User-Friendly Copper-Catalysed Reduction of Azides to Amines

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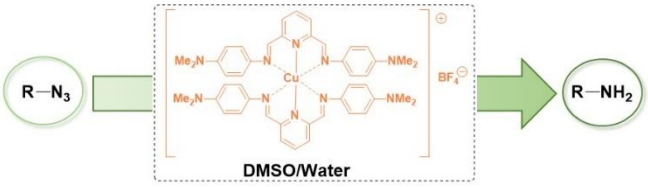
Supporting information and the ORCID identification numbers for the authors of this article can be found under XX. FAIR data for NMR spectra, and crystallographic data is available at 10.14469/hpc/6099.

Graphical Abstract:



The reduction of electron-poor azides into the corresponding amines or amides is presented. The developed catalytic system is based on an air-stable copper(I) catalysts and DMSO/water as both solvent/H-donor.

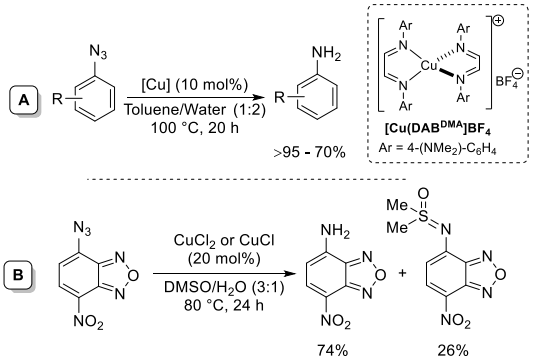
Abstract: Three homoleptic copper(I) complexes have been prepared and applied to the reduction of organic azides. Under optimised conditions, complex $[Cu(^{H}PDI^{DMA})_2]BF_4$ **3** ($^{H}PDI^{DMA}$ = 2,6-bis[*N*-(4-dimethylaminophenyl)carbaldimino]pyridine) could reduce a range of electron-poor azides in a mixture of DMSO and water without the need of an additional H-source.

Introduction

The popularity of organic azides as synthons has raised exponentially in the last two decades, mainly fuelled by the success of the copper-mediated dipolar cycloaddition of azides and alkynes,[1] a powerful exemplification of Click Chemistry.[2] Organic azides are generally stable towards water and oxygen, and safe to use (except those of low molecular weight) and hence their interest as intermediates in the synthesis of nitrogen-containing compounds is long standing.[3] In particular, the reduction of azides to primary amines is a powerful and widespread methodology for accessing this essential family of compounds.[4,5] Indeed, azides can be regarded as convenient amine protecting groups as they are readily accessible and avoid the introduction of additional steric bulk and solubility issues often encounter with carbamate and amide groups.

While a number of catalytic alternatives are available, the Staudinger reaction[6] arguably remains the most reliable strategy for accessing amines from the corresponding azides, particularly in bioconjugation and polysaccharides chemistry.[7] However, the generation of stoichiometric waste from the required phosphine or phosphite reagents is an outstanding concern, even more when the oxidised by-products are not always easy to separate.

We recently reported a [Cu^{I}(DAB)] catalyst (DAB = diazabutadiene) for the reductions of aryl azides into the corresponding anilines in the presence of air and water (Scheme 1A).[8] DFT calculations supported triplet copper(I)-nitrene intermediates as key species in this reaction where both reaction solvents, toluene and water, acted as hydrogen sources. Our results were further supported by an earlier report where nitrobenzoxadiazole azide wasreduced with 20 mol% of simple copper salts in degassed aqueous DMSO in the absence of any additional reducing agent (Scheme 1B).[9] The formation of a DMSO adduct in this system highlighted again the non-innocence of the solvent. Furthermore, this study established the intermediacy of triplet copper–nitrene species by EPR and the importance of water and light in the reaction.



Scheme 1. Reported reductions of aryl azides *via* copper–nitrenes. ^{1}H NMR yields reported.

