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An expeditious N,N-dibenzylation of anilines under ultrasonic irradiation conditions using low loading Cu(II)-clay heterogeneous catalyst

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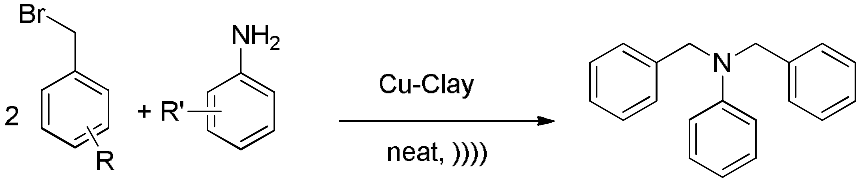
Abstract: A simple one-pot procedure for the direct N,N-dibenzylation of anilines using a catalytic amount of Cu modified montmorillonite-KSF is described. Cu modified montmorillonite-KSF has been proven to be a simple, efficient, mild, convenient and effective catalyst for the selective benzylation of anilines with benzyl bromide. Cu loading plays significant role in product yield and solvents were found to control the selectivity. The catalyst is easy to prepare, heterogeneous, stable and easy to recover.

Key words: Tertiary amines; benzylation; heterogeneous catalyst, solvent effect; neat conditions; clays; ultrasound irradiation

Tertiary amines are extensively found in biologically active natural products, constitutional chemotypes and essential structural motifs in registered drugs and are key structural elements in bioactive synthons.[1] These features of tertiary amines render their synthesis an objective of high priority from the perspective of organic and medicinal chemistry. While many applications for the preparation of primary and secondary amines have been reported, the protocols for the synthesis of tertiary amines are much less developed, due to increased steric hindrance.[2] Last decades have witnessed the successful employment of modern transition-metal-catalyzed processes, like hydroaminations,[3] reductive amination of carbonyls[4] and hydroamino-methylation of olefins or alkynes[5] etc. In these reports metal catalysts like Ni, Ru, Ir, Pd, Au, Cu, and Fe were extensively focused upon. The requirement of organic ligand and additional base as co-catalyst makes these catalyst systems complicated and not practical. A significant synthetic tool to obtain mono- and di-N-benzylated products is the N-benzylation of amines with alkyl halides. However, longer reaction time, higher temperature and lower yields of desired product are associated with this reaction in the presence of a base.[6] So improvements in this protocol are highly demanded and it is highly desirable to replace a successful homogenous catalytic process by a heterogeneous catalyzed reaction, where the solid catalyst is recoverable and reusable.[7]

In organic synthesis the efficiency of metal based heterogeneous catalysis can be improved by employing nano-sized catalysts because of their extremely small size and large surface to volume ratio.[8] Due to its distinctive properties nanocatalysis is one of the growing research areas[9] and during recent times nanoparticles have been attracting much attention as catalysts because they can be easily recovered from the reaction mixture.[10] But the tendency of metal oxide nanoparticles to undergo agglomeration, increases their particle size and therefore, reduces their catalytic activity dramatically.[10] To stabilize the particle size of metal oxide, nanoparticles can be supported in dispersed form on a suitable solid surface.[11] CuO nanoparticles thus can be stabilized by entrapping them inside the clay interlayer, which also combines unique catalytic properties of CuO nanoparticles with the shape-selectivity.[12] Acting as a polar support, the layered structure of montmorillonite facilitates the closer proximity between the reagents. Clays are aluminosilicates possessing lamellar structure with interlayer spacing ranging from 10 to 100 Å, enabling the intercalation of various ions or neutral species, thus can act as support for a large variety of reagents. Smectite clays can also be considered as microreactors because of possessing the ability to concentrate high quantities of reactive species between the aluminosilicate layers.[13] Comparatively high stability of a catalyst on solid support sometimes allows the reaction to be less sensitive to normal ambient conditions. Therefore, substituting clay supported catalysts for a homogeneous catalyst or an expensive heterogeneous catalyst seems highly desirable.[14]

