

A Recyclable Polymer Supported Copper Catalyst for Aza-Michael Reaction with Aromatic Amines and Using Water as a Green Solvent

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Abstract- A simple and green protocol is developed for Aza Michael reaction of aromatic amine with activated olefins in water as a green solvent by using recyclable polymer supported copper acetate as a catalyst.

Index Terms- Aza Michael addition, Water as a Green solvent, Aromatic Amines, Polymer supported Cu(II)

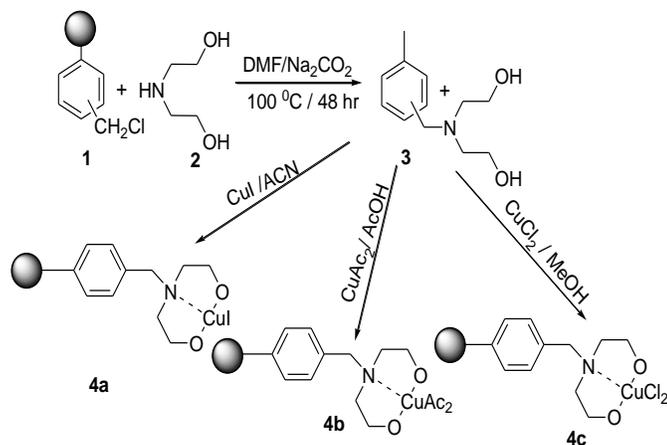
The catalytic addition of an N–H bond across a multiple bond (hydroamination), to give valuable nitrogen-containing molecules is of great interest to both academic and industrial researchers¹. The hydroamination reaction proceeds with 100% atom economy which makes it one of the most desirable processes applicable in the area of natural products, pharmaceuticals, dyes, fine chemicals, polymers and surfactants². There are several reports on hydroamination of unactivated alkenes especially catalyzed by transition metal complexes in homogeneous and heterogeneous conditions^{3–6}. On the other hand, hydroamination of activated olefins (acrylate derivatives) is a Michael type addition reaction, which is a simplistic approach to synthesize amino acid derivatives. These amino acid derivatives have a wide variety of applications in the synthesis of peptide analogues, precursor for amino alcohols, optically active amino acids, lactams and diamines⁷⁻⁸. In earlier studies, Bronsted and Lewis acids such as H₂SO₄, HBF₄ and FeCl₃ have been used for this reaction⁹⁻¹⁰. Recently hydroamination of acrylates with amines has been reported with copper and bismuth salts¹¹⁻¹², and complexes of Ni (II) and Pd (II)¹³⁻¹⁴. Due to the economic attractiveness of copper¹⁵ and by using some special ligands such as N, N- and N, O-bidentate compounds, many CuI-catalyzed C–N¹⁶⁻¹⁷, C–O¹⁸⁻¹⁹, C–S²⁰⁻²¹ and C–C²²⁻²³ bond formation reactions have led to a resurgence of interest in carbon-heteroatom coupling reactions, and their applications seem to be of more and more importance²⁴⁻²⁵.

However homogeneous catalysts have some disadvantages such as they may easily be destroyed during the course of the reaction, contamination in the final products, separation from reaction mass and they cannot be easily recovered after the reaction for reuse. These disadvantages can be overcome by anchoring metal on suitable supports which will allow easy separation and recyclability of the catalyst with minimal amount of product contamination with metal. These

studies confirm that the anchoring of metal on solid support not only exhibits improved catalyst activity, stability and selectivity of the product but also enables easy recovery and reuse of the catalyst. Often heterogeneous organic transformations grow due to their well-documented advantages over homogeneous catalytic systems. But surprisingly there are very few reports available on the use of heterogeneous catalysts for hydroamination of activated olefins. Zeolite beta and clays have been reported so far for this reaction^{26–29}. Zeolites cannot be used for larger substrates because of their smaller pore sizes, whereas clays have low thermal stability which affects the catalyst regeneration. Palladium complexes immobilized on silica and alumina surfaces have been reported for hydroamination of O-activated alkenes³⁰.

On the basis of report on hydroamination of acrylates with amines by using homogeneous “Copper and bismuth salts”³¹⁻³², and Michael addition of aniline is easily proceed in specific polar protic solvents (water as solvent) and fluorinated solvent as reaction promoter. We tried to avoid fluorinated promoter and use recyclable polymer supported copper catalyst³³⁻³⁴.

