1.80–1.90 (m, 1H), 1.60–1.80 (m, 2H); MS (ESI$^+$): *m/z* 326 $[M+H]^+$.

General Procedure for Gold-mediated Bifunctional Modification of D-Raffinose Aldehyde

The reaction was carried by using gold(III) complex **2.1** according to literature procedures.[24] A mixture of D-raffinose aldehyde (10 µL of 100 mM in H_2O), **2.4a** (10 equiv.), **2.5a** (10 equiv.) and **2.1** (1 equiv.) in water (90 µL) was stirred at 40 ^oC for 2 h. The crude reaction mixture was centrifuged. The clear liquor (2 µL) was analyzed by LC-MS for determination of the aldehyde conversion.

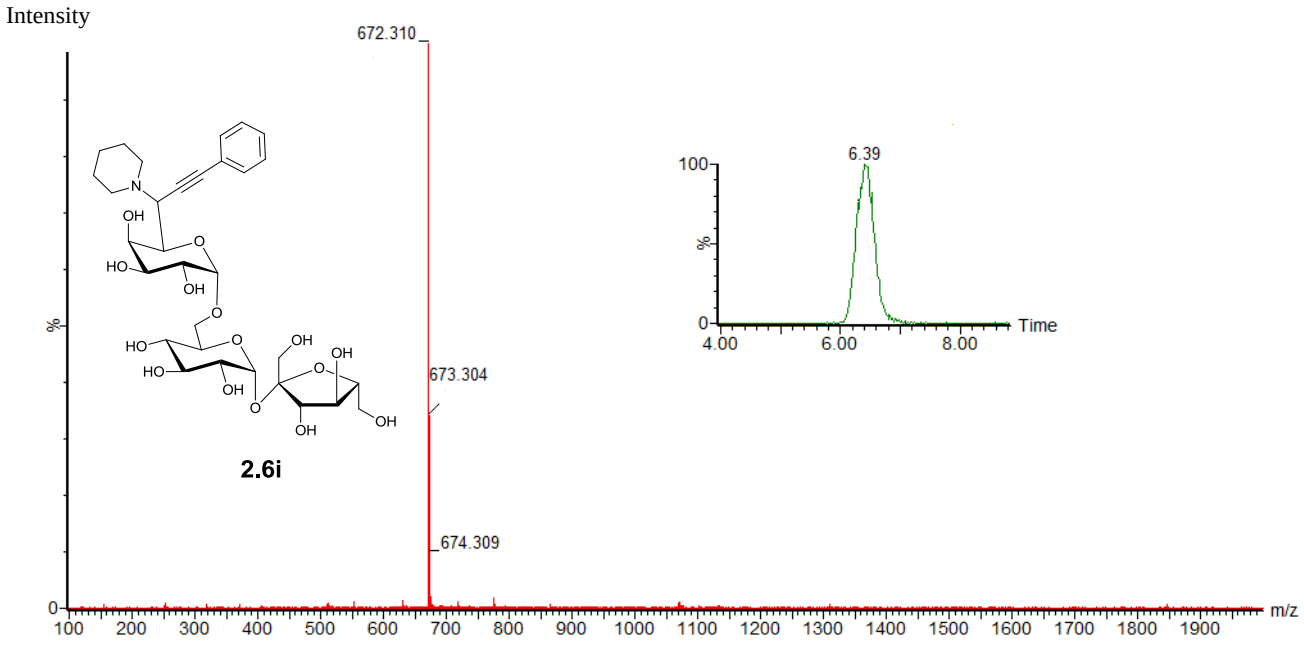


Figure 2.19 LC–MS spectrum of **2.6i** ($[M+H]^+$ = *m/z* 672.31) and the XIC chromatogram of **2.6i** at 6.39 min (inset).

Calculation of Aldehyde Conversion

The crude reaction mixture containing D-raffinose aldehyde and propargylamine-modified D-raffinose after completed reaction was subjected to LC-MS analysis with elution time of 45 min. The raw data was processed by MassLynx 4.1 Transform Program. The aldehyde conversions at different time intervals were determined by measuring the relative peak intensities of aldehyde (substrate) and propargylamine-modified D-raffinose (product) in the mass spectrum as follows:

$$\text{Aldehyde Conversion} = \frac{\text{Relative Intensity of Product}}{\text{Relative Intensities of Aldehyde and Product}} \times 100\%$$

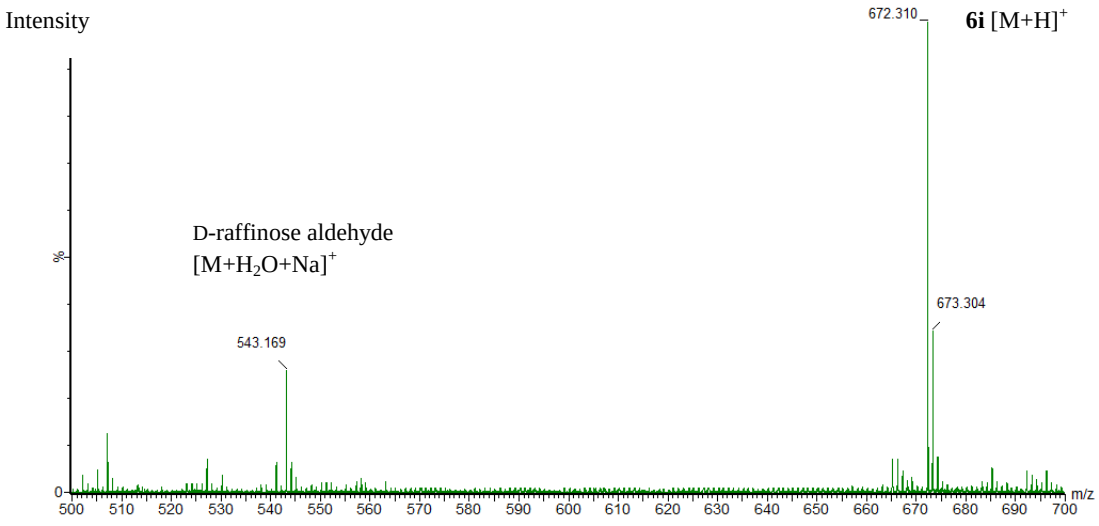
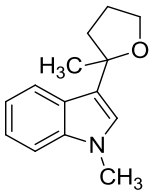


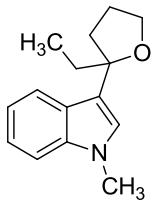
Figure 2.20 LC–MS spectrum of **2.6i (**$[M+H]^+$ = *m/z* 672.31) and D-raffinose aldehyde **(**$[M+H_2O+Na]^+$ = *m/z* 543.17).

General Procedure for Gold(III) Complex-silver Catalysed Synthesis of Alkylated Indoles

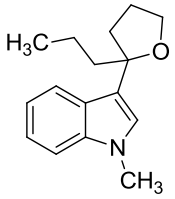
A mixture of alkynyl alcohol **2.7a-g** (0.24 mmol), indole **2.8a-j** (0.2 mmol), gold complex **2.1** or **2.2** (2.5 mol %) and $AgBF_4$ (5 mol %) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 h or until complete conversion of indoles was observed by thin layer chromatography. The solvent was removed under vacuum. The crude mixture was subjected to flash column chromatography to get the purified product.

Compound **2.9a**: 

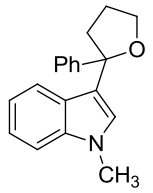
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 1H), 7.28–7.32 (m, 1H), 7.22–7.26 (t, J = 7.0 Hz, 1H), 7.11–7.15 (t, J = 7.0 Hz, 1H), 6.99 (s, 1H), 3.99–4.04 (m, 2H), 3.77 (s, 3H), 2.39–2.44 (m, 1H), 1.95–2.09 (m, 3H), 1.71 (s, 3H); MS (ESI$^+$): *m/z* 216 $[M+H]^+$.

Compound **2.9b**: 

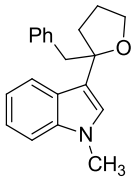
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 1H), 7.28–7.32 (m, 1H), 7.21–7.25 (t, J = 7.2 Hz, 1H), 7.08–7.12 (t, J = 8.0 Hz, 1H), 6.96 (s, 1H), 3.91–3.99 (m, 2H), 3.77 (s, 3H), 2.33–2.37 (m, 1H), 1.90–2.11 (m, 5H), 0.80–0.84 (t, J = 7.4 Hz, 3H); MS (ESI$^+$): *m/z* 230 $[M+H]^+$.

Compound **2.9c**: 

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.20 (m, 1H), 7.05–7.09 (t, J = 7.1 Hz, 1H), 6.91 (s, 1H), 3.87–3.97 (m, 2H), 3.71 (s, 3H), 2.30–2.35 (m, 1H), 1.86–2.05 (m, 5H), 1.27–1.35 (m, 1H), 1.12–1.18 (m, 1H), 0.79–0.83 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 126.3, 125.9, 121.5, 120.8, 120.4, 118.9, 109.5, 85.1, 67.4, 44.0, 37.6, 32.9, 26.1, 18.5, 14.8; MS (ESI^+): *m/z* 244 [M+H^+]; HR-MS (ESI^+): *m/z* 244.1694 $[M+H]^+$, calcd. for $C_{16}H_{21}NO$: *m/z* 244.1701.

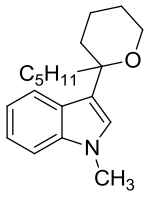
Compound **2.9d**: 

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.30–7.34 (t, J = 7.6 Hz, 2H), 7.17–7.26 (m, 3H), 7.01–7.05 (t, J = 7.1 Hz, 1H), 6.87 (s, 1H), 4.10–4.14 (m, 2H), 3.75 (s, 3H), 2.74–2.81 (m, 1H), 2.47–2.53 (m, 1H), 2.08–2.15 (m, 1H), 1.97–2.04 (m, 1H); MS (ESI^+): *m/z* 278 $[M+H]^+$.

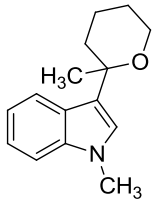
Compound **2.9e**: 

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.0 Hz, 1H), 7.31–7.33 (d, J = 8.0 Hz, 1H), 7.24–7.27 (t, J = 7.5 Hz, 1H), 7.14–7.23 (m, 4H), 7.05–7.07 (m, 2H), 6.79 (s, 1H), 3.91–3.94 (t, J = 6.9 Hz, 2H), 3.73 (s, 3H), 3.25–3.33 (m, 2H), 2.27–3.33 (m, 1H), 2.14–2.21 (m, 1H), 1.75–1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 137.9, 130.8,

127.8, 126.5, 126.2, 125.9, 121.5, 120.7, 120.5, 119.1, 109.6, 85.1, 67.7, 47.4, 36.2, 32.9, 26.1; MS (ESI^+): *m/z* 292 $[M+H]^+$; HR-MS (ESI^+): *m/z* 292.1698 $[M+H]^+$, calcd. for $C_{20}H_{22}NO$: *m/z* 292.1701.

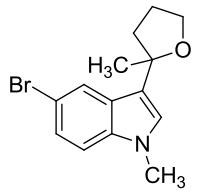
Compound **2.9f**: 

Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.29–7.32 (d, *J* = 8.0 Hz, 1H), 7.22–7.25 (t, *J* = 7.0 Hz, 1H), 7.09–7.12 (t, *J* = 7.0 Hz, 1H), 6.83 (s, 1H), 3.78 (s, 3H), 3.71–3.74 (m, 1H), 3.48–3.55 (m, 1H), 2.17–2.23 (m, 1H), 1.92–2.00 (m, 1H), 1.71–1.78 (m, 4H), 1.38–1.41 (m, 1H), 1.29 (m, 1H), 1.10–1.24 (m, 5H), 0.89–0.93 (m, 1H), 0.78–0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 127.5, 126.8, 121.9, 121.4, 118.9, 116.8, 109.0, 77.3, 62.7, 44.0, 33.9, 32.8, 32.4, 26.1, 23.7, 22.7, 20.2, 14.1; MS (ESI^+): *m/z* 286 $[M+H]^+$; HR-MS (ESI^+): *m/z* 286.2159 $[M+H]^+$, calcd. for $C_{19}H_{27}NO$: *m/z* 286.2171.

Compound **2.9g**: 

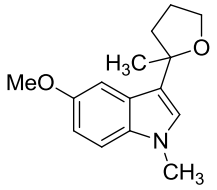
Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.0 Hz, 1H), 6.88 (s, 1H), 3.79 (s, 3H), 3.74–3.77 (m, 1H), 3.50 (td, *J* = 11.3, 2.7 Hz, 1H), 2.24–2.27 (m, 1H), 1.73–1.83 (m, 4H), 1.58 (s, 3H), 1.42–1.46 (m, 1H); MS (ESI^+): *m/z* 230 $[M+H]^+$.

Compound **2.9h**:



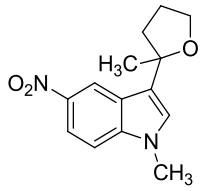
Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (br s, 1H), 7.30 (dd, J = 8.7, 1.8 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 6.97 (s, 1H), 3.94–4.06 (m, 2H), 3.74 (s, 3H), 2.31–2.39 (m, 2H), 2.01–2.09 (m, 2H), 1.91–1.99 (m, 1H), 1.67 (s, 3H); MS (ESI^+): *m/z* 294 $[M+H]^+$.

Compound **2.9i**:



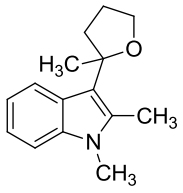
Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.17 (m, 2H), 6.91 (s, 1H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H), 3.93–4.01 (m, 2H), 3.87 (s, 3H), 3.07 (s, 3H), 2.36–2.39 (m, 1H), 1.98–2.04 (m, 2H), 1.93–1.97 (m, 1H), 1.66 (s, 3H); MS (ESI^+): *m/z* 246 $[M+H]^+$.

Compound **2.9j**:



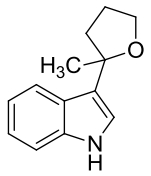
Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 7.11 (s, 1H), 3.95–4.06 (m, 2H), 3.81 (s, 3H), 2.30–2.35 (m, 1H), 2.05–2.14 (m, 2H), 1.92–2.00 (m, 1H), 1.67 (s, 3H); MS (ESI^+): *m/z* 261 $[M+H]^+$.

Compound **2.9k**:

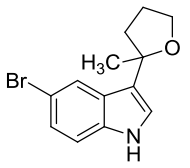


Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.1 Hz, 1H), 7.04 (t, J =7.1 Hz, 1H), 3.98–4.04 (m, 1H), 3.86 (m, 1H), 3.62

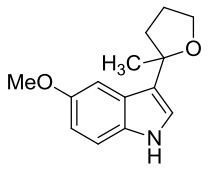
(s, 3H), 2.55 (s, 3H), 2.47–2.52 (m, 1H), 2.15–2.22 (m, 1H), 1.97–2.04 (m, 1H), 1.82–1.92 (m, 1H), 1.63 (s, 3H); MS (ESI^+): *m/z* 230 $[M+H]^+$.

Compound **2.9l**: 

Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.16–7.19 (t, *J* = 7.5 Hz, 1H), 7.08–7.13 (m, 2H), 3.94–4.05 (m, 2H), 2.37–2.42 (m, 1H), 2.01–2.08 (m, 2H), 1.92–1.98 (m, 1H), 1.69 (s, 3H); MS (ESI^+): *m/z* 202 $[M+H]^+$.

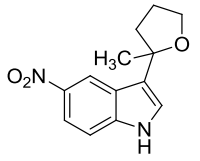
Compound **2.9m**: 

Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (br s, 1H), 7.88 (s, 1H), 7.17–7.25 (dd, *J* = 24.3, 8.6 Hz, 2H), 7.04 (s, 1H), 3.98–4.06 (m, 2H), 2.34–2.38 (m, 1H), 1.97–2.07 (m, 3H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 127.0, 124.8, 123.1, 122.9, 121.9, 112.8, 112.82, 81.8, 67.5, 38.6, 28.6, 26.3; MS (ESI^+): *m/z* 280 $[M+H]^+$; HR-MS (ESI^+): *m/z* 280.0332 $[M+H]^+$, calcd. for $C_{13}H_{14}BrNO$: *m/z* 280.0337.

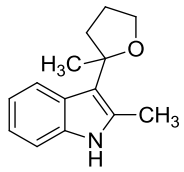
Compound **2.9n**: 

Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.28 (d, *J* = 5.1 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.09 (s, *J* = 2.2 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.95–4.08 (m,

2H), 3.89 (s, 3H), 2.40–2.44 (m, 1H), 2.01–2.07 (m, 2H), 1.96–2.00 (m, 1H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 132.5, 125.7, 122.7, 121.5, 112.1, 111.9, 102.9, 82.0, 67.5, 56.3, 38.4, 28.5, 26.3; MS (ESI^+): *m/z* 232 $[M+H]^+$; HR-MS (ESI^+): *m/z* 232.1334 $[M+H]^+$, calcd. for $C_{14}H_{17}NO_2$: *m/z* 232.1338.

Compound **2.9o**: 

Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 1.7 Hz, 1H), 8.43 (br s, 1H), 8.11 (d, *J* = 6.9 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.25–7.26 (m, 1H), 3.97–4.08 (m, 2H), 2.34–2.38 (m, 1H), 2.08–2.14 (m, 2H), 1.96–1.99 (m, 1H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 140.3, 125.9, 124.7, 123.8, 117.9, 117.7, 111.5, 81.7, 67.6, 38.9, 28.7, 26.3; MS (ESI^+): *m/z* 247 $[M+H]^+$; HR-MS (ESI^+): *m/z* 247.1071 $[M+H]^+$, calcd. for $C_{13}H_{14}NO_3$: *m/z* 247.1083.

Compound **2.9p**: 

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (br s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.03–7.10 (m, 2H), 3.98–4.04 (m, 1H), 3.85–3.90 (m, 1H), 2.52 (s, 3H), 2.43–2.49 (m, 1H), 2.11–2.15 (m, 1H), 1.97–2.04 (m, 1H), 1.84–1.92 (m, 1H), 1.64 (s, 3H); MS (ESI^+): *m/z* 216 $[M+H]^+$.

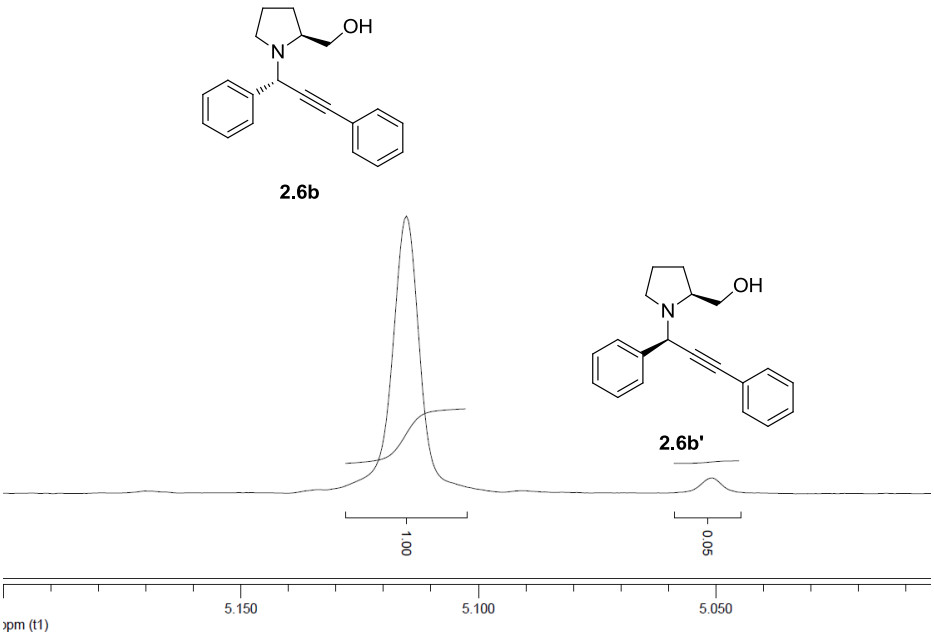
Recyclability Experiment of Gold(III) Catalysts in Synthesis of Propargylamine 2.6a via Three-Component Coupling Reaction

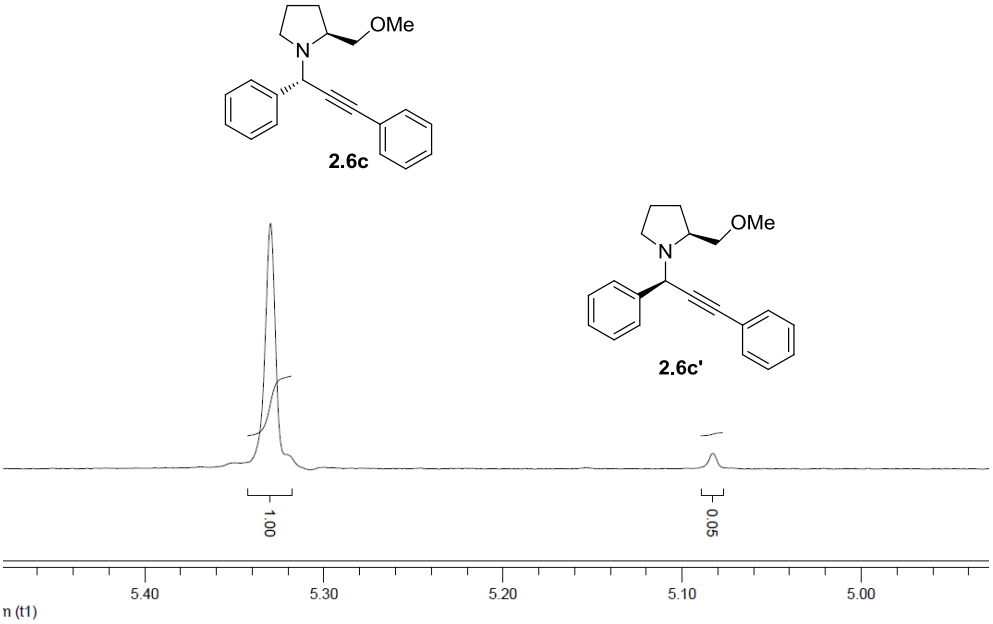
A mixture of cyclometallated gold(III) complex **2.1** or $KAuCl_4$ (1 mol %), benzaldehyde **2.3a** (1 mmol), piperidine **2.4a** (1.1 mmol) and phenylacetylene **2.5a** (1.5 mmol) in water (1 mL) was stirred at 40 ^{o}C for 24 h. After 24 h, the substrate conversion based on benzaldehyde was determined by ^{1}H NMR analysis of an aliquot of reaction mixture taken out from the reaction flask. An additional portion of starting materials was added into the reaction mixture. The reaction was conducted for an additional 24 h.

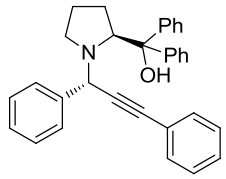
Recyclability Experiment of Gold(III) Catalysts in Synthesis of Alkylated Indole 2.9a

A mixture of alkynyl alcohol **2.7a** (0.24 mmol), indole **2.8a** (0.2 mmol), gold complex **2.1** (2.5 mol %), AgBF4 (5 mol %) and 1,3,5-trimethoxylbenzene (0.2 mmol) in CD_2Cl_2 (2 mL) were stirred at room temperature for 2 h. After 2 h, the substrate conversion was determined by ^{1}H NMR analysis based on the relative peak intensities of product and 1,3,5-trimethoxylbenzene. Another batch of substrates was added for the next cycle of experiments. The reaction was conducted for an additional 2 h. AgBF4 (5 mol %) was added at the 6th and 11th cycles.

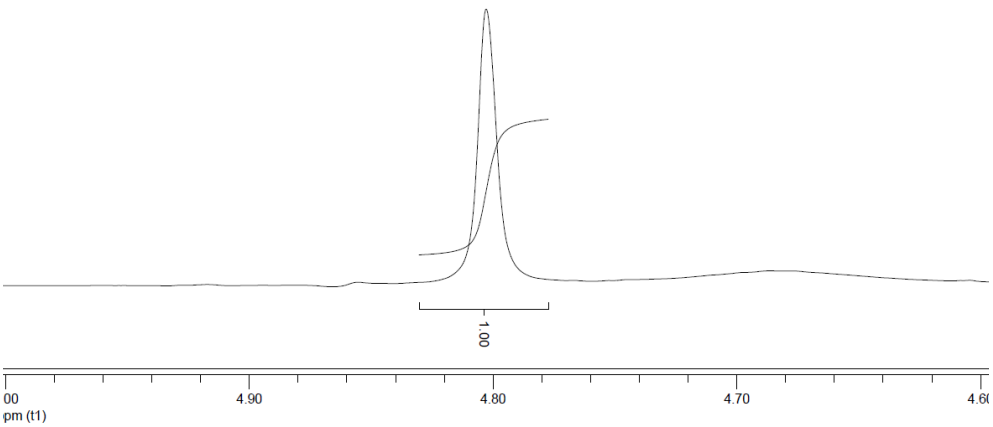
^{1}H NMR Spectra of Diastereomers of Propargylamines in Crude Reaction Mixture (Table 2.3)

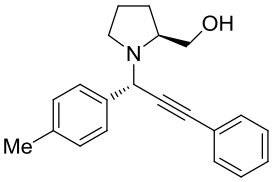




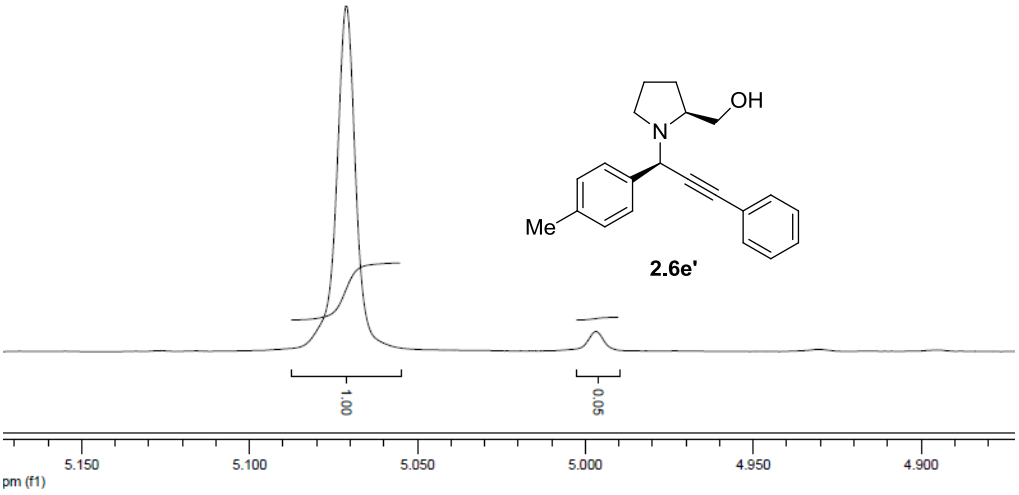


2.6d

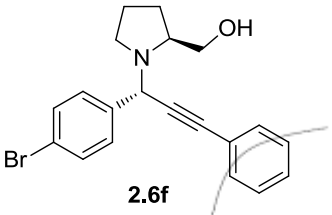




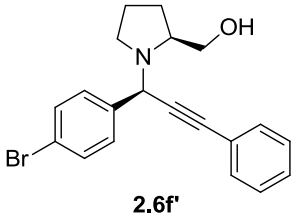
2.6e



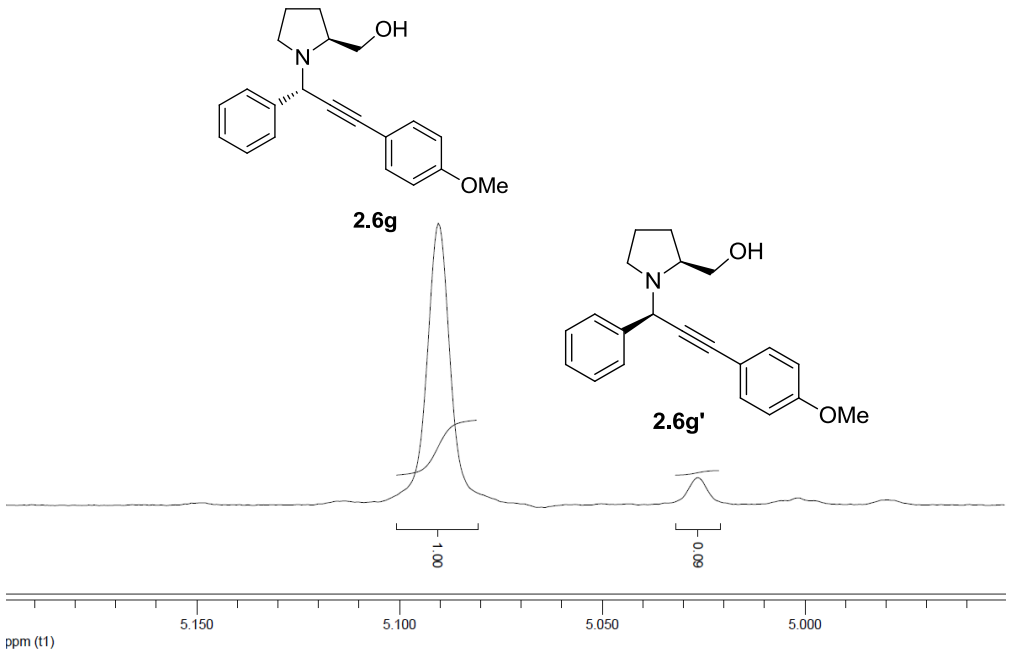
2.6e'

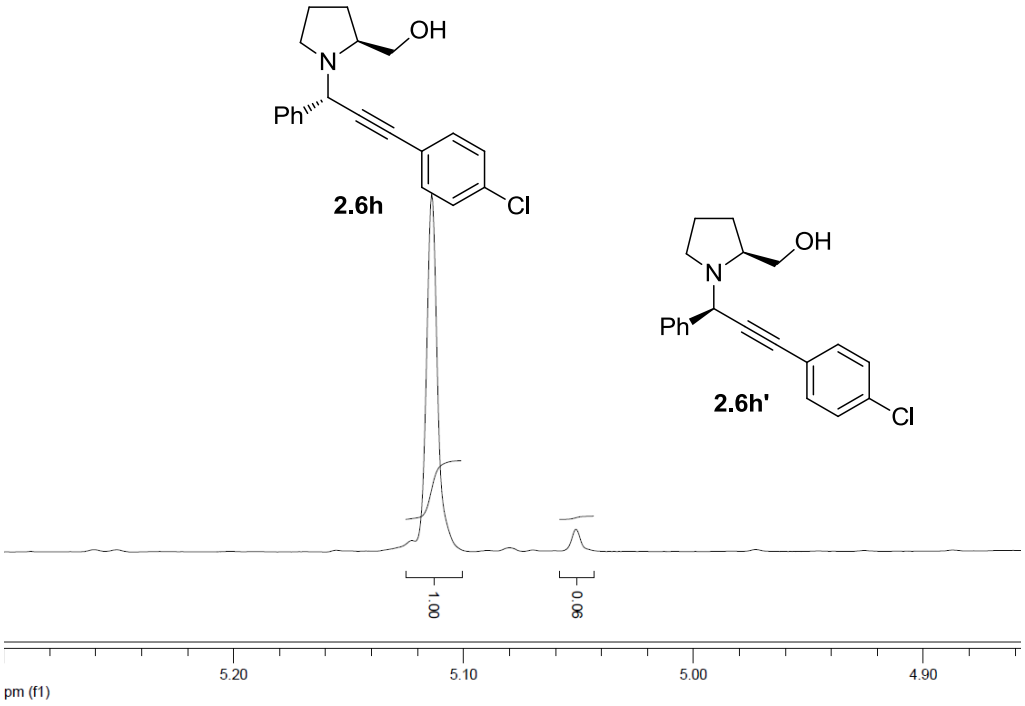


2.6f

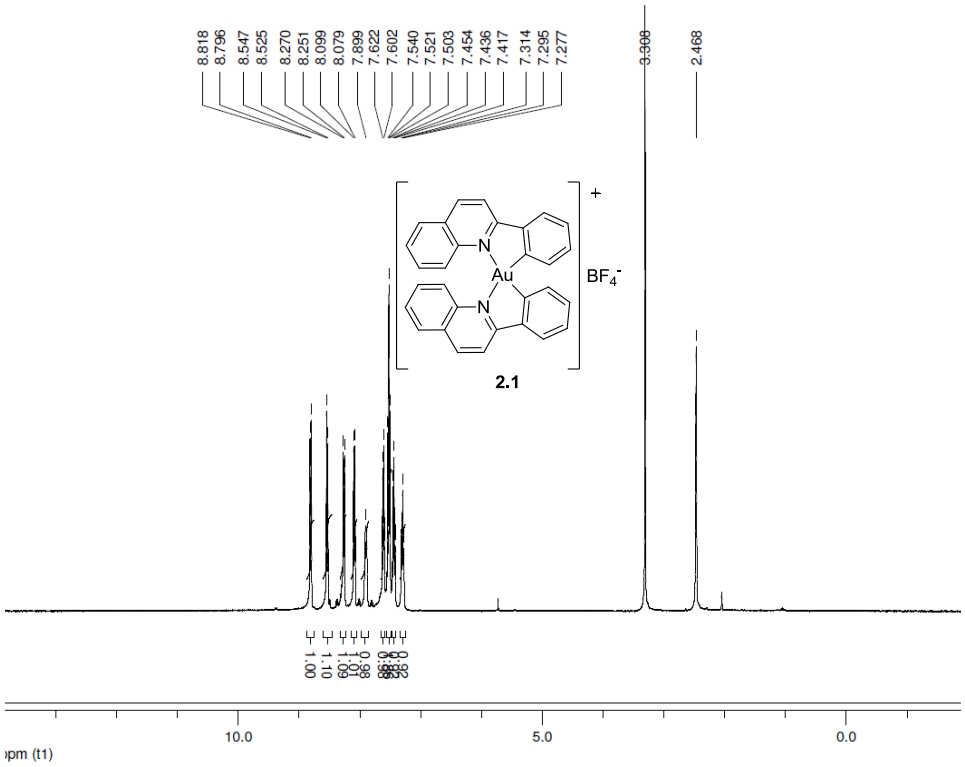


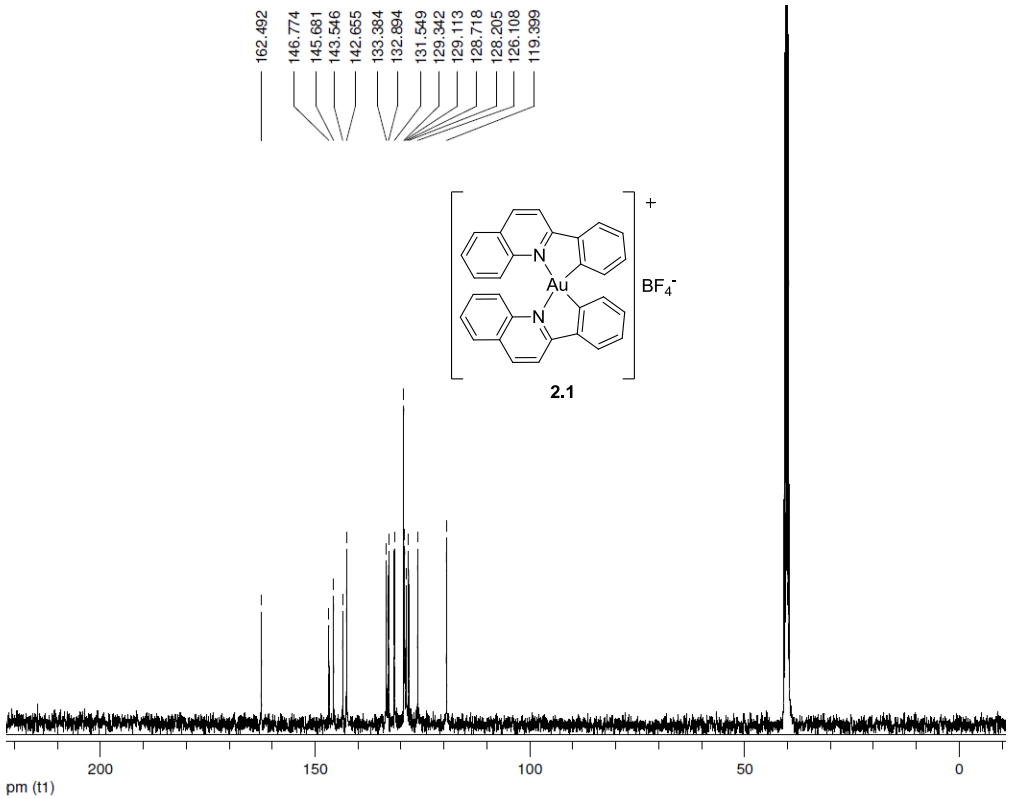
2.6f'

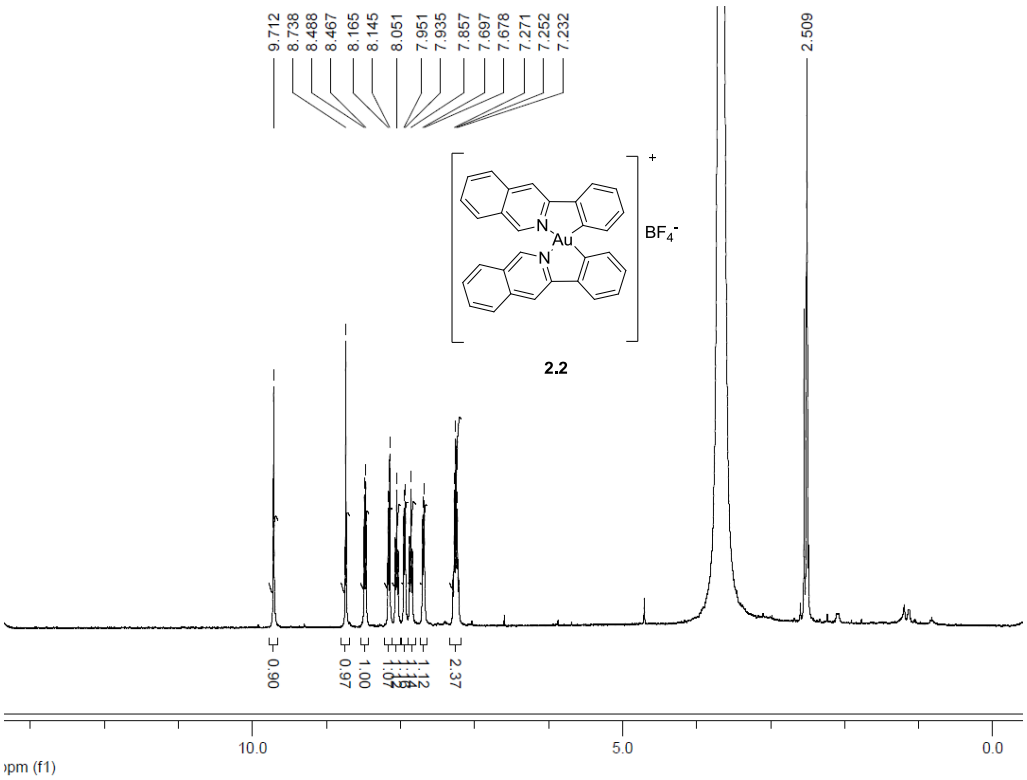

OH
N
OMe
2.6g
OH
N
OMe
2.6g'
1.00
0.09
5.150
5.100
5.050
5.000
ppm (t1)

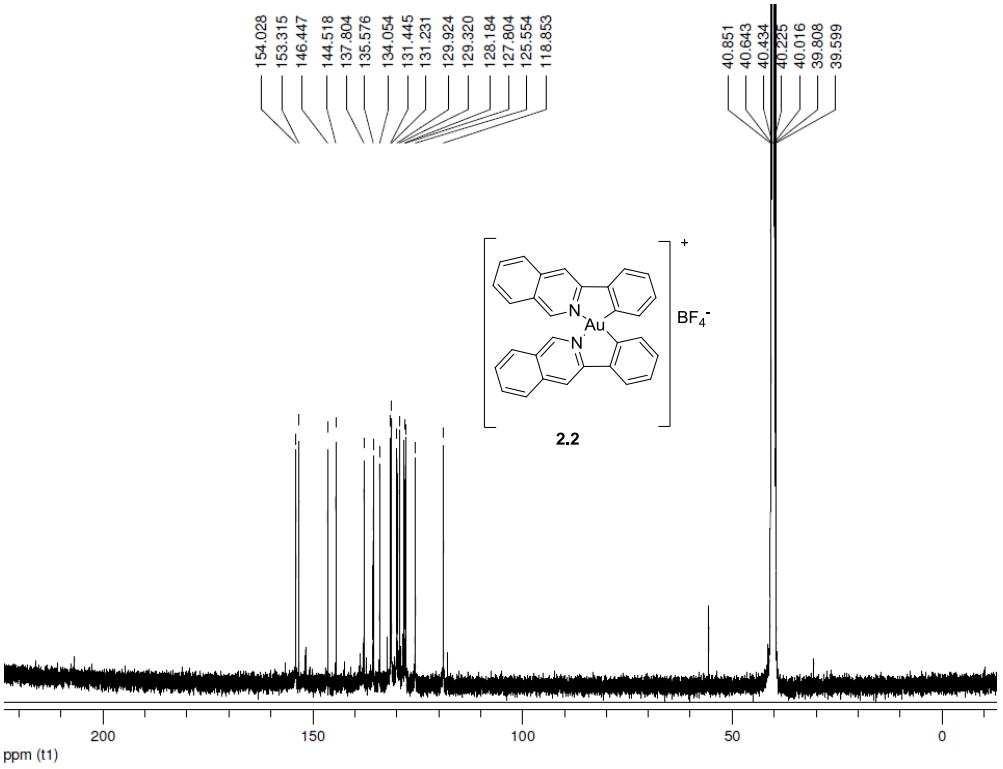

OH
N
Ph
Cl
2.6h
OH
N
Ph
2.6h'
Cl
1.00
0.06
5.20
5.10
5.00
4.90
pm (f1)

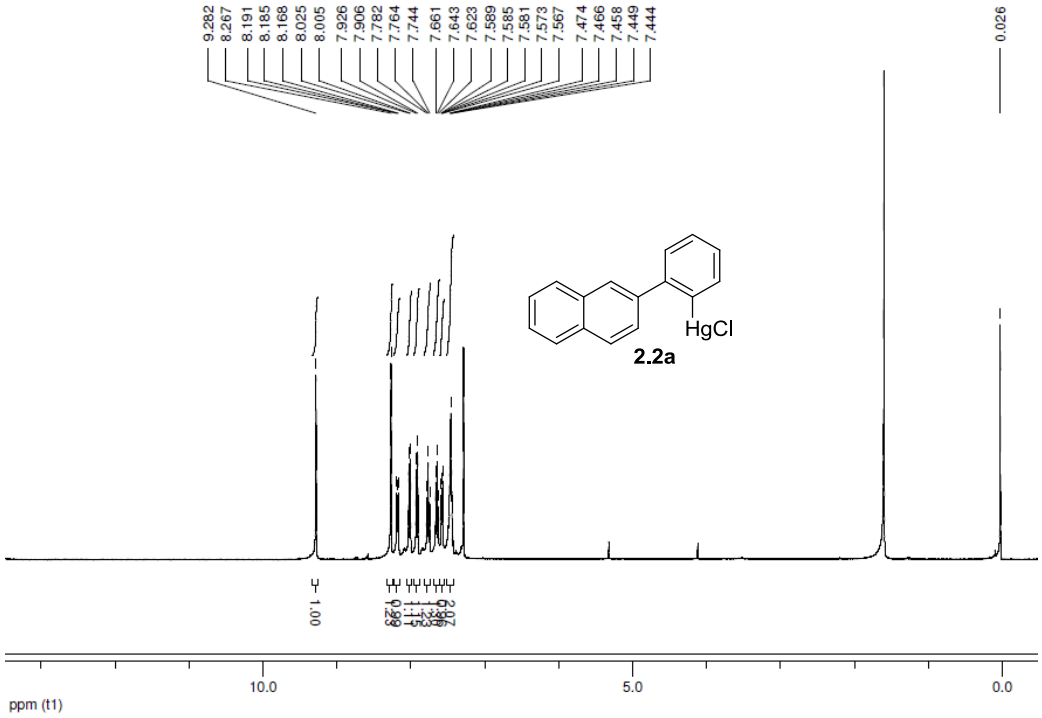
NMR Spectra

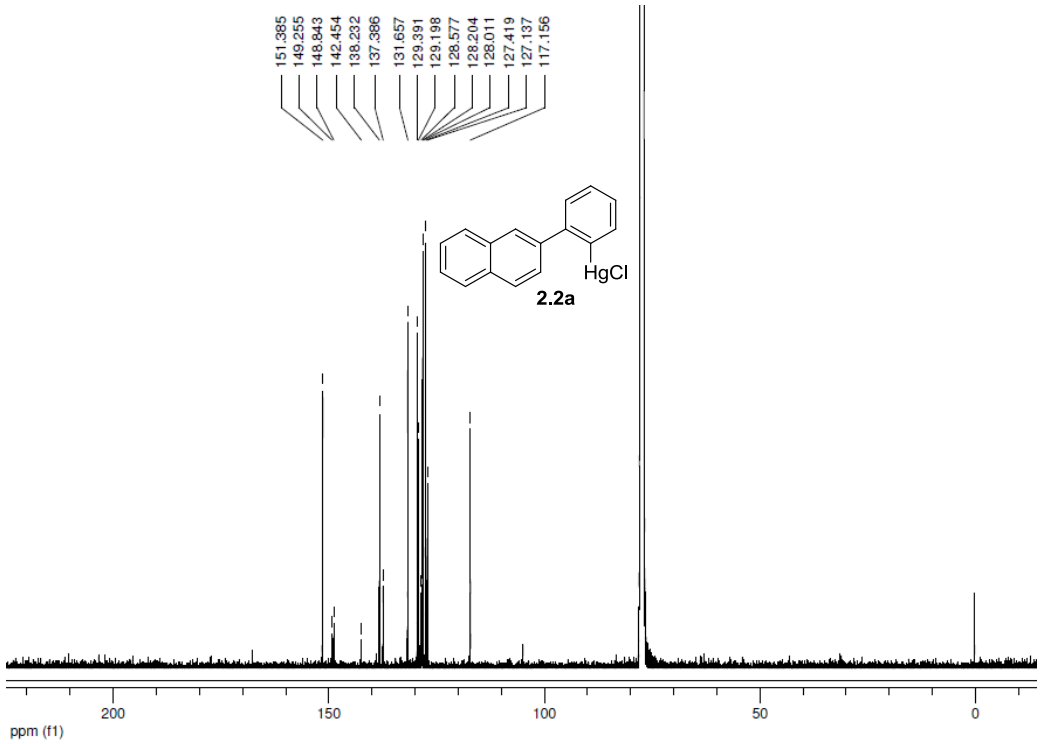

8.818
8.796
8.547
8.525
8.270
8.251
8.099
8.079
7.899
7.622
7.602
7.540
7.521
7.503
7.454
7.436
7.417
7.314
7.295
7.277
3.308
2.468
N
Au
N
BF4-
+
2.1
10.0
5.0
0.0
ppm (t1)

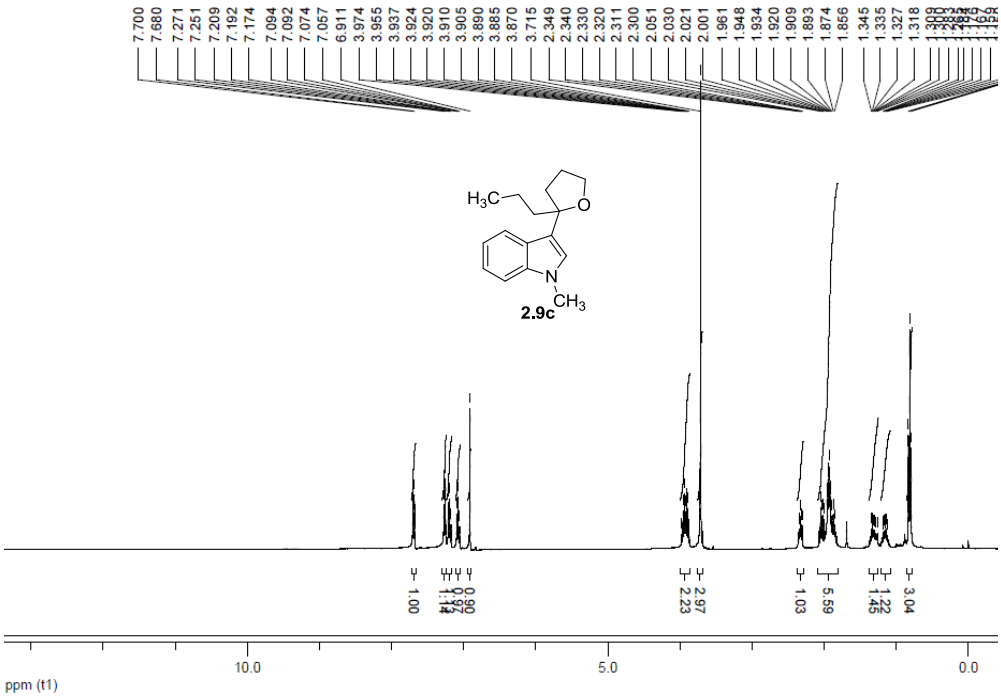

162.492
146.774
145.681
143.546
142.655
133.384
132.894
131.549
129.342
129.113
128.718
128.205
126.108
119.399
N
Au
N
BF4-
+
2.1
200
150
100
50
0
ppm (t1)

