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ARTICLE

Chloromethylated polystyrene immobilized ruthenium complex of 2-(2-Pyridyl)benzimidazole catalyst for the synthesis of bioactive disubstituted ureas by carbonylation reaction

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Abstract

Polymer supported transition metal complex catalysts has enormous applications as heterogeneous catalyst due to ease of synthesis and commercial availability. Ru-Py-Merf was synthesized by anchoring 2-(2-Pyridyl)benzimidazole to the polymer matrix and then loading ruthenium salt on it. This Ru-Py-Merf material was thoroughly characterized by FTIR spectroscopy, UV-Vis absorption spectra, FE-SEM analysis, EDAX analysis, CHN analysis, AAS spectroscopy and TGA. Ru-Py-Merf showed excellent catalytic activity in the synthesis of symmetric and asymmetric disubstituted ureas by reductive carbonylation of nitrobenzenes and anilines. The synthesized Ru-Py-Merf catalyst is entirely heterogeneous in nature, thermally stable and can be easily reused up to six times.

Introduction

Carbonylation reaction using CO as a C_1 source showed their authority in chemical industries for conversion of organic substrate to some new fine chemicals.[1] Specifically, transition metal-catalyzed carbonylation of nitro and amino compounds has been developed as a promising synthetic pathway for the production of carbonyl compounds. Use of Carbon monoxide as a reductant in the past confined to some few reactions, its use in organic synthesis, especially in the reductive carbonylation of nitro aromatics and the oxidative carbonylation of aromatic amines, has increased dramatically.[2] Also use of CO in the industry has been increased in the last decays due to synthesis of aryl carboxylic acids,[3] amides,[4] aldehydes[5] etc. More specifically to say carbonylation of methanol to acetic acids and nitro compounds to disubstituted ureas have gained much more attention. The stunning aspect of fixing carbonyl groups into organic products at the similar time forming new bonds provides this class of transformations tremendously expensive leading scheme for the production of a variety of urea derivatives.

Chemical fixation of carbon monoxide steadily has been a focus of study among researchers for emergent environmentally benign protocols for the production of different biologically active and industrially crucial intermediates. The tremendous binding ability of the disubstituted urea with assured acceptors is an imperative pharmacophore in developing anticancer drugs. The NH functional group present in the disubstituted urea is a supportive hydrogen bond donor, while the oxygen atom is considered as a marvelous acceptor. Furthermore, the structure of aryl urea is helpful for association of alkylating pharmacophores with high affinity DNA binders. Additionally, presence of diaryl urea in many kinase inhibitors, such as RAF, KDR and Aurora kinases made it a novel organic intermediate.[6] The derivatives of disubstituted urea are widely used in the manufacture pharmaceutical composition for the treatment of RET dependent tumor diseases. It is also used for the treatment of protein kinase dependent diseases particularly proliferative diseases, agricultural pesticides,[7] treatment of diabetic neuropathy and as herbicides.[8]

The common synthetic pathway for synthesis of ureas is the reaction of amines with CO by using non metallic catalysts like tert-amine.[9] In this pathway the yield of urea can only be increased by using excess sulfur which leads to the formation of toxic by-product hydrogen sulfide. Shiwei Lu and his coworkers reported the synthetic procedure for the synthesis of symmetrical disubstituted ureas by sulfur-catalyzed carbonylation in ionic liquids.[10] But this methodology requires high CO pressure and high reaction temperature. The other techniques require selenium-catalyst which is toxic in nature and requires continuous oxygen flow in the reaction medium.[11] So, for the large scale synthesis of substituted symmetric ureas and more challenging unsymmetrical ureas[12] design of a new catalytic system is essential. Ru, Pd and Rh incorporated metal complexes are very indispensable for the synthesis of ureas by reductive carbonylation.[13-15] Ru is very promising material for activation of CO_2[16,17] and CO [18] subsequently it converts them into many fine chemicals. Along with this, Ru may also act as photo catalyst[19] and nano reactors[20]. Nowadays, Ru is widely used for the synthesis of methanol from CO_2[21]. But it is also essential to design a suitable support which will influence the catalytic activity of Ru in the disubstituted urea synthesis. Chloromethylated polystyrene is one such true support which will make the catalyst heterogeneous and tailoring of this polymer

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support by suitable ligand in a complexation manner will transform it as an excellent catalytic support.

Transition metals containing Chloromethylated polystyrene supported heterogeneous catalysts are very imperative and gaining huge attention owing to their admirable catalytic activity and easily recoverability. Designing of a catalytic system by loading of ruthenium metal ion on the surface of functionalized chloromethylated polystyrene make it an extremely primitive catalyst for the reductive carbonyltion of disubstituted ureas under mild conditions. Chloromethylated polystyrene can be easily functionalized by imidazole type ligands. Imidazole type ligands are well known due to their superior cross linking with polymers[22,23] and they can easily bind with Ru with their electron enriched nitrogen site. Such type of many chloromethylated polystyrene supported polymer catalyst are reported earlier and they are highly thermal stable and heterogeneous in nature so that they can be reused easily up to 5 times.[18,24-26]

In this context we have reported chloromethylated polystyrene supported Ru-polymer complex for the synthesis of symmetrical and unsymmetrical ureas by carbonylation of nitro and amino compounds under 4 atm pressure and 90 ^{0}C temperature without production of any toxic by-products. The two nitrogen atoms present in the polymer supports facilitates it to bind with ruthenium very strongly so that it cannot get leached to the reaction medium. So choice of ruthenium in this tailoring practice is an appropriate one. Ruthenium is very promising metal in the disubstituted urea synthesis by chemical fixation of carbon monoxide. To get maximum efficiency from the catalyst many parameters are varied. And it is important to say that our prepared catalyst is recyclable up to 6 times without any significant loss of its catalytic activities.