Combination of mildly basic oxyanions of CuO and mildly acidic Cu cation on the polar surface will result in an acid-base bifunctional catalytic system. Using adsorption isotherm and XRD pattern H. Kostelníkova *et al.* have proved that aniline is adsorbed readily into the montmorillonite interlayer and oriented perpendicularly to silicate sheet (with an increase in d001 spacing from 1.26 nm to 1.48 nm, corresponding to on amount of aniline ~11.7 mmol g−1).[15] These concepts encouraged us to develop montmorillonite-KSF clay supported CuO for selective N,N-dibenzylation of aniline and its derivatives (Scheme 1). The Cu(II)-clay catalysts used in this method were prepared by a known method.[16]



Scheme 1: Cu(II)-Clay catalyzed N,N-dibenzylation of aniline

In our initial studies, we attempted to optimize the reaction conditions for the N,N-dibenzylation of anilines using aniline (1eq) and benzybromide (2.2 eq) as model substrates (Scheme 1). In order to find the actual effectiveness of catalyst, the model reaction was first conducted without the use of any catalyst in different solvents under ultrasonic irradiation at room temperature. The reaction failed to produce the desired product in the absence of any catalyst (Table 1, entry 1). Cu(II)-clay catalyzed the reaction efficiently and percentage of copper loading was found to have profound effect on the reaction yield as well as on the selectivity (Table 1, entries 2-7). Using Cu(II)-Clay catalyst with 20 wt% Cu loading yielded 46% conversion containing a mixture of N-benzylaniline and N,N-dibenzylaniline in 3 h under solvent-free ultrasonic conditions (Table 1, entry 2). Decrease of copper loading was found increase in the conversion as well as selectivity of dibenzylated product. With 15 and 10 wt% copper loading the Cu(II)-Clay catalysts furnished 52 and 61 % conversion containing dibenzylated product in increasing proportions respectively (Table 1, entries 3, 4). With 5 wt% copper loading the Cu(II)-Clay catalyst transformed the reactants mainly to the dibenzylated product with 78% conversion within half an hour (Table 1, entry 5). The percentage of conversion remained almost constant when the time of the reaction was increased to 2h. 2.5 wt% Cu loading was found to bring a tremendous increase in the yield (94 %) and dibenzylated product was formed exclusively (Table 1, entry 6). But a further decrease of metal loading leads to decreased yield (Table 1, entry 7). Carrying out the model reaction in presence of unmodified montmorillonite-KSF did not result in the formation of any benzylated product (Table 1, entry 8) and CuO nano-particles furnished 52% conversion containing a mixture of mono and dibenzylated products with mono-benzylated aniline as major product (Table 1, entry 9). When bezylbromide content in model reaction was increased to 2.5 equivalents we obtained 98% conversion containing >99% N,N-dibenzylaniline(Table 1, entry 10).

Table 1. Screening of catalysts[a]

Entry	**Catalyst**	**Time (h)**	**Conversion (%)**	**Yield [b] (%)**	
				Mono	**Di**
1	No catalyst	8	-	-	-
2	20 wt% Cu-Clay	3	46	64	36
3	15 wt% Cu-Clay	1	52	57	43
4	10 wt% Cu-Clay	1	61	36	64
5	5 wt% Cu-Clay	0.5	78	5	95
6	2.5 wt% Cu-Clay	0.5	94	Traces	>99
7	2 Wt% Cu-Clay	0.5	63	9	91

8	MKSF	3	Traces	-	-
9	CuO	3	52	72	28
10 [c]	2.5 Wt% Cu-Clay	0.5	98	Traces	>99

[a] Reaction Conditions: aniline (1 mmol), benzyl bromide (2.2 mmol), solvent-free under sonication, catalyst (2 mol%). [b] Isolated yields. [c] aniline (1 mmol), benzyl bromide (2.5 mmol)