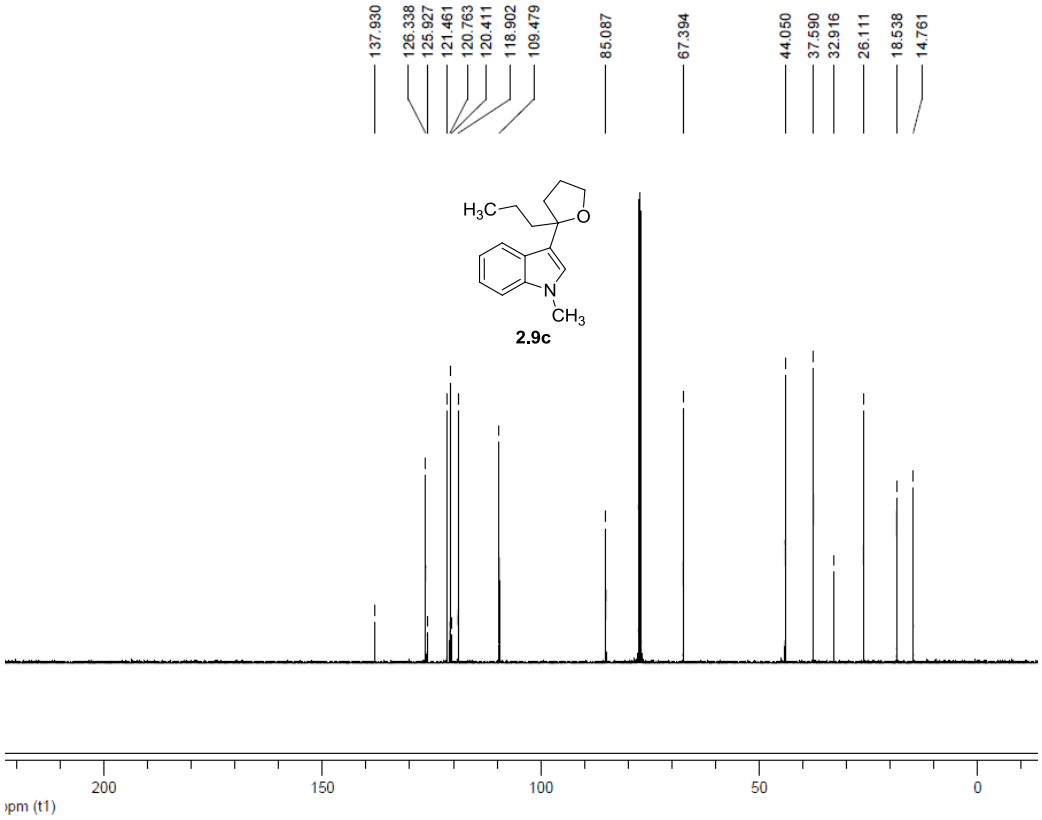

9.712
8.738
8.488
8.467
8.165
8.145
8.051
7.951
7.935
7.857
7.697
7.678
7.271
7.252
7.232
2.509
N
Au
N
BF4-
+
2.2
0.90
0.97
1.00
2.37
10.0
5.0
0.0
ppm (f1)

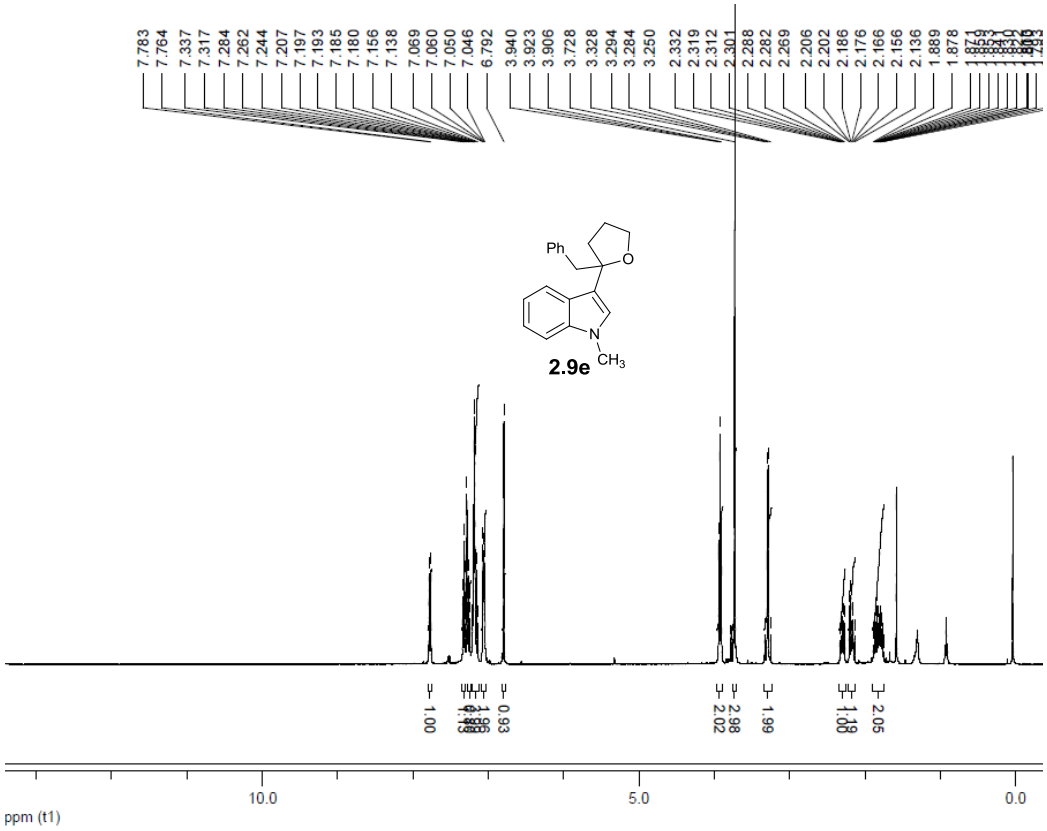

154.028
153.315
146.447
144.518
137.804
135.576
134.054
131.445
131.231
129.924
129.320
128.184
127.804
125.554
118.853
40.851
40.643
40.434
40.225
40.016
39.808
39.599
N
Au
N
BF4-
+
2.2
200
150
100
50
0
ppm (t1)

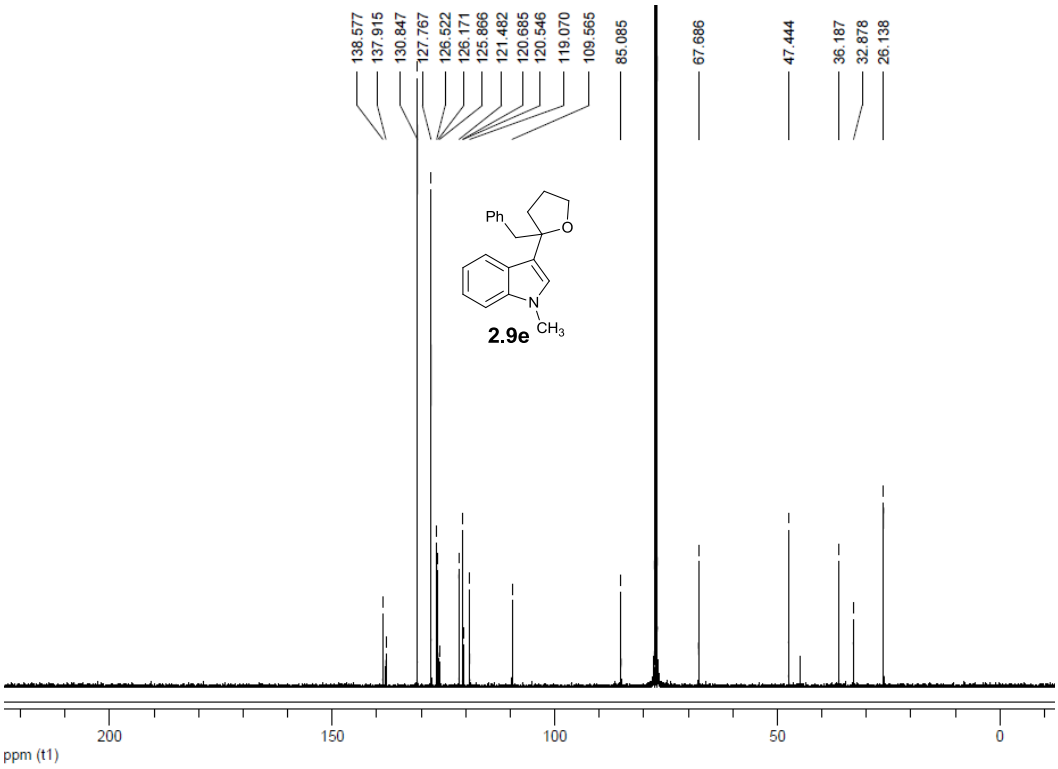

9.282
8.267
8.191
8.185
8.168
8.025
8.005
7.926
7.906
7.782
7.764
7.744
7.661
7.643
7.623
7.589
7.585
7.581
7.573
7.567
7.474
7.466
7.458
7.449
7.444
0.026
HgCl
2.2a
1.00
10.0
5.0
0.0
ppm (t1)

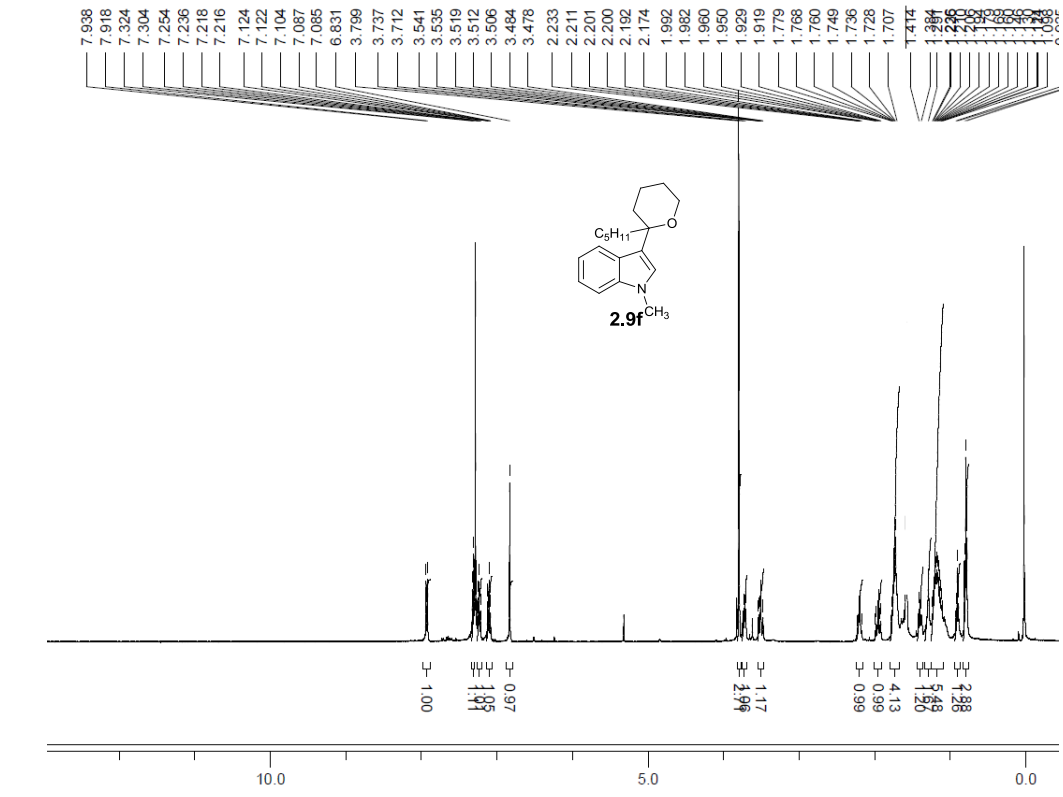

151.385
149.255
148.843
142.454
138.232
137.386
131.657
129.391
129.198
128.577
128.204
128.011
127.419
127.137
117.156
HgCl
2.2a
200
150
100
50
0
ppm (f1)

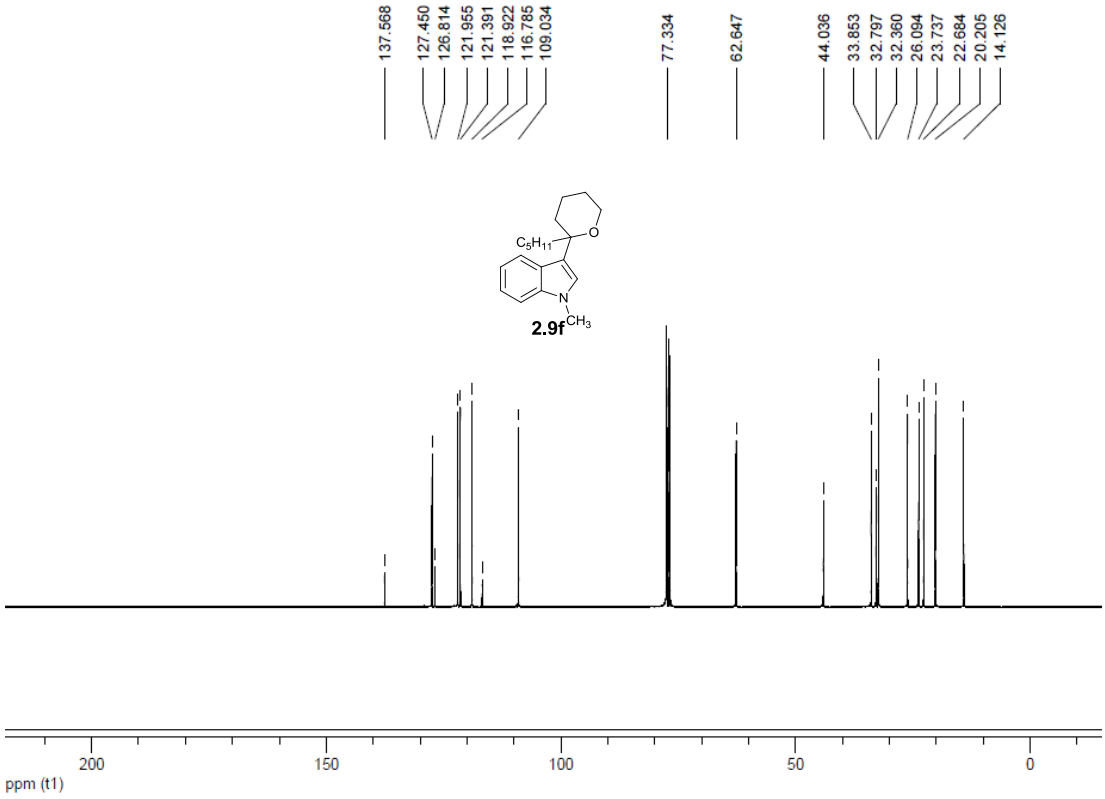

7.700
7.680
7.271
7.251
7.209
7.192
7.174
7.094
7.092
7.074
7.057
6.911
3.974
3.955
3.937
3.924
3.920
3.910
3.905
3.890
3.885
3.870
3.715
2.349
2.340
2.330
2.320
2.311
2.300
2.051
2.030
2.021
2.001
1.961
1.948
1.934
1.920
1.909
1.893
1.874
1.856
1.345
1.335
1.327
1.318
H3C
O
N
CH3
2.9c
1.00
0.90
2.23
2.97
1.03
6.59
1.22
3.04
10.0
5.0
0.0
ppm (t1)

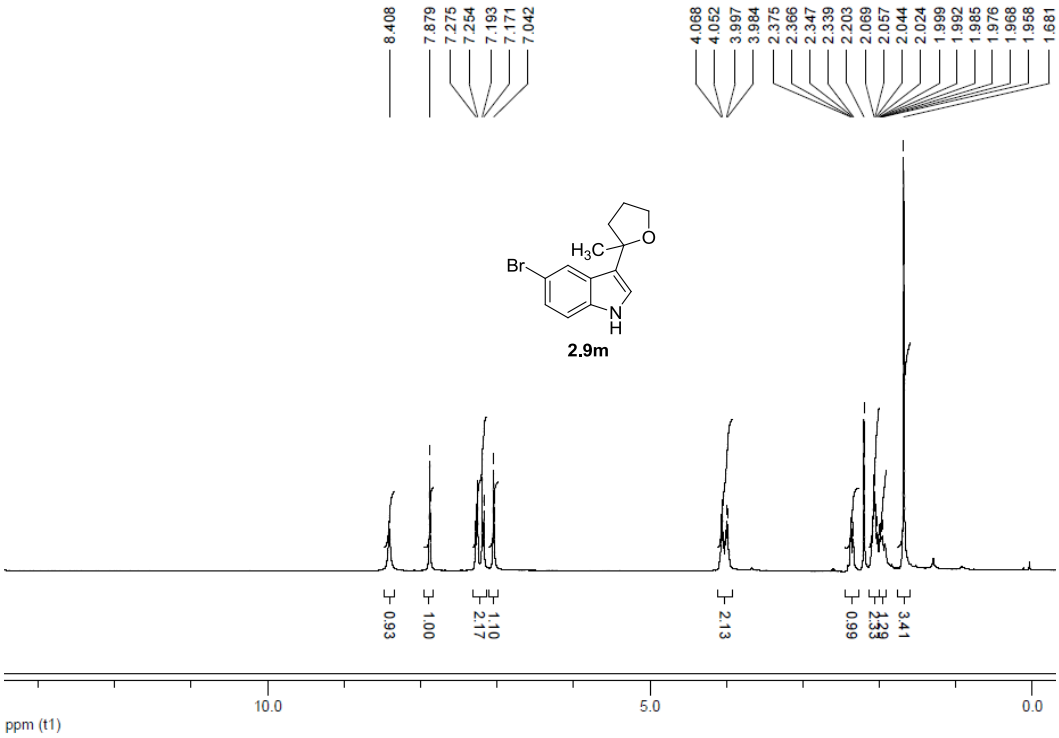

137.930
126.338
125.927
121.461
120.763
120.411
118.902
109.479
85.087
67.394
44.050
37.590
32.916
26.111
18.538
14.761
H3C
O
N
CH3
2.9c
200
150
100
50
0
ppm (t1)

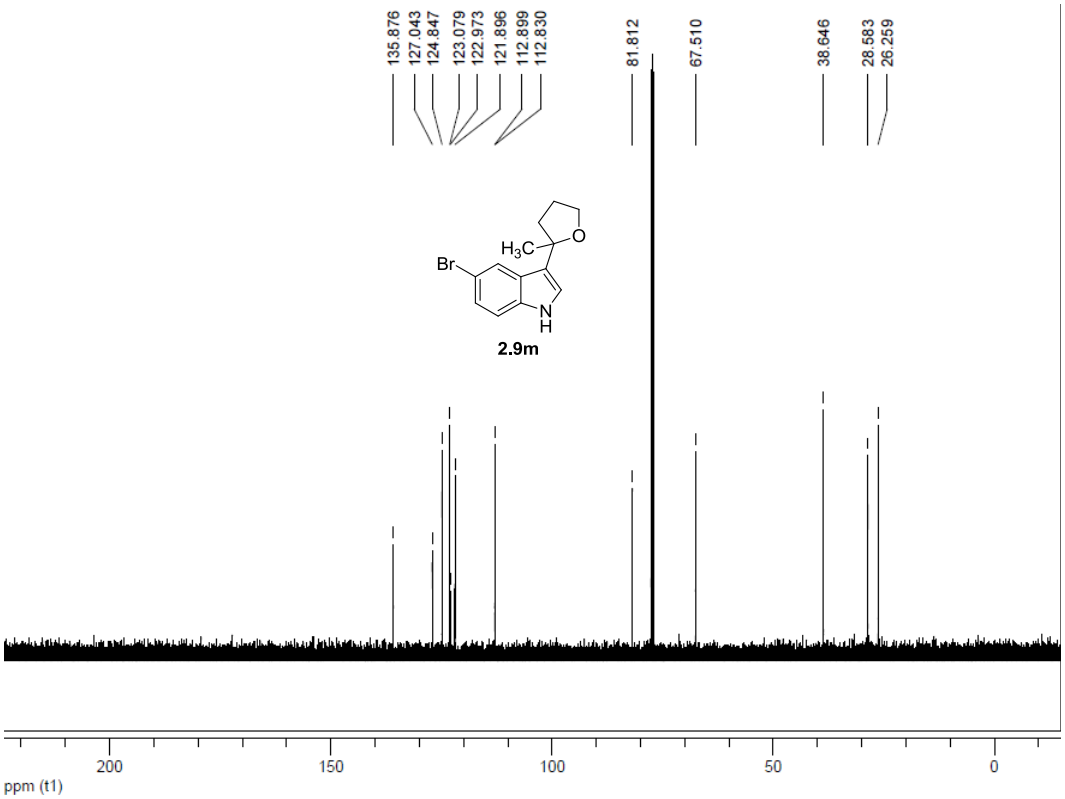

7.783
7.764
7.337
7.317
7.284
7.262
7.244
7.207
7.197
7.193
7.185
7.180
7.156
7.138
7.069
7.060
7.050
7.046
6.792
3.940
3.923
3.906
3.728
3.328
3.294
3.284
3.250
2.332
2.319
2.312
2.301
2.288
2.282
2.269
2.206
2.202
2.186
2.176
2.166
2.156
2.136
1.889
1.878
1.871
Ph
O
N
CH3
2.9e
1.00
0.93
2.02
1.99
1.00
2.05
10.0
5.0
0.0
ppm (t1)

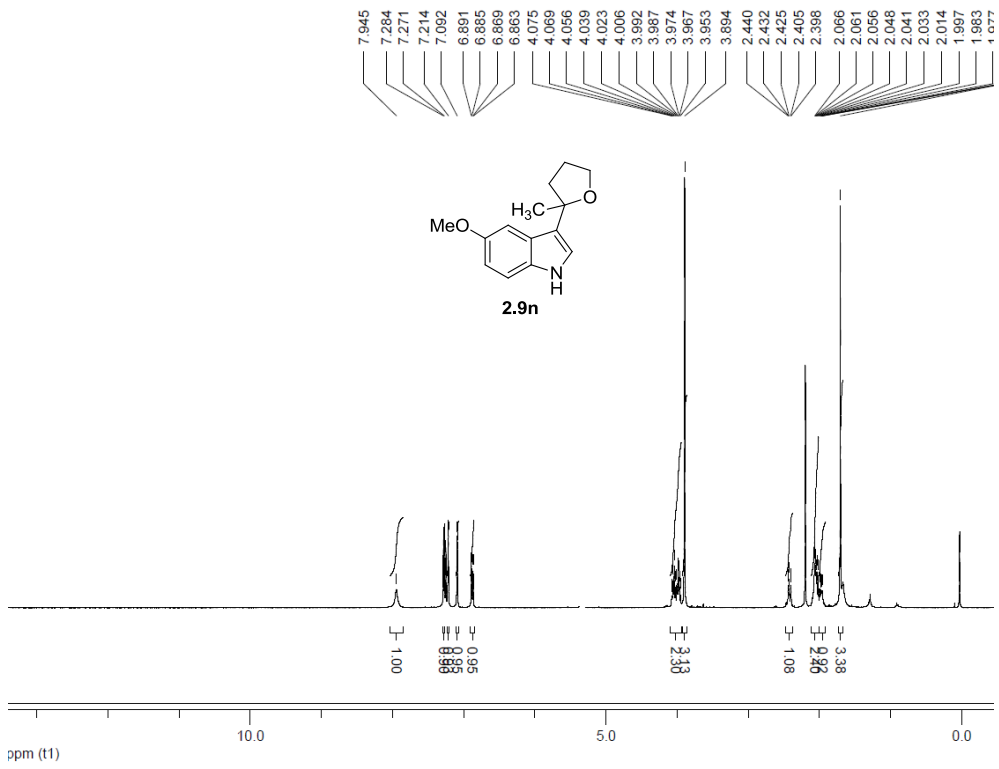

138.577
137.915
130.847
127.767
126.522
126.171
125.866
121.482
120.685
120.546
119.070
109.565
85.085
67.686
47.444
36.187
32.878
26.138
Ph
O
N
CH3
2.9e
200
150
100
50
0
ppm (t1)

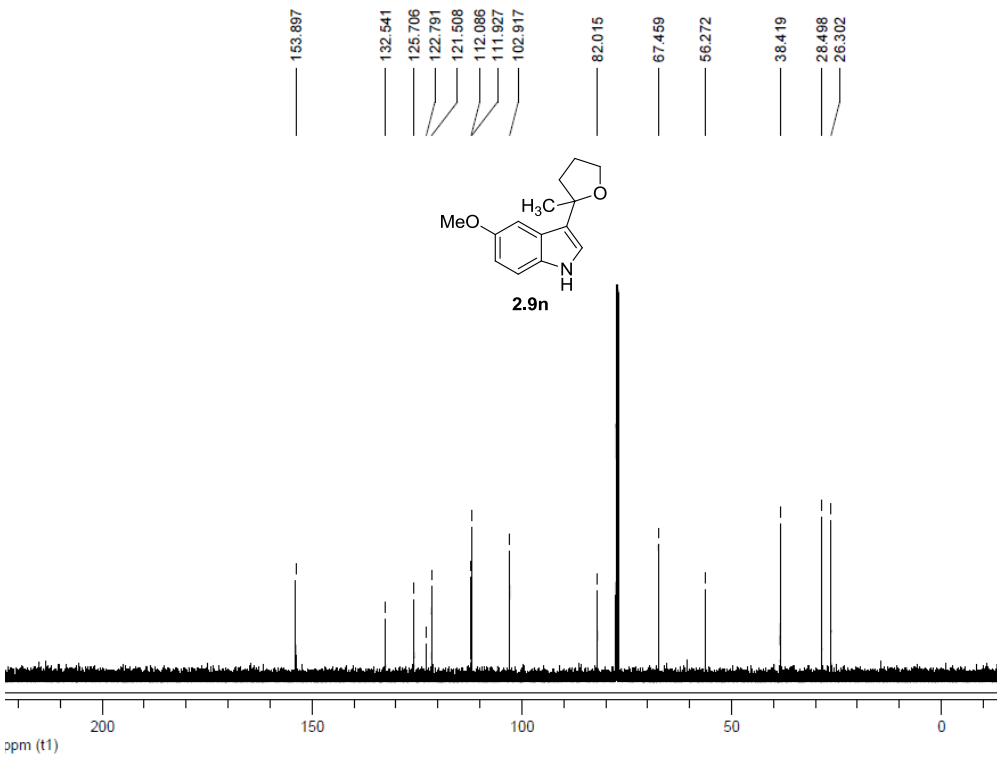

7.938
7.918
7.324
7.304
7.254
7.236
7.218
7.216
7.124
7.122
7.104
7.087
7.085
6.831
3.799
3.737
3.712
3.541
3.535
3.519
3.512
3.506
3.484
3.478
2.233
2.211
2.201
2.200
2.192
2.174
1.992
1.982
1.960
1.950
1.929
1.919
1.779
1.768
1.760
1.749
1.736
1.728
1.707
1.414
C5H11
O
N
CH3
2.9f
1.00
0.97
1.17
0.99
0.99
4.13
2.88
10.0
5.0
0.0

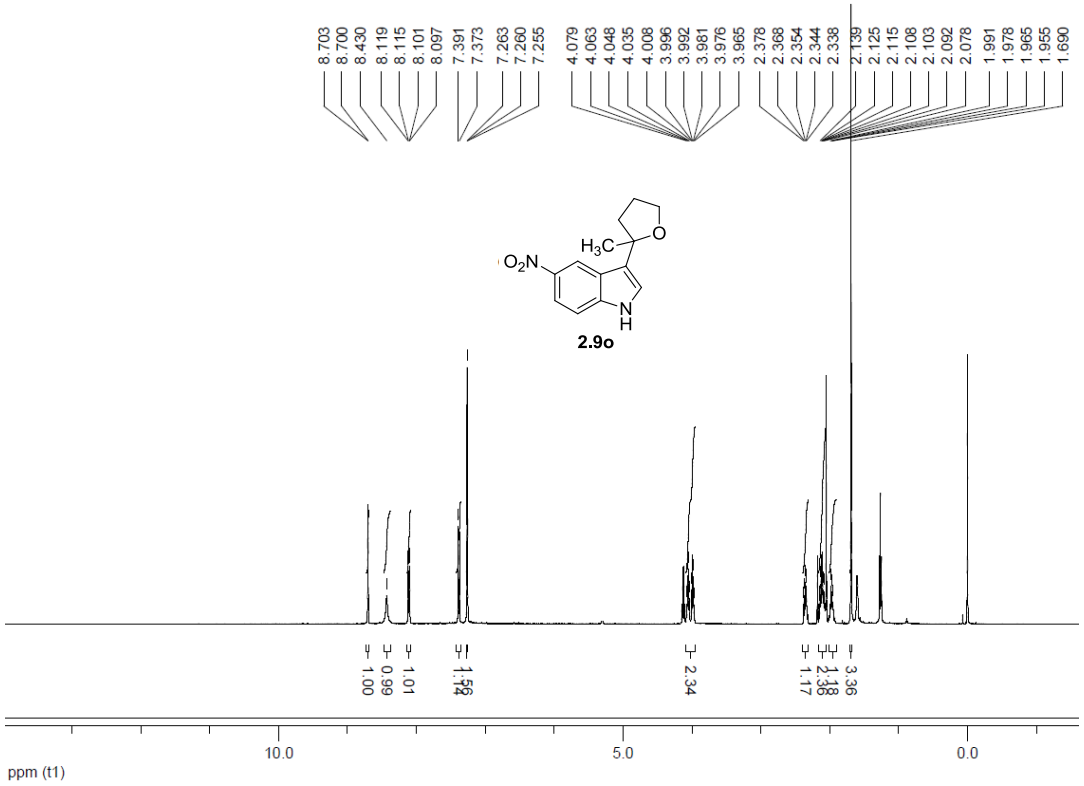

137.568
127.450
126.814
121.955
121.391
118.922
116.785
109.034
77.334
62.647
44.036
33.853
32.797
32.360
26.094
23.737
22.684
20.205
14.126
C5H11
O
N
CH3
2.9f
200
150
100
50
0
ppm (t1)

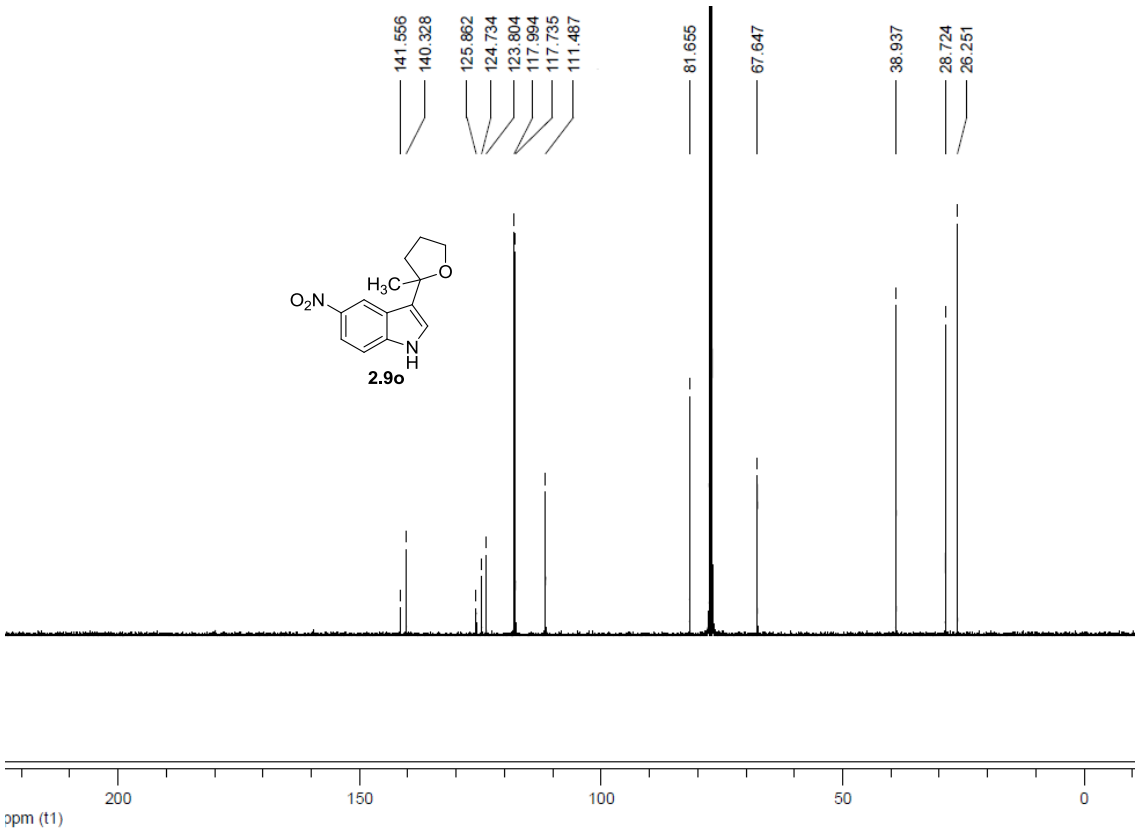

8.408
7.879
7.275
7.254
7.193
7.171
7.042
4.068
4.052
3.997
3.984
2.375
2.366
2.347
2.339
2.203
2.069
2.057
2.044
2.024
1.999
1.992
1.985
1.976
1.968
1.958
1.681
Br
H3C
O
N
H
2.9m
0.93
1.00
2.17
1.10
2.13
0.99
1.23
1.33
3.41
10.0
5.0
0.0
ppm (t1)


135.876
127.043
124.847
123.079
122.973
121.896
112.899
112.830
81.812
67.510
38.646
28.583
26.259
Br
H3C
O
N
H
2.9m
200
150
100
50
0
ppm (t1)


7.945
7.284
7.271
7.214
7.092
6.891
6.885
6.869
6.863
4.075
4.069
4.056
4.039
4.023
4.006
3.992
3.987
3.974
3.967
3.953
3.894
2.440
2.432
2.425
2.405
2.398
2.066
2.061
2.056
2.048
2.041
2.033
2.014
1.997
1.983
MeO
H3C
O
N
H
2.9n
1.00
0.96
3.13
1.08
3.38
10.0
5.0
0.0
ppm (t1)


153.897
132.541
125.706
122.791
121.508
112.086
111.927
102.917
82.015
67.459
56.272
38.419
28.498
26.302
MeO
H3C
O
N
H
2.9n
200
150
100
50
0
ppm (t1)


8.703
8.700
8.430
8.119
8.115
8.101
8.097
7.391
7.373
7.263
7.260
7.255
4.079
4.063
4.048
4.035
4.008
3.996
3.992
3.981
3.976
3.965
2.378
2.368
2.354
2.344
2.338
2.139
2.125
2.115
2.108
2.103
2.092
2.078
1.991
1.978
1.965
1.955
1.690
H_3C
O
O_2N
N
H
2.9o
1.00
0.99
1.01
1.54
1.55
2.34
1.17
3.36
3.38
3.36
10.0
5.0
0.0
ppm (t1)


141.556
140.328
125.862
124.734
123.804
117.994
117.735
111.487
81.655
67.647
38.937
28.724
26.251
H_3C
O
O_2N
N
H
2.9o
200
150
100
50
0
ppm (t1)

2.6 References

[1] (a) Gorin, D. J.; Toste, F. D., *Nature* **2007**, *446*, 395–403; (b) Hashmi, A. S. K., **2007**, *107*, 3180−3211; (c) Li, Z.; Brouwer, C.; He, C., *Chem. Rev.* **2008**, *108*, 3239–3265; (d) Corma, A.; Leyva-Pérez, A.; Sabater, M. J., *Chem. Rev.* **2011**, *111*, 1657–1712.

[2] (a) Dyker, G.; Hildebrandt, D.; Liu, J. H.; Merz, K., *Angew. Chem. Int. Ed.* **2003**, *42*, 4399–4402; (b) Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L., *Adv. Synth. Catal.* **2003**, *345*, 1247–1252; (c) Shi, Z.; He, C., *J. Am. Chem. Soc.* **2004**, *126*, 13596–13597; (d) Georgy, M.; Boucard, V.; Campagne, J. M., *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181; (e) Engel, D. A.; Dudley, G. B., *Org. Lett.* **2006**, *8*, 4027–4029; (f) Krause, N.; Winter, C., *Chem. Rev.* **2011**, *111*, 1994–2009.

[3] (a) Miyaura, N.; Suzuki, A., *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Beletskaya, I. P.; Cheprakov, A. V., *Chem. Rev.* **2000**, *100*, 3009–3066; (c) Littke, A. F.; Fu, G. C., *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211; (d) Cacchi, S.; Fabrizi, G., *Chem. Rev.* **2005**, *105*, 2873–2920; (e) Lyons, T. W.; Sanford, M. S., *Chem. Rev.* **2010**, *110*, 1147–1169.

[4] (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N., *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580; (b) Fagnou, K.; Lautens, M., *Chem. Rev.* **2003**, *103*, 169–196; (c) Hayashi, T.; Yamasaki, K., *Chem. Rev.* **2003**, *103*, 2829–2844; (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A., *Chem. Rev.* **2009**, *110*, 624–655.

[5] (a) Zhang, L.; Sun, J.; Kozmin, S. A., *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; (b) Fürstner, A.; Davies, P. W., *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; (c) Fürstner, A., *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

[6] (a) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W., *Eur. J. Org. Chem.* **2006**, 1387–1389; (b) Aguilar, D.; Contel, M.; Navarro, R.; Urriolabeitia, E. P., *Organometallics*

2007, *26*, 4604–4611; (c) Gorin, D. J.; Sherry, B. D.; Toste, F. D., *Chem. Rev.* **2008**, *108*, 3351–3378; (d) Aguilar, D.; Contel, M.; Navarro, R.; Soler, T.; Urriolabeitia, E. P., *J. Organomet. Chem.* **2009**, *694*, 486–493; (e) Schmidbaur, H.; Schier, A., *Arabian J. Sci. Eng.* **2012**, *37*, 1187–1225.

[7] (a) Mauleón, P.; Zeldin, R. M.; González, A. Z.; Toste, F. D., *J. Am. Chem. Soc.* **2009**, *131*, 6348–6349; (b) Shapiro, N. D.; Toste, F. D., *Synlett* **2010**, *21*, 675–691; (c) Toste, F. D., *Synlett* **2012**, *23*, 46–48; (d) Wang, W.; Hammond, G. B.; Xu, B., *J. Am. Chem. Soc.* **2012**, *134*, 5697–5705; (e) Jaimes, M. C. B.; Bo¨hling, C. R. N.; Serrano-Becerra, J. M.; Hashmi, A. S. K., *Angew. Chem., Int. Ed.* **2013**, *52*, 7963–7966.

[8] Nolan, S. P., *Acc. Chem. Res.* **2010**, *44*, 91–100.

[9] Alvarado, E.; Badaj, A. C.; Larocque, T. G.; Lavoie, G. G., *Chem. Eur. J.* **2012**, *18*, 12112–12121.

[10] (a) Trost, B. M.; Van Vranken, D. L.; Bingel, C., *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343; (b) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R., *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920; (c) Miura, M., *Angew. Chem. Int. Ed.* **2004**, *43*, 2201–2203; (d) Surry, D. S.; Buchwald, S. L., *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361.

[11] Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M., *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406.

[12] (a) Schwerdtfeger, P.; Hermann, H. L.; Schmidbaur, H., *Inorg. Chem.* **2003**, *42*, 1334–1342; (b) Gorin, D. J.; Toste, F. D., *Nature* **2007**, *446*, 395–403.

[13] Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D., *Science* **2007**, *317*, 496–499.

[14] (a) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E., *Angew. Chem. Int. Ed.* **2004**, *43*, 6545–6547; (b) Hashmi, A. S. K.; Rudolph, M.; Weyrauch, J. P.; Wölfle, M.;

Frey, W.; Bats, J. W., *Angew. Chem. Int. Ed.* **2005**, *44*, 2798–2801; (c) Debono, N.; Iglesias, M.; Sánchez, F., *Adv. Synth. Catal.* **2007**, *349*, 2470–2476; (d) Hashmi, A. S. K.; Rudolph, M.; Siehl, H. U.; Tanaka, M.; Bats, J. W.; Frey, W., *Chem. Eur. J.* **2008**, *14*, 3703–3708; (e) Shapiro, N. D.; Shi, Y.; Toste, F. D., *J. Am. Chem. Soc.* **2009**, *131*, 11654–11655; (f) O'Neill, J. A.; Rosair, G. M.; Lee, A. L., *Catal. Sci. Technol.* **2012**, *2*, 1818–1821; (g) Zhang, Y.; Feng, B.; Zhu, C., *Org. Biomol. Chem.* **2012**, *10*, 9137–9141.

[15] (a) Buckley, R. G.; Elsome, A. M.; Fricker, S. P.; Henderson, G. R.; Theobald, B. R. C.; Parish, R. V.; Howe, B. P.; Kelland, L. R., *J. Med. Chem.* **1996**, *39*, 5208–5214; (b) Parish, R. V.; Howe, B. P.; Wright, J. P.; Mack, J.; Pritchard, R. G.; Buckley, R. G.; Elsome, A. M.; Fricker, S. P., *Inorg. Chem.* **1996**, *35*, 1659–1666; (c) Parish, R. V.; Mack, J.; Hargreaves, L.; Wright, J. P.; Buckley, R. G.; Elsome, A. M.; Fricker, S. P.; Theobald, B. R. C., *Dalton Trans.* **1996**, 69–74; (d) Fricker, S. P.; Mosi, R. M.; Cameron, B. R.; Baird, I.; Zhu, Y.; Anastassov, V.; Cox, J.; Doyle, P. S.; Hansell, E.; Lau, G.; Langille, J.; Olsen, M.; Qin, L.; Skerlj, R.; Wong, R. S. Y.; Santucci, Z.; McKerrow, J. H., *Inorg. Biochem* **2008**, *102*, 1839–1845; (e) Albrecht, M., *Chem. Rev.* **2010**, *110*, 576–623; (f) Bertrand, B.; Casini, A., *Dalton Trans.* **2014**, *43*, 4209–4219; (g) Engman, L.; McNaughton, M.; Gajewska, M.; Kumar, S.; Birmingham, A.; Powis, G., *Anti-cancer Drugs* **2006**, *17*, 539–544; (h) Zhu, Y.; Cameron, B. R.; Mosi, R.; Anastassov, V.; Cox, J.; Qin, L.; Santucci, Z.; Metz, M.; Skerlj, R. T.; Fricker, S. P., *J. Inorg. Biochem.* **2011**, *105*, 754–762.

[16] Constable, E. C.; Leese, T. A., *J. Organomet. Chem.* **1989**, *363*, 491–424.

[17] Parish, R. V., *Metal-Based Drugs* **1999**, *6*, 271–276.

[18] (a) Constable, E. C.; Henney, R. P. G.; Leese, T. A.; Tocher, D. A., *J. Chem. Soc., Dalton Trans.* **1990**, 443–449; (b) Cinellu, M. A.; Zucca, A.; Stoccoro, S.; Minghetti, G.;

Manassero, M.; Sansoni, M., *J. Chem. Soc., Dalton Trans.* **1995**, 2865–2872; (c) Cinellu, M. A.; Zucca, A.; Stoccoro, S.; Minghetti, G.; Manassero, M.; Sansoni, M., *J. Chem. Soc., Dalton Trans.* **1996**, 4217–4225.

[19] (a) Wong, K. H.; Cheung, K. K.; Chan, M. C. W.; Che, C. M., *Organometallics* **1998**, *17*, 3505–3511; (b) Yam, V. W. W.; Wong, K. M. C.; Hung, L. L.; Zhu, N. Y., *Angew. Chem., Int. Ed.* **2005**, *44*, 3107–3110; (c) Garg, J. A.; Blacque, O.; Venkatesan, K., *Inorg. Chem.* **2011**, *50*, 5430–5441; (d) Rosca, D. A.; Smith, D. A.; Bochmann, M., *Chem. Commun.* **2012**, 7247–7249.

[20] To, W. P.; Tong, G. S. M.; Lu, W.; Ma, C.; Liu, J.; Chow, A. L. F.; Che, C. M., *Angew. Chem. Int. Ed.* **2012**, *51*, 2654–2657.

[21] Lo, V. K. Y.; Liu, Y. G.; Wong, M. K.; Che, C. M., *Org. Lett.* **2006**, *8*, 1529–1532.

[22] Lo, V. K. Y.; Kung, K. K. Y.; Wong, M. K.; Che, C. M., *J. Organomet. Chem.* **2009**, *694*, 583–591.

[23] Kung, K. K. Y. L., V. K. Y.; Ko, H. M.; Li, G. L.; Chan, P. Y.; Leung, K. C.; Zhou, Z.; Wang, M. Z.; Che, C. M.; Wong, M. K., *Adv. Synth. Catal.* **2013**, *355*, 2055–2070.

[24] Kung, K. K. Y.; Li, G. L.; Zou, L.; Chong, H. C.; Leung, Y. C.; Wong, K. H.; Lo, V. K. Y.; Che, C. M.; Wong, M. K., *Org. Biomol. Chem.* **2012**, *10*, 925–930.

[25] (a) Anderson, M. P.; Casalnuovo, A. L.; Johnson, B. J.; Mattson, B. M.; Mueting, A. M.; Pignolet, L. H., *Inorg. Chem.* **1988**, *27*, 1649–1658; (b) Constable, E. C.; Elder, S. M.; Healy, J.; Ward, M. D.; Tocher, D. A., *J. Am. Chem. Soc.* **1990**, *112*, 4590–4592; (c) Magistrato, A.; Merlin, M.; Pregosin, P. S.; Rothlisberger, U.; Albinati, A., *Organometallics* **2000**, *19*, 3591–3596.

[26] Deuschel-Cornioley, C.; Stoeckli-Evans, H.; von Zelewsky, A., *J. Chem. Soc., Dalton Trans.* **1990**, 121–122.

[27] Kwong, H. L.; Yeung, H. L.; Yeung, C. T.; Lee, W. S.; Lee, C. S.; Wong, W. L., *Coord. Chem. Rev.* **2007**, *251*, 2188–2222.

[28] Gianini, M.; von Zelewsky, A.; Stoeckli-Evans, H., *Inorg. Chem.* **1997**, *36*, 6094–6098.

[29] (a) Kramer, R.; Lehn, J. M.; Marquis-Rigault, A., *PNAS* **1993**, *90*, 5394–5398; (b) Telfer, S. G.; Sato, T.; Kuroda, R., *Angew. Chem. Int. Ed.* **2004**, *43*, 581–584; (c) Miyake, H.; Tsukube, H., *Chem. Soc. Rev.* **2012**, *41*, 6977–6991.

[30] Kwong, H. L.; Yeung, H. L.; Lee, W. S.; Wong, W. T., *Chem. Commun.* **2006**, 4841–4843.

[31] Yeung, C. T.; Yeung, H. L.; Tsang, C. S.; Wong, W. Y.; Kwong, H. L., *Chem. Commun.* **2007**, 5203–5205.

[32] Sham, K. C.; Yeung, H. L.; Yiu, S. M.; Lau, T. C.; Kwong, H. L., *Dalton Trans.* **2010**, *39*, 9469–9471.

[33] Yeung, H. L.; Wong, W. Y.; Wong, C. Y.; Kwong, H. L., *Inorg. Chem.* **2009**, *48*, 4108–4117.

[34] Davies, J.; Wang, H.; Taylor, T.; Warabi, K.; Huang, X. H.; Andersen, R. J., *Org. Lett.* **2005**, *7*, 5233–5236.

[35] Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J., *J. Am. Chem. Soc.* **1990**, *112*, 3715–3716.

[36] Morikawa, S.; Yamazaki, S.; Furusaki, Y.; Amano, N.; Zenke, K.; Kakiuchi, K., *J. Org. Chem.* **2006**, *71*, 3540–3544.

[37] (a) Martin, R.; Jäger, A.; Böhl, M.; Richter, S.; Fedorov, R.; Manstein, D. J.; Gutzeit, H. O.; Knölker, H., *Angew. Chem.* **2009**, *121*, 8186–8190; (b) Zhao, Y. L.; Di, C. H.; Liu, S. D.; Meng, J.; Liu, Q., *Adv. Synth. Catal.* **2012**, *354*, 3545–3550.

[38] Merkul, E.; Muller, T. J. J., *Chem. Commun.* **2006**, 4817–4819.

