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PAPER

Ready synthesis of free *N-H* 2-arylindoles *via* the copper-catalyzed amination of 2-bromo-arylacetylenes with aqueous ammonia and sequential intramolecular cyclization†

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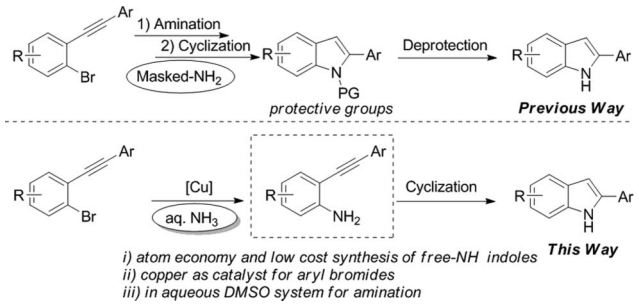
A wide range of free *N-H* 2-arylindoles were synthesised *via* the copper(II)-catalyzed amination of 2-bromo-arylacetylenes with aqueous ammonia and sequential intramolecular cyclization. The convenience and atom economy of aqueous ammonia, and the low cost of the copper catalytic system make this protocol readily superior in practical application.

Introduction

Indoles are one of the most ubiquitous and important structural components found in many biologically-active compounds and natural products.[1] Because of this, a large number of methods have been developed to provide access to a generally applicable synthesis of this structural motif.[2] In this context, transition metal catalysis has played a remarkable and ever growing role. Recently developed metal-catalyzed processes have proved complementary to conventional indole syntheses and allowed reactions to be performed under remarkably mild reaction conditions,[3] particularly protocols relying on addition reactions of nitrogen nucleophiles onto alkynes.[4]

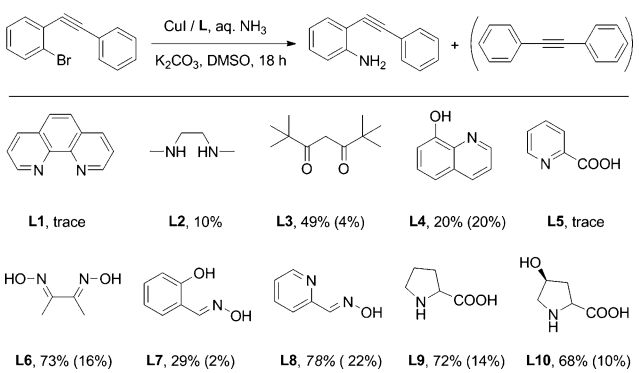
The previous use of masked ammonia apparently suffers from low atom economy and the need for an additional deprotecting step to liberate the primary aryl amine.[3a–c] Ammonia is considered one of the most interesting commodity chemicals due to its great abundance and extremely low cost. Copper-catalyzed amination with ammonium hydroxide as the nucleophile that allows the direct transformation of easily accessible 2-arylhaloarenes into the corresponding *free N-H* indole derivatives is perhaps the most convenient route (Scheme 1). Recently, the palladium- and copper-catalyzed amination of aryl halides with ammonia has gained increased attention.[5]



Scheme 1 Tandem synthesis of free *N-H* indoles from 2-bromo-arylacetylenes.

Results and discussion

We initially tested the amination reaction of 1-bromo-2-(phenylethynyl)benzene with aqueous ammonia (1 mL) by applying 10 mol% of CuI in dimethylsulfoxide (DMSO, 1 mL) at 100 °C in a closed vessel. The investigated reaction parameters included various ligands, copper catalysts, solvents and bases. We realized that the reaction seemed to be affected by sterically-hindered *ortho*-substituents generating some amount of the reduction by-product 1,2-diphenylethyne in most cases. While the most promising preliminary results were obtained using proline and imine as the supporting ligand, we observed that the latter provided superior conversion (100%) and yield (78%) (Scheme 2, **L8**). We postulated that the key point to achieving this transformation is the excellent



Scheme 2 Ligands screened in the amination reaction.

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Table 1 The effect of different catalysts, bases and solvents[a]

Entry	Cu catalyst	Base	Solvent	Yield (%)[b]
1	CuCl	K_2CO_3	DMSO	80 (20)
2	$Cu(OAc)_2$	K_2CO_3	DMSO	86 (13)
3	Cu_2O	K_2CO_3	DMSO	78 (22)
4	$Cu(acac)_2$	K_2CO_3	DMSO	87 (13)
5	$Cu(OTf)_2$	K_2CO_3	DMSO	90 (10)
6	$Cu(OOCCF_3)_2$	K_2CO_3	DMSO	88 (12)
7	$Cu(OAc)_2$	K_3PO_4	DMSO	85 (15)
8	$Cu(OAc)_2$	Cs_2CO_3	DMSO	87 (13)
9	$Cu(OAc)_2$	K_2CO_3	NMP	30 (–)
10	$Cu(OAc)_2$	K_2CO_3	DMF	60 (–)

[a] Reaction conditions: 1-Bromo-2-(phenylethynyl)benzene (0.4 mmol), [Cu] (0.04 mmol), **L8** (0.08 mmol), base (0.5 mmol), aq. NH_3 (1.0 mL) and solvent (1.0 mL) stirred at 100 °C for 18 h under Ar. [b] GC yield (1,2-diphenylethyne observed).

