Chapter 2

‘Clicking’ molecular hooks on silica nanoparticles to immobilize metal complexes: the case of gold catalyst immobilization

In this chapter, we demonstrate that silica chemistry in combination with the [3+2] Huisgen’s cycloaddition could be used to generate a functional group on the surface of silica nanoparticles which can effectively bind to catalytically active metal ions. To show that we have chosen Au(III) ions as an example. The synthesis and characterization of silica nanoparticles in which Au(III) has been immobilized through a 1,2,3-triazole linkage using an alkynlated picolinic acid exploiting ‘click chemistry’ has been discussed. The Au(III) immobilized silica nanoparticles have been thoroughly characterized using FT-IR, $^{13}$C CP MAS NMR and XPS. The utility of these particles as an easily separable catalyst for the Hashmi phenol synthesis is also described.

2.1 Introduction:

Preparation of a multifunctional catalytic system is the grand theme of this thesis. As a first step in that direction in this chapter we describe the preparation of a ‘semi-heterogeneous catalyst’ by immobilizing a catalytically active metal ionic species on silica nanoparticle surface.

Apart from this, immobilization of molecular catalysts onto solid support is of growing commercial and academic interest, because they can combine the advantages of heterogeneous and homogeneous catalysts.\(^1\) It is easy to separate immobilized metal complexes from the reaction mixtures and recycle them. It is also much easier to tailor and fine tune heterogeneous catalysts in such a way that they remain active and selective as their homogeneous counterparts. Thus it is important to develop a methodology for immobilization of those industrially important precious metal complexes.\(^2\) In the recent years, a significant amount of time has been spent to design dispersible matrices for catalyst immobilization.\(^3-5\) Several such dispersible matrices have been explored. Nanoparticles have emerged as alternative dispersible matrix for supporting homogeneous organic reactions.\(^6\) They are considered semi-heterogeneous since they readily disperse in many solvents and the high surface area of these particles allows higher catalyst loading capacity than many conventional support matrices leading to an improved catalytic activity. In the previous chapter we have already discussed that among several nanoparticles that can be used as a support, the use of silica nanoparticles as a matrix for immobilization has been widespread. This can be attributed to the advances made in the last decade or so regarding the development of methodologies that allows easy surface functionalization of silica nanoparticles using well established silane chemistry. Several organic groups can now be covalently attached to silica nanoparticle surface using silanol chemistry discussed in the previous chapter. These organic functionalities can then be used to immobilize metal ions.\(^7-9\) Further, silica particles can also be synthesized with a magnetic core, thus, avoiding catalysts separation by filtration alone. Thus silica nanoparticles have been chosen for immobilization of precious metal complexes.

Bulk gold reveals great stability and chemical inertness, but it has been proved to be an excellent catalyst in the molecular and nanosized form. After the path breaking research done by Haruta et. al. and Hutchings et. al. simultaneously and independently on supported gold nanoparticles catalysts for the selective low-
temperature oxidation of CO,\textsuperscript{10} and the hydrochlorination of ethyne to vinyl chlorides,\textsuperscript{11} scientists have published many reports on the catalytic application of Au nanoparticles.\textsuperscript{12,6} There are numerous examples available in the literature where Au nanoparticles have been immobilized on various kinds of mesoporous solid support\textsuperscript{13} including zeolite,\textsuperscript{14} aluminosilicates,\textsuperscript{15} SBA-15\textsuperscript{16} and MCM-41.\textsuperscript{17} Although heterogeneous catalysis is still predominant, since the last decade or so gold mediated homogeneous reactions emerged as one of the best choices for effecting a variety of chemical transformations with wide range of functional group tolerance such as epoxides, ketones, aldehydes, and acids.\textsuperscript{18-20} Hashmi et al. extended the possibilities of gold-catalyzed reactions to newer avenues, including the conversion of alkyne terminated furan to phenol that combines the C-C and C-O bonds formation.\textsuperscript{21} Since then, it has been found that soluble gold compounds can catalyze many selective organic reactions.\textsuperscript{22} Although molecular Au species have been shown to display excellent reactivity, efforts to make heterogeneous/semi-heterogeneous catalysts based on Au complexes have been rather sparse (Figure 2.1).\textsuperscript{23}

**Figure 2.1:** Current status by gold catalysis. Explored combination (black) and a less explored combination (gray).

**Scheme 2.1:** (A) Au(III) Schiff base complexes synthesized by Corma and co-workers. (Adapted from ref. 25) (B) N-heterocyclic carbone gold complexes synthesized by Corma et al. Adapted from Ref. 24.
Corma and co-workers have immobilized several Au(III) and Au(I) complexes that contain Au(III) Schiff bases onto MCM-41 (Scheme 2.1) and have used them as catalysts for Suzuki, Sonogoshira and Heck C-C bond formation reactions as well as hydroamination reaction.24-28

Among several reactions that have been developed with homogeneous Au catalysts, activation of carbon-carbon π-bonds with Au(III) complexes as electrophiles have been a more recent phenomenon.18 Gold has come to be regarded as an exceedingly mild, relatively carbophilic Lewis acid, leading to the development of a broad array of reactions that proceed by the activation of unsaturated carbon-carbon bonds. Such C-C bond formation reactions are unique for Au which are otherwise very difficult to obtain with other transition metals. The excellent selectivity coupled with interesting possibilities for the synthesis of many novel molecular scaffolds invigorated interest among various scientific disciplines resulting in elegant strategies for easy synthesis of chemical architectures which are otherwise not possible. The dynamic and exorbitant price of gold puts the chemistry of gold in an uncomfortable position though these reactions occur with catalytic quantities of gold. Thus, immobilization of gold could enable the use of gold catalysts with increased efficiency due to the increased local concentration of the Au. However, there are very few reports of heterogenized Au(III) complexes that activate carbon-carbon π-bonds as electrophiles. Nanoparticles of gold supported on nanocrystalline CeO2 have been used to catalyze Hashmi’s phenol synthesis - a reaction in which Au(III) activates a terminal alkyne to isomerizes ω-alkynylfurans to phenols.29 (Scheme 2.2) Further, initial leaching of Au was observed in the first run of the reaction.

