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Selective one-pot synthesis of symmetrical and unsymmetrical di- and triarylamines with a ligandless copper catalytic system†

Anis Tlili, Florian Monnier* and Marc Taillefer*

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The one-pot synthesis of symmetrical or unsymmetrical di- or triarylamines using aryl iodides or bromides and $LiNH_2$ as ammonia source is reported. This highly selective method is based, for the first time, on a copper-catalyzed system, which does not require the presence of any additional ligand.

Among the variety of amines, di- and triarylamines constitute a wide family of active compounds in pharmaceutical and material sciences.[1] They have been commonly prepared *via* Pd-,[2] Ni-[3] or Cu-catalyzed[4] coupling reactions between aryl halides and aniline derivatives. Recently, several approaches employing palladium catalysts have allowed the synthesis of symmetrical di- or triarylamines from aryl halides as the only source of arenes in combination with ammonia or ammonia surrogates. Thus, the preparation of these compounds by Pd-catalyzed arylation of urea and $LiNH_2$ has been described by Beletskaya *et al.*[5a] and Huang and Buchwald.[5b] Although these methods are efficient, their scope is limited to aryl halides possessing electron-donating groups and is strongly dependent on the position of the aryl substituents. More recently, Surry and Buchwald reported a Pd-based catalytic system able to couple ammonia with aryl bromides or chlorides, to produce di- or triarylamines using a multistep protocol.[6] For the synthesis of unsymmetrical molecules, the anilines were first generated from NH_3 and aryl halides with the assistance of a Pd_2dba_3/(*o*-biaryl)-di-*tert*-butylphosphine system. After removing excess ammonia and solvent, another biaryl-dicyclohexylphosphine was in turn added, together with a second aryl halide (diarylamine synthesis), while the further addition of a third aryl halide allowed the formation of unsymmetrical triarylamines. Although this method provides an elegant route to di- and triarylamines, it suffers from drawbacks such as the use of expensive systems based on palladium salts and of two different elaborated phosphine ligands.

As part of our studies on the copper-catalyzed arylation of nucleophiles,[4a,7–9] we now report a new method allowing the one-pot selective synthesis of symmetrical or unsymmetrical di- or triarylamines *via* a very simple ligandless copper-catalyzed system involving aryl iodides and $LiNH_2$ as ammonia source.

CNRS, UMR 5253, Institut Charles Gerhardt Montpellier, ENSCM, 8, rue de l'Ecole Normale, 34296 Montpellier Cedex 5, France. E-mail: florian.monnier@enscm.fr, marc.taillefer@enscm.fr
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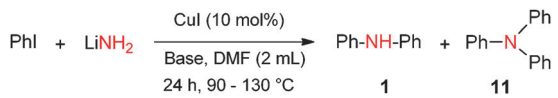
In 2007, our group observed that aqueous ammonia ($NH_3{\cdot}H_2O$) could be coupled with aryl halides to selectively afford the corresponding anilines, using a very simple Cu–diketone catalytic system.[8] We then tried to extend the method *via* a parametric study to the synthesis of symmetrical di- and triarylamines. Unfortunately only non-selective processes were observed, yielding mixtures of anilines and diarylethers, the latter probably resulting from the Cu-catalyzed arylation of water.[9]

We then turned our attention to lithium amide as a potential ammonia source and observed that this compound, already used for the Pd-catalyzed synthesis of anilines[10] and symmetrical diarylamines,[5b] was a preferable candidate to reach our goal. First, we selected PhI as the model substrate and a ligandless copper catalytic system (CuI) for the optimization of the reaction conditions. The preliminary studies showed that with DMF as solvent, the use of an excess of $LiNH_2$ (5 eq.) affords a poor yield of diphenylamine **1** (Table 1, entry 1), together with aniline (20%) and *N*-phenylformamide PhNHCHO (38%). The presence of the latter was not really surprising, as it corresponds to a transamination between an aniline and DMF, a reaction known to be activated under strongly basic conditions (Scheme 1).[11] Decreasing the

Table 1 Selective synthesis of symmetrical di- or triphenylamines (**1** and **11**)[a]



