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Heterogeneous Cu^{II}-Catalysed Solvent-Controlled Selective N-Arylation of Cyclic Amides and Amines with Bromo-iodoarenes

Debasish Kundu,[a] Sukalyan Bhadra,[a] Nirmalya Mukherjee,[a] Bojja Sreedhar,[b] and Brindaban C. Ranu*[a]

Abstract: A selective N-arylation of cyclic amides and amines in DMF and water, respectively, catalysed by Cu^{II}/Al_2O_3 has been achieved. This protocol has been employed for the synthesis of a library of arenes bearing a cyclic amide and an amine moiety at two ends, including a few scaffolds of therapeutic importance. The mechanism has been established based on detailed electron paramagnetic resonance (EPR) spectroscopy, X-ray photoelectron spectroscopy (XPS), UV diffuse reflectance spectroscopy (DRS) and inductively coupled plasma-mass spectrometry (ICP-MS) studies of the catalyst at different stages of the reaction. The Cu^{II}/Al_2O_3 catalyst was recovered and recycled for subsequent reactions.

Keywords: amides · amines · bioactive scaffolds · heterogeneous catalysis · solvent-controlled selectivity

Introduction

The formation of C–N bonds is one of the most important reactions in chemical and pharmaceutical industries,[1] as a majority of the pharmaceutically active molecules are derived from heterocyclic units. In particular, N-arylation of nitrogen heterocycles such as cyclic amides and amines by aryl halides has received current attention as a series of compounds containing both cyclic amides and amines attached with an aromatic ring through a nitrogen centre are found as structural motifs of biologically active molecules and drugs as outlined in Figure 1.[2] Interestingly, no straightforward and efficient methodology was available for the synthesis of these molecules. This prompted us to initiate an investigation to find a suitable protocol for an access to these molecules.

The transition-metal-catalysed cross-coupling reaction is one of the efficient tools for the N-arylation of heterocycles.[3] These reactions are usually mediated by palladium,[4] nickel,[5] copper[6] , more recently, iron[7] catalysts in presence of a ligand. However, copper and iron being less expensive and toxic, have received more attention. Although N-arylation of a variety of cyclic amines such as imidazoles, pyrazoles and indoles were studied extensively by these procedures, less active cyclic amides have not been addressed adequately. In addition, we did not find a single report on the selective N-arylation of a cyclic amide over an amine and vice versa, which would be of much significance towards

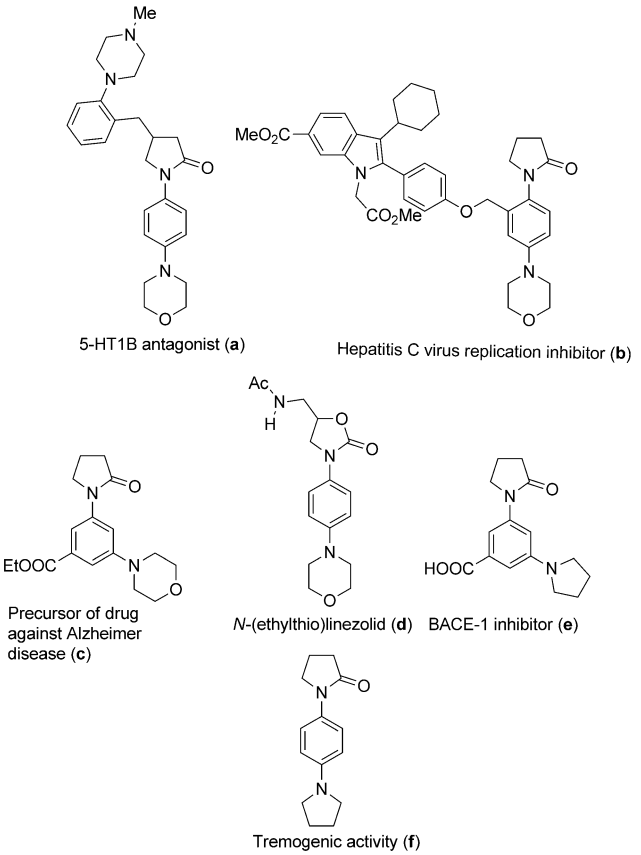

Figure 1. Potent molecules containing both cyclic amide and amine moieties.

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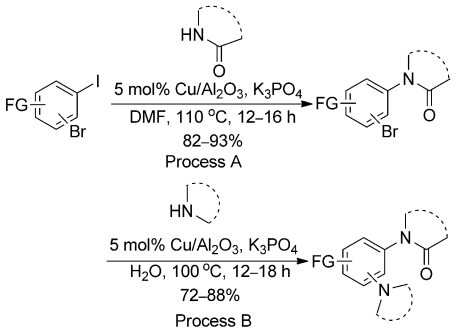
the synthesis of the molecules containing both cyclic amide and amine moieties, as outlined in Figure 1.

A few years back, we have developed a unique Al_2O_3-supported Cu^{II} catalyst that has been successfully used for C–S, C–Se and C–Te cross-coupling reactions.[8] We now report here its application for N-arylation of cyclic amines and amides involving C–N bond formation. Significantly, we have observed that cyclic amides underwent N-arylations by aryl iodides in DMF, whereas amines were arylated marginally under this condition. On the other hand, arylation of amines proceeded efficiently in water by aryl iodide/bromide, whereas amides remained inert. Based on this differential reactivity of iodo- and bromo-arenes, we have developed a simple protocol for the hitherto unreported synthesis of arenes containing both cyclic amide and amine moieties at two ends (Scheme 1), starting from bromo-iodobenzene.



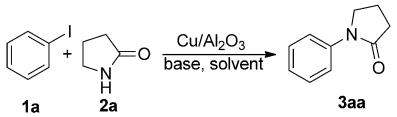
Scheme 1. Solvent-selective differential N-arylations of cyclic amides and amines. FG = functional group.

Results and Discussion

To standardise the reaction conditions for the arylation of cyclic amide a series of experiments for a representative reaction of 2-pyrrolidinone and iodobenzene with variation of the reaction parameters such as solvent, temperature, base, catalyst loading and reaction time were performed. Among DMF, *N*-methylpyrrolidone (NMP), DMSO, CH_3CN, dioxane and water used for this reaction, DMF was found to be the best solvent giving 92% yield at 110°C in presence of K_3PO_4 and Cu/Al_2O_3 (5 mol%) (Table 1, entry 9).Water failed to initiate the reaction (Table 1, entries 5 and 6). The reaction did not proceed at all in the absence of a catalyst and a base (Table 1, entries 16 and 17). Only marginal reaction was observed by using $CuSO_4$ and Al_2O_3 separately (Table 1, entry 14). K_3PO_4 was found to be the most suitable base among other bases tried.