Experimental

Materials and reagents

Chloromethylated polystyrene (5.5% crosslinking), o-phenylenediamine, picolinaldehyde were purchased from Sigma-Aldrich and used without any additional purification. Solvents used like DMF, methanol, ethyl acetate, DCM were purchased from Merck India and used after distillation by standard distillation process and dried by molecular sieve. The derivatives of anilines, nitrobenzenes, p-toluenesulfonic acid were purchased from Alfa-Aesar and used after recrystallization process.

Physical measurements

The FT-IR spectra of the samples were recorded from 450 to 4000 cm^{-1} on a Perkin Elmer FTIR 783 spectrophotometer using KBr pellets. UV-Vis spectra were taken using a Shimadzu UV- 2401PC doubled beam spectrophotometer having an integrating sphere attachment for solid samples. Thermogravimetric analysis (TGA) was carried out using a Mettler Toledo TGA/DTA 851. Surface morphology of the samples was measured using a scanning electron microscope (SEM) (ZEISS EVO40, England) equipped with EDAX facility. Ruthenium content in the catalyst was determined using a Varian AA240 atomic absorption spectrophotometer (AAS). High pressure reactor assembled magnetic stirrer attached with autoclave (AmAr Equipment, model no.SE-1TAP-II) was used to perform the reaction of nitrobenzene and amine derivatives.

Preparation of Catalyst:

The synthesis of Ru-Py-Merf is outlined in Scheme 1.

Preparation of 2-(2-Pyridyl)benzimidazole:

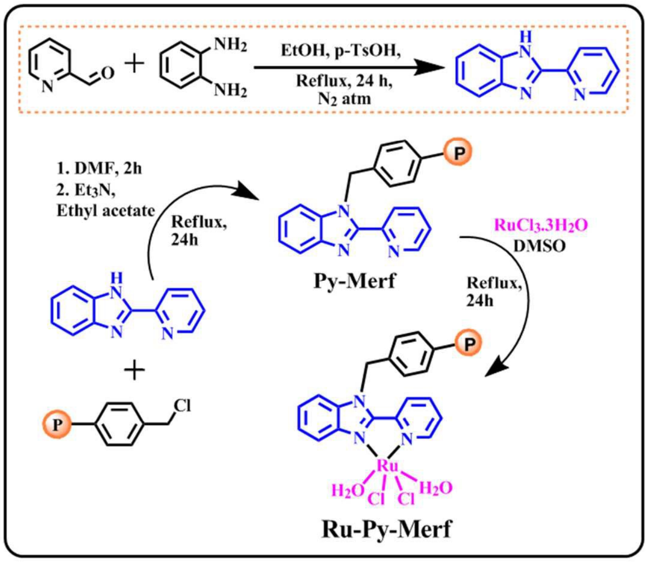
2-(2-Pyridyl)benzimidazole was synthesized by following the procedure mentioned in correlation of previous reported literatures[27]. In a 50 ml round bottomed flask 20 mL of ethanol, o-phenylenediamine (20 mmol) and picolinaldehyde (20 mmol) were added under constant stirring. Then p-toluenesulfonic acid (20 mmol) added drop by drop for 20 minutes. The reaction mixture was refluxed for 24 hour under N_2 atmosphere. The reaction mixture was extracted with DCM in presence of water for at least three times. After complete removal of water the product was purified by column chromatography and analyzed by ^{1}H NMR spectroscopy (supporting information).

Preparation of merrifield anchored 2-(2-Pyridyl) benzimidazole ligand (Py-Merf):

At first 3 g of chloromethylated polystyrene was well swelled in 20 mL DMF and stirred in room temperature for 2 hour. Then 1.625 g of 2-(2-Pyridyl)benzimidazole was dissolved in 15 mL DMF and it was added little by little to the previous suspension. The color of the final solution immediately changed to yellow. After it 4.5 mL triethyl amine and 30 mL ethyl acetate were added and refluxed at 80 ^{0}C for 24 hour. Then it was cooled to room temperature and filtered through a gouch funnel under high vacuum. It was washed with copious amount of DMF and hot ethanol for several times and finally dried in hot air oven at 60 ^{0}C temperature.

Preparation of merrifield anchored 2-(2-Pyridyl) benzimidazole supported ruthenium catalyst (Ru-Py-Merf):

At first $RuCl_3.3H_2O$ (2 mmol) was dissolved in 10 mL DMSO and placed in a magnetic stirrer. Then 1 g of polymeric ligand was added to it and refluxed for 24 h with vigorous stirring. After cooling at room temperature the residue was filtered under vacuum and washed with methanol for three times. Then it was dried in hot oven at 80 ^{0}C for 4 hour.