**Scheme 2.2:** Reaction scheme of Au(III) catalysed phenol synthesis.

We would like to mention that while immobilization of nanoparticles and molecular species on solid supports have been accomplished earlier, creating a
ligating group that can act like hook to attach to the metal ion of interest have not been reported. We envisaged that, Au(III) ion could be immobilized on the surface of silica nanoparticles using Huisgen’s 1, 3 dipolar cycloaddition reaction (Cu(I) catalyzed azide-alkyne cycloaddition reaction, CuAAC). The CaAAC is one of the popular “click” reactions, resulting in 1,2,3-triazoles linkage. (Scheme 2.3) It has been discussed in the previous chapter that among various surface functionalization techniques, CuAAC has become the most powerful “click chemistry” tool for conjugation between appropriately functionalized binding partners on surfaces via a 1,2,3-triazole linkage.\footnote{30,31}

Scheme 2.3: Cu(I) catalysed “click” reaction

In this chapter, the synthesis and characterization of azide grafted silica nanoparticles has been discussed. Au(III) has been immobilized on the surface of silica through a 1,2,3-triazole linkage using an alkynalated picolinic acid exploiting azide-alkyne “click chemistry”. As a model study for the activation of carbon-carbon π-bonds as electrophiles, the catalytic activity of the Au(III) immobilized on silica nanoparticle was investigated for the Hashmi’s phenol synthesis.\footnote{29} The immobilized picolinic acid moiety on the silica surface has a dual role. It anchors the Au(III) and also increases the rate of the isomerisation reaction as has been reported by Hashmi before.\footnote{32} The fate of Au(III) at the end of each run is also discussed.

2.2 Experimental section:

2.2.1 Materials:

Ludox AS40 (50% by weight), 3-hydroxy picolinic acid, o-hydroxy bezoic acid, Sodium tetrachloro aurate (III) dihydtae (NaAuCl\textsubscript{4}), propargyl bromide, chloropropyltriethoxysilane (99%), t-butylammonium chloride, disodium bathophenanthroline sulphonate, copper iodide were obtained from Sigma Aldrich and used as received. Triethylamine was obtained from Spectrochem India. Sodium Azide was obtained from Loba Chemie, India. All other chemicals and solvents were obtained from Merck, India and used as received. 3-azidopropyltriethoxysilane
(AzPTES), sodium dithiocarbamate and azide grafted silica nanoparticles (N$_3$-Silica) were prepared as per the details provided below. Millipore water was used for the preparation and reactions of silica nanoparticles.

2.2.2 Synthesis:

2.2.2.1 Synthesis of 3-azidopropyltriethoxysilane, AzPTES:

3-Chloropropyltriethoxysilane (abbreviated as Cl-PTES; 2 g, 8.3 mmol) was added to a solution of sodium azide (1.08 g, 16.6 mmol) and tetrabutylammonium bromide (0.644 g, 2 mmol) in dry acetonitrile (50 mL), under nitrogen atmosphere. The reaction mixture was stirred under reflux for 18 h. After completion of the reaction, the solvent was removed under reduced pressure. The crude mixture was diluted in n-pentane and the suspension was filtered over Celite. Solvent was removed from the resulting filtrate and the crude oil obtained was distilled under reduced pressure of 0.025 mbar at 62 °C to give AzPTES (3-azidopropyltriethoxysilane) as a colourless liquid. Yield: 1.52 g, 74%. $^1$H NMR (500 MHz, CDCl$_3$): δ 0.66 (t, 2H, J = 8.25 Hz), 1.21 (t, 3H, J = 6.88 Hz), 1.66–1.73 (m, 2H), 3.25 (t, 2H, J = 7.16 Hz), 3.80 (q, 2H, J = 6.88 Hz). $^{13}$C NMR (50 MHz, CDCl$_3$): δ 7.59, 18.23, 22.64, 53.8, 58.41. FT-IR (NaCl, cm$^{-1}$): 2098 (−N=N=−N, s) For the $^1$H and $^{13}$C NMR spectra see Appendix-2.

2.2.2.2 Synthesis of alkyne terminated ligands (L1 and L2):

2.2.2.2a Synthesis of prop-2-ynyl 3-(prop-2-ynyloxy)picolinate (1b):

To an ice cooled suspension of 3-hydroxy picolinic acid 1a (2.5 g, 0.018mol) in 30 mL anhydrous N,N- dimethylformamide was added K$_2$CO$_3$ (11.7 g, 0.085 mol) at 0 °C. After 30 min, propargyl bromide (4.0 mL, 5.3 g, 0.045 mol) was added drop wise and stirred for 5h at room temperature. At the end of the reaction (monitored by TLC), 40 mL water was added and extracted with diethyl ether (3x50mL), combined organic layers were washed with brine solution (2x20mL), dried over anhydrous sodium sulphate and concentrated in vacuo to obtain crude residue that was purified by silica gel column chromatography using ethyl acetate-petroleum ether (1:3) to get the title compound 1b (3.4 g, 89%) as a gum. (Scheme 2.4)

$^1$H NMR (200.13 MHz, CDCl$_3$): δ 2.54(t, 1H, J = 2.5Hz), 2.60(t, 1H, J = 2.4Hz), 4.84(d, 2H, J = 2.4Hz), 4.98(d, 2H, J = 2.5Hz), 7.46(dd, 1H, J = 4.4, 8.6Hz), 7.57(dd, 1H, J = 1.3, 8.6Hz), 8.36(dd, 1H, J = 1.1, 4.4Hz); $^{13}$C NMR (50.32 MHz, CDCl$_3$): δ
2.2.2.2b Synthesis of prop-2-ynyl 3-(prop-2-ynyloxy)picolinic acid (L1):