Entry	$LiNH_2$ (*n* eq.)	Base (*x* eq.)	**1**[b] (%)	**11**[b] (%)
1	5	—	20[c]	0
2	2	—	60[d]	0
3	2	K_2CO_3 (1)	66	0
4	2	Cs_2CO_3 (1)	79	0
5	2	K_3PO_4 (1)	92	0
6	2	K_3PO_4 (1)	68[e], 37[f]	0
7	1	K_3PO_4 (1)	72	0
8	0.5	K_3PO_4 (1)	20	40
9	0.5	K_3PO_4 (2)	10	63
10	0.5	K_3PO_4 (3)	3	87
11	0.5	Cs_2CO_3 (3)	6	67

[a] Performed with 0.1 mmol of CuI (10 mol%), 1 mmol of PhI, *n* equiv. of $LiNH_2$, *x* equiv. of base, 2 mL of solvent at 130 °C for 24 h. [b] GC yield in % determined with 1,3-dimethoxybenzene as an internal standard. [c] Complete conversion of PhI, along with the formation of $PhNH_2$ (20%) and PhNHC(O)H (38%). [d] Formation of PhNHC(O)H (16%). [e] Performed at 110 °C. [f] Performed at 90 °C.

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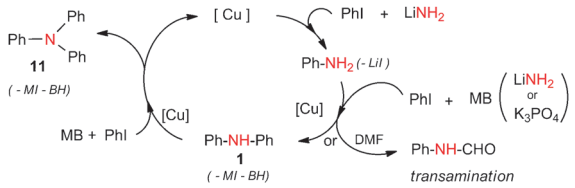
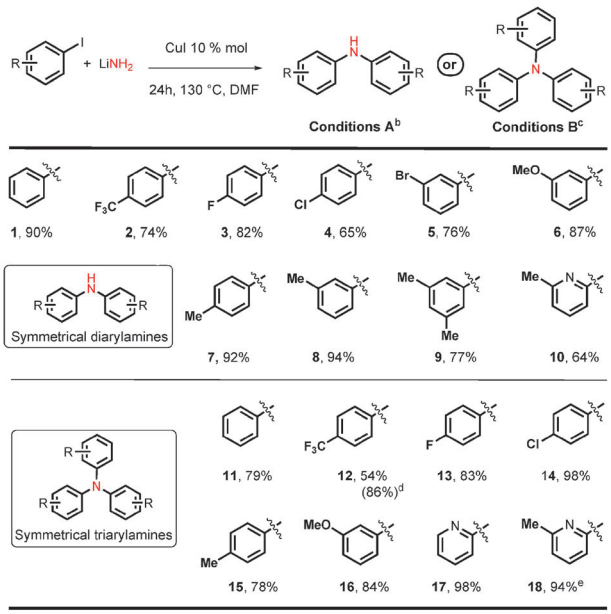


Scheme 1 Possible pathways towards symmetrical di- and triphenylamines.

amount of $LiNH_2$ to two equivalents resulted in a significant increase in the yield of **1** to 60% (Table 1, entry 2), but the undesired phenylformamide was still observed (16%). Finally, we were pleased to find that after the addition of 1 equivalent of an inorganic base (particularly K_3PO_4), iodobenzene can be quantitatively coupled with $LiNH_2$ to selectively afford diphenylamine **1** in 92% yield (entry 5). As a general feature, it should be noted that the reaction can proceed at a lower temperature (110 °C, entry 6) and that DMF was the only solvent[12] that allowed the reaction to proceed to completion. In another set of experiments, we again reduced the amount of $LiNH_2$ to 1 and 0.5 equivalent and observed a decrease in the yield of diphenylamine **1** to 72% and 20%, respectively (entries 7 and 8). This last case was particularly interesting because we detected, for the first time, the formation of a significant amount of triphenylamine **11**. Thereafter, we focused our efforts towards the selective synthesis of this compound and observed that the addition of one more equivalent of K_3PO_4 leads to a 63% yield of **11**, while a 10% yield of diphenylamine **1** was still obtained (entry 9). Finally, we were glad to isolate 87% of **11** by using 3 equivalents of K_3PO_4 (entry 10), this base being the best candidate for achieving the selectivity of this transformation.

In Scheme 1 is represented a plausible general pathway leading to the observed products. Even though it seems obvious that a key factor for the success of our system is the use of a well-defined ratio of $LiNH_2$/inorganic base, the mechanism is not elucidated and particularly the relationship between experimental conditions and reactivity/selectivity is not clear.