Scheme 1: Synthesis of merrifield anchored 2-(2-Pyridyl)benzimidazole supported ruthenium catalyst (Ru-Py-Merf).

General procedure for the synthesis of disubstituted ureas

In a stainless steel high pressure autoclave reactor 4 mL DMF, 4 mL methanol, 5 mmol nitrobenzene and 10 mmol aniline were

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introduced. Then 25 mg of catalyst was added to the mixture and stirred for 10 minutes. Then $FeCl_3$ (300 mg) was added to the reaction mixture. The reactor was then closed and CO was purged in the reactor maintaining the pressure 4 atm and temperature 90 ^{0}C. Then the reaction was carried out for 5 hour. The reactor was cooled to room temperature and the reaction mixture was filtered by a whatman 42 filter paper. The filtrate was then extracted with ethyl acetate for three times and concentrated to get the crude product. A white crystal appeared after cooling which was then washed with diethyl ether and dried in vacuum. The product was characterized by ^{1}H NMR spectroscopy (supporting information).

Results and discussion

Characterization:

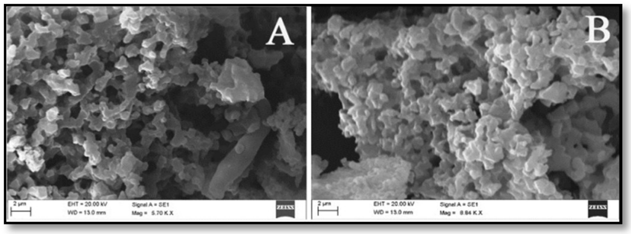

Fig.1 FE-SEM image of (A) Py-Merf, (B) Ru-Py-Merf.

The change in morphology throughout the preparation of catalyst was determined by field emission scanning electron microscope as shown in the Fig. 1. Fig. 1A represents the FESEM image of 2-(2-Pyridyl)benzimidazole bound chloromethylated polystyrene material. It shows the cross linking polymeric nature of Py-Merf material. Fig. 1B shows Ru bound Py-Merf material (Ru-Py-Merf) where change in morphology is clearly observed. The agglomeration of polymeric particles of Ru-Py-Merf is more than that of Py-Merf due to complexation.

The EDAX spectrum of Py-Merf and Ru-Py-Merf are shown in the following Fig. 2 A and 2 B respectively. The spectrum of Py-Merf confirms the presence of carbon, oxygen and chlorine. The peak of chlorine arises probably due to the presence of some unreacted chloromethylated polystyrene. The EDAX spectra of Ru-Py-Merf confirm the presence of ruthenium in the polymeric complex. SEM image and EDAX analysis assured that the attachment of the ruthenium metal onto the merrifield anchored 2-(2-Pyridyl)benzimidazole supported ruthenium catalyst (Ru-Py-Merf).

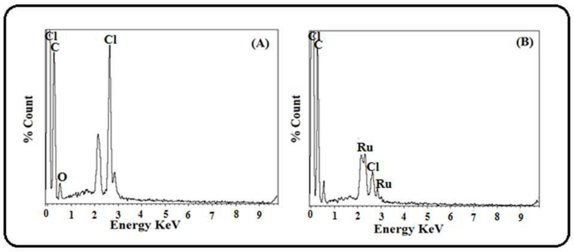

Fig.2 EDAX spectrum of (A) Py-Merf, (B) Ru-Py-Merf

The UV-Vis spectra of Py-Merf and Ru-Py-Merf are represented in the following Fig. 3. The band of Py-Merf showed one major absorption peak at 115 nm and one shoulder at 154 nm. These peaks are due to the intra-ligand charge transfer.[28] The electronic spectrum of Ru-Py-Merf is shown by the red line. It mainly showed two major absorption peaks due to the ligand to metal charge transfer at around 120 and 163 nm. The high resolution bands of Ru-Py-Merf catalyst from 300 to 800 nm are shown in the inset. This image suggests that there are many weak absorption peaks in this above mentioned which are attributed due to the d-d transition (spin allowed) of ruthenium present in the Ru-Py-Merf complex catalyst.

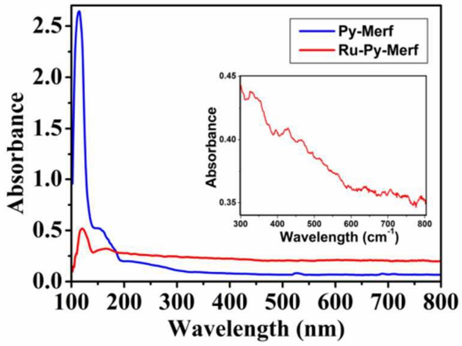

Fig.3 UV-Vis spectra of Py-Merf and Ru-Py-Merf (Inset picture represents high resolution UV-Vis spectra of Ru-Py-Merf)