Copper–nitrenes are accepted intermediates in a range of transformations such as aziridinations or transfer reactions into C–H bonds among others.[10] Their high reactivity offers a convenient alternative for the catalytic reduction of azides without the requirement for an external superstoichiometric hydride source. Indeed, it is widely accepted that in the reported catalytic methodologies, the azido group is reduced by the oxidation of copper(I) to copper(I), which is then reduced back to +I oxidation state upon reaction the reducing agent, such as $NaBH_4$ or sodium ascorbate.[11,12]

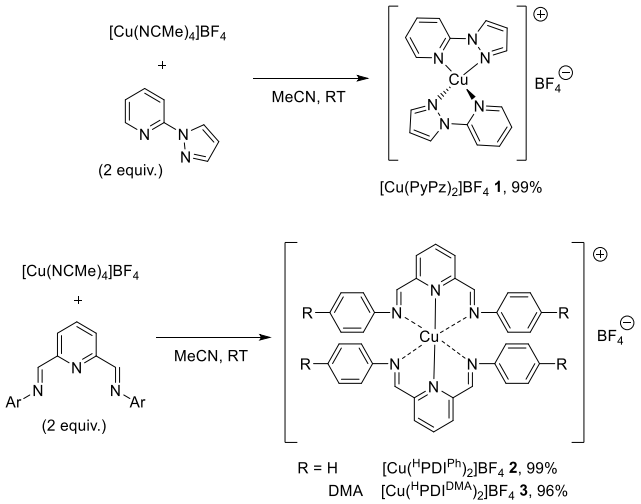
Herein we report the preparation of copper(I) complexes with bi- and tri-dentate N-based ligands and their catalytic activity in the reduction of azides into amines without the addition of any external hydride source.

Results and Discussion

Three known pyridine-containing ligands, 1-(pyridine-2-yl)-1H-pyrazole (PyPz), and two bis(imino)pyridines (^{H}PDI^{Ph} and ^{H}PDI^{DMA}) were selected. In the last 20 years PDI ligands have become increasingly popular ligands for transition metals thanks to their application in ethylene polymerisation processes and their non-innocent redox behaviour,[13] but only a few examples of copper(I) complexes bearing PDI ligands have been reported to date.[14]

The chosen ligands were reacted with $[Cu(NCMe)_4]BF_4$ to prepare three homoleptic complexes (Scheme 2). Compounds **1**–**3** were isolated in excellent yields after a simple precipitation and except for **1**, they were indefinitely stable towards oxygen and moisture and could be handled

with no particular precautions. $[Cu(PyPz)_2]BF_4$ **1**, however, underwent oxidation overnight and has to be kept under inert atmosphere.



Scheme 2. Preparation of cationic homoleptic complexes.

These complexes, whose colours range from yellow to dark brown, were fully characterised by spectroscopic methods. Elemental analysis and HRMS spectra of all complexes agreed with the proposed structures. Also, coordination is supported by the IR spectra as the medium absorption bands around 1576–1623 cm^{-1}, typical for C=N symmetric stretching vibrations, are shifted to lower wavenumbers compared to the corresponding free ligands. A single stretching band for the B-F bonds in complexes **1**–**3** appear at ca. 1025, 1032, 1045 cm^{-1}, respectively. This observation implies that the BF_4^- counter ion does not interact with the copper centre. In the ^1H NMR spectra, the resonances of the ligands appear slightly shifted to lower field upon coordination to the metal centre. For instance, the imino protons in $^{H}PDI^{Ph}$ (8.69 ppm in $CDCl_3$) appear at 8.78 ppm in complex **2**. On the other hand, a slight upfield shift (2–3 ppm) of the CH=N signals in **2** and **3** was observed by ^{13}C NMR. [15]

It is important to note that the ^1H NMR spectra for complexes **2** and **3** showed only a C_2 or *m*-symmetric ligand environment, in spite of the impossibility of featuring an octahedral copper(I) centre. Furthermore, $^1H/^{15}N$ 2D NMR experiments confirmed the magnetic equivalence of both imine nitrogen atoms when **3** is in solution.[16] This is indicative of fluxional behaviour in form of a fast metallotropic shift at room temperature.[17] Indeed, suitable crystals for single crystal X-ray diffraction were obtained for complex **3** by slow diffusion of toluene in a DCM solution (CCDC 1952818) and the obtained structure features a tetra-coordinated copper centre with a distorted tetrahedral geometry (τ_4 = 0.77, Figure 1).[18] No interaction between the copper centre and uncoordinated N(17) or N(47) is evidenced in the solid state since they are *ca*. 4.67 Å away from each other and these imino groups are rotated by *ca*. 180° about the C{ipso}–C{aldimine} single bond so that the lone pairs on these nitrogens are oriented away from the copper atom.[19]