Herein we report the synthesis of novel polymer supported copper catalyst and its application for Aza-Michael reaction in water as a green solvent so that process became a total green process. Our strategy was to modify Merrifield resin (1) with Diethanol amine (2)³⁵ and then allows it to bind copper through ligand exchanged. (Scheme 1)³⁶ The resulting binding interaction also needs to be strong enough to prevent the copper from dissociating from the polymer support under the reaction conditions. Hence, using Cu(OAc)₂ as the source of copper, displacement of acetate would provide a copper-bound polymer-supported catalyst. Here we use copper acetate, copper Iodide, copper Chloride as a source of copper.



Scheme 1. Synthesis of polymer supported Copper catalyst

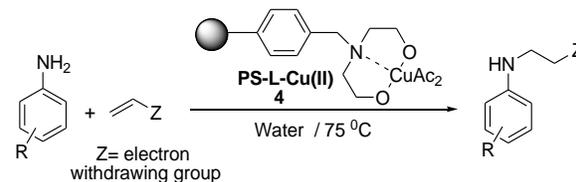
Due to insolubilities of the polymer supported copper catalyst in all common organic solvents, its structural investigation was limited to its physicochemical properties, chemical analysis, SEM, TGA and IR. Table 1 provides the data for elemental analysis of polymer supported ligand and the polymer supported copper catalysts. Copper content in the catalysts determined by EDAX suggests 3.76 wt % Cu in the catalyst. The band at 676 cm^{-1} for C-Cl stretching had disappeared in the polymer anchored ligand. A few new bands appeared, e.g. those at 3311 cm^{-1} (broad) along with bands at 1641 cm^{-1} showed the presence of free -OH groups in the ligand. On complexation with copper, the frequency of free -OH groups are reduced in intensity. In FT-IR spectra of PS-L-CuCl₂ and PS-L-CuI complexes, all bands were almost same as PS-L-Cu(OAc)₂ complex. FT-IR spectra of the polymer supported ligand and copper catalysts are given in Fig.1. FTIR spectra of Merrifield resin and modified Merrifield resin shows no peak at 865 cm^{-1} peak (CH₂-Cl), indicating replacement of CH₂Cl group by CH₂-N group. The scanning electron micrographs (Fig. 2) of the polymer supported ligand and supported copper catalysts clearly show the morphological change which occurred on the surface of polystyrene after loading of metal on it. Energy dispersive spectroscopy analysis of X-rays (EDAX) data for the polymer anchored ligand and copper catalysts are given in Fig. 3. The EDX data also inform that the attachment of copper metal on the surface of the polymer matrix. Thermal stability of the complexes was investigated using DSC at a heating rate of 10 deg C/min in the air over a temperature range of 30-300 C. DSC curves of the polymer supported ligand and supported copper catalysts are shown in Fig. 5. The ligand and copper complexes were stable up to 200-250 °C and above this temperature they decomposed. Differential scanning Chromatography study suggests that the polymer supported copper complexes degrade at considerably higher temperature.

Table 1. Chemical composition of polymer anchored ligand and polymer supported Cu (II) catalyst

Compound	Color	C%	H%	Cl%	N%	Cu%
PS-L	White	73.16	6.42	3.11	(5.54)	-
LCu(OAc) ₂	Green	63.09	5.88	3.17	4.81	5.17,4.73,4.71*
L-CuI	Bluish	65.68	5.62	3.20	4.97	4.53

L-CuCl ₂	Green	Light Green	67.73	5.75	8.01	5.01	4.64
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*used catalyst



Scheme 2. Aza Michael addition using polystyrene supported Cu(OAc)₂ as a catalyst and water as solvent

Table 2. Effect of catalysts on the Aza Michael addition reaction

Entry	Catalyst	Yield ^b (%)
1	PS-L-CuI	82
2	PS-L-CuAc ₂	89
3	PS-L-CuCl ₂	79

^aReaction Conditions: Aniline (1.5 mmol), Ethyl Acrylate (4.5 mmol), Water (3 mL), catalyst (25 mol %) at 75°C temperature for 16h.

^bIsolated yield.

The reaction of aniline with Ethyl acrylate was chosen as a model reaction. Initially in an effort to develop an efficient catalyst various copper based catalysts were scanned for Aza Michael addition reaction, where polymer supported Cu(OAc)₂ gave the maximum yield of 89% (Table 2, entry 2).