LiOH (223mg, 9.3 mmol) in water (5 mL) was added to solution of compound 1b (1.0 g, 4.65 mmol) in 15 mL of CH₃OH:THF (1:2) at 0 °C. The reaction mixture was stirred at room temperature until the complete consumption of starting material (TLC) and then solution was neutralized using amberlite IR120 (H⁺), filtered and the resin was washed with water and MeOH. The combined methanolic solution was concentrated under reduced pressure and the crude product (0.9 g) was recrystallized from aqueous ethanol to give the compound L1 (0.6 g, 73%) as a solid. (Scheme 2.4) m.p 63 °C ; ¹H NMR (200.13 MHz, CDCl₃): δ 2.75(t, 1H, J = 2.4Hz), 4.06(d, 2H, J = 2.4Hz), 6.67(dd, 1H, J = 4.5, 8.6Hz), 6.80(dd, 1H, J = 1.2, 8.6Hz), 7.34(dd, 1H, J = 1.2, 4.5Hz); ¹³C NMR (50.32 MHz, CDCl₃): δ 56.5, 78.9, 79.6, 122.3, 126.7, 141.7, 142.1, 151.6, 167.0; For the ¹H and ¹³C NMR spectra see Appendix-2. Mol. Wt. Calcd for C₁₂H₉NO₃Na:238.204; Found, 238.162

2.2.2.2c Synthesis of prop-2-ynyl 2-(prop-2-ynyloxy)benzoate (2b):

It has been synthesized according to the above procedure. (Scheme 2.4) m.p. 167 °C; ¹H NMR (200.13 MHz, CDCl₃): δ 2.52(t, 1H, J = 2.5Hz), 2.55(t, 1H, J = 2.4Hz), 4.80(d, 2H, J = 2.4Hz), 4.89(d, 2H, J = 2.5Hz), 7.04(t, 1H, J = 7.5Hz), 7.13(d, 1H, J = 8.5Hz), 7.49(t, 1H, J = 7.7Hz), 7.86(dd, 1H, J = 1.6, 7.7Hz); ¹³C NMR (50.32 MHz, CDCl₃): δ 52.3, 56.8, 74.9, 76.1, 77.8, 78.1, 114.4, 119.9, 121.3, 132.0, 133.8, 157.3, 164.8; For the ¹H and ¹³C NMR spectra see Appendix-2. LRMS Calcd for C₁₃H₁₀O₃Na:237.217; Found, 237.062

Scheme 2.4: Synthesis of ligand L1 and ligand L2
2.2.2.2d Synthesis of prop-2-ynyl 2-(prop-2-ynyloxy)benzoic acid (L2):

It has been prepared by following the above procedure (for L1) from compound 2b (Scheme 2.4).

m.p 65 °C; \(^1\)H NMR (200.13 MHz, CDCl\(_3\)): δ 2.58(t, 1H, J = 2.4Hz), 4.74(d, 2H, J = 2.4Hz), 7.20-7.35(m, 2H), 8.27(dd, 1H, J = 1.7, 4.3Hz), 8.38(d, 1H, J = 2.6Hz); \(^{13}\)C NMR (50.32 MHz, CDCl\(_3\)): δ 55.9, 76.7, 77.5, 121.5-123.7, 138.2, 142.7, 153.6; For the \(^1\)H and \(^{13}\)C NMR spectra see Appendix-2. Mol. Wt. Calcd for C\(_{10}\)H\(_8\)O\(_3\):176.169; Found, 177.108

2.2.2.3 Synthesis of azide-grafted silica nanoparticles (N\(_3\)-Silica):

Ludox silica sol (2.4 g) was diluted with 30 mL of a DI water ethanol (1:1) mixture and placed in a Teflon beaker. AzPTES (494 mg, 2 mmol) was added to the homogeneous dispersion. The reaction mixture was stirred for 23 h at room temperature, after which the reaction mixture was centrifuged at 12000 rpm for 30 min. The clear supernatant liquid was decanted from the solid deposit. The solid mass obtained was sonicated with ethanol for 20 min and then centrifuged three times. It was then dried at 50 °C under high vacuum for 6 h. The particles were characterized by NMR, FT-IR, TEM and elemental analysis. Yield: 0.512 g

2.2.2.4 Synthesis of ligand (L1 or L2) functionalized Silica nanoparticles using CuAAC:

For CuAAC, the azide functionalized silica nanoparticles were incubated with 5 equivalents of the alkyne substituted ligand (L1 or L2) in DMF: H\(_2\)O solvent mixture (8:2) containing CuI (2.0 equivalent), disodium bathophenanthroline sulphonate (2.0 equivalent), sodium ascorbate (4 equivalent) and triethylamine (5.0 equivalents). In a typical reaction, azide grafted silica nanoparticles (150 mg, 0.1071 mmol of azide) was incubated with L1 (94.78 mg, 0.5355 mmol, 5 eq) in 12ml DMF/3ml H\(_2\)O mixture containing sodium ascorbate (84.82 mg, 0.4284 mmol, 4 eq) and copper iodide (40.698 mg, 0.2142 mmol, 2 eq) and disodium sulphonated bathophenanthroline (115.56 mg, 0.2142 mmol, 2 eq) and triethylamine (54 mg, 0.5355 mmol, 5 eq). The reaction mixture was subjected to three freeze-pump-thaw cycles for rigorous exclusion of dioxygen. The CuAAC was allowed to proceed for 24 h with stirring. After completion of the reaction, the mixture was taken into a centrifuge tube and centrifuged for 20 min at 12000 rpm. The supernatant liquid was decanted off and the solid residue was washed with DMF (2 times), ethanol (2 times),
0.1 M sodium ascorbate (2 times), 0.1 M N,N-diethyldithiocarbamate sodium in ethanol (4 times) and ethanol (2 times). It was finally washed with 0.1 M HCl (2 times) and then stored as a suspension in ethanol. This sample will henceforth be called as Silica-L1. For preparation of samples for NMR and IR, a part of the functionalized silica nanoparticles solution was washed in ethanol and dried under vacuum at 60 ºC. Yield: 123 mg

Similar protocol was adopted for CuAAC of the ligand L2 with Silica-Azide to afford the conjugate Silica-L2. Yield: 112 mg

