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N-Alkylation of poor nucleophilic amines and derivatives with alcohols by a hydrogen autotransfer process catalyzed by copper(II) acetate: scope and mechanistic considerations

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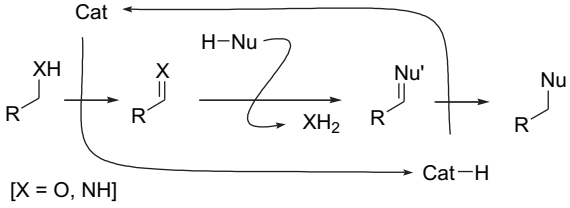
ABSTRACT

Copper(II) acetate is a versatile, cheap and simple catalyst for the selective N-monoalkylation of amino derivatives with poor nucleophilic character, such as aromatic and heteroaromatic amines as well as carboxamides, phosphinamides, sulfonamides, and phosphazenes, using in all cases primary alcohols as initial source of the electrophiles, through a hydrogen autotransfer process. In the case of sulfonamides, the monoalkylation process followed by a naphthalene-catalyzed reductive deprotection gives primary amines, which is an indirect alternative to the direct monoalkylation of ammonia. A study of the reaction using deuterium labelled reagents was performed, indicating that the dehydrogenation and hydrogenation steps do not take placed on the same copper-atom coordination sphere, with the condensation step occurring out of the dehydrogenating catalytic species.

1. Introduction

The hydrogen autotransfer,[1] also called borrowing-hydrogen, is an old reaction[2] with a great interest nowadays in C–C bond formation processes (Scheme 1).[3] This interest leans now towards the use of amines, and other nitrogenated compounds, as nucleophiles to yield the corresponding *N*-alkylated products.[4] The reason of this change takes root in the great variety of amines present in Nature, as well as their relevant importance in the pharmaceutical and agrochemical industries as usual building blocks. The extremely high advantage of this N-alkylation process, compare with classical protocols,[5] is based, on one hand, in the simplicity of the protocol and, on the other hand, in the avoidance of using either mutagenic alkyl halides, sulfates, etc., or difficult storable carbonyl compounds, as well as the reduction of wastes.

Many different complexes have been proposed as catalysts for this thrifty process.[6] However, only a few examples of copper-containing catalysts have been proposed for this reaction and all of them are used in heterogeneous phase. Thus, a copper–chromite catalyst ($CuCr_2O_4$–$BaCr_2O_4$) has been used in the N-alkylation of high nucleophilic aliphatic amines with alcohols in the presence of hydrogen (125 atm) at 180–250 °C with modest results (lower than



Scheme 1. General scheme for a hydrogen autotransfer process.

70% yield).[7] Other catalysts such as CuO–Cr_2O_3 on silica[8] or CuO on alumina[9] have been also tested in similar conditions giving better results, in all cases with the temperature being higher than 220 °C.

The obtained results using copper(II) carboxylates were more interesting. For instance, the reaction of dimethylamine with dodecylalcohol at 210 °C using copper stearate gave the expected tertiary amine in 40% yield, while the same reaction failed using copper acetylacetonate.[10] A further improvement of the system was the use of mixtures from 5:1 to 8:1 of $Cu(C_{17}H_{35}CO_2)_2$ and $Ni(C_{17}H_{35}CO_2)_2$, which increased the above yield up to 72%.[10,11] It should be pointed out that the presence of other stearate salts such barium and calcium derivatives, permitted to increase the yields up to 99%.[12] This colloidal catalytic system, presenting Cu–Ni nanoparticles of about 125 nm, could be recovered by a complicated distillation of all reagents and products.[13]

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Notwithstanding these partially successful examples, there are practically no studies on the synthetic possibilities of other most simpler and cheaper copper salts, for the reaction with less nucleophilic aromatic and heteroaromatic amines,[14] amides[15–17] and phosphazene derivatives[18] having been unexplored.[19] With this paper, we would like to fill this lack, presenting copper(II) acetate as a simple, selective and economical catalyst for the N-alkylation of a wide range of poor nucleophilic nitrogen-containing derivatives using alcohols as source of electrophiles.[20]

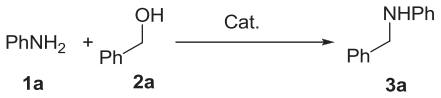
2. Results and discussion

2.1. N-Alkylation of amines

Initially, the reaction outlined in Table 1 was used as the standard one for the reaction-condition optimization. Firstly, we proceeded to perform the reaction using nearly equimolecular amount of aniline and benzyl alcohol catalyzed by 10 mol % of different catalysts in the presence of 1 equiv of base in dioxane.

The first tested catalyst was aluminium isopropoxide, which rendered the expected amine but with a modest yield (entry 1 in Table 1). Then, other catalysts were tested with cobalt, copper, ruthenium[3] and palladium giving the best results (compare entries 1–8 in Table 1). After that, the reduction of the catalyst amount to 1 mol % for this set of catalyst only produces slightly changes on the results, except for copper salt. In this case, the compound **3a** was obtained in practically quantitative yield (compare entries 9–12). Then, we focused on the copper salt effect, and it was clear that copper(II) acetate is better catalyst than other tested salts (compare results of entries 13–16). The yield using KOH as base was similar to that using ^{t}BuOK but superior to either using less basic K_2CO_3 or substoichiometric amounts of ^{t}BuOK (entries 17–19). Other solvents or temperatures did not improve the aforementioned result (compare entries 10 and 20–23), with the increase of the amount of alcohol (400 mol %) decreasing only the reaction time to one day (96% of **3a**).

Table 1
Reaction-condition optimization

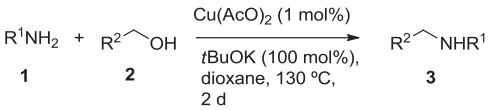


Entry	Cat. (mol %)	Base	Solvent	T (° C)	t (d)	Yield **3a**[a] (%)
1	$Al(O^iPr)_3$ (10)	^{t}BuOK	Dioxane	130	2	30
2	VCl_2 (10)	^{t}BuOK	Dioxane	130	2	5
3	$Fe(acac)_3$ (10)	^{t}BuOK	Dioxane	130	2	<5
4	$CoCl_2$ (10)	^{t}BuOK	Dioxane	130	2	83
5	$NiCl_2$ (10)	^{t}BuOK	Dioxane	130	2	<5
6	$Cu(AcO)_2$ (10)	^{t}BuOK	Dioxane	130	1	92
7	$RuCl_2(DMSO)_4$ (10)	^{t}BuOK	Dioxane	130	2	85
8	$Pd(AcO)_2$ (10)	^{t}BuOK	Dioxane	130	2	80
9	$CoCl_2$ (1)	^{t}BuOK	Dioxane	130	2	30
10	$Cu(AcO)_2$ (1)	^{t}BuOK	Dioxane	130	2	>99
11	$RuCl_2(DMSO)_4$ (1)	^{t}BuOK	Dioxane	130	2	82
12	$Pd(AcO)_2$ (1)	^{t}BuOK	Dioxane	130	2	80
13	$CuCl_2$ (1)	^{t}BuOK	Dioxane	130	2	40
14	$Cu(TfO)_2$ (1)	^{t}BuOK	Dioxane	130	2	60
15	CuCl (1)	^{t}BuOK	Dioxane	130	2	50
16	CuI (1)	^{t}BuOK	Dioxane	130	4	60
17	$Cu(AcO)_2$ (1)	KOH	Dioxane	130	2	95
18	$Cu(AcO)_2$ (1)	K_2CO_3	Dioxane	130	2	15
19	$Cu(AcO)_2$ (1)	^{t}BuOK[b]	Dioxane	130	2	40[c]
20	$Cu(AcO)_2$ (1)	^{t}BuOK	PhMe	130	2	84
21	$Cu(AcO)_2$ (1)	^{t}BuOK	DMSO	130	2	15
22	$Cu(AcO)_2$ (1)	^{t}BuOK	Dioxane	170	1	95
23	$Cu(AcO)_2$ (1)	^{t}BuOK	Dioxane	90	2	48

[a] Reaction performed using 130 mol % of **2a** and 100 mol % of base and isolated yields after column chromatography (silica gel: hexane/ethyl acetate).
[b] Reaction performed using 10 mol %.
[c] Benzylidene aniline (35%) was detected.

Once the reaction conditions were optimized, we faced the problem of the reaction scope using poor electrophilic amines (Table 2), starting by changing the electronic nature of substituent on the benzylic alcohol **2**. The reaction using different 4-substituted benzylic alcohols gave nearly the same results (Table 2, entries 1, 2 and 4), even using a polisubstituted derivative (entry 3), independent of the electron-donating or withdrawing character of the substituent. However, it should be pointed out that in the case of the 4-chlorobenzyl alcohol (entry 4), the dehalogenation process occurred as a by-reaction, decreasing the yield of the expected compound **3c**. In the case of the using sensitive furan-2-ylmethanol (entry 5) as electrophilic partner, the yield was somehow lower. The obtained yields using aliphatic alcohols were even lower (entries 6 and 7).

Table 2
Copper(II) acetate catalyzes the N-alkylation of aromatic amines



Entry	R^1	R^2	Product	Yield[a] (%)
1	Ph	Ph	**3a**	>99
2	Ph	4-$MeOC_6H_4$	**3b**	85
3	Ph	3,4-$(OCH_2O)C_6H_3$	**3c**	90
4	Ph	4-ClC_6H_4	**3d**	60[b]
5	Ph	2-furyl	**3e**	55
6	Ph	$Me(CH_2)_5$	**3f**	7
7	Ph	$(CH_2)_5CH$	**3g**	40
8	4-$MeOC_6H_4$	Ph	**3h**	>99
9	2-$MeOC_6H_4$	Ph	**3i**	90[c]
10	3-ClC_6H_4	Ph	**3j**	99
11	2-Pyridyl	Ph	**3k**	>99[d]
12	2-Pyridyl	4-$MeOC_6H_4$	**3l**	>99[d]
13	2-Pyridyl	4-MeC_6H_4	**3m**	>99
14	2-Pyridyl	4-ClC_6H_4	**3n**	90[e]
15	2-Pyridyl	2-$MeOC_6H_4$	**3o**	>99
16	2-Pyridyl	$Me(CH_2)_5$	**3p**	69[f]
17	4-Pyridyl	Ph	**3q**	>99
18	4-Pyridyl	3,4-$(OCH_2O)C_6H_3$	**3r**	>99
19	2-Pyrimidyl	Ph	**3s**	>99
20	2-Pyrimidyl	3,4-$(OCH_2O)C_6H_3$	**3t**	95
21	5-Methylthiazol-2-yl	Ph	**3u**	0[f]
22	^{t}Bu	Ph	**3v**	0[f]

[a] Reaction performed using 130 mol % of **2** and isolated yields after column chromatography (silica gel: hexane/ethyl acetate).
[b] Compound **3a** (30%) was isolated.
[c] After 5 days.
[d] After 1 day.
[e] After 1 day, and 8% of **3k** detected.
[f] After 6 days.