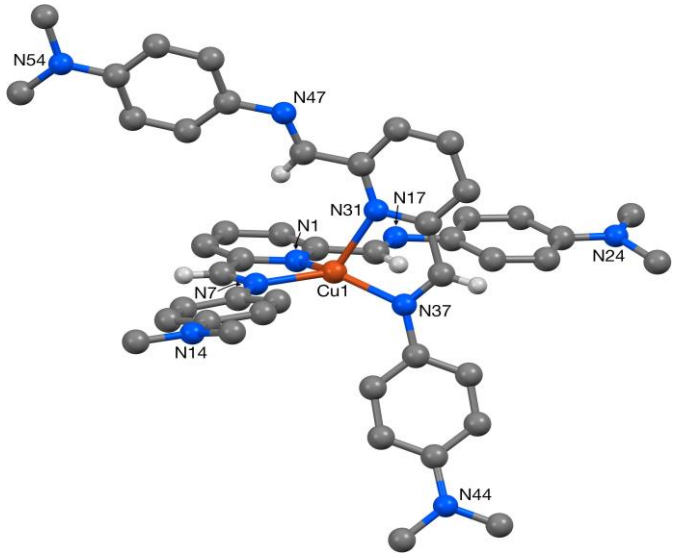
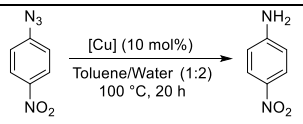


Figure 1. Structure of the cation present in the crystal of **3**. Most hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): Cu–N1 2.041(4), Cu–N7 2.035(5), Cu–N31 2.108(6), Cu–N37 2.007(4), N1–Cu–N7 82.4(2), N1–Cu–N31 113.9(2), N7–Cu–N37 132.1(2), N7–Cu–N31 119.2(2), N7–Cu–N37 131.0(2), N31–Cu–N37 81.7(2).

With this set of complexes in hand, their activity in the reductions of aryl azides was next investigated. With 4-nitrophenyl azide **4a** as model substrate, we first screened our catalysts using the conditions previously optimised for copper-DAB complexes,[8] and 10 mol% of each complex was used in a mixture of toluene and water at 100 °C in the presence of air (Table 1). Only a poor conversion into aniline **5a** was observed with catalysts **1**, which is not surprising considering its sensitivity towards oxidation. Still, a very similar outcome was obtained with **2**. Fortunately, a much more promising result was obtained with complex **3** bearing two $^{H}PDI^{DMA}$ ligands (Table 1, entry 3)

Table 1. Catalyst screening[a]



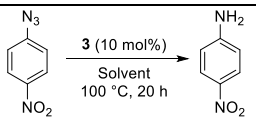
4a **5a**

Entry	[Cu]	Recov. **4a** (%)[b]	Conv. **5a** (%)[b]
1	$[Cu(PyPz)_2]BF_4$ **1**	73	13
2	$[Cu(^{H}PDI^{Ph})_2]BF_4$ **2**	71	18
3	$[Cu(^{H}PDI^{DMA})_2]BF_4$ **3**	-	53 (49)[c]

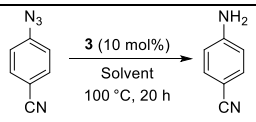
[a] Azide (0.5 mmol), catalyst (10 mol%) in toluene/water (1:2, 1 mL). [b] ^{1}H NMR recoveries/conversions are the average of two independent reactions and are calculated with respect to 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yield.

Catalyst **3** was selected for further optimisation, as it delivered the highest aniline conversion. Still, significant decomposition in this reaction led to almost 50% of the mass balance missing and therefore alternative solvents were next tested (Table 2). Lower conversions were obtained with toluene and water separately (Table 2, entries 1 and 2), and while expected **5a** was produced in all tested solvents, the highest conversions were observed in DMSO and ethanol (Table 2, entries 5 and 6). While considerable decomposition was still observed in all of these reactions, changing the model azide to the cyano analogue **5b** led to comparable amine conversions while significantly improving the azide recovery (Table 2, entries 9–10). A mixture of DMSO and water (4:1) further improved the amine conversion up to 89% (Table 2, entry 15), while the same positive effect was not observed with ethanol/water mixtures (Table 2, entries 10 and 16).[20]

Table 2. Solvent screening[a]