2.2.2.5 Synthesis of Silica-Au-L1:

Functionalized silica nanoparticle Silica-L1 was dispersed in methanol and then NaAuCl4 was added and heated at 60 ºC. In a typical reaction, 50 mg of Silica-L1 (0.03882 mmol) was dispersed in 2.5ml methanol followed by the addition of 16.85 mg NaAuCl4 (0.0465 mmol, 1.2 eq). The reaction mixture was heated to 60 ºC for 10 hrs. After completion of the reaction, the mixture was taken into a centrifuge tube and centrifuged for 10 min at 12000 rpm. The supernatant liquid was decanted off and the solid residue was washed with methanol (5 times) to afford Silica-Au-L1. It was finally stored as a suspension in ethanol. For preparation of samples for IR, a part of the Silica-Au-L1 solution was washed in ethanol and dried under vacuum at 60 ºC. Yield: 41 mg

2.2.2.6 General procedure of Hashmi reaction for the synthesis of 4-methyl-1, 3-dihydroisobenzofuran-5-ol using Silica-Au-L1:

Catalyst silica-Au-L1 (2 mol% Au, 28.2 mg, 0.01027 mmol) in acetonitrile (1mL) was added to solution of 2-methyl-5-(prop-2-ynyloxy) methyl furan (75 mg, 0.5136 mmol) in acetonitrile (0.5 mL) at 0 ºC. The reaction mixture was stirred at room temperature and periodically monitored by LC-MS until the complete consumption of starting material. After the completion of starting material catalyst was separated by centrifuging at 6000 rpm and then washed with acetonitrile, sonicated and dried for 30min. Recovered catalyst was reused for one more cycle of same reaction.

A number of catalysis reactions have been done using silica-Au-L1 with the help of Dr. Srinivas Hotha, National Chemical Laboratory, using same protocol discussed above. The reactions will be discussed in detail later in this chapter (Scheme 2.6). The NMR of the final products is listed below.
2-methyl-5-(prop-2-ynyloxy) methyl furan (3)

To an ice cooled solution of (5-methylfuran-2-yl)methanol 3 (400mg, 3.6mmol) in 5 mL anhydrous N,N-dimethyl formamide at 0 °C NaH (60% in mineral oil) (168 mg, 4.2mmol) was added. After 30 min, at 0 °C propargyl bromide (500mg, 4.2 mol) was added drop wise and stirred for 2h at room temperature. At the end of reaction (monitored by TLC), 6 mL water was added and extracted with diethyl ether (3x10mL), combined organic layers were washed with brine (2x5mL), dried over anhydrous sodium sulphate and concentrated in vacuo, crude residue was purified by silica gel column chromatography to get 2-methyl-5-(prop-2-ynyloxy)methyl furan 4 (478mg, yield 89%).

\(^1\)H NMR (200.13 MHz, CDCl\(_3\)): δ 2.28(d, 3H, J = 0.8Hz), 2.45(t, 1H, J = 2.4Hz), 4.14(d, 2H, J = 2.4Hz), 4.49(s, 2H), 5.91(m, 1H), 6.24(d, 1H, J = 3.0Hz); \(^13\)C NMR (50.32 MHz, CDCl\(_3\)): δ 13.6, 58.4, 63.1, 74.7, 79.4, 106.2, 111.1, 148.8, 152.9; Mol. Wt. Calcd for C\(_9\)H\(_{10}\)O\(_2\):150.068; Found, 149.176

4-methyl-1, 3-dihydroisobenzofuran-5-ol (4)

AuCl\(_3\) (4mg, 0.013mmol) in acetonitrile (0.5mL) was added to a solution of 2-methyl-5-(prop-2-ynyloxy)methyl furan 4 (100mg, 0.67mmol) in acetonitrile (1mL) at 0 °C. The reaction mixture was stirred at room temperature until the complete consumption of starting material and then quenched with Et\(_3\)N and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using ethyl acetate-petroleum ether (1:20) to get the title product 5 (90mg, 90%).

Mp 71°C; \(^1\)H NMR (200.13 MHz, CDCl\(_3\)): δ 2.25(s, 3H), 5.13(bs, 2H), 5.14(bs, 2H), 5.77(s, 1H), 6.70(d, 1H, J = 7.5Hz), 7.04(d, 1H, J = 7.5Hz); \(^13\)C NMR (50.32 MHz, CDCl\(_3\)): δ 15.2, 71.7, 74.0, 112.7, 122.2, 124.9, 130.5, 138.6, 148.4; For the \(^1\)H and \(^13\)C NMR spectra see Appendix-2. Mol. Wt. Calcd for C\(_9\)H\(_{10}\)O\(_3\):150.174; Found, 150.938

5-methyl-2-tosylisoindolin-4-ol (6)

Reaction was carried out for 5 h with substrate 5. The reaction conditions were kept similar to those followed in the reaction of 3 to give 4 as delineated above. m.p. 178 °C; \(^1\)HNMR (200.13MHz, CDCl\(_3\)): δ 2.19 (s, 3 H), 2.40 (s, 3 H), 4.60 (m, 4H), 5.00 (brs, 1H), 6.64 (d, 1 H, J = 7.6 Hz), 6.99 (d, 1 H, J = 7.5 Hz), 7.30 (d, 2 H, J = 8.0 Hz), 7.75 (d, 2 H, J = 8.4 Hz); \(^13\)C NMR (100.61 MHz, CDCl\(_3\)): δ 15.1, 21.5, 51.6,
For the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra see Appendix-2; M\textsubscript{w} Calcd for C\textsubscript{16}H\textsubscript{17}NO\textsubscript{3}S: 303.092; Found, 304.291 (M\textsuperscript{+} + 1).

When the reaction was carried out with substrate 7 two products 8 and 9 were obtained. The reaction conditions were again kept the same as those delineated above.

\textit{Dihydroisobenzofuran-4-ol (8)}

m.p. 130–135 \textdegree C; \textsuperscript{1}H NMR (400.13 MHz, CDCl\textsubscript{3}): \(\delta\) 5.13, 5.15 (2s, 4 H), 5.67 (brs, 1 H), 6.66 (d, 1 H, J = 8.1 Hz), 6.81 (d, 1 H, J = 7.6 Hz), 7.15 (t, 1 H, J = 7.8 Hz); \textsuperscript{13}C NMR (100.61 MHz, CDCl\textsubscript{3}): \(\delta\) 71.4, 73.7, 112.8, 113.4, 124.9, 128.8, 141.2, 149.9. For the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra see Appendix-2; M\textsubscript{w} Calcd for C\textsubscript{8}H\textsubscript{8}O\textsubscript{2}: 136.052; Found, 137.114 (M\textsuperscript{+} + 1).