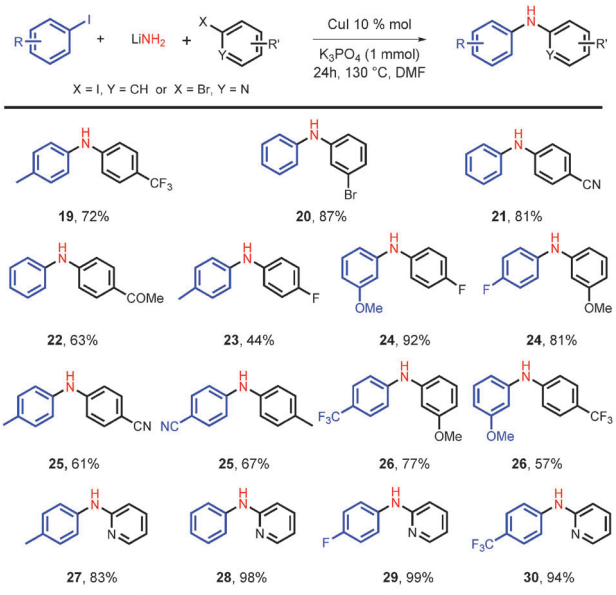
On the basis of these results, we developed two highly selective conditions for the synthesis of various symmetrical diarylamines **1–10** and symmetrical triarylamines **11–18** (Scheme 2). Under condition A, 10 mol% of CuI efficiently promotes cross-coupling between $LiNH_2$ and aryl iodides bearing electron-withdrawing groups (Scheme 2, **2–5**) to afford the corresponding diarylamines in good to excellent isolated yields (65 to 82%). Similar results were obtained starting from aryl iodides substituted by electron-donating groups in *para* or *meta*-positions (Scheme 2, **6–9**, yields 77–94%). On the other hand, we have shown that under condition B, the corresponding triarylamines are obtained in good yields with high selectivities. The reactions well tolerate substituents on the starting aryl iodides (Scheme 2, **11–16**, yields 78–98%), while the presence of an additional ligand (DMEDA) is required to obtain a good yield (86%) in the particular case of *p*-trifluoromethyliodobenzene. It is noteworthy that the method was also efficient for the synthesis of secondary dipyridylamine **10** and tertiary tripyridylamines **17–18**, obtained from 2-bromo-6-methyl pyridine (Scheme 2, **10** and **18**) and 2-bromopyridine (Scheme 2, **17**). The family of polypyridylamines has found a wide variety of applications as ligands in coordination chemistry and in organometallic catalysis.[13]



[a] Isolated yields. [b] Conditions A (table 1, entry 5): reactions with 0.1 mmol of CuI (10 mol%), 1 mmol of ArI, 2 mmol of $LiNH_2$, 1 mmol of K_3PO_4 at 130 °C for 24 h. [c] Conditions B (table 1, entry 10): reactions with 0.1 mmol of CuI (10 mol%), 1 mmol of ArI, 0.5 mmol of $LiNH_2$ and 3 mmol of K_3PO_4 at 130 °C for 24 h. [d] Conditions B with 0.5 mmol of DMEDA as ligand. [e] Conditions B with 2 mmol of $LiNH_2$.

Scheme 2 Selective one-pot access to symmetrical di- and triarylamines **1–18**.

We then focused our research on the synthesis of unsymmetrical arylated amines, which constitute another stimulating challenge in terms of selectivity and applications. Under the conditions given in Scheme 3 involving two different aryl halides, $LiNH_2$ and the ligandless copper system allowing the synthesis of symmetrical diarylamines (Scheme 2, A), we were pleased to obtain the various



[a] Isolated yields. [b] Reactions conducted with 0.1 mmol of CuI (10 mol%), 1 mmol of RC_6H_4I, 2 mmol of $LiNH_2$, 0.7 mmol of $R'C_6H_4I$ (or 2-BrPy), 1 mmol of K_3PO_4 at 130 °C for 24 h. $R'C_6H_4I$ (or 2-BrPy) was added *in situ* after 6 h without any modification of the reaction mixture and without any additional work-up.

Scheme 3 Selective one-pot access to unsymmetrical diarylamines **19–30**.

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unsymmetrical diarylamines **19–30** in good to excellent yields with a high selectivity.