4a **5a**



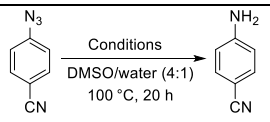
4b **5b**

Entry	Solvent	Recov. **4a** (%)[b]	Conv. **5a** (%)[b]	Entry	Solvent	Recov. **4b** (%)[b]	Conv. **5b** (%)[b]
1	Toluene	47	17	9[c]	DMSO	54	48
2	Water	9	39	10	Ethanol	19	63
3	1,4-Dioxane	24	35	11	Water	27	42
4	MeCN	35	38	12	DMSO/water (1:2)	25	48
5[c]	DMSO	3	49	13	DMSO/water (2:1)	17	78
6	EtOH	1	67	14	DMSO/water (3:1)	--	89
7	iPrOH	31	36	15	DMSO/water (4:1)	5	89
8	Glycerol	15	32	16	EtOH/water (2:1)	0	59

[a] Azide (0.5 mmol), **3** (10 mol%) in technical solvent (1 mL). [b] ^{1}H NMR recoveries/conversions are the average of two independent reactions and are calculated with respect to 1,3,5-trimethoxybenzene as the internal standard. [c] Traces of a DMSO adduct were also observed, see Scheme 1B.

Reducing the copper loading or temperature led to a decrease in aniline conversion, while the absence of light had no effect on the reaction (Table 3, entries 1–4). Both the ligand and copper are essential in this transformation as only 13% of **5b** was produced with a simple copper salt and the starting azide was quantitatively recovered in the absence of copper (Table 3, entries 5 and 6). Since no additional reagents are available in this system, only DMSO and water can act as H-donors. While it has been proposed that DMSO is a more likely H-donor in this transformation,[9] a hydrogen peroxide test showed that H_2O_2 was formed in the model reaction, albeit in low concentration (1–3 mg/L).

Table 3. Further optimisation[a]

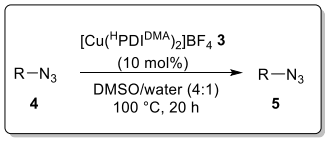


4b **5b**

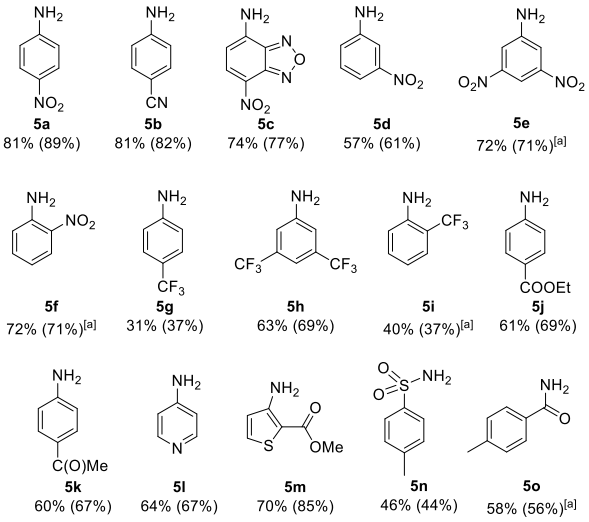
Entry	Conditions	Recov. **4b** (%)[b]	Conv. **5b** (%)[b]
1	**3** (10 mol%), 100 °C	5	89
2	**3** (10 mol%), 80 °C	33	62
3	**3** (5 mol%), 100 °C	30	57
4[c]	**3** (10 mol%), 100 °C	--	90
5	$[Cu(NCMe)_4]BF_4$ (10 mol%), 100 °C	79	13
6	No copper, 100 °C	>95	--

[a] Azide (0.5 mmol), [Cu] in DMSO/water (4:1, 1 mL). [b] ^{1}H NMR recoveries/conversions are the average of two independent reactions and are calculated with respect to 1,3,5-trimethoxybenzene as the internal standard. [c] Reaction carried out in the absence on light.