1,3-\textit{Dihydroisobenzofuran-5-ol (9)}

m.p. 120 \textdegree C; \textsuperscript{1}H NMR (200.13 MHz, CDCl\textsubscript{3}): \(\delta\) 5.06 (s, 4 H), 5.50 (brs, 1 H), 6.66–6.78 (m, 2 H), 7.08 (d, 1 H, J = 8.0 Hz); \textsuperscript{13}C NMR (50.32 MHz, CDCl\textsubscript{3}): \(\delta\) 73.3, 73.4, 107.9, 114.6, 121.8, 130.7, 140.7, 155.5. For the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra see Appendix-2; M\textsubscript{w} Calcd for C\textsubscript{8}H\textsubscript{8}O\textsubscript{2}: 136.052; Found, 137.020 (M\textsuperscript{+} + 1).

When the reaction was carried out with substrate 10 two products 11 and 12 were obtained. The reaction conditions were again kept the same as those delineated above.

\textit{2-Tosylisoindolin-4-ol (11)}

m.p. 145–150 \textdegree C; \textsuperscript{1}H NMR (200.13 MHz, CDCl\textsubscript{3}): \(\delta\) 2.40 (s, 3 H), 4.53 (s, 4 H), 5.27 (s, 1 H), 6.68 (td, 2 H, J=2.4, 8.2 Hz), 7.00 (d, 1 H, J=8.2Hz), 7.31 (m, 2 H), 7.75 (m, 2 H); \textsuperscript{13}C NMR (100.61 MHz, CDCl\textsubscript{3}): \(\delta\) 21.5, 53.2, 53.7, 109.5, 115.2, 123.6, 127.6(2C), 127.9, 129.9(2C), 133.6, 137.7, 143.8, 155.6. For the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra see Appendix-2; M\textsubscript{w} Calcd for C\textsubscript{15}H\textsubscript{15}NO\textsubscript{3}S: 289.077; Found, 290.203 (M\textsuperscript{+} + 1).

\textit{2-Tosylisoindolin-5-ol (12)}

m.p. 170 \textdegree C; \textsuperscript{1}H NMR (200.13 MHz, CDCl\textsubscript{3}): \(\delta\) 2.40 (s, 3 H), 4.67 (s, 4 H), 5.52 (brs, 1 H), 6.64 (d, 1 H, J=8.1 Hz), 6.72 (d, 1 H, J=7.6 Hz), 7.10 (t, 1 H, J = 7.9 Hz), 7.31 (m, 2 H), 7.77 (m, 2 H); \textsuperscript{13}C NMR (50.32 MHz, CDCl\textsubscript{3}): \(\delta\) 21.6, 51.6, 54.1, 114.1, 114.7, 122.8, 127.6 (2C), 129.4, 129.9 (2C), 133.6, 138.3, 143.8, 150.9. For the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra see Appendix-2; M\textsubscript{w} Calcd for C\textsubscript{15}H\textsubscript{15}NO\textsubscript{3}S: 289.077; Found, 290.276 (M\textsuperscript{+} + 1).
2.3 Results and Discussion:

Our strategy to prepare the desired “molecular hook” for immobilizing gold (III) complex onto silica is displayed in Scheme 2.5. The first step in this endeavor was the synthesis of azide grafted silica particles. The azide grafted silica nanoparticles (N₃-silica) were synthesized by the condensation of azidopropyltriethoxysilane (AzPTES) onto commercially available silica colloidal particles (Ludox AS40; 22±3 nm particle size) as presented in Scheme 2.5. The organosilica precursor AzPTES was obtained by the displacement of the chloro group in 3-chloropropyltriethoxysilane with an azido group using sodium azide. The azide grafted silica nanoparticles were characterized by TEM (Figure 2.2), TGA (Figure 2.4 b), FT-IR (Figure 2.5 b), multinuclear (²⁹Si, ¹³C) solid state NMR (Figure 2.6 a and 2.7 a).

![Scheme 2.5: Synthesis of Silica-Au-L1 conjugate](image)

The second step in our strategy was to modify the silica surface to bear the moieties L₁ or L₂ that would serve as hooks/anchors to immobilize Au(III). The ligand L₁ was chosen such that a robust five membered ring would form once the...
Au(III) ligates. For doing control experiment ligand L2 was anchored on the surface of silica nanoparticles. Due to the absence of nitrogen in L2, it can be expected that five membered ring will not form with Silica-Au-L2 and hence Au(III) anchoring may not be facile. Ligands L1 and L2 were immobilized on silica surface applying “Click Reaction”. The CuAAC reaction was carried out using CuI/sulfonated bathophenanthroline in DMF and H2O mixture at a ratio of 80:20 for 24 hrs. After the reaction, an extensive washing protocol was followed to remove the Cu(I), ascorbate and any unreacted starting materials. One of the key steps in the washing was the usage of dithiocarbamate to remove the Cu(I), as reported earlier. The ligand grafted silica nanoparticles Silica-L1 and Silica-L2 were characterized by TGA (Figure 2.4 c), FT-IR (Figure 2.5 c), multinuclear (29Si, 13C) solid state NMR (Figure 2.6 b and 2.7 b). The extent of the reaction was estimated using FT-IR spectroscopy, by monitoring the decrease in the integrated intensity of the νas(N3) at 2100 cm⁻¹. XPS analysis was done to know the chemical composition of the surface (Figure 2.8).

In the final step, after thorough optimization, Au(III) was incorporated onto silica-L1 nanoparticle by incubating them with NaAuCl₄ in methanol solution at 55 °C to afford Silica-Au-L1 (Scheme 2.5). Control reactions were performed with Silica-L2 keeping same reaction condition. As expected Au(III) did not bind with Silica-L2 because of absence of picolinic acid moiety. All these materials were characterized FT-IR (Figure 2.5 e) spectroscopy. ICP analysis was done to know the amount of Au present in the Silica-Au-L1 and Silica-Au-L2 (Table 2.2). Chemical composition of the surface was determined using XPS analysis (Figure 2.9).