For the optimisation of the reaction conditions for the arylation of amines, similar experiments for a representative reaction of 1-(4-bromophenyl)pyrrolidin-2-one (**3ha**) (obtained by arylation of pyrrolidinone) and morpholine were carried out with variation of solvent, base, catalyst loading, time and temperature. The results are summarised in Table 2. It was revealed that the best yield was obtained

Table 1. Standardisation of the amide coupling reaction.[a]



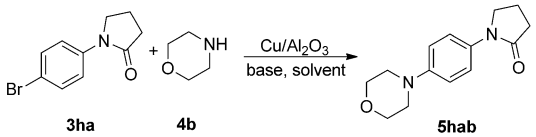
1a 2a 3aa

Entry	Catalyst [mol%]	Solvent	Base	T [°C]	Yield [%][b]
1	5	NMP	K_3PO_4	110	90
2	5	DMSO	K_3PO_4	110	53
3	5	CH_3CN	K_3PO_4	110	72
4	5	toluene	K_3PO_4	110	0
5	5	H_2O	K_3PO_4	110	0
6	5	H_2O	KOH	110	0
7	5	dioxane	K_3PO_4	110	38
8	5	THF	K_3PO_4	reflux	traces
9	5	DMF	K_3PO_4	110	92
10	5	DMF	K_2CO_3	110	0
11	5	DMF	Cs_2CO_3	110	86
12	5	DMF	KOH	110	76
13[c]	2	DMF	K_3PO_4	110	66
14[d]	5	DMF	K_3PO_4	110	20
15[c]	5	DMF	K_3PO_4	80	traces
16	0	DMF	K_3PO_4	110	0
17	5	DMF	none	110	0

[a] Reaction conditions: iodobenzene (1.0 mmol), 2-pyrrolidinone (1.2 mmol), 12 h, under an argon atmosphere. [b] Yields of the isolated pure products. [c] 24 h. [d] $CuSO_4$ was used as catalyst and basic alumina (0.1 mmol) was used as additive.

when the reaction was performed in water at 100°C in the presence of K_3PO_4 and 5 mol% of the catalyst (Table 2, entry 10). Significantly in a sharp contrast, DMF, which works most efficiently for the arylation of amides, did not initiate the arylation reaction for the amine at all (Table 2, entries 1–3 and 5). On the other hand, water, which was

Table 2. Standardisation of the amine coupling reaction.[a]



3ha 4b 5hab

Entry	Catalyst [mol%]	Solvent	Base	T [°C]	Yield [%][b]
1	5	DMF	K_2CO_3	110	0
2	5	DMF	K_3PO_4	110	traces
3	5	DMF	Cs_2CO_3	110	traces
4	5	NMP	K_3PO_4	110	traces
5	5	DMF	K_3PO_4	140	0
6	5	DMSO	K_3PO_4	110	20
7	5	CH_3CN	K_3PO_4	110	45
8	5	Toluene	K_3PO_4	110	0
9	5	THF	K_3PO_4	reflux	traces
10	5	H_2O	K_3PO_4	100	86
11	5	H_2O	Cs_2CO_3	100	78
12	5	H_2O	None	100	traces
13	5	H_2O	KOH	100	60
14	2	H_2O	K_3PO_4	100	53
15	0	H_2O	K_3PO_4	100	0
16	5	H_2O	K_3PO_4	RT	0

[a] Reaction conditions: 1-(4-bromophenyl)pyrrolidine-2-one (1.0 mmol), morpholine (2.0 mmol), 12 h, under an argon atmosphere. [b] Yields of the isolated pure products.

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found to be inactive for the arylation of the amide, worked successfully for the arylation of amines.

Thus, in a typical reaction procedure a mixture of a cyclic amide and an aryl iodide was heated in DMF at 110 °C in the presence of K_3PO_4 and Cu/Al_2O_3 for a certain period of time as required to complete the reaction (TLC) (procedure A). On the other hand, arylation of an amine was performed by using aryl iodide/bromide in water at 100 °C under similar conditions (procedure B).

A series of 5-, 6-, 7- and 8-membered cyclic amides underwent reactions with several diversely substituted aryl and heteroaryl iodides by procedure A to give the corresponding N-arylated or heteroarylated amides. The results are summarised in Table 3. Both electron-donating and electron-withdrawing groups on the aryl iodide are compatible in this procedure giving uniform yields. The reaction is highly chemoselective being successful for the coupling of an amide with an iodo-moiety leaving Br unaffected in the bromo-iodobenzene.

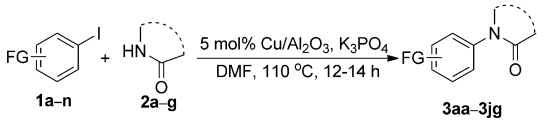
The heteroaryl iodides bearing thiophenyl (**1e**) and pyridinyl (**1f**) units also underwent facile reactions. Sterically hindered iodides, such as 2-bromo-4-methyl-iodobenzne (**1k**) and 2-bromoiodobenzene (**1i**), reacted with 5- and 6-membered cyclic amides (i.e., compounds **2a** and **2c**) without any difficulty. The bridged cyclic amide **1g** is also equally reactive to form compound **3jg**. The arylation of the eight-membered cyclic amide **2f** is reported for the first time.