[39] (a) Nakamura, H.; Ishikura, M.; Sugiishi, T.; Kamakura, T.; Biellmann, J. F., *Org. Biomol. Chem.* **2008**, *6*, 1471–1477; (b) Kuang, J.; Ma, S., *J. Am. Chem. Soc.* **2010**, *132*, 1786–1787; (c) Lo, V. K. Y.; Zhou, C. Y.; Wong, M. K.; Che, C. M., *Chem. Commun.* **2010**, *46*, 213–215; (d) Ye, J.; Li, S.; Chen, B.; Fan, W.; Kuang, J.; Liu, J.; Liu, Y.; Miao, B.; Wan, B.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Ma, S., *Org. Lett.* **2012**, *14*, 1346–1349.

[40] Martin, R.; Jäger, A.; Böhl, M.; Richter, S.; Fedorov, R.; Manstein, D. J.; Gutzeit, H. O.; Knölker, H., *Angew. Chem. Int. Ed.* **2009**, *48*, 8042–8046.

[41] (a) Boulton, A. A.; Davis, B. A.; Durden, D. A.; Dyck, L. E.; Juorio, A. V.; Li, X. M.; Paterson, I. A.; Yu, P. H., *Drug Develop. Res.* **1997**, *42*, 150–156; (b) Yogev-Falach, M.; Amit, T.; Bar-Am, O.; Youdim, M. B. H., *FASEB J.* **2003**, *17*, 2325–2327.

[42] (a) Wei, C. M.; Li, Z. G.; Li, C. J., *Synlett* **2004**, 1472–1483; (b) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V., *Chem. Soc. Rev.* **2012**, *41*, 3790–3807.

[43] (a) Wei, C.; Li, Z.; Li, C. J., *Org. Lett.* **2003**, *5*, 4473–4475; (b) Ji, J.-X.; Au-Yeung, T. T.-L.; Wu, J.; Yip, C. W.; Chan, A. S. C., *Adv. Synth. Catal.* **2004**, *346*, 42–44; (c) Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C. J., *Tetrahedron Lett.* **2004**, *45*, 2443–2446; (d) Yao, X.; Li, C. J., *Org. Lett.* **2005**, *7*, 4395–4398; (e) Jeganathan, M.; Dhakshinamoorthy, A.; Pitchumani, K., *ACS Sustainable Chem. Eng.* **2014**, *2*, 781–787.

[44] (a) Li, C.-J.; Wei, C., *Chem. Commun.* **2002**, 268–269; (b) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A., *Org. Lett.* **2004**, *6*, 1001–1003; (c) Park, S. B.; Alper, H., *Chem.*

Commun. **2005**, *1315–1317*; (d) Sreedhar, B.; Reddy, P. S.; Prakash, B. V.; Ravindra, A., *Tetrahedron Lett.* **2005**, *46*, 7019–7022; (e) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H., *J. Am. Chem. Soc.* **2005**, *127*, 10804–10805; (f) Kidwai, M.; Bansal, V.; Mishra, N. K.; Kumar, A.; Mozumdar, S., *Synlett* **2007**, 1581–1584.

[45] (a) Sakai, N.; Hirasawa, M.; Konakahara, T., *Tetrahedron Lett.* **2003**, *44*, 4171–4174; (b) Fischer, C.; Carreira, E. M., *Org. Lett.* **2004**, *3*, 4319–4321; (c) Sakaguchi, S.; Mizuta, T.; Furuwan, M.; Kubo, T.; Ishii, Y., *Chem. Commun.* **2004**, 1638–1639; (d) Kamtam, M. L.; Balasubrahmanyam, V.; Kumar, K. B. S.; Venkanna, G. T., *Tetrahedron Lett.* **2007**, *48*, 7332–7334; (e) Ramu, E.; Varala, R.; Sreelatha, N.; Adapa, S. R., *Tetrahedron Lett.* **2007**, *48*, 7184–7190; (f) Lanke, S. R.; Bhanage, B. M., *Appl. Organomet. Chem.* **2013**, *27*, 729–733.

[46] (a) Koradin, C.; Polborn, K.; Knochel, P., *Angew. Chem. Int. Ed.* **2002**, *41*, 2535–2538; (b) Wei, C.; Li, C. J., *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639; (c) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P., *Angew. Chem. Int. Ed.* **2003**, *42*, 5763–5766; (d) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P., *Chem. Eur. J.* **2003**, *9*, 2797–2811; (e) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M., *Org. Lett.* **2006**, *8*, 2437–2440; (f) Gommermann, N.; Knochel, P., *Chem. Eur. J.* **2006**, *12*, 4380–4392; (g) Wei, C.; Mague, J. T.; Li, C. J., *Proc. Natl. Acad. Sci.* **2004**, *101*, 5749–5754; (h) Bisai, A.; Singh, V. K., *Org. Lett.* **2006**, *8*, 2405–2408.

[47] (a) J. A. Mao; P. F. Zhang, *Tetrahedron: Asymmetry* **2009**, *20*, 566–569; (b) B. Roy; R. Raj; B. Mukhopadhyay, *Tetrahedron Lett.* **2009**, *50*, 5838–5841; (c) K. Karthik Kumar; T. Mohan Das, *Carbohydr. Res.* **2011**, *346*, 728–732.

[48] (a) Kidwai, M.; Bansal, V.; Kumar, A.; Mozumdar, S., *Green Chemistry* **2007**, *9*, 742–745; (b) Zhang, X.; Corma, A., *Angew. Chem. Int. Ed.* **2008**, *47*, 4358–4361; (c) Datta, K. K. R.; Reddy, B. V. S.; Ariga, K.; Vinu, A., *Angew. Chem. Int. Ed.* **2010**, *49*, 5961–5965.

[49] Juwarker, H.; Suk, J. M.; Jeong, K. S., Indoles and Related Heterocycles. In *Anion Recognition in Supramolecular Chemistry*, Gale, P. A.; Dehaen, W., Eds. Springer Berlin Heidelberg: 2010; Vol. 24, pp 177–204.

[50] (a) Pflugrath, J. W.; Quiocho, F. A., *Nature* **1985**, *314*, 257–260; (b) He, J. J.; Quiocho, F. A., *Science* **1991**, *251*, 1479–1481.

[51] Barluenga, J.; Valdés, C., Five-Membered Heterocycles: Indole and Related Systems. In *Modern Heterocyclic Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA: 2011; pp 377–531.

[52] (a) B. Cardillo; G. Casnati; A. Pochini; A. Ricca, *Tetrahedron* **1967**, *23*, 3771–3783; (b) S. Hayat; Atta-Ur-Rahman; M. I. Choudhary; K. M. Khan; W. Schumann; E. Bayer, *Tetrahedron* **2001**, *57*, 9951–9957; (c) X. Zhu; A. Ganesan, *J. Org. Chem.* **2002**, *67*, 2705–2708; (d) Z. G. Le; Z. C. Chen; Y. Hu; Zheng, Q. G., *Synthesis* **2004**, 208–212.

[53] Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C., *Tetrahedron Lett.* **2003**, *44*, 4589–4591.

[54] Yadav, J. S.; Reddy, B. V. S.; Praneeth, K., *Tetrahedron Lett.* **2008**, *49*, 199–202.

[55] (a) J. S. Yadav; B. V. S. Reddy; G. Narasimhulu; G. Satheesh, *Synlett* **2009**, 727–730; (b) K. Rad-Moghadam; M. Sharifi-Kiasaraie, *Tetrahedron* **2009**, *65*, 8816–8820; (c) M. -Z. Wang; C. -Y. Zhou; M. -K. Wong; C. -M. Che, *Chem. Eur. J.* **2010**, *16*, 5723–5735; (d) V. Cadierno; J. Francos; J. Gimeno, *Chem. Commun.* **2010**, *46*, 4175–4177; (e) T. Tsuchimoto; M. Kanbara, *Org. Lett.* **2011**, *13*, 912–915.

[56] Bandini, M.; Eichholzer, A., *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644.

[57] Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T., *J. Am. Chem. Soc.* **2006**, *128*, 8146–8147.

[58] (a) Li, Z.; Shi, Z.; He, C., *J. Organomet. Chem.* **2005**, *690*, 5049–5054; (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M., *Chem. Eur. J.* **2007**, *13*, 1358–1373; (c) Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J., *J. Organomet. Chem.* **2009**, *694*, 546–550.

[59] (a) Ferrer, C.; Echavarren, A. M., *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109; (b) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M., *J. Org. Chem.* **2008**, *73*, 7721–7730.

[60] Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H., *Chem. Eur. J.* **2007**, *13*, 8285–8293.

[61] Zanardi, A.; Mata, J. A.; Peris, E., *Chem. Eur. J.* **2010**, *16*, 13109–13115.

[62] (a) Al-Salim, N.; West, A. A.; McWhinnie, W. R.; Hamor, T. A., *J. Chem. Soc., Dalton Trans.* **1988**, 2363–2371; (b) Constable, E. C.; Leese, T. A., *J. Organomet. Chem.* **1987**, *335*, 293–299; (c) Wehman, E.; van Koten, G.; Jastrzebski, J. T. B. H.; Ossor, H.; Pfeffer, M., *J. Chem. Soc., Dalton Trans.* **1988**, 2975–2981; (d) Vicente, J.; Abad, J. A.; Gutierrez-Jugo, J. F.; Jones, P. G., *J. Chem. Soc., Dalton Trans.* **1989**, 2241–2245; (e) Wu, Y.; Ding, K.; Yang, W.; Zhu, Y.; Yang, L., *J. Organomet. Chem.* **1994**, *468*, 13–19.

[63] Parish, R. V.; Wright, J. P.; Pritchard, R. G., *J. Organomet. Chem.* **2000**, *596*, 165–176.

[64] Ko, H. M.; Kung, K. K. Y.; Cui, J. F.; Wong, M. K., *Chem. Commun.* **2013**, *49*, 8869–8871.

[65] (a) D. Fan; C. -T. Yang; J. D. Ranford; Lee, P.-F.; J. J. Vittal, *Dalton Trans.* **2003**, 2680–2685; (b) K. J. Kilpin; W. Henderson; B. K. Nicholson, *Inorg. Chim. Acta*, **2009**, *362*,

3669–3676; (c) P. A. Bonnardel; Parish, R. V.; R. G. Pritchard, *J. Chem. Soc., Dalton Trans.* **1996**, 3185–3193.

[66] Wang, Y.-Z.; Liu, L.-Z.; Zhang, L.-M., *Chem. Sci.* **2013**, *4*, 739–746.

Chapter 3

Cyclometallated Gold(III) Complexes for Chemoselective Cysteine Modification via Ligand Controlled C-S Bond-Forming Reductive Elimination

3.1 Introduction

3.1.1 Applications of Cyclometallated Gold(III) Complexes

Gold-based therapeutic agents have been on the market for decades. The application of gold compounds was first used in the treatment of rheumatoid arthritis and sold under the trade names of Myochrysine, Solgonal and Ridaura. Later studies revealed that the gold compounds also provided promising treatment for asthma, pemphigus and arthritis.[1] Notably, square planar gold(III) compounds having d^8 system are isoelectronic and isostructural with Pt(II) compounds such as *cis*-platin.

Some gold compounds were found to exhibit anti-cancer properties[2] as well as anti-HIV activities.[3] The gold(III) complex [$AuCl_2$damp] (damp = 2-[(dimethylamino)methyl]phenyl) complex was one of the most representative examples of gold(III) complexes showing anti-cancer properties (Figure 3.1a). It was found to cause damaging of cancer cells by its modest DNA binding properties.[4] Later, Che and Sun reported that gold(III) porphyrin complexes as potential anti-cancer drugs (Figure 3.1b). The complexes showed high stability against

glutathione and gave cytotoxic effects against human cancer cell lines.[5] Furthermore, binuclear gold(III) oxo complexes were tested as anti-cancer agents which showed different antiproliferative properties towards human cell lines compared to the mononuclear analogues (Figure 3.1c).

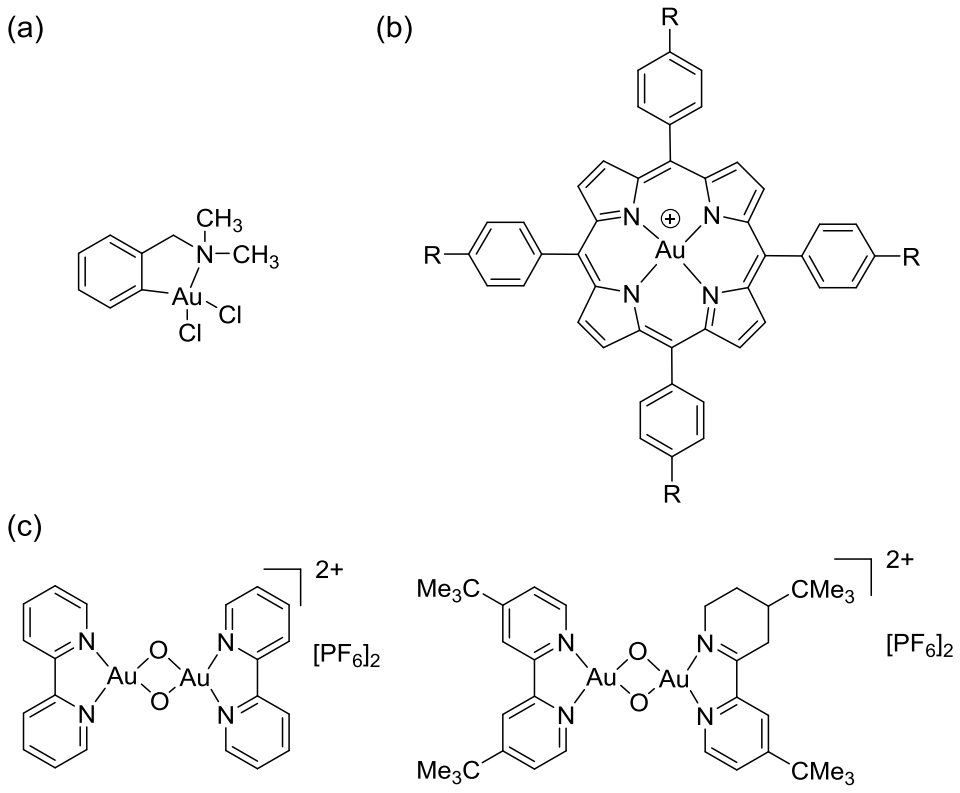
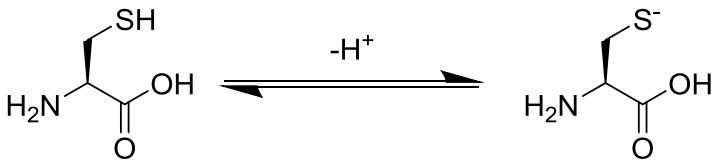


Figure 3.1 Examples of gold(III) complexes as therapeutic agents.

The use of gold complexes has also been expanded to electrochemical[6] and luminescent[7] applications. As mentioned in the previous chapter, cyclometallated gold(III) compounds offer excellent chemoselectivity, reactivity and compatibility in catalytic organic transformations.[8] Modular design of square planar gold(III) complexes taking advantages of their four coordination sites allows fine-tuning of the stability and reactivity of the gold catalysts.[9] However, the use of gold(III) complexes in selective biomolecule modification remains unexplored.

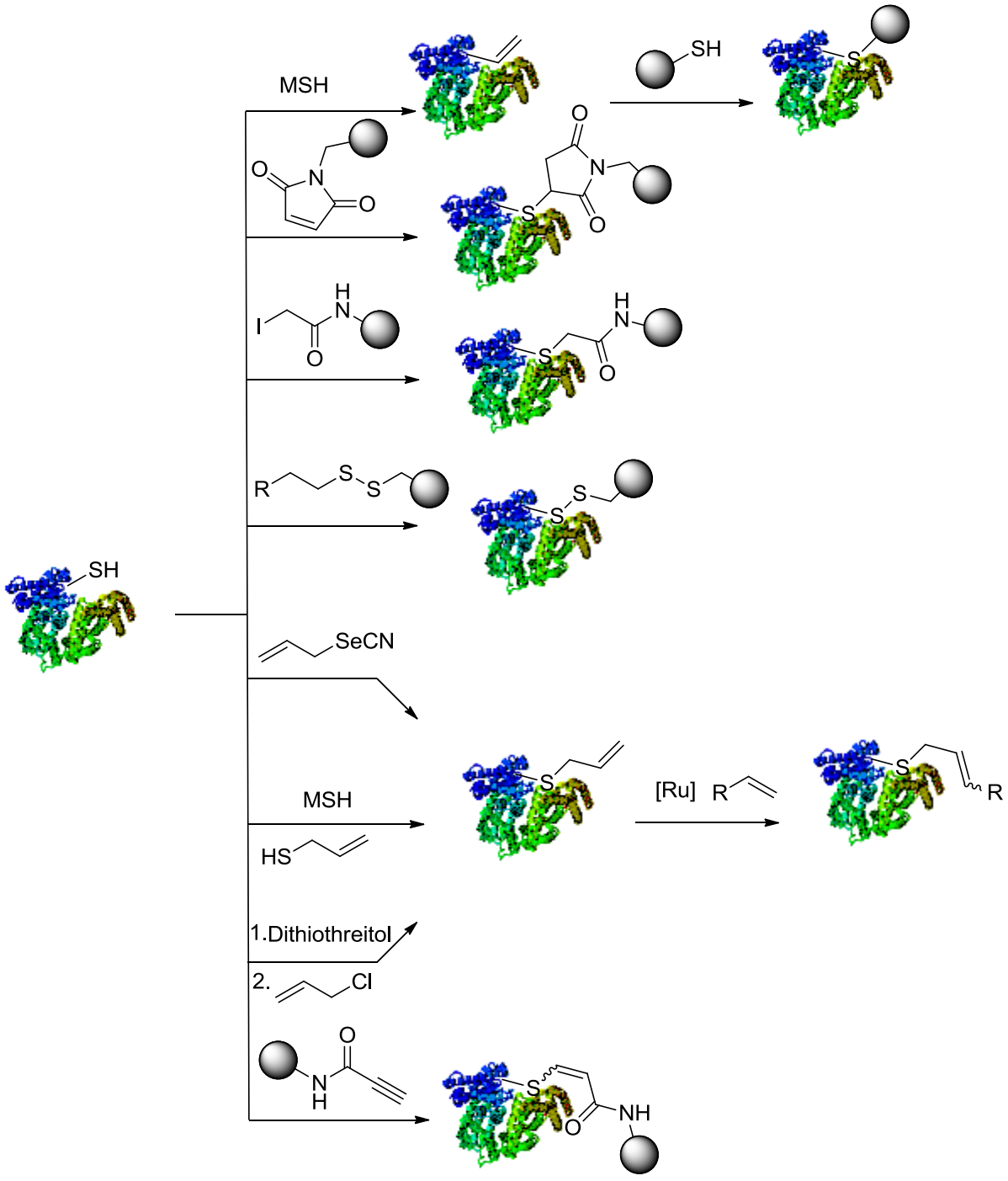
3.1.2 Selective Cysteine Modification

Cysteine, a naturally occurring amino acid, contains a highly nucleophilic thiol group which is the strongest nucleophilic among the natural amino acids. The pKa value of the cysteine thiol group is close to natural (pH~8.5). In biological environment, cysteine always occurs as thiolate form which is highly nucleophilic that leads to wide range of biological functions of cysteine (Scheme 3.1).



Scheme 3.1 Deprotonation of thiol group of cysteine.

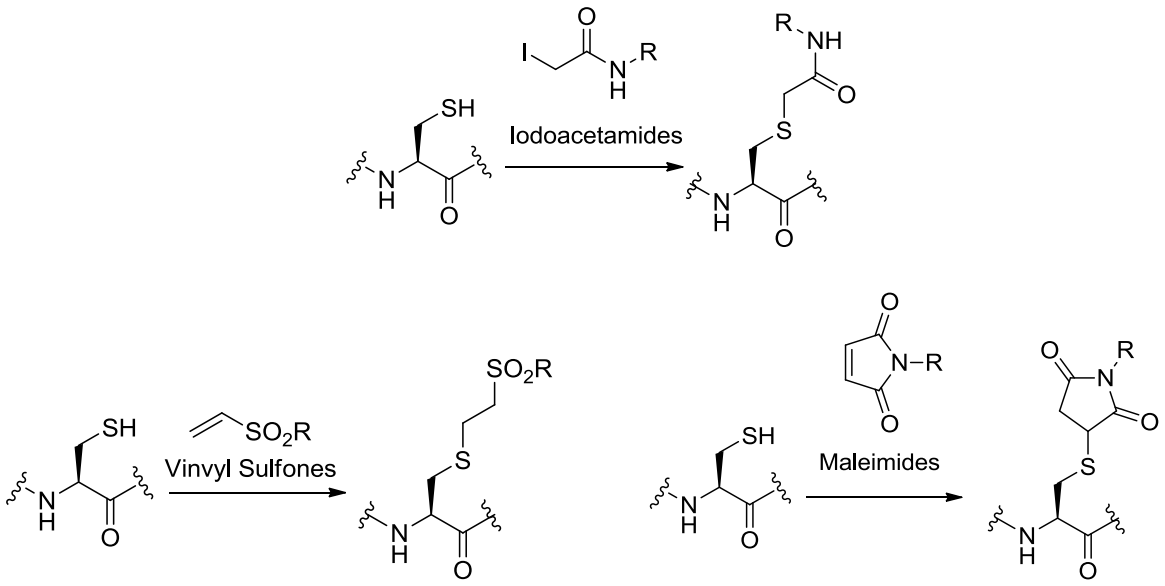
Because of the stronger nucleophilicity of -SH group among other nucleophilic residues such as R-NH_2 and –OH groups, the site selective modification of cysteine over other amino acids is possible by choosing suitable chemical reagents. Moreover, the low natural abundance (~1.7 %) of cysteine in protein sequences makes it as a useful handle for modification of target protein containing cysteine residues. Various methods for cysteine modification have been developed based on the unique reactivity of cysteine. Selective cysteine modification can be achieved by alkylation, disulfide bond formation, dehydroalanine formation, metal mediated reaction with cysteine and formation of vinyl sulfide linkages (Scheme 3.2).[10]



Scheme 3.2 Various routes for cysteine modification.

3.1.2.1 Conventional Approaches for Cysteine Modification

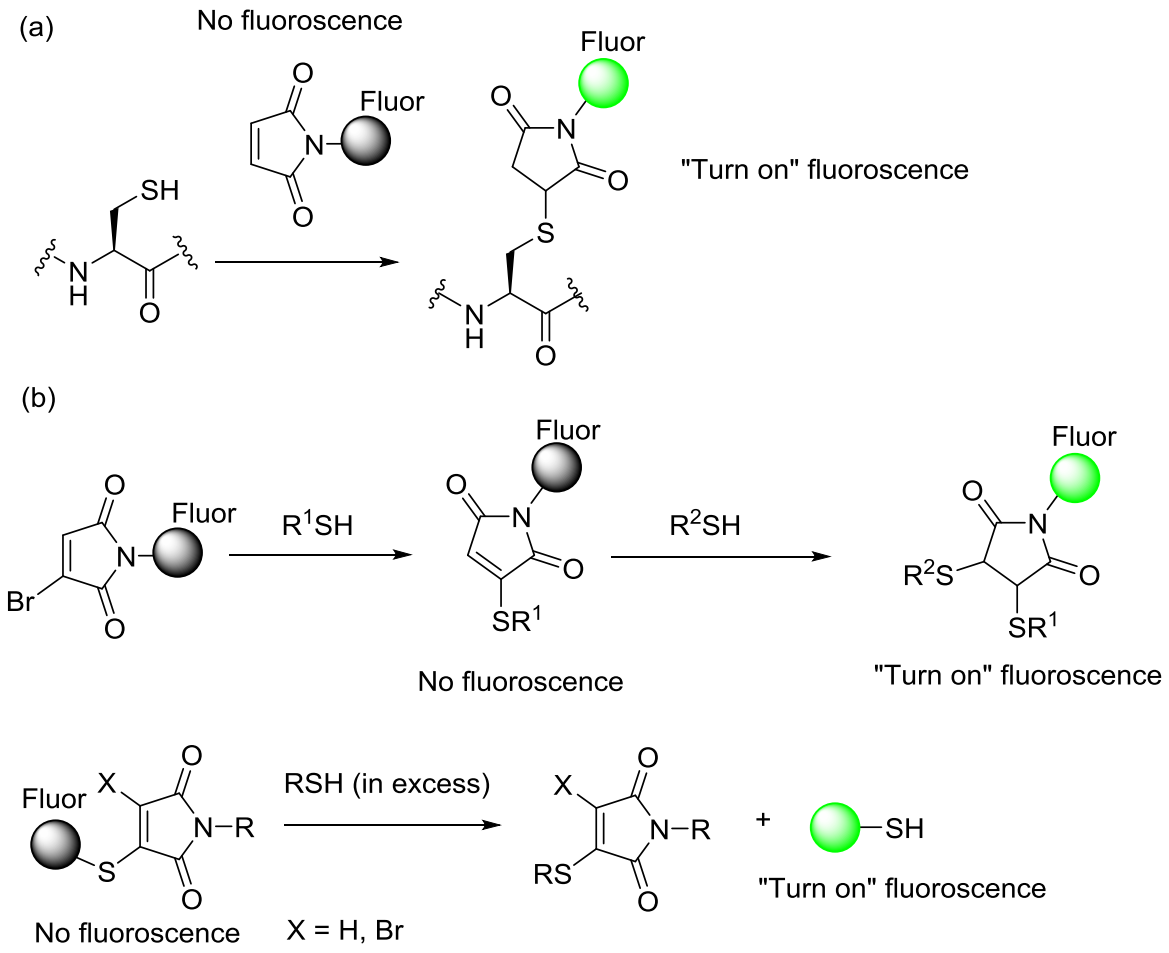
By using suitable electrophiles, alkylation of nucleophilic cysteine is a common cysteine modification technique.[11] Michaelis *et.al.* pioneered the modification of cysteine residue in a protein by using electrophilic α-halocarbonyl compounds (i.e. iodoacetamides) in nucleophilic substitution reaction with cysteine (Scheme 3.3, upper).[12] However, the cross-reactivity of this reaction with other amino acids such as methionine, lysine, histidine and tyrosine was observed.



Scheme 3.3 Conventional approaches for modification of cysteine by alkylating agents.

Furthermore, conjugate addition reaction of cysteine to Michael acceptors can produce alkylated cysteine side chains. Maleimides[13] and vinyl sulfones[14] are widely used as Michael acceptors for conjugate addition of cysteine to give C-S bonds (Scheme 3.3, lower). Maleimides were found to react selectively with thiol and stable under biological conditions while other amino acid side chain such as lysine fails to react with maleimides because of protonation of the primary amine of lysine under pH 9.[10] However, cross-reactivity with other amino acids side chains such as lysine and tyrosine was observed, especially in high pH

medium. Maleimides recently have been developed as an important component in “turn on” fluorophores (Fluor) for detection of cysteine -SH based on quenching properties of maleimide to the excited fluorophores by photo induced electron transfer (PET) or intramolecular charge transfer (ICT).[15] After the 1,4-addition of maleimide by cysteine –SH to generate the thiosuccinimide product losing the quenching ability, the fluorescence of the resulting compound is “turned on” (Scheme 3.4).[16]

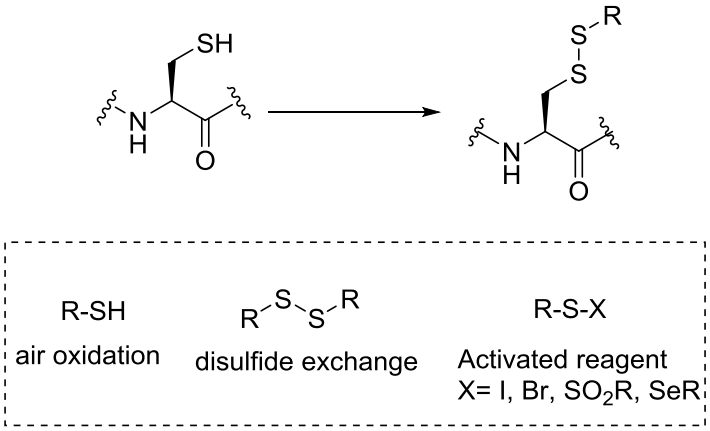


Scheme 3.4 “Turn on” fluorescent strategies for cysteine sensing using **(a)** maleimides, **(b)** bromomaleimides and thiomaleimides.

More recently, bromomaleimides have been designed for thiol sensing and intercellular reporting.[17] The substitution of the bromides by thiol groups afford non-fluorescent compounds which can be “turn on” by reacting with another equivalent of thiol compounds to afford fluorescent dithiosuccinimides (Scheme 3.4b, upper). Furthermore, fluorophore-linked thiomaleimides can be synthesized by using bromomaleimides (Scheme 3.4b, lower), which were found to be useful as reporter molecules in the biological studies because of high thiol selectivity in cells.

3.1.2.2 Oxidation of Cysteine: Disulfide Bond Formation

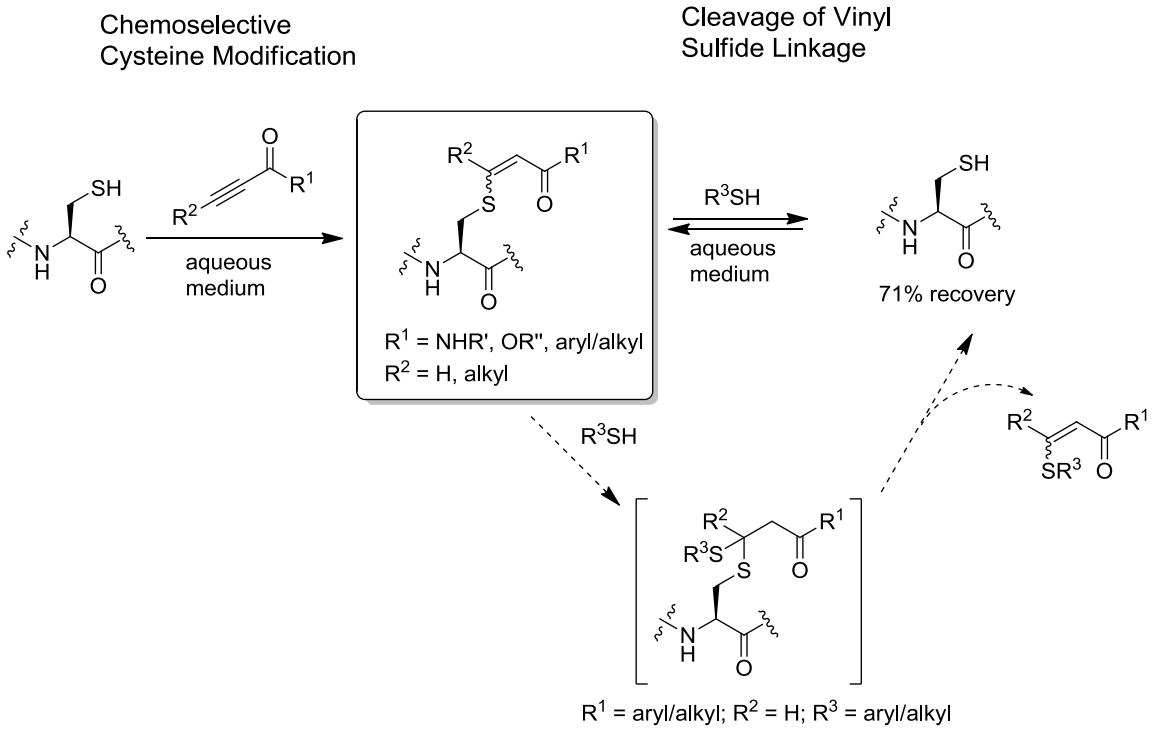
Free thiols in proteins are relative rare compared with the oxidized form (disulfide) in view of gaining stability of proteins. Addition of reducing agents such as dithiothreitol (DTT) is generally required to generate free thiol groups by breaking some of the disulfide linkages within the proteins. However, the free thiols would be oxidized back to disulfide linkages quickly in air. This natural activity of cysteine has been adopted as a chemical strategy for the modification of proteins. The cysteine thiol group can also be modified through the formation of disulphide (S-S) bond by using reactive disulfide reagents (i.e. Ellman's reagent)[18] in a thiol-disulfide exchange process or reacting with some activated reagents (i.e. sulfenyl halides, methanethiosulfonate reagents)[19] (Scheme 3.5). However, this required relatively long reaction time and led to limited control of selectivity of product resulted by mixed disulfides and dimers in the crude reaction mixture. Moreover, the S-S bond is unstable and susceptible to bond breaking in the presence reducing agents. Methods for conversion of disulfides into more stable thioether derivatives have been developed.[20] Conversion of cysteine into dehydroalanine followed by conjugate addition of thiol nucleophiles also provides facile approaches in cysteine modification.[21]



Scheme 3.5 Various approaches for cysteine modification via disulfide formation.

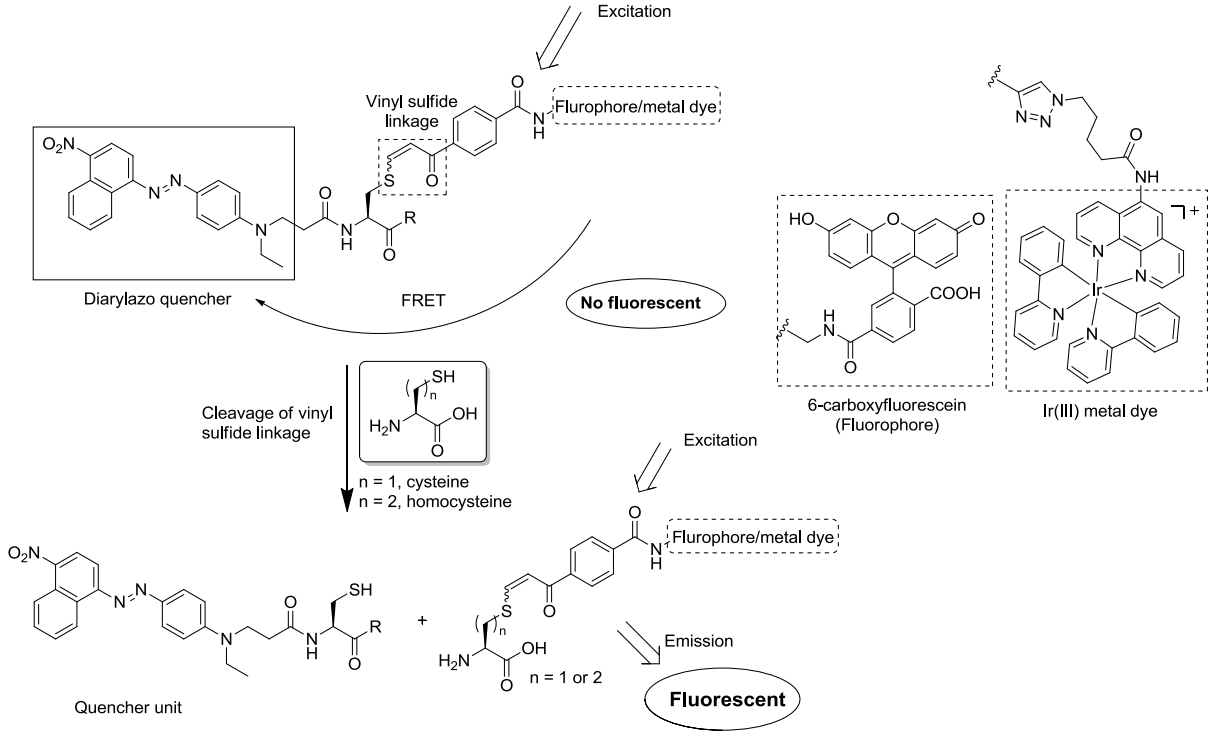
3.1.2.3 Formation of Vinyl Sulfide Linkage by Electron Deficient Alkynes

According to literatures, the vinyl sulfide linkage could be formed by conjugation addition of nucleophilic thiols to electron-deficient alkynes (i.e. alkynoic amides esters and alkynones).[22] Wong and Che first reported the use of electron deficient alkynes as cleavable reagents for chemoselective cysteine modification of peptides/proteins in aqueous medium.[23] The reaction proceeded smoothly in various pH values with highly chemoselective to cysteine without side products generated by other nucleophilic side chains such as serine -OH and lysine ε-NH_2. Furthermore, the vinyl sulfide linkage can be cleaved by addition of excess thiols under mild conditions to regenerate the native peptides with up to 71% recovery. It was noted that the cleavage reaction was selective to thiol containing reagents.



Scheme 3.6 Chemoselective cysteine modification by formation of cleavable vinyl sulfide linkage.

The application of thiol-specific cleavage reaction was further extended by Wong and Che to the design of thiol selective 'turn-on' fluorescent probes for detection of cysteine or homocysteine in biological samples. It has been achieved by connecting a fluorophore (6-carboxyfluorescein) with a diarylazo quencher together via the vinyl sulfide linkage (Scheme 3.7).[24] More recently, a 'turn-on' fluorescent iridium(III) probe has been developed showing advantages of significantly low background emission signal and large Stokes shift between excitation and emission wavelengths.[25]

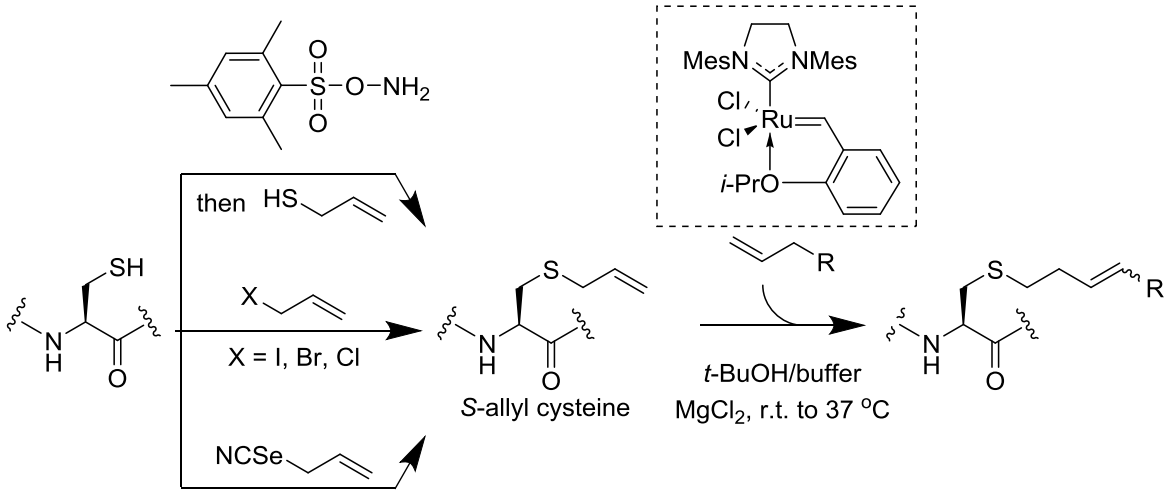


Scheme 3.7 The principle of the 'turn-on' fluorescent probes for detection of cysteine and homocysteine by organic or metal dyes.

3.1.2.4 Transition Metal Mediated Modification of Cysteine

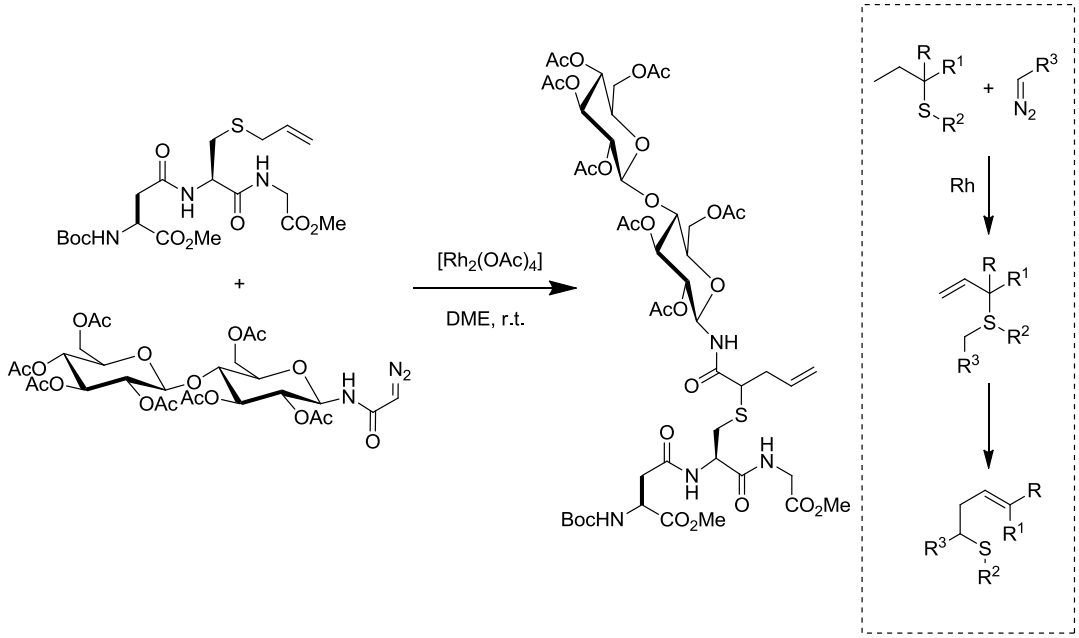
Recently, employing transition metal catalysis as a strategy in peptide/protein modification has become promising by rendering large reaction scopes and giving excellent chemoselectivity and reactivity.[26] The modification of cysteine can be achieved by metal-mediated transformation reactions, by utilizing the affinity of soft metals and sulphur containing compounds.[11a, 27] For examples, nickel and palladium catalysts have been used to prepare alanine residue in peptides and proteins through the desulfurization of cysteine after the native chemical ligation (NCL) where NCL is a effective strategy for the total chemical synthesis of proteins from two peptides.[28]

Davis *et.al.* reported the application of olefin cross metathesis in aqueous medium with allyl sulfides in site-selective modification of cysteine-containing proteins.[26d] The reaction required the transformation of cysteine -SH into *S*-allyl cysteines in the protein by **1)** 1,4-addition of allyl thiols to dehydroalanines generated by the reaction of the cysteine residues with *O*-mesitylenesulfonylhydroxylamine (MSH)[29] and **2)** nucleophilic addition of cysteine to allyl halides or allyl selenocyanate (Scheme 3.8, left).[20a, 20b, 29] The ruthenium catalysed olefin metathesis was achieved by using Hoveyda-Grubbs catalyst and allyl sulphides. The olefins were found to chemoselectively react with *S*-allyl cysteines rather than their carbon or heteroatom counterparts (Scheme 3.8, right). Such a chemoselective olefin metathesis results in post-translational modification of proteins via C-C bond formation. Glycosylation and PEGylation on the protein surface by this method are the most representative examples of the application of metal mediated cysteine modification.[21c, 26d]



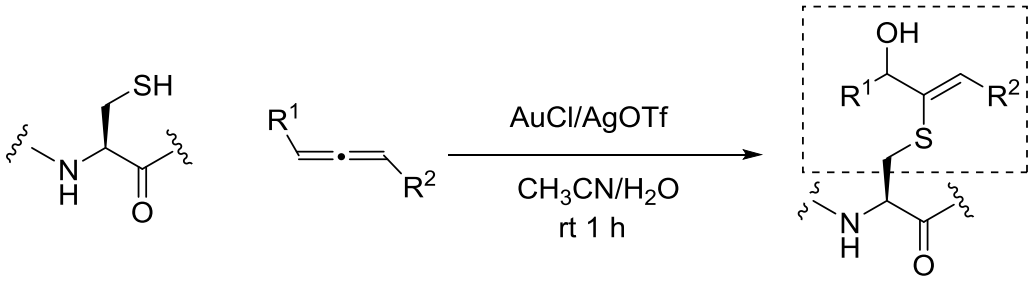
Scheme 3.8 Chemoselective cysteine modification by Ru-mediated olefin metathesis.

$[Rh_2(OAc)_4]$-catalysed Kirmse-Doyle reaction can also be applied in the modification *S*-allyl cysteine by diazo compounds (Scheme 3.9, left).[26c] The rhodium carbenoid generated by reacting of $Rh_2(OAc)_2$ with a sugar-functionalized diazo compound reacted with the *S*-allyl cysteine to give an allylic sulphur ylide which underwent rearrangement to afford product (Scheme 3.9, right).



Scheme 3.9 Rh-catalysed Kirmse-Doyle reaction for cysteine modification.

More recently, Wong and Che have reported the novel gold(I) mediated selective cysteine modification by addition reaction of cysteine thiols to allenes.[30] Different from transition metal catalysed nucleophilic addition of allenes, hydroxyl vinyl thioethers were formed instead of 1,2 or 1,3 addition products (Scheme 3.10). The strategy was employed to modification cysteine-containing peptide RNaseA.



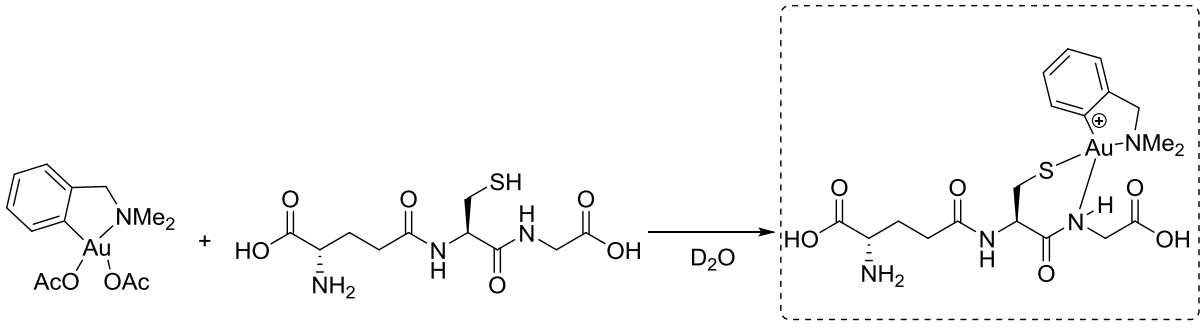
Scheme 3.10 Gold-mediated chemoselective cysteine modification by using allenes.

In spite of this progress, the advance of highly effective and chemoselective modification of cysteine-containing peptides and proteins by metal mediated C-S bond formation in biological compatible conditions is still a great challenge.

3.1.3 Interaction between Cyclometallated Gold(III) Complexes and Cysteine

Lewis acidic gold ions are highly reactive towards soft lewis bases such as sulfhydryl (-SH) groups to give Au-S bond.[31] The design and synthesis of cyclometallated gold(III) compounds bearing various biological sources such as cysteine containing peptides/proteins have drawn attentions due to novel applications of metalloprotein synthesis in asymmetric catalysis[32] and drugs development.[33]

Parish *et. al.* discovered that a gold(III) complex [Au(dmamp)$(OAc)_2$] (dmamp = 2-(dimethylaminomethyl)-phenyl) reacted chemoselectively with thiol-containing biological ligands, such as cysteine and Glutathione (GSH) , rather than biological amine ligands, such as adenine, adenosine, inosine and caffeine. Furthermore, the structural study of interaction of gold(III) and cysteine has been studied by Parish *et. al.* through the substitution reactions of [Au(dmamp)$(OAc)_2$] complex with GSH (Scheme 3.11).[29] The possible structure of the substituted product $[Au(dmamp)(GSH)]^+$ was proposed based on the ^1H and ^{13}C NMR analysis of the crude reaction mixture. However, the remaining signals in the NMR spectra were too complex to be interpreted for confirming the proposed structure.



Scheme 3.11 Formation of $[Au(dmba)(GSH)]^+$ complex.

Recently Che's group has reported the synthesis of cyclometallated gold(III) complexes with lipophilicity, and study of the interaction between cyclometallated gold(III) complexes, such as $[Au(C^N)L]^{n+}$ where HC^N = 2-(4-*n*-butylphenyl)pyridine or 2-phenylpyridine, L = biguanide or biuret, n = 0-1) and $[Au(C^N)(R_2NCS_2)]^+$ (Figure 3.2), with GSH and cysteine-containing peptides/proteins in cancer cell lines.[34] However, the rationale of how these gold complexes interact with the -SH group of cysteine has not been found out.

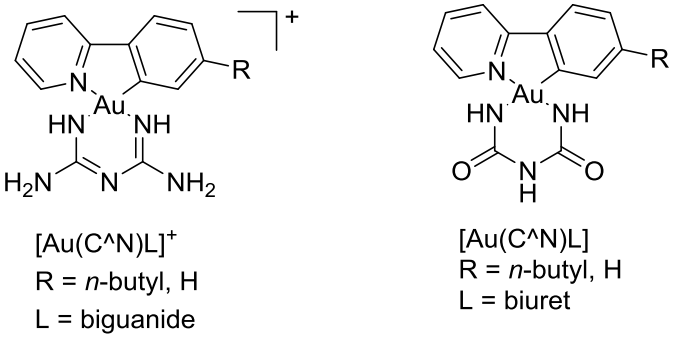


Figure 3.2 Structures of $[Au(C^N)L]^{n+}$ complexes.

Compound $[Au(C^N)(GSH)]^+$ was identified by ESI-MS in the substitution reaction of the cyclometallated gold(III) complex, $[Au(BCN)biguanide]^+$ (BCN = 2-(4-*n*-butylphenyl)pyridine) by addition of GSH. Structural studies in the binding of cysteine-containing peptides to cyclometallated gold(III) complexes remain a challenge.