The catalytic activity of Silica-Au-L1 was studied on Hashmi’s phenol synthesis using different substrates. Control experiments were performed using Silica-Au-L2. The reactions were monitored by LC-MS analysis. (Figure 2.11 and Figure 2.12) The detailed characterizations of different materials are discussed below.

### 2.4 Characterizations:

#### 2.4.1 Transmission electron microscopy:

The TEM of azide grafted silica nanoparticles is shown in Figure 2.2. The size of commercially available silica colloidal solution is around 22 nm. The size of the azide grafted silica nanoparticles was determined to be about 22±3 nm from TEM
studies. This indicates that after azide grafting the size and morphology of silica particles remains same.

### 2.4.2 N\textsubscript{2} Adsorption isotherm:

The N\textsubscript{2} adsorption and desorption isotherm of Ludox Silica particles are presented in Figure 2.3. This isotherm signifies that the particles are not porous and solid in nature. This also agrees well with the TEM presented in Figure 2.2.

![Figure 2.2: TEM of Silica-azide](image)

**Figure 2.2:** TEM of Silica-azide

![Figure 2.3: Nitrogen adsorption-desorption isotherms of Silica Nanoparticles](image)

**Figure 2.3:** Nitrogen adsorption-desorption isotherms of Silica Nanoparticles
2.4.3 Elemental and Thermo gravimetric analysis:

![Thermo gravimetric analysis](image)

**Figure 2.4:** Thermo gravimetric analysis (TGA) of (a) bare Ludox, (b) N\textsubscript{3}-silica, (c) Silica-L1

The thermo gravimetric analysis of the different functionalized silica materials are presented in Figure 2.4. Elemental and thermogravimetric analyses confirmed a grafting ratio of 0.7 mmol of azidopropyl group per gram of silica particle (Figure 2.4 a and 2.4 b). The nitrogen content was found out to be 3.4\% while the TGA data displayed a loss of 7.2 \% weight. Taking into consideration that the average particle size is 22 nm and a surface area of 110 m\textsuperscript{2}/g, (surface area was calculated from N\textsubscript{2} adsorption, Figure 2.3) the grafting density was determined to be 3.7 azidopropyl groups/nm\textsuperscript{2}. It has been calculated that 3-5 silanol sites/nm\textsuperscript{2} are available for condensation of organosilane molecules on the silica surface for monolayer coverage.\textsuperscript{35,36} Therefore, the grafting density of 3.7 azidopropyl groups/nm\textsuperscript{2} signifies monolayer coverage of the azidopropyl groups on the silica surface. The TG-DTA analysis of Silica-L1 (Figure 2.4 c) indicated a mass loss of 20 \% between 200 °C and
600 °C which corresponds to a loading of 0.65 mmol of L1/gm of silica. The graft density was estimated to be about 3.6 group/nm² (6 µmol/m²).

<table>
<thead>
<tr>
<th></th>
<th>Weight Loss (%)</th>
<th>Ligand Grafting Density (mmol/gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludox</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>N₃-Silica</td>
<td>7.2</td>
<td>0.684</td>
</tr>
<tr>
<td>Silica-L1</td>
<td>19.62</td>
<td>0.65</td>
</tr>
<tr>
<td>Silica-Au-L1</td>
<td>-</td>
<td>0.65</td>
</tr>
<tr>
<td>Silica-L2</td>
<td>-</td>
<td>0.59</td>
</tr>
<tr>
<td>Silica-Au-L2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2.1:** The calculated ligand grafting density and gold loading on different functionalized silica particles

### 2.4.4 FT-IR spectroscopy

The FT-IR spectra of the various functionalized silica nanoparticles are presented in the Figure 2.5. In the FT-IR spectrum, the peak at ~2100 cm⁻¹ (which is absent in the starting Ludox particle) is the characteristic stretching vibration of organic azide (Figure 2.5 a and 2.5 b). Other significant peaks were observed at 1210, 1070, 800 and 466 cm⁻¹ respectively. These peaks are typical of Si-O-Si bands that are associated with the formation of the silica networks. Therefore, the FT-IR spectra indicate that the azido group was efficiently incorporated on the surface of the silica nanoparticles.

The FT-IR spectra of Silica-L₁ and Silica-L₂ show a decrease in the azide peak intensity. The extent of “click” reaction was estimated using IR spectroscopy by monitoring the decrease in the integrated intensity of the νₘ(N₃) at 2100 cm⁻¹ (Figure 2.5). Control reactions performed in the absence of CuI showed no conversion of the azide. The attachment of L₁ was further confirmed by the appearance of the ν(C=O) at 1610 cm⁻¹ arising from the carboxylic moiety present in L₁. The amount of grafted ligand in silica-L₁ was determined to be 0.53 mmol/g of silica by semi-quantitative IR.³⁷ This corresponds to a conversion of 75% of the available azides to the
corresponding triazoles. The grafting density of Silica-L1 obtained by FT-IR was slightly lower than that estimated by TG-DTA. This could be due to the fact that the increase in the molar mass of the nanoparticle due to the addition of L1 was not considered during the estimation of the extent of reaction. For control experiments, ligand L2 was grafted onto the silica nanoparticles using similar methodology described above. It should be noted that L2 has only one carboxylate ligand and hence is not expected to bind Au(III). The grafting density of ligand in Silica-L2 was determined to be 0.59 mmol/g of silica which corresponds to the conversion of 85% of the available azides to the corresponding triazoles.

![Infrared spectra](image)

**Figure 2.5:** Infrared spectra of (a) bare Ludox, (b) N3-silica, (c) Silica-L1 (d) Silica-L2 (e) Silica-Au-L1, and (f) Silica-Au-L2

The IR spectra of Silica-Au-L1 showed that the \( \gamma(\text{CO}) \) shifted significantly from 1610 cm\(^{-1}\) to 1720 cm\(^{-1}\), suggesting the binding of Au(III) to the O-atom of carboxylic acid of L1. Such shifts have been reported before for related Au(III) complexes with carboxylic containing ligands.\(^{38,39}\) Similar attempts were made to incorporate Au(III) onto Silica-L2. However, the FT-IR of the resultant compound
formed (Silica-Au-L2) displayed no shift in the \(\gamma(\text{CO})\) stretch as observed in Silica-Au-L1. This was expected since the ligand L2 does not have the bidentate picolinic acid moiety present as in L1 that was necessary to bind the Au(III).

