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Metal Acetylacetonates Covalently Anchored onto Amine Functionalized Silica/Starch Composite for the One-Pot Thioetherification and Synthesis of 2*H*-Indazoles

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Abstract This paper reports a series of novel metal acetylacetonates covalently anchored onto amine functionalized silica/starch composite, prepared by the Schiff condensation of metal acetylacetonates [$Co(acac)_2$, $Cu(acac)_2$, $Pd(acac)_2$, $Ru(acac)_3$, $Mn(acac)_3$, $Co(acac)_3$] with organically modified 3-aminopropyl silica/starch composite. Different metal acetylacetonates have been chosen with a view to select the most active heterogeneous catalyst. Among various catalysts, covalently anchored $Cu(acac)_2$ onto amine functionalized silica/starch composite [ASS-$Cu(acac)_2$] was found to be the most active and recyclable catalyst for the one-pot thioetherification and one-pot three component synthesis of 2*H*-indazoles via consecutive C–N and N–N bond formations. All the catalysts were characterized by FTIR, TGA and AAS analysis and the most active catalyst, [ASS-$Cu(acac)_2$] was further characterized by SEM and TEM. The catalyst could be recovered by simple filtration and reused with almost consistent activity for four consecutive runs.

Keywords Metal acetylacetonates · Amine functionalized silica/starch composite · Thioetherification · 2*H*-indazoles · Heterogeneous catalysis · Recyclability

1 Introduction

Heterogeneous catalysis for the synthesis of fine chemicals is an attractive area of research playing a crucial role in the chemical industry with significant economic and environmental impact [1–9]. In recent years, the emphasis of science and technology is shifting more towards environmentally friendly and sustainable resources, and processes. The preparation of porous materials from renewable resources such as starch is a relatively new area and its applications are developing, mainly as a consequence of a demand for biodegradable and naturally-derived products [10, 11]. Developing applications of biomaterials include new support materials for catalysts, as support for sensors and nano-materials for microbial culture. The use of biopolymers as support material for metal catalyst has attracted a wide attention in 1990's, however their application in organic syntheses started only in 2000 but this has been growing steadily ever since. Nowadays, catalysts based on silica/biomaterial composites are being used to meet the practical catalytic requirements in the chemical industry. The combination of high surface area inorganic mesoporous materials with organic polymer systems is an emerging class of hybrid materials with numerous potential applications [12–18]. They combine the advantages of inorganic material (rigidity, thermal stability) and the organic polymer (e.g., flexibility, ductility, and processability). Furthermore, these systems often possess the capability for recovery, high activity, selectivity, good accessibility and chemical versatility which is an important factor for the development of green catalysts. Despite of these potentialities, only few catalytic systems have been reported using silica/biomaterial supported metal as heterogeneous catalysts [19–21].

The construction of C–S bond represents an indispensable tool for the synthesis of new drugs and functionalized moieties [22]. The preparation of thioethers has been under consideration and widely studied in recent years using palladium [23], nickel [24], cobalt [25], copper [26] and iron

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salts [27] as catalysts. Migita et al. [28] first reported the coupling of aryl halides with thiols using $Pd(PPh_3)_4$ as a catalyst. Recent methodologies include general protocols by Zheng et al. using aryl triflates [29], coupling using DPE-Phos as ligand [30]; thioetherification using CyPF-*t*-Bu as ligand [23]. However, the harsh reaction conditions such as high temperature, use of strong bases, stoichiometric amounts of metal salts, and long reaction times are some of the disadvantages of such protocols. Bhaumik et al. have developed a novel protocol for one-pot thioetherification of different aryl halides with thiourea in water [31]. Thus, designing an efficient and environmentally friendly catalytic process for C–S coupling reactions is highly desirable.

In heterocyclic chemistry, indazole unit has been recognized as a "privileged structure", and is an important pharmacophore in medicinal chemistry [32–35]. 2*H*-Indazoles are less studied as compared to 1*H*-indazoles due to the difficulty in their preparation [36]. Hence, the formation of 2*H*-indazoles still remains a challenging task. Recently, several promising synthetic routes have been developed for the synthesis of 2*H*-indazoles, such as palladium-catalyzed intramolecular amination of the corresponding *N*-aryl-*N*-(*o*-bromobenzyl) hydrazines [37]; Fe-catalyzed intramolecular N–N bond formation from aryl azides [38]; reaction of highly functionalized zinc reagents with aryldiazonium salts [39]; [3 + 2] dipolar cycloaddition of arynes and sydnones [33]; reaction of sodium hydride or DBU catalyzed 2-nitrobenzyl triphenylphosphonium bromide with aryl isocyanates [40]; synthesis of 2*H*-indazoles using Suzuki–Miyaura and Sonogashira couplings [41]. However, most of the existing methods exhibit several drawbacks, such as requirement of additives, low functional group tolerance; and need several steps to synthesize the starting materials. Furthermore, most of these methods are homogeneous in nature. Therefore, there is a need for the development of novel and selective approach for the synthesis of 2*H*-indazoles.

In this paper, we report the synthesis of different metal acetylacetonate complexes covalently anchored onto amine-functionalized silica/starch composite [ASS-M(acac)$_n$, n = 2 or 3, M=Co, Cu, Pd, Mn, Ru] and their catalytic activities were evaluated for the one-pot thioetherification of aryl halides with benzyl bromide and thiourea, and one-pot three component synthesis of 2*H*-indazoles from 2-bromobenzaldehyde, primary amines and sodium azide through consecutive C–N and N–N bond formations, with a view to select the most effective recyclable and stable heterogeneous catalyst. These heterogeneous catalysts were developed via surface functionalization with 3-aminopropylsilica/starch composite, followed by Schiff condensation of the surface $-NH_2$ with M(acac)$_n$. The amine functionalized silica/starch support can stabilize the metal acetylacetonate complexes effectively and prevent the aggregation of metal particles.