We then turned our attention to the arylation of amines. The *N*-(bromophenyl) cyclic amides, prepared earlier, were then subjected to reaction with cyclic amines by following procedure B to provide the corresponding products involving a coupling through a Br functionality. The results are reported in Table 4. A variety of amines such as pyrrolidine (**4a**), piperidine (**4c**), morpholine (**4b**), thiomorpholine (**4d**) and 4-methyl piperidine (**4e**) have been used for this coupling reaction. All the products were characterised by their spectroscopic data. In addition, the X-ray structures of two of these products (Table 4, **5kab** and **5hfc**) also confirmed their identities (Figure 2).[9]

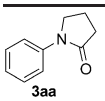
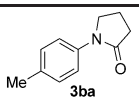
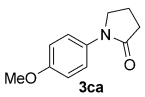
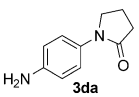
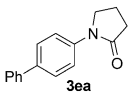
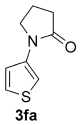
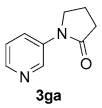
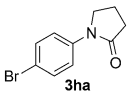
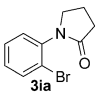
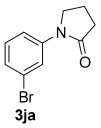
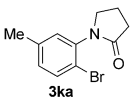
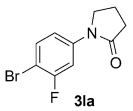
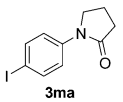
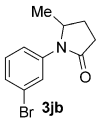
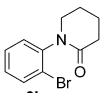
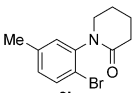
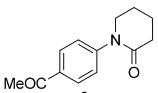
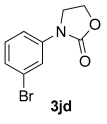
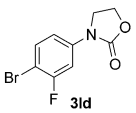
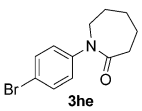
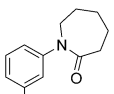
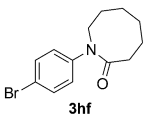
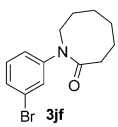
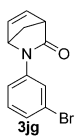
These products, the arenes bearing an amide and an amine moiety at two ends, are of much potential as therapeutic agents. Several such compounds have been obtained by this reaction. Product **5hab** (Table 4) constitutes the core unit of the 5-HT1B antagonist (**a**, Figure 1) and the hepatitis C virus replication inhibitor (**b**, Figure 1) and product **5jdb** resembles linezolid (**d**, Figure 1). Product **5jab** is a precursor to a drug against Alzheimer disease (**c**, Figure 1) and product **5jba** resembles the BACE-1 inhibitor (**e**, Figure 1) and the products **5haa** and **5laa** resemble the compound showing tremogenic activity (**f**, Figure 1).

In general, both reactions are clean and high yielding. The products are obtained in high purity. Thus, this protocol provides an efficient synthesis of arenes containing a cyclic amide on one end and a cyclic amine at the other for the first time through a unique solvent-controlled sequential N-arylation of cyclic amides and amines. The catalyst was

Table 3. N-Arylations of cyclic amides.[a]



1a–n 2a–g 3aa–3jg

Product	Yield [%]	Product	Yield [%]
 3aa	92	 3ba	90
 3ca	89	 3da	80
 3ea	86	 3fa	92
 3ga	81	 3ha	93
 3ia	83	 3ja	90
 3ka	80	 3la	90
 3ma	82	 3jb	88[b]
 3ic	80[c]	 3kc	81[c]
 3nc	83[c]	 3jd	85
 3ld	80	 3he	84[d]
 3je	86[d]	 3hf	85[e]
 3jf	83[e]	 3jg	82[e]

[a] Reaction conditions: iodoarene (1.0 mmol), amide (1.2 mmol), K_3PO_4 (1.5 mmol), DMF (3.0 mL), 110 °C, 12 h, under an argon atmosphere. [b] 13 h time is required. [c] 14 h time is required. [d] 15 h time is required. [e] 16 h time is required.

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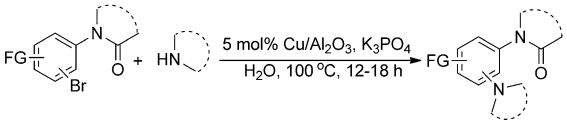
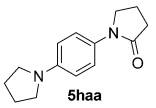
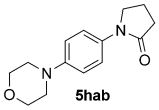
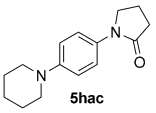
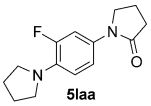
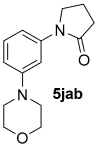
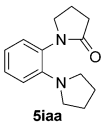
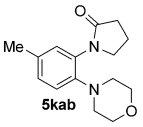
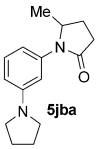
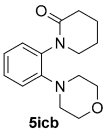
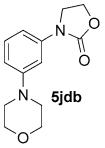
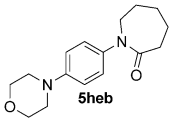
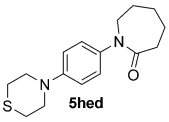
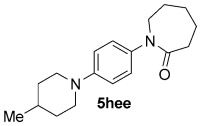
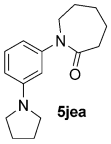
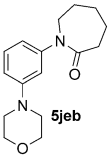
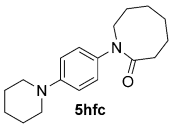
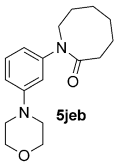
Table 4. N-Arylations of cyclic amines.[a]



3ha–3jf 4a–4e 5haa–5jeb

Product	Yield [%]	Product	Yield [%]
 5haa	82	 5hab	86
 5hac	83	 5laa	88
 5jab	85	 5iaa	82
 5kab	86	 5jba	78
 5icb	72[b]	 5jdb	74
 5heb	78[c]	 5hed	76[c]
 5hee	72[c]	 5jea	84[d]
 5jeb	88[d]	 5hfc	87[e]
 5jeb	85[e]		

[a] Reaction conditions: bromoarene (1.0 mmol), amine (2.0 mmol), K_3PO_4 (1.5 mmol), water (3 mL), 100 °C, 12 h, 1 atm argon. [b] 14 h time is required. [c] 15 h time is required. [d] 16 h time is required. [e] 18 h time is required.

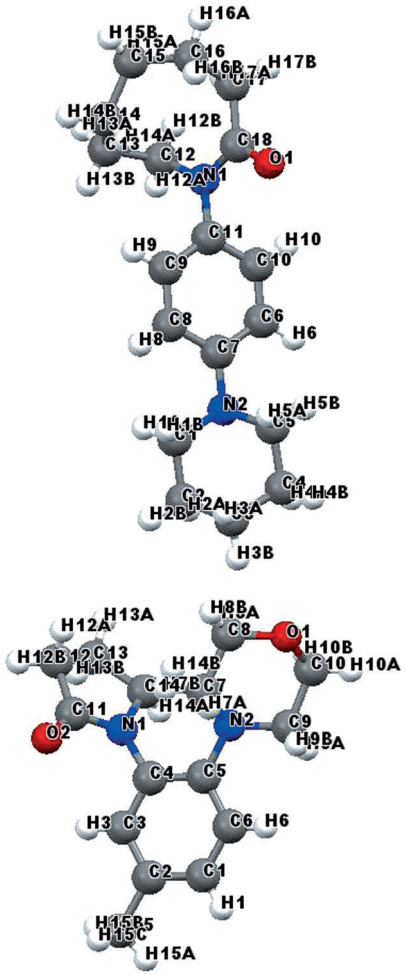


Figure 2. Top: ORTEP diagram of compound **5hfc**. Bottom: ORTEP diagram of compound **5kab**.

recycled for five times without any appreciable loss of activity (Figure 3).