### 2.4.5 Solid state CP-MAS NMR spectroscopy

#### 2.4.5.1 \(^{13}\text{C}\) CP-MAS NMR spectroscopy

Figure 2.6 represents the solid state \(^{13}\text{C}\) CP-MAS NMR spectra of the functionalized silica materials. The solid state \(^{13}\text{C}\) CP-MAS NMR spectrum of the azide grafted silica particles shows three peaks corresponding to C1 (10.81 ppm), C2 (23.66 ppm), C3 (54.95 ppm) that can be assigned to the three C-atoms of the azido-propyl chain. This spectra conclusively proves the incorporation of azide group on the silica surface.

![Figure 2.6: \(^{13}\text{C}\) CP-MAS NMR of (a) N\(_3\)-silica and (b) Silica-L1](image)

The solid state 13C CP-MAS NMR spectra of silica-L1 displayed extra peaks in addition to the C1, C2 and C3 observed in N\(_3\)-silica (Figure 2.6 b). The extra resonances at 128 ppm and 144 ppm correspond to the C4 and C5 atoms of the
triazole indicating a covalent linkage of L1 via the triazole ring. The C7 peak observed at 183 ppm is due to the presence of the C=O group of the carboxylic acid.

2.4.5.2 \(^{29}\text{Si CP-MAS NMR spectroscopy}\)

The \(^{29}\text{Si CP MAS NMR} \) spectra of the different functionalized silica materials are presented in Figure 2.7. The \(^{29}\text{Si CP MAS NMR} \) spectra of N\textsubscript{3}-Silica exhibit prominent peaks at around -111, -101, -67 and -58 ppm (Figure 2.7 a). The peaks at -111 and -101 ppm are assigned to the different types of the Si-sites namely Q3 \([(\text{SiO})_3\text{Si(OH)}] \) and Q4 \([(\text{SiO})_4\text{Si}] \). Two other distinct peaks observed at -58 and -67 ppm are ascribed to the functionalized sites of the Si-framework namely T2 \([R(\text{SiO})_2\text{Si(OH)}] \) and T3 \([R(\text{SiO})_3\text{Si}] \) respectively, where R is the azidopropyl group. Thus, all these data conclusively proves that the azidopropyl group was grafted successfully onto the silica nanoparticle.
The $^{29}\text{Si}$ CP MAS spectrum of silica-\textbf{L1} showed little or no change from the starting azide grafted silica particles indicating that the Si-sites do not undergo any chemical change during the reaction and its work-up (Figure 2.7 b). This is expected since the T1 and T2 Si-sites are that from the azido-propyl modified silica and should not undergo any change during the course of the click reaction.

2.4.6 ICP analysis:

ICP analysis was carried out to determine the amount of Cu and Au present in the materials (Table 2.1). After click reaction the presence of Cu in Silica-\textbf{L1} and Silica-\textbf{L2} was tested using ICP analysis. No appreciable amount of Cu was found which indicates that the extensive washing protocol used was sufficient to remove all the Cu from these hybrid materials.

<table>
<thead>
<tr>
<th></th>
<th>[Au] (mmol/gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludox</td>
<td>-</td>
</tr>
<tr>
<td>\textbf{N}_3\text{-Silica}</td>
<td>0.005</td>
</tr>
<tr>
<td>Silica-L1</td>
<td>-</td>
</tr>
<tr>
<td>Silica-Au-L1</td>
<td>0.339</td>
</tr>
<tr>
<td>Silica-L2</td>
<td>-</td>
</tr>
<tr>
<td>Silica-Au-L2</td>
<td>0.09</td>
</tr>
</tbody>
</table>

\textbf{Table 2.2:} The calculated Au concentration in different functionalized silica particles.

From the ICP analysis, Au concentration was determined to be 0.34 mmol/g of Silica-\textbf{L1}. This corresponds to the fact that Au(III) was bound to 55% of the available sites of the picolinic acid moiety of silica-\textbf{L1}. The Au concentration determined by ICP was found out to be only 0.09 mmol/g of Silica-Au-\textbf{L2}. This was expected since the ligand \textbf{L2} does not have the bidentate picolinic acid moiety present as in \textbf{L1}. The small amount of Au(III) seen from ICP was probably due to some non-specific binding to the surface silanol groups.

2.4.7 X-ray photoelectron spectroscopy:

The chemical composition of silica-\textbf{L1} was also verified with X-ray photoelectron spectroscopy. All the pristine spectra have been background corrected using the Shirley algorithm\textsuperscript{40} and the curves deconvoluted using standard curve fitting.
programs. The signals from Si 1s core level could be resolved into three components mainly occurring at 102.0, 103.4, 105.1 eV (Figure 2.8 A). These are assigned to Si-O-H, Si-O-Si, Si-O-C respectively. Three chemically distinct components are observed at 284.3, 285.7 and 287.9 eV in the case of the C1s core level spectrum (Figure 2.8 B). The peak at ~284 eV was ascribed to the adventitious carbon. The peak at higher binding energy at ~286 eV could be ascribed to the carbon bound to N. On the other hand the peak at ~288eV could be ascribed to the –C=O carbon. The O1s signals can be deconvoluted to three components at 531.1, 532.6, 533.8 eV which proves the presence of different components of O1s (Figure 2.8 D). The high BE component at 533.8 eV is accredited to the loading of L1 onto Silica azide. Two chemically distinct components are observed at 399.1, 400.2 and 402.0 eV in the case of the N1s core level spectrum (Figure 2.8 C). The higher binding energy was assigned to the pyridine N present in the L1 molecule attached to silica.