From FTIR spectroscopy the functional groups present in the merrifield anchored 2-(2-Pyridyl)benzimidazole supported ruthenium catalyst complex can be identified precisely. In Fig. 4 the FTIR spectrum of Py-Merf and Ru-Py-Merf are represented. Spectrum (A) shows two sharp band at 2995 and 2924 cm^{-1} due to the presence of aromatic C-H bonds and CH_2 bond respectively. The band at 1613 cm^{-1} is due to the stretching mode of vibration of C=N bond. The stretching mode of vibration of C-N bond shows a small intense peak at 1397 cm^{-1}. Spectrum (b) represents the FTIR spectra of Ru-Py-Merf. The stretching frequency of aromatic C-H bonds and CH_2 bond are now slightly shifted to 3022 and 2918 cm^{-1} in the desired catalyst. The stretching frequency of C=N bond and C-N bond are also shifted to 1606 and 1421 cm^{-1}.[29,30] The presence of Ru-N bond is confirmed by the presence of a band at 544 cm^{-1}. Also there is Ru-O bond which is confirmed by the band at 470 cm^{-1}.

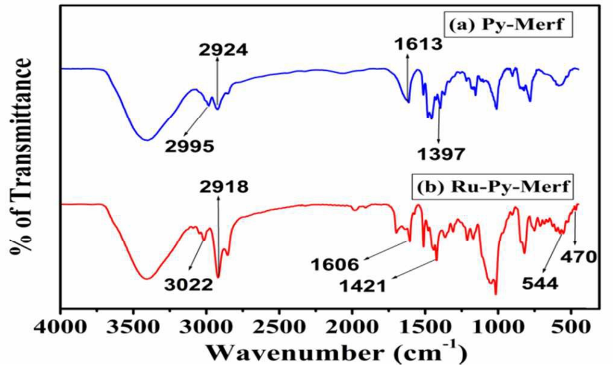

Fig.4 FTIR spectra of (A) Py-Merf and (B) Ru-Py-Merf

Thermogravimetric analysis was executed to ascertain the stability of Py-Merf and Ru-Py-Merf maintaining a heating rate 10 ^{0}C/minute in an air oven from 30 ^{0}C to 600 ^{0}C. Py-Merf started to decompose from 175 ^{0}C and then decomposition continues till it completely diminishes. It is also important to say that a small weight loss of Py-Merf also observed in the around 100 ^{0}C due to presence of moisture. But a dramatical change was observed when Ru was incorporated in the polymeric support. The Ru-Py-Merf catalyst was

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thermally stable upto 330 ^{0}C after which it started to degrade (Fig. 5). So, our prepared catalyst is more stable than the supported ligand.

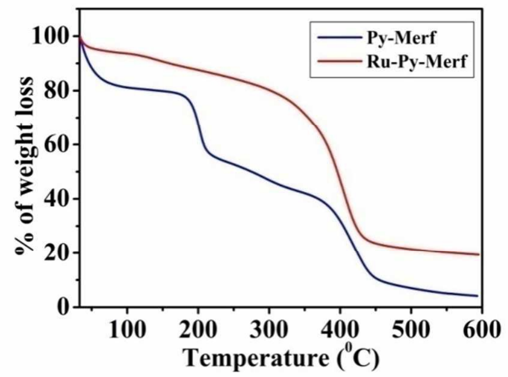


Fig.5 TGA plot of (A) Py-Merf and (B) Ru-Py-Merf

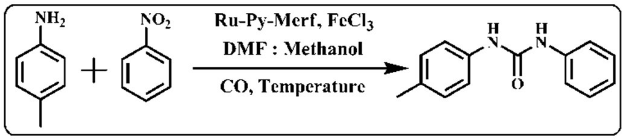
The metal content of the Ru-Py-Merf was measured by atomic absorption spectroscopy and the percentage of carbon, hydrogen and nitrogen was measured by CHN analyzer. The data of the mentioned analysis are represented in Table 1.

Table 1: Elemental analysis

Compound	C %	H %	N %	Ru %
Py-Merf	74.31	4.42	13.51	-
Ru-Py-Merf	66.13	5.34	11.92	6.42

The emergence of new FTIR bands and shift in other FTIR bands of Ru-Py-Merf catalyst has been used as additional evidence for grafting of the metal in Py-Merf. In addition the polymer supported ruthenium complex was also characterized by UV, FTIR, AAS, CHN and analysis to forecast the complexation of metal ions as well as to establish the structures of the complex.

Catalytic Activity



Scheme 2: Synthesis of 1-phenyl-3-p-tolylurea catalysed by Ru-Py-Merf

In the 1-phenyl-3-p-tolylurea urea synthesis effect CO pressure and reaction temperature are the very important parameters. To find out the best optimized pressure and temperature a series of experiments were performed varying pressure from 2 atm to 6 atm and temperature from 80 ^{0}C to 95 ^{0}C. The data of these experiments are summarized in the Figure 6. It is clear that at 90 ^{0}C temperature and 4 atm CO pressures are the optimum condition for 1-phenyl-3-p-tolylurea synthesis. Bellow this temperature and pressure a lower yield was observed. But above 90 ^{0}C and 4 atm the yields are almost remained unaltered. All the reactions were performed in this experiment temperature and pressure are strictly maintained.