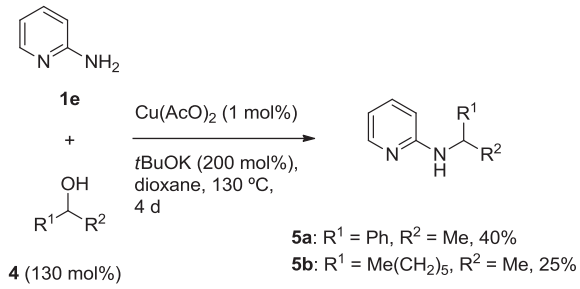
As in the previous cases, when different substituted anilines were used as nucleophiles the results were practically the same independent of the electronic nature of substituent (entries 8–10 in Table 2). It should be pointed out, however, that the reaction with more hindered 2-substituted anilines took place in a longer reaction time and the dehalogenation side-reaction of the 3-chloroaniline derivative did not occur here (entry 10), as in the case of the chlorinated alcohol (entry 4). The reaction can also be performed using electron-poor heteroaromatic amines: for instance, the reaction with the 2-pyridyl derivative gave quantitative yield, practically independent of the benzylic alcohol **2** used (entries 11–15). A small amount of the by-product **3k** was detected by GC–MS in the case of using 4-chlorobenzyl alcohol as electrophile (entry 14). As in the previous cases, the reaction could be also carried out with aliphatic alcohols, such as 1-heptanol, although in

this case the reaction time should be increased up to 6 days and the yields was somehow lower (entry 16).

The position of this extra-nitrogen atom in the aromatic ring of the nucleophilic partner, as well as the existence of two nitrogen atoms, seems to have no influence on these good results (entries 17–20 in Table 2). By the contrary, the reaction with electron-rich heteroaromatic amines, such as thiazolamine or highly nucleophilic *tert*-butylamine failed after six reaction days (entries 21 and 22).

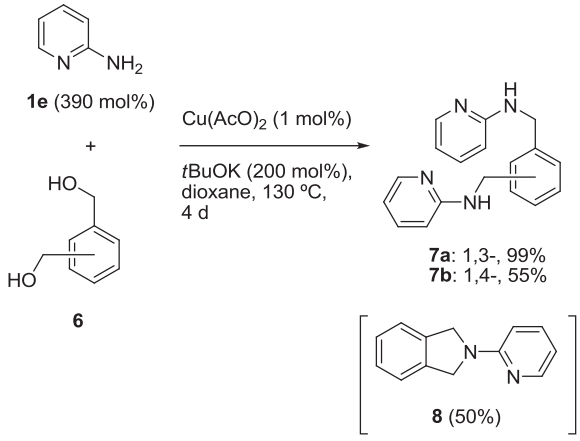
The reaction of the secondary *N*-methylaniline with benzyl alcohol failed after 6 days under standard conditions, showing the selectivity of the process, and permitting to perform the alkylation of primary anilines in the presence of secondary ones.

The same protocol could be applied to secondary alcohols as electrophiles, as it is depicted in Scheme 2. However, the reaction time should be increased compared with the standard one presented in Table 2, and the obtained yields were accountability lower than for primary alcohols, independently of the use of aromatic or aliphatic ones **4**.



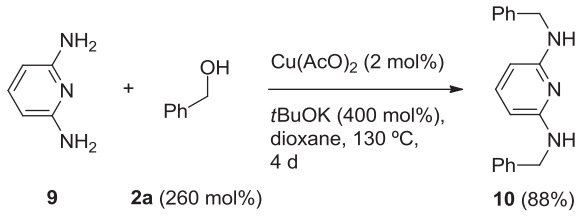
Scheme 2. N-Alkylation of the amine **1e** using secondary alcohols **4**.

We studied then the use of 1,*n*-di(hydroxymethyl)benzene derivatives **6** in their reaction with pyridin-2-amine (**1e**). The reaction using stoichiometric amounts of amine (200 mol %) gave a mixture of products including compounds of type **7** as well as products containing only one unit of pyridine. However, when the amount of amine **1e** was increased to 390 mol % only one product arising from the hydrogen autotransfer process was isolated. The reaction using 1,3-(dihydroxymethyl)benzene gave the product **7a** with a excellent yield (Scheme 3). However, the related 1,4-product **7b** was obtained with lower yield. These compounds have a special interest since they could be used as chelating agent for different metal atoms[21] and for hydrogen-bonding recognition of molecules.[22] The reaction using 1,2-(dihydroxymethyl)benzene (**6a**) gave the cyclic compound 2-(pyridin-2-yl)isoindoline (**8**) in 50% yield and nothing of the corresponding derivative **7**, with the use of stoichiometric amount of amine **1e** having influence only on the final chemical yield (25%), but not in the products detected.



Scheme 3. N-Alkylation of the amine **1e** using diols **6**.

Once we found possible the dialkylation process using diols, we faced the problem of using diamines as nucleophiles.[23] The reaction of the diamine **9** with a large excess of benzyl alcohol (520 mol %) gave the expected compound **10** with good results (Scheme 4). As in the aforementioned case, this type of subunit has an important role in process of self-assembly.[24]

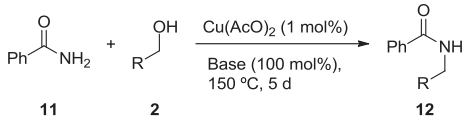


Scheme 4. N-Alkylation of diamine **9**.

2.2. N-Alkylation of amides

Once the catalytic activity and scope of the copper(II) acetate was demonstrated, we faced the problem of using other less nucleophilic amino derivatives such as amides, starting from carboxamides.[15] The reaction using acetamide failed under standard conditions, recovering the initial amide practically in quantitative yields, and we attributed this results to the presence of acidic protons at the α-position. Therefore, we changed the initial amide by benzamide **11** (Table 3).

Table 3
N-Alkylation of benzamide

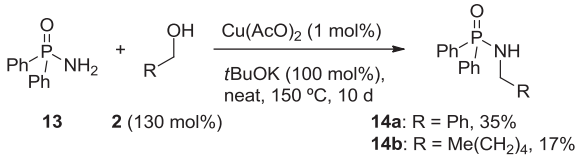


Entry	R	Base	Solvent	No.	Yield[a] (%)
1	Ph	^{t}BuOK	Dioxane	**12a**	40
2	Ph	^{t}BuOK	PhMe	**12a**	85
3	Ph	^{t}BuOK	—	**12a**	40
4	Ph	K_2CO_3	PhMe	**12a**	60
5	Ph	NaAcO	PhMe	**12a**	35
6	3,4-$(OCH_2O)C_6H_3$	^{t}BuOK	PhMe	**12b**	55
7	1-Naphthyl	^{t}BuOK	PhMe	**12c**	40

[a] Reaction performed using 130 mol % of **2** and isolated yields after column chromatography (silica gel: hexane/ethyl acetate).

The reaction under standards conditions using benzylic alcohol (**2a**) gave a modest yield, which could be improved by using toluene as solvent, with other reaction media (compare entries 1–3 in Table 3), bases (entries 4 and 5) and amounts of bases giving lower yields. The reaction could be performed with other benzylic alcohols giving modest results (entries 6 and 7), due to the presence of different hydrolysis by-products.

Then, we perform the N-alkylation reaction of phosphinamide[16] **13** (Scheme 5). The reaction under different reaction conditions failed, and only in the case of using solvent-free conditions the expected alkylated product **14** could be isolated, with different amount of the amine arising from the hydrolysis. The direct acidic

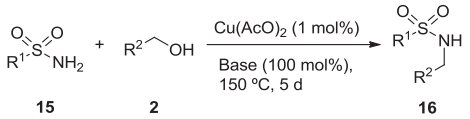


Scheme 5. N-Alkylation of phosphinamide **13**.

hydrolysis of compounds **14** using hydrochloric acid in methanol to give only the corresponding amine[25] did not improve the above yields accountably.

The above low yields were due, in part, to the hydrolysis process and/or a nucleophilic substitution process by the base on the nucleophilic amide. For this reason, we studied the reaction with sulfonamides[17] (which are difficult to be hydrolyzed and their electrophilic character is lower than the previous amides) to give the corresponding *N*-alkylated sulfonamides[26] (Table 4).

Table 4
N-Alkylation of sulfonamides

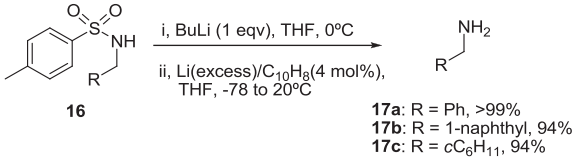


Entry	R^1	R^2	Solvent	Base	No.	Yield[a] (%)
1	4-MeC_6H_4	Ph	Dioxane	^{t}BuOK	**16a**	40
2	4-MeC_6H_4	Ph	PhMe	^{t}BuOK	**16a**	92
3	4-MeC_6H_4	Ph	PhMe	K_2CO_3	**16a**	71
4	4-MeC_6H_4	Ph	—	K_2CO_3	**16a**	85
5	4-MeC_6H_4	4-$MeOC_6H_4$	PhMe	^{t}BuOK	**16b**	85
6	4-MeC_6H_4	3-ClC_6H_4	PhMe	^{t}BuOK	**16c**	>99
7	4-MeC_6H_4	3,4-$(OCH_2O)C_6H_3$	PhMe	^{t}BuOK	**16d**	>99
8	4-MeC_6H_4	1-Naphthyl	PhMe	^{t}BuOK	**16e**	94
9	4-MeC_6H_4	$(CH_2)_5CH$	PhMe	^{t}BuOK	**16f**	84
10	4-$MeOC_6H_4$	Ph	PhMe	^{t}BuOK	**16g**	78
10	4-$MeOC_6H_4$	Ph	PhMe	K_2CO_3	**16g**	81
11	4-$MeOC_6H_4$	3,4-$(OCH_2O)C_6H_3$	PhMe	^{t}BuOK	**16h**	89
12	Me	Ph	PhMe	^{t}BuOK	**16i**	93

[a] Reaction performed using 130 mol % of **2** and isolated yields after column chromatography (silica gel: hexane/ethyl acetate).