Figure 2.8: XPS of Silica-L1 (A) Si 2p (B) C 1s (C) N 1s (D) O 1s core levels Silica-L1

The chemical composition of silica-Au-L1 was also probed using X-Ray photoelectron spectroscopy (Figure 2.9). The spectra have been background corrected
using the Shirley algorithm prior to curve resolution. The signals from the Si 2p, C1s, O1s and N1s were more or less similar to the earlier peaks observed for the starting silica-L1. (Figure 2.9 A, B, C, D) Further, the Au 4f core level signals could be resolved into two chemically distinct species corresponding to Au(I) and Au (III) (Figure 2.9 E). The pair at 84.6 and 88.2 eV can be assigned as the spin orbit coupling of Au 4f_{7/2} and Au 4f_{5/2} respectively of Au(I).

**Figure 2.9:** XPS of Silica-Au-L1 (A) Si 2p (B) C 1s (C) N 1s (D) O 1s (E) Au 4f (F) Cl 2p core levels of Silica-Au-L1.
The presence of signals at 85.5 eV and 89.1 eV is related to the presence of Au (III). It can be clearly seen that the Au (III) component is less when compared to Au (I) which is unusual. To probe this further, we prepared the complex bis(pyridine-2-carboxylato)-gold(III) perchlorate and recorded its XPS.\textsuperscript{39} Interestingly, here also we could see peaks corresponding to Au (III) and Au (I) which is similar to the XPS of Silica-Au-L\textsubscript{1} (Figure 2.10). The ambiguous detection of Au(I) can be attributed to the electron donating capability of L\textsubscript{1} to Au(III) and strong X-ray radiation while recording XPS.\textsuperscript{41} However, we would like to mention that this did not influence in anyway the catalytic nature of the complex as can be seen further. The presence of chloride was confirmed from the peak at 198.8 eV (Figure 2.9 F).

**Figure 2.10:** XPS of Au 4f of the complex bis(pyridine-2-carboxylato)-gold(III) perchlorate.

### 2.5 Hashmi phenol synthesis by Au immobilized silica nanoparticles

The catalysts silica-Au-L\textsubscript{1} and silica-Au-L\textsubscript{2} were then evaluated for their ability to activate alkyne moiety of furanyl propargyl ether to trigger intramolecular Diels-Alder reaction to give isobenzofuran (Scheme 2.6). Accordingly, 5-methylfuranyl propargyl ether (3) was treated with silica-Au-L\textsubscript{1} (2 mol% Au) in acetonitrile leading to the formation of the isobenzofuran (4). The reaction was found
to be very exothermic and hence it was carried out at 0 °C. The reaction was complete in about 100 min as was observed from complete disappearance of the starting material, compound 3, by LC-MS analysis (Figure 2.11). Isolation of the product showed the yield of the reaction to be 90%. The same reaction, carried out using AuCl₃ as the catalyst, took more than 3 h to undergo completion clearly exemplifying the advantages of silica-Au-L1 over AuCl₃. This is expected since the picolinic acid ligand that binds the Au(III) in silica-Au-L1 is known to accelerate the rate of the reaction as has been shown by Hashmi et. al. In the control experiment, formation of isobenzofuran was not observed using silica-Au-L2. The catalyst silica-Au-L2 does not contain appreciable amounts of Au(III) since L2, a monodentate ligand having only carboxylic acid moiety, is unable to bind Au(III) effectively. This also clearly shows that the presence of Au(III) in silica-Au-L1 is key to the progress of this reaction.

Scheme 2.6: Experimental details of the Hashmi reaction performed using silica-Au-L1 conjugate on various substrates.
Cycle 1: Hashmi Reaction (Time Course Study)

![Reaction Scheme]

Figure 2.11: Time dependent LC-MS spectra for 1st cycle
Cycle 2: Hashmi Reaction (Time Course Study)

Ph.D Thesis  Chapter 2  ‘Clicking’ molecular hooks

Figure 2.12: Time dependent LC-MS spectra for 2$^{nd}$ cycle
At the end of the reaction, the silica-Au-L1 could be isolated from the reaction mixture by centrifugation. Isolated silica-Au-L1 particles were washed three times with acetonitrile, sonicated and then resuspended in acetonitrile to perform the Hashmi’s reaction on compound 3 again (Figure 2.12). This isolated catalyst was again found to be active for the synthesis of isobenzofuran 4 albeit taking longer periods of time for completion (16 hrs). Subsequently, this catalyst was found to be inactive for the synthesis of isobenzofurans. Therefore it was obvious that the catalyst was losing activity during the progress of the reaction. One possibility for this deactivation might be the leaching of Au during the progress of the reaction. The amount of Au present in silica-Au-L1 was estimated after each catalytic cycle by ICP. It was determined that the amount of gold even after three cycles of reaction was within 15% of the initial loading. This negates the possibility of Au leaching as the reaction progresses.

![Figure 2.13: XPS of Au 4f of the spent catalyst after 2nd run](image)

Then, to find the reasons for the loss of catalytic activity after the second cycle, the XPS of the spent catalyst has been analyzed (Figure 2.13). Unfortunately it displayed the spin orbit pair at 84.1 and 87.7 eV that can be assigned to Au(0). The presence of Au(0) indicates that during the progress of the reaction, the Au(III) complex was getting reduced to Au(0) thereby slowly rendering the catalyst inactive.
As mentioned earlier, the reaction is very exothermic, and the heat generated during the reaction may have reduced Au(III) to Au(0) which corroborate the recent findings by Shi and co-workers.42

2.6 Conclusion:

In conclusion, a successful strategy to immobilize Au(III) onto silica nanoparticles through CuAAC “click chemistry” protocol has been demonstrated. The catalyst has been thoroughly and extensively characterized using a variety of analytical and spectroscopic techniques. The catalyst was found to activate the carbon-carbon π-bond of alkynyl group in Hashmi’s phenol synthesis. The same catalyst is being evaluated for other Au(III) catalyzed cascade reactions initiated by heteroatom nucleophiles with π-electrophiles. The developed methodology is a generic one and can be extended to immobilizing other metal complexes and/or other surfaces including magnetic core-shell systems. Moreover, this study allowed to gain enough expertise in silica functionalization that was necessary for our further investigations.

2.7 References:

3. Dickerson, T. J.; Reed, N. N.; Janda, K. D., Soluble polymers as scaffolds for recoverable catalysts and reagents. Chemical Reviews, 2002, 102, (10), 3325-3344.


Ph.D Thesis  Chapter 2  ‘Clicking’ molecular hooks