2 Experimental

2.1 General Remarks

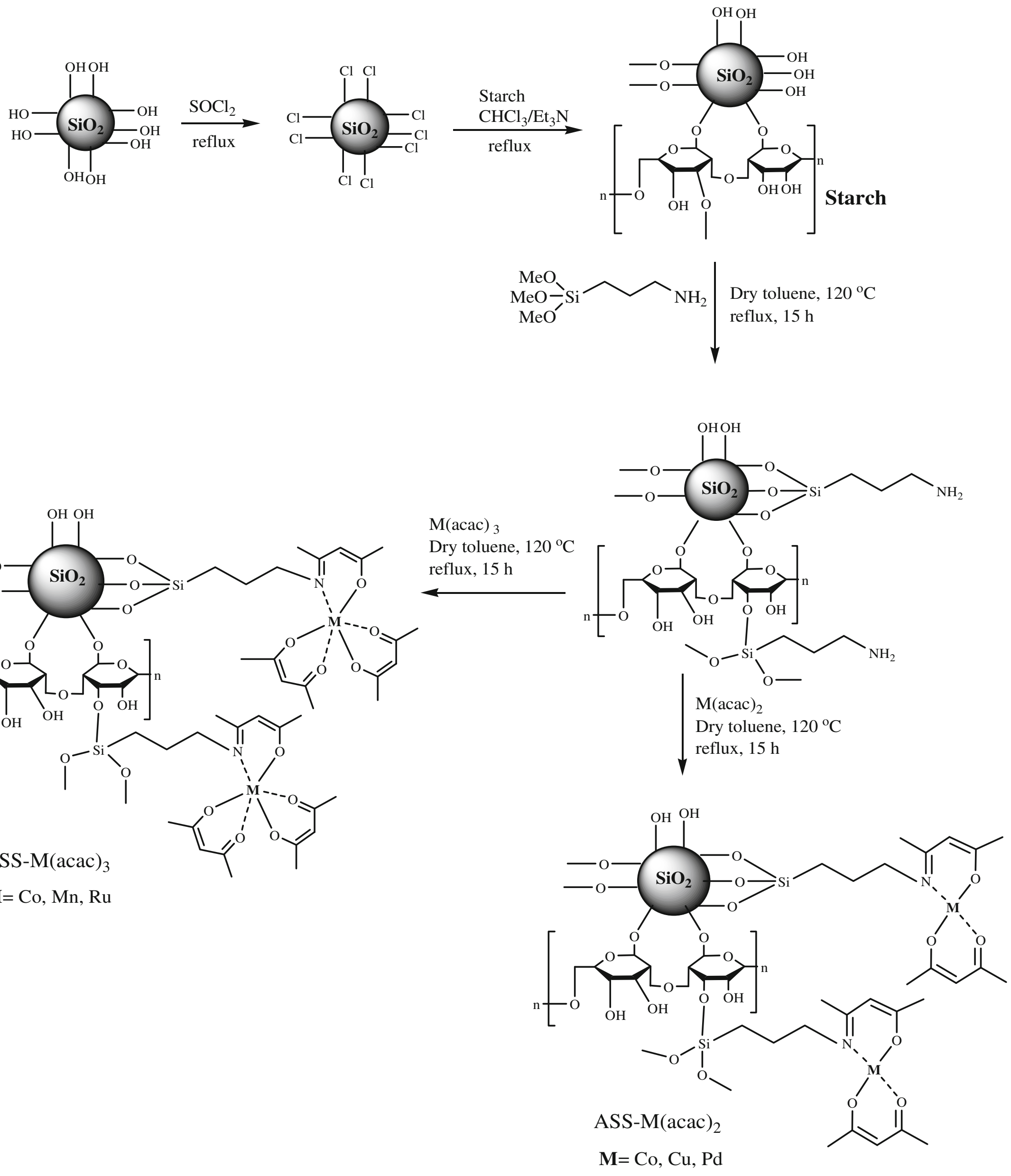
The chemicals used were either prepared in our laboratory or purchased from Aldrich Chemical Company or Merck. Metal acetylacetonates used for the preparation of catalyst were purchased from Aldrich Chemical Company. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on Bruker Avance III 400 MHz spectrometer. The FTIR spectra were recorded on Perkin-Elmer FTIR spectrophotometer and mass spectral data were recorded on Bruker Esquires 3000 (ESI). SEM images were taken on FEG SEM JSM-7600F Scanning electron microscope and Transmission electron micrographs (TEM) on H7500 Hitachi. The amount of metal in catalysts was determined by AAS analysis and thermal analysis was carried out on Linsesis STA PT-1000 make thermal analyzer. The CHNS elemental analysis was carried out on Vario MICRO Cube. Microwave synthesizer used was manufactured by CEM (DISCOVER SYSTEM) and products were purified using Flash chromatography (BIOTAGE).

2.2 General Procedure for the Synthesis of Amine Functionalized Silica/Starch-M(acac)$_n$ [ASS-M(acac)$_n$]

Activated silica (5 g) was charged to the three-neck flask (100 mL), equipped with a dropping funnel containing thionyl chloride (20 mL) and a gas inlet tube for conducting HCl over an absorbing solution of 10 % aqueous NaOH. Thionyl chloride was added drop-wise over a period of 15 min at room temperature followed by stirring for 10 h at 80 °C. The untreated $SOCl_2$ was removed by distillation and the resulting silica chloride was vacuum dried at 90 °C [42].

Silica/starch composite was prepared by refluxing mixture of silica chloride (5 g), corn starch (2 g), and triethyl amine (0.5 mL) in $CHCl_3$ (30 mL) for 10 h. The reaction mixture was filtered, washed with chloroform (3 × 10 mL) and water (3 × 20 mL) followed by drying in the oven at 120 °C for 2 h. To silica/starch composite (5 g) in dry toluene (100 mL), 3-aminopropyl(trimethoxy) silane (0.89 g, 5 mmol) was added and the reaction mixture was refluxed for 12 h. The 3-aminopropylsilica/starch substrate was filtered off, washed with hot toluene (50 mL) and dried at 110 °C for 5 h to get the surface bound amino groups.

For the preparation of amine functionalized silica/starch-M(acac)$_n$, a mixture of 3-aminopropylsilica/starch substrate (3 g) and M(acac)$_n$ [0.5 mmol, 0.12 g Co(acac)$_2$, 0.13 g Cu(acac)$_2$, 0.15 g Pd(acac)$_2$, 0.19 g Ru(acac)$_3$, 0.12 g Co(acac)$_3$ and 0.17 g Mn(acac)$_3$] in dry toluene (50 mL) was refluxed at 120 °C for 12 h (Scheme 1). The ASS-M(acac)$_n$

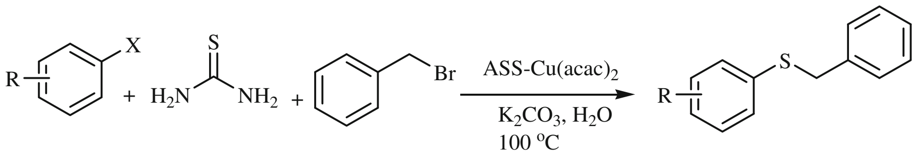


Scheme 1 General procedure for the synthesis of amine functionalized silica/starch-M(acac)$_n$

was filtered off, washed with hot toluene (50 mL) till the washings were colorless and dried in a hot air oven at 110 °C for 5 h. In order to remove any physisorbed M(acac)$_n$, the catalysts were conditioned by refluxing for a total of 9 h in xylene at 130 °C (2 × 2 h), ethanol at 78 °C (2 × 2 h) and acetonitrile at 80 °C (2 × 2 h). Finally, ASS-M(acac)$_n$ were dried in a hot air oven at 110 °C for 4 h.

2.3 General Procedure for the Thioetherification of Aryl Halides

To a mixture of aryl halide (1 mmol), benzyl bromide (1.1 mmol), K_2CO_3 (2 mmol), thiourea (1.2 mmol) and ASS-Cu(acac)$_2$ (0.2 g, 3.5 mol % Cu) in a round-bottom flask (25 mL), water (5 mL) was added and the reaction mixture was stirred at 100 °C for an appropriate time (Scheme 2). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate and filtered. The residue was treated with hot ethyl acetate (3 × 10 mL) and the organic layer was washed with water (100 mL) and dried over anhyd. Na_2SO_4. Finally, the product was obtained after removal of the solvent under reduced pressure followed by purification using flash chromatography on silica gel (EtOAc-Petroleum ether).