Firstly, the reaction conditions were optimized,[19] finding that the best conditions were obtained when a strong base in toluene was used (Table 4, compare entries 1–4). Under these conditions other amides and alcohols were submitted to the alkylation process, obtaining similar results independently on the used either aliphatic or aromatic sulfonamides or alcohols (entries 5–12).

Finally, the above sulfonamides **16** were deprotected to give the corresponding primary amines **17** with excellent results,[27] by a protocol, which implied the initial deprotonation of the amide followed by a reductive cleavage of N–S bond through a naphthalene-catalyzed lithiation[28] reaction (Scheme 6). The whole process, N-alkylation of sulfonamide and deprotective reduction, is an interesting alternative to the direct mono alkylation of ammonia, which is a difficult task using the hydrogen autotransfer strategy.[29]

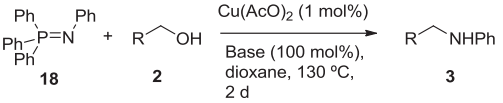


Scheme 6. N-Deprotection of sulfonamides **16**.

2.3. N-Alkylation of amines by a indirect aza-Wittig process

The indirect aza-Wittig reaction could be carried out using this strategy,[18] and to study the scope of copper(II) acetate as catalyst for different hydrogen autotransfer process, we faced the possible utilization of it in the reaction of N-(triphenylphosphoranylidene) aniline (**18**) with different primary alcohols to give the corresponding secondary amines **3** (Table 5).

Table 5
Copper(II) acetate catalyzes the N-alkylation process using phosphazene **18**



Entry	R^2	Base	Product	Yield[a] (%)
1	Ph	—	**3a**	10
2	Ph	K_2CO_3	**3a**	15
3	Ph	KOH	**3a**	25
4	Ph	^{t}BuOK	**3a**	77
5	4-$MeOC_6H_4$	^{t}BuOK	**3b**	90
6	3,4-$(OCH_2O)C_6H_3$	^{t}BuOK	**3c**	95
7	4-ClC_6H_4	^{t}BuOK	**3d**	46[b]
8	2-furyl	^{t}BuOK	**3e**	62
9	$Me(CH_2)_5$	^{t}BuOK	**3f**	65
10	*c*-C_6H_{11}	^{t}BuOK	**3g**	42

[a] Reaction performed using 130 mol % of **2** and isolated yields after column chromatography (silica gel: hexane/ethyl acetate).
[b] Compound **3a** (30%) was isolated.

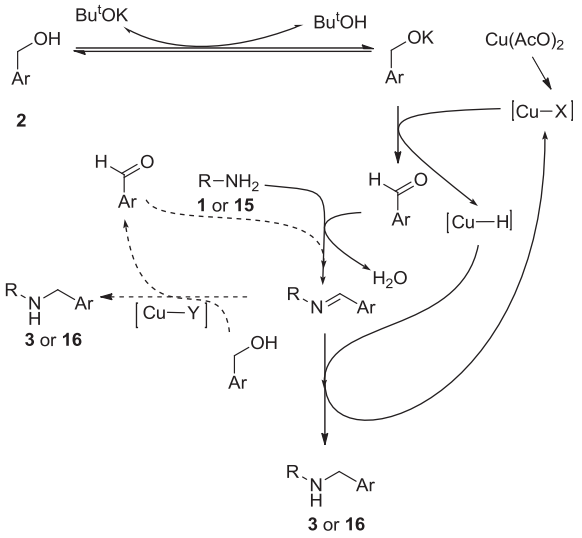
The reaction of compound **18** with benzyl alcohol gave the expected amine **3a** with very low yield in the absence of base. The use of stoichiometric amounts of bases such as potassium carbonate or hydroxide did not produce the expected improvement in the results. However, the reaction with potassium *tert*-butoxide gave the amine **3a** with good chemical yield (compare entries 1–4). It should be pointed out that the same reaction but using substoichiometric amounts of base gave worse results. The reaction could be performed with other benzylic alcohols having electron-donating groups with similar chemical yields (entries 5 and 6). In the case of using 4-chlorobenzil alcohol, together with the expected product **3d** an important amount of dehalogenated amine **3a** was also isolated (entry 7), as in the of the direct alkylation of aniline. The reaction gave satisfactory yields when sensitive furan-2-ylmethanol or aliphatic alcohols were used as initial source of electrophile (entries 8–10).

2.4. Mechanistic considerations

Finally we try to understand the possible mechanism pathway. For the case of using sulfonamides as nucleophile in air at 150 °C in the presence of K_2CO_3, a tentative mechanism has been proposed.[19] The formation of *N*,*N*′-ditosylbenzimidamide, arising from tosylamide and oxidation of benzyl alcohol to benzoic derivative was detected only in the presence of base or air, and it was assumed that this compound was a stabilizer of the copper catalyst. In our reaction conditions, we could not detected the imidamide by neither ^{1}H NMR nor GC–MS spectra.

The real role of the base is not clear but it seems to be connected with the deprotonation of the primary alcohol and to force the dehydrogenation step, forming the aldehyde, since the reaction of *para*-toluenesulfonamide with benzyl alcohol failed in the absence of ^{t}BuOK. However, the same reaction using the in situ prepared lithium alkoxide (by deprotonation of benzyl alcohol with buthyllithium) yields the expected product **16a** with good yield. Moreover, when the reaction was performed using an equimolecular amount of benzaldehyde and benzyl alcohol and in the absence of base, **16a** was obtained in 75% after 9 days, indicating that two catalytic cycles might be possible. The initial one would take place in the absence of aldehyde and would need the presence of base. The second possible catalytic cycle would proceed when there is aldehyde in the media. It should be pointed out that the reaction of *para*-toluenesulfonamide (**15a**) with benzaldehyde and benzyl alcohol in the presence of ^{t}BuOK, but in the absence of copper salt, failed, yielding only the corresponding sulfonylimine. The reaction

of an equal mixture of 1-naphthylmethanol (60 mol %) and α,α-dideuterobenzyl alcohol (60 mol %) with of *para*-toluenesulfonamide (**15a**, 100 mol %) under standard conditions gave a mixture of the related monodeuteated products **16** at the benzylic position, with the incorporation of deuterium in the benzyl sulfonamide **16a′** being about 90% and in the naphthyl derivative **16e′** being only about 70%, according to GC–MS spectrum. This indicates that between the copper-catalyzed steps of dehydrogenation of alcohol and of the hydrogenation of imine there is one step, which occurs out of the cooper coordination sphere, with the condensation reaction being this step (Scheme 7, Fig. 1).



Scheme 7. Tentative catalytic cycles. The main cycle is drawn using plain arrows and the secondary one in dashed arrows.

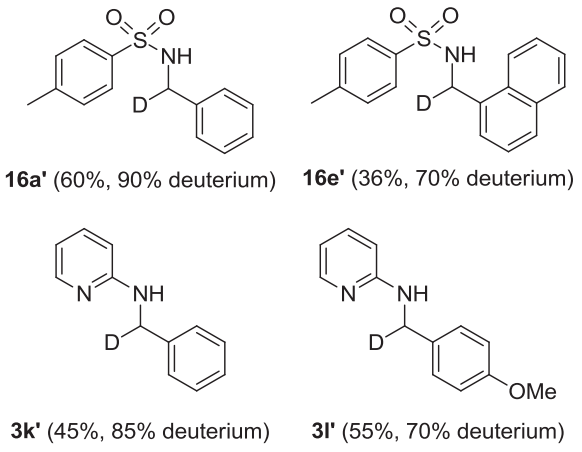


Fig. 1. Detected deuterated compounds.

In the case of using amines as nucleophiles, we found that the reaction between the amine **1e** and benzyl alcohol (**2a**) failed in the absence of ^{t}BuOK. As in the previous case, the reaction using a mixture of alcohol and aldehyde did not need the presence of base, indicating the presence of at least two parallel mechanism pathways. Moreover, when a equimolecular amount of α,α-dideuterobenzyl alcohol (60 mol %) and 4-methoxybenzyl alcohol (60 mol %) was reacted with 2-aminopyridine (**1e**) a similar mixture of mono deuterated products **3k′** (85% deuterium incorporation) and **3l′** (70% deuterium incorporation) were detected and isolated (Fig. 2).

This labelled experiments showed that after the dehydrogenation step to form the corresponding aldehyde, the condensation with amine also took place out of copper coordination sphere, the imine coming back to the copper hydride (deuteride) complex to be reduced. It should be pointed out that dioxane could act also as initial hydrogen source[30] for the formation of the corresponding metal hydride (Scheme 7).

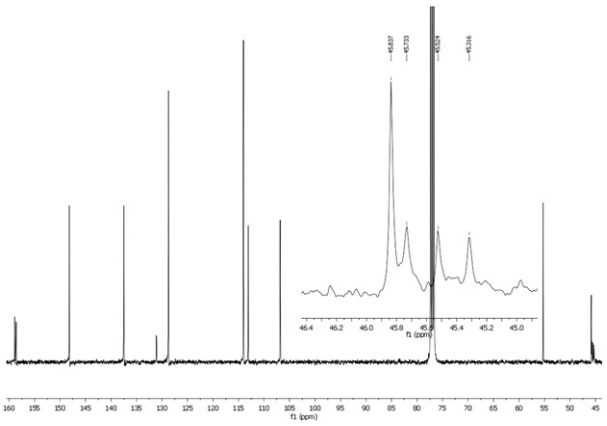


Fig. 2. ^{13}C NMR of compound **3l′**.

Finally, in order to exclude the reversibility of the reaction as the cause of labelling product processes, the reaction of alkylated amine **3l** with α,α-dideuterobenzyl alcohol under standards conditions was conducted and, after three days of reaction time, the initial amine **3l** was recovered unchanged (amine **3l′** was not detected by GC–MS spectrum), meanwhile the alcohol was transformed to deuteriated benzaldehyde (PhCDO).

3. Conclusion

In conclusion, cheap and commercially available copper(II) acetate has been shown to be an active, stable, versatile and highly selective catalyst for the selective monoalkylation of aromatic amines and amides thought a hydrogen autotransfer process. The simplicity of the protocol and the wide scope of substrates, which could be used, permitted us to anticipate a good future for the process shown in this article not only in the academia but also in industries. The combined alkylation–deprotection process is an alternative to the direct monoalkylation of ammonia.