Study of the mechanism: To understand this solvent-selective N-arylation of amides and amines a detailed investigation on the mechanism was undertaken. To check whether the reaction is going through the heterogeneous or homogeneous catalysis pathway inductively coupled plasma (ICP) MS studies of the catalyst at different stages of the reaction were carried out. The fresh catalyst is found to contain 0.518 mmol g^{-1} of copper whereas the recovered one from the amide coupling after fourth cycle contains 0.502 mmol g^{-1} of copper and that from the amine reaction contains 0.496 mmol g^{-1} of copper. These data indicate marginal loss of catalyst in the process, which might be due to loss during handling. In another experiment for homogeneity test, a coupling reaction of 2-pyrrolidinone and 4-methyl iodobenzene was stopped at 3.5 h after 26% conversion (NMR spectroscopy). The catalyst was separated and the reaction mixture was allowed to run further. Even after 12 h no formation of product was observed and the separated

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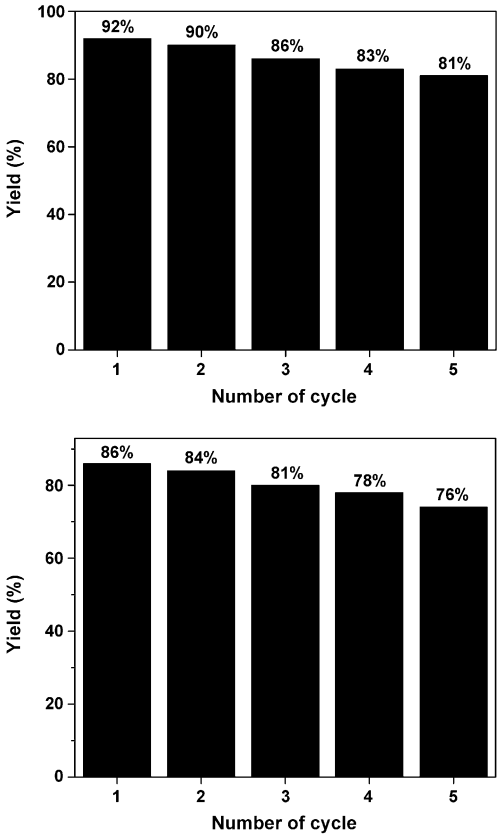
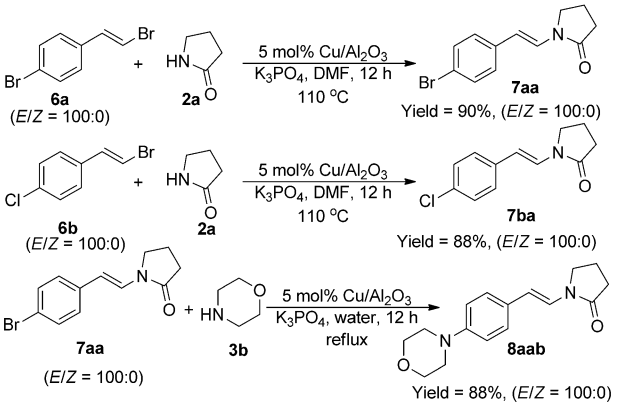
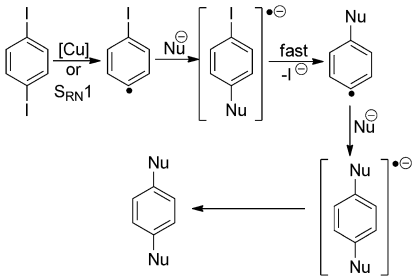


Figure 3. Top: Recyclability diagram of the catalyst in the amide coupling. Bottom: Recyclability diagram of the catalyst in the amine coupling.



Scheme 2. Coupling of styryl derivatives with retention of the stereoselectivity.



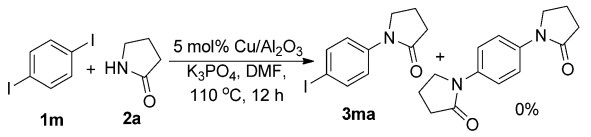
Scheme 3. Expected behaviour of 1,4-diiodobenzene under a radical–anion mechanistic pathway.

catalyst was found to contain 0.514 mmol g^{-1} of copper by ICP-MS analysis. Thus, this study clearly establishes heterogeneous catalysis in this process.

As the reactions did not occur in the absence of catalyst (Tables 1 and 2), uncatalysed pathways such as S_NAr[10] or $S_{RN}1$[11] (thermal or photochemical) are unlikely. Thus, in this copper-catalysed process three paths involving 1) radical intermediates, 2) oxidative addition/reductive elimination and 3) metal-assisted nucleophilic displacement, are considered.

To check the possibility of a radical process we performed the coupling reaction of 2-pyrrolidinone and 4-methyl iodobenzene in the presence of a nitroarene (electron acceptor) and THF (radical scavenger)[12] and practically no effect was observed. These results did not support the involvement of radicals. In another experiment, the coupling of 2-pyrrolidinone and *trans*-4-chlorostyrenyl bromide led to the *trans* product (Scheme 2) only (100%). This observation too does not support the radical pathway as the involvement of vinyl radials would provide mixture of stereoisomers undergoing a rapid inversion of the configuration.[13]

To find the involvement of a radical anion we have also carried out the Cu^{II}-catalysed reaction of 2-pyrrolidinone (2 equivalents) and 1,4-diiodobenzene (1 equivalent) under the same conditions (Scheme 3) and we have observed the formation of a mono-N-arylated product (Scheme 4). The reaction through a radical anion intermediate would lead to the disubstitution product in place of a monosubstituted one.[14] Thus, a radical anion pathway for this reaction is unlikely.



Scheme 4. Behaviour of 1,4-diiodobenzene under standardised reaction condition.

If an oxidative addition–reductive elimination pathway is considered, it would involve a Cu^{II}/Cu^{IV} transition, which is unusual. The other possibility is initial reduction of Cu^{II} to Cu^{I}[15] or Cu^0 followed by oxidative addition involving a Cu^{I}/Cu^{III}[6e] or Cu^0/Cu^{II} pathway. However, the EPR and XPS studies of the catalyst at intermediate stage of the reaction did not show the presence of any Cu^{I} or Cu^0 species. Hence, the oxidative addition–reductive elimination pathway is also ruled out.