Scheme 2 ASS-Cu(acac)$_2$ catalyzed one-pot thioetherification of arylhalides using thiourea as the source of sulfur

Scheme 3 ASS-Cu(acac)$_2$ catalyzed one-pot synthesis of 2*H*-indazoles via consecutive C–N and N–N bond formations

2.4 General Procedure for the Synthesis of 2*H*-Indazoles Under Thermal Conditions

A mixture of 2-bromobenzaldehyde (1.5 mmol), primary amine (1.8 mmol), sodium azide (2 mmol) and ASS-Cu(acac)$_2$ (0.2 g, 3.5 mol% Cu) in DMSO (5 mL) was stirred at 100 °C for an appropriate time (Scheme 3). After completion of the reaction, the reaction mixture was diluted with ethyl acetate and filtered. The residue was washed with hot ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with water (100 mL) and dried over anhyd. Na_2SO_4. Finally, the product was obtained after removal of the solvent under reduced pressure followed by purification in a flash chromatography on silica gel (EtOAc-Petroleum ether). The catalyst was washed with EtOAc (3 × 5 mL) followed by double distilled water (3 × 10 mL) and dried at 100 °C for 2 h, and reused for subsequent reactions.

2.5 General Procedure for the Synthesis of 2*H*-Indazoles Under Microwave Irradiation

A mixture of 2-bromobenzaldehyde (1.5 mmol), primary amine (1.8 mmol), sodium azide (2 mmol) and ASS-Cu(acac)$_2$ (0.2 g, 3.5 mol% Cu) in DMSO (5 mL) was placed in a closed vial (10 mL) and irradiated in a microwave synthesizer at 100 °C for an appropriate time (monitored by TLC). The product was obtained after the similar work-up as given in Sect. 2.4.

The structure of the products were confirmed by ^{1}H and ^{13}C NMR, mass spectral data and comparison with authentic samples obtained commercially or prepared according to the literature methods [43–45].

3 Results and Discussion

3.1 Characterization of Covalently Anchored M(acac)$_n$ onto Amine Functionalized Silica/Starch Composite [ASS-M(acac)$_n$]

Covalently bonded silica/starch composite contains several free hydroxy groups on their backbone which have the potential for chelation with other functional groups/reagents/metal ions. Starch is composed of two polymers: amylose, a linear polymer and amylopectin which is highly branched polysacchride. Highly branched structure of amylopectin can supply more hydroxy groups that can better interact and facilitates the grafting of chemical species to achieve different surface properties (surface functionalization). It is rather surprising that despite the abundant functional groups present in biopolymers, the successful method for functionalization has not been reported yet. The functionalization of silica/starch composite with 3-aminoproplytrimethoxy silane introduces free –NH$_2$ groups onto the surface of the silica/starch composite. The functionalized silica/starch composite containing surface –NH$_2$ could bind with the M(acac)$_n$ strongly, as a result, the possibility of the leaching of the active metal from the catalyst surface would be slow during the liquid phase reactions. The general procedure for the synthesis of amine functionalized silica/starch-M(acac)$_n$ is represented in Scheme 1. It involves the preparation of amine functionalized silica/starch substrate followed by Schiff condensation of the surface –NH$_2$ with M(acac)$_n$. The metal is a lewis acid which is being an electron acceptor while the ligand being lewis base can donate the electron pair to central metal. The bond between metal and ligand is a lewis acid–base interaction. First, activated silica was converted to silica chloride using thionyl chloride [46], followed by reaction with starch in chloroform and triethylamine to obtain the silica/starch substrate. M(acac)$_n$ (where M=Co, Cu, Pd, n = 2; Co, Mn, Ru, n = 3) was refluxed with amine functionalized silica/starch substrate in dry toluene followed by simple filtration and drying in the oven at 110 °C. All the six heterogeneous catalysts were characterized by FTIR, TGA and AAS analysis. In addition to this, the most active catalyst was further characterized by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) [48]. Among the various supported metal acetylacetonates tested, ASS-Cu(acac)$_2$ was found to be the most active.

The FTIR of silica/starch composite showed bands in the range 3700–3200 cm^{-1} which were assigned to surface –OH groups, and 1101 and 804 cm^{-1} due to ν_{as}(Si–O–Si)

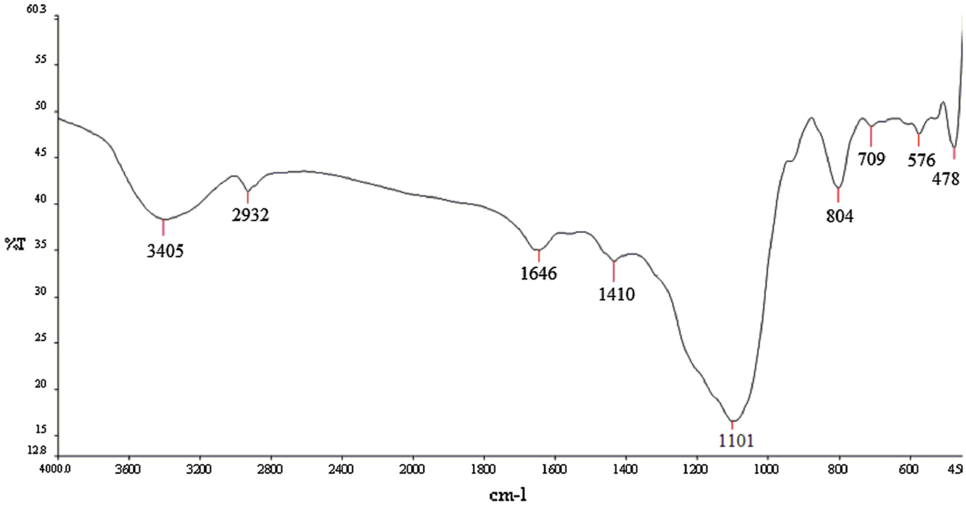


Fig. 1 FT-IR of ASS-Cu(acac)$_2$

Table 1 Characterization of covalently anchored M(acac)$_n$ onto amine functionalized silica/starch composite by FTIR, AAS and thermal analysis

Entry	Catalyst	FTIR[a]	AAS analysis[b]	TGA[c] (°C)	
		(C=N, υ_{max} in cm^{-1})	(Metal wt%)	Loss of residual solvent	Loss of organic functionality
1	ASS-Cu(acac)$_2$	1646	1.1	100	250–300
2	ASS-Co(acac)$_2$	1658	1	90	280–300
3	ASS-Pd(acac)$_2$	1642	1.8	90	250–290
4	ASS-Mn(acac)$_3$	1637	0.9	95	230–300
5	ASS-Co(acac)$_3$	1650	1.1	90	250–280
6	ASS-Ru(acac)$_3$	1620	1.7	70	220–300

[a] FTIR was recorded on Perkin-Elmer FTIR spectrophotometer using KBr discs

[b] AAS analysis was carried on GBC Avanta-M atomic absorption spectrometer. The catalyst was stirred in dil. HCl for 10 h and then subjected to AAS analysis