The reaction was optimized for various reaction parameters such as temperature, solvent and catalyst loading. The Amine remains unconsumed when the reaction was done at room temperature (Table 3, entry 7). The effect of temperature on the yield of product was monitored from 50°C to 90°C (Table 3, entry 5, 8, 9). However, no further increase in the yield was obtained by increasing temperature from 75°C to 90°C. Hence 75°C was chosen as optimum reaction temperature.

Among the solvent system studied, water ethanol mixture was found to be the best solvent (Table 4, entry 4) giving a maximum yield of the desired product. However water alone also giving good result (Table 4, entry 3).

Table 3. Effect of Time and Temperature on Aza-Michael reaction

Entry	Temp(°C)	Time hrs	Yield ^b (%)
1	75	05	66
2	75	08	78
3	75	11	85
4	75	14	94
5	75	16	95
6	75	18	95
7	R.T.	16	Nil
8	50	16	56
9	90	16	93

^aReaction Conditions: Aniline (1.5 mmol), Ethyl Acrylate (4.5 mmol), Water (3 mL), catalyst (25 mol %).

^bIsolated yield.

Table 4. Effect of solvent^a on Aza Michael Reaction

Entry	Solvent	Temp(°C)	Yield ^b (%)
1	Water	75	44
2	Water + Ethanol	75	65
3	Water + catalyst	75	89
4	Water + Ethanol + catalyst	75	98
5	Ethanol	75	-

^aReaction Conditions: Aniline (1.5 mmol), Ethyl Acrylate (4.5 mmol), catalyst (25 mol %) at 75°C temperature for 16h.

^bIsolated yield.

Catalyst concentration was optimized by varying its concentration from 0.05 gm to 0.3 gm (Table 5, entry 1-6). An increase in the product yield was observed in 0.05 to 0.02 gm of catalyst amount. Hence 0.2 gm was considered as an optimum catalyst concentration. (Table 5, entry 4)

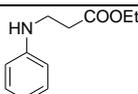
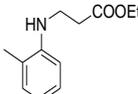
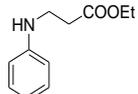
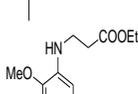
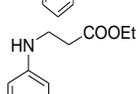
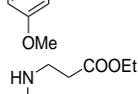
Table 5. Effect of catalyst for Aza Michael Reaction^a

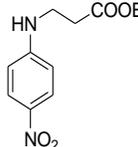
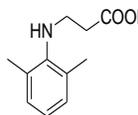
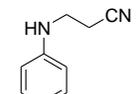
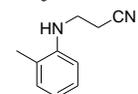
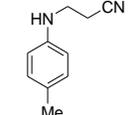
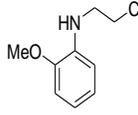
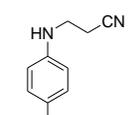
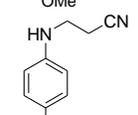
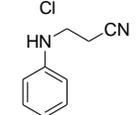
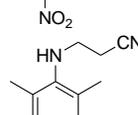
Entry	Catalyst in gm	Yield ^b (%)
1	0.05	66
2	0.1	78
3	0.15	85
4	0.2	95
5	0.25	94
6	0.30	96

^aReaction Conditions: Aniline (1.5 mmol), Ethyl Acrylate (4.5 mmol), Water (3 mL), at 75°C temperature for 16h.

^bIsolated yield.

Table 6. Aza-Michael Reaction of Aromatic amine with Activated olefins in presence of PS-L-CuAc₂.

Entry	R =	R ₁ =	Time(h)	Product	Yield ^b (%)
1	H	COOEt	16		84
2	2-Me	COOEt	20		64
3	4-Me	COOEt	16		85
4	2-MeO	COOEt	16		81
5	4-MeO	COOEt	12		99
6	4-Cl	COOEt	24		25

7	4-NO ₂	COOEt	24		15
8	2,6-di-Me	COOEt	24		10
9	H	-CN	16		89
10	2-Me	-CN	24		70
11	4-Me	-CN	16		84
12	2-MeO	-CN	16		85
13	4-MeO	-CN	12		99
14	4-Cl	-CN	24		32
15	4-NO ₂	-CN	24		15
16	2,6-di-Me	-CN	24		10

^aReaction Conditions: Aniline (1.5 mmol), Ethyl Acrylate (4.5 mmol), Water (3 mL), catalyst (25 mol %) at 75°C temperature..