Thus 2.5 wt% Cu loaded clay is a true catalyst for the N,N-dibenzylation of aniline. The probable reason for the high yield of dibenzylation product in presence of this catalyst may be the synergistic relation between CuO nano-particles and the clay support in presence of ultrasound radiations. Aniline is adsorbed perpendicularly on the silicate layer of clay[15] and the CuO nano-particles in vicinity activate the C-X bond of benzyl halides thus facilitate a faster reaction. A higher metal loading leads to lower metal dispersion as well as increase in particle size, thus is responsible for lower surface area of CuO nano-particles. These factors may be responsible for lesser conversion and lower yield of di-benzylated products. A lower metal loading may decrease the number of activated C-X bonds in vicinity of anilines adsorbed, due to extra high dispersion of metal oxide nano particles.

Reactions under different conditions were studied using Cu(II)-clay catalyst with 2.5 wt%. When this catalyst was used for the model reaction with different solvents under ultrasonic conditions at room temperature, some interesting results were obtained. Solvents like methanol, ethanol and dimethylformamide (DMF) promoted the reaction towards mono benzylated products selectively but the yields were very low. In these solvent systems decomposition of benzyl bromide to benzyl alcohol was also observed (Table 2, entries 2, 3 and 9). Formation of benzyl alcohol was stopped in solvents like hexane, toluene and ethylacetate, but the yield still remained the matter of concern (Table 2, entries 1, 10, 11). In tetrahedydrofuran (THF) the conversion increased to a great extent but the selectivity was disrupted, resulting in the formation of a mixture of mono and di-benzylated products along with some benzyl alcohol (Table 2, entry 5). However in this case dibenzylated product was formed in higher ratio. Similar results were obtained when the reaction was conducted in acetonitrile as solvent, but the major product N,N-dibenzylaniline was formed in better proportion (Table 2, entry 12). Using dimethylsulfoxide (DMSO) as solvent for the model reaction, we obtained the mono-benzylated and di-benzylated products in almost 1:9 ratio (Table 2, entry 13). The higher yield of di-benzylated products in acetonitrile and DMSO may be attributed to the basic nature of these solvents. Basic nature of solvents may buffer out the HBr produced during the reaction, thus facilitating the reaction in forward direction according to Le Chatlier's principle. Under solvent-free condition the sole product formed is N,N-dibenzylaniline, which may be due to high collision frequency and direct interaction between the catalyst and the reactants without any interference of solvent.

Table.2: Benzylation of aniline in presence of 2.5 wt% of Cu(II)-clay catalyst under ultrasonic condition using various solvents [a]

Entry	**Solvent**	**Time (min)**	**Yield [b] (%)**
1	Hexane	120	75 [c]

2	DCM	120	80[d]
3	Methanol	120	33[e]
4	Ethanol	120	62[e]
5	THF	120	55[f]
6	Chloroform	120	60[d]
7	Water	120	70[d]
8	Without solvent	30	98[g]
9	DMF	60	21[e]
10	Toluene	120	64[c]
11	Ethylacetate	120	58[c]
12	Acetonitrile	60	78[f]
13	DMSO	60	83[f]