[c] Thermal analysis was carried out on Linsesis STA PT-1000 make thermal analyzer with heating rate of 10 °C/min

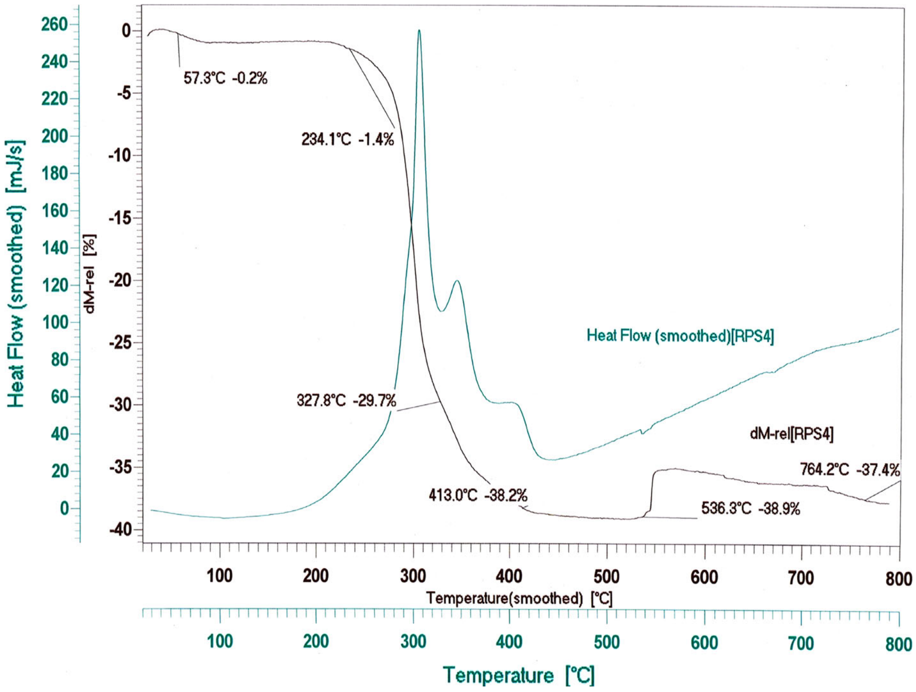


Fig. 2 Thermo-gravimetric analysis of ASS-Cu(acac)$_2$

Table 2 Elemental analysis of ASS composite and ASS-Cu(acac)$_2$

Elemental analysis	Component	Element %
CHNS[a] (ASS composite)	Carbon	13.82
	Hydrogen	2.40
	Nitrogen	1.55
AAS[b] [ASS-Cu(acac)$_2$]	Copper	1.1

[a] CHN elemental analysis was carried out on vario MICRO Cube CHNS analyzer

[b] AAS analysis was carried on GBC Avanta-M atomic absorption spectrometer

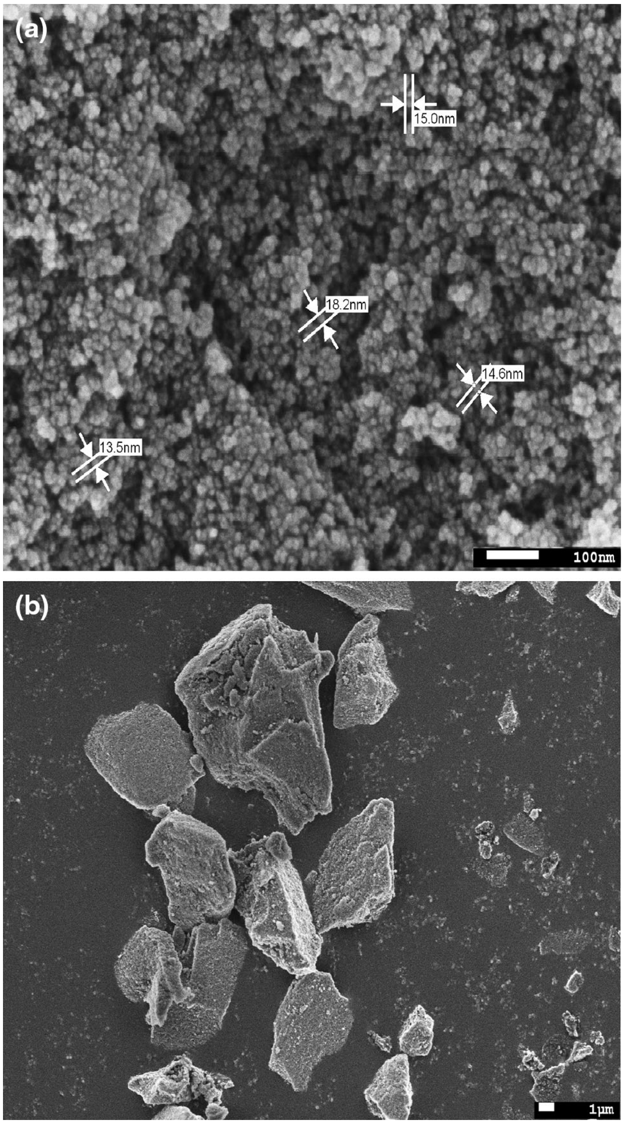


Fig. 3 SEM images of covalently anchored Cu(acac)$_2$ onto amine functionalized silica/starch composite [ASS-Cu(acac)$_2$]

and ν_s(Si–O–Si), respectively. After functionalization of silica/starch substrate with 3-aminopropyltrimetoxysilane, some slight changes were observed in the spectrum due to partial coverage of the silica/starch surface with aminopropyl groups. The two broad bands at 3434 and 1630 cm^{-1} can be ascribed to the N–H stretching vibration and NH$_2$ bending mode of free NH$_2$ group, respectively. The presence of the anchored propyl group was confirmed by C–H stretching vibrations that appeared at 2924 and 2851 cm^{-1}. After complexation with M(acac)$_n$, the –CH$_2$ stretching band got shifted to 2932 cm^{-1}. ASS-Cu(acac)$_2$ exhibits well defined bands at