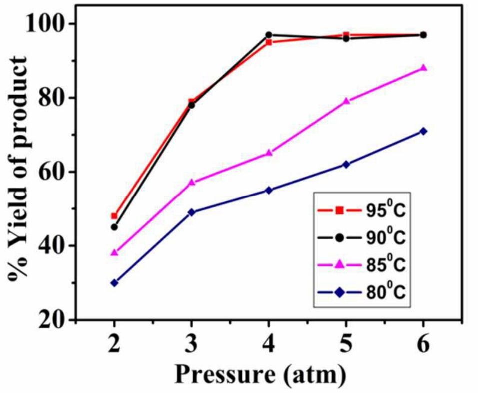


Fig.6 Effect of pressure and temperature on 1-phenyl-3-p-tolylurea synthesis

Reaction conditions: Nitrobenzene (5 mmol), p-toluidine (10 mmol), DMF (4 mL), MeOH (4 mL), FeCl$_3$ (300 mg), catalyst (25 mg), time (5 h).

Table 2: Effect of solvent and co-solvent in the synthesis of disubstituted urea

Entry	Solvent	Co solvent	Solvent : Co solvent	Yield (%)^b
1.	Benzene	MeOH	1:1	38
2.	DMSO	MeOH	1:1	92
3.	Acetonitrile	MeOH	1:1	79
4.	DMF	MeOH	1:1	97
5.	DMF	EtOH	1:1	89
6.	DMF	MeOH	1:2	96
7.	DMF	MeOH	2:1	94
8.	DMF	-	-	22

Reaction conditions: Nitrobenzene (5 mmol), p-toluidine (10 mmol), FeCl$_3$ (300 mg), catalyst (25 mg), 4 atm pressure, 90 ^{0}C, 5 h. ^{b}isolated yield of product.

Effect of solvent is also an important parameter for this experiment. Choice of appropriate solvent and co solvent promotes the yield of this reaction. We have performed this reaction by varying different solvents and co-solvents taking p-toluidine and nitrobenzene as a model reaction and the results are tabulated in Table 2. Interestingly we have found that using DMF as a solvent and methanol as a co solvent maximum yield was obtained. When we used non polar solvent like benzene the yield was extremely low. Also we performed this reaction without co-solvent and it was found that without co solvent the yield of the product was poor. The role of co-solvent is vital for this reaction and choice of best co-solvent is also crucial part to get maximum yield of product. Alcohols are subjected as best co-solvent and their presence in the reaction medium can leap the yield of product massively. In this reaction methanol acts as best co-solvent because of its highly polar nature. The yield of product in presence of ethanol as a co-solvent slightly lowers down due to polarity change from methanol to ethanol. Also, the DMF: MeOH molar ratio controls the yield of the

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reaction as on increasing the molar ratio from 1:1 to 1:2, the yield slightly lowers down. This may be due to dilution of the reaction medium or increasing of polarity than the optimum value. So, the above data establish that use of DMF as solvent and MeOH as co-solvent in 1:1 proportion is the best choice for significant yield of product.

Table 3: Optimization for amount of Catalyst and Co-catalyst

Entry	Amount of catalyst (g)	Amount of co-catalyst (g)	Yield (%)^{b}
1.	0.05	0.4	97
2.	0.04	0.4	97
3.	0.03	0.4	97
4.	0.025	0.3	97
5.	0.025	0.25	82
6.	0.02	0.3	79

Reaction conditions: Nitrobenzene (5 mmol), p-toluidine (10 mmol), DMF (4 mL), MeOH (4 mL), 4 atm CO pressure, 90 ^{0}C, 5 h. ^{b}isolated yield of product.

The effect of amount catalyst and co catalyst has great influence in the 1-phenyl-3-p-tolylurea urea synthesis. Here $FeCl_3$ is chosen to perform the role of co-catalyst. Lewis acidic nature of $FeCl_3$ makes the reaction condition milder and promotes the yield of product exceptionally. As $FeCl_3$ is easily commercially available and very cheap than the other Lewis acids, it is used as co-catalyst to perform this reaction. The reaction was also performed in absence of $FeCl_3$ maintaining the same reaction conditions but the yield of product was very low. So to expose the accurate amount of co-catalyst and catalyst for this reaction a set of reactions were performed varying different amount of catalyst and co-catalyst. The results are represented in the Table 3. It was experimentally observed that only 25 mg of catalyst and 300 mg of co catalyst ($FeCl_3$) is sufficient to carry out the reaction. When the amount of co-catalyst decreased from 300 mg to 250 mg maintaining same amount of catalyst the yield of the reaction also decreased from 97% to 82%. So, $FeCl_3$ plays a crucial role in the disubstituted urea synthesis.

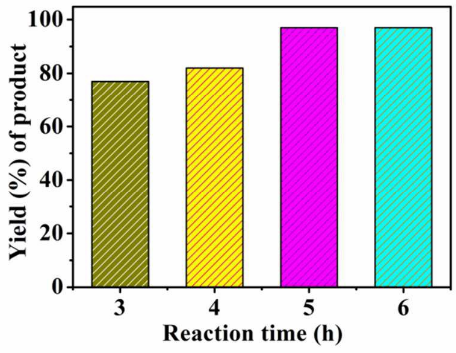


Fig.7 Effect of reaction time on 1-phenyl-3-p-tolylurea synthesis
Reaction conditions: Nitrobenzenes (5 mmol), p-toluidine (10 mmol), $FeCl_3$ (300 mg), catalyst (25 mg), DMF (4 mL), MeOH (4 mL), 4 atm CO pressure, temperature (90 ^{0}C).