Table 2 Effect of the volume ratio of aq. NH_3/DMSO[a]

Entry	Aq. NH_3 : DMSO	Yield (%)[b]
1	1 : 9	70 (30)
2	1 : 3	88 (12)
3	2 : 3	92 (8)
4	1 : 1	90 (10)
5	2 : 1	50 (–)
6	3 : 1	20 (–)

[a] Reaction conditions: 1-Bromo-2-(phenylethynyl)benzene (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol), **L8** (0.08 mmol), K_2CO_3 (0.5 mmol), aq. NH_3 and DMSO stirred at 100 °C for 18 h under Ar. [b] GC yield (1,2-diphenylethyne observed).

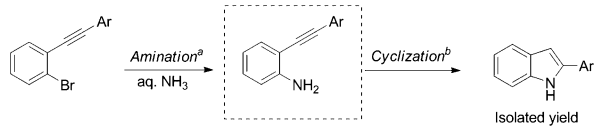
coordination of ligand **L8** to the Cu catalyst and its high solubility in the aqueous DMSO system.[6]

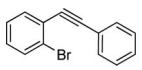
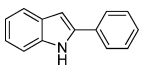
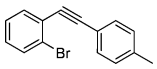
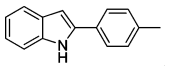
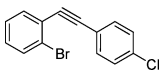
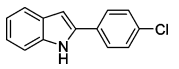
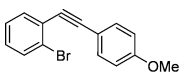
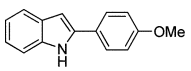
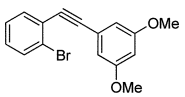
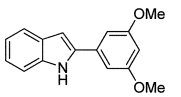
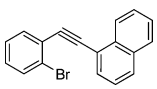
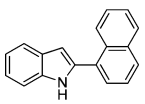
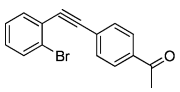
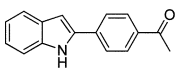
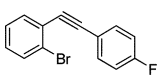
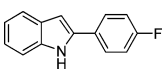
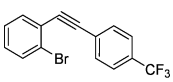
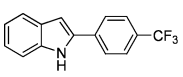
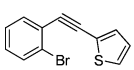
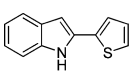
The development of an applicable *ortho*-hindered amination procedure requires further assessment of the catalyst activity. Studies revealed that reactions conducted with water-soluble Cu(II) catalysts resulted in high reactivities in aqueous DMSO. It was found that $Cu(OTf)_2$ was the most efficient catalyst, producing the corresponding primary aryl amine in 90% yield (Table 1, entry 5). Bases have an insignificant influence on the catalyst activity (Table 1, entries 7 and 8), while solvents play an important role in the chemical process (Table 1, entries 9 and 10). DMSO turns out to be the most efficient solvent among the solvents DMF, NMP and DMSO.

The effect of the volume ratio of aq. NH_3 to DMSO on the model reaction was further investigated. The results described below indicate that the balance between the reactivity and selectivity is important. Generally, the more that DMSO added, the higher the reactivity and the lower the selectivity. Initially, increasing the volume ratio of aq. NH_3/DMSO resulted in a positive effect on the reaction selectivity and yield (Table 2, entries 1–3). As expected, an excess of ammonium hydroxide also introduced an excess of water into the system, resulting in a low conversion. An aq. NH_3/DMSO volume ratio of 2 : 3 proved to be the best combination. In a typical protocol, 10 mol% $Cu(OTf)_2$, 20 mol% ligand **L8** and K_2CO_3 in DMSO/aq. NH_3 (3 : 2) at 100 °C were employed.