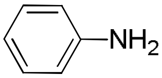
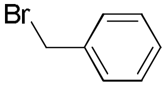
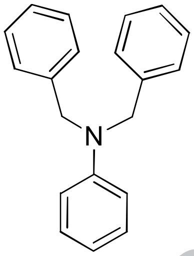
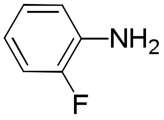
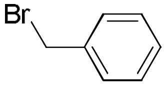
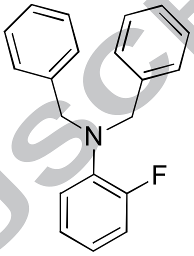
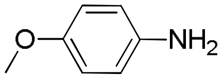
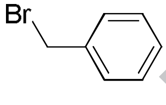
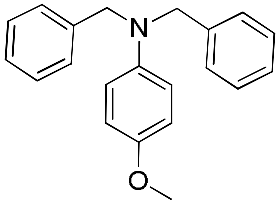
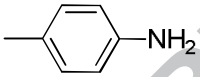
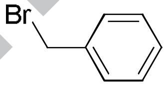
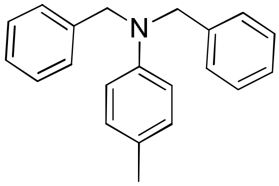
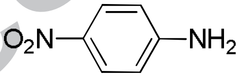
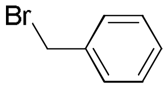
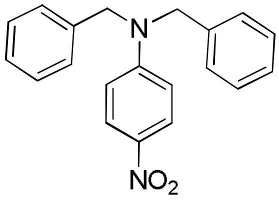
[a] Reaction conditions: all the reactions were carried out using benzyl bromide 1 (2.5 mmol) and Aniline (1.0 mmol), at sonication. [b] Isolated yield. [c] N-benzylaniline. [d] mixture of N-benzylaniline (major) and N,N'-dibenzylaniline (minor). [e] mixture of N-benzylaniline and benzylalcohol. [f] mixture of N-benzylaniline (minor) and N,N'-dibenzylaniline (major).

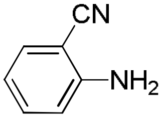
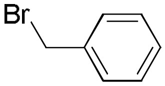
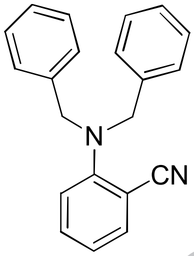
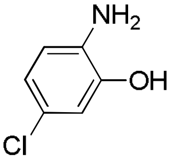
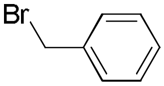
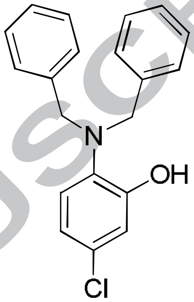
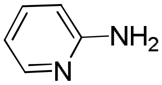
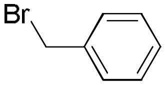
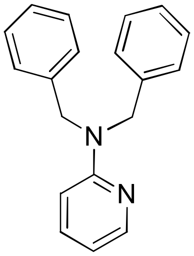
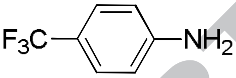
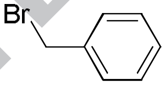
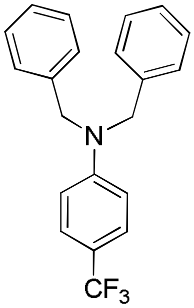
As part of our research interest directed towards the development of highly expedient methods for the green chemical transformation through heterogeneous catalysis[17] and our focus on N,N-dibenzylation of anilines, we proceeded with the Cu(II)-clay catalyst containing 2.5 wt% copper.