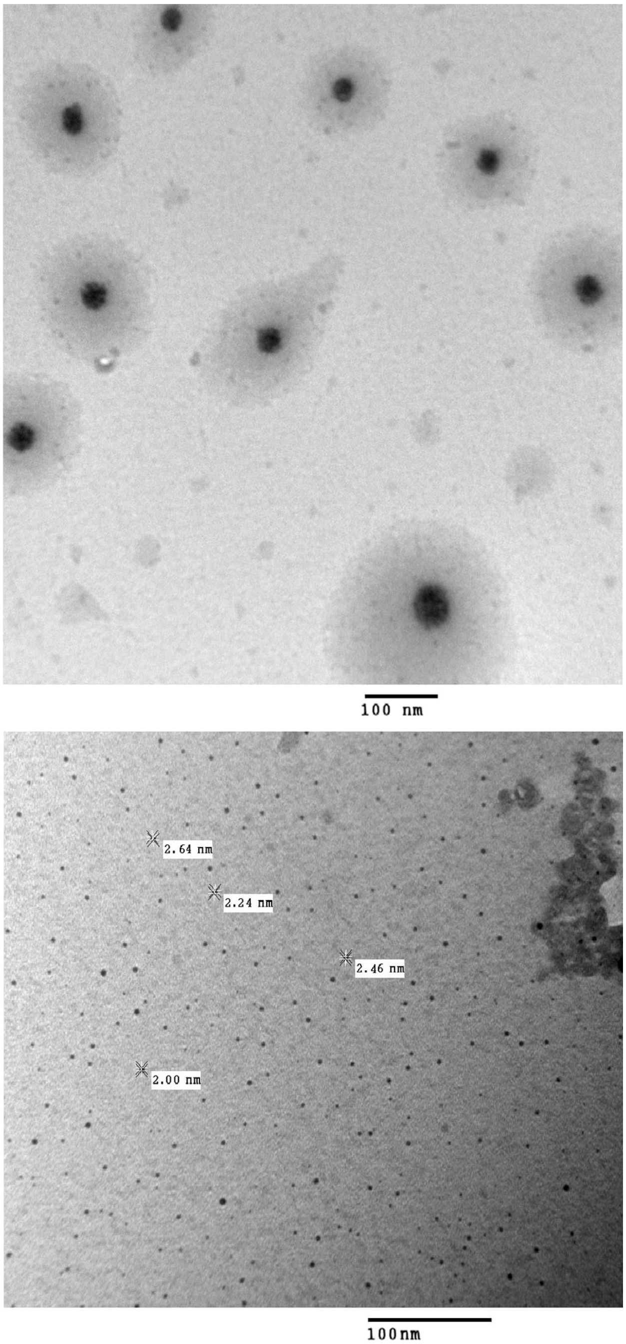


Fig. 4 TEM images of covalently anchored Cu(acac)$_2$ onto amine functionalized silica/starch composite [ASS-Cu(acac)$_2$]

Table 3 Comparison of catalytic activities of different covalently anchored $M(acac)_n$ complexes onto aminefunctionalized silica/starch composite for one- pot thioetherification and synthesis of 2*H*-indazoles

Entry	Catalyst	Thioethers[a]		2H-indazoles[b]	
		Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)
1	ASS-$Cu(acac)_2$	1.25	92	6	85
2	ASS-$Co(acac)_2$	2	75	6	50
3	ASS-$Pd(acac)_2$	2	75	6	55
4	ASS-$Mn(acac)_3$	2	70	6	40
5	ASS-$Co(acac)_3$	2	70	6	50
6	ASS-$Ru(acac)_3$	2	60	6	20

[a] Reaction conditions: bromobenzene (1 mmol), benzyl bromide (1.1 mmol), thiourea (1.2 mmol), K_2CO_3 (2 mmol), ASS-$M(acac)_n$ (1.1 wt% M) [M=Cu, Ru, Pd, Co, Mn; n = 2 or 3] at 100 °C in water (5 mL)

[b] Reaction conditions: 2-bromobenzaldehyde (1.5 mmol), aniline (1.8 mmol), sodium azide (2 mmol), ASS-$M(acac)_n$ (1.1 wt% M) [M=Cu, Ru, Pd, Co, Mn; n = 2 or 3] at 100 °C in DMSO (5 mL)

[c] Isolated yield

1646 and 1410 cm^{-1} due to C=O and/or C=N and C=C respectively. This is a strong evidence for anchoring of $Cu(acac)_2$ onto the surface of amine functionalized silica/starch composite through Schiff condensation of NH_2 and C=O (Fig. 1). The characteristic C=N bands for supported metal acetylacetonates are presented in Table 1. The stability of the catalysts was determined by thermogravimetric analysis. The TGA was recorded by heating the sample at the rate of 10 °C min^{-1}. The TGA curve of ASS-$Cu(acac)_2$ showed an initial weight loss up to 100 °C, which was attributed to the loss of residual solvent and water trapped onto the surface. The major weight loss from 250 to 300 °C was due to the decomposition of starch and chemisorbed material i.e. aminopropyl group from the silica/starch substrate (Fig. 2). Thus, the catalyst is stable up to 250 °C and it is safe to carry out the reaction at 100 °C under heterogeneous conditions. The major weight losses of all the six catalysts are presented in Table 1.

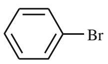
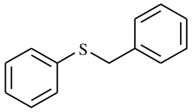
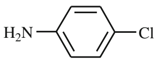
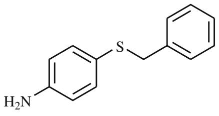
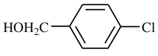
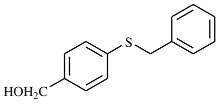
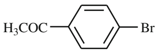
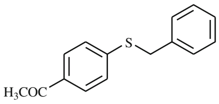
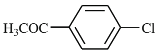
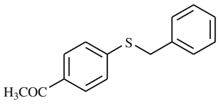
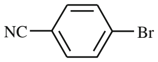
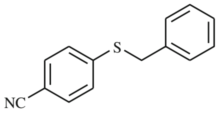
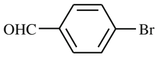
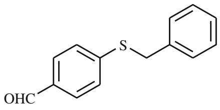
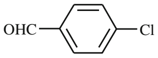
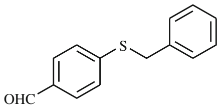
The loading of aminopropyl group onto silica/starch composite was determined from C, H, N elemental analysis and the loading of Cu was determined by AAS analysis (Table 2). ASS-$Cu(acac)_2$ contained 1.1 wt% copper per g of the catalyst which is very close to the theoretical value of 1.5 wt%. The AAS of all the six catalysts is presented in Table 1. In order to understand the surface morphology and to assess the surface dispersion of metal onto amine functionalized silica/starch composite, the systematic study on SEM analysis was done. SEM images showed wooly cloud like clusters with somewhat spherical morphology (Fig. 3a). The SEM images of ASS-$Cu(acac)_2$ showed a very slight roughening of the surface of the catalyst which may possibly be due to the interaction of $Cu(acac)_2$ with the surface of the support material (Fig. 3b). The TEM images provided a direct observation of the morphology and distribution of copper onto the surface of amine functionalized silica/starch composite. Particle size was derived from TEM micrographs, which indicated that the individual particles have spherical shape with an average diameter of 2–2.5 nm (Fig. 4). The regular arrangement of the pores can be clearly observed. In the TEM images, the black colored spots could be attributed to the presence of grafted Cu-sites formed due to the coordination of Cu(II) with the surface of the support. No bulk aggregation of the metal occurred indicating that copper is dispersed evenly onto the surface of support material with near spherical morphology.

3.2 Catalytic Testing for the One-Pot Thioetherification and Synthesis of 2*H*-Indazoles

Initially, to select the most appropriate heterogeneous metal acetylacetonate catalyst, the thioetherification in case of test substrates (4-bromobenzaldehyde, benzyl bromide and thiourea) was carried out using different amine functionalized silica/starch-$M(acac)_n$ [ASS-$M(acac)_n$ (M=Co, Cu, Mn, Pd and Ru, n = 2 or 3, 3.5 mol% metal] at 100 °C in water. The screening of various catalysts allowed us to select ASS-$Cu(acac)_2$ as the most effective catalyst for one-pot thioetherification of aryl halides with thiourea and benzyl bromide in water (Table 3).