4. Experimental section

4.1. General Information

Melting points were obtained with a Reichert Thermovar apparatus. NMR spectra were recorded on a apparatus (300 MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$ as a solvent and TMS as internal standard for ^{1}H and ^{13}C; chemical shifts are given in δ (parts per million) and coupling constants (J) in hertz. Mass spectra (EI) were obtained at 70 eV on a spectrometer, giving fragment ions in m/z with relative intensities (%) in parentheses. Thin layer chromatography (TLC) was carried out on plates coated with a 0.2 mm layer of silica gel; detection by UV_{254} light, staining with phosphomolybdic acid [25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2 \cdot 4H_2O$, 60 mL of concentrated H_2SO_4 and 940 mL H_2O]. Column chromatography was performed using silica gel 60 of 35–70 mesh. All reagents were commercially available and were used as received.

4.2. General procedure for N-alkylation of amines 1

To a solution of $Cu(OAc)_2$ (0.025 mmol, 0.0046 g) and potassium *tert*-butoxide (0.175 g, 2.5 mmol) in anhydrous dioxane (3 mL), the

corresponding amine **1** (2.5 mmol) or the triphenylphosphoranylidenaniline **18** (2.5 mmol) and the correspondent alcohol **2** or **4** (3.75 mmol) were added successively under inert argon atmosphere. After 2 or 5 days of reaction at 130 °C (see Table 2 and Scheme 2), the resulting mixture was hydrolyzed with a saturated solution of ammonium chloride (10 mL). The mixture was extracted with AcOEt (3×10 mL) and washed with brine (10 mL), after drying with anhydrous $MgSO_4$, was filtered on Celite and the solvents were removed under low pressure(15–18 Torr). The resulting mixture was purified by column chromatography (if needed).

*4.2.1. N-Benzylbenzenamine (**3a**)*[14f]. Yellow oil. t_R 15.9; R_f 0.90 (hexane/ethyl acetate 1:1); IR (film): 3404, 3053, 1601, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (s, 1H, NH), 4.30 (s, 2H, CH_2), 6.61 (d, 2H, J=7.5, NCCH), 6.70 (t, 1H, J=7.3, NCCHCHC*H*), 7.15–7.20 (m, 2H, NCCHC*H*), 7.25–7.40(m, 5H, CH_2CC*HCHCH*); ^{13}C NMR ($CDCl_3$) δ 48.20, 112.80 (2C), 117.50, 127.20, 127.40 (2C), 128.60 (2C), 129.20 (2C), 139.40, 148.10; MS (EI) m/z 183 (M^+, 42%), 182 (27), 181 (84), 180 (100), 104 (13), 91 (46), 77 (44), 51 (15).

*4.2.2. N-(4-Methoxybenzyl)benzenamine (**3b**)*[14f]. Yellow oil; t_R 18.1; R_f 0.83 (hexane/ethyl acetate 1:1); IR (film): 3428, 3084, 2844, 1597, 1499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H, CH_3), 3.90 (s, 1H, NH), 4.24 (s, 2H, CH_2), 6.63 (d, 1H, J=8.7, NCCH), 6.71 (t, 1H, J=7.4, NCCHCHC*H*), 6.87 (d, 2H, J=8.6, OCCH), 7.17 (dd, 2H, J=7.4 8.7, NCCHC*H*), 7.28 (d, 2H, J=8.6, CH2CC*H*); ^{13}C NMR ($CDCl_3$) δ 47.80, 55.28, 112.80 (2C), 114.00 (2C), 117.50, 128.80 (2C), 129.20 (2C), 131.40, 148.20, 158.80; MS (EI) m/z 213 (M^+, 19%), 212 (13), 211 (13), 210 (100), 167 (12), 121 (84), 171 (40), 51 (13).

*4.2.3. N-(Benzo[d][1,3]dioxol-5-ylmethyl)benzenamine (**3c**)*[31]. White solid; t_R 16.3; mp=80–81 °C; R_f 0.42 (hexane/ethyl acetate 8:2); IR (KBr): 3411, 3116, 1603, 1504, 918, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (s, 1H, NH), 4.23 (s, 2H, CH_2), 5.94 (s, 2H, OCH_2), 6.60–6.65 (m, 2H, NCCH), 6.68–6.75 (m, 1H, NCCHCHC*H*), 6.80–6.90 (m, 3H, (C*H*)$_2$CH$_2$(C*H*)), 7.15–7.20 (m, 2H, NCCHC*H*); ^{13}C NMR ($CDCl_3$) δ 48.15, 100.95, 108.05, 108.30, 112.85 (2C), 117.60, 129.25 (2C), 133.30, 146.70, 147.90, 148.00; MS (EI) m/z 227 (M^+, 40%), 136 (10), 135 (100), 77 (17).

*4.2.4. N-(4-Chlorobenzyl)benzenamine (**3d**)*[14f]. Yellow oil; t_R 17.7; R_f 0.87 (hexane/ethyl acetate 1:1); IR (film): 3427, 3041, 1602, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.05 (s, 1H, NH), 4.31 (s, 2H, CH_2), 6.60–6.65 (m, 2H, NCCH), 6.70–6.75 (m, 1H, NCCHCHC*H*), 7.15–7.20 (m, 2H, NCCHC*H*), 7.25–7.30 (m, 4H, ClCCHCH); ^{13}C NMR ($CDCl_3$) δ 47.60, 112.85 (2C), 117.80, 128.65 (2C), 128.70 (2C), 129.30 (2C), 132.50, 137.95, 147.80; MS (EI) m/z 219 (M^++2, 11%), 218 (11), 217 (65), 216 (52), 215 (94), 214 (100), 127 (22), 125 (66), 104 (18), 89 (18), 77 (70), 76 (10), 51 (23).

*4.2.5. N-[(Tetrahydrofuran-2-yl)methyl]benzenamine (**3e**)*[32]. Yellow oil; t_R 12.4; R_f 0.29 (hexane/ethyl acetate 9:1); IR (film): 3411, 3052, 1603, 1504, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.01 (s, 1H, NH), 4.31 (s, 2H, CH_2), 6.23 (d, 1H, J=2.8, CH_2CC*H*), 6.32 (dd, 1H, J=2.8 1.1, OCHC*H*), 6.68 (d, 2H, J=8.6, NCC*H*), 6.74 (t, 1H, J=7.4, NCCHCHC*H*), 7.18 (dd, 2H, J=7.4 8.6, NCCHC*H*), 7.36 (d, 1H, J=1.1, OCH); ^{13}C NMR ($CDCl_3$) δ 14.10, 106.95, 110.30, 113.10 (2C), 118.00, 129.20 (2C), 141.90, 147.60, 152.70; MS (EI) m/z 173 (M^+, 55%), 172 (54), 171 (51), 170 (25), 144 (13), 143 (12), 142 (12), 117 (11), 115 (17), 105 (10), 91 (10), 82 (10), 81 (100), 77 (41), 65 (13), 63 (11), 53 (26), 52 (14), 51 (34).

*4.2.6. N-Heptylbenzenamine (**3f**)*[33]. Yellow oil; t_R 12.4; R_f 0.43 (hexane/ethyl acetate 7:3); IR (film): 3414, 2926, 1603, 1506, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J=6.7, CH_3), 1.30–1.35 (m, 8H, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.60–1.65 (m, 2H, NCH_2CH_2), 3.09 (t, 2H, J=7.2, NCH_2), 4.70 (s, 1H, NH), 6.60 (d, 2H, J=7.6, NCCH), 6.68 (t, 1H, J=7.3, NCCHCHC*H*), 7.40–7.45 (m, 2H, NCCHC*H*); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.60, 27.15, 29.10, 29.55, 31.80, 44.00, 112.65 (4C), 129.20 (2C); MS (EI) m/z 191 (M^+, 16%), 106 (100), 77 (14).

*4.2.7. N-(Cyclohexylmethyl)benzenamine (**3g**)*[34]. Yellow oil; t_R 13.5; R_f 0.55 (hexane/ethyl acetate 1:1); IR (film): 3419, 3051, 2922, 2850, 1602, 1505, 747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95–1.00 (m, 2H, $CHCH_2CH_2CH_2$), 1.20–1.30 (m, 8H, $CH_2CHCH_2CH_2$), 1.65–1.70 (m, 1H, CH_2CH), 2.94 (d, 2H, J=6.7, $NHCH_2$), 3.62 (s, 1H, NH), 6.58 (dd, 2H, J=8.5 0.9, NCCH), 6.66 (td, 1H, J=7.3 0.9, NCCHCHC*H*), 7.15–7.20 (m, 2H, NCCHC*H*); ^{13}C NMR ($CDCl_3$) δ 25.95 (2C), 26.55, 31.25 (2C), 37.50, 50.55, 112.55 (2C), 116.80, 129.15 (2C), 148.60; MS (EI) m/z 189 (M^+, 21%), 107 (10), 106 (100).

*4.2.8. N-Benzyl-4-methoxybenzenamine (**3h**)*[14f]. Yellow oil; t_R 18.0; R_f 0.76 (hexane/ethyl acetate 1:1); IR (film): 3377, 2947, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 6.59 (d, 2H, J=8.85, NCCH), 6.77 (d, 2H, J=8.85, NCCHC*H*), 7.25–7.40 (m, 5H, CH_2CC*HCHCH*); ^{13}C NMR ($CDCl_3$) δ 49.20, 55.80, 114.05 (2C), 114.85 (2C), 127.10 (2C), 127.50, 128.55 (2C), 139.65, 195.85, 152.15; MS (EI) m/z 213 (M^+, 12%), 212 (15), 211 (90), 210 (15), 197 (15), 196 (100), 167 (24).

*4.2.9. N-Benzyl-2-methoxybenzenamine (**3i**)*[14f]. Yellow oil; t_R 17.4; R_f 0.85 (hexane/ethyl acetate 1:1); IR (film): 3411, 2948, 1601, 1513 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 4.63 (s, 1H, NH), 6.55–6.60 (m, 1H, NCCH), 6.65–6.70 (m, 1H, NCCHC*H*), 6.75–6.85 (m, 2H, OCCHCH), 7.25–7.40 (m, 5H, CH_2CC*HCHCH*); ^{13}C NMR ($CDCl_3$) δ 48.00, 57.35, 109.30, 110.05, 116.60, 121.20, 127.10, 127.50 (2C), 128.50 (2C), 138.05, 139.50, 146.50; MS (EI) m/z 213 (M^+, 32%), 212 (21), 211(100), 210 (20), 196 (20), 1995(10), 182 (13), 180 (30), 167 (26), 134 (15), 120 (41), 106 (16), 105 (15), 104 (33), 92 (14), 91 (37), 89 (10), 77 (25), 65 (18), 63 (12), 51 (12).