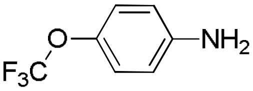
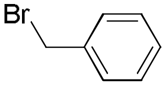
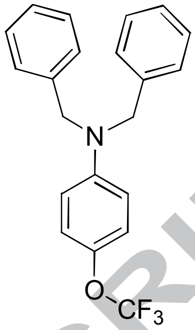
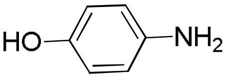
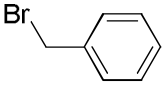
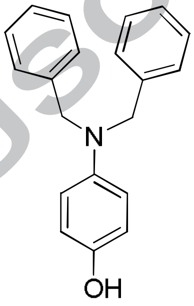
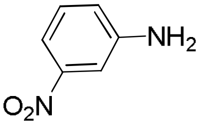
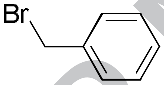
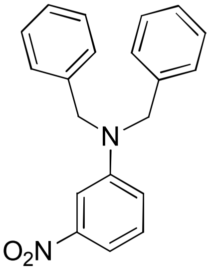
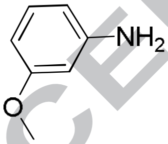
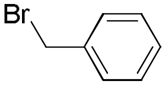
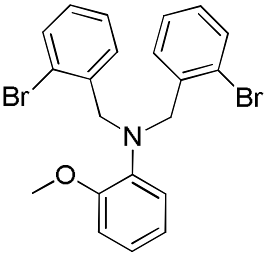
Scope and limitations of the protocol were studied on a series of anilines and benzylbromide derivatives under ultrasonic and solvent-free conditions at room temperature without using additional base, ligands or any other additives. The reaction was found to be compatible with various functional groups such as Cl, Br, F, OMe, OEt, NO_2, CN and OH with excellent chemo-selectivity. The method proved to be compatible with a wide range of benzyl bromide derivatives also and the desired products were obtained in good to excellent yields (47–98%) in very short reaction times. Simple aniline was converted into corresponding N,N-dibenzylated product with 98% yield within 30 min. (Table 3, entry 1). Aniline derivatives with electron donating groups were found to react slightly faster than those with electron withdrawing groups. The reaction was also compatible with heteroarylamines (Table 3, entries 3, 13-16, 19). Ortho substituted anilines as well as ortho substituted benzyl bromides reacted slower as compared to their meta and para substituted congeners. The tolerance of different functional groups to these reaction conditions illustrates the flexibility and generality of Cu(II)-clay catalyst. All the compounds so prepared were stable and were characterized by NMR and MS analysis and compared with reported data.

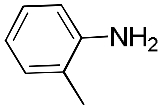
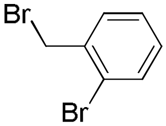
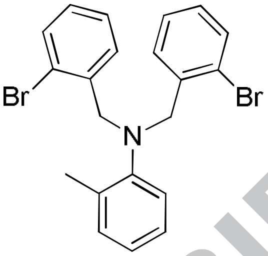
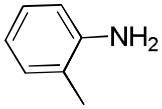
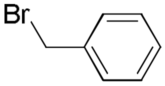
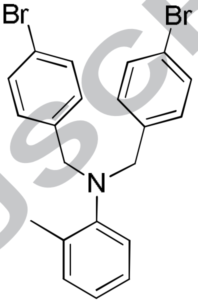
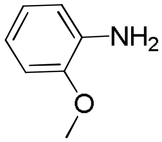
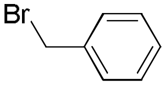
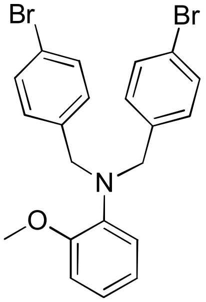
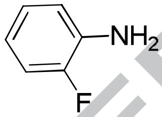
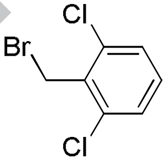
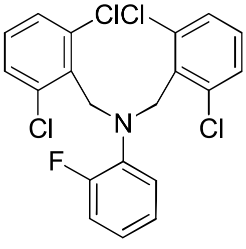
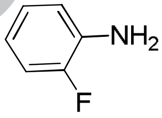
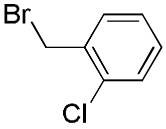
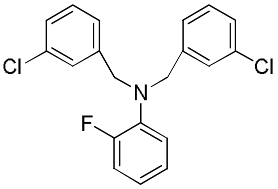
Table 3: Cu(II)-clay catalyzed synthesis of N,N-dibenzylanilines