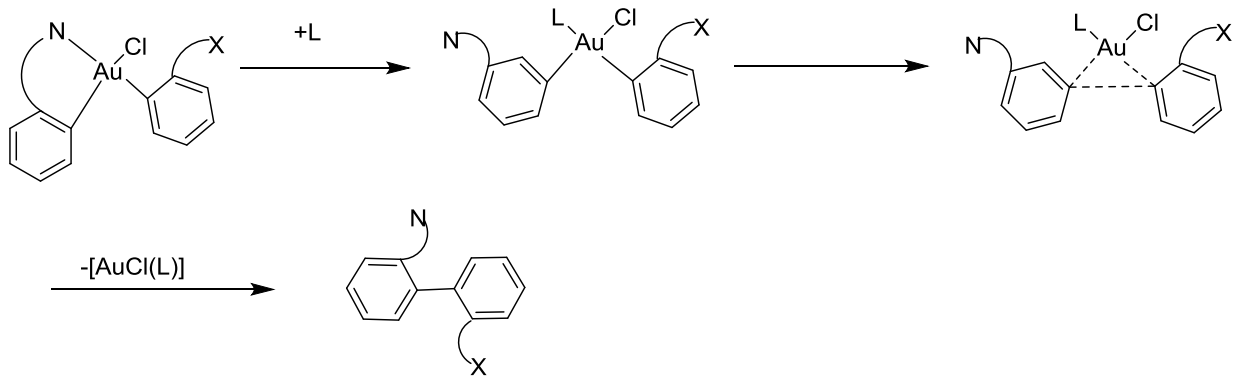
3.1.4 Gold(III) Reductive Elimination

Reductive elimination of transition metal complexes is one of the well-studied reactions in the advance of organometallic chemistry. Nevertheless, studies on the this fundamental reaction of gold(III) complexes were relatively confined. Kochi first have reported the mechanistic studies of gold(III) reductive elimination by preparing a trialkyl(triphenylphosphine) gold(III) complex in 1970s. The gold(III) complex was found to undergo reductive elimination in three consecutive steps: (a) the rearrangement of alkyl groups σ-bonded to gold(III), (b) the *cis*-trans isomerisation of the alkyl groups, and (c) the reductive elimination of two *cis*-alkyl groups to form dialkyls and alkylgold(I) species.[35] Later, they have studied these steps separately and they found that the reductive elimination of gold(III) was through a three-coordinated trialkyl gold intermediate which was supported by kinetic experiment of addition of phosphine in the reaction mixture and theoretical studies.[36]

Tobias have designed and synthesized a series cationic gold(III) complex with *cis*-alkyl groups and studied the rate of reductive elimination of these complexes in various of solvents, temperatures, sizes of ligands.[37] There was no further study until the effects of steric and electronic factors of the ligands as well as the leaving group selectivity of gold(III) complexes in reductive elimination were studied by Komiya and Shibue after a decade.[38]

Vicente *et. al.* have started to study the formation of biaryls from reductive elimination of dialky gold(III) compounds in 1990s.[39] They have reported the formation of biaryls by reductive elimination from cyclometallated gold(III) complexes [Au(C_6H_4N=NPh)ArCl] and [Au($C_6H_4CH_2NMe_2$)ArCl] (C_6H_5N=NPh = diazobenzene, $C_6H_4CH_2NMe_2$ = *N*,*N*-dimethylbenzylamine) with addition of phosphine or other ligands.[39-40] Gold(III) complexes

were relatively stable towards reductive elimination indicated by these studies. However, the slow reductive elimination process was considered to hinder the development of gold-catalysed C-C coupling.

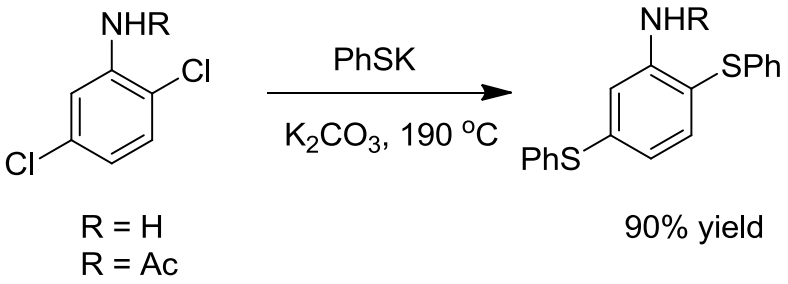


Scheme 3.12 Proposed pathway to the synthesis of biaryls from reductive elimination of a diarylgold(III) complex.

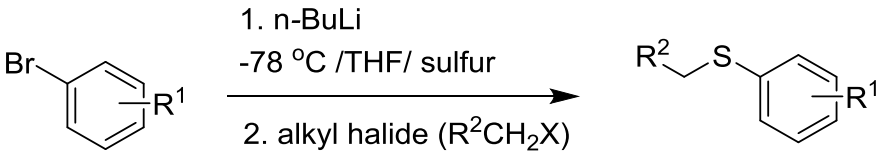
Interestingly, recent advances suggested the formation of C-C, C-I and C-F bonds can be achieved by gold(III) reductive elimination without the addition of ligands.[41] Moreover, Toste and Mankad reported that an alkyl gold(III) fluoride complex was found to be a possible intermediate in gold(I) catalyzed C-C coupling with arylboronic acid which facilitated the C-C reductive elimination to afford products.[41a] More recently, Toste's group has reported that the observed reductive elimination of biaryl gold(III) compounds with electron withdrawing substituents to afford biaryls was the fastest among other transition metals.[41e] In this connection, development of gold catalysis by utilizing the redox cycle of Au(I)/Au(III) was ongoing by continuous mechanistic studies in depth.

3.1.5 C-S Bond Formation

In literature, nucleophilic substitution of halides by thiolates,[42] reactions of sulfur with Grignard reagents and organolithium compounds[43] were common methods for C-S bond formation (Scheme 3.13 & 3.14). However, these methods required harsh reaction conditions and usually resulted in poor product selectivity.



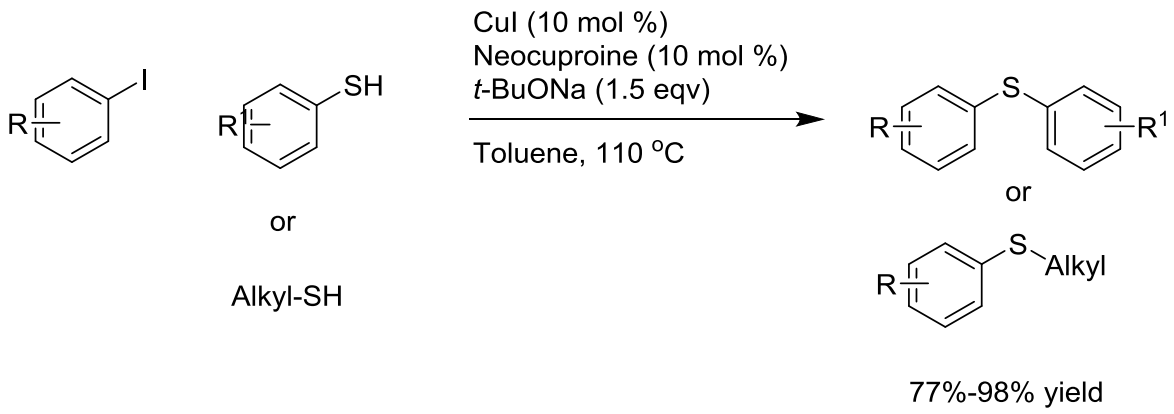
Scheme 3.13 Formation of C-S bonds by nucleophilic substitution of haildes by thiolates.[42]



R^1 = CH_3, OCH_3, CF_3, Ph, COOH, Br
R^2 = alkyl, allyl, aryl, carboxyl, caronyl, heterocyclic
X = Cl, Br, I

Scheme 3.14 Formation of C-S bond by nucleophilic substitution of halides by organolithium reagents.[43b]

A breakthrough in C-S bond formation was brought by Cu-catalysed Ullmann coupling reactions using thiols and aryl halides (Scheme 3.15).[44] Later, transition metal-catalysed C-S bond formation reactions were achieved by using other transition metals (e.g. Cu, Pd, Ir, Ni, Co) via cross coupling reactions[45] or reactions of sulfur containing compounds with C-C multiple bonds[46] to give various sulfide compounds.

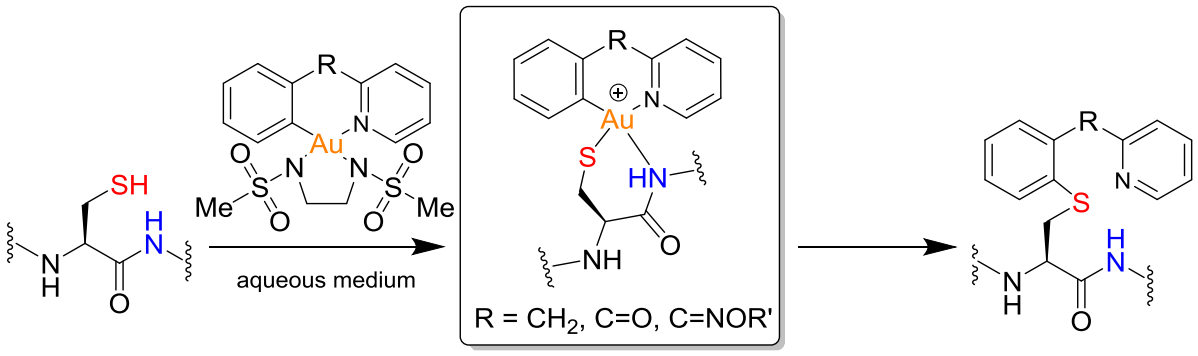


Scheme 3.15 Cu(I) catalyzed Ullmann coupling reactions for C-S bond formation.[44b]

On the contrary, examples of C-S bond formation by gold catalysis are rare[47] and a promising approach for C-S bond formation utilizing the chemistry of gold has not been developed yet. According to studies in C-S bond reductive elimination from square planar cyclometallated Pd(IV) complexes reported by Hartwig and Dong,[48] formation of C-S bonds via reductive elimination from highly valent metal sulfides was highly efficient in mild conditions. Moreover, combining with a recent report of fast gold(III) C-C bond reductive elimination,[41e] the urge of studies in the formation of carbon-heteroatom bonds especially C-S bond are inspired. We are of the opinion that the study in reductive elimination of gold(III) sulfides would provide a direction for further development of gold-catalysed cross-coupling reactions for carbon-heteroatom bond formation.

3.2 Objectives

Cyclometallated gold(III) complexes with different ancillary ligands would be synthesized and the chemoselectivity towards cysteine modification would be studied by conducting control experiments. The interaction between the cyclometallated gold(III) complexes and cysteine would be studied by conducting model reactions. The ease of formation of *S*-arylated peptides from reactions between cysteine-containing peptides and different cyclometallated gold(III) complexes would be studied under various conditions.



3.3 Results and Discussion

Along with our ongoing researches in the reactivity of cyclometallated gold(III) complexes with 5- and 6-membered rings in organic synthesis[49] and developing reactions for modification of biomolecules,[23, 30, 49b, 50] herein, we present the modular design of cyclometallated gold(III) complexes for modification of cysteine by C-S bond formation from cyclometallated gold-cysteine adducts (Figure 3.3). In this work, chemoselective cysteine modification of peptides by ligand controlled C-S bond reductive elimination was accomplished by the design of ancillary ligands in cyclometallated gold(III) complexes [Au(C^N)msen] (Scheme 3.16). Note that suitable choice of arylpyridine ligands can enhance the stability of the cationic gold-cysteine intermediates towards reductive elimination. *To the best of our knowledge, this work is the first example of employing gold(III)-mediated C-S bond formation from arylpyridines and sulfhydryl compounds for bioconjugation.*

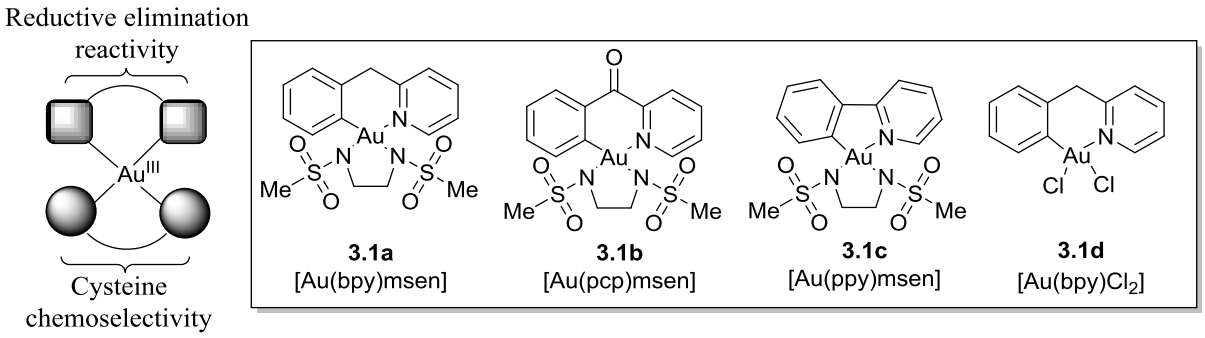
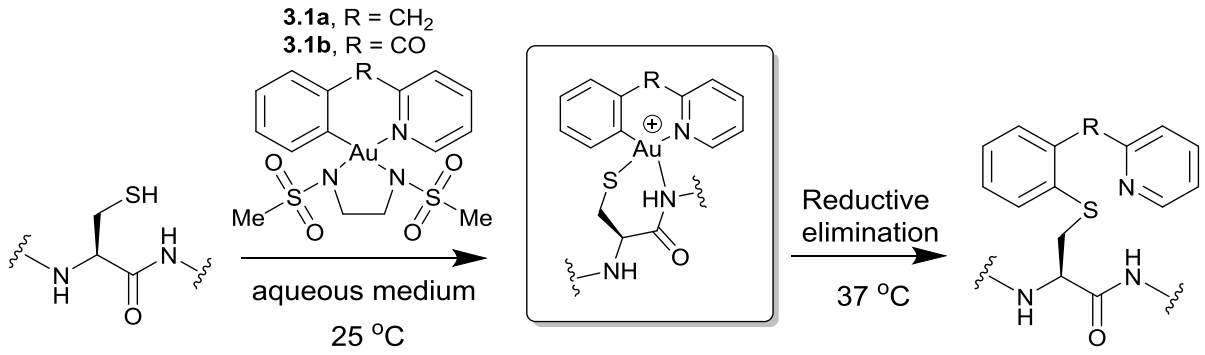


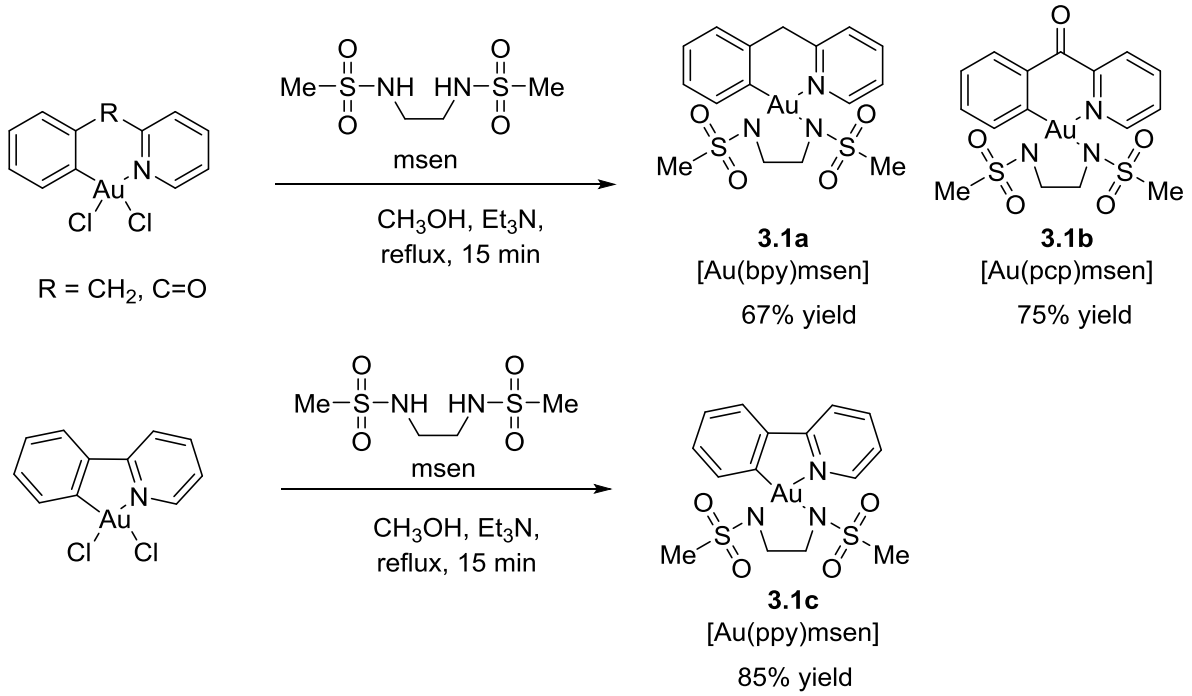
Figure 3.3 Design of cyclometallated gold(III) complexes.



Scheme 3.16 Chemoselective modification of cysteine by cyclometallated gold(III) complexes via C-S bond formation.

3.3.1 Synthesis of Cyclometallated Gold(III) Complexes with Cysteine Chemoselectivity

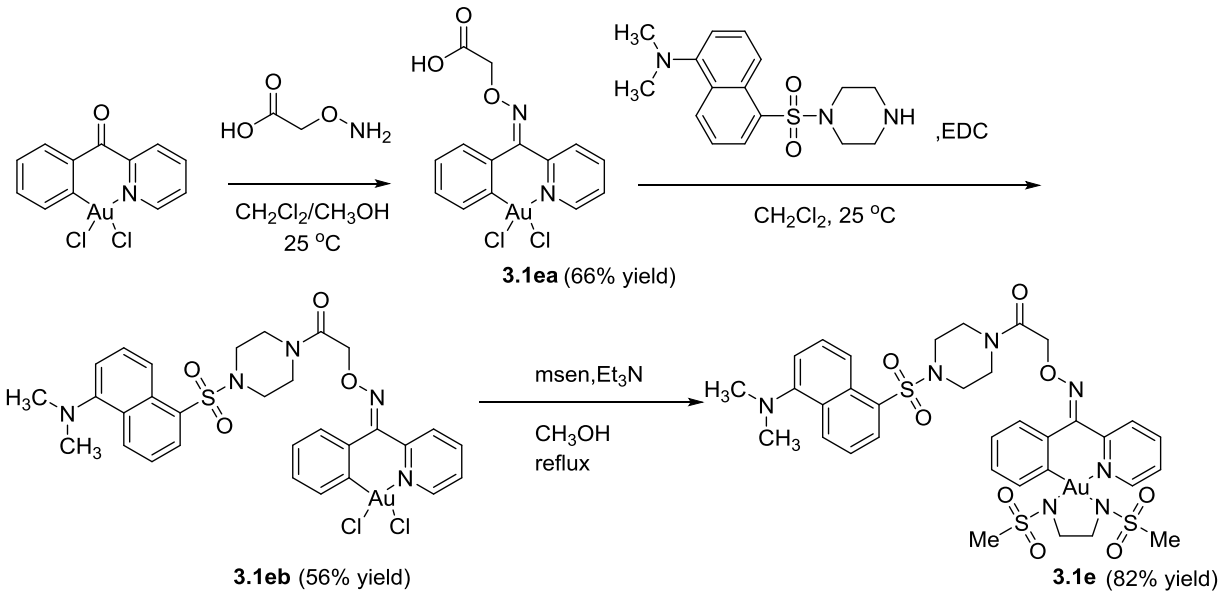
Cyclometallated gold(III) complexes [Au(bpy)msen] **3.1a**, [Au(pcp)msen] **3.1b** and [Au(ppy)msen] **3.1c** (msen = *N*,*N*'-bis(methanesulfonyl) ethylenediamine) were synthesized according to literature procedures (Scheme 3.17).[51]



Scheme 3.17 Synthesis of cyclometallated gold(III) complexes with msen ligand.

The dansyl functionalized cyclometallated gold(III) complexes was synthesized by reacting Au(pcp)Cl_2 with *O*-(carboxymethyl)hydroxylamine to give **3.1ea**. **3.1ea** was then reacted with dansyl piperidine obtained to give dansyl-functionalized gold(III) complex **3.1eb**.

Replacing the ancillary ligand with msen based on the previous procedure for synthesizing **3.1a-c** obtained complex **3.1e** in 85% yield **(**Scheme 3.18).

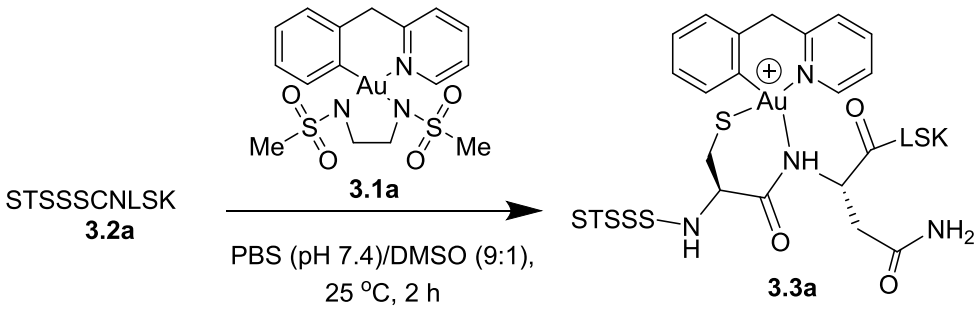


Scheme 3.18 Synthesis of dansyl-functionalized cyclometallated gold(III) complex **3.1e**.

3.3.2 Chemoselective Modification of Cysteine-containing Peptide via Formation of Gold-peptide Adducts

Mixing of a peptide sequence STSSSCNLSK (**3.2a**; 0.1 mM, M.W. = 1012) with [Au(bpy)msen] **3.1a** (1 equiv.) in PBS (50 mM, pH 7.4)/DMSO (9:1) at 25 ^{o}C for 2 h gave gold-peptide adduct **3.3a** with 99% substrate conversion (Table 3.1, entry 1) and the resulting products were confirmed by LC-MS. Moreover, gold-peptide adducts **3.3b**-**e** of peptides AYEMWCFHQK **3.2b**, ASCGTN **3.2c**, KSTFC **3.2d** and CSKFR **3.2e** could also be produced by the reaction with [Au(bpy)msen] **3.1a**. The substrate conversions to the corresponding cysteine-modified peptides were found to be 99, 99, 95 and 92%, respectively by LC-MS analysis (Entries 2-5). The above reaction was found to be exclusive to cysteine-containing peptides shown in LC-MS/MS analysis which implied the good cysteine selectivity of gold(III) complexes. However, no gold-peptide adduct was detected for non-cysteine-containing peptides YTSSSKNVVR **3.2f**, DSKFR **3.2g** and PSKFR **3.2h** (Entries 6-8), suggesting the excellent cysteine selectivity.

Table 3.1 Formation of gold-peptide adducts by [Au(bpy)msen] **3.1a**.[a]



Entry	Peptide sequence	Product	Conversion (%)[b]
1	STSSSCNLSK (**3.2a**)	**3.3a**	99
2	AYEMWCFHQK (**3.2b**)	**3.3b**	99
3	ASCGTN (**3.2c**)	**3.3c**	99
4	KSTFC (**3.2d**)	**3.3d**	95
5	CSKFR (**3.2e**)	**3.3e**	92
6	YTSSSKNVVR (**3.2f**)		-
7	DSKFR (**3.2g**)		-
8	PSKFR (**3.2h**)		-

[a] Peptide **3.2** (0.1 mM) and [Au(bpy)msen] **3.1a** (1 equiv.) in PBS (pH 7.4)/DMSO (9:1) solution (100 μL) at 25 °C for 2 h. [b] Determined by LC-MS analysis.

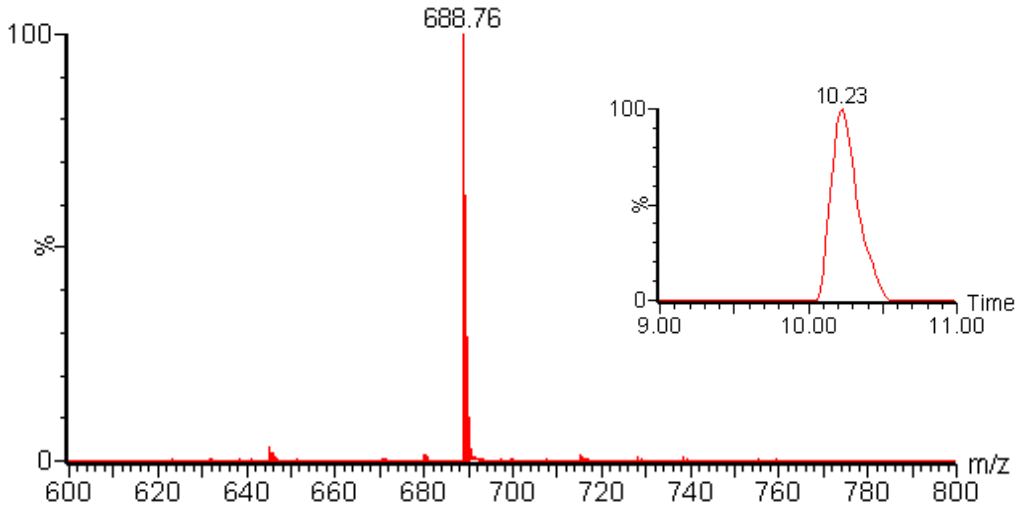
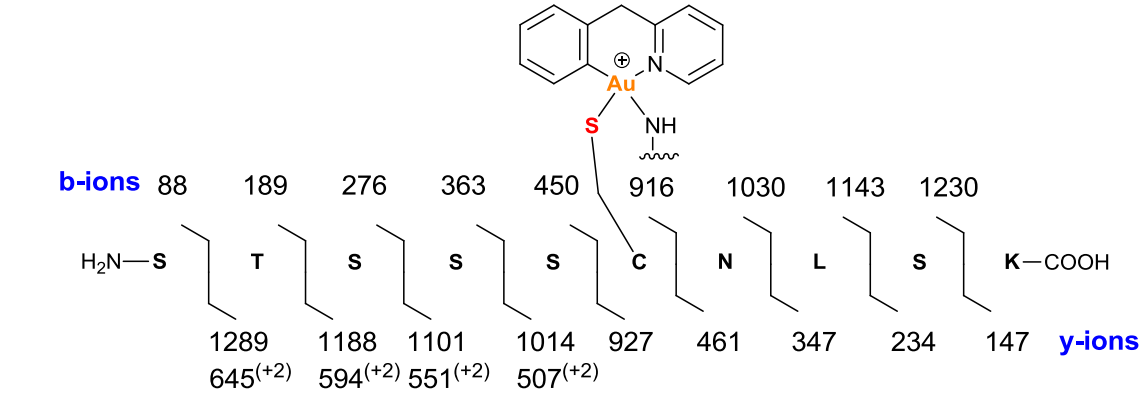


Figure 3.4. MS spectrum of **3.3a** (Doubly charged ion of *m/z* = 688.8) and XIC chromatogram of **3.3a** at t = 10.27 min (inset).



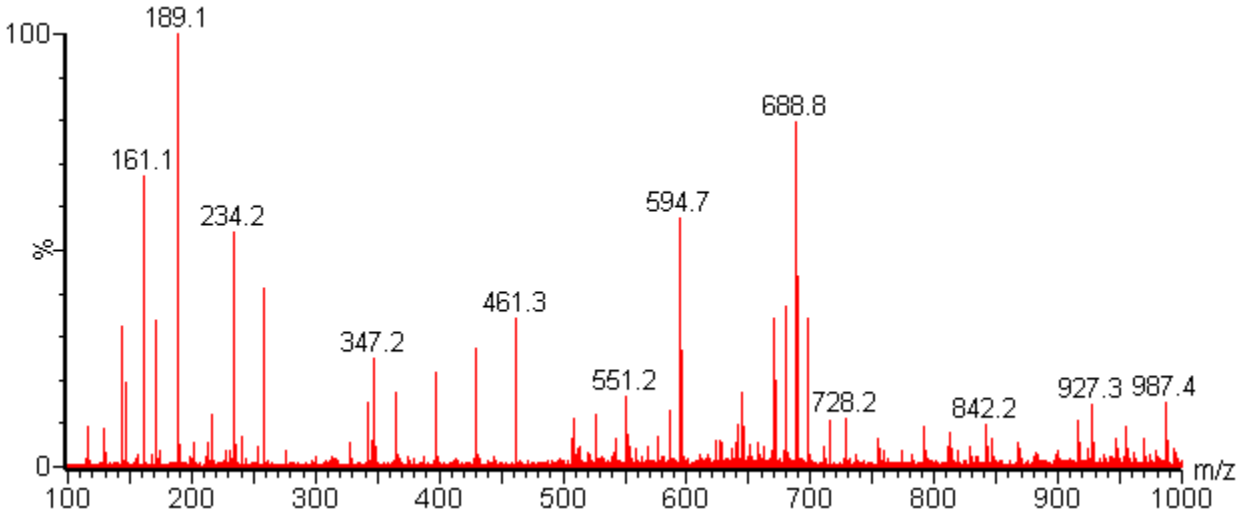


Figure 3.5. MS/MS spectrum of **3.3a** (ESI source, doubly charged ion of *m/z* = 688.8).

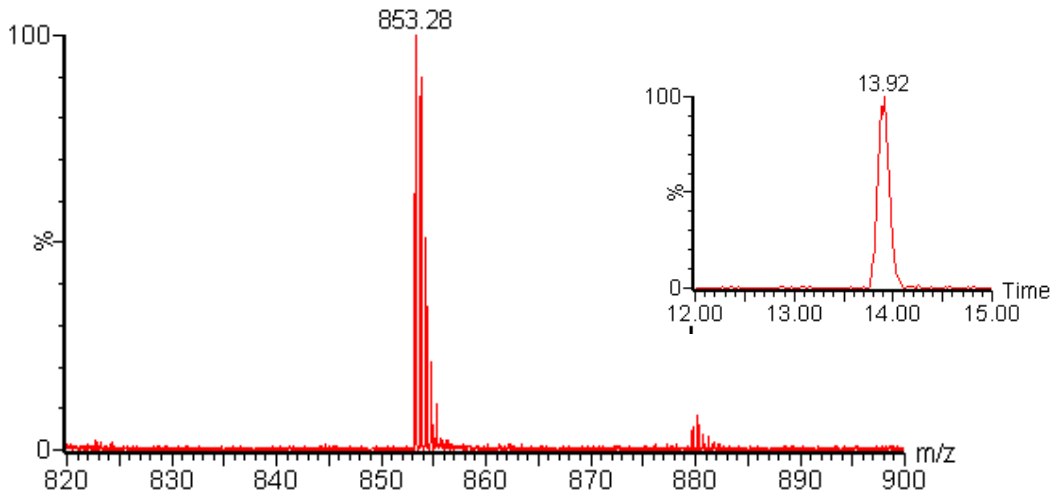


Figure 3.6 MS spectrum of **3.3b** (Doubly charged ion of *m/z* = 853.2) and XIC chromatogram of **3.3b** at t = 13.92 min (inset).

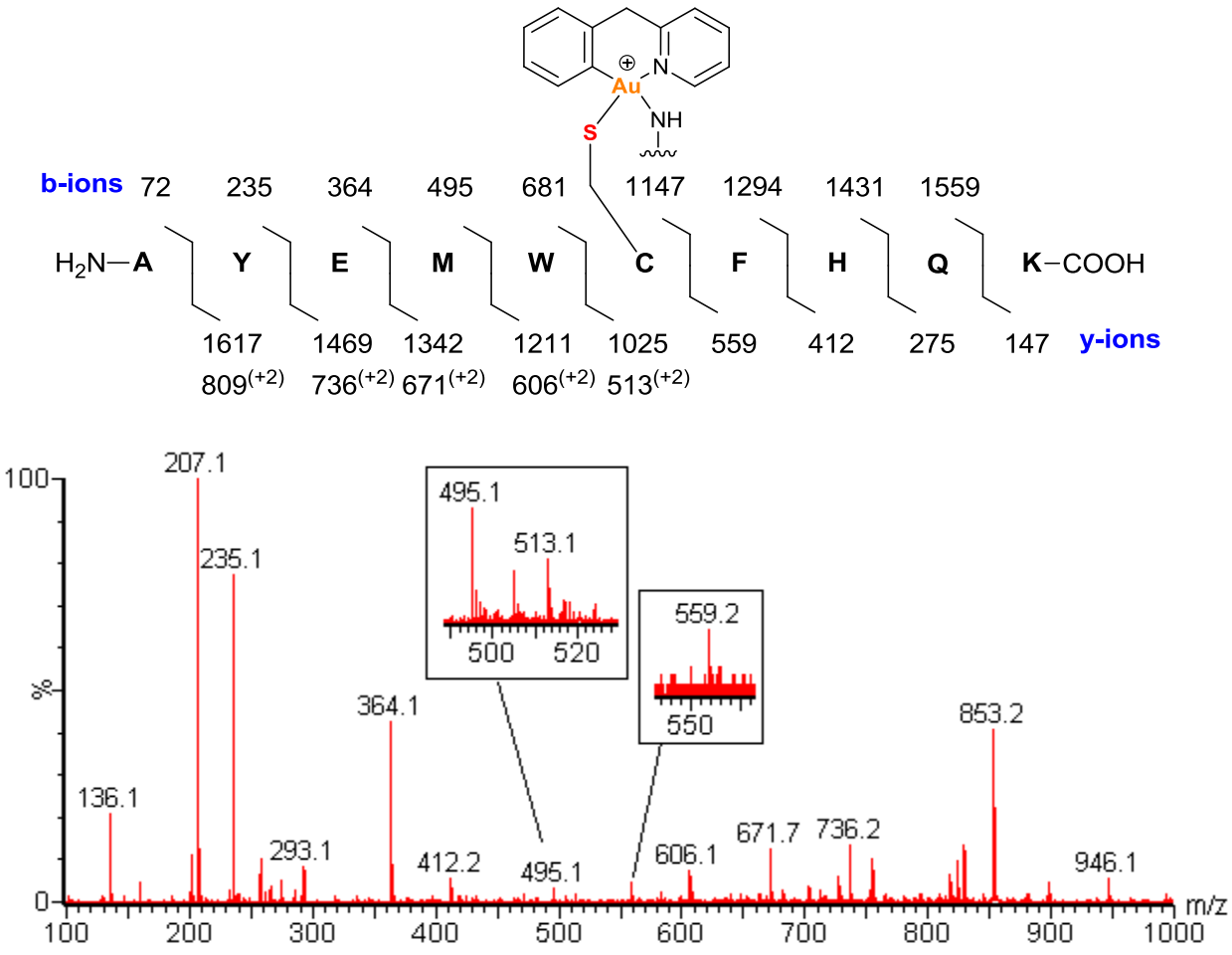


Figure 3.7 MS/MS spectrum of **3.3b** (ESI source, doubly charged ion of *m/z* = 853.2).

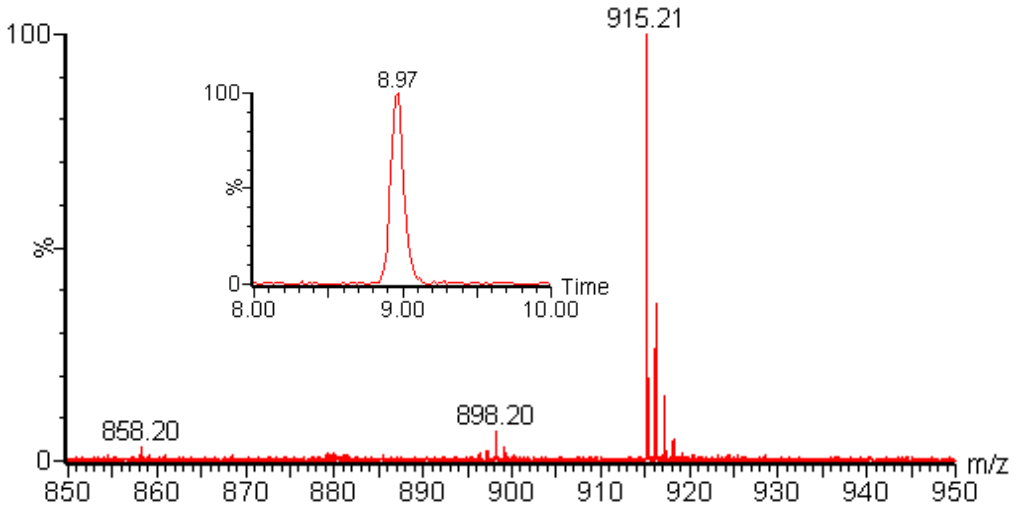


Figure 3.8 MS spectrum of **3.3c** (Singly charged ion of *m/z* = 915.2) and XIC chromatogram of **3c** at t = 8.97 min (inset).

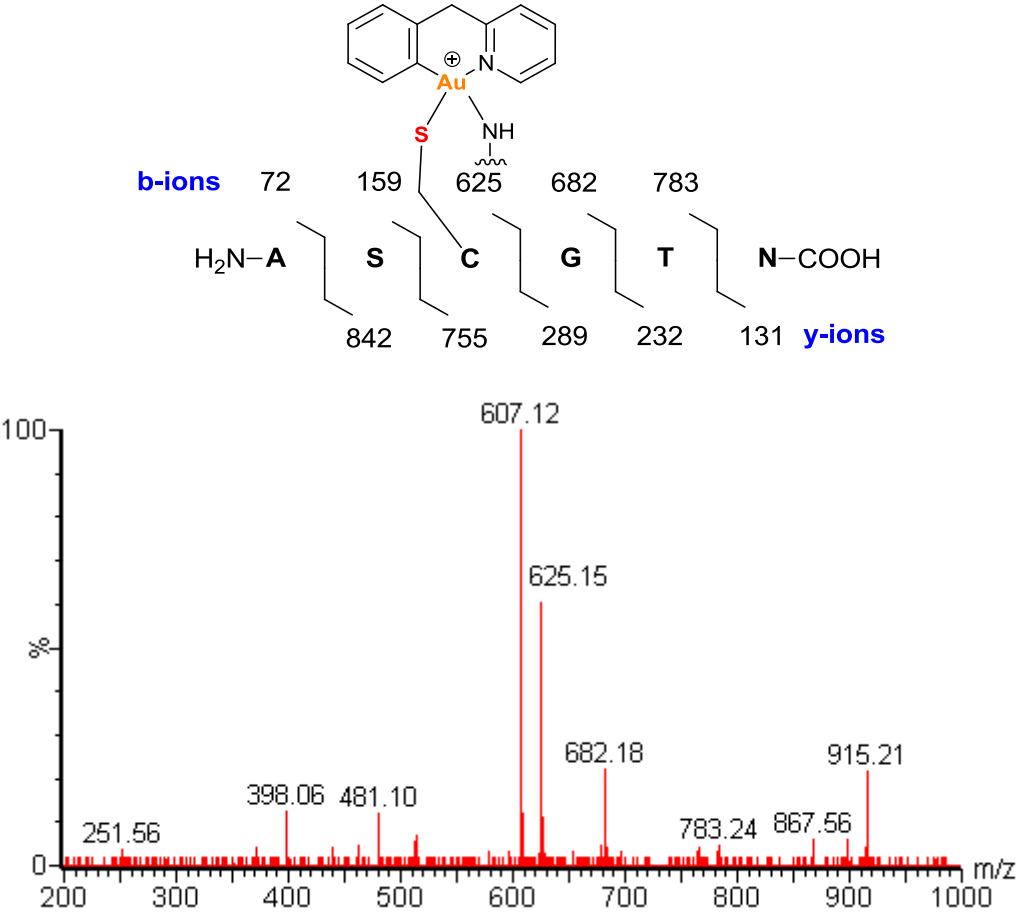


Figure 3.9 MS/MS spectrum of **3.3c** (ESI source, singly charged ion of *m/z* = 915.2).

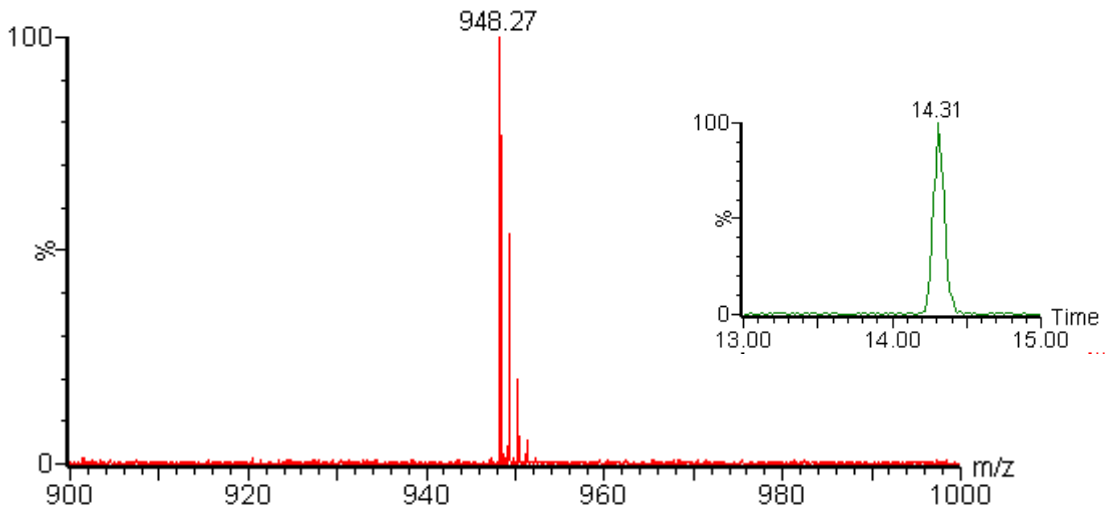


Figure 3.9 MS spectrum of **3.3d** (Singly charged ion of *m/z* = 948.2 and XIC chromatogram of **3.3d** at t = 14.31 min (inset).

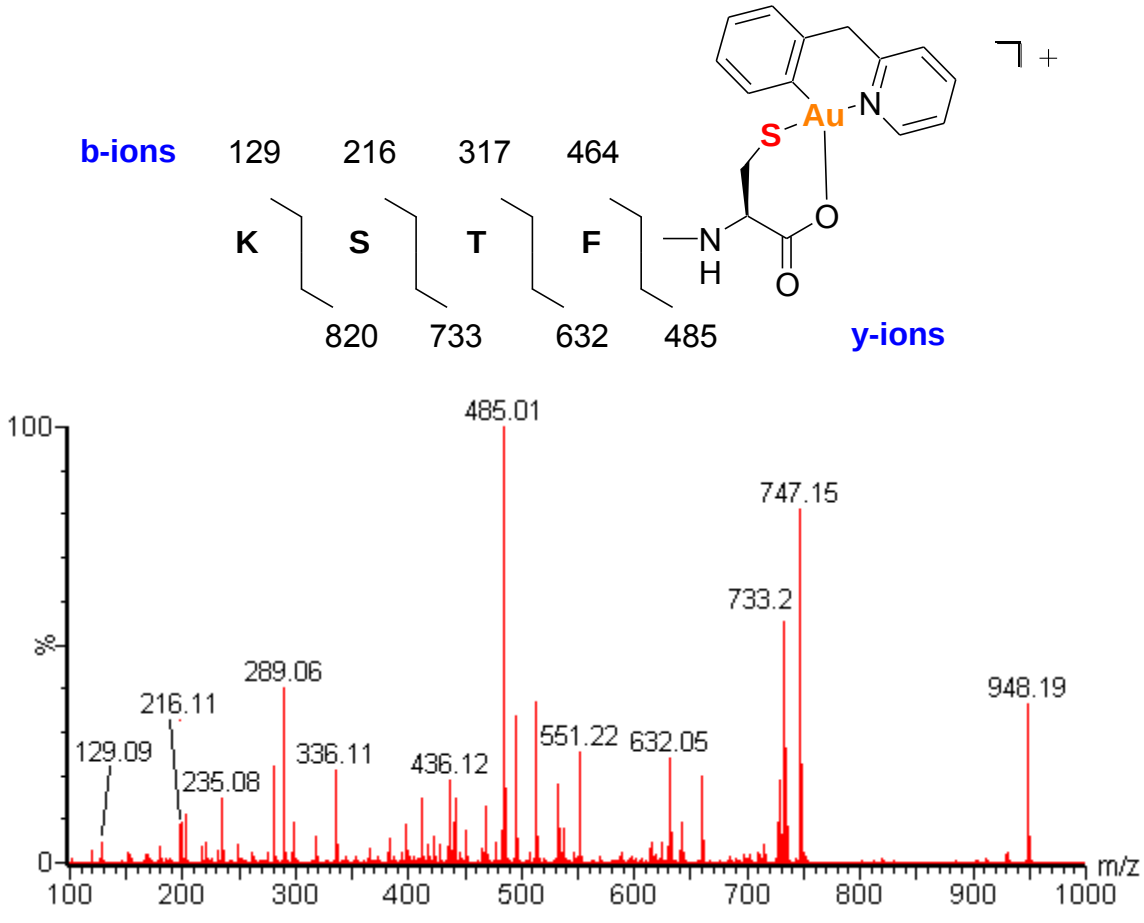


Figure 3.10 MS/MS spectrum of **3.3d** (ESI source, singly charged ion of *m/z* = 948.2)

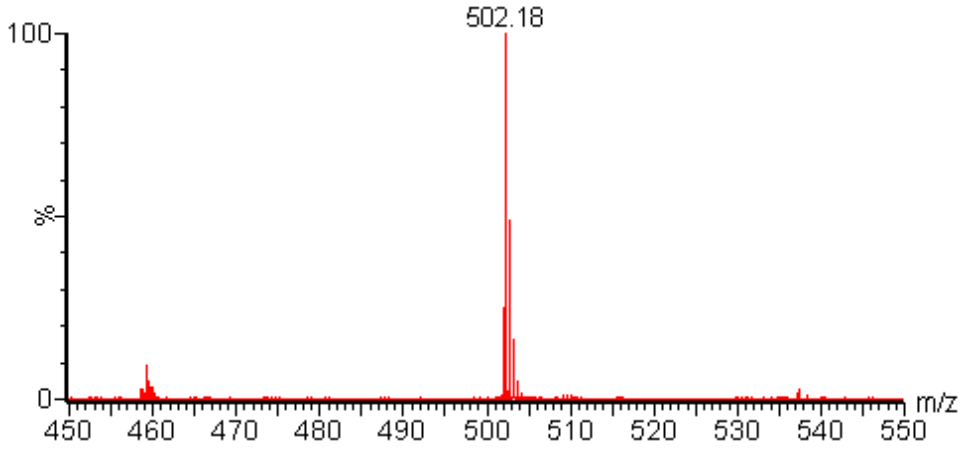


Figure 3.11 MS spectrum of **3.3e** (Singly charged ion of *m/z* = 502.2) and XIC chromatogram of **3.3e** at t = 10.89 min (inset).

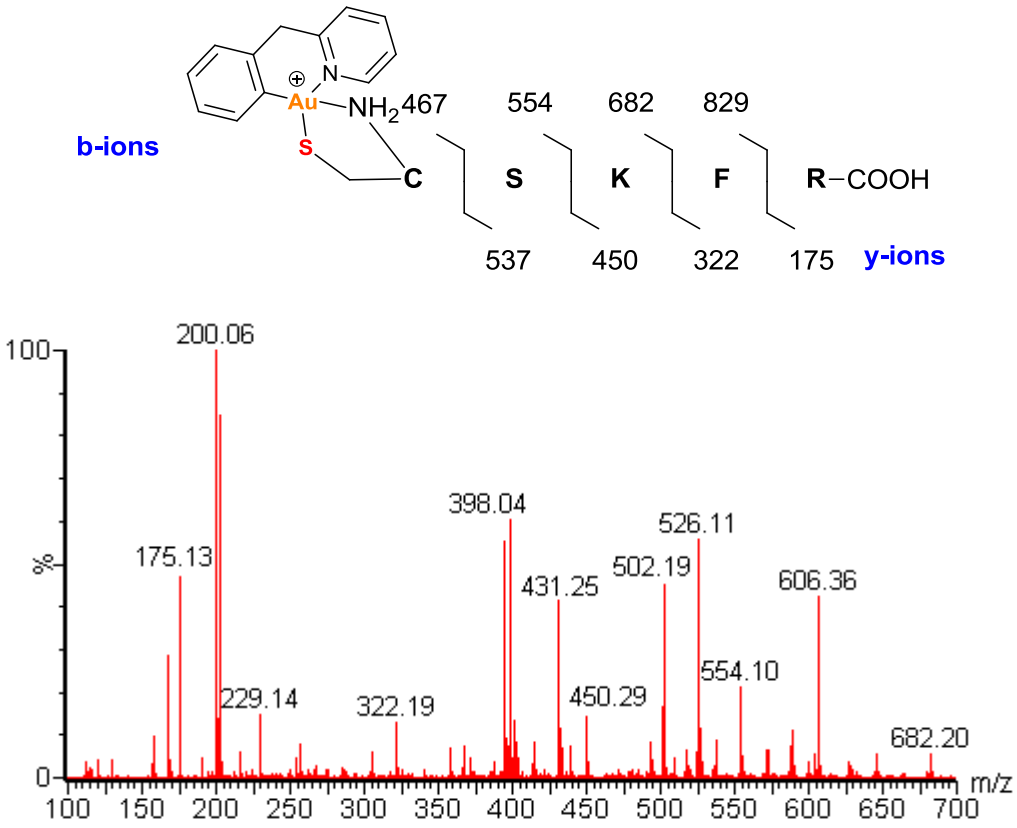


Figure 3.12 MS/MS spectrum of **3.3e** (ESI source, singly charged ion of *m/z* = 502.2).