To further exploit this new methodology, a tandem protocol was developed for the conversion of 2-bromo-arylacetylenes to 2-arylindoles, where the initially formed 2-arylethynylaniline was treated with toluene, facilitated by the Lewis acid catalyst $ZnBr_2$.[7]

Table 3 Synthesis of 2-arylindoles with different acetylene substituents[a]



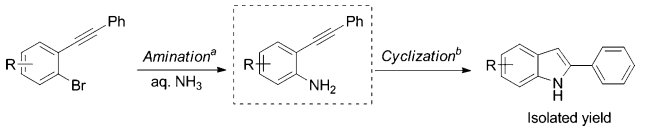
Entry	Aryl bromide	Indole		Yield (%)
1			**3a**	87
2			**3b**	85
3			**3c**	84
4			**3d**	87
5			**3e**	83
6			**3f**	83
7			**3g**	68[c]
8			**3h**	88[c]
9			**3i**	83[c]
10			**3j**	57

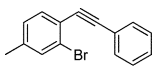
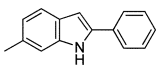
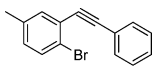
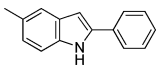
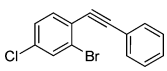
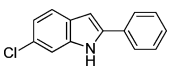
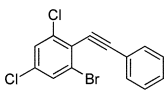
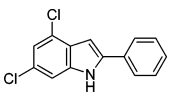
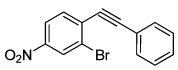
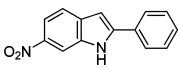
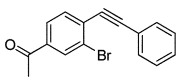
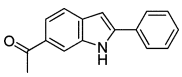
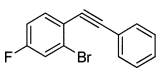
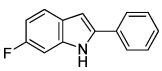
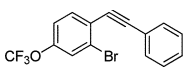
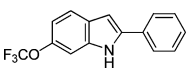
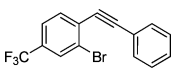
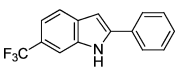
[a] Reaction conditions: 2-Arylhaloarene (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol), **L8** (0.08 mmol), K_2CO_3 (0.5 mmol), aq. NH_3 (1.0 mL) and DMSO (1.5 mL) stirred at 100 °C for 18 h under Ar. [b] Reaction conditions: After removing the water by extraction, the residue was treated with $ZnBr_2$ (0.2 mmol) and toluene (4 mL), and refluxed 110 °C for 6 h. [c] Refluxed at 110 °C for 15 h.

Sequential intramolecular cyclization *via* the addition reactions of aryl amines with 2-ethynylarenes allowed the direct synthesis of free *N-H* indoles in good yields. Of importance is that chloro, fluoro, trifluoromethyl, trifluoromethoyl, methyl ketone, nitro and thienyl substituents were well tolerated under the reaction conditions employed (Table 3 and Table 4).

As shown in Table 3, under these conditions, the reaction tolerates a number of different substituents, either on the nucleophile or the electrophile, providing the corresponding indole. In general, different acetylene substituents on the 1-bromo-2-ethynylarene have no significant influence at the amination stage, and both electron-rich and electron-deficient arylacetylenes worked well, as detected by GC or LC. However, for the stage of the nitrogen

Table 4 Synthesis of 2-arylindoles with different aryl bromides[a]



Entry	Aryl bromide	Indole		Yield (%)
1			**4a**	82
2			**4b**	90
3			**4c**	82
4			**4d**	80
5			**4e**	69[c]
6			**4f**	69[c]
7			**4g**	88[c]
8			**4h**	77[c]
9			**4i**	70[c]

[a] Reaction conditions: 2-Arylhaloarene (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol), **L8** (0.08 mmol), K_2CO_3 (0.5 mmol), aq. NH_3 (1.0 mL) and DMSO (1.5 mL) stirred at 100 °C for 18 h under Ar. [b] Reaction conditions: After removing the water by extraction, the residue was treated with $ZnBr_2$ (0.2 mmol) and toluene (4 mL), and refluxed at 110 °C for 6 h. [c] Refluxed at 110 °C for 15 h.

addition reaction, the electron-deficient arylacetylenes proceeded slower than the electron-rich and electron-neutral arylacetylenes (Table 3, **3g–3i**). In this situation, a longer time for complete cyclization was required, presumably due to the reduced electron density of the acetylene.

Under similar conditions, we were able to extend this copper catalytic protocol to the coupling of ammonia with the aryl bromide moiety bearing various functional groups. We found that the electronic and steric effects of the attached groups at the aryl bromide moiety were not ignored for either the initial amination or the sequential cyclization. The yields of products bearing a strong electron-withdrawing substituent were diminished (Table 4, **4e** and **4f**), a trend opposite to that observed for the copper-catalyzed coupling of ammonia with aryl halides.[5] The high reactivity of the amination for electron-deficient aryl bromides was also accompanied by an increase of the dehalogenation side reaction. For the complete cyclization, prolonging the time of the addition reaction is also suggested (Table 4, **4d–4g**). We also observed that aryl bromides were more reactive substrates. Consequently, amination reactions of aryl bromides with chloro substituents showed an interesting chemoselectivity, proceeding exclusively at the bromo group (Table 4, **4c** and **4d**).