We realized that the use of a small excess of the first introduced aryl iodide R–C_6H_4I was needed to almost fully eliminate the formation of symmetrical diarylamines, which can result from each of the two aromatic partners. Another key element for this easy-to-operate protocol was the *in situ* introduction of the second (hetero-) aryl iodide or bromide after 6 h of the reaction without any modification or additional work-up of the reaction mixture. It is noteworthy to mention that this simple catalytic system is tolerant towards both electron-donating (4-CH_3, 3-OMe) or withdrawing (F, Br, CF_3, CN, COMe) substituents on the two aryl halide derivatives, the expected products being always obtained in good to excellent yields (Scheme 3, **19–30**). Interestingly, the latter could be sometimes optimized by changing the introduction order of the two aromatic partners (Scheme 3, **24–26**). Finally, of particular interest is the possibility to build various mixed unsymmetrical aryl–heteroaryl(2-pyridyl)amines (Scheme 3, **27–30**) in almost quantitative yields using this method.

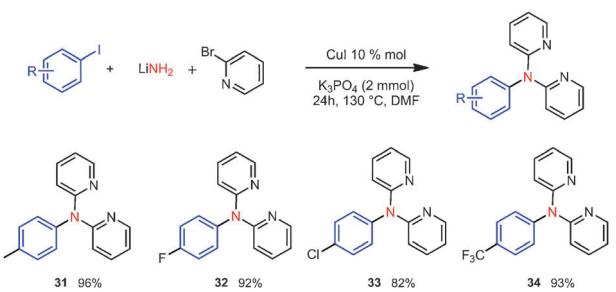
Another challenging task in the synthesis of triarylamines was to devise a method for the one-pot synthesis of tertiary amines bearing at least two different aromatic cycles. Among them, we chose to consider the case of aryldipyridylamines that are, as outlined above,[13] ligands with high potential in transition metal coordination chemistry and in catalysis.

As a result of various experimentations, it proved possible to synthesize these molecules from aryl iodides and 2-bromopyridine in excellent yields (Scheme 4, **31–34**). The catalytic system is quite similar to the one that allowed the synthesis of unsymmetrical diarylamines, the difference lying in the use of one additional equivalent of K_3PO_4, presumably to facilitate the deprotonation of the diarylamine intermediate. It is worthy of note that this one-pot ligandless copper-catalyzed system is compatible with electron-donating or withdrawing groups present on the aryl iodide (Scheme 4).

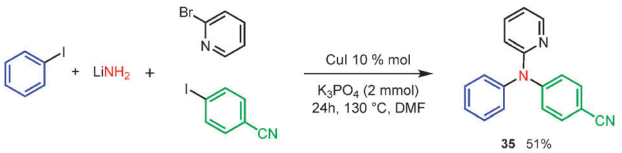
Finally, we have tried to synthesize, in one step, an even more challenging triarylamine bearing three different aromatic groups.

By using the former catalytic system, in which a slight excess of iodobenzene was reacted with 2-bromopyridine and 4-iodobenzonitrile, we could conduct the direct one-pot synthesis of tertiary phenyl(4-cyanophenyl)(pyridin-2-yl)amine **35**, obtained in 51% yield (42% isolated) (Scheme 5). Studies are in progress to render this method more general and to rationalise the selectivity obtained.[14]

In summary, we have disclosed a versatile method allowing the one-pot synthesis of various symmetrical or unsymmetrical di- or triarylamines using a simple ammonia source ($LiNH_2$) and aryl halides. This controlled and highly selective process is based,



Scheme 4 New one-pot access to triarylamines aryldipyridylamines **31–34**.



[a] Isolated yields. [b] Reactions conducted with 0.1 mmol of CuI (10 mol%), 1 mmol of PhI, 0.7 mmol of 2-BrPy and 0.7 mmol of 4-iodobenzonitrile (both added after 6 h), 2 mmol of $LiNH_2$ and 2 mmol of K_3PO_4 at 130 °C for 24 h.

Scheme 5 One-pot access to unsymmetrical triarylamine **35**.

for the first time, on a Cu-catalyzed system, which does not require the presence of any additional ligand. Thus, the low cost, the low toxicity and the simplicity of this catalytic system render the method competitive with comparable Pd-based protocols, which require the presence of sophisticated ligands. Work is in progress to broaden the application field of the method, particularly for the synthesis of totally unsymmetrical triarylamines.

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