The influence of reaction time for the synthesis of 1-phenyl-3-p-tolylurea a representative bar diagram is shown in the Fig. 7 from the experimental observation by varying the reaction time from 3 to 6 hour. It is clearly observed that only at 5 hour the reaction gave maximum yield and there was no increase in yield of product when the reaction time was elaborated. So prolonging of reaction time has not any influence on the disubstituted urea synthesis. Also when the reaction time decreases from 5 hour to 4 hour the yield of the product lowers down.

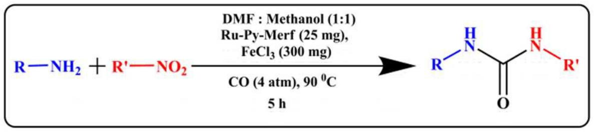
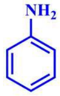
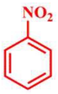
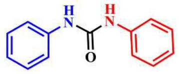
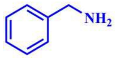
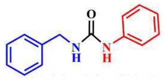
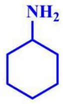
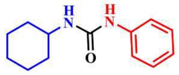
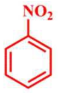
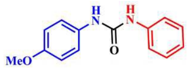
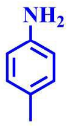
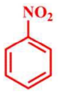
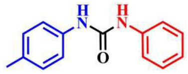
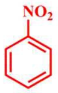
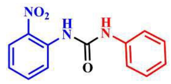
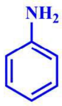
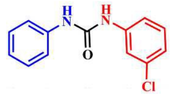
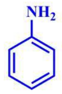
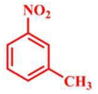
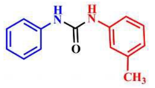
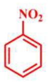


Table 4: Synthesis of di-substituted ureas in the presence of Ru-Py-Merf catalyst

Entry	Amines	Nitros	Product	Yield (%)^{b}
1.				93
2.				96
3.				99
4.				98
5.				97
6.				trace
7.				92
8.				trace
9.	$H_3C\text{-}NH_2$			93

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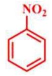
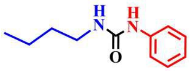
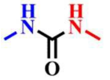
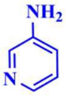
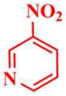
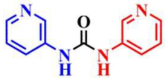
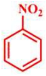
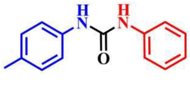
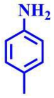
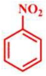
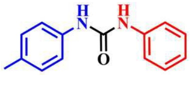
10.				95
11.	$H_3C\text{-}NH_2$	H_3C-NO_2		28
12.				trace
13.				48[c]
14.				trace[d]

Reaction conditions: Nitrobenzenes (5 mmol), amines (10 mmol), $FeCl_3$ (300 mg), Ru-Py-Merf catalyst (25 mg), DMF (4 mL), MeOH (4 mL), 4 atm CO pressure, temperature (90 ^{0}C), time (5 h). [b]isolated yield of product. [c]isolated yield of product without $FeCl_3$. [d]isolated yield of product without Ru-Py-Merf but in presence of $FeCl_3$.

To discover the scope of this reaction several derivatives of amines and nitrobenzenes were used including aliphatic and aromatic amines. The isolated yields of the respective products are represented in Table 4. All the reactions were performed under optimized conditions. Primarily different amines were used (Table 4, Entries 1-6, 9-10) to find out the effect of electron withdrawing, electron donating functional groups, aliphatic and aromatic amines in the disubstituted ureas synthesis catalyzed by Ru-Py-Merf. It was established that aliphatic amines give elevated yield than aniline and among them cyclohexyl amine (Table 4, Entry 3) gave the maximum yield. On increasing the chain length from methyl amine to butyl amine (Table 4, Entries 9,10) the yield of product gradually increases. The reason behind this consequence is inductive effect, as inductive effect increases on nitrogen atom of amine the yield of respective product increases gradually. The presence of electron withdrawing nitro group in the ortho position (Table 4, Entry 6) highly deactivates the aniline group, as a result very trace amount of product was found. So electron withdrawing groups present in the amine lowers down the yield of product but electron donating groups present in the amine highly elevates the yield of product for example 4-methoxyaniline, p-toluidine (Table 4, Entries 4,5). Benzylamine also gives higher yield than aniline (Table 4, Entry 3) due to the more active $-NH_2$ group. When the functional group of nitrobenzene was varied we found an interesting result that electron donating group present in nitrobenzene extremely decreases the yield of product (Table 4, Entry 8). But electron withdrawing group moderately gave better yield (Table 4, Entry 7) with respect to the others. When non aromatic nitro compound like nitromethane was used the yield of product was found to be extremely low (Table 4, Entry 11). In addition to this when hetero amine and hetero nitro compounds were used it was found that they are extremely inert for this reaction (Table 4, Entry 12). As the electron density decreases from the $-NO_2$ group the possibility of the reduction of nitro to amine group increases. So, higher yield was observed for electron withdrawing groups present in the nitro derivatives than the electron donating groups. In addition it is essential to mention that when the reaction was performed without any addition of $FeCl_3$, the yield of isolated product lowers down to 48 % from 97 % . But in presence of $FeCl_3$ when no catalyst was added during the course of reaction only trace amount of product was found. So $FeCl_3$ only promotes the yield of reaction but if there is no catalyst in reaction medium there will be no product formation. In this reaction $FeCl_3$ act as a co-catalyst during reformation of urea from carbamate it may facilitate the reaction.