Entry	Arylamine	Alkylbromide	Time (min)	Product	Yield[a] %

1.			30		98
2.			45		82
3			45		83
4			45		78
5			50		64

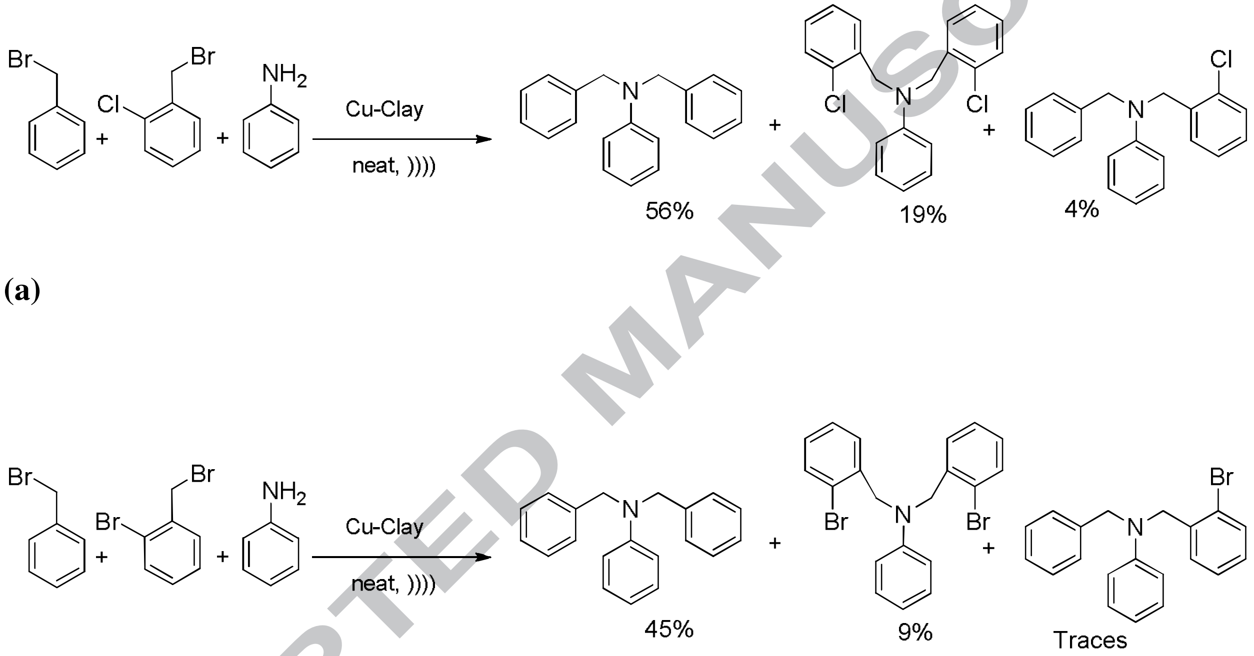
6			50		61
7			60		52
8			60		52
9			45		80

10			45		96
11			60		63
12			50		68
13			60		54

14			60		67
15			60		66
16			60		72
17			60		47
18			60		66

[a] Isolated yield

Cross reactions for the synthesis of unsymmetrical dibenzylation products were also carried out, but analysis results of the reaction mixture revealed that the unsymmetrical products are obtained with very low yield (as given in scheme 2).



(a)

(b)

Scheme 2: Cu(II)-Clay catalyzed unsymmetrical N,N-dibenzylation of aniline

Cu(II)-clay being a solid heterogeneous catalyst could be easily recovered by simple filtration; thus the recyclability of the catalyst was investigated for model reaction. The catalyst was washed with ethyl acetoacetate before each new cycle. This experiment proved that the catalyst has excellent recycling capability as no significant loss of activity was observed even after 10 consecutive cycles (Fig. 1). The ICP-MS analysis of the used catalyst after 10th consecutive cycle showed negligible loss of active metal from the catalyst (< 0.08 wt. % from 2.5 wt. %), which attributes to the stability of the catalysts even after recycling. To evaluate the heterogeneity of catalyst, we performed filtration test on model reaction. After 15 minutes (almost 50% conversion), the catalyst was filtered off and the filtrate was allowed to react further, but no further reaction was observed even after 8 h (GC analysis) suggesting that the copper catalyst remains on the support during the reaction.