*4.2.10. N-Benzyl-3-chlorobenzenamine (**3j**)*[14f]. Yellow oil; t_R 17.8; R_f 0.83 (hexane/ethyl acetate 1:1); IR (film): 3428, 3051, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (s, 1H, NH), 4.30 (s, 2H, CH_2), 6.45–6.50 (m, 1H, NCC*H*CH), 6.60–6.65 (m, 1H, NCCHCl), 6.65–6.68 (m, 1H, NCCHCClC*H*), 7.05–7.10 (m, 1H, NCCHC*H*), 7.25–7.40 (m, 5H, CH_2CC*HCHCH*); ^{13}C NMR ($CDCl_3$) δ 48.05, 111.10, 112.45, 117.40, 127.40, 127.45 (2C), 128.70 (2C), 130.20, 135.00, 138.70, 149.20; MS (EI) m/z 218 (M^++1, 11%), 217 (61), 216 (52), 215 (92), 214 (100), 138 (12), 113 (11), 111 (34), 91 (75), 89 (13), 77 (14), 76 (11), 75 (21), 51 (10).

*4.2.11. N-Benzylpyridin-2-amine (**3k**)*[14f]. Colourless solid; t_R 17.8; mp=99–101 °C (ethyl acetate); R_f 0.64 (hexane/ethyl acetate 1:1); IR (KBr): 3313, 3194, 1597, 1573, 1532 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.49 (d, 2H, J=5.8, CH_2), 4.98 (s, 1H, NH), 6.35 (d, 1H, J=8.4, NCCH), 6.55–6.60 (m, 1H, NCCHC*H*), 7.25–7.30 (m, 1H, NCNCHC*H*), 7.30–7.40 (m, 5H, CH_2CC*HCHCH*), 8.08(d, 1H, J=5.12, NCH); ^{13}C NMR ($CDCl_3$) δ 46.25, 106.70, 113.10 (2C), 127.20, 127.35 (2C), 128.60, 137.40, 139.10, 148.15, 158.60; MS (EI) m/z 185 (M^++1, 13%), 184 (100%), 183 (54), 182 (19), 181 (45), 154 (10), 107 (20), 106 (86), 91 (46), 79 (82), 78 (35), 77 (11), 65 (16), 52 (14), 51 (18).

*4.2.12. N-(4-Methoxybenzyl)pyridin-2-amine (**3l**)*[14f]. Colourless solid; t_R 18.3; mp=125–126 °C (ethyl acetate); R_f 0.52 (hexane/ethyl acetate 1:1); IR (KBr): 3584, 3236, 1601, 1573 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H, CH_3), 4.41 (d, 2H, J=5.7, CH_2), 4.90 (s, 1H, NH), 6.35 (d, 2H, J=8.6, NCCH), 6.55–6.60 (m, 1H, NCCHC*H*), 6.86 (d, 2H, J=8.4, CH_2CCHC*H*), 7.27 (d, 2H, J=8.4, CH_2CC*H*), 7.35–7.40 (m, 1H, NCNCHC*H*); 8.08 (d, 1H, J=5.1, NCNCH); ^{13}C NMR ($CDCl_3$) δ 45.75, 55.20, 106.70, 113.00, 113.95 (2C), 128.65 (2C), 131.10, 137.40, 148.10, 158.60, 158.80; MS (EI) m/z 214 (M^+, 57%), 213 (34), 136 (22), 121 (100), 79 (30), 78 (23).

*4.2.13. N-(4-Methylbenzyl)pyridin-2-amine (**3m**)*[14f]. Colourless solid; t_R 16.9; mp=77–79 °C (ethyl acetate); R_f 0.52 (hexane/ethyl

acetate 1:1); IR (KBr): 3432, 3230, 1603, 1574 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 4.45 (d, 2H, J=5.8, CH_2), 4.88 (s, 1H, NH), 6.37 (d, 1H, J=8.5, NCCH), 6.50–6.60 (m, 1H, NCCH*CH*), 7.15 (d, 2H, J=7.9, CH_2CCH), 7.23 (d, 2H, J=7.9, CH_2CCHCH), 7.35–7.45 (m, 1H, NCNCH*CH*), 8.10 (d, 1H, J=4.1, NCNCH); ^{13}C NMR ($CDCl_3$) δ 20.85, 45.85, 106.45, 112.65, 127.15 (2C), 128.90, 129.10 (2C), 135.80, 137.50, 147.60, 158.50; MS (EI) m/z 199 (M^+, 14%), 198 (100), 197 (45), 196 (16), 195 (33), 183 (16), 120 (83), 105 (60), 103 (11), 91 (14), 79 (76), 78 (34), 77 (20), 52 (11), 51 (12).

*4.2.14. N-(4-Chlorobenzyl)pyridin-2-amine (**3n**)[14f].* Colourless solid; t_R 17.8; mp=104–105 °C (ethyl acetate); R_f 0.50 (hexane/ethyl acetate 1:1); IR (KBr): 3449, 3016, 1602, 1509 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.49 (d, 2H, J=5.9, CH_2), 4.92 (s, 1H, NH), 6.36 (d, 1H, J=8.4, NCCH), 6.60–6.65 (m, 1H, NCCHC*H*), 7.25–7.30 (m, 4H, CH_2CCHCH), 7.30–7.45 (m, 1H, NCNCH*CH*), 8.10 (d, 1H, J=4.0, NCNCH); ^{13}C NMR ($CDCl_3$) δ 45.55, 106.65, 113.05, 128.65 (2C), 128.75 (2C), 132.80, 137.45, 147.95, 148.00, 159.10; MS (EI) m/z 220 (M^++2, 20%), 219 (19), 218 (64), 217 (31), 2216 (10), 215 (15), 142 (27), 140 (83), 127 (15), 125 (40), 107 (11), 89 (20), 80 (10), 79 (100), 78 (32), 52 (15), 51 (15).

*4.2.15. N-(2-Methoxybenzyl)pyridin-2-amine (**3o**)[14f].* Colourless solid; t_R 17.8; mp=75–76 °C (ethyl acetate); R_f 0.66 (hexane/ethyl acetate 1:1); IR (KBr): 3521, 2969, 1603, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H, CH_3), 4.49 (d, 2H, J=6.0, CH_2), 5.0 (s, 1H, NH), 6.40 (d, 1H, J=8.4, NCCH), 6.55–6.60 (m, 1H, NCCHC*H*), 6.85–6.95 (m, 2H, OCC*H*CHC*H*), 7.20–7.30 (m, 2H, OCCHC*H*CHC*H*), 7.30–7.40 (m, 1H, NCNCH*CH*), 8.09 (d, 1H, J=4.06, NCNCH); ^{13}C NMR ($CDCl_3$) δ 41.50, 51.10, 99.00, 112.10, 123.00, 123.20, 124.00, 125.80, 141.35, 143.35, 147.95, 158.05, 159.05; MS (EI) m/z 215 (M^++1, 11%), 214 (76), 213 (18), 199 (26), 184 (15), 183 (100), 182 (14), 181 (64), 180 (12), 136 (44), 121 (34), 107 (18), 105 (16), 91 (91), 80 (47), 77 (15), 65 (20), 52 (15), 51 (19).

*4.2.16. N-Heptylpyridin-2-amine (**3p**)[35].* Colourless solid; t_R 15.3; mp=106–107 °C (ethyl acetate); R_f 0.64 (hexane/ethyl acetate 1:1); IR (KBr): 3263, 1605, 1431, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=6.8, CH_3), 1.25–1.45 (m, 8H, $CH_3CH_2CH_2CH_2CH_2$), 1.60–1.65 (m, 2H, NCH_2CH_2), 3.20–3.25 (m, 2H, NCH_2), 4.92 (s, 1H, NH), 6.36 (d, 1H, J=8.4, NCC*H*), 6.50–6.55 (m, 1H, NCCHC*H*), 7.40–7.45 (m, 1H, NCNCH*CH*), 8.07 (d, 1H, J=4.8, NCNCH); ^{13}C NMR ($CDCl_3$) δ 14.05, 22.60, 27.00, 29.05, 29.55, 31.75, 42.30, 106, 25, 112.55, 137.40, 148.20, 158.90; MS (EI) m/z 192 (M^+, 15%), 121(27), 108 (23), 107 (100), 94 (39), 80 (27).

*4.2.17. N-Benzylpyridin-4-amine (**3q**)[14f].* Colourless solid; t_R 15.8; mp=83–84 °C (ethyl acetate); R_f 0.61 (hexane/ethyl acetate 1:1); IR (KBr): 3229, 3100, 1597, 1533, 1448.92 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.37 (d, 2H, J=5.5, CH_2), 4.52 (s, 1H, NH), 6.47 (d, 2H, J=6.4, NCCH), 7.30–7.40 (m, 5H, $CH_2CCHCHCH$), 8.20 (d, 2H, J=6.4, NCH); ^{13}C NMR ($CDCl_3$) δ 42.60, 110.35, 127.45 (2C), 127.85, 128.64 (2C), 139.05, 158.15 (2C), 168.35; MS (EI) m/z 186 (M^++1, 13%), 185 (100), 184 (71), 108 (13), 106 (56), 91 (30), 80 (21), 79 (20), 77 (10), 65 (13), 53 (10).

*4.2.18. N-(Benzo[d][1,3]dioxol-5-ylmethyl)pyridin-4-amine (**3r**).* Yellow oil; t_R 17.5; R_f 0.12 (ethyl acetate); IR (film): 3327, 3028, 2920, 1600, 1501, 923, 763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (d, 2H, J=4.6, CH_2), 5.23 (s, 1H, NH), 5.91 (s, 2H, OCH_2), 6.44 (d, 2H, J=4.9, NCC*H*), 6.75–6.80 (m, 3H, $(CH)_2CH_2(CH)$), 8.12 (d, 2H, J=4.9, NCH); ^{13}C NMR ($CDCl_3$) δ 46.45, 100.95, 107.60 (2C), 108.25, 120.30, 131.70, 146.80, 147.90, 149.40 (2C), 153.30; MS (EI) m/z 228 (M^+, 26%), 135 (100), 77 (15), 51 (10); HRMS: M^+ found 228.0895 $C_{13}H_{12}N_2O_2$ requires 228.0899.