Plausible mechanism

The plausible mechanism for the synthesis of disubstituted ureas are proposed in Fig. 8. Mechanism of any catalytic reaction is important for better understanding of chemistry behind every explanation. Our proposed mechanism explains the role of Ru-Py-Merf in the reductive carbonylation pathway for the synthesis of disubstituted ureas. The reaction initiates by the complex formation of nitrobenzene with Ru-Py-Merf complex catalyst. In this process carbon monoxide is converted to carbon dioxide. This only happens in presence of Ru-Py-Merf. After it the formed complex further get carbonylated by insertation of CO moiety and the carbon monoxide group get attached with the nitrogen atom of nitrobenzene. Further an aniline molecule reacts with the carbonylated complex compound and produces disubstituted urea by removing catalyst from its moiety. But the reaction does not seize here because the co-solvent methanol takes a major role in the mechanism. Presence of MeOH seriously increases the yield of product by forming an ester compound. This ester compound is formed when some amount of disubstituted urea reacts with methanol by releasing an aniline moiety. Finally the ester compound then again reacts with aniline releasing the desired product in large scale. So this path i.e. the involvement of methanol in the reaction pathway increases the rate of the reaction and acts as a finest co-solvent.[31-33] So, the proposed reaction mechanism is in good agreement with the results discussed earlier.

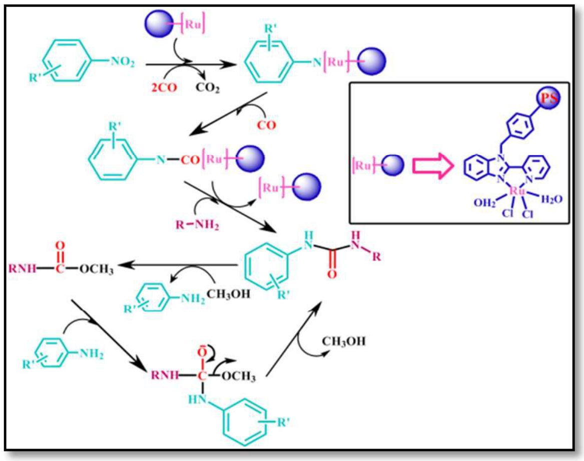


Fig.8 Plausible mechanism of disubstituted urea synthesis catalysed by Ru-Py-Merf complex

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Comparison of catalytic effectiveness of polymer supported ruthenium catalyst with the other reported systems

Table 5 represent the efficiency for the synthesized Ru-Py-Merf catalyst with the other reported catalyst performed for the synthesis of diphenyl urea. It is obvious from the following table that the present merrifield anchored 2-(2-Pyridyl)benzimidazole supported ruthenium catalyst is more mesmerizing and well proficient one than previous catalysts.

Table 5: Comparison with other reported systems for diphenyl urea synthesis

Sl. No.	Catalyst	Reaction condition	Yield (%)	Ref.
1.	PdI_2	Aniline, DME, 100 ^{0}C, 16 atm of CO, 4 atm of air, and 40 atm of CO_2, 10 h.	90	34
2.	K_2PdI_4	Aniline, 110 ^{0}C, 170 atm of CO and O_2, 60 h.	96	35
3.	$Pd(OAc)_2$	Aniline, Nitrobenzene, Xylene, 110 ^{0}C, 40 atm of CO, 2 h.	98	36
4.	1-n-butyl-3-methyl imidazolium hydroxide [Bmim]OH	n-butylamine, 170 ^{0}C, 9.86 atm of CO_2, 19 h.	55.1	37
5.	BMImCl /CsOH	Aniline, room temperature, CO_2, 36 h.	27	38
6.	$[Ru(PSimd)(CO)_2Cl_2]$	Nitrobenzene, aniline, CH_3OH $FeCl_3$, DMF, 120 ^{0}C, 5 h, 60 atm CO pressure.	92	18
7.	Ru-Py-Merf	Nitrobenzene, Aniline, $FeCl_3$, DMF, MeOH, 4 atm CO pressure, 90 ^{0}C, 5 h.	93	In this study

Heterogeneity test

Whether the synthesized catalyst completely works as heterogeneous manner or not, a heterogeneity test was performed for 1-phenyl-3-p-tolylurea synthesis from p-toluidine and nitrobenzene in the presence of ruthenium catalyst. At first the catalyst was carried out for 2 h then removed from the reaction mixture and the yield of the product was found to be 68 %. Then the reaction was again continued for 3 hour without catalyst. After 5 h the yield of the product was determined and no alteration of yield. So it can be concluded that there was no leaching of metal from the polymer support. This was also confirmed by AAS that there is no significance amount of ruthenium metal in the reaction mixture.