In order to optimize the protocol and to understand the influence of different variables on this reaction, several components were studied to increase its efficiency. Choice of a solvent plays an important role in multi-component reactions. To choose the appropriate solvent for this reaction, we carried out the test reaction in a variety of protic and aprotic solvents, and water was found to be the best solvent in terms of reaction time and yield. K_2CO_3 showed the best performance, furnishing the desired product in quantitative yield. However, in the absence of a base no product formation takes place. Temperature is considered as a major factor that affects the rate of a reaction. The reaction with the test substrate was tried at room temperature but unfortunately reaction did not go to completion. With the increase in temperature to 50 or 70 °C, the rate of the reaction was very slow. However, the reaction at 100 °C provided the highest yield with maximum selectivity. Using the optimized conditions, the present reaction was further extended to a broader range of substituted aryl halides in order to evaluate the scope of the method (Scheme 2, Table 4) and found that the reaction works well for both electron-donating and electron-withdrawing

Table 4 ASS-Cu(acac)$_2$ catalyzed thioetherification of different aryl halides using thiourea under aqueous medium at 100 °C

Entry	Aryl halide	Product	Time (h)	Yield (%)[a]
1			1.25	92
2			2.50	87
3			1.50	82
4			2	88
5			1	87
6			2.50	90
7			3.50	90
8			2	85

Reaction conditions: aryl halide (1 mmol), benzyl bromide (1.1 mmol), thiourea (1.2 mmol), K_2CO_3 (2 mmol), ASS-Cu(acac)$_2$ (0.2 g, 1.1 wt% Cu) at 100 °C in water (5 mL)

[a] Isolated yield

groups. In general, the reaction is clean and high yielding. In order to select the optimum amount of catalyst, reaction in case of test substrates was carried out with varying amount of catalysts and found that 3.5 mol% Cu gave the best results in terms of reaction time and yield. With this protocol, the preparation of structurally diverse thioethers becomes more practical and easier than available protocols in which thiols are directly used for the preparation of aryl alkyl thioethers.

The reaction proceeds by the generation of *S*-alkylisothiouronium salt **A** which was hydrolyzed in the reaction mixture to produce a thiolate moiety and urea. Urea was hydrolyzed to produce carbon dioxide gas and ammonia as the final products of the hydrolysis reaction. The generated thiolate ion react by the oxidative addition reaction with Cu(II) to form intermediate **B**, which undergoes reaction with aryl halide to form arylorganocopper **C.** Intermediate C undergoes reductive elimination resulting in the

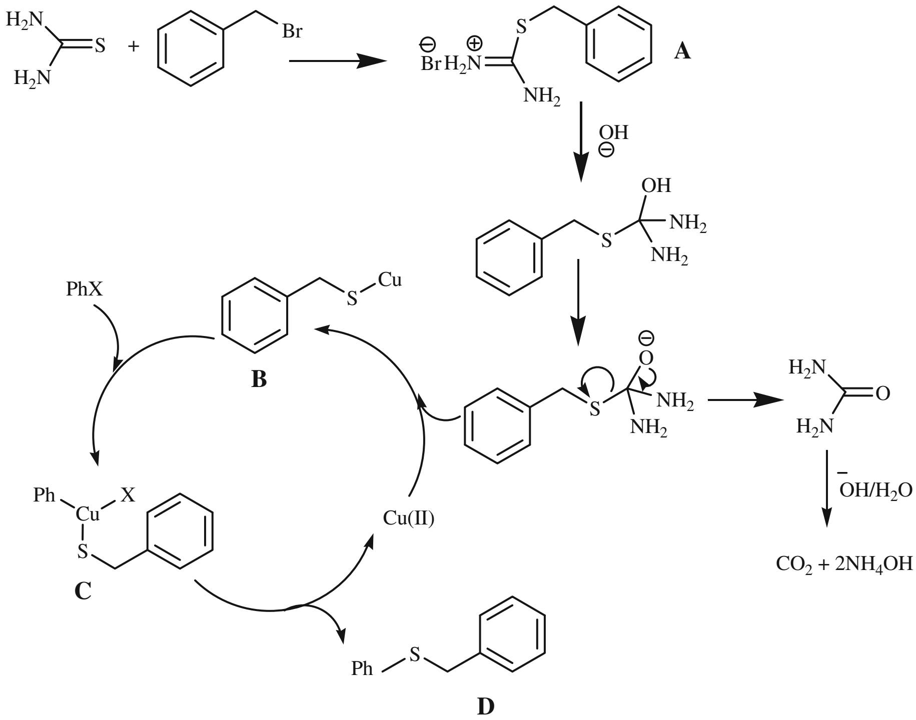


Fig. 5 Proposed mechanism for ASS-Cu(acac)$_2$ catalyzed thioetherification of aryl halides with thiourea and benzyl bromide

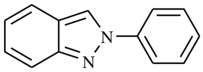
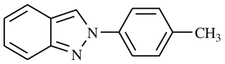
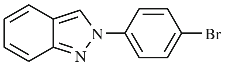
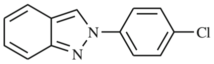
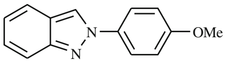
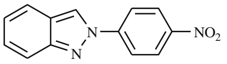
formation of thioether **D** with the regeneration of the catalyst (Fig. 5).

Initial attempts to optimize the reaction conditions for the synthesis of 2*H*-indazoles (Scheme 3), aniline and 2-bromobenzaldehyde were chosen as the test substrates and the reaction was carried out in the presence of different amine functionalized silica/starch-M(acac)$_n$ catalysts (Table 3). ASS-Cu(acac)$_2$ was again turned out to be the best catalyst for the synthesis of 2*H*-indazoles. After identifying the most efficient catalyst (Table 3), we further screened different solvents in order to enhance the reaction rate. Among the various solvents examined (acetonitrile, water, ethanol, DMSO), the reaction proceeded well in DMSO, which was found to be the most appropriate solvent. Furthermore, reaction of most of the substrates with several aromatic amines bearing electron-donating as well as electron-withdrawing groups were performed smoothly and the corresponding 2*H*-indazoles were obtained in good yields (Table 5).

For the synthesis of 2*H*-indazoles, reactions have also been carried out under microwave irradiation (Table 5). The comparison between conventional and microwave-assisted method showed that, the microwave protocol predate the conventional method by significantly reducing reaction time with remarkable improvements in efficiency, yields and energy consumption.