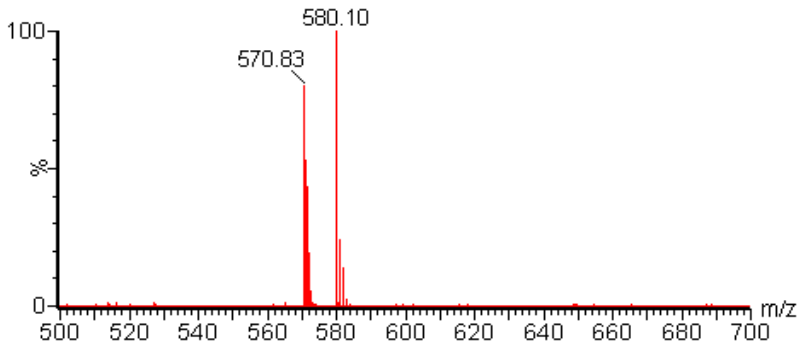


Figure 3.13 MS spectrum of YTSSSKNVVR **3.2f** (Doubly charged ion of *m/z* = 570.8) after mixing with cyclometallated gold(III) complex **3.1a** (Singly charged ion of *m/z* = 580.1).

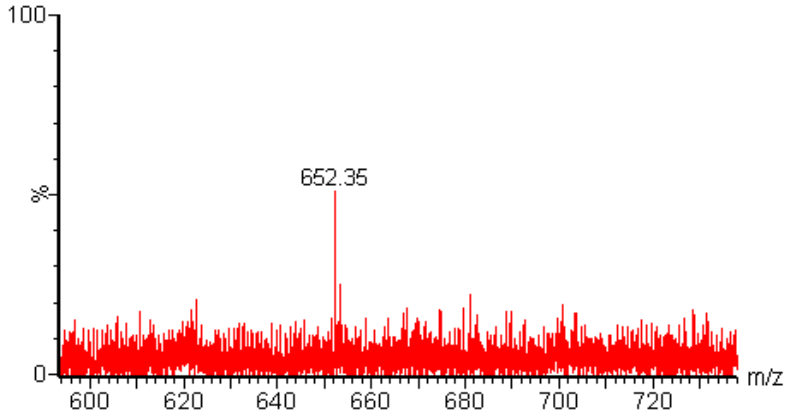


Figure 3.14 MS spectrum of DSKFR **3.2g** (Singly charged ion of *m/z* = 652.4) after mixing with cyclometallated gold(III) complex **3.1a**.

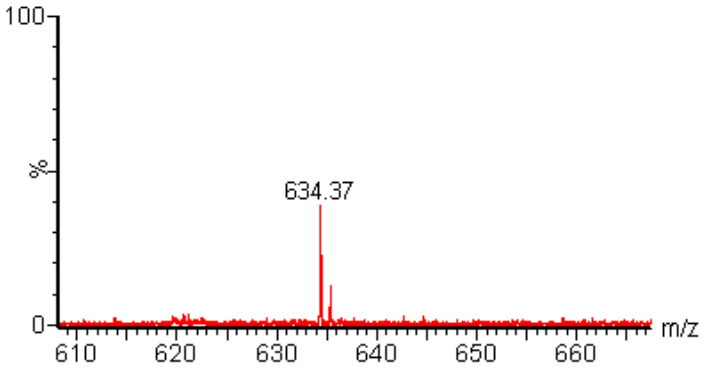
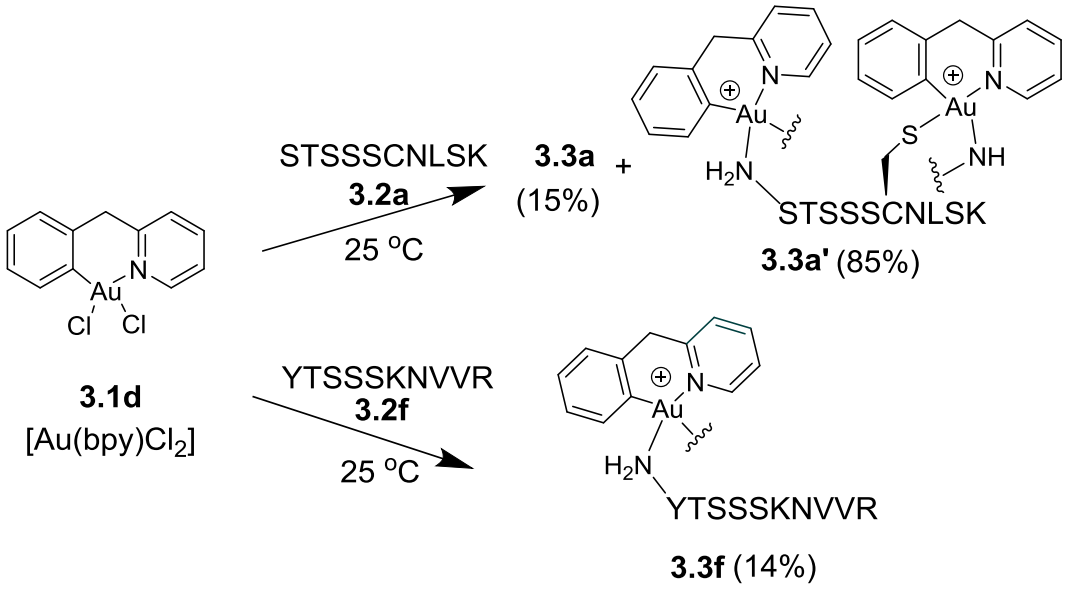


Figure 3.15 MS spectrum of PSKFR **3.2h** (Singly charged ion of *m/z* = 634.4) after mixing with cyclometallated gold(III) complex **3.1a**.

To demonstrate the excellent chemoselectivity of complex **3.1a** for cysteine modification, control experiments using cyclometallated gold(III) complex **3.1d** were conducted (Scheme 3.19). Reaction of complex **3.1d** with cysteine-containing peptide **3.2a** gave gold-cysteine adducts **3.3a** (15%) and **3.3a'** (85%). On the other hand, it was found that complex **3.1d** reacted with non-cysteine containing peptide YTSSSKNVVR **3.2f** to give *N*-terminal modified gold-peptide adduct **3.3f** with 14% conversion. Unlike **3.1a**, complex **3.1d** exhibited poor cysteine selectivity.



Scheme 3.19 Non-selective modification of peptides by cyclometallated gold(III) complex **3.1d**.

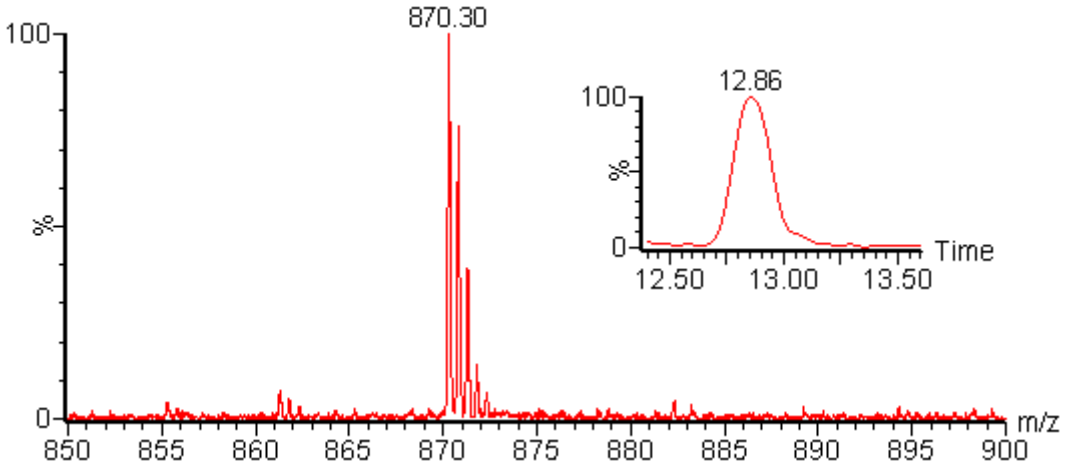


Figure 3.16 MS Spectrum of **3.3a'** (Doubly charged ions of m/z = 870.3) and XIC chromatogram of **3.3a'** at t = 12.86 min.

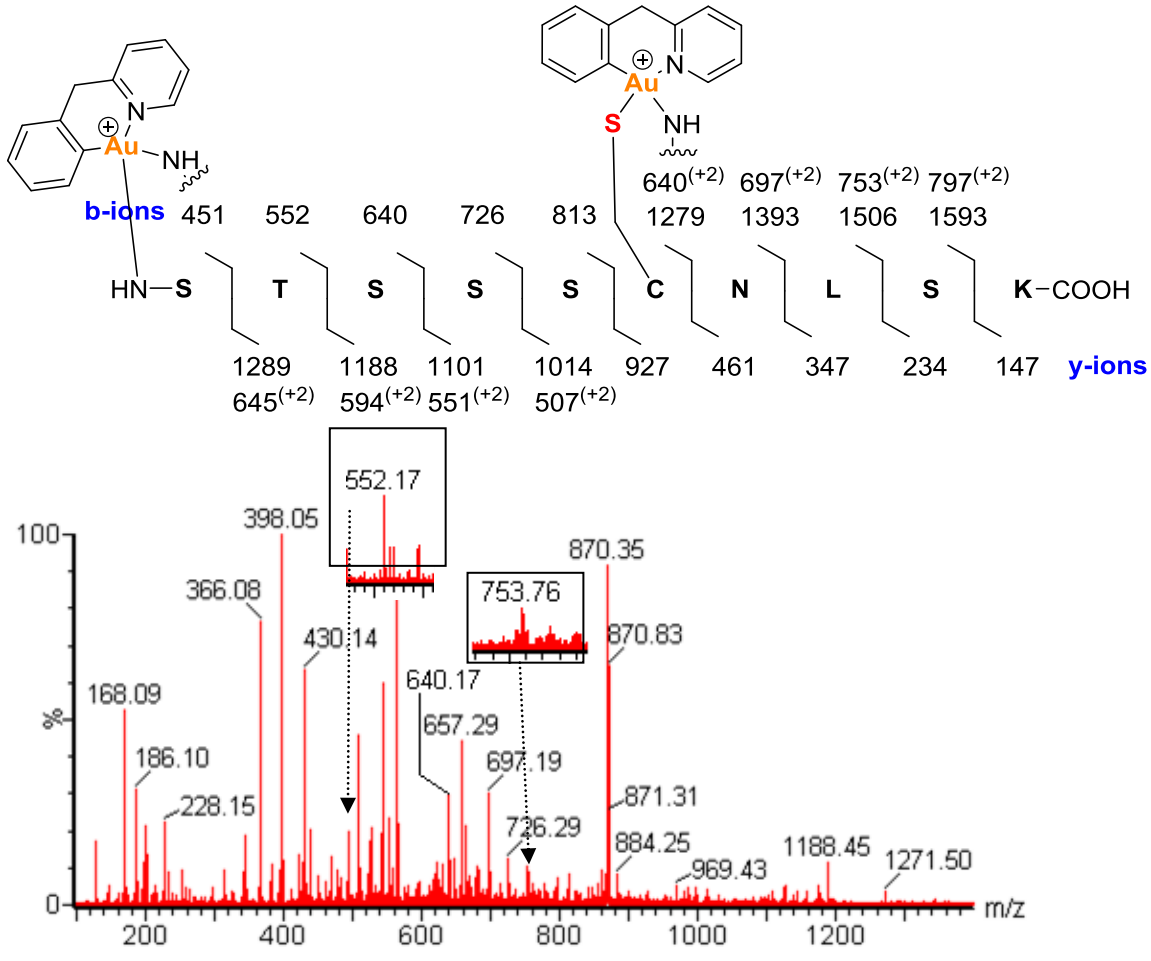


Figure 3.17 MS/MS spectrum of **3.3a'** (ESI source, doubly charged ion of *m/z* = 870.3).

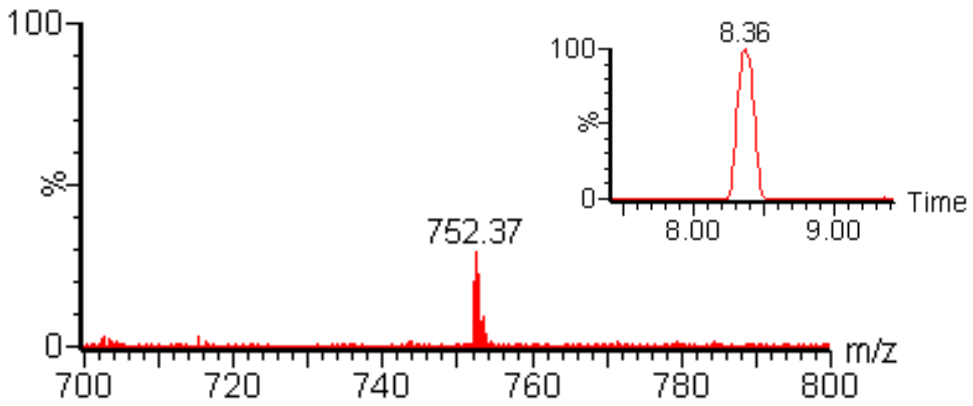


Figure 3.18 MS spectrum of **3.3f** (Doubly charged ion of *m/z* = 752.3) and XIC chromatogram of **3.3f** at t = 8.36 min (inset).

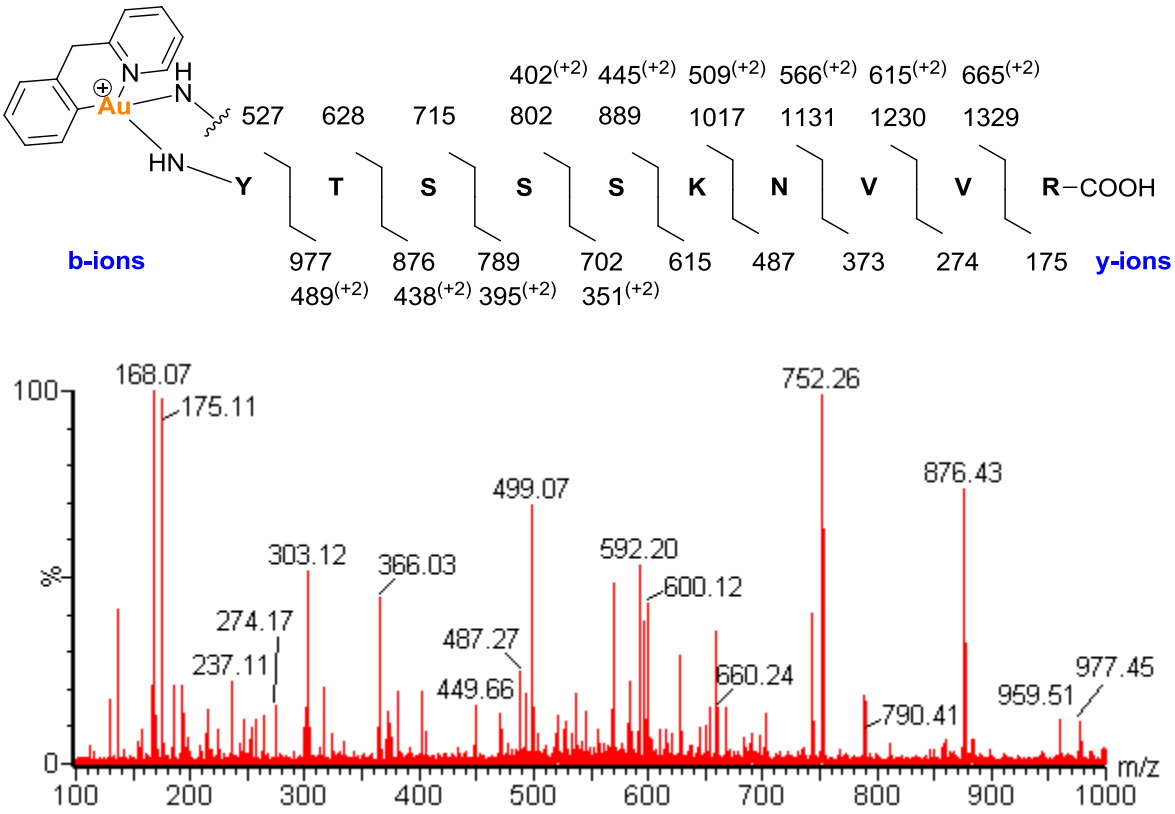


Figure 3.19 MS/MS spectrum of **3.3f** (ESI source, doubly charged ion of m/z = 752.3).

The above findings indicated that complex **3.1a** with msen as the ancillary ligand exhibits excellent chemoselectivity in cysteine modification while complex **3.1d** with chloride ions as the ancillary ligands gives poor cysteine selectivity. It could be explained by the chemical hardness[52] together with the chelating effect of the ancillary ligands in the cyclometallated gold(III) complexes **3.1a** and **3.1d**. According to the relative "hardness" of the ligands listed in below, the msen ligand has moderate "hardness" among sulfhydryl (-SH), amines (RNH_2) and chlorides (Figure 3.20).

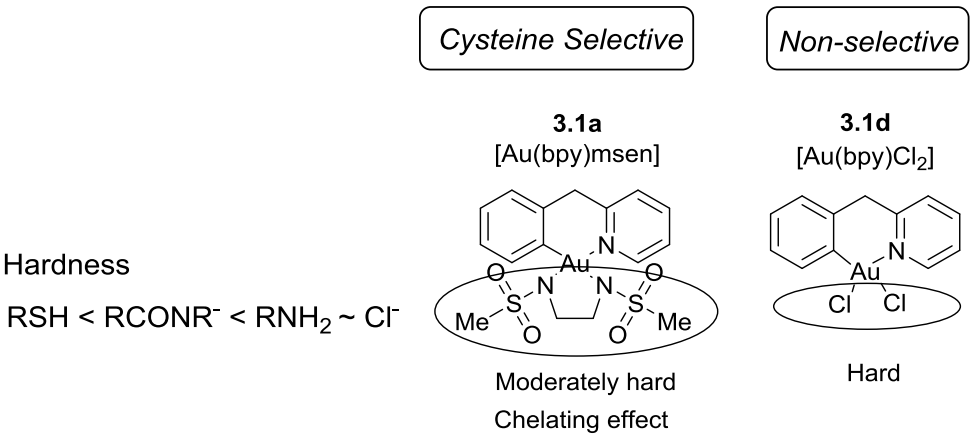
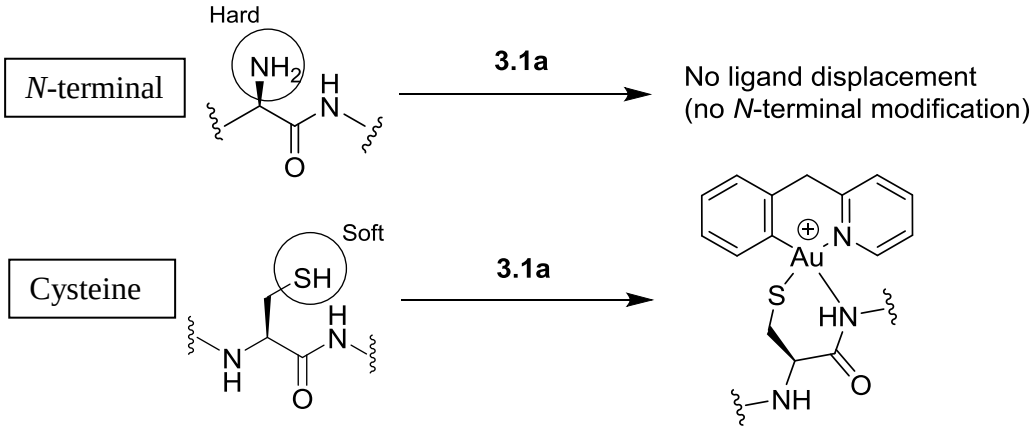


Figure 3.20 Relative hardness of the ancillary ligands in gold(III) complexes.

Deprotonated sulfonamide groups of the msen ligand (chemically "softer" than chloride ions) of complex **3.1a** bind to the soft gold(III) centre to give stronger Au-N bonds. Furthermore, the chelating effect of the bidentate msen ligand makes it difficult to dissociate and hence offers extra stability to complex **3.1a**. Thus, hard monodentate ligands such as ROH and RNH_2 from peptides could not displace the msen ligand from complex **3.1a**. As shown in Table 1, the msen ligand only can be substituted by the "softer" RS^- group in the peptide sequence to give the gold-peptide adducts that renders cysteine selectivity. *N*-Terminal α-amino group of peptides is a hard base and hence ligand substitution to the msen

ligand of complex **3.1a** is difficult (i.e. no *N*-terminal modification) (Scheme 3.20). On the contrary, the hard chloride ions in complex **3.1d** could be substituted easily by the hard *N*-terminal α-amino group of peptides, resulting in non-selective cysteine and *N*-terminal modification.



Scheme 3.20 Ligand displacement reactions of "hard" ligand (R-NH_2) and "soft" ligand (R-S^-) with complex **3.1a**.

A time course experiment monitoring the formation of gold-peptide adduct **3.3a** from [Au(bpy)msen] **3.1a** and peptide **3.2a** in various pH values was conducted at 25 ^{o}C (Figure 3.21). In 1 h, the conjugation reaction gave around 80% conversions at pH 7.4-9.3, while only 65% conversion was observed at pH 6.2. After 2 h, quantitative substrate conversions were achieved at pH 6.2-9.3. These results indicated that the formation of gold-peptide adducts in a wide physiological pH range could proceed smoothly at 25 ^{o}C.

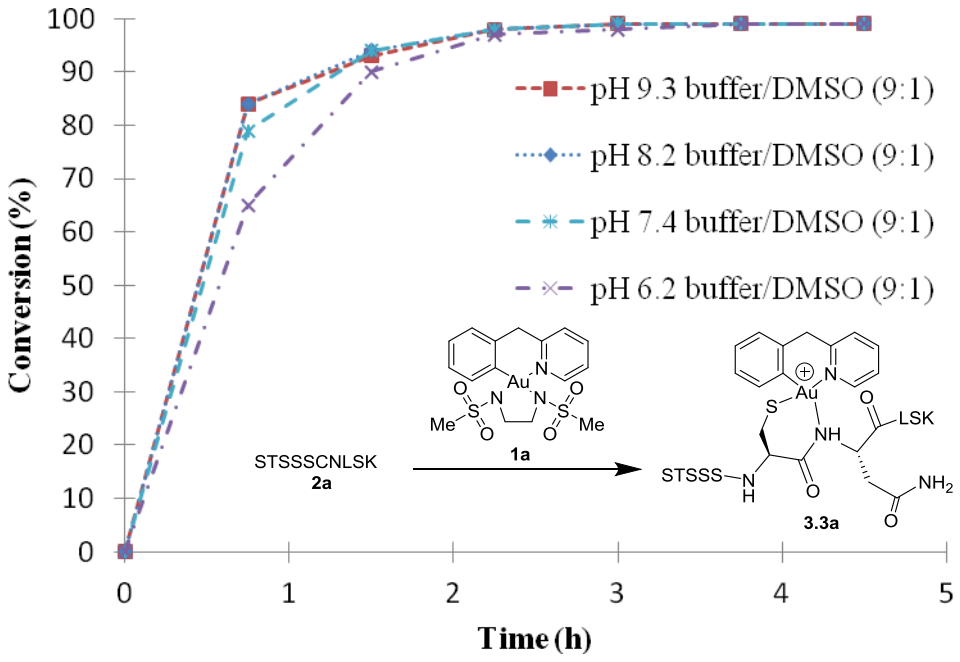
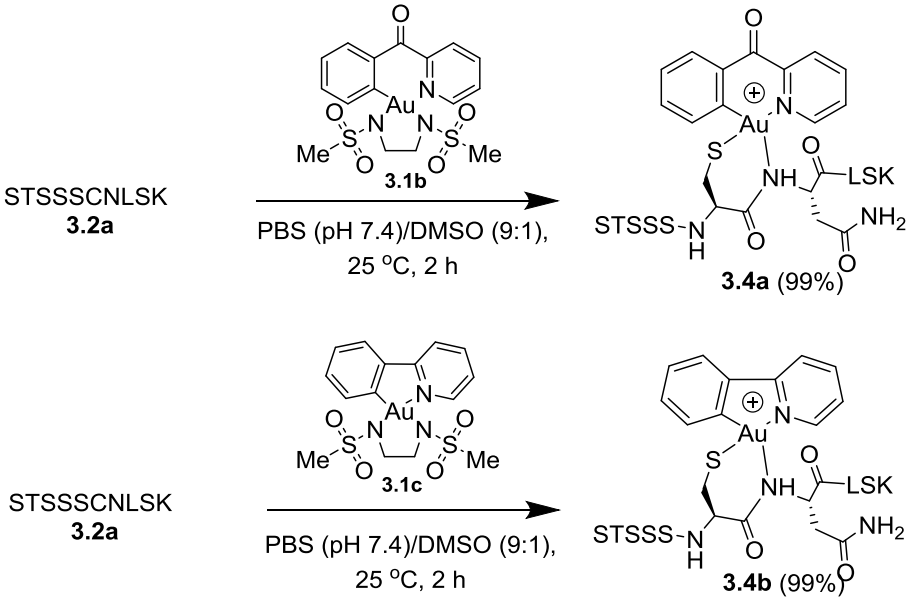


Figure 3.21 The formation of **3.3a** in various pH values.

Cyclometallated gold(III) complexes [Au(pcp)msen] (**3.1b**, Hpcp = 2-benzoylpyridine) and [Au(ppy)msen] (**3.1c**, Hppy = 2-phenylpyridine) were employed in modification of peptide **3.2a** to afford gold-peptide adducts **3.4a** and **3.4b** quantitatively in the same reaction condition as **3.1a** (Scheme 3.21). The cysteine selectivity of gold complexes **3.1b-c** to peptide **3.2a** was confirmed by LC-MS/MS analysis of the corresponding gold-peptide adducts.



Scheme 3.21 Modification of peptide **3.2a** by gold complexes **3.1b** and **3.1c**.

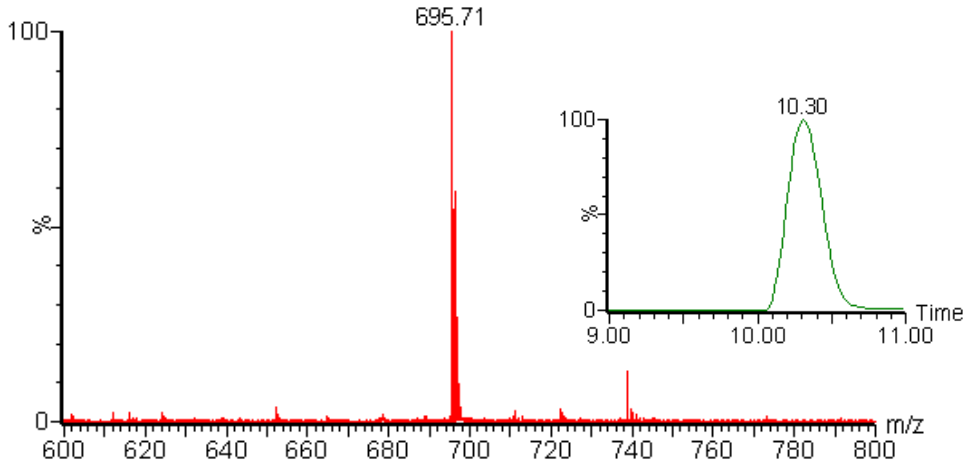


Figure 3.22 MS spectrum of **3.4a** (Doubly charged ion of *m/z* = 695.7) and XIC chromatogram of **3.4a** at t = 10.30 min (inset).

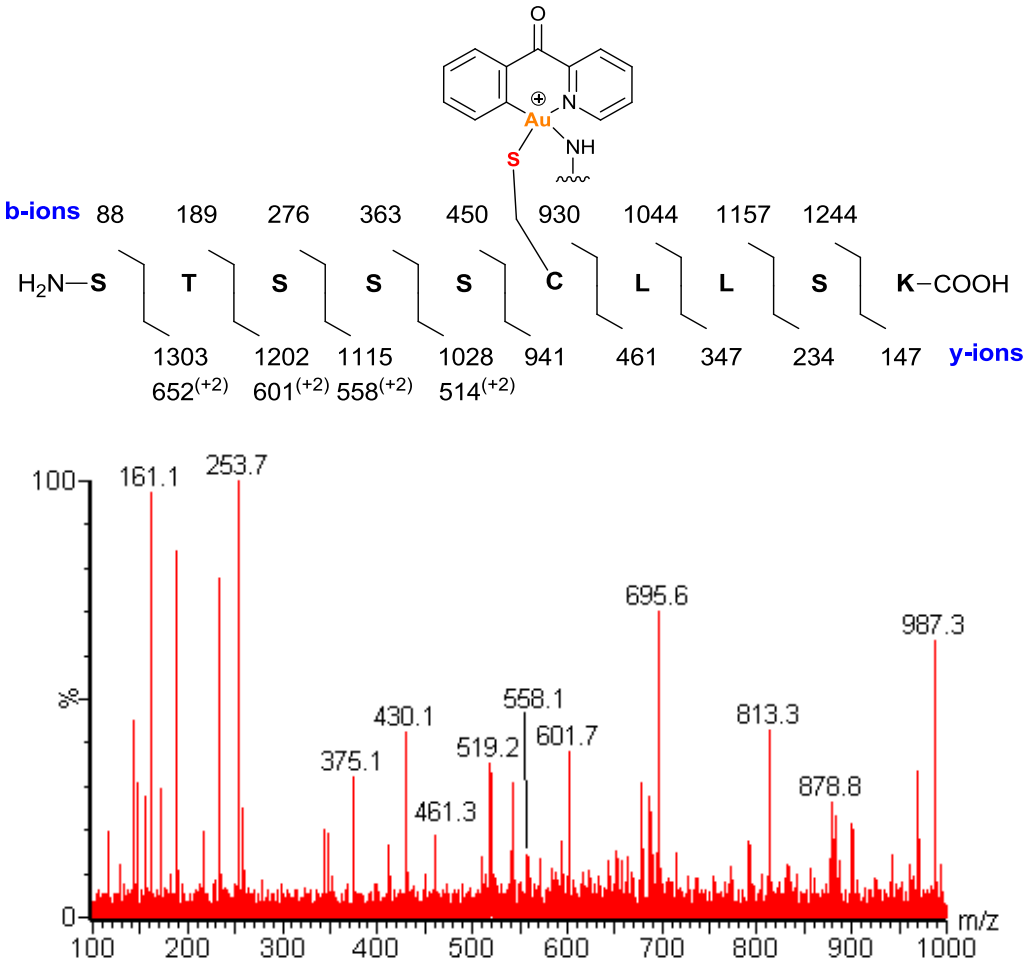


Figure 3.23 MS/MS spectrum of **3.4a** (ESI source, doubly charged ion of *m/z* = 695.6).

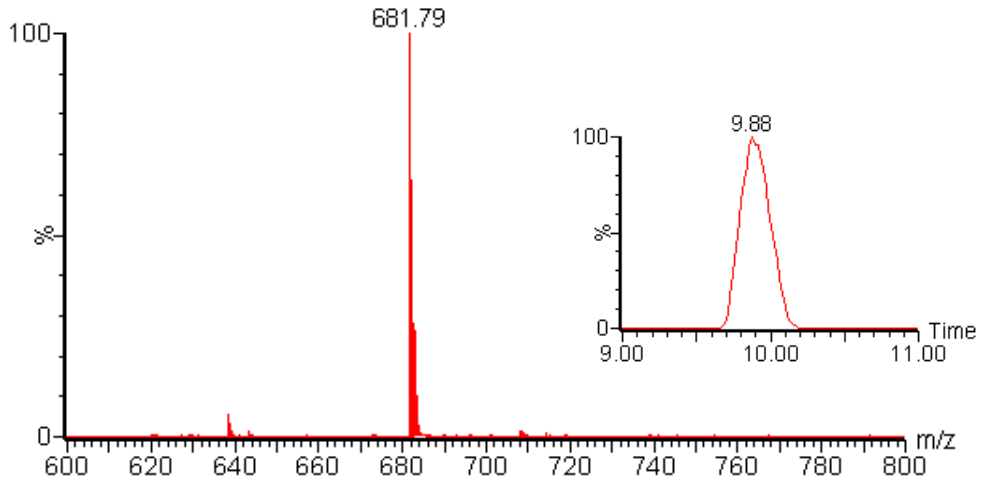
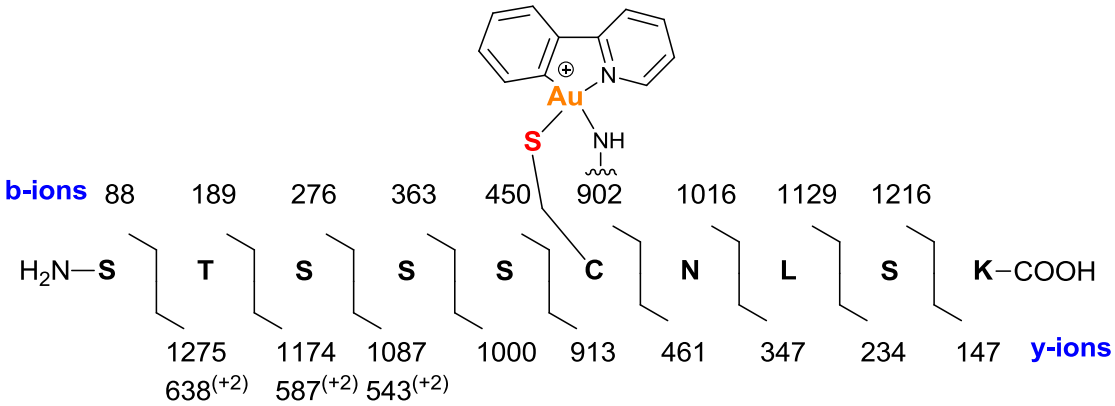


Figure 3.24 MS spectrum of **3.4b** (Doubly charged ion of *m/z* = 681.8) and XIC chromatogram of **3.4b** at t = 9.88 min (inset).



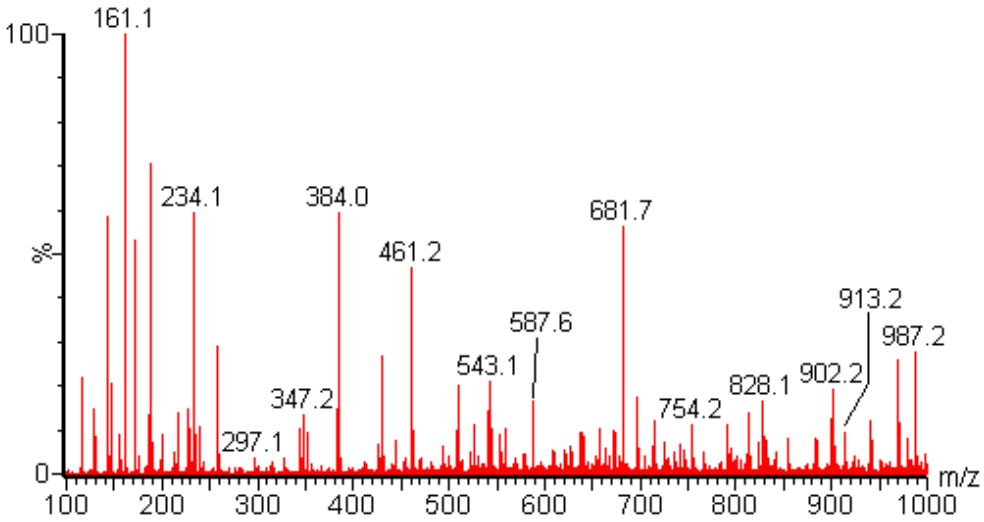


Figure 3.25 MS/MS spectrum of **3.4b** (ESI source, doubly charged ion of *m/z* = 681.8).

3.3.3 Model Studies of Interactions between Cysteine-containing Peptides and Gold(III) Complexes

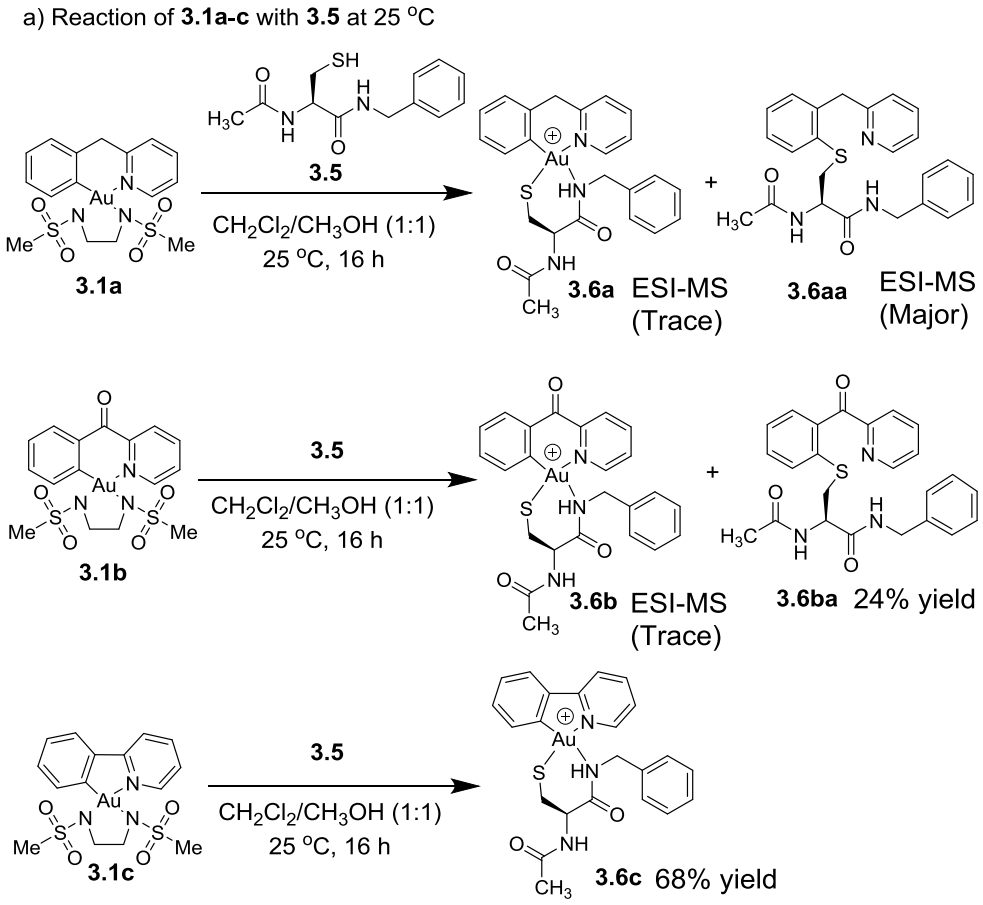
Model studies of gold-cysteine interaction using *N*-acetyl-L-cysteine benzyl amide **3.5** as a cysteine model were conducted (Scheme 3.22). Treatment of complex **3.1a** with cysteine amide **3.5** in CH_2Cl_2/CH_3OH (1:1) at 25 ^oC for 16 h gave product mixtures containing a trace amount of gold-cysteine adduct **3.6a** and reductive elimination product **3.6aa** as the major product as indicated by ESI-MS analysis of the crude mixture (Scheme 3.22a). [Au(pcp)msen] **3.1b** reacted with **3.5** in CH_2Cl_2/CH_3OH (1:1) at 25 ^oC for 16 h to afford a trace amount of gold-cysteine adduct **3.6b** (by ESI-MS analysis) and reductive elimination product **3.6ba** in 24% isolated yield (Scheme 3.22a). In contrast, no reductive elimination product was found when [Au(ppy)msen] **3.1c** and **3.5** were mixed in CH_2Cl_2/CH_3OH (1:1) at 25 ^oC for 16 h. Instead, a gold-cysteine adduct **3.6c** was found in 68% isolated yield (Scheme 3.22a).

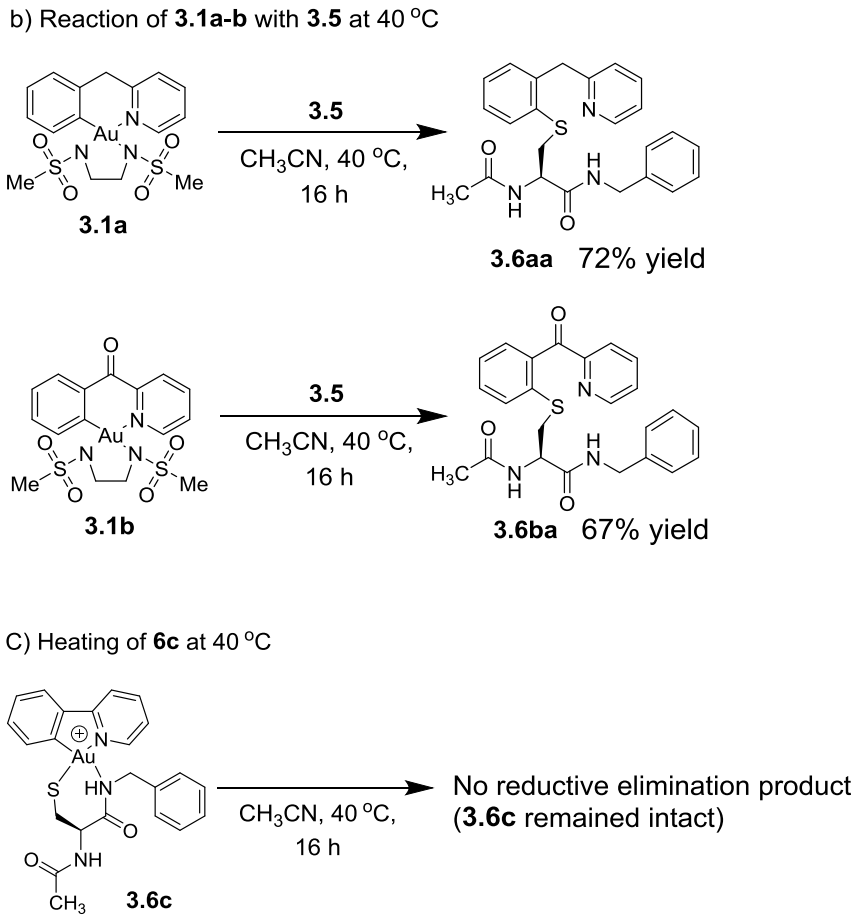
We found that the reductive elimination reactions occurred easily at 40 ^oC. By heating a mixture of **3.1a** and **3.5** in CH_3CN at 40 ^oC for 16 h, reductive elimination product **3.6aa** was formed in 72% isolated yield (Scheme 3.22b). Under the same reaction conditions, [Au(pcp)msen] **3.1b** reacted with **3.5** to give **3.6ba** in 67% isolated yield (Scheme 3.22b). However, gold-cysteine adduct **3.6c** remained intact when it was heated at 40 ^oC for 16 h (Scheme 3.22c).

Purple-coloured precipitates were found in the reaction mixture at the end of the reactions. We suggest that these precipitates would consist of metallic gold or gold nanoparticles with aggregates. According to literatures of C-C bond formation by reductive elimination of gold(III) compounds, cyclometallated gold(III) complexes would undergo C-S

bond formation to form *S*-arylated products together with gold(I) species.[36b, 40c, 41b, 41e] The gold(I) species without stabilization by ligands would further reduce to metallic form or nanoparticles under heating.

As ligands such as phosphine are needed in the reaction mixture in order to enhance the stability of Au(I) species, we have conducted reactions of gold(III) complex **3.1a** (or **3.1b**) with *N*-acetyl-L-cysteine benzyl amide **3.5** in the presence of an equivalent of triphenylphosphine (PPh_3) in CH_3CN at 40 ^oC for 24 h. the *S*-arylated product **3.6aa** (or **3.6ba**), gold(I) phosphine species (i.e. $[PPh_3Au]^+$ and $[(PPh_3)_2Au]^+$) were detected by ESI-MS (Figure 3.26).





Scheme 3.22 Model studies of gold-cysteine interaction using **3.5**.

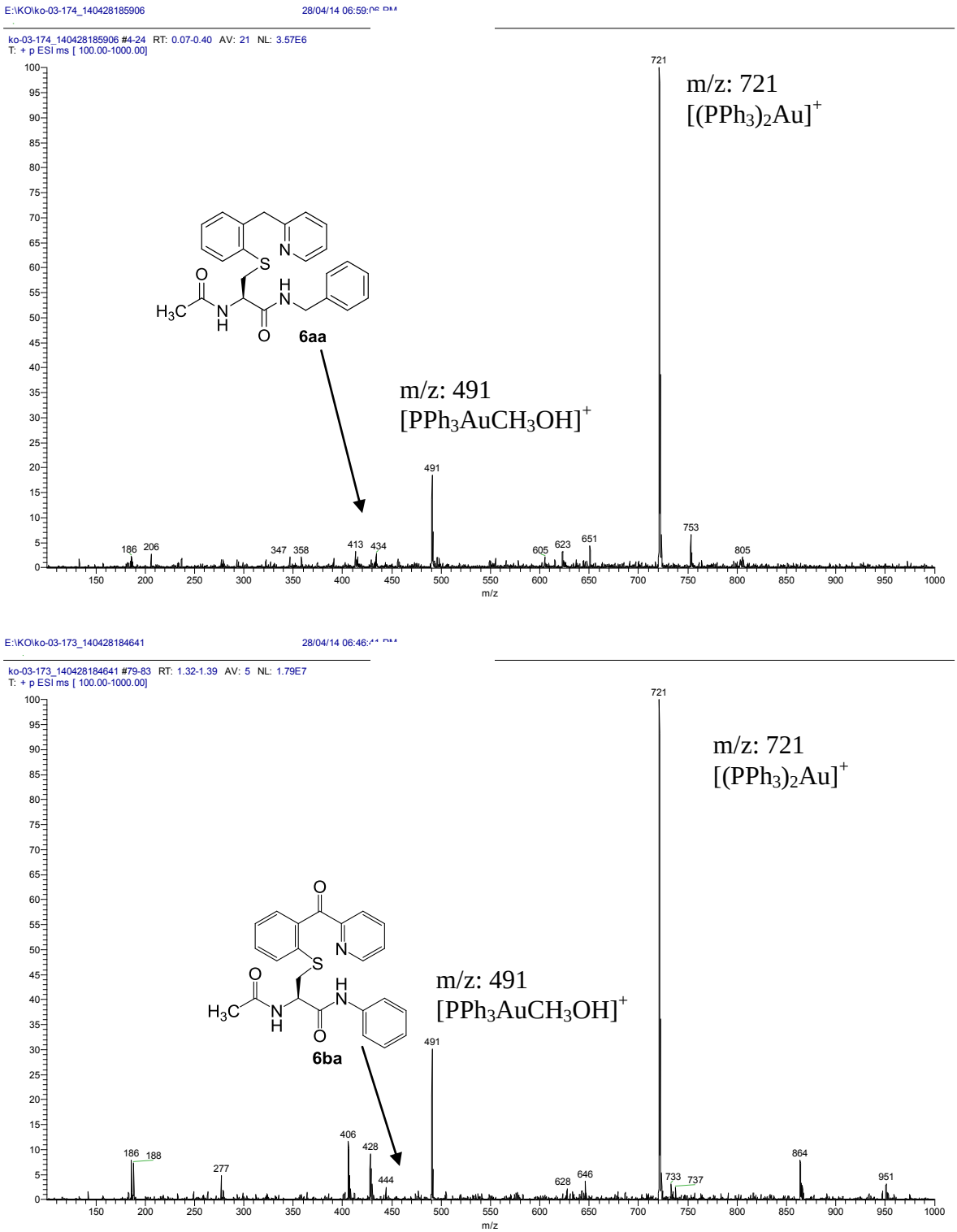


Figure 3.26 ESI-MS spectra of the crude mixture of reactions of **1a** (or **1b**) with **5** in the presence of PPh_3.