^bIsolated yield.

To explore the general applicability of the catalyst, hydroamination's of EA with different amines were carried out and the mono-addition product yield after 16 h of reaction was compared (Table 6). The nature of substituent's on the aromatic ring of aniline derivatives has considerable effect over the reactivity. The electron-donating groups at the -Para positions gave higher yields of mono-addition while -Ortho position substituted because of steric factors gave lower conversion, anti-Markovnikov products. The aromatic amines with electron withdrawing substituent such as 4-Chloro-aniline (25%) were less reactive, P-nitroaniline showed traces of reactivity with EA.

These results indicate that the amine reactivity depends on their basicity. It is well known that aromatic amines with electron donating substituent are more basic than amines with electron withdrawing substituent. As the basicity of amines increased their reactivity also increased in hydroamination of activated olefins and vice versa.

In conclusion, we have reported the novel catalyst and simple method for preparation of chloro-methylated polystyrene supported copper (II) complex and its successful application for the Aza Michael addition reaction of various aromatic amines with activated olefins. The present system is moisture stable and the catalyst can be synthesized readily from inexpensive and commercially available starting materials. Moreover the catalyst was reused for several consecutive cycles with consistent catalytic activity. Further work is in progress to broaden the scope of this catalytic system for other organic transformation.

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References and notes

- [1] Herr, R. J. Bioorg. Med. Chem. 2002, 10, pp. 3379-3393.
- [2] T.E. Muller, M. Beller, Chem. Rev., 1998, 98, pp. 675.
- [3] J.J. Brunet, D. Neibecker, in: A. Togni, H. Grutzmacher (Eds.), Catalytic Hetero functionalization, Wiley-VCH, Weinheim, 2001, pp. 91-141
- [4] L.L. Anderson, J. Arnold, R.G. Bergman, J. Am. Chem. Soc. 2005, 127, pp. 14543.
- [5] J.A. Bexrud, J.D. Beard, D.C. Leitch, L.L. Schafer, Org. Lett 2005, 7, pp. 1959.
- [6] L. Ackermann, L.T. Kaspar, A. Althammer, Org. Biomol. Chem. 2007, 5, pp. 1975.
- [7] O. Jimenez, T.E. Muller, C. Sievers, A. Spirkel, J.A. Lercher, Chem. Commun. 2006, pp. 2974
- [8] N. Sewald, Amino Acids 1996, 11, pp. 397.
- [9] E. Juaristi, H.L. Ruiz, Curr. Med. Chem. 1999, 6, pp. 983.
- [10] M. Perez, R. Pleixats, Tetrahedron 1995, 51, pp.8355.
- [11] T.C. Wabnitz, J.B. Spencer, Org. Lett. 2003, 5, 2141.
- [12] L.W. Xu, J.W. Li, C.G. Xia, S.L. Zhou, X.X. Hu, Syn. Lett. 2003, 15, pp. 2425.
- [13] J. Monfray, A.M.P. Koskinen, Lett. Org. Chem. 2003, 3, pp. 324.
- [14] J.J. Bozell, L.S. Hegedus, 1981, 46, pp. 2561.
- [15] L. Fadini, A. Togni, Chem. Commun. 2003, pp. 30.
- [16] H.J. Cristau, P.P. Cellier, J.F. Spindler, M. Taillefer, Chem. Eur. J. 2004, 10, pp. 5607-5622.
- [17] Q. Cai, W. Zhu, H. Zhang, Y. Zhang, D. Ma, Synthesis 2005, pp. 496-499.
- [18] W. Deng, Y. Wang, W. Zou, L. Liu, Q. Guo, Tetrahedron Lett. 2004, 45, pp. 2311-2315.
- [19] G. Nordmann, S.L. Buchwald, J. Am. Chem. Soc. 2003, 125, pp. 4978-4979.
- [20] Z. Wan, P.P. Cellier, S. Hamada, J.F. Spindler, M. Taillefer, Org. Lett. 2004, 6, pp. 913-916.
- [21] C.G. Bates, P. Saejueng, M.Q. Doherty, D. Venkataraman, Org. Lett. 2004, 6, pp. 5005-5008.
- [22] W. Zhu, D. Ma, J. Org. Chem. 2005, 70, pp. 2696-2700.
- [23] E.J. Hennessy, S.L. Buchwald, Org. Lett. 2002, 4, pp. 269-272.
- [24] C.G. Bates, P. Saejueng, D. Venkataraman, Org. Lett. 2004, 6, pp. 1441-1444.
- [25] Z. Zhang, J. Mao, D. Zhu, F. Wu, H. Chen, B. Wan, Tetrahedron 2006, 62, pp. 4435-4443.