In order to find out the role of ASS-Cu(acac)$_2$ as the heterogeneous catalyst, the test reaction was carried out in the presence of silica/starch composite, amine functionalized silica/starch composite, silica supported Cu(acac)$_2$, starch supported Cu(acac)$_2$, Cu(acac)$_2$ and without using catalyst (for thioethers, 4-bromobenzaldehyde, benzyl bromide and thiourea; for 2*H*-indazoles, aniline, 2-bromobenzaldehyde). Starch by itself could not give the satisfactory results. Starch supported Cu(acac)$_2$ suffered with several disadvantages such as hydrophilic nature of starch and poor mechanical stability especially under aqueous medium. Silica supported Cu(acac)$_2$ was found to be active under the optimized conditions and provided good yield in reasonable time (Fig. 6). The results are summarized in Table 6, which indicated that Cu(acac)$_2$ under homogeneous conditions gave the best results, but since they were miscible in the reaction medium so it was a painstaking process to remove and retain it for reuse. The use of heterogeneous systems would be more advantageous as catalyst recovery is easier, process is more efficient and moreover, the catalyst could be recycled for several runs. The biopolymer containing hybrid material of silica has drawn attention owing to their promising properties and creative alternatives to design new materials for academic research and innovative industrial applications. Thus, we have selected ASS-Cu(acac)$_2$ as the heterogeneous catalyst for both these reactions. Recyclability and operational stability of ASS-Cu(acac)$_2$ was tested in case of entry 1 (Table 1, thioether; Table 2, 2*H*-indazole) (Fig. 5). It was found that ASS-Cu(acac)$_2$ could be recycled for four consecutive runs without loss of significant activity.

Table 5 ASS-Cu(acac)$_2$ catalyzed one-pot synthesis of 2H-indazoles from 2-bromo-benzaldehydes, various primary amines and sodium azide in DMSO

Entry	Product	Time (h)		Yield (%)[a]	
		Δ	MW	Δ	MW
1		6	0.5	85	85
2		8	0.75	75	82
3		12	1	75	80
4		14	1.15	73	82
5		10	0.75	70	80
6		13	1.20	70	75

Reaction conditions: 2-bromobenzaldehyde (1.5 mmol), primary amine (1.8 mmol), sodium azide (2 mmol), ASS-Cu(acac)$_2$ (0.2 g, 1.1 wt% Cu) at 100 °C in DMSO (5 mL)

[a] Isolated yield

3.2.1 Spectral Data of Compounds

3.2.1.1 Benzyl Phenyl Sulfide (Table 3, entry 1) White solid, M.p./Lit. M.p. 42–43/40–43 °C [47]. ^{1}H NMR (CDCl$_3$): δ 3.70 (*s*, 2H, –CH$_2$), 7.35–7.48 (*m*, 10H, H$_{\text{arom}}$). ^{13}C NMR (CDCl$_3$): δ 35.71, 127.08, 127.53, 128.50, 129.13, 139.70. MS (ESI): 200 (M)$^+$.

3.2.1.2 Benzyl 4-Aminophenyl Sulfide (Table 3, entry 2) Brown oil, [48]. ^{1}H NMR (CDCl$_3$): δ 3.45 (*s*, 2H, –CH$_2$), 4.47 (*s*, 2H, –NH$_2$), 6.36–6.43 (*t*, 2H, H$_{\text{arom}}$), 6.92–6.96 (*m*, 2H, H$_{\text{arom}}$), 7.06–7.20 (*m*, 5H, H$_{\text{arom}}$). ^{13}C NMR (CDCl$_3$): δ 43.10, 116.02, 122.71, 126.45, 127.54, 128.9, 129.31, 138.02, 145.22. MS (ESI): 217 (M)$^+$.

3.2.1.3 4-(Benzylthio)phenyl Methanol (Table 3, entry 3) Brown oil, [49]. ^{1}H NMR (CDCl$_3$): δ 3.69 (*s*, 2H, -CH$_2$), 4.53 (*s*, 2H, –CH$_2$OH), 7.35–7.45 (*m*, 9H, H$_{\text{arom}}$). ^{13}C NMR (CDCl$_3$): δ 35.69, 64.45, 122.24, 123.47, 125.57, 127.04, 127.49, 129.49, 137.47, 138.24, 139.57. MS (ESI): 233 (M + 2).

3.2.1.4 Benzyl 4-Acetylphenyl Sulfide (Table 3, entry 4) White soild, M.p./Lit. M.p. 112-114/113–115 °C [50]. ^{1}H NMR (CDCl$_3$): δ 2.15 (*s*, 3H, –COCH$_3$), 3.59 (*s*, 2H, –CH$_2$), 7.22–7.39 (*m*, 5H, H$_{\text{arom}}$), 7.50–7.62 (*m*, 4H, H$_{\text{arom}}$). ^{13}C NMR (CDCl$_3$): δ 35.55, 57.22, 115.13, 127.33, 127.94, 128.59, 128.99, 138.11, 152.33. MS (ESI): 241 (M)$^{+\cdot}$

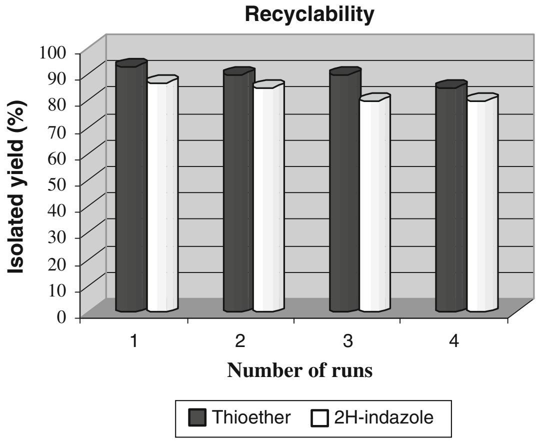


Fig. 6 Recyclibility of ASS-Cu(acac)$_2$: Reaction conditions- bromobenzene (1 mmol), benzyl bromide (1.1 mmol), thiourea (1.2 mmol), K_2CO_3 (2 mmol), ASS-Cu(acac)$_2$ (0.2 g, 1.1 wt % Cu) at 100 °C in water (5 mL) [for thioethers]; 2-bromobenzaldehyde (1.5 mmol), Aniline (1.8 mmol), sodium azide (2 mmol), ASS-Cu(acac)$_2$ (0.2 g, 1.1 wt % Cu) at 100 °C in DMSO (5 mL) [for 2*H*-indazoles]

3.2.1.5 Benzyl 4-Cyanophenyl Sulfide (Table 3, entry 6) White solid, M.p./Lit. M.p. 83–84/84–85 °C [51]. ^{1}H NMR ($CDCl_3$): δ 3.62 (*s*, 2H, –CH_2), 7.26–7.32 (*m*, 4H, H$_{arom}$), 7.33–7.37 (m, 5H, H$_{arom}$). ^{13}C NMR ($CDCl_3$): δ 38.73, 109.03, 115.64, 127.46, 128.83, 129.03, 137.38, 138.15. MS (ESI): 226 (M)$^+$.

3.2.1.6 Benzyl 4-Formylphenyl Sulfide (Table 3, entry 7) White solid, M.p./Lit. M.p. 70–71/70–72 °C [52]. ^{1}H NMR ($CDCl_3$): δ 3.61 (*s*, 2H, –CH_2), 7.26-7.35 (*m*, 5H, H$_{arom}$), 7.69–7.72 (*m*, 4H, H$_{arom}$), 9.17 (*s*, 1H, –CHO). ^{13}C NMR ($CDCl_3$): δ 35.58, 127.42, 128.66, 130.14, 137.37, 138.14, 142.18, 171.18. MS (ESI): 227 (M)$^+$.