The structure of the gold-peptide adduct intermediates was studied by a model reaction of [Au(ppy)msen] **3.1c** with *N*-acetyl-L-cysteine benzyl amide **3.5** to give the corresponding gold-cysteine adduct **3.6c** which was characterized by ^{1}H, ^{13}C NMR as well as ESI-MS. The structure of **3.6c** was suggested to contain bidentate coordination of 2-phenylpyridine to the Au centre via C,N-donors. Two amide –NH protons (H^5 and H^6) were found to be retained in **3.6c** and assigned by 2D COSY experiments (Figure 3.27). ^{1}H NMR spectra of **3.6c** showed downfield chemical shifts of H^1, H^2 ($\Delta\delta$ = +0.60, +0.57) and H^3 ($\Delta\delta$ = +0.14) compared to *N*-acetyl-L-cysteine benzyl amine **3.5** (Table 3.2). These changes in chemical shifts combining with the disappearance of –SH signal in ^{1}H NMR and downfield shift of C_2 ($\Delta\delta$ = +8.1) in ^{13}C NMR (Table 3.3) indicated the formation of a Au-S bond. Furthermore, the slightly upfield chemical shifts of H^5 ($\Delta\delta$ = -0.04) and the benzylic protons H^4 ($\Delta\delta$ = -0.03) suggested the coordination of the neighbour –NH to the gold centre. On the basis of the NMR spectra and literatures,[53] it was suggested that **3.5** coordinates to the Au(III) centre via S,N-donors to afford a metallocycle. The sulfur ligand was proposed to be *cis* to the sp^2 carbon in 2-phenylpyridine because of the strong *trans* effect of RS^- and Ph^-. No reductive elimination product was found when compound **3.6c** was heated at 40 ^{o}C for 16 h. This suggested that gold-cysteine adduct with 2-phenylpyridine ligand was stable towards reductive elimination under the reaction conditions.

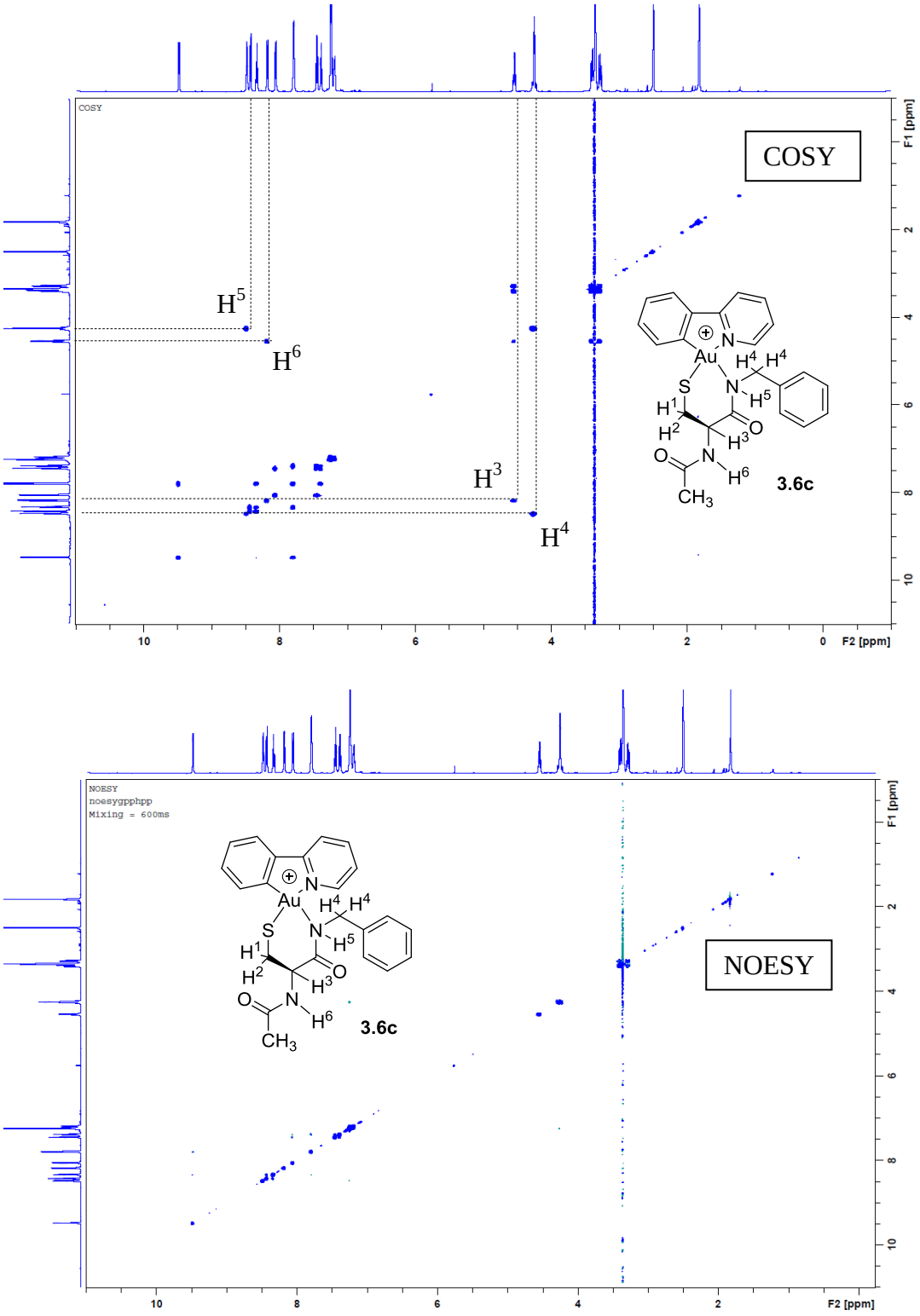


Figure 3.27 2D COSY and NOESY spectra of gold-cysteine adduct **3.6c**.

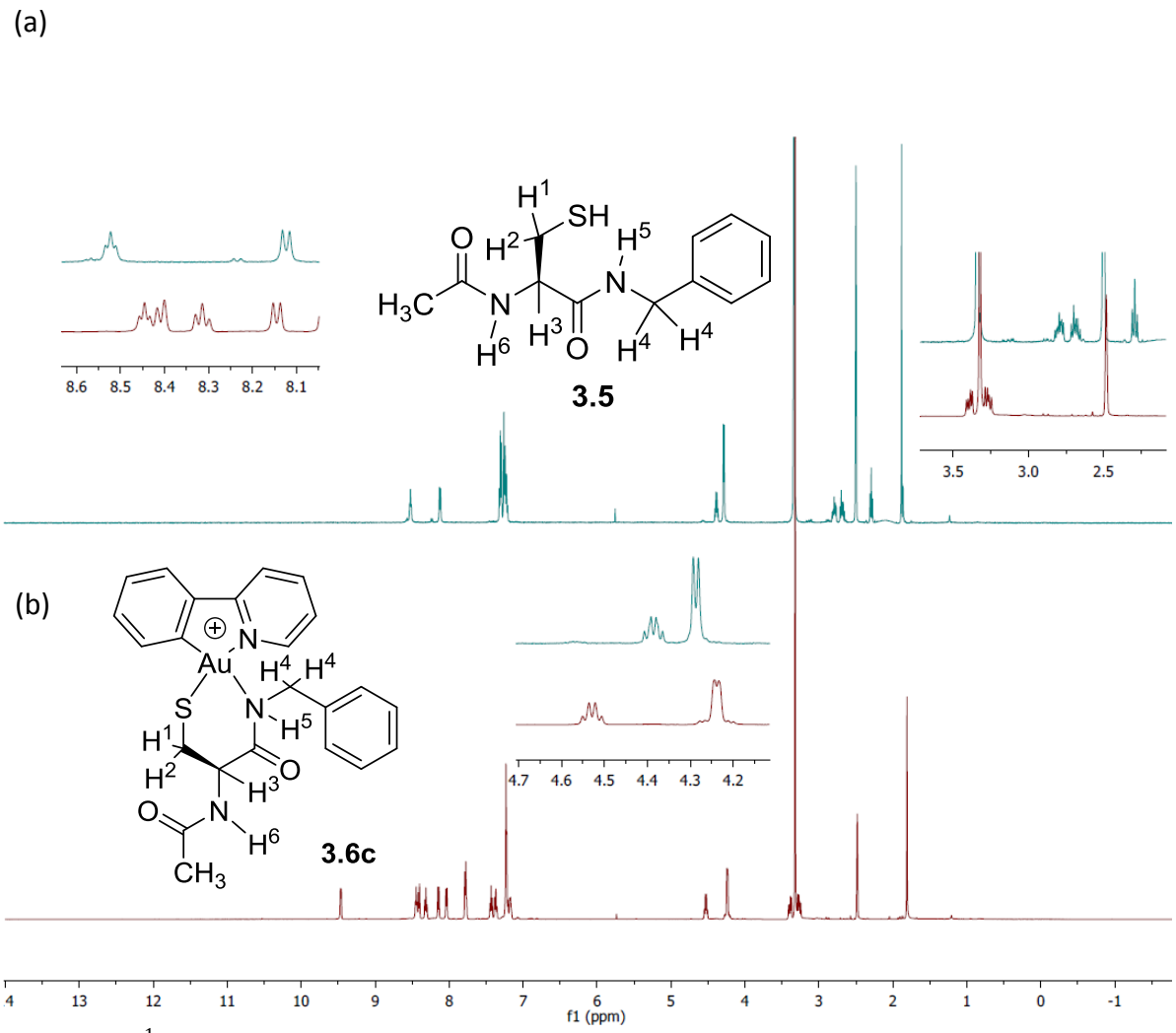


Figure 3.28 ^{1}H NMR spectra of compound **3.5** (a) and **3.6c** (b).

Table 3.2 ^{1}H NMR chemical shifts (δ) for compound **3.5** and gold-cysteine adduct **3.6c**.

δ (ppm)	H^1, H^2	H^3	H^4	H^5	H^6	S*H*
3.5	2.79, 2.70	4.39	4.29	8.52	8.13	2.29
3.6c	3.39, 3.27	4.53	4.24	8.48	8.14	/[a]
$\Delta\delta$[b]	+0.60, +0.57	+0.14	-0.03	-0.04	+0.01	/[a]

[a] '/'= a peak is missing. [b] $\Delta\delta = \delta$(complex) - δ(ligand).

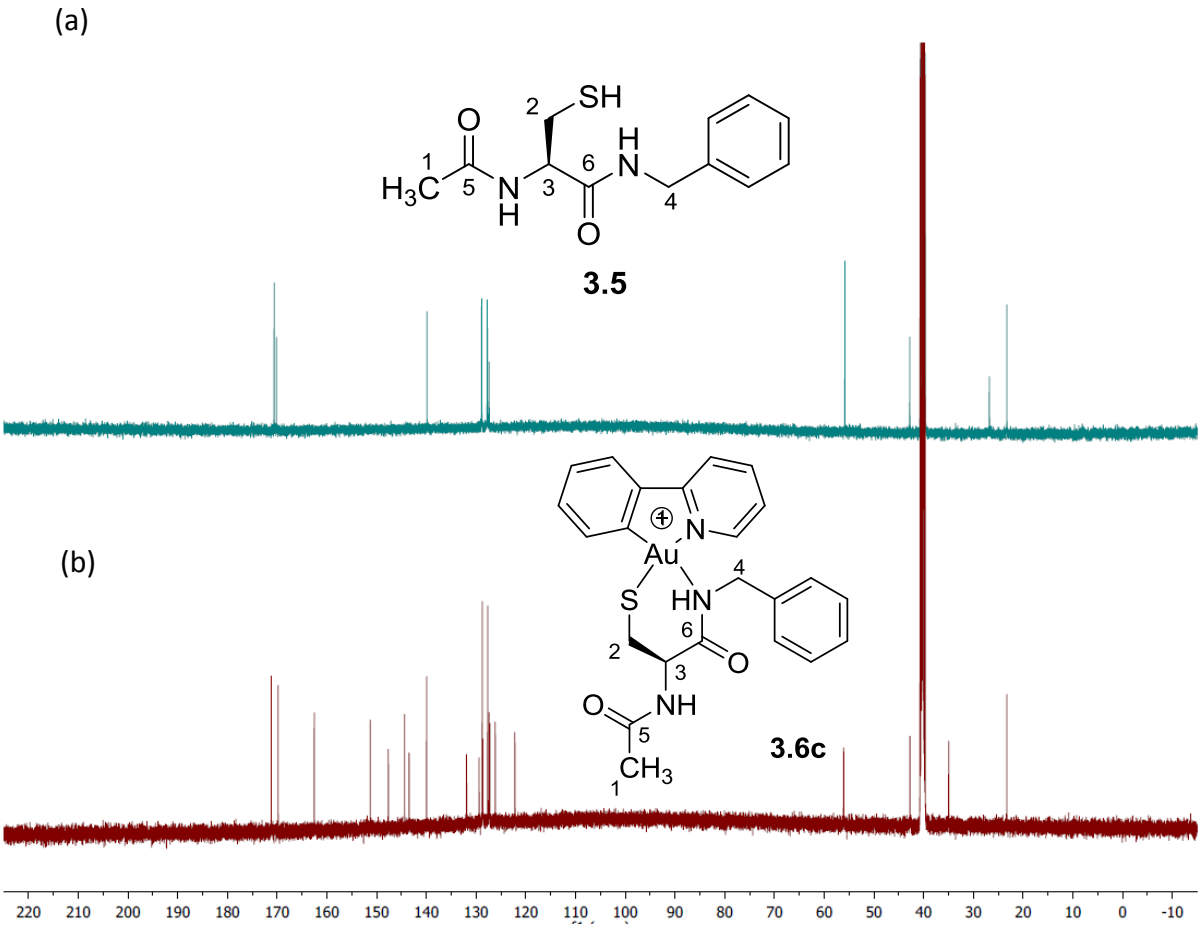


Figure 3.29 ^{13}C NMR spectra of compound **3.5** (a) and **3.6c** (b).

Table 3.3 ^{13}C NMR chemical shifts (δ) for compound **3.5** and gold-cysteine **3.6c**.

δ (ppm)	C^1	C^2	C^3	C^4	C^5, C^6 (ambiguous)
3.5	23.3	26.8	42.8	55.9	170.1, 170.6
3.6c	23.3	34.9	42.8	56.1	169.8, 171.2
$\Delta\delta^b$	0	+8.1	0	+0.2	-0.3, + 0.6

[a] '/'= a peak is missing. [b] Δδ = δ(complex) - δ(ligand).

Explanation of tendency towards reductive elimination in model studies

The above model studies indicated that gold-cysteine adducts with 2-benzylpyridine (**3.6a**) or 2-benzyolpyridine (**3.6b**) ligands easily underwent reductive elimination to give *S*-arylated cysteines while gold-cysteine adduct **3.6c** with 2-phenylpyridine ligand resisted to undergo reductive elimination. As all the complexes **3.1a-c** have the same msen ancillary ligand, the different reactivities in reductive elimination would be attributed to the arylpyridine ligands. Comparing the lengths of the Au-C bond of [Au(ppy)Cl_2] (1.950 Å)[54] with [Au(mppy)Cl_2] (2.021 Å)[55] (Hmppy = 2-(1-methyl-1-phenylethyl)pyridine) and [Au(pcp)Cl_2] (2.033 Å),[56] it is noted that the gold(III) complexes with 2-phenylpyridine ligand have shorter Au-C bond lengths than the other (C,N) cyclometallated gold(III) complexes (Figure 3.30). The differences in the Au-C bond lengths could be related to the tendency of these gold complexes to afford *S*-arylated cysteine products.[40b] It would be reasonable to assume that weakening of the Au-C bond (i.e., longer bond length) would facilitate the reductive elimination reaction. Thus, the Au-C bond of gold-cysteine adduct **3.6b** with 2-benzyolpyridine ligand was weaker than that of gold cysteine adducts **3.6a** and **3.6c**, resulting in facile reductive elimination of **3.6b** at 25 ^{o}C.

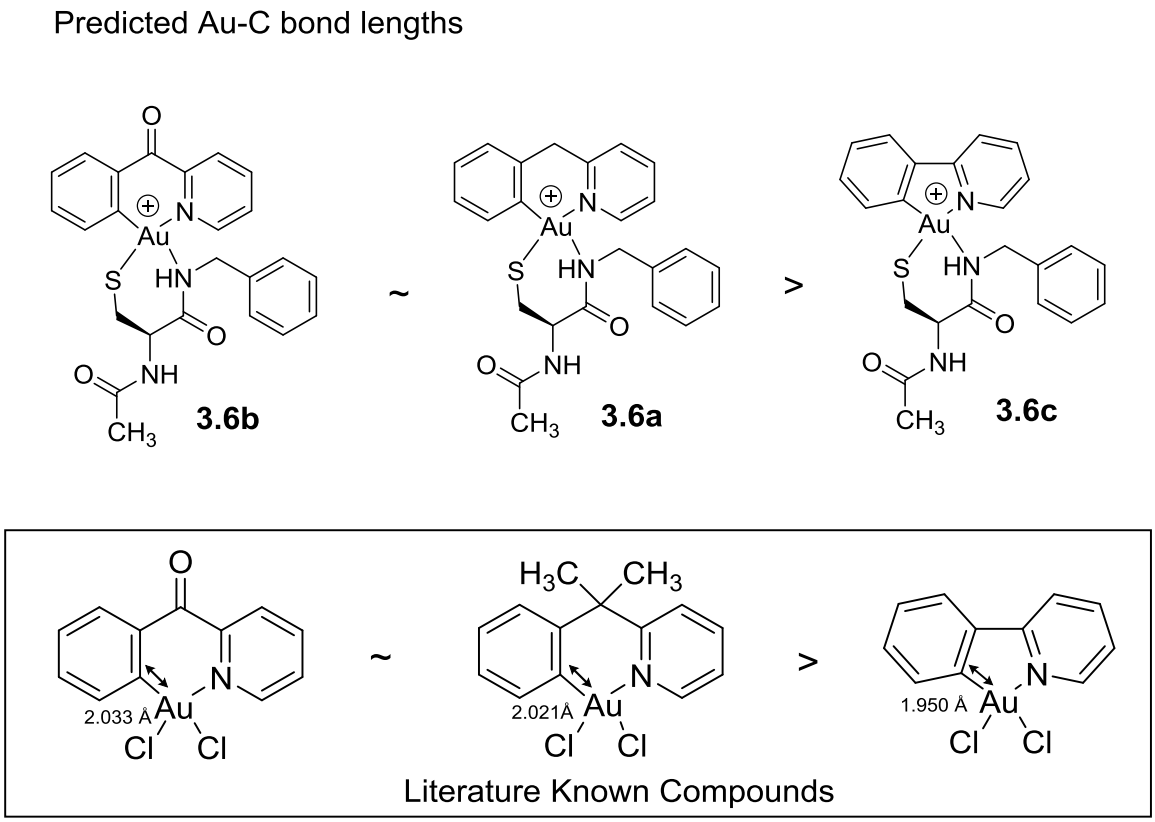
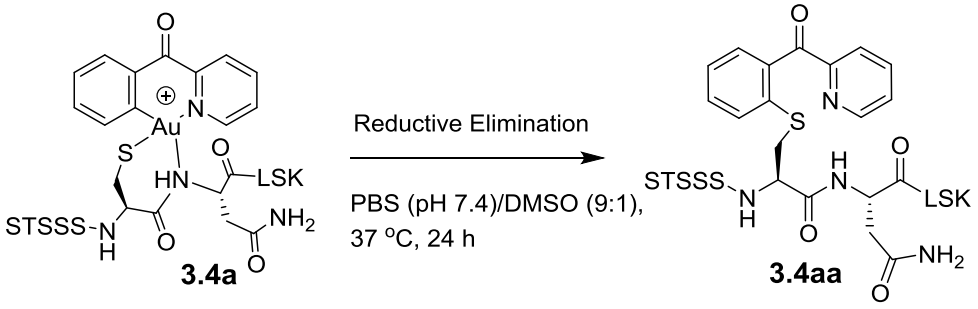


Figure 3.30 Comparison of Au-C bond lengths of gold-cysteine adducts based on the gold(III) dichloride analogues.

3.3.4 Reductive Elimination of Gold-peptide Adducts

Studies on modification of cysteine-containing peptides by C-S bond formation form the gold-peptide adducts **3.3a**, **3.4a** and **3.4b** at 37 ^{o}C for 24 h were performed. Gold-peptide adduct **3.4a** with 2-benzoylpyridine ligand, showing the highest tendency towards reductive elimination in the previous studies, successfully modified peptide **3.2a** to afford *S*-arylated peptide **3.4aa** by ligand controlled C-S bond formation from **3.4a** in 67% conversion at 37 ^{o}C for 24 h (Scheme 3.23). There was no *S*-arylated peptide detected when crude mixtures of corresponding gold(III) adducts **3.3a** and **3.4b** were heated at 37 ^{o}C for 24 h (Figure 3.31). Time course experiments of the formation of *S*-arylated peptide **3.4aa** from gold-peptide adduct **3.4a** at 37 ^{o}C for various pH values were carried out. The reaction was found to proceed smoothly in pH 6.2-9.3 (Figure 3.32). These findings suggested that the reductive elimination from gold-peptide adducts to give *S*-arylated adducts could be achieved under mild reaction conditions and a wide pH range with complex **3.1b**.



Scheme 3.23 Reductive elimination of gold-peptide adduct **3.4a** to *S*-arylated peptide **3.4aa**.

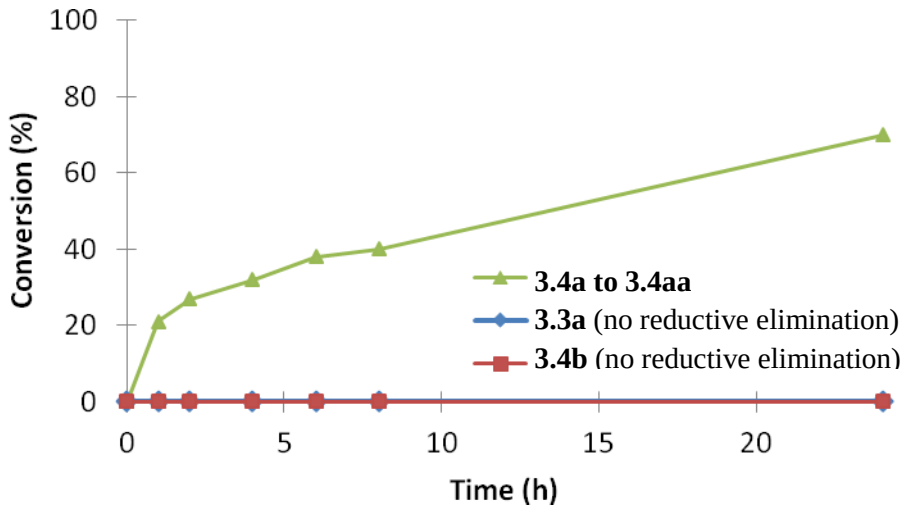


Figure 3.31. Time course studies of conversions of gold-cysteine adduct **3.4a** to *S*-arylated-**3.4aa** by C-S bond formation reaction at 37 ^{o}C.

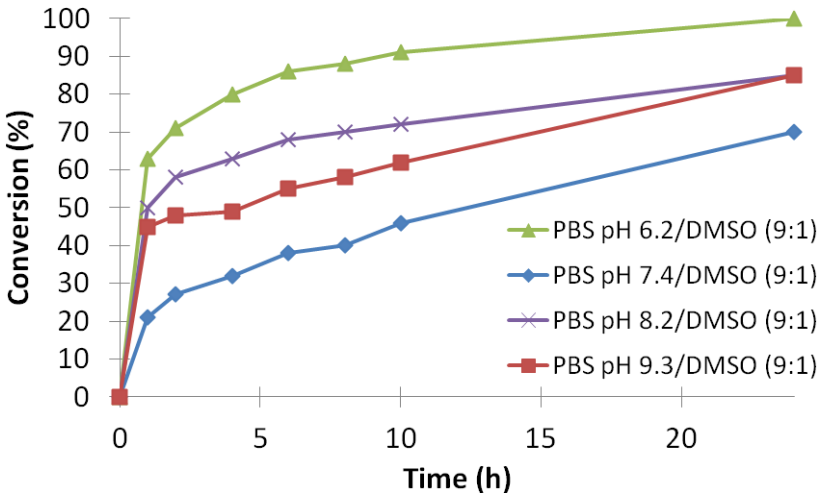
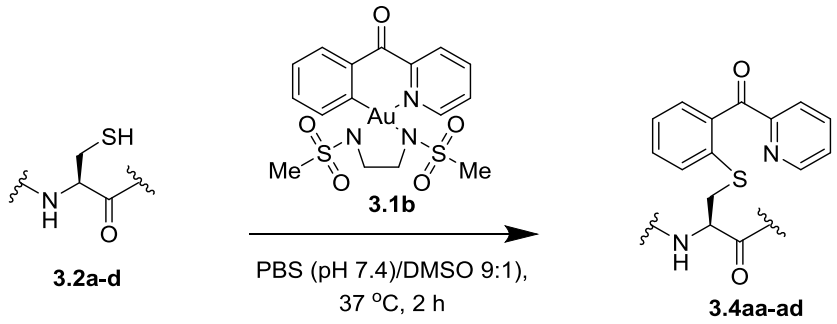


Figure 3.32. Conversions of gold-cysteine adduct **3.4a** to *S*-arylated-**3.4aa** by reductive elimination in various pH values at 37 ^{o}C.

3.3.5 Modification of Cysteine-containing Peptides via C-S Bond-Forming Reductive Elimination

The ligand-controlled C-S bond formation for modification of peptides STSSSCNLSK **3.2a**, AYEMWCFHQK **3.2b**, ASCGTN **3.2c**, and KSTFC **3.2d** were carried out with gold complex **3.1b** in PBS buffer (pH 7.4) by heating at 37 ^{o}C for 18 h (Table 3.4). Qunatitative conversions of corresponding peptides were achieved (Entries 1-4). The cysteine chemoselective modification by gold(III) mediated C-S bond formation from their corresponding gold-peptide adducts were confirmed by LC-MS/MS analysis.

Table 3.4 Modification of peptides using complex **3.1b** at 37 ^{o}C.[a]



Entry	Peptide sequence	Product	Conversion (%)[b]
1	STSSSCNLSK (**3.2a**)	**3.4aa**	67
2	AYEMWCFHQK (**3.2b**)	**3.4ab**	99
3	ASCGTN (**3.2c**)	**3.4ac**	92
4	KSTFC (**3.2d**)	**3.4ad**	99

[a] Peptide **3.2** (0.1 mM) and [Au(pcp)msen] **3.1b** (1 equiv.) in PBS (pH 7.4)/DMSO (9:1) solution (100 μL) at 37 ^{o}C for 2 h. [b] Determined by LC-MS analysis.

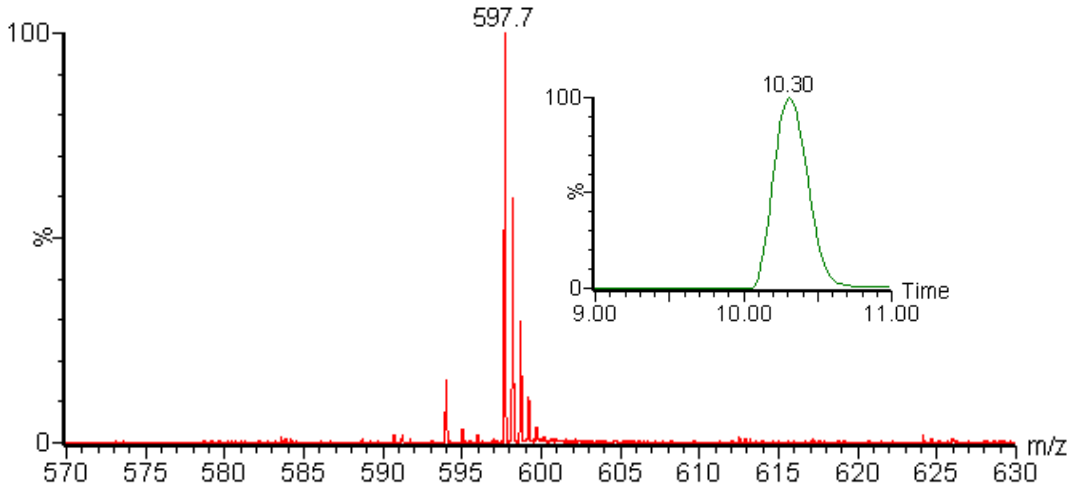


Figure 3.33 MS spectrum of **3.4aa** (Doubly charged ion of *m/z* = 597.7) and XIC chromatogram of **3.4aa** at t = 10.30 min (inset).

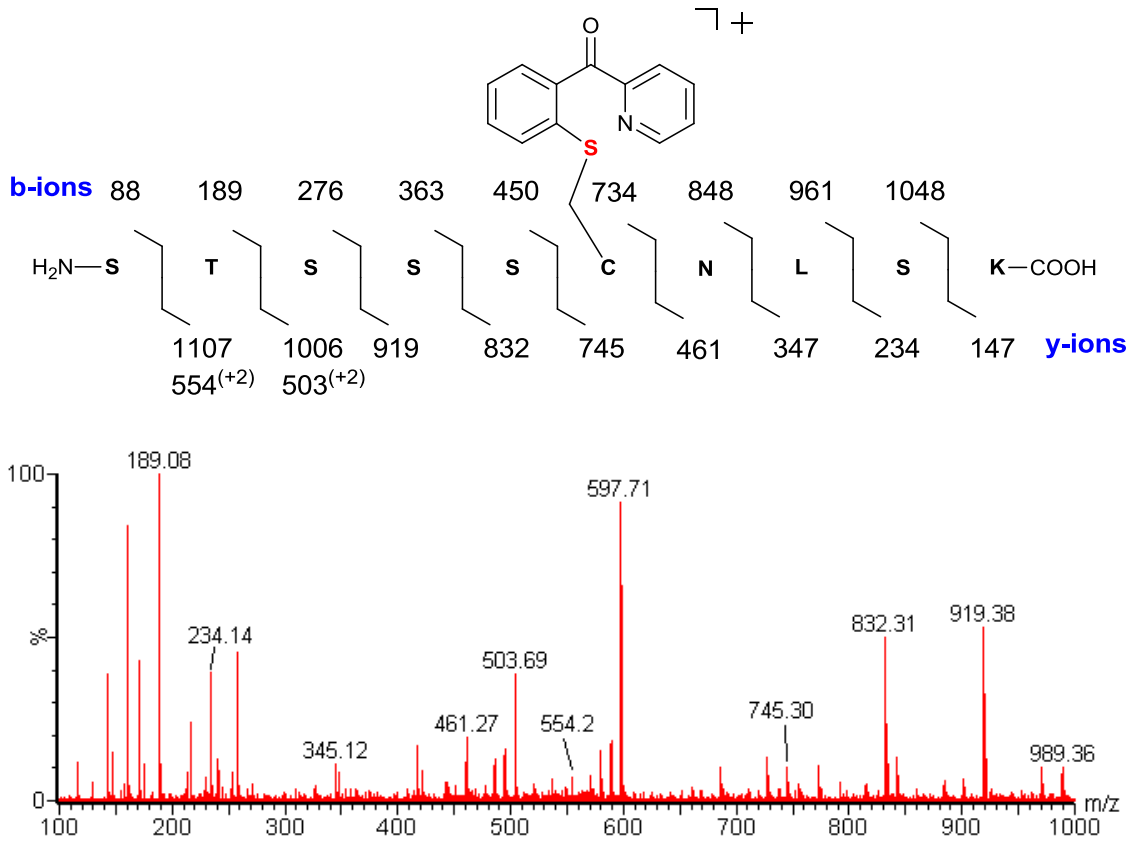


Figure 3.34 MS/MS spectrum of **3.4aa** (ESI source, doubly charged ion of *m/z* = 597.7).

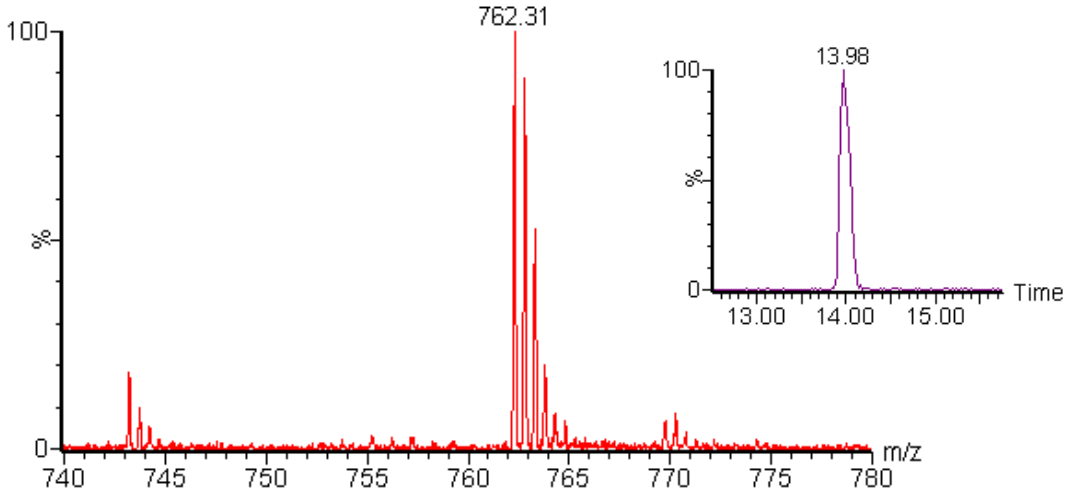
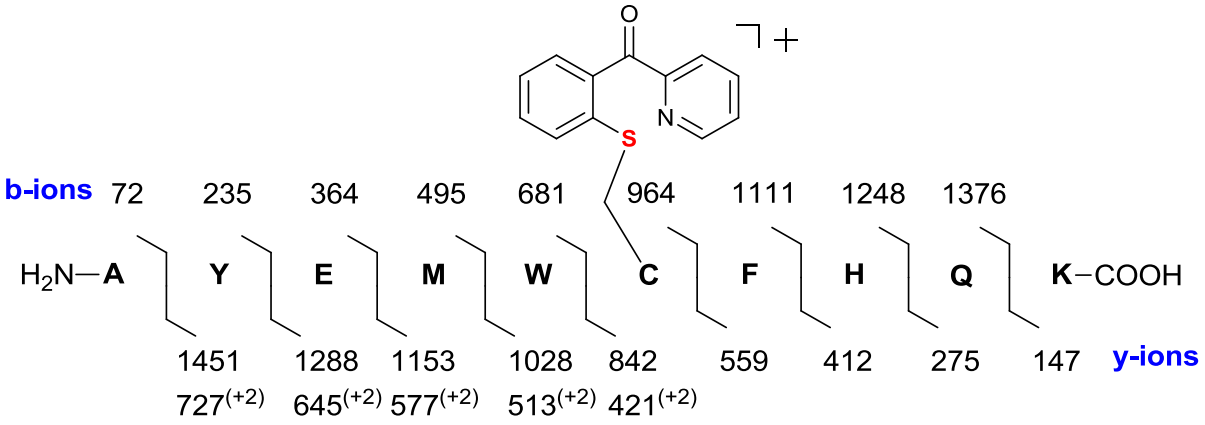


Figure 3.35 MS spectrum of **3.4ab** (Doubly charged ion of *m/z* = 762.3) and XIC chromatogram of **3.4ab** at t = 13.98 min (inset).



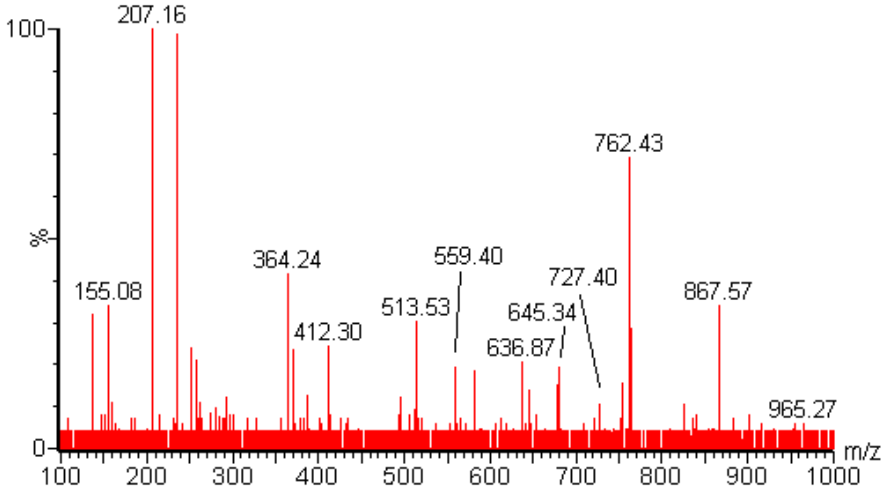


Figure 3.36 MS/MS spectrum of **3.4ab** (ESI source, doubly charged ion of *m/z* = 762.3).

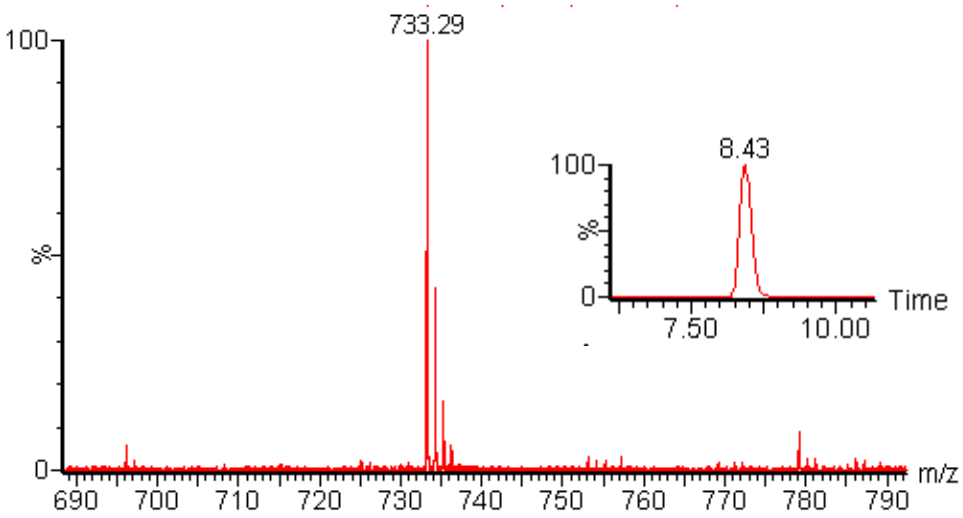


Figure 3.37 MS spectrum of **3.4ac** (Singly charged ion of *m/z* = 733.2) and XIC chromatogram of **3.4ac** at t = 8.43 min (inset).

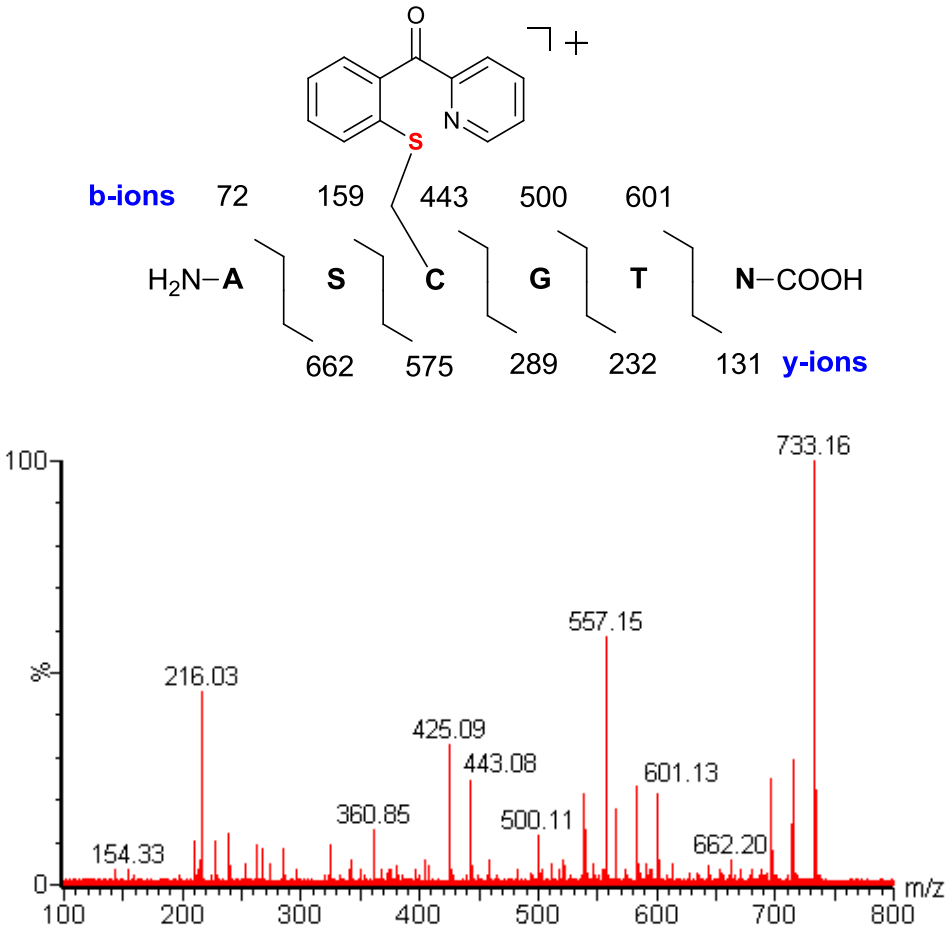


Figure 3.38 MS/MS spectrum of **3.4ac** (ESI source, singly charged ion of *m/z* = 733.2).

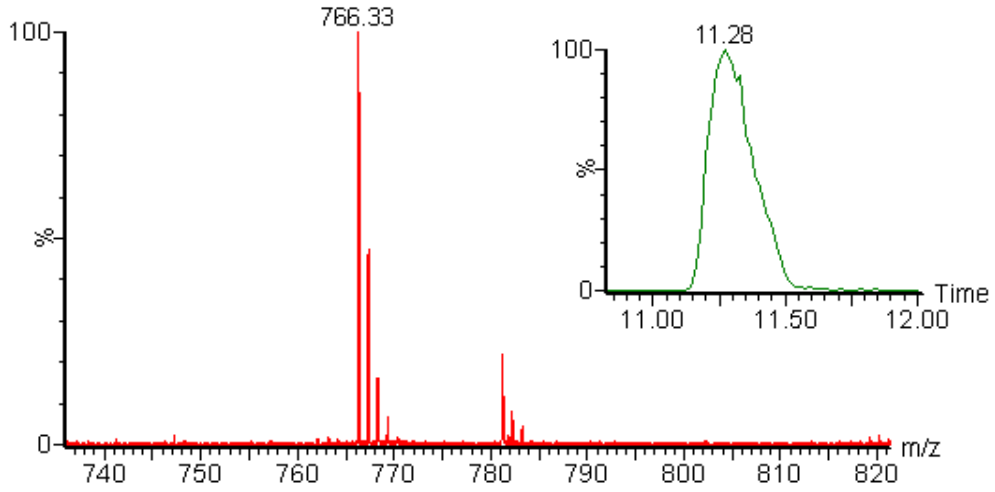


Figure 3.39 MS spectrum of **3.4ad** (Singly charged ion of *m/z* = 766.3) and XIC chromatogram of **3.4ad** at t = 11.28 min (inset).

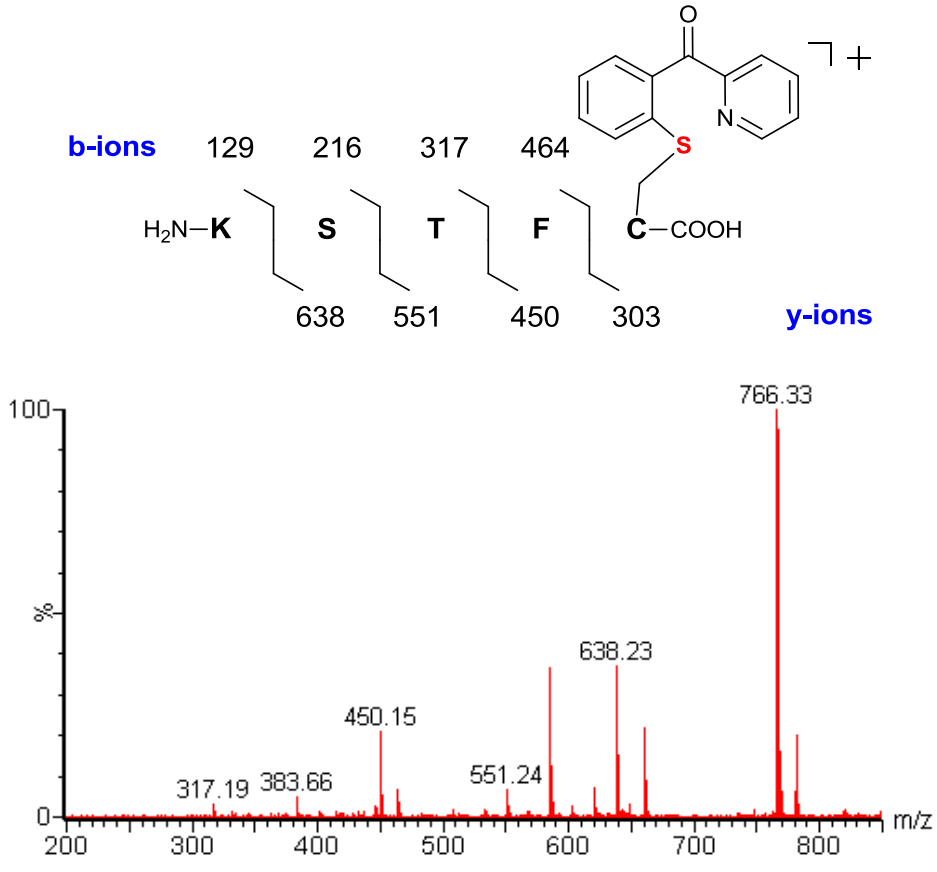
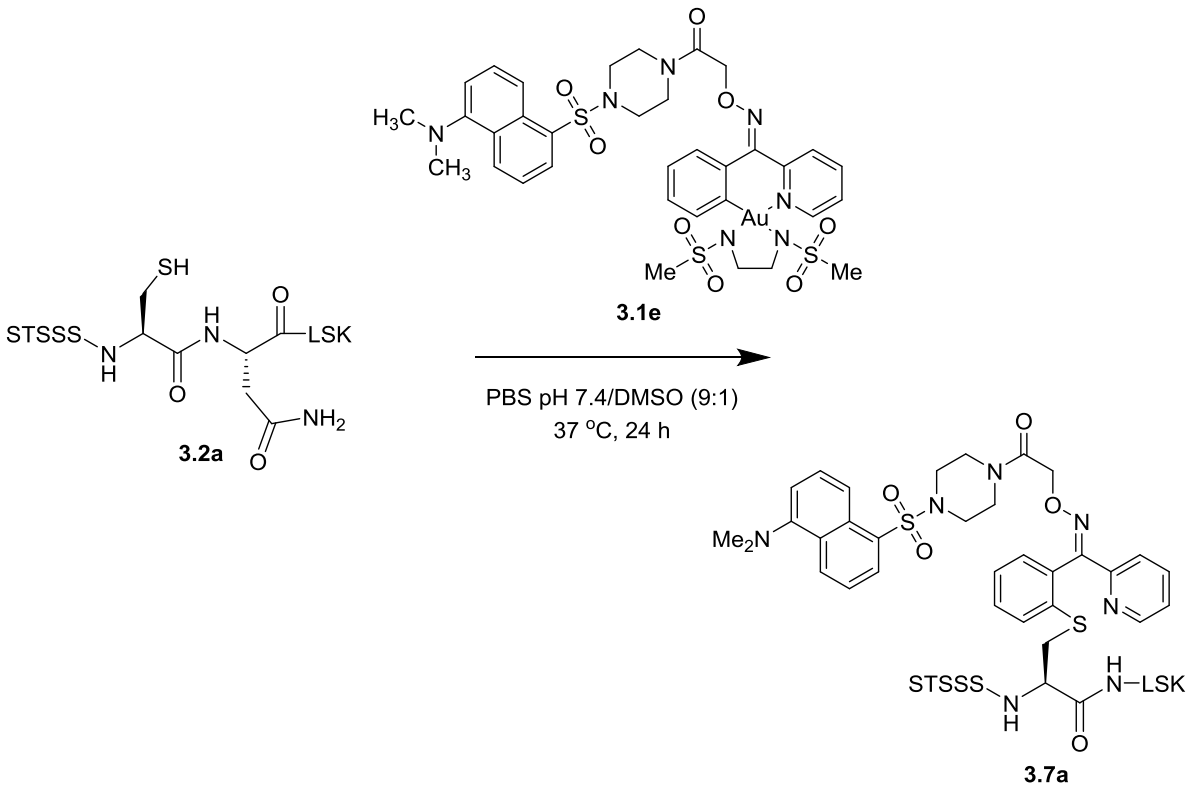


Figure 3.40 MS/MS spectrum of **3.4ad** (ESI source, doubly charged ion of *m/z* = 766.3).

The chemoselective cysteine modification via C-S bond-forming reductive elimination can be further extended by using dansyl-functionalized gold(III) complex **3.1e**. Under the same reaction conditions, it was found that the functionalized gold complex can also exhibit excellent reactivity towards peptide **3.2a**, giving dansyl-linked gold peptide adducts with 78% conversion (Scheme 3.24). This implied that the gold(III) chemoselective cysteine modification strategy can afford bioconjugation of cysteine containing peptides with biophysical probes. The strategy is potentially useful for selective protein modification which is of importance to study the biological systems.



Scheme 3.24 Modification of peptide **3.2a** with dansyl-functionalized gold(III) complex **3.1e**.