Next, we focussed our attention to a Cu-assisted nucleophilic displacement process.[16] Thus, a more detailed investigation on the nature of the catalyst and reaction was undertaken. The XPS study of the fresh catalyst at the Cu 2p

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level shows the $2p_{3/2}$ line at 934.556 with characteristic shake up feature at 942.969 (Figure 4a),[17] which suggests the presence of the oxidation state +2 of copper. The X-band EPR spectrum of the alumina-supported copper catalyst exhibits a broad four-line hyperfine splitting for solid sample at 77 K (Figure 4b).[18] The g values with $g_{||} > g_{\perp} > 2.0023$ indicate that an unpaired electron resides in a $d_{x^2-y^2}$ orbital with the copper centre in axial symmetry. The $g_{||}$, $g_{\perp}$ and $A_{||}$ values of 2.318, 2.143 and $114.9 \times 10^{-4}\,cm^{-1}$ suggest a tetrahedrally distorted copper(II) species with the presence of an in-plane sigma bonding interaction. This fact is also supported by a UV-DRS study, where we got an absorption peak for Cu^{II} in the region of $\lambda = 750$ nm[19] (Figure 4c).

To conclude whether the copper centre is interacting with the electrophile or nucleophile in the first stage of the reaction, we have performed a reaction of iodobenzene and bromobenzene in presence of Cu^{II}/Al_2O_3 in DMF and water, respectively, without any nucleophile and base at 100–110 °C. After 2 h the EPR spectrum of the catalyst, suspended in DMF and water, shows similar kinds of X-bands as found in the fresh catalyst (Figure 5). The EPR spectrum of the catalyst at intermediate stages of the reaction with the amide and amine in DMF and water, respectively, in the absence of any electrophile, suggest a change in the coordination environment of the Cu^{II} centre (Figure 6a). The EPR spectral pattern of the species generated upon treatment of the copper catalyst with amine in water changed dramatically. The EPR parameters ($g_{\|} = 2.229$, $g_{\perp} = 2.049$ and $A_{||} = 171.1 \times 10^{-4}$ cm-1) clearly suggest a change in the coordination environment resulting in a square-planar coordination geometry at the copper(II) centre. On the other hand, the EPR spectrum of catalyst after addition of amide in DMF suggests a change in coordination geometry at the copper centre with a tetrahedral distortion ($g_{||} = 2.298$, $g_{\perp} = 2.075$ and $A_{||} = 144.1 \times 10^{-4}\,cm^{-1}$). However, the extent of the tetrahedral distortion gets reduced in the latter stage. In both cases, however, the nucleophiles get coordinated at the metal centre with a concomitant change in the coordination environment. The EPR parameters indicate the binding of the amine through the nitrogen atom and of the amide through the anionic oxygen atom, or the nitrogen atom or through the N-C-O π cloud to the copper(II) centre. Binding or coordination of the amide, a bulky ligand, (Figure 7) results in a tetrahedrally distorted copper(II) centre in order to alleviate steric repulsion between the ligands. It was observed that an increase in the ring size of the cyclic amide led to a reduction of the rate of the reaction because of steric strain.

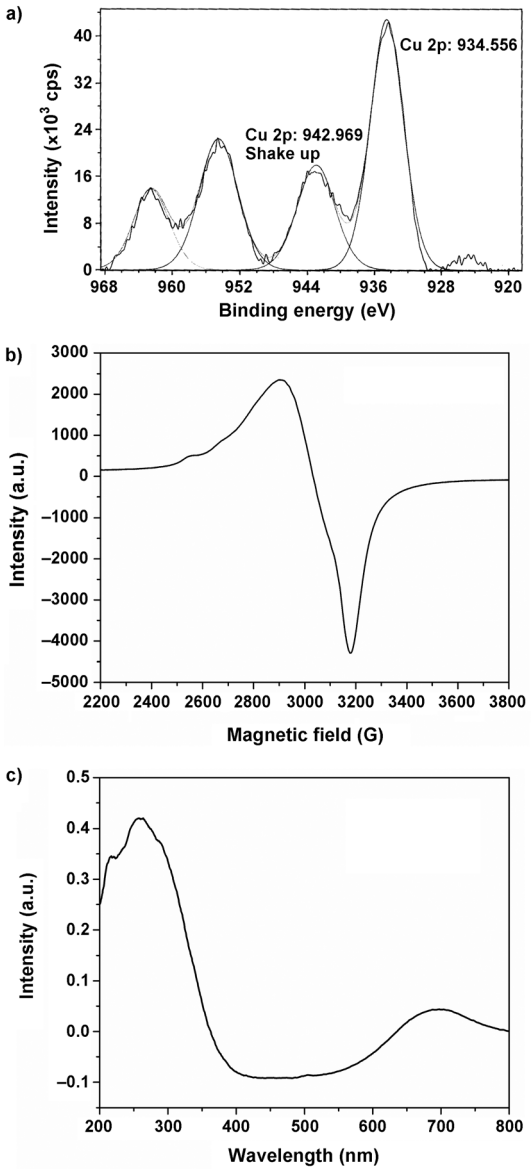

Figure 4. a) XPS study of the fresh catalyst. b) X-band EPR spectrum of the fresh catalyst. c) UV diffuse reflectance spectrum (DRS) of the fresh catalyst.

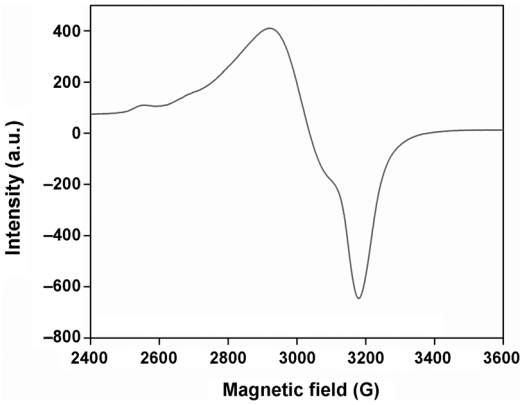

Figure 5. EPR pattern of the catalyst with bromobenzene in water.