With an optimised set of conditions in hand, the scope of the reaction was next explored (Scheme 3). Good to high yields were obtained in general, even if the catalytic system remains limited to electron-poor aromatic azides.[21] Not only aryl azides, but also sulfonyl and acyl azides could be reduced under these conditions (*i.e.* **5n** and **5o**). In some cases, better conversions were observed at 80 °C as a lower temperature minimised azide decomposition (*i.e.* **5f**, **5i** and **5o**), although this effect was not general. All reactions were completely chemoselective and only azide groups were reduced under these conditions. Also, only traces of a urea derivative, issue of a Curtius rearrangement,[22] were observed in the formation of amide **5o**. Furthermore, despite the presence of water and oxygen, products **5** were stable and did not undergo oxidative hydrogenative couplings to produce either aromatic azo compounds or diaryl hydrazines.[23]



4 **5**



5a 81% (89%) **5b** 81% (82%) **5c** 74% (77%) **5d** 57% (61%) **5e** 72% (71%)[a]

5f 72% (71%)[a] **5g** 31% (37%) **5h** 63% (69%) **5i** 40% (37%)[a] **5j** 61% (69%)

5k 60% (67%) **5l** 64% (67%) **5m** 70% (85%) **5n** 46% (44%) **5o** 58% (56%)[a]

Scheme 3. [Cu(^{H}PDI^{DMA})$_2$]BF$_4$ **3** mediated reduction of azides. Isolated yields (^{1}H NMR conversions). [a] Reaction carried out at 80 °C.

Conclusions

Three complexes of general formulae [CuL$_2$]BF$_4$ have been prepared and fully characterised. Crystals grown for [Cu(^{H}PDI^{DMA})$_2$]BF$_4$ **3** confirmed the PDI ligands act as bidentate ones in this case, and that these complexes are highly fluxional in solution since only highly symmetrical ligand environments can be evidenced by ^{1}H and ^{13}C or ^{1}H/^{15}N NMR. Under optimised conditions, complex **3** could promote the reduction of a range of electron-poor organic azides. Even if its scope remains limited, complex **3** is a promising step towards the development of a sustainable alternative to the Staudinger reaction since it is active in all tested solvents, and therefore is it less sensitive to the nature of the H-donor, unlike our previously reported system.[8]

Experimental Section

General remarks

All chemicals were obtained from commercial sources and used without further purification. Copper complex syntheses were performed using standard Schlenk line techniques. Anhydrous acetonitrile was dried passing them through columns of molecular sieves in a solvent purification system. Column chromatography and TLC were performed on silica gel (Kieselgel 60), using UV light visualise the products. NMR spectra were measured on Bruker AVANCE 400 spectrometers (^{1}H: 400 MHz, ^{13}C: 100 MHz, ^{15}N: 50 MHz) at 20 °C, unless stated otherwise. The chemical shifts (δ) are given in ppm relatively to a tetramethylsilane standard or the residual solvent signal. The multiplicity is given in br, s, d, t, q, sept, and m for broad, singlet, doublet, triplet, quartet, septet, and multiplet. Mass spectra (MS) were recorded on a Micromass Autospec Premier, Micromass LCT Premier or a VG Platform II spectrometer using EI or ESI techniques at the Mass Spectroscopy Service of Imperial College London. Infrared spectra were recorded using a Perkin Elmer 100 series FT-IR spectrometer, equipped with a beam condensing accessory, and samples were sandwiched between diamond compressor cells. Melting points (uncorrected) were determined on an Electrothermal Gallenhamp apparatus. Single crystal X-ray diffraction data was collected using Oxford Diffraction Xcalibur PX Ultra and Xcalibur 3 diffractometers, and the structures were refined using the SHELXTL v5.1,[24] and SHELX-2013[25] program systems.

[Cu(PyPz)$_2$]BF$_4$ (1): PyPz (73 mg, 0.5 mmol) was added into the solution of [Cu(NCMe)$_4$]BF$_4$ (79 mg, 0.25 mmol) in 50 mL of dry acetonitrile and stirred for 16 h at room temperature under a nitrogen atmosphere. The reaction mixture was then filtered through Celite and concentrated to 10 mL. Petroleum ether (40 mL) was added and the resulting precipitate was filtered and dried under vacuum to isolate the title compound as a light yellow solid (101 mg, 99%(. mp 165 –166 ºC. ^{1}H NMR (400 MHz, CDCl$_3$, 223 K): δ 8.63 (br s, 2H), 8.39 (br s, 2H), 8.04 (br s, 3H), 7.82 (br s, 2H), 7.37 (br s, 3H), 6.69 (br s, 2H). ^{13}C NMR could not be recorded due to the low solubility in CDCl$_3$, CD$_3$CN, acetone-*d*$_6$, methanol-*d*$_4$, DMSO-*d*$_6$. IR (KBr) ν 3134,

1733, 1602, 1573, 1485, 1444, 1350, 1326, 1210, 1025, 946, 914, 901, 762, 713 cm^{-1}. HRMS (ESI-MS): *m/z* calcd for $C_{16}H_{14}N_6Cu$ 353.0576, found 353.0580 ($[Cu(PyPz)_2]^+$). Anal. Calcd for $C_{16}H_{14}F_4BCuN_6$: C, 43.61; H, 3.20; N, 19.07. Found: C, 43.73; H, 3.41; N, 18.90.