- [26] A. Ouali, R. Laurent, A.-M. Caminade, J.-P. Majoral, M. Taillefer, J. Am. Chem. Soc. 2006, 128, pp. 15990-15991
- [27] N.S. Shaikh, V.H. Deshpande, A.V. Bedekar, Tetrahedron 2001, 57, pp. 9045.
- [28] J. Horniakova, K. Komura, H. Osaki, Y. Kubota, Y. Sugi, Catal. Lett. 2005, 102, pp. 191.
- [29] M.L. Kantam, B. Nilima, C.V. Reddy, J. Mol. Catal. A Chem. 2005, 241, pp. 147.
- [30] T. Joseph, G.V. Shanbhag, D.P. Sawant, S.B. Halligudi, J. Mol. Catal. A Chem. 2006, pp. 250, 210.
- [31] M. Tada, M. Shimamoto, T. Sasaki, Y. Iwasawa, Chem. Commun. 2004, pp. 2562.
- [32] L.W. Xu, J.W. Li, C.G. Xia, S.L. Zhou, X.X. Hu, Syn. Lett. 2003, 15, pp. 2425.
- [33] J. Monfray, A.M.P. Koskinen, Lett. Org. Chem. 2006, 3, pp. 324.
- [34] Kavita De, J. Legros, B. Crousse, J. Org. Chem. 2009, 74, pp. 6260-6265
- [35] **Synthesis of modified Merrifield Resin with Diethanol Amine (3):** The preparation procedure followed to obtain the catalyst is given in Scheme 1. The catalyst was readily prepared in two steps. Firstly, the 2 g of 2% Di-vinyl benzene cross linked Merrifield resin (1) treated with 0.979 g of Diethanol amine (2) to produce a corresponding polymer anchored ligand (3) in the presence of sodium carbonate base (0.759 g) using N,N-dimethylformamide as solvent (DMF) at 100 deg. C for 48 h to obtain a light brown polymer (L). The polymer was washed thoroughly with DMF to remove excess Diethanol amine and then with 1 M HCl to remove the excess base. Finally, it was washed with double distilled water, dried and stored at room temperature for further use.
- [36] **Synthesis of the metal complexes (4)**
This Polymer anchored Diethanol amine ligand 3 (1 g) in acetic acid (20 mL) was treated with 5 mL 1% (w/v) acetic acid solution of copper acetate over a period of nearly 30 min under constant stirring. Then the reaction mixture was refluxed for 24 h. The greenish yellow copper complex (CuL(Ac)₂) 4b thus formed was filtered and washed thoroughly with ethanol and dried in room temperature under vacuum.
The Polymer anchored Diethanol amine ligand 3 (1 g) in acetonitrile (20 mL) was treated with 5 mL 1% (w/v) acetonitrile solution of copper iodide over a period of nearly 30 min under constant stirring. Then the reaction mixture was refluxed for 24 h. The green color copper complex (CuLI) 4a thus formed was filtered and washed thoroughly with ethanol and dried at room temperature under vacuum.
The Polymer anchored Diethanol amine ligand 3 (1 g) in methanol (20 mL) was treated with 5 mL 1% (w/v) methanolic solution of copper chloride over a period of nearly 30 min under constant stirring. Then the reaction mixture was refluxed for 24 h. The light green color copper complex (CuLCI₂) 4c thus formed was filtered and washed thoroughly with ethanol and dried at room temperature under vacuum
- [37] **General procedure for addition of aromatic amine to activated olefins:** In an oven dried 100 mL RB flask, polymer supported Cu(II) catalyst (200 mg, 0.0329 mmol), activated olefin (3 mmol), aromatic amines (1 mmol), and 6 ml solvent were stirred, at 75°C. The reaction mixtures were collected at different time intervals and after extraction with MDC identified by GCMS and quantified by GC. After the completion of the reaction, the catalyst was filtered off and washed with water followed by ethanol and dried in oven. The filtrate was extracted with Methyl Dichloride (3*20 mL) and the combined organic layers were dried with anhydrous Na₂SO₄ by vacuum. The filtrate was concentrated by vacuum and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

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