The X-band EPR spectrum of the catalyst at the intermediate stage of the amide and amine coupling in presence of both an electrophile and a nucleophile under standardised reaction conditions in DMF and water, respectively, after 4 h shows similar types of results with that taken in absence of an electrophile (Figure 6b). In case of amide coupling the catalyst suffers a tetrahedral distortion ($g_{\|} = 2.307$,

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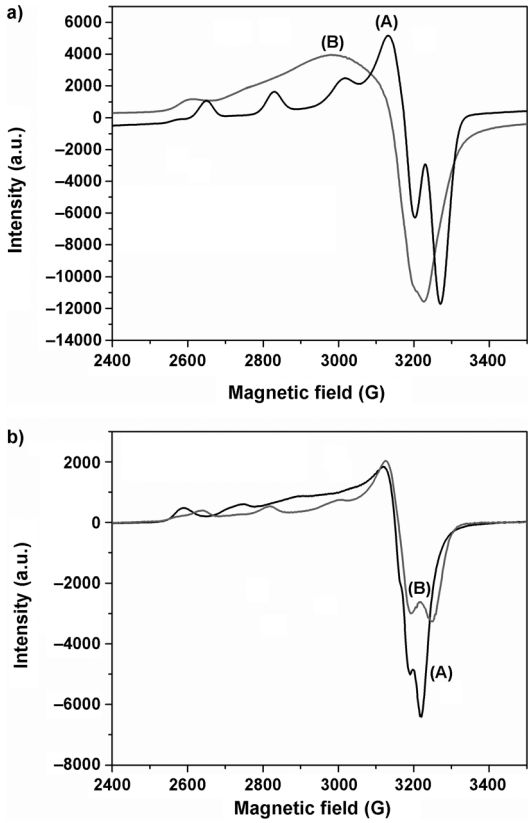

Figure 6. a) X-band EPR pattern of the catalyst at the stage of (A) the amine–Cu and (B) the amide–Cu intermediate in DMF and water, respectively, without any electrophile. b) X-band EPR pattern of the catalyst at the intermediate stage of (A) the amide-Cu and (B) the amine-Cu in DMF and water, respectively, in the presence of iodobenzene as electrophile.

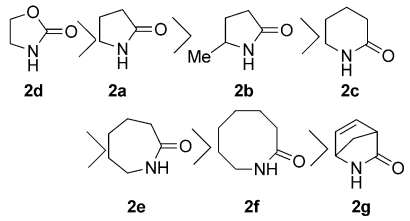

Figure 7. Reactivity order of different cyclic amides with respect to iodobenzene.

$g_{\perp}=2.063$ and $A_{||}=137.64\times10^{-4}\,cm^{-1}$) and in case of amine coupling in water the catalyst achieves a square-planner geometry ($g_{\parallel}=2.230$, $g_{\perp}=2.057$ and $A_{||}=167.4\times10^{-4}\,cm^{-1}$). This clearly suggests that the nucleophilic activation by the metal centre is the first and key step in this reaction.

In case of the amide–copper intermediate the XPS shows the Cu $2p_{3/2}$ and N 1s lines at 935.081 and 401.842 eV, respectively, with the characteristic shake up feature of copper(II) (see Figure S1 a and b in the Supporting Information). On the other hand, for the amine–copper intermediate the XPS shows the Cu $2p_{3/2}$ and N 1s lines at 935.023 and 400.474 eV, respectively, (see Figure S1 c and d in the Supporting Information) with the characteristic shake up feature of copper(II). These facts indicate that copper is in the oxidation state +2 at the intermediate stage of the reaction.

The UV-DRS spectrum of the amine intermediate shows a strong N–Cu charge transfer (ligand-to-metal charge transfer, LMCT)[20] band in the region of $\lambda=450$–600 nm, which indicates that copper is bound to the amine nitrogen atom.

In case of the amide intermediate, the spectral pattern is quite similar to that of the fresh catalyst; however a weak band is present in the region of $\lambda=450$–550 nm (Figure 8).

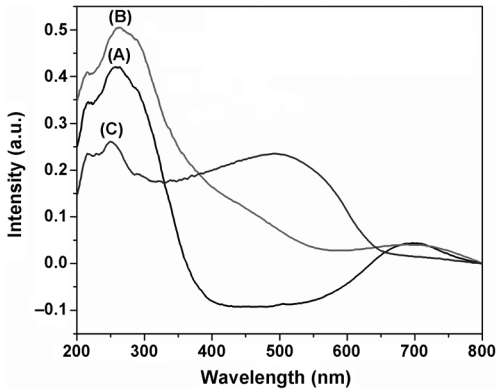

Figure 8. Comparative UV-DRS study of (A) the fresh catalyst, (B) the amide intermediate and (C) the amine intermediate.

In line with the EPR findings the UV-DRS study also suggests that, in case of amine coupling, the amine is interacting with copper directly through the nitrogen centre, but in case of the amide the binding possibly occurs through the oxygen centre, which could also be preferable due to hard–hard interaction or the N-C-O π cloud.

After activation of the nucleophile by the Cu catalyst, the aryl halide and the base come close to the metal centre and a metal-assisted nucleophilic displacement leads to the formation of the product. The catalyst is regenerated and takes part in the next cycle. The regenerated catalysts from both the amide and the amine coupling in DMF and water, respectively, are characterised by EPR (see Figure S2 in the Supporting Information) and XPS (see Figure S3 a and b in the Supporting Information). The X-band EPR spectrum of the recycled catalyst in the amide coupling ($g_{\parallel}=2.336$, $g_{\perp}=2.066$ and $A_{\parallel}=122.3\times10^{-4}\,cm^{-1}$) indicates that the Cu^{II} centre remains in a tetrahedral environment with some short tetragonal distortion with respect to the fresh catalyst. This distortion is due to the presence of solvent in the coordination environment of copper(II). The EPR parameters of the recycled catalyst in the amine coupling ($g_{\parallel}=2.338$, $g_{\perp}=2.067$ and $A_{\parallel}=127.2\times10^{-4}\,cm^{-1}$) show the similar result, and in both cases the copper centre remains in the same coordination environment, which is quite expected.

The XPS study of the regenerated catalyst in the amide coupling in DMF and the amine coupling in water at the Cu 2p level shows the $2p_{3/2}$ lines at 934.006 and 934.355 eV, respectively, with characteristic shake-up features at 943.494

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and 944.002 eV, respectively, after the fourth catalytic cycle. This clearly shows that copper remains in the oxidation state +2 after the reaction (See Figure S3 a and b in the Supporting Information).