$[Cu(^{H}PDI^{Ph})_2]BF_4$ (2): Following the procedure described for the synthesis of **1** from $^{H}PDI^{Ph}$ (143 mg, 0.5 mmol), the title compound was isolated as dark brown solid (179 mg, 99%). mp 117 – 118 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 2H), 8.27 (d, *J* = 8.0 Hz, 2H), 8.20 (t, *J* = 8.0 Hz, 1H), 7.33–7.28 (m, 6H), 7.03 (d, *J* = 8.0 Hz, 4H). ^{13}C NMR (100 MHz, CD_3CN) δ 158.9, 152.2, 149.4, 140.1, 130.5, 129.8, 129.2, 122.4. IR (KBr) ν 3053, 2918, 1576, 1483, 1449, 1419, 1363, 1263, 1047, 1032, 954, 855, 759, 734, 686 cm^{-1}. HRMS (ESI-MS): *m/z* calcd for $C_{38}H_{30}N_6Cu$ 633. 1828, found 633. 1818 ($[Cu(^{H}PDI^{Ph})_2]^+$). Anal. Calcd for $C_{38}H_{30}F_4BCuN_6$: C, 63.30; H, 4.19; N, 11.66. Found: C, 62.99; H, 4.29; N, 11.53.

$[Cu(^{H}PDI^{DMA})_2]BF_4$ BF_4 (3): Following the procedure described for the synthesis of **1** from $^{H}PDI^{DMA}$ (186 mg, 0.5 mmol), the title compound was isolated as dark brown solid (428 mg, 96%). CCDC 1952818. mp 163 – 164 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 2H), 8.21 (d, *J* = 8.0 Hz, 2H), 8.07 (t, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 4H), 6.59 (d, *J* = 12.0 Hz, 4H), 2.97 (s, 12H). ^{13}C NMR (100 MHz, CD_3CN): δ 152.0, 150.9, 150.5, 138.3, 135.9, 125.8, 123.2, 111. 8, 39. 2. IR (KBr) ν 2856, 2800, 1610, 1591, 1559, 1517, 1360, 1271, 1162, 1121, 1090, 1045, 815, 739, 713 cm^{-1}. HRMS (ESI-MS): *m/z* calcd for $C_{46}H_{50}N_{10}Cu$ 805. 3516, found 805. 3526 ($[Cu(^{H}PDI^{DMA})_2]^+$). Anal. Calcd for $C_{46}H_{50}F_4BCuN_{10}$: C, 61.85; H, 5.64; N, 15.68. Found: C, 61.68; H, 5.55; N, 15.56.

General procedure for the reduction of azides: In a microwave vial, azide (1.0 mmol) and catalyst **3** (10 mmol%(were suspended in DMSO (1.6 mL) and water (0.4 mL) and sealed with a crimped cap. The reaction mixture was heated to 100 °C for 20 h before being cooled and filtered through Celite and washed with EtOAc. The filtrate was washed with saturated, aqueous Na_4EDTA (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Reported ^{1}H NMR yields are the average of at least two independent reactions and were calculated with respect to 1,3,5-trimethoxybenzene as internal standard. Isolated yields were obtained after purification by column chromatography.

4-Nitroaniline (5a): Following the general procedure from 1-azido-4-nitrobenzene (164 mg, 1.0 mmol), **5a** was isolated as a brown solid (224 mg, 81%) after purification by column chromatography (petroleum ether/EtOAc = 1:2, R_f = 0.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 2H), 6.63 (d, *J* = 8.0 Hz, 2H), 4.36 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 139.1, 126.4, 113.4. Spectroscopic data were consistent with previously reported data for this compound.[26]

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Conflict of interest

The authors declare no conflict of interest

Keywords: Amines – Azides – Reduction – Copper – Pyridyldi(imine) Ligands

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