*4.2.19. N-Benzylpyrimidin-2-amine (**3s**)[14f].* Colourless solid; t_R 17.5; mp=109–111 °C (ethyl acetate); R_f 0.61 (hexane/ethyl acetate 1:1); IR (KBr): 3467, 3183, 1602, 1521 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.37 (d, 2H, J=5.5, CH_2), 4.52 (s, 1H, NH), 6.47 (t, 1H, J=6.4, NCCH*CH*), 7.25–7.40 (m, 5H, $CH_2CCHCHCH$), 8.20 (d, 2H, J=6.4, NCH); ^{13}C NMR ($CDCl_3$) δ 44.70, 107.60 (2C), 127.15 (2C), 127.45, 128.65 (2C), 137.90, 149.65 (2C), 153.35; MS (EI) m/z 184 (M^+, 73%), 183 (18), 182 (10), 91 (100), 78 (14), 65 (12), 51 (12)

*4.2.20. N-(Benzo[d][1,3]dioxol-5-ylmethyl)pyrimidin-2-amine (**3t**)[36].* Colourless solid; t_R 16.2; mp=120–121 °C (ethyl acetate); R_f 0.40 (ethyl acetate); IR (KBr): 3256, 3012, 2927, 1598, 1494, 916, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.54 (d, 2H, J=3.2, CH_2), 5.63 (s, 1H, NH), 5.93 (s, 2H, OCH_2), 6.54 (t, 1H, J=4.7, NCH*CH*), 6.75–6.85 (m, 3H, $(CH)_2CH_2(CH)$), 8.27 (d, 2H, J=4.7, NCH); ^{13}C NMR ($CDCl_3$) δ 45.15, 100.90, 108.15, 120.60, 132.95, 146.70, 147.75, 158.00 (2C), 162.15; MS (EI) m/z 230 (M^++1, 14%), 229 (100), 228 (40), 150 (33), 135 (82), 79 (14), 77 (18).

*4.2.21. N-Benzylpyridin-2-amine (**3k′**).* Colourless solid; t_R 17.8; mp=99–101 °C (ethyl acetate); R_f 0.64 (hexane/ethyl acetate 1:1); IR (KBr): 3223, 3055, 1597, 1574, 1529 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.49 (d, 1.7H, J=5.7, CH_2), 4.96 (s, 1H, NH), 6.36 (d, 1H, J=8.4, NCCH), 6.56–6.59 (m, 1H, NCCHC*H*), 7.25–7.30 (m, 1H, NCNCHC*H*), 7.30–7.40 (m, 5H, $CH_2CCHCHCH$), 8.05–8.10 (m, 1H, NCNCH); ^{13}C NMR ($CDCl_3$) δ 45.30, 45.50, 45.70 (C–D), 55.30, 106.80, 113.10, 114.00, 128.70, 131.10(2C), 137.45, 148.15 (2C), 158.60; MS (EI) m/z 186 (M^++1, 11%), 185 (49), 184 (100), 183 (43), 182 (26), 181 (29), 154 (11), 108 (13), 107 (53), 79 (86), 78 (59), 77 (23), 66 (12), 65 (25), 63 (12), 52 (26), 51 (39). HRMS: M^+ found 185.1061 $C_{12}H_{11}DN_2$ requires 150.1063.

*4.2.22. N-(4-Methoxybenzyl)pyridin-2-amine (**3l′**).* Colourless solid; t_R 18.3; mp=125–126 °C (ethyl acetate); R_f 0.52 (hexane/ethyl acetate 1:1); IR (KBr): 3235, 3012, 1603, 1572, 1507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H, CH_3), 4.41 (d, 2H, J=5.7, CH_2), 4.90 (s, 1H, NH), 6.35 (d, 1H, J=8.6, NCCH), 6.55–6.60 (m, 1H, NCCHC*H*), 6.86 (d, 2H, J=8.4, OCCH), 7.27 (d, 2H, J=8.4, CH_2CCH), 7.35–7.40 (m, 1H, NCNCH*CH*); 8.08 (d, 1H, J=5.1, NCNCH); ^{13}C NMR ($CDCl_3$) δ 45.75, 55.20, 106.70, 113.00, 113.95 (2C), 128.65 (2C), 131.10, 137.40, 148.10, 158.60, 158.80; MS (EI) m/z 216 (M^++1, 20%), 215 (57), 214 (50), 213 (13), 137 (20), 136 (18), 123 (30), 122 (100), 121 (81), 80 (22), 79 (42), 78 (51), 77 (16), 52 (52), 51 (17). HRMS: M^+ found 215.1168 $C_{13}H_{13}DN_2O$ requires 215.1169.

*4.2.23. N-(Octan-2-yl)pyridin-2-amine (**5a**).* Colourless solid; t_R 12.9; mp=46–47 °C (ethyl acetate); R_f 0.81 (hexane/ethyl acetate 8:2); IR (KBr): 3411, 2955, 2918, 2846, 1643, 1466, 1382, 1255, 802 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=6.8, CH_2CH_3), 0.99 (m, 3H, $CHCH_3$), 1.25–1.45 (m, 8H, $CH_3CH_2CH_2CH_2CH_2$), 1.58–1.65 (m, 2H, $NCHCH_2$), 3.23 (m, 1H, $NCHCH_2$), 4.92 (s, 1H, NH), 6.36 (d, 1H, J=8.4, NCCH), 6.50–6.55 (m, 1H, NCCHC*H*), 7.40–7.45 (m, 1H, NCNCHC*H*), 8.07 (d, 1H, J=4.8, NCNCH); ^{13}C NMR ($CDCl_3$) δ 14.05, 21.30, 22.60, 27.00, 29.05, 29.55, 31.75, 42.30, 106, 25, 112.55, 137.40, 148.20, 158.90; MS (EI) m/z 206 (M^+, 13%), 121(100), 108 (23), 94 (14), 78 (11). HRMS: M^+ found 206.1779 $C_{13}H_{22}N_2$ requires 206.1783.

*4.2.24. N-(1-Phenylethyl)pyridin-2-amine (**5b**)[37].* Yellow oil; t_R 13.6; R_f 0.82 (hexane/ethyl acetate 8:2); IR (film): 3416, 2974, 2936, 2736, 1652, 1474, 1397, 1238, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (d, 3H, J=6.9, CH_3), 4.70–4.75 (m, 1H, NCH), 4.94 (s, 1H, NH), 6.15–6.20 (m, 1H, NCCH), 6.50–6.55 (m, 1H, NCCHC*H*), 7.20–7.25 (m, 1H, NCNCHC*H*), 7.30–7.40 (m, 5H, $CH_2CCHCHCH$), 8.05–8.10 (m, 1H, NCNCH); ^{13}C NMR ($CDCl_3$) δ 24.40, 51.95, 106.65, 113.05, 125.80 (2C), 127.00, 128.65 (2C), 137.45, 144.60, 148.15, 157.95; MS (EI) m/z 198 (M^+, 65%), 197 (12), 184 (12%), 183 (100), 121 (13), 120 (36), 105 (38), 103 (12), 94 (24), 79 (18).

4.3. General procedure for synthesis of amines 7, 8 and 10

To a solution of $Cu(OAc)_2$ (0.05 mmol, 0.0092 g) and potassium *tert*-butoxide (0.175 g, 2.5 mmol) in anhydrous dioxane (3 mL), the

amine **1e** (9.75 mmol) or the diamine **7** (2.5 mmol) and the correspondent alcohol **6** (2.5 mmol) or **2a** (13 mmol) were added successively under inert argon atmosphere. After 4 days of reaction at 130 °C, it was hydrolyzed with a saturated solution of ammonium chloride (10 mL). The mixture was extracted with AcOEt (3×10 mL) and washed with brine (10 mL), after drying with anhydrous $MgSO_4$ and filtering on Celite, the solvents were removed under low pressure (15–18 Torr). The resulting mixture was purified by column chromatography (if needed).

*4.3.1. N,N′-(1,3-Phenylenebis(methylene))dipyridin-2-amine (**7a**)*[38]. Colourless solid; t_R 23.2; mp=132–133 °C (ethyl acetate); R_f 0.57 (ethyl acetate); IR (KBr): 3257, 3022, 2889, 2856, 1604, 1575, 1519, 2941, 1342, 771 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.50 (d, 4H, J=5.4, CH_2), 4.90 (s, 2H, NH), 6.40–6.45 (m, 2H, NCCH), 6.60–6.65 (m, 2H, NCCHC*H*), 7.26–7.36 (m, 4H, Ph), 7.45–7.50 (m, 2H, NCNCHC*H*), 8.00–8.05 (m, 2H, NCNCH); ^{13}C NMR ($CDCl_3$) δ 46.15 (2C), 107.45 (2C), 113.00 (2C), 126.20 (2C), 126.35 (2C), 129.05, 138.50 (2C), 139.10, 146.30 (2C), 157.75 (2C); MS (EI) m/z 290 (M^+, 23%), 197 (17), 196 (100), 195 (23), 78 (13).

*4.3.2. N,N′-(1,4-Phenylenebis(methylene))dipyridin-2-amine (**7b**)*[39]. Colourless solid; t_R 24.8; mp=191–193 °C (ethyl acetate); R_f 0.41 (ethyl acetate); IR (KBr): 3233, 3016, 1602, 1578, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.49 (d, 4H, J=5.8, CH_2), 4.92 (s, 2H, NH), 6.35–6.40 (m, 2H, NCCH), 6.55–6.65 (m, 2H, NCCHC*H*), 7.25–7.35 (m, 4H, Ph), 7.40–7.45 (m, 2H, NCNCHC*H*), 8.05–8.10 (m, 2H, NCH); ^{13}C NMR ($CDCl_3$) δ 46.00 (2C), 106.90 (2C), 113.20 (2C), 119.95, 127.55 (2C), 127.70 (2C), 137.60 (2C), 138.15, 148.00 (2C), 158.50 (2C); MS (EI) m/z 290 (M^+, 2%), 197 (26), 196 (100), 192 (12), 78 (13).