To find a rationale for the selective N-arylation of the amide in DMF over water, the X-band EPR spectrum of the catalyst at the intermediate stage of amide coupling in water was taken. This gives a similar result as that of the interaction of the catalyst with water only without an amide or an electrophile (Figure 9). This suggests that in water the metal

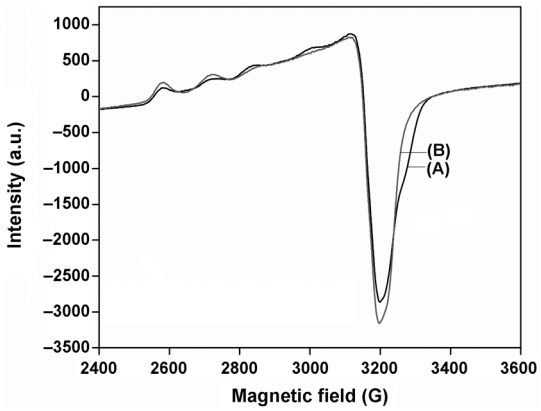
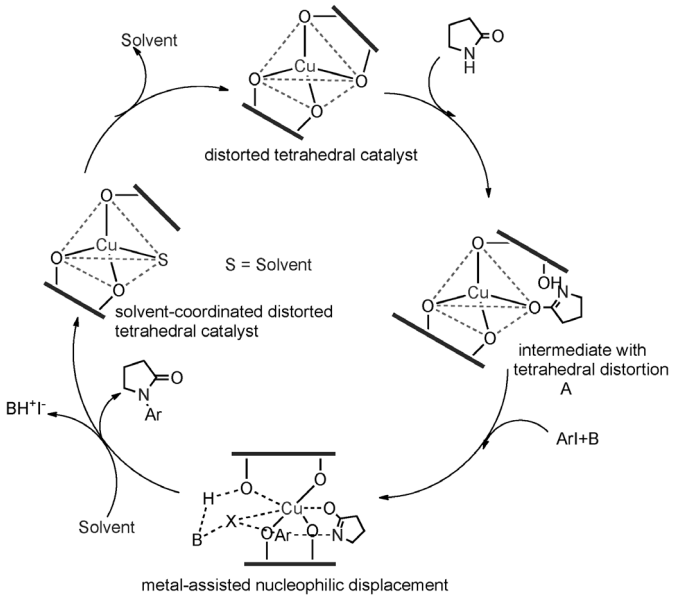


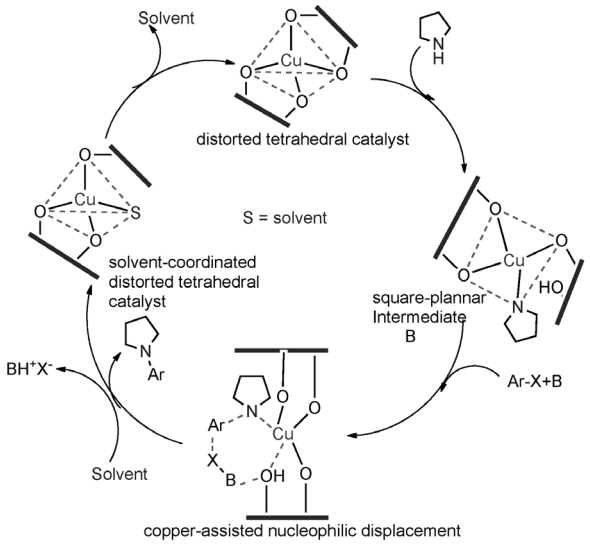
Figure 9. Comparative EPR study of the catalyst in water in the presence (A) and the absence (B) of a cyclic amide with base.

catalyst is not binding to the amide, which is the initial step of the reaction (Scheme 5) and hence in water the amide coupling did not occur. Moreover, the XPS spectrum of the catalyst at the intermediate stage of the amide coupling in water does not show any N 1s line, suggesting no Cu–amide interaction is formed. To validate this finding, a reaction of



Scheme 5. Probable mechanism of the amide coupling. Ar = aryl.

bromobenzene in water in the presence of 2-pyrrolidinone was performed and 15% of phenol was obtained as product. This indicates that in this case water is activated by the catalyst over the amide. So, on the basis of above experiments we have proposed the following mechanism (Schemes 5 and 6) in case of the amide and the amine coupling.



Scheme 6. Probable mechanism of the amine coupling.

In the amide coupling, the copper catalyst activates the amide through the oxygen centre or the N-C-O π-electron cloud. The coordination of a bulky ligand like an amide results in a tetragonally distorted copper–amide intermediate. Then, the iodoaryl electrophile comes close to the metal centre and in the presence of a base, copper-assisted nucleophilic displacement takes place. The extent of the tetragonal distortion is then reduced by the expulsion of the product from the metal coordination environment, which leads to a solvent-coordinated distorted tetrahedral catalyst. The catalyst is then regenerated through the exclusion of the solvent to take part in the next reaction cycle.

On the other hand, a cyclic amine is coordinated through the nitrogen centre, which leads to a square-planar copper–amine intermediate. The bromo- or iodoaryl electrophile interacts with the metal centre and in the presence of a base, nucleophilic displacement takes place. The catalyst attained its original distorted tetrahedral geometry through the release of the product from its coordination environment.

The morphology of the Cu catalyst remained unaltered before and after the reaction as revealed by SEM images (see Figure S4 a–c) and the XRD pattern (see Figure S5).

Conclusion

We have developed a convenient and efficient protocol for the selective N-arylation of a cyclic amide and an amine in DMF and water, respectively. We have outlined possible re-

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action pathways for both reactions based on detailed EPR, XPS, UV-DRS and ICP-MS analysis of the catalyst at different stages of the reaction. A logical explanation for the preferential reaction of the amide in DMF over water was also provided. This strategy has been successfully employed for the synthesis of several scaffolds of potent therapeutically active arenes bearing cyclic amide and amine moieties at two ends (Figure 1). To the best of our knowledge, we are not aware of any report demonstrating such solvent-selective N-arylation of amides and amines and such an efficient synthesis of the therapeutically important amide, amine-substituted arenes by a two-step procedure from readily available materials. The other attractive features of this procedure are the simple operation, the recyclability of the catalyst, high yields and the scope for versatile manipulations. We believe this strategy will find useful applications in organic synthesis.