Conclusions

In conclusion, we have explored a convenient, efficient and atom economic synthesis of free *N-H* 2-arylindoles from 2-arylhaloarenes *via* a sequential amination and cyclization. By applying this elegant protocol, a wide range of electron-rich and electron-deficient 2-phenylindoles were obtained. We believe that this simple and effective catalyst system will find wide applications in the synthesis of related indoles.

Experimental

General information

All reagents were obtained from commercial sources (>99%) and used without further purification unless otherwise noted. The reactions were carried out under an argon atmosphere and the products were isolated by column chromatography on silica gel (200–300 mesh) using petroleum ether (60–90 °C) and ethyl acetate as eluates. Compounds described in the literature were characterized by comparison of their ^1H and ^{13}C NMR spectra with the reported data. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 and chemical shifts are reported in parts per million relative to TMS. MS data were gathered on a HP1100 instrument. High resolution mass spectrometric data (HRMS) were gathered on an HPLC-Q-Tof MS. HPLC analyses were tested on a Waters 2695–2996 instrument.

General procedure for the synthesis of 2-arylhaloarenes

2-Bromo-anilines were obtained from commercial sources or were conveniently be prepared by the NBS bromination of anilines along with a catalytic amount of ammonium acetate (NH_4OAc) in CH_3CN, as described in the literature.[8]

2-Bromo-iodides were prepared based on the Sandmeyer reaction, as described in the literature.[3f]

2-Arylhaloarenes were prepared based on the Sonogashira coupling reaction, as described in the literature.[9]

General procedure for the synthesis of 2-arylindoles

Amination. A flame-dried test tube with a magnetic stirring bar was charged with 2-arylhaloarene (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol), picolinaldehyde oxime (0.08 mmol), K_2CO_3 (0.5 mmol) and aq. NH_3 (1.0 mL) in DMSO (1.5 mL), and stirred at 100 °C under argon. The mixture was reacted at 100 °C for 18 h and then cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated under vacuum.

Cyclization. The residue was direct treated with $ZnBr_2$ (0.2 mmol) and toluene (4 mL), and refluxed at 110 °C for 6 or 15 h. After cyclization completion had been detected by HPLC, the toluene was removed under vacuum and the residue then

purified by column chromatography on silica gel with an eluent of petroleum ether and ethyl acetate. All the physical data of the known compounds were in agreement with values reported in the literature.

2-(3,5-Dimethoxyphenyl)-1*H*-indole (3e)

Following the general procedure, the crude product was purified by a silica gel column using ethyl acetate/petroleum ether (1 : 5–1 : 1), giving a pale orange solid. Yield: 83 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (br, 1H), 7.62 (d, J = 7.6, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.81–6.80 (m, 3H), 6.4 (s, 1H), 3.86 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.2, 137.8, 136.7, 134.3, 129.1, 122.4, 120.7, 120.3, 110.9, 103.6, 100.4, 99.7, 55.5. HR-ESI-MS: $[M - H]^-$ m/z calc. for $C_{16}H_{14}NO_2$ 252.1025, found: 252.1023. GC-MS (EI) m/z: 253 (M^+, 100%). m.p.: 124–125 °C.

1-(2-Phenyl-1*H*-indol-6-yl)ethanone (4f)

Following the general procedure, the crude product was purified by a silica gel column using ethyl acetate/petroleum ether (1 : 5–1 : 1), giving a orange solid. Yield: 65 mg, 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.84 (br, 1H), 8.14 (s, 1H), 7.76–7.72 (m, 3H), 7.65 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 6.87 (s, 1H), 2.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.3, 141.8, 136.3, 133.2, 131.6, 131.5, 129.2, 128.6, 125.5, 120.8, 120.2, 111.9, 100.2, 26.84. HR-ESI-MS: $[M + Na]^+$ m/z calc. for $C_{16}H_{14}NO_2$ 258.0895, found: 258.0897. GC-MS (EI) m/z: 220 (100%), 235 (M^+, 70%). m.p.: 212–213 °C.

2-Phenyl-6-(trifluoromethoxy)-1*H*-indole (4h)

Following the general procedure, the crude product was purified by a silica gel column using ethyl acetate/petroleum ether (1 : 3), giving a white solid. Yield: 85 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (br, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.26 (s, 1H), 7.00 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 6.80 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.15, 139.43, 136.36, 131.88, 129.14, 128.12, 127.97, 125.19, 124.62, 121.88 (q, J = 255 Hz, 1C), 114.39, 103.96, 99.87. ^{19}F NMR (400 MHz, $CDCl_3$) δ = −57.9. MS (API, m/z): 278.0 $[M + H]^+$. HR-ESI-MS: $[M + H]^+$ m/z calc. for $C_{16}H_{11}NOF_3$ 278.0793, found: 278.0788. m.p.: 167–168 °C.

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