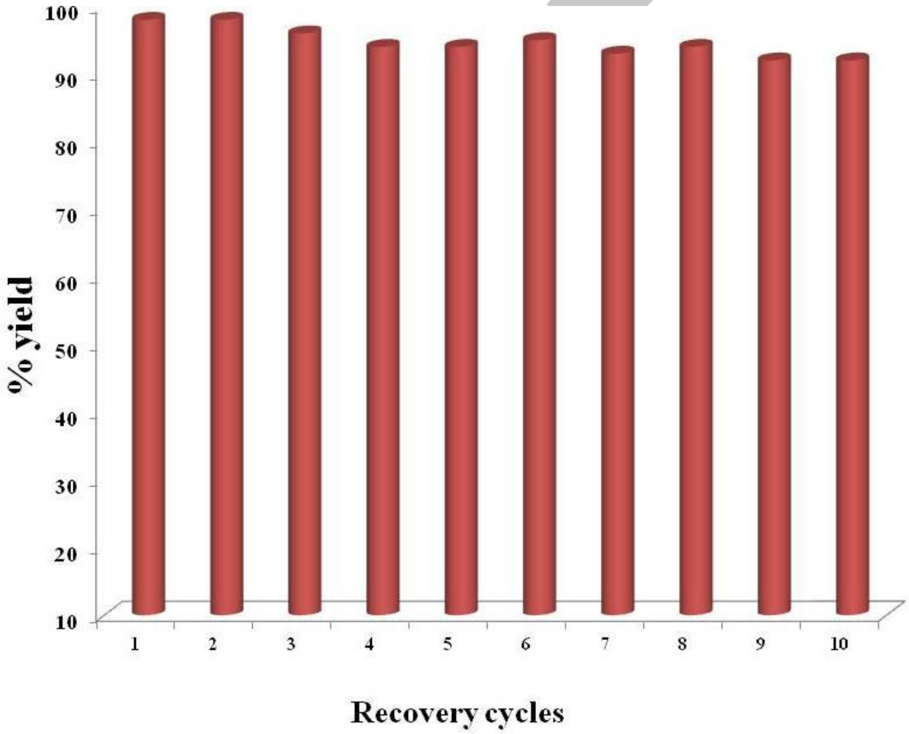


Fig. 1: Recyclability of Cu(II)-clay catalyst

The catalyst was characterized by different techniques to know the nature of the Cu species. The powder X-ray diffraction of the catalyst was recorded on a D-8 ADVANCE (BRUKER AXS, Germany) X-ray diffractometer using Ni filter and Gobel Mirror parallel beam geometry (CuKα: $\lambda = 0.15418$ nm) in the 2θ range 2–80° in step scan mode (Step Size: 0.011°, Scan Speed: 13.6 s/step). The phases are identified by search match procedure with the help of DIFFRACPLUS software using JCPDS databank. The XRD clearly indicates that there are no sharp crystalline phases, indicating that CuO is supported on MKSF in the form highly dispersed fine particles as shown in Fig. S1 (Supplementary). The reducible character of catalyst was determined by CHEMBET-3000 TPR/TPD/TPO instrument, containing a quartz reactor (i.d. = 4 mm) and a T.C.D. detector. The temperature programmed reduction (TPR) curve of the catalyst given in Fig. S2 (Supplementary), shows a broad peak at 380 °C, which may be assigned to the reduction of highly dispersed CuO to Cu.[18] X-ray photoelectron spectroscopy is a surface technique which provides valuable information about the oxidation state and chemical environment of atoms due to the shift in binding energies. Fig. S3 shows the high resolution narrow X-ray photoelectron spectra (XPS) for Cu(II)-clay catalyst, recorded to know the oxidation state of Cu. As observed in this figure, binding energy peaks at 935.6 eV and 955.3 eV can be attributed to 2p3/2 and 2p1/2 spin–orbit split-doublets, respectively, which are characteristic of Cu in +2 oxidation state.