Recyclability of catalyst

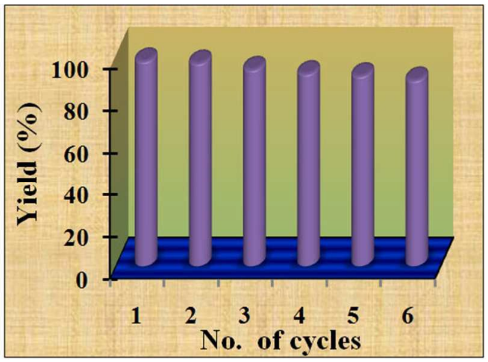

Fig.9 Recycling diagram of Ru-Py-Merf complex catalyst

Recyclability is also an important parameter to prove the novelty of any catalyst. Our prepared catalyst is also highly reusable (up to 6 times) without any large change of its efficiency. The catalyst can be easily recovered by centrifugation of the reaction mixture. Then after washing with hot methanol and followed by drying in hot air oven at 60 ^{0}C for 3 hour the catalyst is ready to use for next reaction. The recyclability curve of Ru-Py-Merf in 1-phenyl-3-p-tolylurea synthesis is shown Fig. 9.

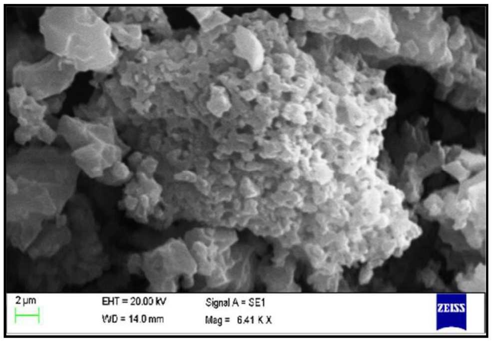

Fig.10 FESEM image of Ru-Py-Merf after sixth recycle

The FE-EM image of Ru-Py-Merf catalyst after 6 recycles is shown in Fig. 10. So it can be concluded that no appreciable change in morphology of Ru-Py-Merf was found after 6 recycle which prove that the heterogeneous catalyst is adequately done the reaction for several times.

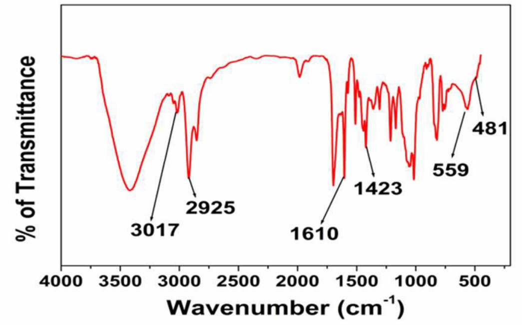

Fig.11 FTIR spectra of Ru-Py-Merf after sixth recycle

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After sixth recycle the FTIR spectra of Ru-Py-Merf was measured and represented in Fig. 11. It was clearly observed that there is no change in bonding framework of synthesized Ru-Py-Merf catalyst after sixth recycle.

Conclusion

In summary, it can be concluded that Ru-Py-Merf is an outstanding polymeric transition metal complex which show excellent catalytic activity for the synthesis of symmetric and asymmetric disubstituted ureas by reductive carbonylation under mild pressure and temperature (4 atm of CO pressure and 90 ^{0}C temperature). Fixation of carbon monoxide in organic substrate for the production of fine chemicals is very challenging and our synthesized catalyst is appropriate contender for the disubstituted urea synthesis. In this reaction $FeCl_3$ acts as co-catalyst and methanol acts as co-solvent which promotes the yield of the reaction. The effect of electron donating and electron withdrawing groups present in the amines and nitrobenzenes are well studied and the reason behind them are well explained. The synthesized catalyst is stable up to 330 ^{0}C and can be reused up to 6 times without any significant loss of its catalytic activity due to its heterogeneous nature. Also it is imperative to state that no leaching of metal ion occurs from the functionalized polymeric support. So our synthesized Ru-Py-Merf catalyst opened a new strategic method of reductive carbonylation near the researchers and industries.

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Graphical Abstract

Chloromethylated polystyrene immobilized ruthenium complex of 2-(2-Pyridyl)benzimidazole catalyst for the synthesis of bioactive disubstituted ureas by carbonylation reaction

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Ru-Py-Merf complex heterogeneous catalyst is synthesized by three step process. At first 2-(2-Pyridyl)benzimidazole is synthesized from o-phenylenediamine and picolinaldehyde then it is tailored with chloromethylated polystyrene to get Py-Merf. Finally ruthenium ion is loaded in Py-Merf to get Ru-Py-Merf complex. The synthesized Ru-Py-Merf exhibited maximum catalytic efficiency for the synthesis of symmetric and asymmetric disubstituted ureas by reductive carbonylation of nitrobenzenes and amines under 4 atm CO pressure and 90 ^{0}C temperature using $FeCl_3$ as co-catalyst and MeOH as co-solvent.