*4.3.3. 2-(Pyridin-2-yl)isoindoline (**8**)*[40]. Colourless solid; t_R 15.4; mp=160–161 °C (ethyl acetate); R_f 0.82 (ethyl acetate); IR (KBr): 3217, 3023, 2940, 2915, 2862, 1597, 1528, 1325, 891 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (s, 4H, CH_2), 6.65–6.70 (m, 1H, NCCH), 6.70–6.80 (m, 1H, NCCHC*H*), 6.95–7.00 (m, 1H, NCNCHC*H*), 7.25–7.50 (m, 4H, Ph), 8.15–8.20(m, 1H, NCH); ^{13}C NMR ($CDCl_3$) δ 61.50 (2C), 108.25, 115.00, 121.30 (2C), 127.75 (2C), 137.85, 140.25 (2C), 148.30, 157.05; MS (EI) m/z 196 (M^+, 62%), 195 (35), 194 (13), 181 (21), 180 (100), 168 (27), 167 (20), 118 (52), 117(18), 107 (13), 98 (12), 90 (11), 89 (10), 79 (60), 78 (27), 63 (10), 52 (12), 51 (21).

*4.3.4. N^2,N^6-Dibenzylpyridine-2,6-diamine (**10**)*[41]. Colourless solid; t_R 21.6; mp=73–74 °C (ethyl acetate); R_f 0.73 (ethyl acetate); IR (KBr): 3288, 3020, 1630, 1580, 1503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.45 (d, 4H, J=5.1, CH_2), 4.73 (s, 2H, NH), 5.73 (d, 2H, J=7.9, NCCH), 7.20–7.25 (m, 1H, NCCHC*H*), 7.25–7.40 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 46.35 (2C), 95.10 (2C), 127.05 (2C), 127.40 (4C), 128.50 (4C), 139.25 (2C), 139.62 (2C), 157.83; MS (EI) m/z 290 (M^++1, 22%), 289 (100%), 288 (11), 272 (38), 198 (47), 183 (11), 106 (33), 94 (10), 91 (67), 65 (12).

4.4. General procedure for synthesis of amides 12, 14 and 16

To a solution of $Cu(OAc)_2$ (0.05 mmol, 0.0092 g) and potassium *tert*-butoxide (0.175 g, 2.5 mmol) in anhydrous dioxane (3 mL), the corresponding amide **11**, **13** or **15** (2.5 mmol) and the corresponding alcohol **2** (3.25 mmol) were added successively under inert argon atmosphere. After 5 days of reaction at 150 °C, it was hydrolyzed with a saturated solution of ammonium chloride (10 mL). The mixture was extracted with AcOEt (3×10 mL) and washed with brine (10 mL), after drying over anhydrous $MgSO_4$ and filtering on Celite, the solvents were removed under low pressure (15–18 Torr). The resulting mixture was purified by column chromatography (if needed).

*4.4.1. N-Benzylbenzamide (**12a**)*[42]. White solid; t_R 18.6; mp=115–116 °C (ethyl acetate); R_f 0.51 (hexane/ethyl acetate 1:1); IR (KBr): 3331, 1640, 1543, 1313 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.66 (d, 2H, J=5.7, CH_2), 6.37 (s, 1H, NH), 7.30–7.40 (m, 5H, $CH_2CCHCHCH$), 7.40–7.45 (m, 2H, CCCHC*H*), 7.50–7.55 (m, 1H, CCCHCHC*H*), 7.75–7.80(m, 2H, CCCH); ^{13}C NMR ($CDCl_3$) δ 44.20, 127.10 (2C), 127.70 (2C), 128.00 (2C), 128.80 (2C), 128.80 (2C), 131.60 (2C), 134.50, 138.40, 169.60; MS (EI) m/z 212 (M^++1, 10%), 211 (69), 210 (27), 106 (26), 105 (100), 103 (17), 77 (52), 51 (13).

*4.4.2. N-(Benzo[d][1,3]dioxol-5-ylmethyl)benzamide (**12b**)*[43]. Yellow oil; t_R 18.6; R_f 0.32 (hexane/ethyl acetate 1:1); IR (film): 3309, 2969, 2926, 3067, 1739, 1633, 1548, 1370, 922, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.55 (d, 2H, J=5.6, CH_2), 5.95 (s, 2H, OCH_2), 6.34 (s, 1H, NH), 6.76–6.86 (m, 3H, (CH)$_2CH_2$(CH)), 7.40–7.55 (m, 3H, CCCHC*HCH*), 7.75–7.80 (m, 2H, CCC*H*); ^{13}C NMR ($CDCl_3$) δ 44.00, 101.10, 108.40, 108.45, 108.55, 115.90, 121.25, 126.90 (2C), 128.60 (2C), 131.55, 132.00, 144.75, 161.53; MS (EI) m/z 256 (M^++1, 17%), 255 (100), 254 (12), 150 (30), 135 (18), 105 (70), 77 (36).

*4.4.3. N-(Naphthalen-1-ylmethyl)benzamide (**12c**)*[42]. White solid; t_R 22.9; mp=122–123 °C (ethyl acetate); R_f 0.41 (hexane/ethyl acetate 1:1); IR (KBr): 3381, 3046, 2957, 2917, 2842, 1681, 1537, 1504, 1337, 872 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.77 (s, 1H, NH), 5.10 (s, 2H, CH_2), 7.15–7.25 (m, 2H, CH_2CCHCH), 7.30–7.45 (m, 10H, $COCCHCHCH$ and $CH_2CCCHCHCHCHCCH$); ^{13}C NMR ($CDCl_3$) δ 42.45, 123.50, 124.10, 125.45, 126.10, 126.40, 126.80, 126.95 (2C), 127.21 (2C), 128.60, 128.80 (2C), 129.18, 131.55, 134.45, 167.80; MS (EI) m/z 262 (M^++1, 20%), 261 (100), 260 (11), 156 (42), 154 (14), 141 (14), 129 (19), 128 (12), 127 (11), 115 (11), 105 (82), 77 (33).

*4.4.4. N-Benzyl-P,P-diphenylphosphinic amide (**14a**)*[44]. Yellow oil; t_R 25.1; R_f 0.33 (hexane/ethyl acetate, 1:1); IR (film): 3526, 1217 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.06 (s, 1H, NH), 5.06 (d, 2H, J=6.77, CH_2), 7.25–7.35(m, 5H, $CH_2CCHCHCH$), 7.40–8.00 (m, 10H, PCCHCHCH); ^{13}C NMR ($CDCl_3$) δ 66.30, 127.85 (2C), 128.25, 128.35, 128.50 (2C), 128.55 (2C), 128.60 (2C), 131.65 (2C), 131.75 (2C), 132.20; MS (EI) m/z 308 (M^++1, 24%) (3), 203 (12), 202 (100), 201 (25), 167 (12), 155 (20), 105 (25), 91 (41), 78 (12), 77 (37), 65(14), 51 (23).

*4.4.5. N-Hepthyl-P,P-diphenylphosphinic amide (**14b**).* Yellow oil; t_R 15.2; R_f 0.18 (hexane/ethyl acetate, 8:2); IR (film): 3447, 3058, 1592, 1465, 1227 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–0.90 (m, 3H, CH_3), 1.25–1.35 (m, 6H, $CH_3(CH_2)_3$), 1.35–1.45 (m, 4H, $NCH_2CH_2CH_2$), 1.70–1.75 (m, 2H, $NHCH_2$), 4.00 (s, 1H, NH), 7.40–7.85 (m, 10H, PCCHCHCH); ^{13}C NMR ($CDCl_3$) δ 14.05, 22.55, 25.55, 28.80, 29.70, 30.50, 31.70, 128.40 (2C), 128.55 (4C), 131.55 (2C), 131.70 (4C); MS (EI) m/z 315 (M^+, 24%), 220 (13), 219 (100), 217 (16), 201 (221), 141 (13), 77(15). HRMS: M^+ found 315.1740 $C_{19}H_{26}NOP$ requires 315.1742.

*4.4.6. N-Benzyl-4-methylbenzenesulfonamide (**16a**)*[45]. White solid; t_R 21.6; mp=115–117 °C (ethyl acetate); R_f 0.60 (hexane/ethyl acetate 1:1); IR (KBr): 3265, 3028, 1597, 1324, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 4.10 (d, 2H, J=7.3, CH_2), 4.90 (t, 1H, J=7.3, NH), 7.15–7.25 (m, 5H, $CH_2CCHCHCH$), 7.28 (d, 2H, J=8.2, SCCHC*H*), 7.74 (d, 2H, J=8.2, SCCH); ^{13}C NMR ($CDCl_3$) δ 21.45, 47.15, 127.10 (2C), 127.80 (2C), 128.60 (2C), 129.70 (2C), 136.25, 136.75, 143.45; MS (EI) m/z 261 (M^+, 0.13%), 106 (100), 92 (13), 91 (44), 79 (10), 77 (13), 65 (13).

*4.4.7. N-(4-Methoxybenzyl)-4-methylbenzenesulfonamide (**16b**)*[46]. White solid; t_R 19.8; mp=122–123 °C (ethyl acetate); R_f 0.21 (hexane/ethyl acetate 7:3); IR (KBr): 3301, 3070, 1602, 1456, 1306, 1011 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H, CCH_3), 3.77 (s, 3H, OCH_3), 4.11 (d, 2H, J=6, CH_2), 4.62 (t, 1H, J=6, NH), 6.80 (d, 2H, J=8.6,

CH_2CCHCH), 7.10, (d, 2H, J=8.6, CH_2CCH), 7.32 (d, 2H, J=8.3, SCCHCH), 7.72 (d, 2H, J=8.3, SCCH); ^{13}C NMR ($CDCl_3$) δ 21.50, 46.80, 55.25, 114.05 (2C), 127.17 (2C), 128.25, 129.25(2C), 129.70 (2C), 136.90, 143.45, 159.30; MS (EI) m/z 291 (M^+, 7%), 136 (8721), 135 (100), 134 (54), 121 (20), 91 (23), 65 (11).