In conclusion, we have developed ultrasound promoted N,N-dibenzylation of anilines. Use of heterogeneous catalyst with very low metal loading, excellent yields, short reaction times and solvent-free conditions are the main advantages of this method. The Cu(II)-clay is an efficient and eco-friendly heterogeneous catalyst. The catalyst is easy to recover and can be reused several times without any significant loss in catalytic activity.

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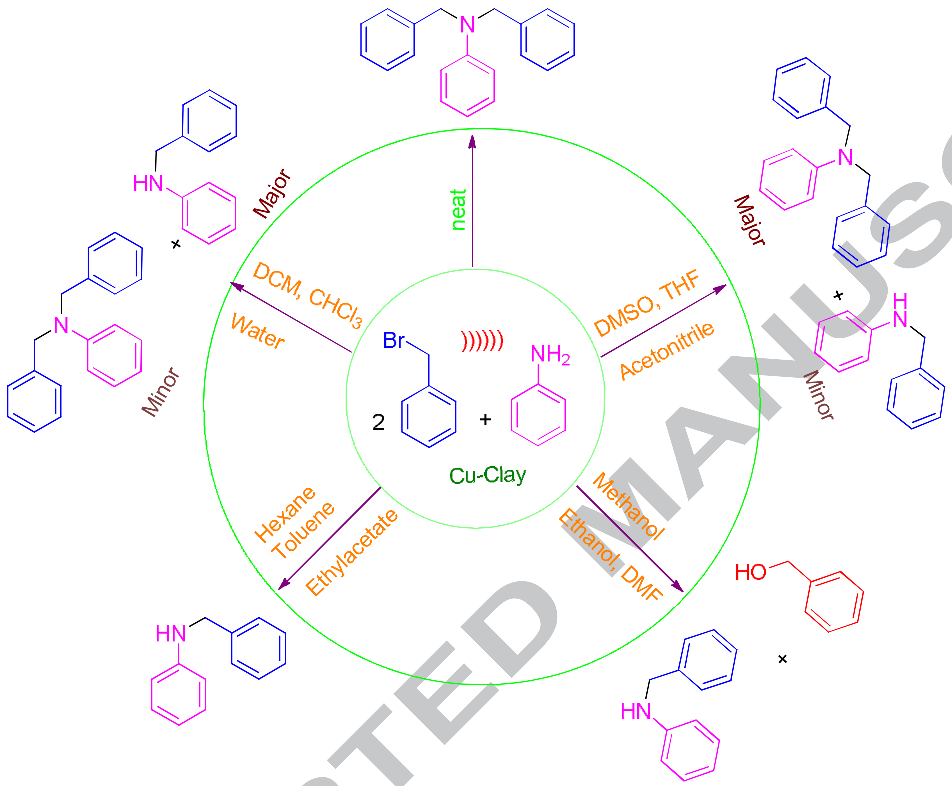
19. *Typical experimental procedure:* Benzyl bromide (2.5 eq.), aniline (1 equiv), catalyst (2 mol %) was sonicated at room temperature for a specified period of time. After the completion of the reaction (indicated by the TLC), the catalyst was filtered and washed with ethyl acetate and the resulting filtrate diluted with ethyl acetate and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and the excess solvent was removed under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography eluting with ethyl acetate and petroleum ether (1:2) to afford the desired products. The products thus obtained are characterized by HRMS and NMR. The spectral data are found to be consistent with authentic samples.

An expeditious N,N-dibenzylation of anilines under solvent free ultrasonic irradiation conditions using low loading Cu(II)-Clay heterogeneous catalyst.



20.