Experimental Section

IR spectra were taken as thin films for liquid compounds and as KBr pellets for solids. NMR spectra were recorded at 300 and 500 MHz for ^{1}H NMR spectra and at 75 and 125 MHz for ^{13}C NMR spectra in $CDCl_3$ solutions. XPS measurements were performed with a spectrometer fitted with an EA125 hemispherical analyser and a monochromatised Al KR (1486.6 eV) source. X-Band EPR measurements were carried out at 77 K. The Cu/Al_2O_3 catalyst was prepared following our procedure reported earlier.[8a]

Representative experimental procedure for the coupling of 2-pyrrolidinone and iodobenzene to 1-phenylpyrrolidin-2-one (Table 3, entry 1): In a 10 mL round bottom flask, a mixture of iodobenzene (204 mg, 1 mmol), 2-pyrrolidinone (102 mg, 1.2 mmol), K_3PO_4 (425 mg, 2 mmol), Cu/Al_2O_3 (100 mg, 5 mol%) and DMF (3 mL) was heated at 110°C for 12 h (TLC) in an oil bath. The reaction mixture was then allowed to cool down and was extracted with EtOAc (3×20 mL). The extract was washed with water (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by column chromatography over silica gel (hexane/ethyl acetate 80:20) to provide the pure 1-phenylpyrrolidin-2-one as a white solid (148 mg, 92%). M.p. 68–69°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.11–2.17 (m, 2H), 2.58–2.61 (m, 2H), 3.83–3.86 (m, 2H), 7.13 (t, J=7.0 Hz, 1H), 7.34–7.37 (m, 2H), 7.59–7.61 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ= 18.1, 32.8, 48.9, 120.0 (2C), 124.6, 128.9 (2C), 139.5, 174.3 ppm; IR (KBr): $\tilde{\nu}$=3059, 2916, 2898, 1680, 1171 cm^{-1}; HRMS: m/z calcd for $C_{10}H_{12}NO$: 162.0193 $[M+H]^+$; found: 162.0194.

This procedure was followed for all the reactions listed in Table 3. Many of these compounds are not reported earlier and these unknown compounds were characterised properly by their spectroscopic and spectrometric data (IR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS). The known compounds were identified by comparison of their spectroscopic and spectrometric data with those reported earlier.[21] All these data are provided in the Supporting Information.

Representative experimental procedure for the coupling of 1-(4-bromophenyl)pyrrolidin-2-one and morpholine to 1-(4-morpholinophenyl)pyrrolidin-2-one (Table 4, entry 3): In a 10 mL round bottom flask, a mixture of 1-(4-bromophenyl)pyrrolidin-2-one (240 mg, 1 mmol), morpholine (174 mg, 2 mmol), K_3PO_4 (425 mg, 2 mmol), Cu/Al_2O_3 (100 mg, 5 mol%) and water (4 mL) was heated at 100°C for 12 h (TLC) in an oil bath. The reaction mixture was then allowed to cool to room temperature and after evaporation of water under vacuum the product was extracted with EtOAc (3×20 mL). The extract was washed with brine (2×10 mL). The organic phase was dried over Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography over silica gel (hexane/ethyl acetate 30:60) to provide the pure 1-(4-morpholinophenyl)-pyrrolidin-2-one as a white solid (212 mg, 86%),. M.p. 102–104°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.10–2.16 (m, 2H), 2.57 (t, J=8.0 Hz, 2H), 3.11 (t, J=5.0 Hz, 4H), 3.80–3.85 (m, 6H), 6.90 (d, J=9.0 Hz, 2H), 7.48 ppm (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.0, 32.5, 49.2 (2C), 49.6, 66.9 (2C), 116.1 (2C), 121.6 (2C), 132.1, 148.5, 174.2 ppm; IR (KBr): $\tilde{\nu}$=2975, 2842, 1679, 1515, 1226, 833 cm^{-1}; HRMS: m/z calcd for $C_{14}H_{19}N_2O_2$: 247.1441 $[M+H]^+$; found: 247.1442.

This procedure was followed for all the reactions listed in Table 4. All of these compounds are new and were not reported earlier. They were characterised properly by their spectroscopic and spectrometric data (IR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS). All these data are provided in the Supporting Information.

Although these procedures were described with a 1 mmol scale, 10 mmol scale reactions also provided uniform results.

Recyclability of the catalyst: After workup the residual catalyst was washed with water (3 mL), EtOAc (3 mL) and acetone (4 mL). The solid was then dried at 100°C for 8 h for further use. The catalyst was recycled five times without appreciable loss of activity.

Preparation of the amide complex in DMF: A mixture of the Cu/Al_2O_3 catalyst (100 mg, 5 mol%) and 2-pyrrolidinone (102 mg, 1.2 mmol) in DMF (3 mL) was heated at 110°C for 8 h. The mixture was cooled to room temperature and the supernatant liquid was filtered off. The dirty brownish solid residue was thoroughly washed with water (4 mL), ethyl acetate (4 mL) and acetone (3 mL) and dried to get the intermediate A.

Preparation of the amine complex in water: A mixture of the Cu/Al_2O_3 catalyst (100 mg, 5 mol%) and morpholine (174 mg, 2 mmol) in water (4 mL) was heated at 100°C for 8 h. The mixture was cooled to room temperature and the supernatant liquid was filtered off. The orange solid residue was thoroughly washed with water (4 mL), ethyl acetate (3 mL) and acetone (3 mL) and dried to get the intermediate B.

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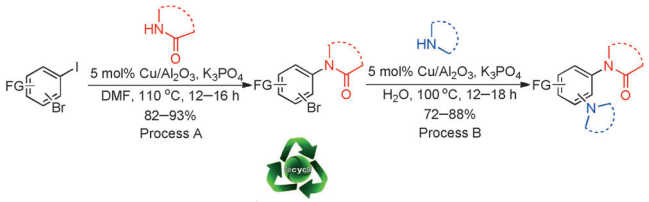

One over the other: A selective N-arylation of cyclic amides and amines in DMF and water, respectively, catalyzed by Cu^{II}/Al_2O_3 has been achieved (see scheme). This protocol has been employed for the synthesis of a library of arenes bearing cyclic amide and amine moieties at two ends including a few scaffolds of therapeutic importance. The mechanism has been established based on detailed spectroscopic studies (FG = functional group).

Catalysis

*D. Kundu, S. Bhadra, N. Mukherjee, B. Sreedhar, B. C. Ranu**.... ▮▮▮▮–▮▮▮▮

Heterogeneous Cu^{II}-Catalysed Solvent-Controlled Selective N-Arylation of Cyclic Amides and Amines with Bromo-iodoarenes

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