*4.4.8. N-(3-Chlorobenzyl)-4-methylbenzenesulfonamide (**16c**)*[46]. Yellow oil; t_R 17.8; R_f 0.27 (hexane/ethyl acetate 8:2); IR (film): 3066, 2922, 1725, 1352, 1077 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3), 4.43 (d, 2H, J=5.5, CH_2), 5.04 (s, 1H, NH), 6.33 (d, 2H, J=8.5, CH_2CCHCH), 6.50–6.55 (m, 1H, CH_2CCHCH), 7.12 (d, 2H, J=7.9, SCCHCH), 7.23 (d, 2H, J=7.9, SCCH), 7.35–7.40 (m, 1H, $CH_2CCHCCl$), 8.05–8.10 (m, 1H, $CH_2CCHCHCH$); ^{13}C NMR ($CDCl_3$) δ 21.00, 46.00, 106.60, 112.90 (2C), 127.30 (2C), 129.20 (2C), 136.00, 136.75, 137.35, 148.10, 158.65; MS (EI) m/z 277 (M^+ −35, 3%), 171 (21), 155 (18), 122 (27), 108 (29), 107 (28), 106 (100), 92 (22), 91 (19), 79 (10), 77 (43), 64 (12), 51 (12).

*4.4.9. N-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-methylbenzenesulfonamide (**16d**)*[46]. White solid; t_R 24.2; mp=142–143 °C (ethyl acetate); R_f 0.39 (hexane/ethyl acetate 7:3); IR (KBr): 3257, 2798.61, 1596, 1398, 1032, 925.58 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.98 (d, 2H, J=7.1, $NHCH_2$), 5.12 (s, 1H, NH), 5.98 (s, 2H, OCH_2), 6.60–6.70 (m, 3H), 7.28 (d, 2H, J=8.2, SCCHCH), 7.72 (d, 2H, J=8.2, SCCH); ^{13}C NMR ($CDCl_3$) δ 21.50, 45.30, 123.25, 125.15, 125.95, 126.60, 126.90, 127.20 (2C), 128.65, 128.95, 129.65 (2C), 131.11, 131.30, 133.70, 136.45, 143.50; MS (EI) m/z 311 (M^+, 11%), 156 (49), 155 (55), 154 (100), 153 (19), 141 (15), 129 (15), 128 (24), 127 (28), 126 (13), 115 (11), 91 (30).

*4.4.10. 4-Methyl-N-(naphthalen-1-ylmethyl)benzenesulfonamide (**16e**)*[45]. White solid; t_R 21.6; mp=158–159 °C (ethyl acetate); R_f 0.65 (hexane/ethyl acetate 1:1); IR (KBr): 3324, 3291, 1596, 1317, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 4.50 (d, 2H, J=7.1, CH_2), 4.84 (t, 1H, J=7.1, NH), 7.20–7.30 (m, 4H, CH_2CCHCH and $CH_2CCCHCHCH$), 7.45–7.50 (m, 2H, SCCHCH), 7.70–7.75 (m, 3H, SCCCH and $CH_2CCHCHCH$), 7.75–7.80 (m, 1H, $CH_2CCCHCHCHCH$), 7.85–7.90 (m, 1H, CH_2CCCH); ^{13}C NMR ($CDCl_3$) δ 21.50, 45.30, 123.25, 125.15, 125.95, 126.60, 126.90, 127.20 (2C), 128.65, 128.95, 129.65 (2C), 131.11, 131.30, 133.70, 136.45, 143.50; MS (EI) m/z 311 (M^+, 11%), 156 (49), 155 (55), 154 (100), 153 (19), 141 (15), 129 (15), 128 (24), 127 (28), 126 (13), 115 (11), 91 (30).

*4.4.11. N-(Cyclohexylmethyl)-4-methylbenzenesulfonamide (**16f**)*[46]. Yellow oil; t_R 17.5; R_f 0.74 (hexane/ethyl acetate 1:1); IR (film): 3284, 2922, 1599, 1448, 1322, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–0.90, 1.05–1.25, 1.35–1.45 and 1.60–1.70 (4 m, 2, 3, 1 and 5H, $NHCH_2CHCH_2CH_2CH_2$), 2.43 (s, 3H, CH_3), 2.70–2.75 (m, 2H, NCH_2), 4.55 (t, 1H, J=6.4, NH), 7.30 (d, 2H, J=8.2, SCCHCH), 7.74 (d, 2H, J=8.2, SCCH); ^{13}C NMR ($CDCl_3$) δ 21.50, 25.60 (2C), 26.22, 30.50 (2C), 37.70, 49.40, 127.05 (2C), 129.60 (2C), 137.05, 143.25; MS (EI) m/z 269 (M^+ −2, 0.39%), 186 (10), 184 (99), 155 (100), 96 (11), 92 (12), 91 (81), 65 (13), 55 (21).

*4.4.12. N-Benzyl-4-methoxybenzenesulfonamide (**16g**)*[46]. White solid; t_R 18.4; mp=112–113 °C (ethyl acetate); R_f 0.18 (hexane/ethyl acetate 7:3); IR (KBr): 3267, 3064, 1596, 1456, 1302, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 4.11 (d, 2H, J=6, CH_2), 4.62 (t, 1H, J=6, NH), 6.97 (d, 2H, J=8.9, SCCHCH), 7.15–7.35 (m, 5H, $CH_2CCHCHCH$), 7.81 (d, 2H, J=8.9, SCCH); ^{13}C NMR ($CDCl_3$) δ 47.25, 55.60, 114.25 (2C), 127.85, 127.90 (2C), 128.70 (2C), 129.30 (2C), 131.35, 133.65, 136.25; MS (EI) m/z 277 (M^+, 3%), 171 (21), 155 (18), 122 (27), 108 (29), 107 (28), 106 (100), 92 (22), 91 (19), 79 (10), 77 (43), 64 (12), 51 (12).

*4.4.13. N-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-methoxybenzenesulfonamide (**16h**).* White solid; t_R 23.5; mp=137–138 °C (ethyl acetate); R_f 0.48 (ethyl acetate); IR (KBr): 3255, 3012, 2832, 1597, 1324, 1025, 916 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 4.01 (d, 2H, J=6.1, $NHCH_2$), 4.73 (t, 1H, J=6.1, NH), 5.92 (s, 2H, OCH_2), 6.60–6.70 (m, 3H, $(CH)_2CCH_2(CH)$), 6.95–7.00 (m, 2H, SCCHCH), 7.75–7.80 (m, 2H, SCCH); ^{13}C NMR ($CDCl_3$) δ 47.10, 55.60, 101.10, 108.20, 108.45, 114.25 (2C), 121.30, 129.25 (2C), 130.05, 131.45, 147.25, 147.85, 162.90; MS (EI) m/z 321 (M^+, 21%), 150 (53), 149 (100), 148 (31), 135 (16), 77 (14). HRMS: M^+ found 321.0677 $C_{15}H_{15}NO_5S$ requires 321.0671.

*4.4.14. N-Benzylmethanesulfonamide (**16i**)*[46]. Yellow oil; t_R 13.1; R_f 0.12 (hexane/ethyl acetate 8:2); IR (film): 3227, 3021, 1605, 1493, 1293, 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.85 (s, 3H, CH_3), 4.31 (d, 2H, J=6.0, CH_2), 4.88 (s, 1H, NH), 7.20–7.40 (m, 5H, $CH_2CCHCHCH$); ^{13}C NMR ($CDCl_3$) δ 41.05, 47.15, 127.90 (2C), 128.10, 128.90 (2C), 136.70; MS (EI) m/z 185 (M^+, 1.32%), 106 (100), 105 (24), 104 (70), 91 (34), 79 (35), 78 (17), 77 (44), 65 (12), 51 (25).

4.5. General procedure for synthesis of amines 17

To a solution of the corresponding sulfonamide **16** (1 mmol) in anhydrous THF (10 mL) was added *n*-buthyl lithium (1 mmol, 0.625 mL) at 0 °C under inert argon atmosphere. After 10 min, the resulting solution was added to a suspension of lithium powder (7.2 mmol, 50 mg) and naphthalene (0.08 mmol, 10 mg) in anhydrous THF (5 mL) at −78 °C. The mixture was stirred during 12 h, reaching temperature to rise to 25 °C, and finally was hydrolyzed with water (10 mL). The mixture was extracted with AcOEt (3×10 mL) and washed with brine (10 mL), after drying with anhydrous $MgSO_4$, ands filtering on Celite, the solvents were removed under low pressure(15–18 Torr). The resulting mixture was purified by column chromatography.

*4.5.1. Phenylmethanamine (**17a**)*[45]. Yellow oil; t_R 7.0; R_f 0.71 (ethyl acetate); IR (film): 3365, 3026, 1643, 1218 cm^{-1}; 2916, 2849, 1382, 736; ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 2H, NH_2), 3.76 (s, 2H, CH_2), 7.15–7.40 (m, 5H, $CH_2CCHCHCH$); ^{13}C NMR ($CDCl_3$) δ 45.90, 129.40 (2C), 127.60, 127.90 (2C), 142.70; MS (EI) m/z 107 (M^+, 57%), 106 (100), 91 (12), 79 (32), 77 (19).

*4.5.2. Naphthalen-1-ylmethanamine (**17b**)*[46]. Yellow oil; t_R 12.6; R_f 0.72 (ethyl acetate); IR (film): 3372, 3048, 2926, 2815, 1597, 1393, 1262, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 2H, NH_2), 4.20 (s, 2H, CH_2), 7.35–7.50 (m, 4H, CH_2CCHCH and $CH_2CCCHCHCH$), 7.60–7.70 (m, 1H, $CH_2CCHCHCH$), 7.75–7.80 (m, 1H, $CH_2CCCHCHCHCH$), 7.95–8.00 (m, 1H, CH_2CCCH); ^{13}C NMR ($CDCl_3$) δ 43.70, 122.90, 124.10, 125.40, 125.85, 127.20, 128.55, 130.90, 133.55, 138.65; MS (EI) m/z 157 (M^+, 0.33%), 145 (12), 144 (100), 143 (16), 130 (12), 129 (84), 128 (24), 155 (13), 91 (12).

*4.5.3. Cyclohexylmethanamine (**17c**)*[29d]. Yellow oil; t_R 5.2; R_f 0.23 (hexane/ethyl acetate 1:1); IR (film): 3373, 3295, 2921, 2851, 1614, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–0.95 (m, 2H, CHCHH), 1.05–1.30 (m, 6H, $CHCH_2CH_2CH_2$), 1.70–1.80 (m, 5H, NCH_2CHCHH and NH_2), 2.30–2.50 (m, 2H, NCH_2); ^{13}C NMR ($CDCl_3$) δ 25.15 (2C), 25.80, 29.90 (2C), 40.45, 48.00; MS (EI) m/z 114 (M^++1, 14%), 113 (100), 96 (46), 95 (12), 82 (18), 81 (41), 79 (10), 68 (19), 67 (74), 56 (23), 55 (64), 54 (40), 53 (18).

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