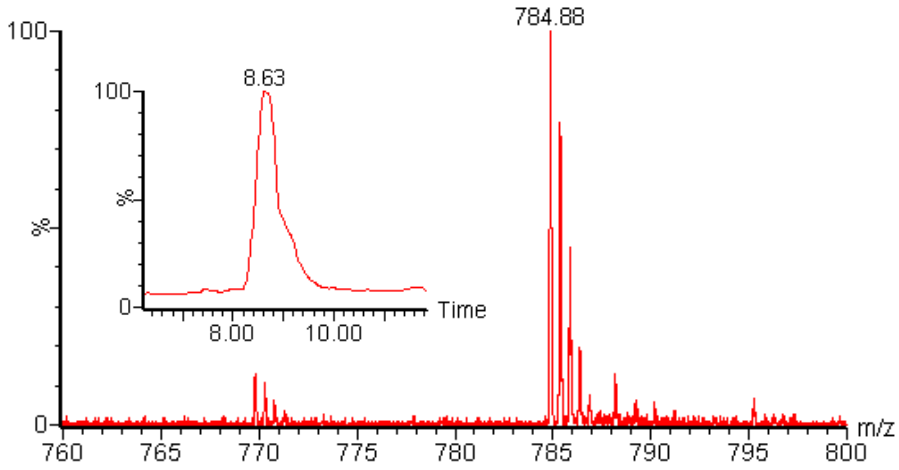


Figure 3.41 MS spectrum of **3.7a** (Doubly charged ion of *m/z* = 784.9) and XIC chromatogram of **3.7a** at t = 8.63 min (inset).

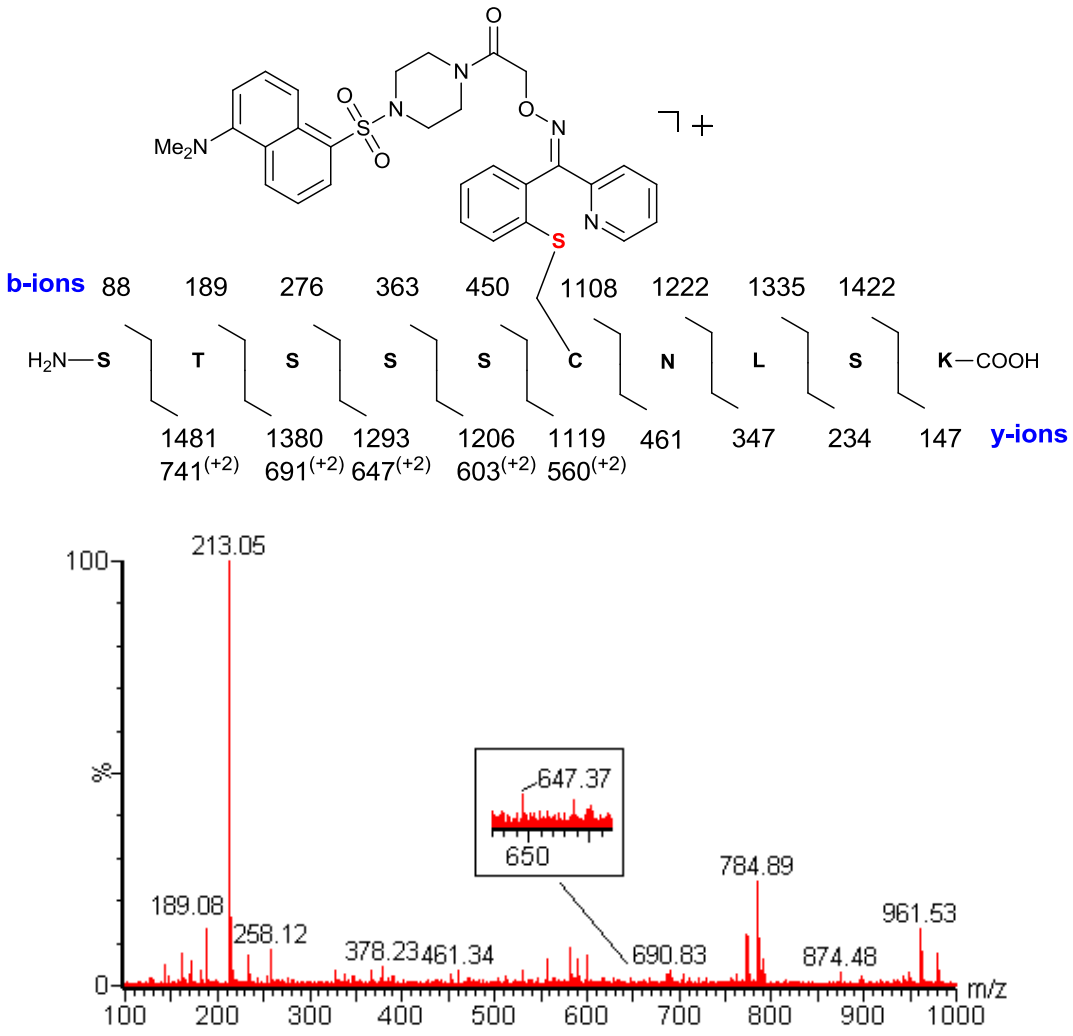


Figure 3.42 MS/MS spectrum of **3.7a** (ESI source, doubly charged ion of *m/z* = 784.9).

3.4 Conclusion

In summary, ligand controlled C-S bond formation reaction from gold-peptide adducts for chemoselective cysteine modification has been developed. This gold-mediated bioconjugation could proceed smoothly in excellent conversion (up to 99%) with high functional group tolerance under mild reaction conditions in aqueous medium. The present work indicates that modular ligand design of gold(III) complexes will provide a new approach for biomolecules modification which is an unexplored area of studies in bioconjugation chemistry.

This work regarding the use of cyclometallated gold(III) complexes for chemoselective cysteine modification has been accepted for publishing in *Chem. Commun.* **2014**, *50*, 11899-11902.

3.5 Future Works

Based on the above results, we suggest to prepare other functionalized cyclometallated gold(III) complexes [Au(C^N)msen] for selective labelling of cysteine-containing peptides by using Biotin or PEG probes (Figure 3.43).

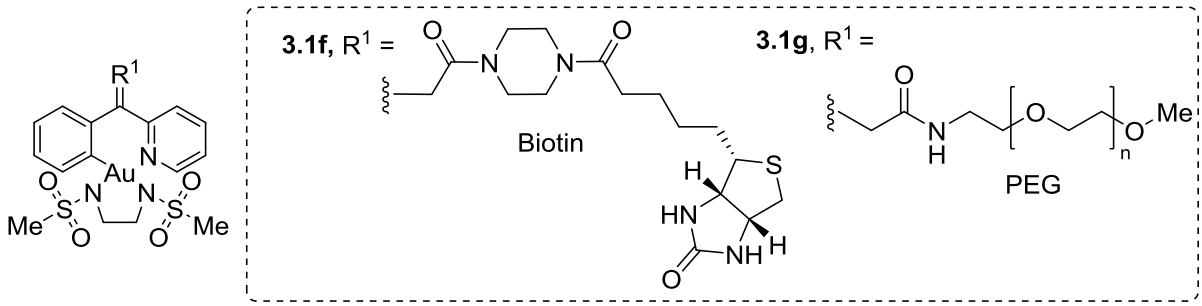


Figure 3.43 Design of new [Au(C^N)msen] complexes **3.1f-g**.

The ligation products formed could be useful for applications of biological studies, pharmaceuticals, materials chemistry as well as catalysis. Furthermore, as the cysteine modification by C-S bond formation via reductive elimination was achieved for cysteine-containing peptides, the next step for examining the strategy is to modify more complex biomolecules (i.e. proteins with surface exposed cysteine residues).

We envision that this gold-mediated modification is fascinating to be developed as an efficient and versatile method for chemoselective labeling of cysteine-containing peptides/proteins which is important to develop novel bioconjugates for studying the interactions within the biological systems. The synthesis and study of metallopeptides as well as their stability towards reductive elimination are ongoing.

3.6 Experimental Section

General Procedure

The chemicals/reagents were bought from commercial sources and used without further purification and characterization. Milli-Q® water was used as reaction medium in peptide modification and LC-MS. The Milli-Q® water was deionised by using a Milli-Q® Gradient A10 system (Millipore, Billerica, USA). Flash column chromatography was conducted using silica gel 60 (230-400 mesh ASTM) and ethyl acetate/*n*-hexane or methanol/dichloromethane were used as eluent. ^{1}H and ^{13}C NMR spectra were performed by Bruker DPX-400 or DPX-600, Varian Unity Inova 400 NB or 500 NB spectrometers. Chemical shifts are quoted on the scale in ppm and calibrated by TMS or solvent residue as the internal standard. Coupling constants (*J*) are reported in Hertz (Hz) and the multiplicity was described as abbreviations: s = singlet, br s = broad singlet, d = doublet, dd= double doublet, t = triplet and m = multiplet. Low resolution and high resolution mass spectra were obtained on an ESI source of Q-TOF 2™ mass spectrometer (Waters-Micromass, Manchester, United Kingdom) in the positive ion mode.

LC–MS Analysis of Peptides

The LC system was based on CapLC® system from Waters (Manchester, UK). The system was equipped with a Poroshell 300SB-C18 column with 1.0 mm ID ×75 mm, 5μm) and ZORBAX Poroshell guard column with 1.0 mm ID ×17 mm, 5 μm (Agilent-Technologies Inc., Wilmington, United States of America). Mass spectrometry analysis was conducted by using Q-TOF 2™ (Waters-Micromass, Manchester, UK) as the ESI source in the positive ion mode. The mobile phase solvent system included solvent A, Milli-Q® water with 0.1%

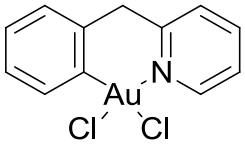
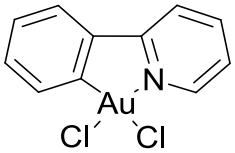
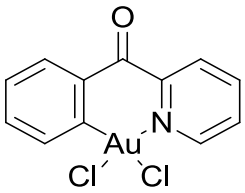
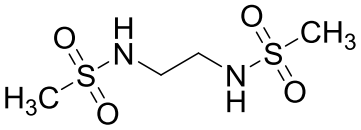
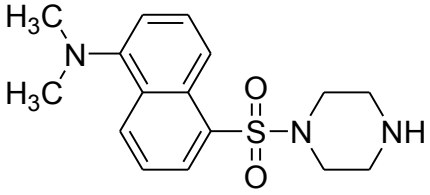
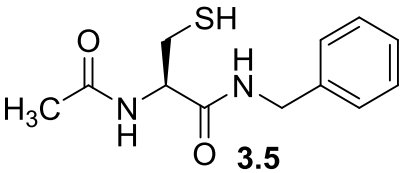
formic acid, and solvent B, acetonitrile with 0.1% formic acid. The samples were first desalted with 3% solvent B for 3 minutes, and then eluted with a 26 minute linear gradient of 3% to 70% solvent B and restored to 3% solvent B for last 15 minute. Desolvation and source temperatures were set at 150 ℃ and 80 ℃ respectively. Operating conditions optimized for the detection of reaction mixture were as follows: capillary voltage 3 kV, sample cone voltage 30 V, extraction voltage 4 V and collision cell voltage 10 eV.

Calculation of Peptide Conversion

The crude reaction mixture of cysteine-containing peptide (peptide) and modified peptide (product) after completed reaction was subjected to LC-MS analysis with elution time of 45 min. The raw data was processed by MassLynx 4.1 Transform Program and peptide conversion at different time intervals was determined by measuring the relative peak intensities of aldehyde and product in the mass spectrum as follows:

$$Peptide\ Conversion\ (\%) = \left(1 - \frac{Relative\ Peak\ Intensity\ of\ Peptide}{Relative\ Peak\ Intensities\ of\ Peptide\ and\ Product}\right) \times 100\%$$

Literature References

 [Au(bpy)Cl_2] **3.1d**	M. A. Cinellu, A. Zucca, S. Stoccoro, G. Minghetti, M. Manassero, M. Sansoni, *J. Chem. Soc., Dalton Trans.* **1995**, *17*, 2865–2872.
 [Au(ppy)Cl_2]	E. C. Constable, T. A. Leese, *J. Organomet. Chem.* **1989**, *363*, 419–424.
 [Au(pcp)Cl_2]	Y. Fuchita, H. Ieda, Y. Tsunemune, J. Kinoshita-Nagaoka, H. Kawano, *J. Chem. Soc., Dalton Trans.* **1998**, 791–796.
 *N*,*N*′-bis(methanesulfonyl) ethylenediamine (msen)	H. Alyar, A. Ü nal, N. Ö zbek, S. Alyar, N. Karacan, *Spectrochim. Acta, Part A*, **2012**, *91*, 39–47.
	V. Sashuk, D. Schoeps, and H. Plenio, *Chem. Commun*. **2009**, *7*, 770–772.
 **3.5**	L. M. Tedaldi, A. E. Aliev, J. R. Baker, *Chem. Commun.* **2012**, *48*, 4725–4727.

Synthesis of [Au(C^N)msen] 3.1a-c

Cyclometallated gold(III) complex [Au(C^N)Cl_2] (HC^N = 2-arylpyridines) (0.229 mmol) and *N*,*N*'-bis(methanesulfonyl) ethylenediamine (msen) (142 mg, 0.341 mmol) were stirred in refluxing methanol (30 mL). A mixture of trimethylamine/water (1:1, 2 mL) was added, resulting in the formation of a milky yellow suspension. This mixture was stirred until cool down, filtered, and the product washed with water (2 × 10 mL) and diethyl ether (10 mL) then dried under vacuum to give [Au(C^N)msen] as a product.

Synthesis of Dansyl-linked Cyclometallated Gold(III) Complex 3.1e

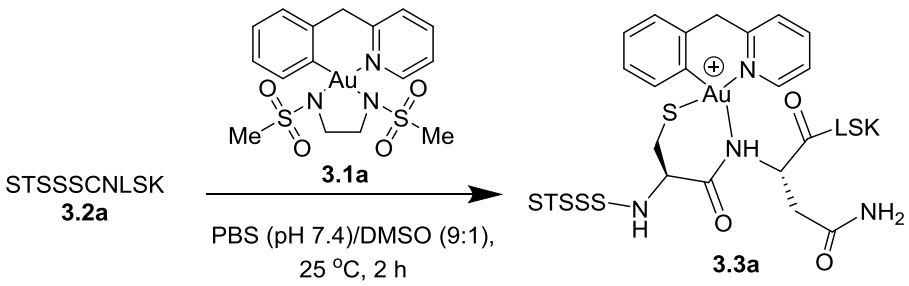
Cyclometallated gold(III) complex [Au(pcp)Cl_2] (0.2 mmol) was added to *O*-(carboxymethyl)hydroxylamine hemihydrochloride in a mixture of 1:1 CH_2Cl_2/CH_3OH (50 mL). The resulting mixture was stirred for overnight at 25 ^oC to give white precipitate. The solvent was removed under vacuum to give white solid. The product was further purified by washing with CH_3OH (10 mL) to give **3.1ea.**

1-Dansylpiperazine (0.1 mmol), **3.1ea** (0.1 mmol) and EDC (0.2 mmol) was stirred in anhydrous CH_2Cl_2 (20 mL) for 20 h under nitrogen atmosphere. The resulting mixture was extracted with water (20 mL) three times. The solvent was removed under vacuum to give yellow solid. The purified product **3.1eb** was obtained by flash column chromatography using CH_2Cl_2/CH_3OH as eluent.

Complex **3.1eb** (0.05 mmol) and bis(methanesulfonyl) ethylenediamine (msen) (0.1 mmol) were stirred in refluxing methanol (10 mL) to give a cloudy mixture. A mixture of triethylamine/water (1:1, 1 mL) was added and the mixture turned clear. The resulting mixture was refluxed for further 15 minutes. Complex **3.1e** was obtained by flash column

chromatography using CH_2Cl_2/CH_3OH as eluent. ^1H NMR spectrum showed the presence of diastereomers in the ratio of 1:5 which could not be separated in flash column chromatography.

Chemoselective Modification of cysteine by Formation of Gold-Peptide Adducts (3.3a-e, 3.4a-b)



A mixture of peptide STSSSCNLSK **3.2a** (10 μL of 1 mM in H_2O) and [Au(bpy)msen] **3.1a** (Hbpy = 2-benzylpyridine) (10 μL of 1 mM in DMSO, 1 equiv.) in a PBS solution (pH 7.4, 80 μL) was stirred at 25 ^oC. After 2 h, the crude reaction mixture was analysed by LC-MS and MS/MS. The above reaction was repeated by using peptides AYEMWCFHQK **3.2b**, ASCGTN **3.2c**, KSTFC **3.2d**, CSKFR **3.2e**, YTSSSKNVVR **3.2f**, DSKFR **3.2g** and PSKFR **3.2h**.

The formation of gold-peptide adducts **3.4a** and **3.4b** were conducted under the same reaction conditions by using [Au(pcp)msen] **3.1b** and [Au(ppy)msen] **3.1c**, respectively.

Procedure for Time Course Experiments of Studying The Formation of 3.3a in Different pH Values

A mixture of peptide STSSSCNLSK **3.2a** (10 μL of 1 mM in H_2O) and [Au(bpy)msen] **3.1a** (Hbpy = 2-benzylpyridine) (10 μL of 1 mM in DMSO, 1 equiv.) in a PBS solution (50 mM, pH 7.4, 80 μL) was stirred at 25 ^oC. The crude reaction mixture was analysed by LC-MS analysis within 5 h. The above reaction was repeated by using PBS solutions with different pH values (50 mM, pH 6.2, 8.2 and 9.3).

Procedure for Control Experiments Using [Au(bpy)Cl_2] 3.1d

A mixture of peptide STSSSCNLSK **3.2a** (10 μL of 1 mM in H_2O) and [Au(bpy)Cl_2] **3.1d** (Hbpy = 2-benzylpyridine) (15 μL of 1 mM in DMSO, 1.5 equiv.) in a PBS solution (pH 7.4, 75 μL) was stirred at 25 ^oC. After 2 h, the crude reaction mixture was analysed by LC-MS analysis. The above reaction was repeated by using peptides YTSSSKNVVR **3.2f**.

Procedure for Reaction of *N*-Acetyl-L-cysteine Benzyl Amide 3.5 with 3.1a (or 3.1b)

A mixture of *N*-acetyl-L-cysteine benzyl amide **3.5** (0.1 mmol) and **3.1a** (or **3.1b)** (0.1 mmol) were stirred in CH_3CN (4 mL) at 40 ^oC for 16 h. After the reaction, the solvent was removed under vacuum. The residue was dissolved in 10 mL of CH_2Cl_2 and extracted with saturated $Na_2S_2O_3$ solution (10 mL) followed by distillated water (10 mL x 2). The combined organic layer was then subjected to flash column chromatography with CH_2Cl_2/CH_3OH as eluent and the reductive elimination product **3.6a** (or **3.6b)** was then obtained.

Procedure for Reactions of *N*-Acetyl-L-Cysteine Benzyl Amide 3.5 with 3.1c

A mixture of *N*-acetyl-L-cysteine benzyl amide **3.5** (0.1 mmol) and **3.1c** (0.1 mmol) were dissolved in CH_2Cl_2/CH_3OH (1:1) (4 mL) and the resulting mixture was stirred at 25 ^oC for 16 h for complete conversion of **3.5**. After the reaction, the crude reaction mixture was subjected to flash column chromatography with CH_2Cl_2/CH_3OH as eluent and the purified gold-cysteine adduct **3.6c** was then obtained. Heating of compound **3.6c** in CH_3CN (4 mL) at 40 ^oC for 16 h gave no reductive elimination product.

3.1c and **3.5** were mixed in CH_2Cl_2/CH_3OH (1:1) at 25 ^oC for 16 h. Instead, a gold-cysteine adduct **3.6c** was found in 68% isolated yield.

Procedure for Ligand Controlled C-S Bond Formation from Gold-peptide Adducts

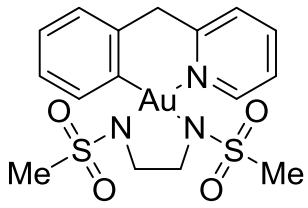
Crude mixtures of gold-peptide adducts **3.3a**, **3.4a** or **3.4b** (100 μL of 0.2 mM in H_2O) obtained from reactions of peptide **3.2a** with complexes **3.1a-c** were heated at 37 ^oC, respectively. The reactions were monitored by LC-MS for 24 h.

Procedure for Time Course Experiments of Studying The Reductive Elimination of 3.4a to 3.4aa in Different pH Values

A mixture containing **3.4a** in a PBS solution (50 mM, pH 7.4, 80 μL) was stirred at 37 ^oC. The crude reaction mixture was analyzed by LC-MS analysis within 24 h. The above reaction was repeated by using PBS solutions with different pH values (50 mM, pH 6.2, 8.2 and 9.3).

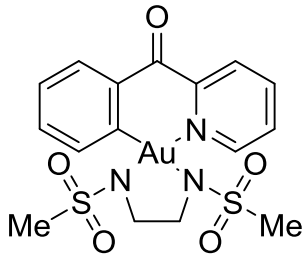
Procedure for Modification of Cysteine-containing Peptides 3.2a-d by Complex 3.1b via C-S Bond-Forminng Reductive Elimination

A mixture of peptide STSSSCNLSK **3.2a** (10 μL of 1 mM in H_2O) and [Au(pcp)msen] **3.1b** (10 μL of 1 mM in DMSO, 1 equiv.) in a PBS solution (pH 7.4, 80 μL) was stirred at 37 ^oC. After 2 h, the crude reaction mixture was analyzed by LC-MS and MS/MS analysis. The above reaction was repeated by using peptides AYEMWCFHQK **3.2b**, ASCGTN **3.2c**, and KSTFC **3.2d**.



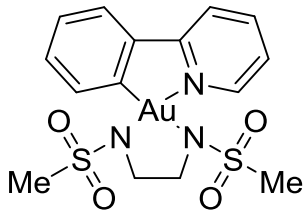
[Au(bpy)msen] **3.1a**

67% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$): δ 9.08 (d, *J* = 6 Hz, 1H), 7.92–7.96 (m, 1H), 7.61 (d, *J* = 7 Hz, 1H), 7.56 (dd, *J* = 8, 1 Hz, 1H), 7.38–7.42 (m, 1H), 7.21 (dd, *J* = 7, Hz, 1H), 7.13–7.18 (m, 1H), 7.06–7.10 (m, 1H), 4.49 (d, *J* = 15 Hz, 1H), 3.97 (d, *J* = 15 Hz, 1H), 3.81 (dd, *J* = 11, 5 Hz, 1H), 3.56–3.65 (m, 1H), 3.31–3.38 (m, 1H), 3.14 (dd, *J* = 11, 5 Hz, 1H), 2.89 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 153.6, 141.8, 138.8, 133.0, 128.4, 128.1, 127.0, 125.3, 123.4, 56.8, 51.8, 47.8, 43.1, 38.6; MS (ESI^+): *m/z* = 580 $[M + H]^+$; HRMS (ESI^+) calcd. for $C_{16}H_{21}AuN_3O_4S_2$ $[M + H]^+$ 580.0639, found 580.0652.



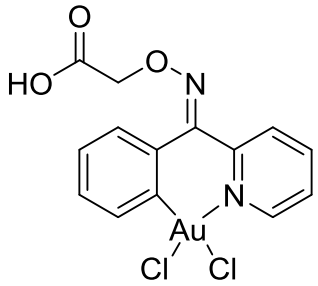
[Au(pcp)msen] **3.1b**

75% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (d, *J* = 7 Hz, 1H), 8.29 (dd, *J* = 8, 2 Hz, 1H), 8.25 (dd, *J* = 8, 2 Hz, 1H), 7.90 (dd, *J* = 7, 2 Hz, 2H), 7.76–7.80 (m, 1H), 7.40–7.44 (m, 2H), 3.70 (t, *J* = 6 Hz, 2H), 3.29 (t, *J* = 6 Hz, 2H), 2.86 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 146.6, 142.6, 137.5, 133.9, 133.0, 130.5, 130.4, 129.9, 128.6, 128.2, 126.6, 56.7, 51.4, 42.3, 38.3; MS (ESI^+): *m/z* = 594 $[M + H]^+$; HRMS (ESI^+) calcd. for $C_{16}H_{19}AuN_3O_5S_2$ $[M + H]^+$ 594.0432, found 594.0386.



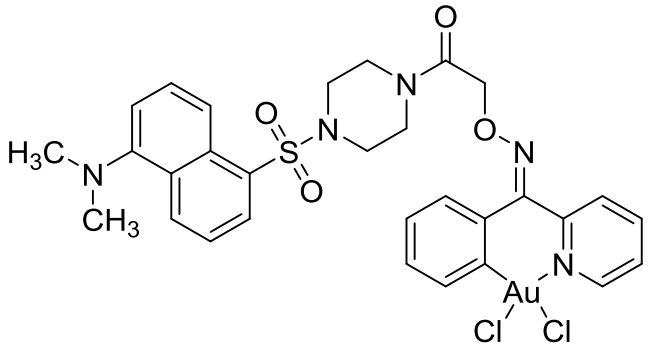
[Au(ppy)msen] **3.1c**

85% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, *J* = 6 Hz, 1H), 8.04–8.08 (m, 1H), 7.82 (dd, *J* = 8, 1 Hz, 1H), 7.75 (dd, *J* = 8, 1 Hz, 1H), 7.54 (dd, *J* = 8, 1 Hz, 1H), 7.30–7.34 (m, 2H), 7.29, (m, 1H), 3.50 (t, *J* = 6 Hz, 2H), 3.35 (t, *J* = 6 Hz, 2H), 3.22 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 153.2, 151.3, 142.6, 142.5, 134.6, 131.6, 128.8, 124.8, 123.4, 119.9, 55.9, 50.3, 42.7, 40.0; MS (ESI^+): *m/z* = 566 $[M + H]^+$; HRMS (ESI^+) calcd. for $C_{15}H_{19}AuN_3O_4S_2$ $[M + H]^+$ 566.0483, found 566.0473.



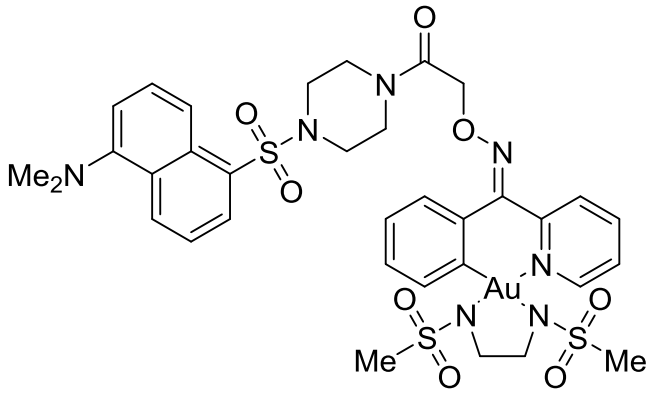
3.1ea

66% yield; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9. 33 (d, J = 6 Hz, 1H), 8.48 (d, J = 4 Hz, 2H), 7.95 (dd, J = 10, 5 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.23–7.39 (m, 3H), 4.91 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.2, 153.7, 153.3, 143.9, 138.1, 134.1, 130.6, 130.4, 129.4, 129.3, 128.9, 128.4, 72.4; MS (ESI$^+$): m/z = 487 [M - Cl]$^+$; HRMS (ESI$^+$) calcd. for $C_{14}H_{11}N_2O_3Cl$ [M - Cl]$^+$ 487.0124, found 487.0127.



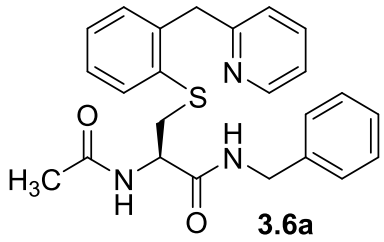
3.1eb

56% yield; pale yellow solid; analytical TLC (silica gel 60) (CH_2Cl_2/MeOH = 19:1, R_f = 0.5) ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.80 (d, J = 8 Hz, 1H), 8.60 (d, J = 8 Hz, 1H), 8.37 (d, J = 9 Hz, 1H), 8.22 (d, J = 7 Hz, 1H), 8.08 (t, J = 7 Hz, 1H), 7.63–7.69 (m, 1H), 7.53–7.61 (m, 3H), 7.30–7.37 (m, 1H), 7.14–7.23 (m, 3H), 4.95 (dd, J = 133, 15 Hz, 2H), 3.64–3.80 (m, 2H), 3.40–3.48 (m, 2H), 3.17–3.36 (m, 4H), 2.90 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 153.3, 152.1, 151.6, 145.5, 141.7, 138.5, 133.4, 132.1, 131.2, 130.9, 130.3, 130.2, 130.1, 129.8, 128.6, 128.5, 128.4, 127.4, 126.8, 123.2, 119.2, 115.4, 72.3, 45.4, 45.3, 44.1, 41.4; MS (ESI$^+$): m/z = 788 [M - Cl]$^+$; HRMS (ESI$^+$) calcd. for $C_{30}H_{30}N_5O_4SAuCl$ [M - Cl]$^+$ 788.1381, found 788.1373.



3.1e

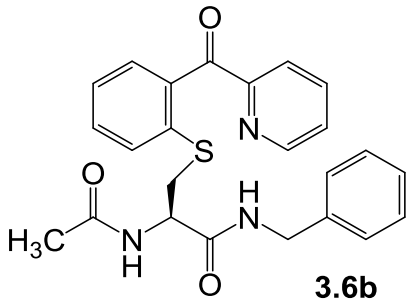
82% yield; pale yellow solid; analytical TLC (silica gel 60) (CH_2Cl_2/MeOH = 19:1, R_f = 0.6); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (d, *J* = 6 Hz, 1H), 8.72 (d, *J* = 8 Hz, 1H), 8.60 (d, *J* = 8 Hz, 1H), 8.37 (d, *J* = 9 Hz, 1H), 8.22 (d, *J* = 7 Hz, 1H), 8.03 (t, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.56 (t, *J* = 7 Hz, 2H), 7.50 (t, *J* = 7 Hz, 1H), 7.44–7.49 (m, 1H), 7.18–7.24 (m, 3H), 4.93 (dd, *J* = 136, 15 Hz, 2H), 3.57–3.80 (m, 4H), 3.45 (s, 2H), 3.15–3.38 (m, 6H), 2.90 (s, 6H), 2.81 (s, 3H), 2.64 (s, 3H); MS (ESI$^+$): *m/z* = 968 $[M + H]^+$; HRMS (ESI$^+$) calcd. for $C_{34}H_{41}N_7O_8S_3Au$ $[M + H]^+$ 968.1844, found 968.1840.



3.6a

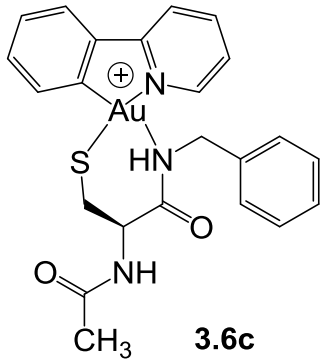
72% yield; yellow solid; analytical TLC (silica gel 60) (CH_2Cl_2/MeOH = 9:1, R_f = 0.65); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 5 Hz, 1H), 7.54–7.63 (m, 3H), 7.50 (d, *J* = 8 Hz, 1H), 7.21 (m, 5H), 7.14 (m, 3H), 7.06 (m, 2H), 4.67 (dd, *J* = 13, 6 Hz, 1H), 4.46 (d, *J* = 15 Hz, 1H), 4.32 (dd, *J* = 15, 6 Hz, 1H), 4.25 (d, *J* = 15 Hz, 1H), 4.19 (dd, *J* = 15, 5 Hz, 1H), 3.49 (dd, *J* = 14, 5 Hz, 1H), 3.28 (dd, *J* = 14, 6 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.3, 160.9, 149.1, 140.9, 138.1, 137.3, 134.6, 132.5, 130.8, 128.7, 127.9, 127.8,

127.7, 127.5, 123.9, 121.8, 54.3, 43.8, 41.5, 36.4, 22.9; MS (ESI^+): *m/z* = 420 $[M + H]^+$; HRMS (ESI^+) calcd. for $C_{24}H_{26}N_3O_2S$ $[M + H]^+$ 420.1746, found 420.1753.



3.6b

52% yield; white solid; analytical TLC (silica gel 60) (CH_2Cl_2/MeOH = 9:1, R_f = 0.6); ^1H NMR (500 MHz, $CDCl_3$): δ 8.52 (d, *J* = 4 Hz, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.89 (t, *J* = 8 Hz, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.52 (t, *J* = 8 Hz, 1H), 7.42–7.48 (m, 1H), 7.39 (d, *J* = 7 Hz, 1H), 7.33 (t, *J* = 7 Hz, 1H), 7.20–7.29 (m, 3H), 7.18 (d, *J* = 7 Hz, 2H), 7.08–7.15 (m, 1H), 6.87 (d, *J* = 7 Hz, 1H), 4.54 (dd, *J* = 12, 7 Hz, 1H), 4.31 (dd, *J* = 15, 6 Hz, 1H), 4.15 (dd, *J* = 15, 5 Hz, 1H), 3.38–3.49 (m, 1H), 3.11–3.24 (m, 1H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.8, 170.6, 170.0, 154.3, 149.2, 140.8, 137.9, 137.5, 134.4, 131.8, 131.5, 129.6, 128.8, 127.8, 127.5, 127.3, 126.7, 124.4, 53.5, 43.7, 36.5, 23.1; MS (ESI^+): *m/z* = 434 $[M + H]^+$; HRMS (ESI^+) calcd. for $C_{24}H_{24}N_3O_3S$ $[M + H]^+$ 434.1538, found 434.1527.

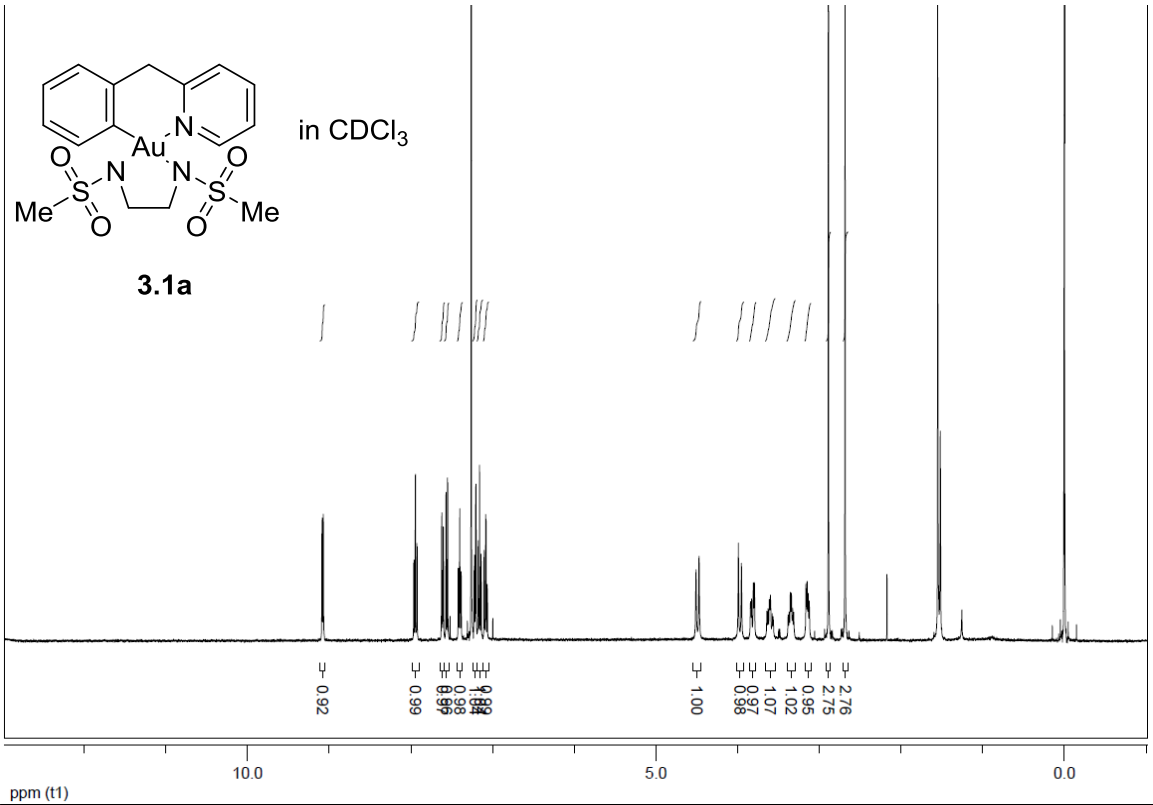


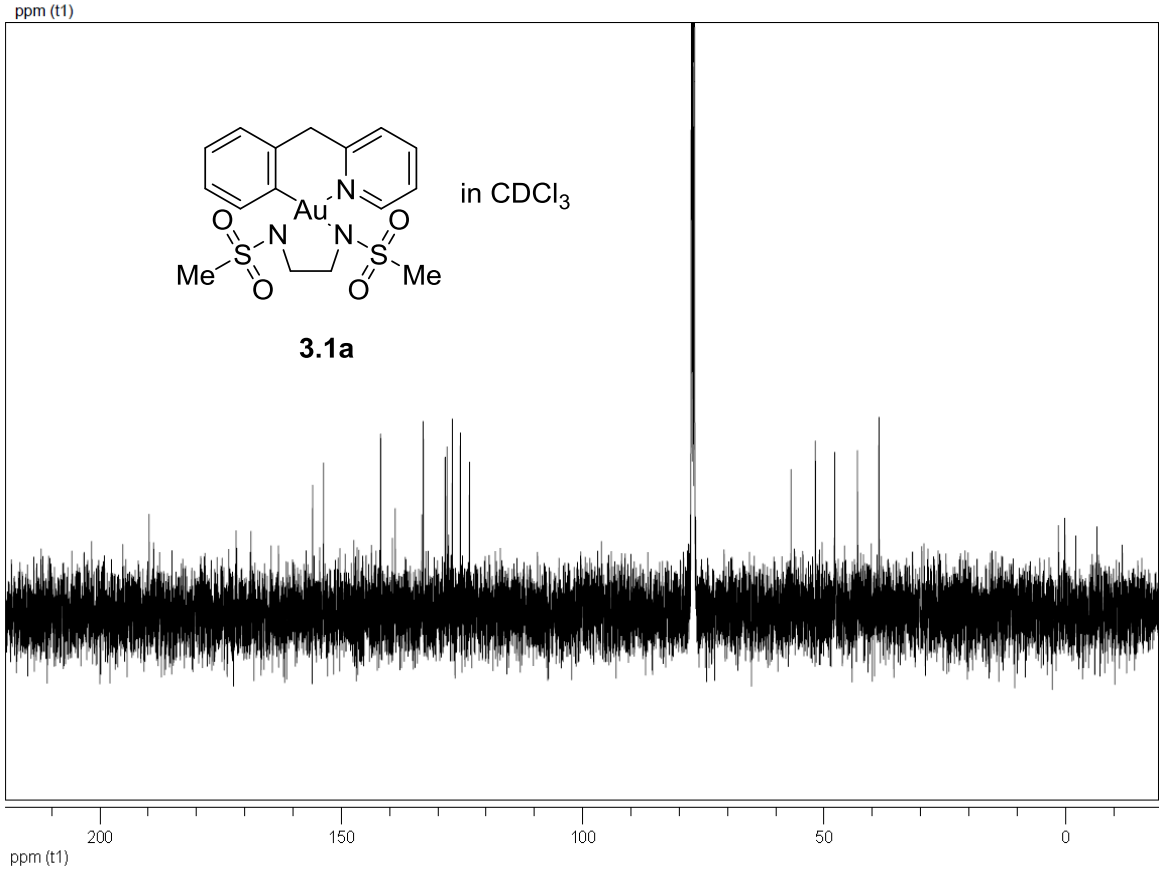
3.6c

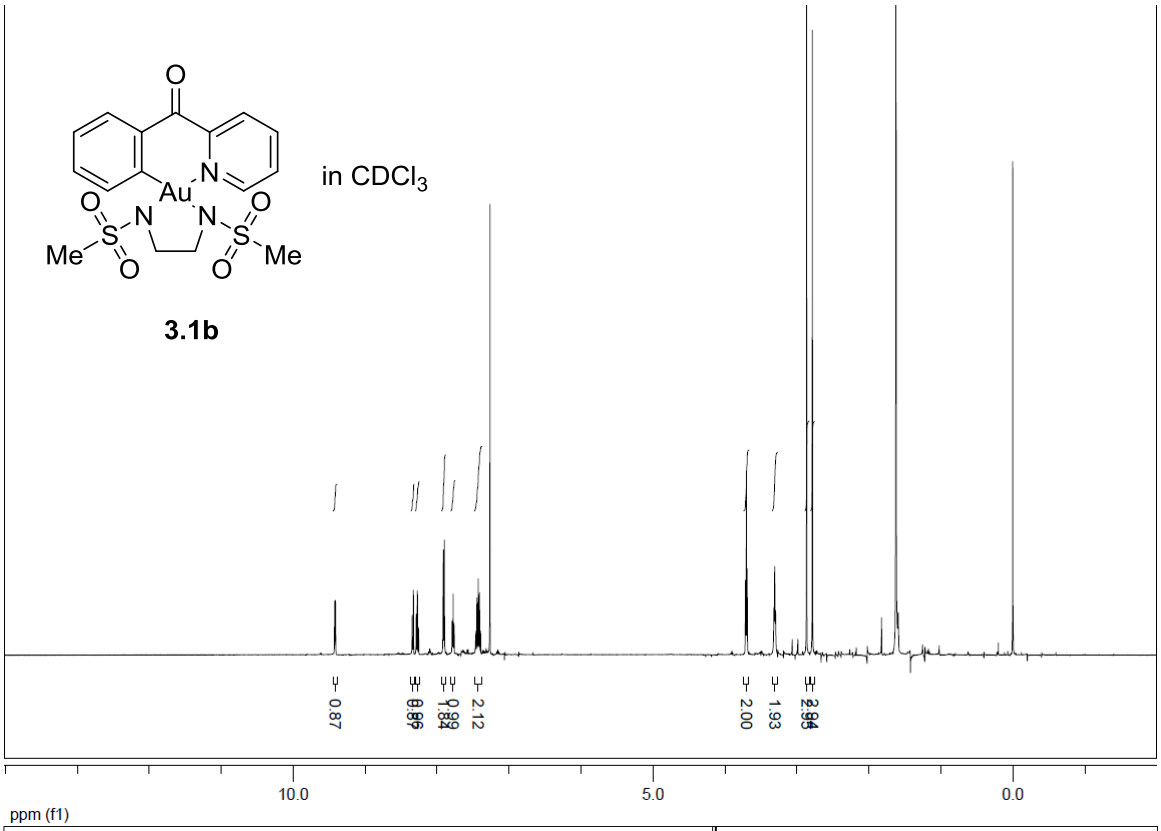
68% yield; pale yellow solid; analytical TLC (silica gel 60) (CH_2Cl_2/MeOH = 9:1, R_f = 0.5); ^1H NMR (500 MHz, DMSO-d_6): δ 9.46 (d, *J* = 6 Hz, 1H), 8.45 (t, *J* = 6 Hz, 1H), 8.41 (d, *J* =

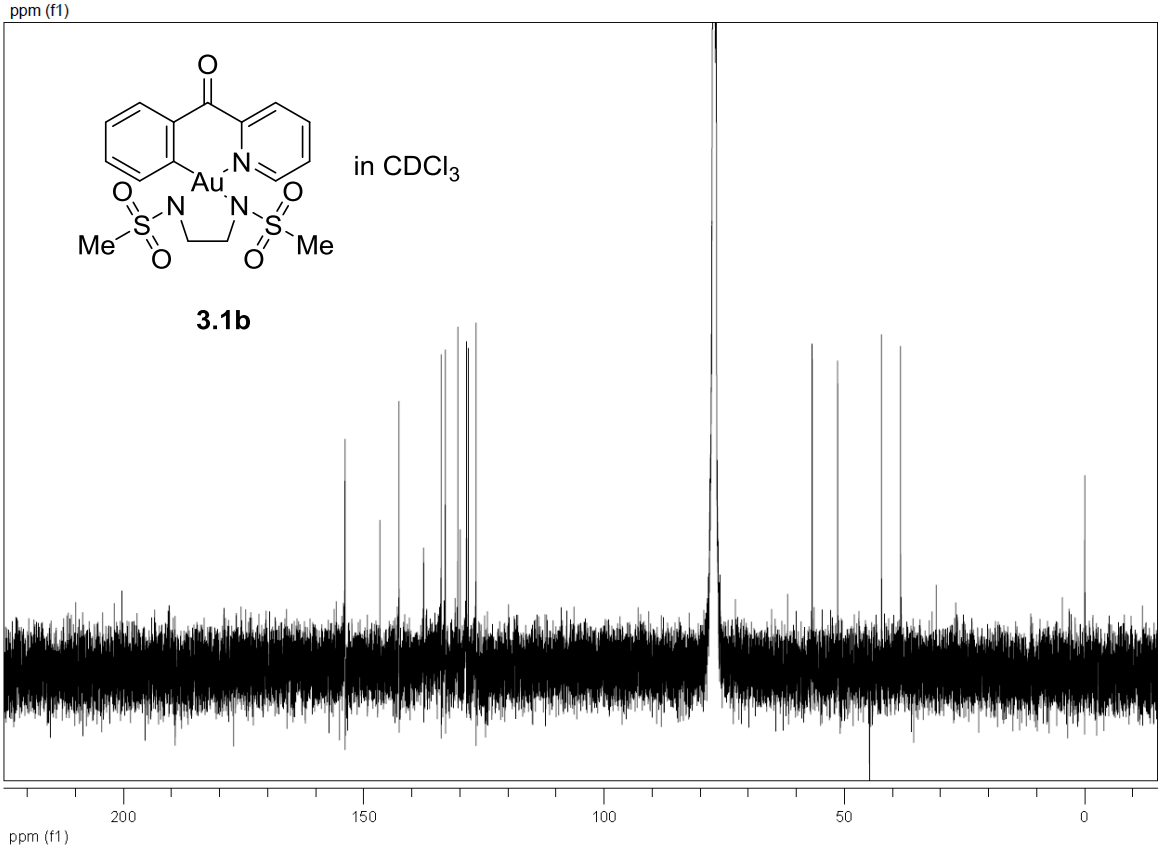
8 Hz, 1H), 8.31 (t, *J* = 8 Hz, 1H), 8.14 (d, *J* = 8 Hz, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.77 (t, *J* = 6 Hz, 2H), 7.43 (t, *J* = 7 Hz, 1H), 7.37 (t, *J* = 7 Hz, 1H), 7.20–7.26 (m, 4H), 7.14–7.20 (m, 1H), 4.53 (q, *J* = 8, 8 Hz, 1H), 4.19–4.29 (m, 2H), 3.39 (dd, *J* = 13, 6 Hz, 1H), 3.27 (dd, *J* = 13, 8 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.2, 169.8, 162.5, 151.3, 147.7, 144.4, 143.5, 139.9, 131.9, 129.4, 128.8, 128.7, 127.7, 127.4, 127.2, 126.2, 122.2, 56.1, 42.76 34.9, 23.2; MS (ESI$^+$): *m/z* = 602 $[M]^+$; HRMS (ESI$^+$) calcd. for $C_{23}H_{23}AuN_3O_2S$ $[M]^+$ 602.1177, found 602.1172.