3.2.1.7 2-Phenyl-2H-Indazole (Table 4, entry 1) White solid, M.p./Lit. M.p. 81–82/81–82 °C [53]. ^{1}H NMR ($CDCl_3$): δ 7.12–7.14 (*t*, 1H, H$_{arom}$), 7.33–7.34 (*t*, 1H, H$_{arom}$), 7.41–7.45 (*t*, 1H, H$_{arom}$), 7.54–7.57 (*t*, 2H, H$_{arom}$), 7.73–7.75 (*d*, 1H, H$_{arom}$), 7.80–7.82 (*d*, 1H, H$_{arom}$), 7.92–7.94 (*d*, 2H, H$_{arom}$), 8.4 (*s*, 1H, H$_{arom}$). ^{13}C NMR ($CDCl_3$): δ 117, 122, 126.8, 127.9, 129.6, 140.5, 149.8. MS (ESI): 195 (M + 1)$^+$.

3.2.1.8 2-(4-Methyl)-2H-Indazole (Table 4, entry 2) White solid, M.p./Lit. M.p. 100–102/101–103 °C [53]. ^{1}H NMR ($CDCl_3$): δ 2.45 (*s*, 1H, -CH_3), 7.11–7.15 (*t*, 1H, H$_{arom}$), 7.34–7.36 (*m*, 3H, H$_{arom}$), 7.72–7.74 (*d*, 1H, H$_{arom}$), 7.79–7.81 (*m*, 3H, H$_{arom}$), 8.4 (*s*,1H, H$_{arom}$). ^{13}C NMR ($CDCl_3$): δ 21.01, 113.5, 120.8, 125.5, 126.6, 130, 137.9, 138.2, 149.6. MS (ESI): 209 (M + 1)$^+$.

Table 6 Comparison of activity of ASS-Cu(acac)$_2$ with silica/starch composite, amine functionalized silica/starch composite and homogeneous Cu(acac)$_2$ for the synthesis of thioethers and 2*H*-indazoles

Entry	Catalyst	Thioether[a]		2*H*-Indazole[b]	
		Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]
1	No catalyst	4	NR[d]	10	NR[d]
2	Silica/starch composite	4	5	10	Traces
3	Amine functionalized silica/starch composite	4	15	10	5
4	SiO_2-Cu(acac)$_2$	4	75	6	70
5	Starch-Cu(acac)$_2$	4	60	6	50
6	Cu(acac)$_2$	0.8	90	6	80
7	ASS-Cu(acac)$_2$	1.25	92	6	85

[a] Reaction conditions: bromobenzene (1 mmol), benzyl bromide (1.1 mmol), thiourea (1.2 mmol), K_2CO_3 (2 mmol), and catalyst (0.2 g for entries 1-3; 0.002 g, 3.5 mol% Cu for entry 4; and 0.2 g, 3.5 mol% Cu for entry 5) at 100 °C in water (5 mL)

[b] Reaction conditions: 2-bromobenzaldehyde (1.5 mmol), aniline (1.8 mmol), sodium azide (2 mmol), and catalyst (0.2 g for entries 1–3; 0.002 g; 3.5 mol% Cu for entry 4; and 0.2 g, 3.5 mol % Cu for entry 5) at 100 °C in DMSO (5 mL)

[c] Isolated yield

[d] *NR* No reaction

3.2.1.9 2-(4-Methoxyphenyl)-2H-Indazole (Table 4, entry 3) White solid, M.p./Lit. M.p. 146–147/146–148 °C [53]. ^{1}H NMR ($CDCl_3$): δ 3.22 (*s*, 3H, –OCH_3), 7.11–7.13 (*d*, 2H, H$_{arom}$), 7.15–7.17 (*d*, 2H, H$_{arom}$), 7.32–7.36 (*t*, 2H, H$_{arom}$), 7.72–7.74 (*d*, 1H, H$_{arom}$), 7.79–7.81 (*d*, 1H, H$_{arom}$), 8.52 (*s*, 1H, H$_{arom}$). ^{13}C NMR ($CDCl_3$): δ 55.20, 113.12, 114.20, 120.34, 122.3, 126.69, 130.12, 149.66, 155.33. MS (ESI): 225 (M + 1)$^+$.

3.2.1.10 2-(4-Chlorophenyl)-2H-indazole (Table 4, entry 4) White solid, M.p./Lit. M.p. 130–131/130–132 °C [53]. ^{1}H NMR ($CDCl_3$): δ 7.12–7.14 (*d*, 2H, H$_{arom}$), 7.14–7.16 (*d*, 2H, H$_{arom}$), 7.33–7.35 (*t*, 2H, H$_{arom}$), 7.35–7.37 (*t*, 2H, H$_{arom}$), 8.43 (*s*, 1H, H$_{arom}$). ^{13}C NMR ($CDCl_3$): δ 113.5, 120, 121.7, 125, 126, 130, 131, 138, 150. MS (ESI): 229 (M)$^+$, 230 (M + 1).

3.2.1.11 2-(4-Bromophenyl)-2H-indazole (Table 4, entry 5) Yellow solid, M.p./Lit. M.p. 140–142/141–143 °C [54]. ^{1}H NMR ($CDCl_3$): δ 7.13–7.16 (*t*, 1H, H$_{arom}$), 7.35–7.37 (*t*, 1H, H$_{arom}$), 7.67–7.69 (*d*, 2H, H$_{arom}$), 7.71–7.74 (*d*, 2H, H$_{arom}$), 7.78–7.80 (*d*, 1H, H$_{arom}$), 7.82–7.84 (*d*, 1H, H$_{arom}$), 8.42 (*s*, 1H, H$_{arom}$). ^{13}C NMR ($CDCl_3$): δ 117, 120, 122, 123, 127, 132.6, 139.5, 149.9. MS (ESI): 273 (M + 1)$^+$, 275 (M + 2).

3.2.1.12 2-(4-Nitrophenyl)-2H-indazole (Table 4, entry 6) Yellow solid, M.p./Lit. M.p. 219–220/218–220 °C [55]. ^{1}H NMR ($CDCl_3$): δ 7.07–7.08 (*t*, 1H, H_{arom}), 7.30–7.33 (*t*, 1H, H_{arom}), 7.64-7.66 (*d*, 1H, H_{arom}), 7.70–7.72 (*d*, 1H, H_{arom}), 8.06–8.09 (*m*, 2H, H_{arom}), 8.33–8.36 (*m*, 2H, H_{arom}), 8.4 (*s*, 1H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 128.5, 131, 131.8, 135, 135.4, 137, 141, 161.7, 164, 169. MS (ESI): 240 $(M + 1)^+$.

4 Conclusions

In conclusion, we have reported the synthesis of a series of novel metal acetylacetonates covalently anchored onto amine functionalized silica/starch composite and its catalytic activity was studied for the one-pot thioetherification of aryl halides with benzyl bromide using thiourea in water, and for the one-pot three component synthesis of 2*H*-indazoles by consecutive C–N and N–N bond formations. This procedure is free from foul-smelling thiols and work-up becomes easy, practical and eco-compatible, diminishing environmental concerns. Compared with literature protocols, our approach offers very mild reaction conditions and affords the corresponding products in moderate to excellent yields. The catalyst was found to be highly active and could be recycled for four consecutive runs without significant loss of activity.

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