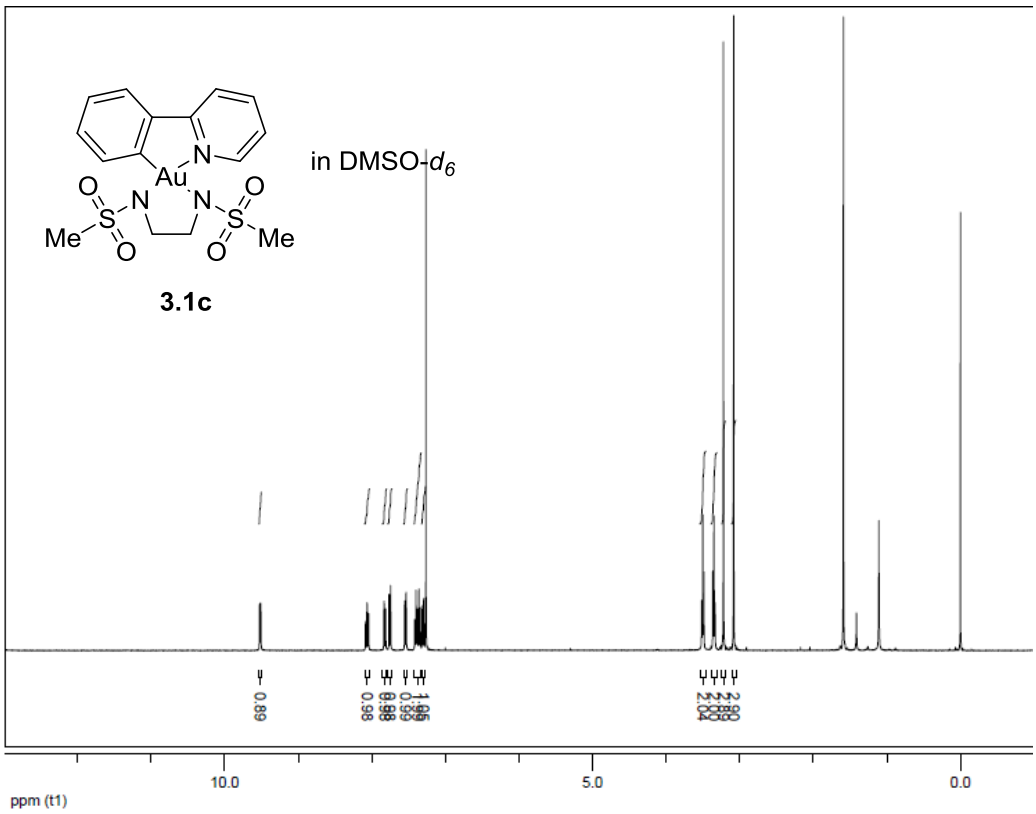
NMR spectra

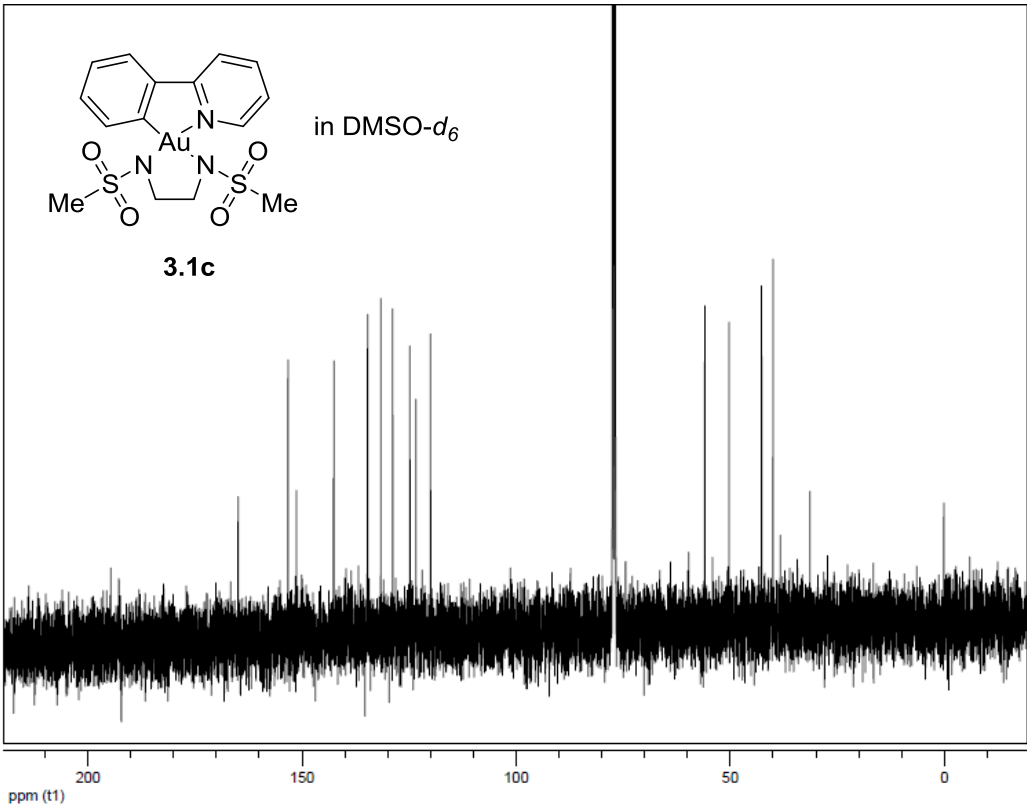

in $CDCl_3$
3.1a
0.92
0.99
1.00
0.98
1.07
1.02
0.95
2.75
2.76
10.0
5.0
0.0
ppm (t1)

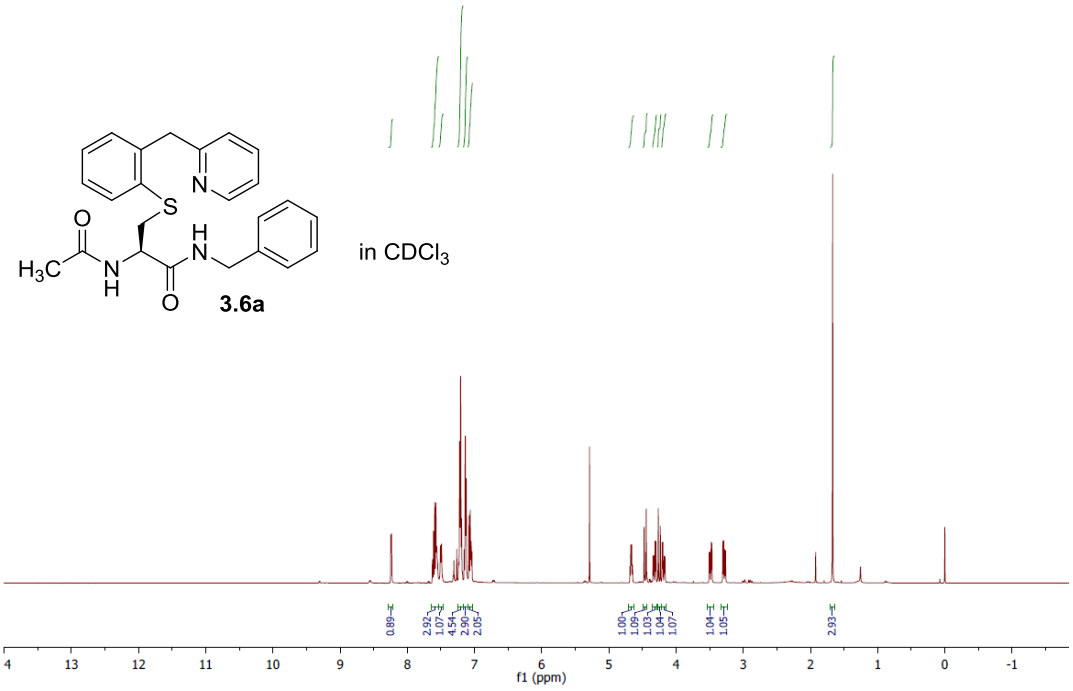

in $CDCl_3$
3.1a
200
150
100
50
0
ppm (t1)

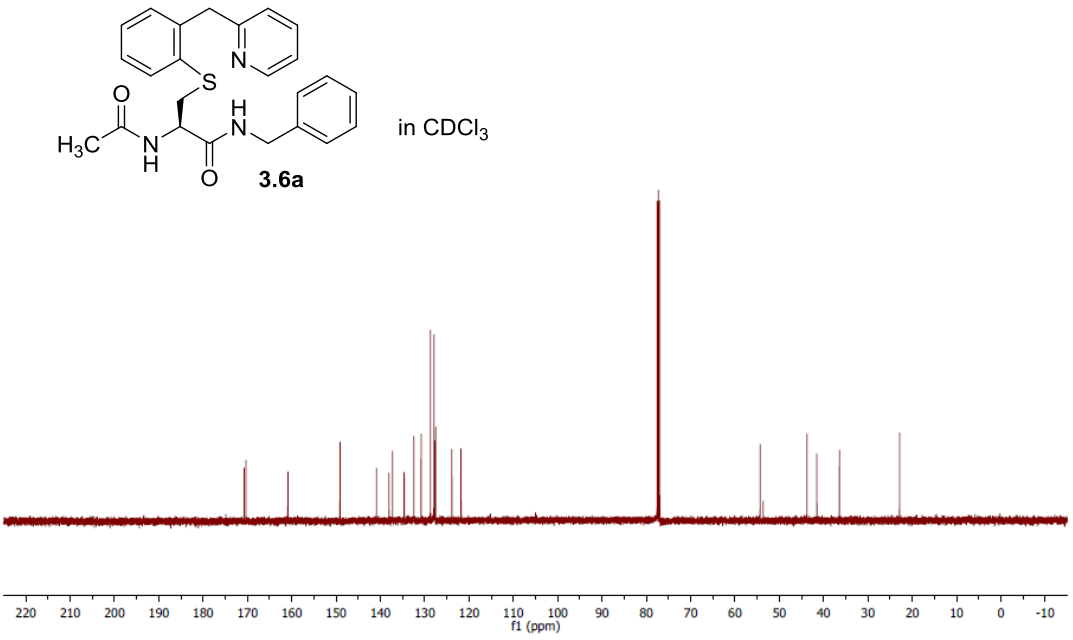

in CDCl3
3.1b
0.87
2.12
2.00
1.93
10.0
5.0
0.0
ppm (f1)

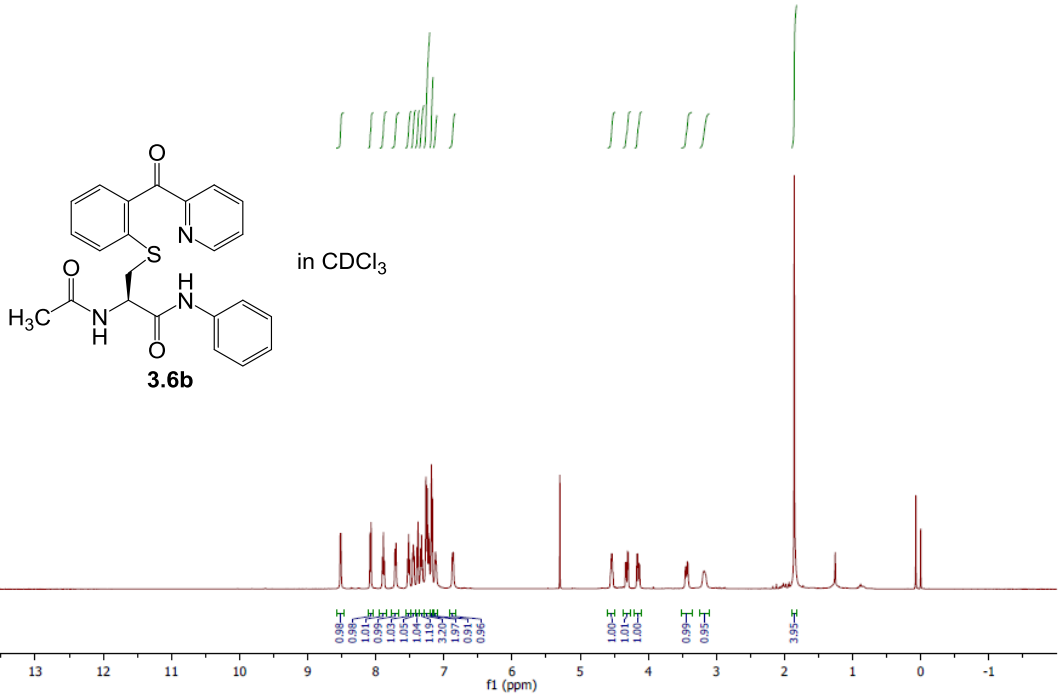

in CDCl3
3.1b
200
150
100
50
0
ppm (f1)

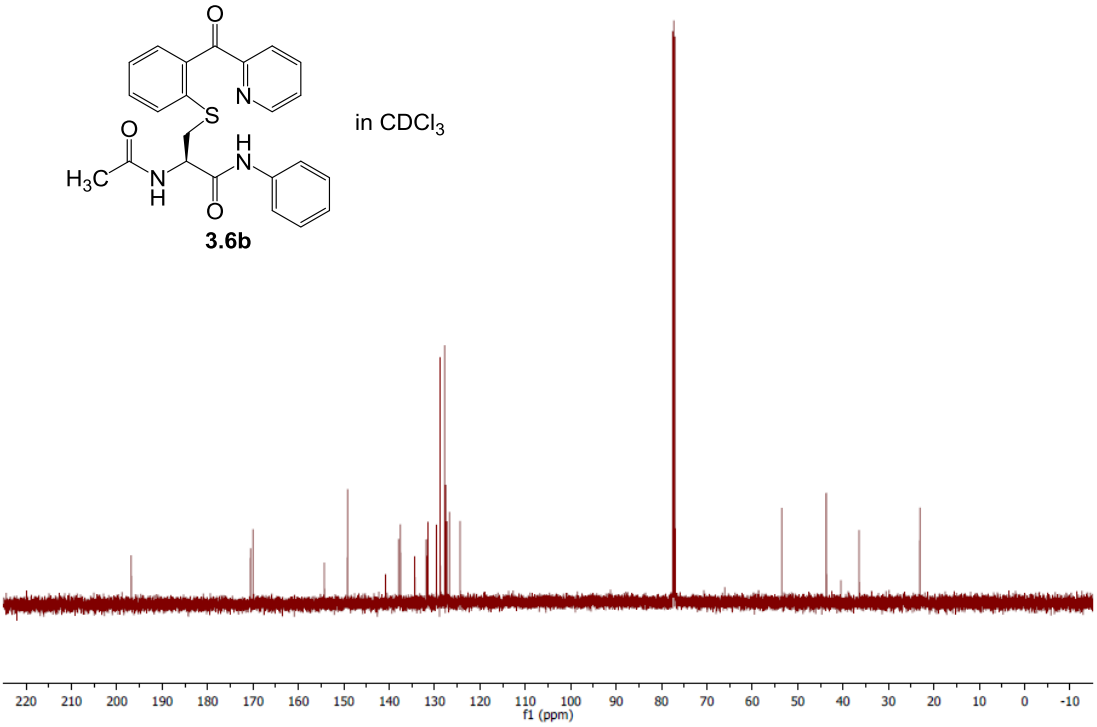

in DMSO-d_6
3.1c
10.0
5.0
0.0
ppm (t1)

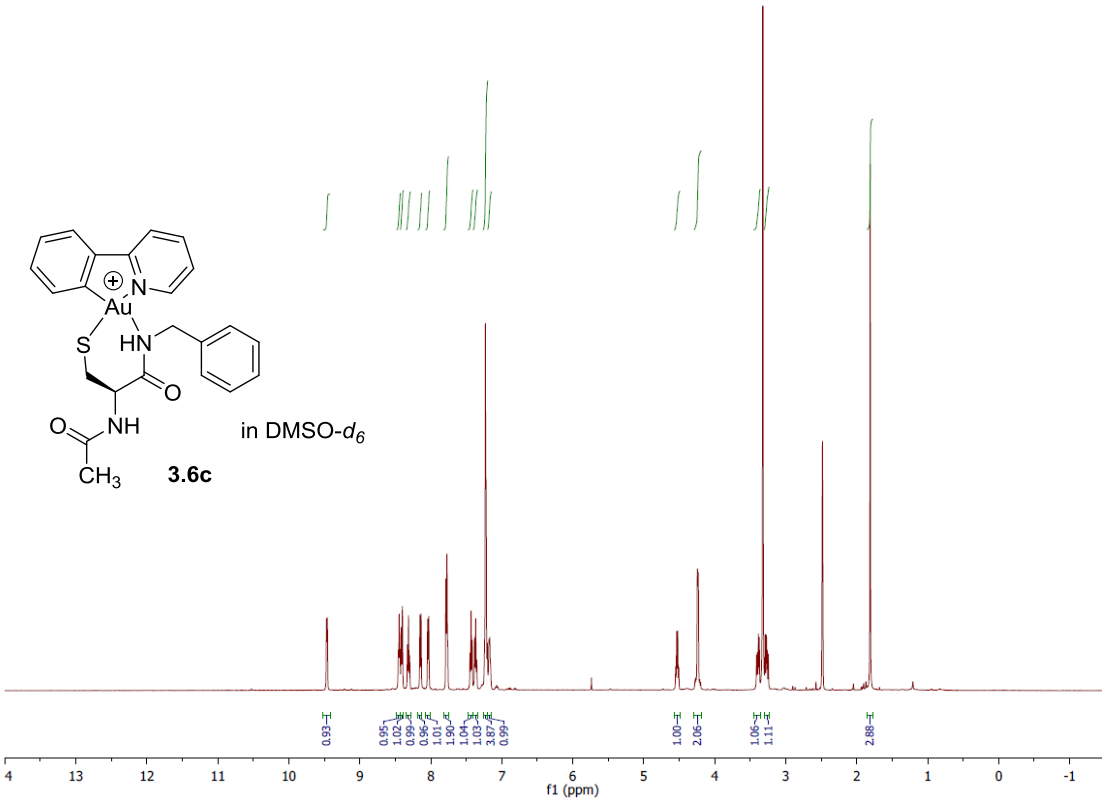

in DMSO-d_6
3.1c
200
150
100
50
0
ppm (t1)

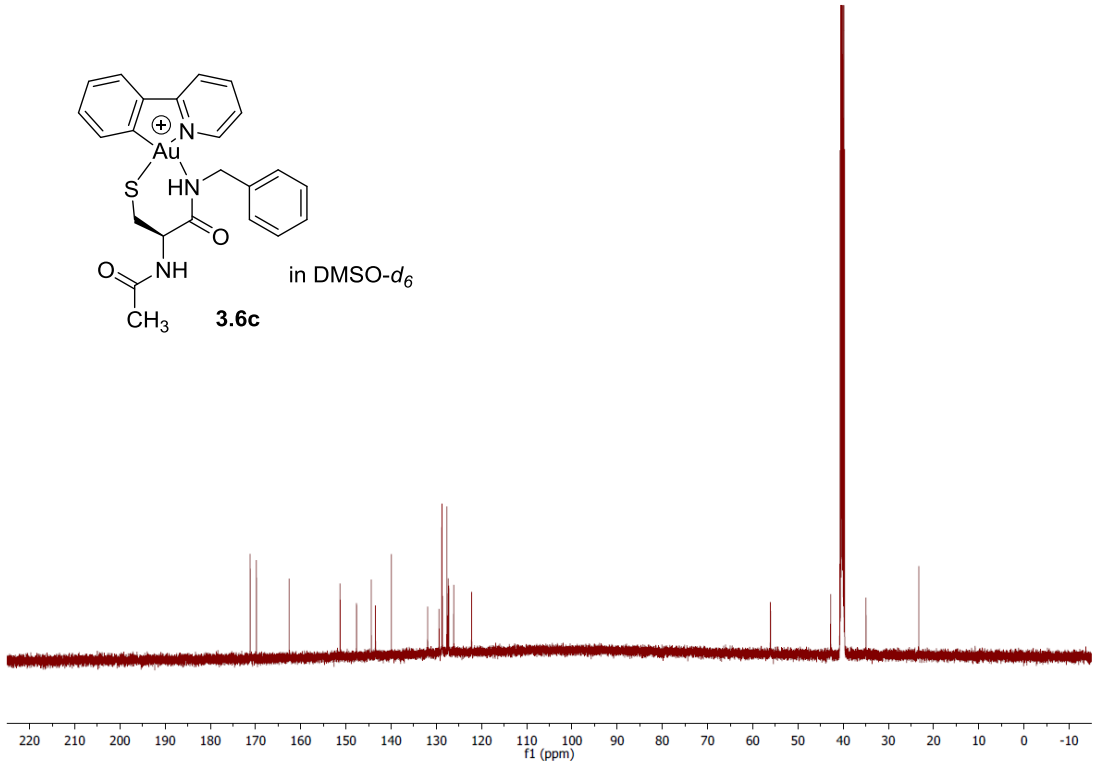

in CDCl3
3.6a
f1 (ppm)

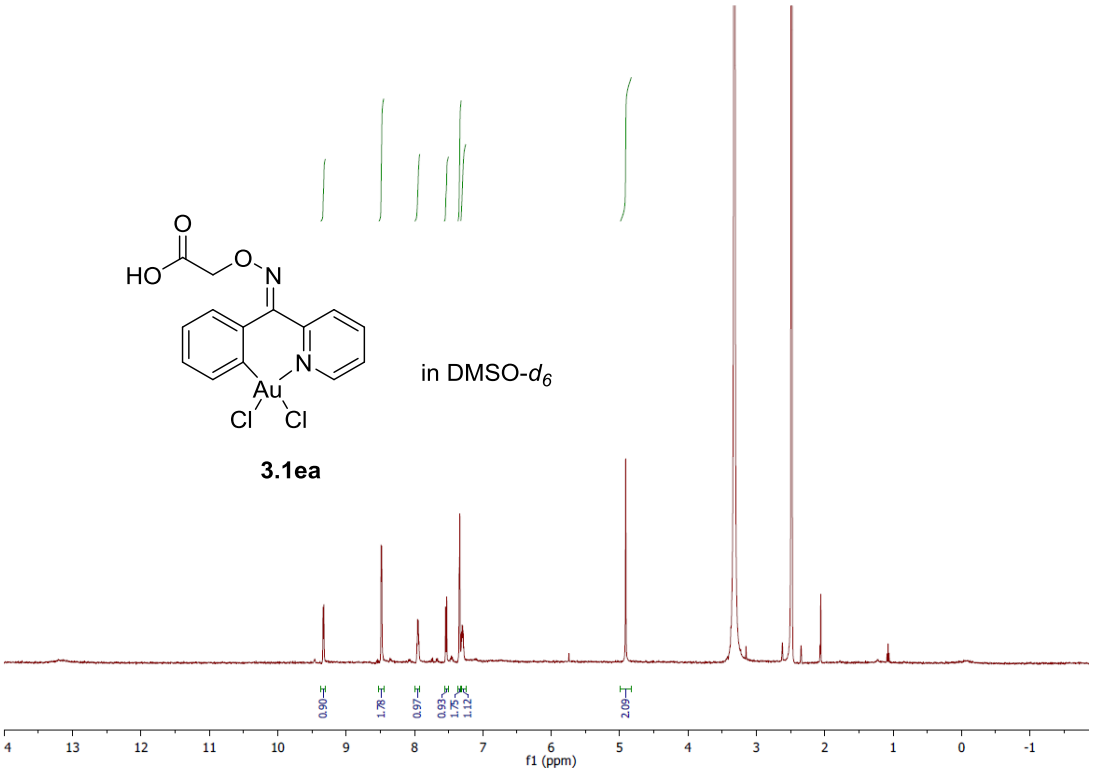

in CDCl3
3.6a
f1 (ppm)


in CDCl3
3.6b
f1 (ppm)

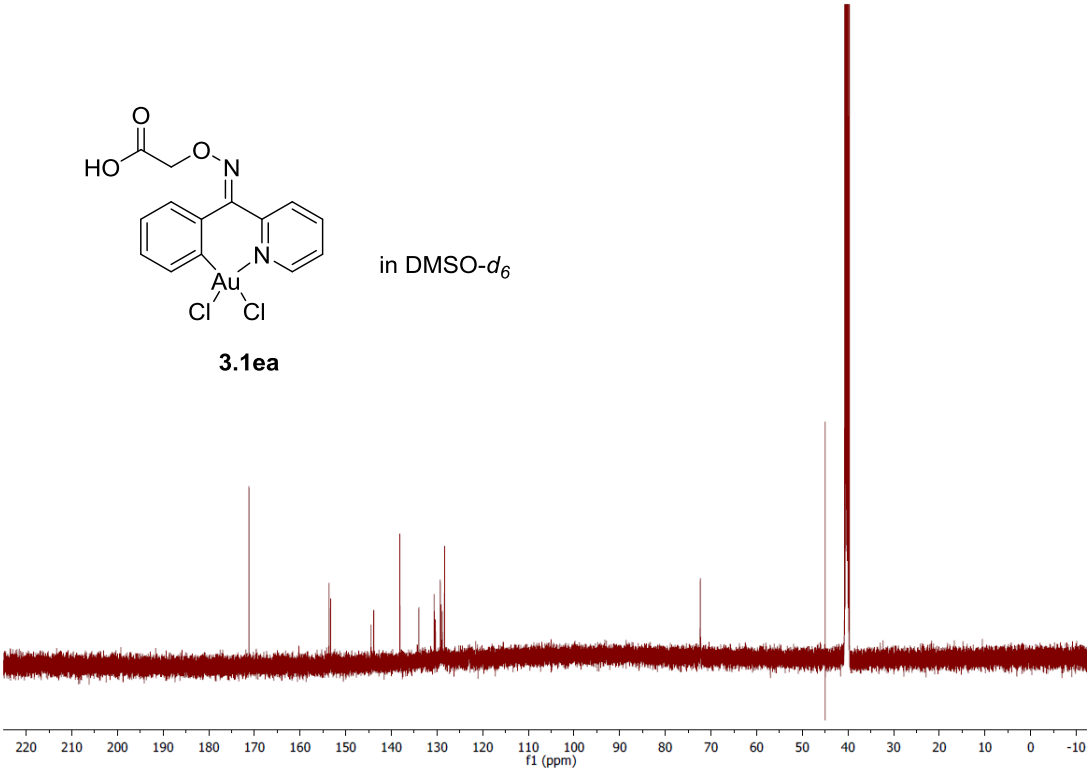

in CDCl3
3.6b
f1 (ppm)


in DMSO-d_6
3.6c
0.93
0.95
1.02
0.99
0.96
1.01
1.90
1.04
1.03
3.57
0.99
1.00
2.06
1.06
1.11
2.88
f1 (ppm)

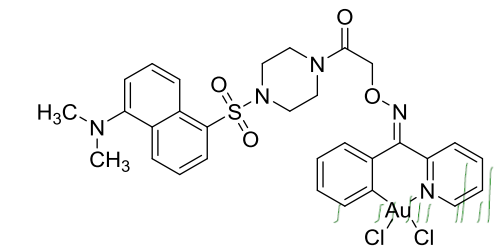

in DMSO-d_6
3.6c
f1 (ppm)


HO
O
O
N
N
Au
Cl
Cl
in DMSO-d_6
0.90
1.78
0.97
0.93
1.12
2.09
f1 (ppm)

3.1ea

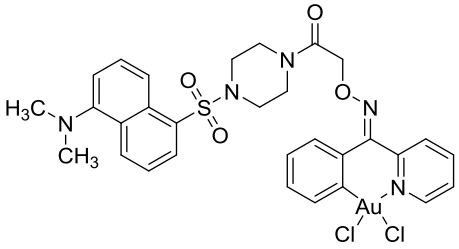

HO
O
O
N
N
Au
Cl
Cl
in DMSO-d_6
f1 (ppm)

3.1ea



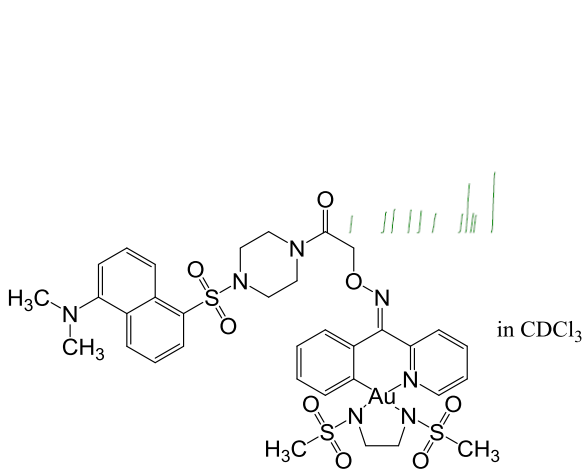
in $CDCl_3$

3.1eb



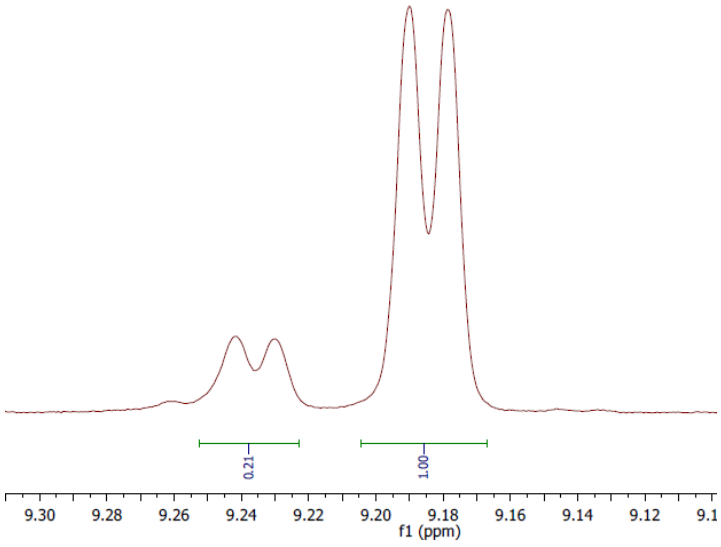
in $CDCl_3$

3.1eb


in $CDCl_3$

3.1e

0.70
0.85
0.97
0.95
0.92
0.79
2.04
0.82
0.72
2.52
2.21
3.70
2.00
6.27
6.26
2.39
2.39
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


0.21
1.00
9.30
9.28
9.26
9.24
9.22
9.20
9.18
9.16
9.14
9.12
9.1
f1 (ppm)

3.7 References

[1] Shaw, C. F., *Chem. Rev.* **1999**, *99*, 2589–2600.

[2] (a) Buckley, R. G.; Elsome, A. M.; Fricker, S. P.; Henderson, G. R.; Theobald, B. R. C.; Parish, R. V.; Howe, B. P.; Kelland, L. R., *J. Med. Chem.* **1996**, *39*, 5208–5214; (b) Parish, R. V.; Howe, B. P.; Wright, J. P.; Mack, J.; Pritchard, R. G.; Buckley, R. G.; Elsome, A. M.; Fricker, S. P., *Inorg. Chem.* **1996**, *35*, 1659–1666; (c) Parish, R. V.; Mack, J.; Hargreaves, L.; Wright, J. P.; Buckley, R. G.; Elsome, A. M.; Fricker, S. P.; Theobald, B. R. C., *Dalton Trans.* **1996**, 69–74; (d) Parish, R. V., *Metal-Based Drugs* **1999**, *6*, 271-276; (e) Engman, L.; McNaughton, M.; Gajewska, M.; Kumar, S.; Birmingham, A.; Powis, G., *Anti-cancer Drugs* **2006**, *17*, 539–544; (f) Gabbiani, C.; Casini, A.; Messori, L., *gold bull.* **2007**, *40*, 73−81; (g) Fricker, S. P.; Mosi, R. M.; Cameron, B. R.; Baird, I.; Zhu, Y.; Anastassov, V.; Cox, J.; Doyle, P. S.; Hansell, E.; Lau, G.; Langille, J.; Olsen, M.; Qin, L.; Skerlj, R.; Wong, R. S. Y.; Santucci, Z.; McKerrow, J. H., *Inorg. Biochem* **2008**, *102*, 1839–1845; (h) Milacic, V.; Dou, Q. P., *Coord. Chem. Rev.* **2009**, *253*, 1649–1660; (i) Zhu, Y.; Cameron, B. R.; Mosi, R.; Anastassov, V.; Cox, J.; Qin, L.; Santucci, Z.; Metz, M.; Skerlj, R. T.; Fricker, S. P., *J. Inorg. Biochem.* **2011**, *105*, 754–762; (j) Zhang, J. J.; Sun, R. W. Y.; Che, C. M., *Chem. Commun.* **2012**, *48*, 3388–3390; (k) Bertrand, B.; Casini, A., *Dalton Trans.* **2014**, *43*, 4209–4219.

[3] (a) Sun, R. W. Y.; Ma, D. L.; Wong, E. L. M.; Che, C. M., *Dalton Trans.* **2007**, 4884–4892; (b) Fonteh, P. N.; Keter, F. K.; Meyer, D., *J. Inorg. Biochem.* **2011**, *105*, 1173–1180; (c) Mphahlele, M.; Papathanasopoulos, M.; Cinellu, M. A.; Coyanis, M.; Mosebi, S.; Traut, T.; Modise, R.; Coates, J.; Hewer, R., *Bioorg. Med. Chem* **2012**, *20*, 401–407.

[4] Buckley, R. G.; Elsome, A. M.; Fricker, S. P.; Henderson, G. R.; Theobald, B. R. C.; Parish, R. V.; Howe, B. P.; Kelland, L. R., *J. Med. Chem.* **1996**, *39*, 5208–5214.

[5] Che, C. M.; Sun, R. W. Y.; Yu, W. Y.; Ko, C. B.; Zhu, N.; Sun, H., *Chem. Commun.* **2003**, 1718–1719.

[6] (a) Constable, E. C.; Henney, R. P. G.; Leese, T. A.; Tocher, D. A., *J. Chem. Soc., Dalton Trans.* **1990**, 443–449; (b) Cinellu, M. A.; Zucca, A.; Stoccoro, S.; Minghetti, G.; Manassero, M.; Sansoni, M., *J. Chem. Soc., Dalton Trans.* **1995**, 2865–2872; (c) Cinellu, M. A.; Zucca, A.; Stoccoro, S.; Minghetti, G.; Manassero, M.; Sansoni, M., *J. Chem. Soc., Dalton Trans.* **1996**, 4217–4225.

[7] (a) Wong, K. H.; Cheung, K. K.; Chan, M. C. W.; Che, C. M., *Organometallics* **1998**, *17*, 3505–3511; (b) Yam, V. W. W.; Wong, K. M. C.; Hung, L. L.; Zhu, N. Y., *Angew. Chem., Int. Ed.* **2005**, *44*, 3107–3110; (c) Garg, J. A.; Blacque, O.; Venkatesan, K., *Inorg. Chem.* **2011**, *50*, 5430–5441; (d) Rosca, D. A.; Smith, D. A.; Bochmann, M., *Chem. Commun.* **2012**, 7247–7249.

[8] (a) A. S. K. Hashmi; M. Rudolph; J. P. Weyrauch; M. Wölfle; W. Frey; J. W. Bats, *Angew. Chem. Int. Ed.* **2005**, *44*, 2798–2801; (b) N. Debono; M. Iglesias; F. Sánchez, *Adv. Synth. Catal.* **2007**, *349*, 2470–2476; (c) A. S. K. Hashmi; M. Rudolph; H. U. Siehl; M. Tanaka; J. W. Bats; W. Frey, *Chem. Eur. J.* **2008**, *14*, 3703–3708; (d) N. D. Shapiro; Y. Shi; F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 11654–11655; (e) J. A. O'Neill; G. M. Rosair; A. L. Lee, *Catal. Sci. Technol.* **2012**, *2*, 1818–1821; (f) Y. Zhang; B. Feng; C. Zhu, *Org. Biomol. Chem.* **2012**, *10*, 9137–9141; (g) Schmidbaur, H.; Schier, A., *Arabian J. Sci. Eng.* **2012**, *37*, 1187–1225.

[9] Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E., *Angew. Chem., Int. Ed.* **2004**, *43*, 6545–6547.

[10] Baslé, E.; Joubert, N.; Pucheault, M., *Chem. Biol.* **2010**, *17*, 213−227.

[11] (a) Chalker, J. M.; Bernardes, G. J. L.; Lin, Y. A.; Davis, B. G., *Chem. Asian J.* **2009**, *4*, 630–640; (b) Chalker, J. M.; Bernardes, G. J. L.; Davis, B. G., *Acc. Chem. Res.* **2011**, *44*, 730–741.

[12] Goddard, D. R.; Michaelis, L., *J. Biol. Chem.* **1935**, *112*, 361–371.

[13] Crankshaw, M. W.; Grant, G. A., Modification of Cysteine. In *Curr. Protoc. Protein Sci.*, John Wiley & Sons, Inc.: 2001.

[14] Masri, M. S.; Friedman, M., *J. Protein Chem.* **1988**, *7*, 49–54.

[15] Chen, X.; Zhou, Y.; Peng, X.; Yoon, J., *Chem. Soc. Rev.* **2010**, *39*, 2120−2135.

[16] Matsumoto, T.; Urano, Y.; Shoda, T.; Kojima, H.; Nagano, T., *Org. Lett.* **2007**, *9*, 3375−3377.

[17] Youziel, J.; Akhbar, A. R.; Aziz, Q.; Smith, M. E. B.; Caddick, S.; Tinker, A.; Baker, J. R., *Org. Biomol. Chem.* **2014**, *12*, 557−560.

[18] (a) Ellman, G. L., *Arch. Biochem. Biophys.* **1959**, *82*, 70–77; (b) Pollack, S. J.; Schultz, P. G., *J. Am. Chem. Soc.* **1989**, *111*, 1929–1931.

[19] (a) Kenyon, G. L.; Bruice, T. W., *Methods Enzymol.* **1977**, *47*, 407−430; (b) Davis, B. G.; Maughan, M. A. T.; Green, M. P.; Ullman, A.; Jones, J. B., *Tetrahedron: Asymmetry* **2000**, *11*, 245−262.

[20] (a) Crich, D.; Krishnamurthy, V.; Hutton, T. K., *J. Am. Chem. Soc.* **2006**, *128*, 2544–2545; (b) Crich, D.; Krishnamurthy, V.; Brebion, F.; Karatholuvhu, M.; Subramanian, V.; Hutton, T. K., *J. Am. Chem. Soc.* **2007**, *129*, 10282–10294; (c) Bernardes, G. J. L.; Grayson, E. J.; Thompson, S.; Chalker, J. M.; Errey, J. C.; Oualid, F. E.; Claridge, T. D. W.; Davis, B. G., *Angew. Chem.* **2008**, *120*, 2276–2279.

[21] (a) Okeley, N. M.; Zhu, Y.; van der Donk, W. A., *Org. Lett.* **2000**, *2*, 3603–3606; (b) Seebeck, F. P.; Szostak, J. W., *J. Am. Chem. Soc.* **2006**, *128*, 7150–7151; (c) Bernardes, G. J. L.; Chalker, J. M.; Errey, J. C.; Davis, B. G., *J. Am. Chem. Soc.* **2008**, *130*, 5052–5053; (d) Chalker, J. M.; Gunnoo, S. B.; Boutureira, O.; Gerstberger, S. C.; Fernandez-Gonzalez, M.; Bernardes, G. J. L.; Griffin, L.; Hailu, H.; Schofield, C. J.; Davis, B. G., *Chem. Sci.* **2011**, *2*, 1666–1676; (e) Chalker, J. M.; Lercher, L.; Rose, N. R.; Schofield, C. J.; Davis, B. G., *Angew. Chem. Int. Ed.* **2012**, *51*, 1835–1839.

[22] (a) Truce, W. E.; Tichenor, G. J. W., *J. Org. Chem.* **1972**, *37*, 2391−2396; (b) Halphen, P. D.; Owen, T. C., *J. Org. Chem.* **1973**, *38*, 3507–3510; (c) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G., *J. Org. Chem.* **1986**, *51*, 1457−1466; (d) Journet, M.; Rouillard, A.; Cai, D.; Larsen, R. D., *J. Org. Chem.* **1997**, *62*, 8630−8631.

[23] Shiu, H. Y.; Chan, T. C.; Ho, C. M.; Liu, Y.; Wong, M. K.; Che, C. M., *Chem. Eur. J.* **2009**, *15*, 3839–3850.

[24] Shiu, H. Y.; Chong, H. C.; Leung, Y. C.; Wong, M. K.; Che, C. M., *Chem. Eur. J.* **2010**, *16*, 3308−3313.

[25] Shiu, H. Y.; Wong, M. K.; Che, C. M., *Chem. Commun.* **2011**, *47*, 4367−4369.

[26] (a) Antos, J. M.; Francis, M. B., *Curr. Opin. Chem. Biol.* **2006**, *10*, 253–262; (b) van Maarseveen, J. H.; Reek, J. N. H.; Back, J. W., *Angew. Chem. Int. Ed.* **2006**, *45*, 1841–1843; (c) Crich, D.; Zou, Y.; Brebion, F., *J. Org. Chem.* **2006**, *71*, 9172−9177; (d) Lin, Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J. L.; Davis, B. G., *J. Am. Chem. Soc.* **2008**, *130*, 9642−9643.

[27] Jacob, C.; Giles, G. I.; Giles, N. M.; Sies, H., *Angew. Chem. Int. Ed.* **2003**, *42*, 4742−4758.

[28] Yan, L. Z.; Dawson, P. E., *J. Am. Chem. Soc.* **2001**, *123*, 526−533.

[29] Chalker, J. M.; Lin, Y. A.; Boutureira, O.; Davis, B. G., *Chem. Commun.* **2009**, 3714–3716.

[30] Chan, A. O. Y.; Tsai, J. L. L.; Lo, V. K. Y.; Li, G. L.; Wong, M. K.; Che, C. M., *Chem. Commun.* **2013**, *49*, 1428–1430.

[31] (a) Henderson, W., *Adv. Organomet. Chem.* **2006**, *54*, 207–265; (b) Janzen, D. E.; Doherty, S. R.; VanDerveer, D. G.; Hinkle, L. M.; Benefield, D. A.; Vashi, H. M.; Grant, G. J., *J. Organomet. Chem.* **2014**, *755*, 47–57.

[32] (a) Collot, J.; Gradinaru, J.; Humbert, N.; Skander, M.; Zocchi, A.; Ward, T. R., *J. Am. Chem. Soc.* **2003**, *125*, 9030−9031; (b) Carey, J. R.; Ma, S. K.; Pfister, T. D.; Garner, D. K.; Kim, H. K.; Abramite, J. A.; Wang, Z.; Guo, Z.; Lu, Y., *J. Am. Chem. Soc.* **2004**, *126*, 10812−10813; (c) Letondor, C.; Humbert, N.; Ward, T. R., *PNAS* **2005**, *102*, 4683−4687; (d) Wang, Z. J.; Clary, K. N.; Bergman, R. G.; Raymond, K. N.; Toste, F. D., *Nat. Chem.* **2013**, *5*, 100−103.

[33] (a) Meggers, E., *Curr. Opin. Chem. Biol.* **2007**, *11*, 287−292; (b) Haas, K. L.; Franz, K. J., *Chem. Rev.* **2009**, *109*, 4921−4960; (c) Meggers, E., *Chem. Comm.* **2009**, 1001−1010; (d) Crassous, J., *Chem. Commun.* **2012**, *48*, 9687−9695.

[34] (a) J. J. Zhang; R. W. Y. Sun; C. M. Che, *Chem. Commun.* **2012**, *48*, 3388–3390; (b) J. J. Zhang; K. M. Ng; C. N. Lok; R. W. Y. Sun; C. M. Che, *Chem. Commun.* **2013**, *49*, 5153–5155.

[35] Tamaki, A.; Magennis, S. A.; Kochi, J. K., *J. Am. Chem. Soc.* **1974**, *96*, 6140–6148.

[36] (a) Komiya, S.; Albright, T. A.; Hoffmann, R.; Kochi, J. K., *J. Am. Chem. Soc.* **1976**, *98*, 7255–7265; (b) Komiya, S.; Kochi, J. K., *J. Am. Chem. Soc.* **1976**, *98*, 7599–7607.

[37] Kuch, P. L.; Tobias, R. S., *J. Organomet. Chem.* **1976**, *122*, 429–446.

[38] (a) Komiya, S.; Shibue, A., *Organometallics* **1985**, *4*, 684−687; (b) Komiya, S.; Ozaki, S.; Shibue, A., *J. Chem. Soc., Chem. Commun.* **1986**, 1555−1556.

[39] Vicente, J.; Chicote, M. T.; Bermudez, M. D.; Sanchez-Santano, M. J.; Jones, P. G.; Fittschen, C.; Sheldrick, G. M., *J. Organomet. Chem.* **1986**, *310*, 401−409.

[40] (a) Vicente, J.; Bermúdez, M. D.; Chicote, M. T.; Sánchez-Santano, M. J., *J. Organomet. Chem.* **1990**, *381*, 285–292; (b) Vicente, J.; Bermudez, M. D.; Escribano, J.; Carrillo, M. P.; Jones, P. G., *J. Chem. Soc., Dalton Trans* **1990**, 3083−3089; (c) Vicente, J.; Bermudez, M. D.; Escribano, J., *Organometallics* **1991**, *10*, 3380–3384.

[41] (a) Mankad, N. P.; Toste, F. D., *J. Am. Chem. Soc.* **2010**, *132*, 12859–12861; (b) Scott, V. J.; Labinger, J. A.; Bercaw, J. E., *Organometallics* **2010**, *29*, 4090–4096; (c) Mankad, N. P.; Toste, F. D., *Chem. Sci.* **2012**, *3*, 72–76; (d) Winston, M. S.; Wolf, W. J.; Toste, F. D., *J. Am. Chem. Soc.* **2014**; (e) Wolf, W. J.; Winston, M. S.; Toste, F. D., *Nature Chem.* **2014**, *6*, 159–164.

[42] Caruso, A. J.; Colley, A. M.; Bryant, G. L., *J. Org. Chem.* **1991**, *56*, 862−865.

[43] (a) Sandrinelli, F.; Perrio, S.; Averbuch-Pouchot, M. T., *Org. Lett.* **2002**, *4*, 3619−3622; (b) Ham, J.; Yang, I.; Kang, H., *J. Org. Chem.* **2004**, *69*, 3236–3239.

[44] (a) Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E., *Tetrahedron lett,* **2000**, *41*, 1283−1286; (b) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D., *Org. Lett.* **2002**, *4*, 2803–2806; (c) Kwong, F. Y.; Buchwald, S. L., *Org. Lett.* **2002**, *4*, 3517–3520.

[45] (a) Wong, Y. C.; Jayanth, T. T.; Cheng, C. H., *Org. Lett.* **2006**, *8*, 5613–5616; (b) Ke, F.; Qu, Y.; Jiang, Z.; Li, Z.; Wu, D.; Zhou, X., *Org. Lett.* **2010**, *13*, 454−457; (c) Ananikov, V. P.;

Zalesskiy, S. S.; Kachala, V. V.; Beletskaya, I. P., *J. Organomet. Chem.* **2011**, *696*, 400–405; (d) Bastug, G.; Nolan, S. P., *J. Org. Chem.* **2013**, *78*, 9303−9308.

[46] (a) Gao, N.; Zheng, S.; Yang, W.; Zhao, X., *Org. Lett.* **2011**, *13*, 1514−1516; (b) Liu, W.; Zhao, X., *Synthesis* **2013**, *45*, 2051–2069.

[47] (a) Morita, N.; Krause, N., *Angew. Chem. Int. Ed.* **2006**, *45*, 1897–1899; (b) Brouwer, C.; Rahaman, R.; He, C., *Synlett* **2007**, 1785–1789; (c) Ando, K., *J. Org. Chem.* **2010**, *75*, 8516–8521; (d) Menggenbateer; Narsireddy, M.; Ferrara, G.; Nishina, N.; Jin, T.; Yamamoto, Y., *Tetrahedron lett.* **2010**, *51*, 4627–4629.

[48] (a) Baranano, D.; Hartwig, J. F., *J. Am. Chem. Soc.* **1995**, *117*, 2937−2938; (b) Hartwig, J. F., *Acc. Chem. Res.* **1998**, *31*, 852−860; (c) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A., *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219; (d) Zhao, X.; Dong, V. M., *Angew. Chem. Int. Ed.* **2011**, *50*, 932–934.

[49] (a) Lo, V. K. Y.; Kung, K. K. Y.; Wong, M. K.; Che, C. M., *J. Organomet. Chem.* **2009**, *694*, 583–591; (b) Kung, K. K. Y.; Li, G. L.; Zou, L.; Chong, H. C.; Leung, Y. C.; Wong, K. H.; Lo, V. K. Y.; Che, C. M.; Wong, M. K., *Org. Biomol. Chem.* **2012**, *10*, 925–930; (c) Ko, H. M.; Kung, K. K. Y.; Cui, J. F.; Wong, M. K., *Chem. Commun.* **2013**, *49*, 8869–8871; (d) Kung, K. K. Y.; Lo, V. K. Y.; Ko, H. M.; Li, G. L.; Chan, P. Y.; Leung, K. C.; Zhou, Z.; Wang, M. Z.; Che, C. M.; Wong, M. K., *Adv. Synth. Catal.* **2013**, *355*, 2055–2070.

[50] (a) Chan, W. K.; Ho, C. M.; Wong, M. K.; Che, C. M., *J. Am. Chem. Soc.* **2006**, *128*, 14796−14797; (b) Chan, A. O. Y.; Ho, C. M.; Chong, H. C.; Leung, Y. C.; Huang, J. S.; Wong, M. K.; Che, C. M., *J. Am. Chem. Soc.* **2012**, *134*, 2589−2598; (c) Li, G. L.; Kung, K. K. Y.; Zou, L.; Chong, H. C.; Leung, Y. C.; Wong, K. H.; Wong, M. K., *Chem. Commun.*

2012, *48*, 3527−3529; (d) Kung, K. K. Y.; Wong, K. F.; Leung, K. C.; Wong, M. K., *Chem. Commun.* **2013**, *49*, 6888−6890.

[51] Kilpin, K. J.; Henderson, W.; Nicholson, B. K., *Polyhedron* **2007**, *26*, 434–447.

[52] (a) Pearson, R. G., *J. Am. Chem. Soc.* **1963**, *85*, 3533−3539; (b) Pearson, R. G., *J. Am. Chem. Soc.* **1988**, *110*, 7684−7690.

[53] Parish, R. V.; Mack, J.; Hargreaves, L.; Wright, J. P.; Buckley, R. G.; Elsome, A. M.; Fricker, S. P.; Theobald, B. R. C., *J. Chem. Soc., Dalton Trans.* **1996**, 69−74.

[54] Fan, D.; Yang, C. T.; Ranford, J. D.; Lee, P. F.; Vittal, J. J., *Dalton Trans.* **2003**, 2680−2685.

[55] Cinellu, M. A.; Zucca, A.; Stoccoro, S.; Minghetti, G.; Manassero, M.; Sansoni, M., *J. Chem. Soc., Dalton Trans.* **1995**, 2865−2872.

[56] Fuchita, Y.; Ieda, H.; Tsunemune, Y.; Kinoshita-Nagaoka, J.; Kawano, H., *J. Chem. Soc., Dalton Trans.* **1998**, 791−796.