A convenient copper-catalyzed direct amination of nitroarenes with *O*-alkylhydroxylamines

Shinzo Seko,* Kunihito Miyake and Norio Kawamura

Organic Synthesis Research Laboratory, Sumitomo Chemical Co., Ltd., Tsukahara, Takatsuki, Osaka 569-1093, Japan

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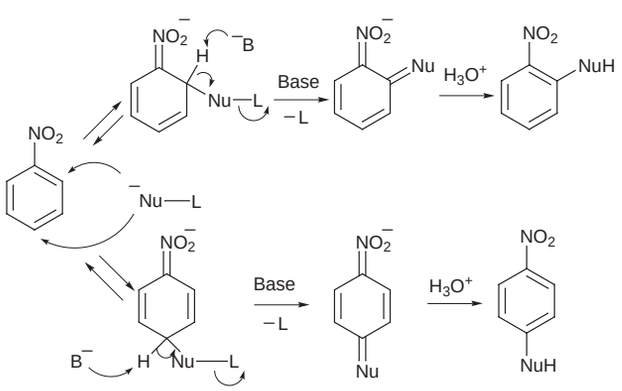
O-Alkylhydroxylamines, particularly *O*-methylhydroxylamine, aminate nitroarenes in the presence of a strong base and a copper catalyst to give aminonitroarenes in good yields. *ortho*- or *para*-Amination with respect to the nitro group takes place, and in some cases the *ortho*-aminated product is preferentially obtained. With 3-substituted nitrobenzenes where the substituent has a lone pair of electrons, preferential amination occurs at the 2-position to give the sterically most congested **3c**–**f**, **14** and **22g**.

Introduction

Aromatic amines represent an important class of compounds for a wide variety of pharmaceuticals, pesticides, additives and dyes. They have been synthesized in the chemical industry for a long time by such classical methods as the sequence of nitration–reduction, and substitution reactions of aromatic halides or hydroxides with amines.[1] Although direct amination of aromatic compounds, which is the most simple synthetic method for aromatic amines, is of great interest, there have been no general and practical methods for it in spite of considerable efforts in its exploitation.[2] Vicarious nucleophilic substitution (VNS),[3] which has been intensely studied by Makosza and coworkers, significantly serves as one of the nucleophilic substitutions for aromatic hydrogen,[4] although a nitro group in the substrate is necessary. The VNS reaction consists of treatment of nitroarenes with nucleophiles bearing a good leaving group at the nucleophilic center to furnish the corresponding *ortho*- or *para*-substituted nitroarenes (Scheme 1). VNS alkylations,[5]

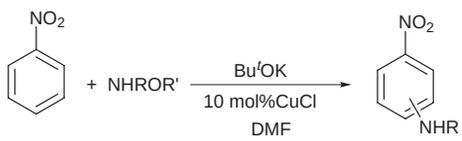


Scheme 1

hydroxylation[6] and aminations[7] have been reported so far. Among them, amination is of great importance as a direct introduction of an amino group into an aromatic ring to give aminonitroarenes. 4-Amino-1,2,4-triazoles,[7a] sulfenamides[7b,c] and 1,1,1-trimethylhydrazinium iodide[7d] are known as aminating agents. However, since these agents have a complicated leaving group of high molecular weight, additional treatment and separation of the eliminated residue from the products are necessary in the work-up procedures. On the other hand, although it is known that unsubstituted hydroxylamine aminates 1,3-dinitrobenzene and bicyclic nitroarenes,[8] it cannot aminate mononitrobenzenes.

In our preliminary communication[9] we briefly reported the direct amination of nitrobenzenes with *O*-alkylhydroxylamines in the presence of a copper catalyst to give nitroanilines in excellent yields. *ortho*-Nitroanilines thus obtained are important as precursors of *o*-phenylenediamines, which are readily converted into benzimidazole or quinoxaline derivatives often found in numerous pharmaceuticals.[10] This paper gives a full account of our studies on the amination of nitroarenes with *O*-alkylhydroxylamines, in particular, *O*-methylhydroxylamine.

Table 1 Direct amination of nitrobenzene with *O*-alkylhydroxylamines[a]



Entry	R	R′	Yield (%)[b]	*o*:*p*[c]
1	H	Me	93 (60)[d]	71:29 (65:35)[d]
2	H	Et[e]	68 (38)[d]	68:32 (61:39)[d]
3	H	Bn[e]	41	76:24
4	H	Bu^t[e]	40	27:73
5	Me	Me	22[f]	0:100
6	H	H	0[g]	

[a] Unless otherwise stated, reactions were performed with nitrobenezene (1 equiv.), NHROR′ (1.25 equiv.), Bu^{t}OK (3 equiv.) and CuCl (0.1 equiv.) in DMF at room temperature for 1–24 h. [b] GC yields. [c] The *o*:*p* ratios were determined by GC. [d] Results when CuCl was not used are in parentheses. [e] Amine hydrochloride and an additional base (1.25 equiv.) were used. [f] Isolated yield. [g] Starting material was recovered.

Results and discussion

We initially examined commercially available primary amines with a N–N, N–O, N–S or N–halogen bond, as VNS aminating agents for the amination of nitrobenzene in the presence of Bu^{t}OK in DMF. After screening many candidates we found that *O*-methylhydroxylamine[11] can efficiently aminate nitrobenzene in the presence of Bu^{t}OK (3 equiv.) in DMF at room temperature to give *ortho*- and *para*-nitroanilines (*o*:*p* = 65:35) in 60% yield (Table 1, Entry 1, values in parentheses). Some metal catalysts such as zinc, copper, nickel and manganese salts were next examined in order to improve the unsatisfactory

Table 2 The effect of experimental conditions on the yields of nitroanilines in the direct amination of nitrobenzene with *O*-methylhydroxylamine[a]

Entry	Bu^{t}OK (equiv.)	CuCl (equiv.)	Solvent	Yield (%)[b]	*o*:*p*[b]
1	1	0.1	DMF	50	69:31
2	2	0.1	DMF	84	70:30
3	3	0.1	DMF	93	71:29
4	3	0.01	DMF	83	73:27
5	3	0.1	Toluene	59	80:20
6	3	0.1	Hexane	71	81:19

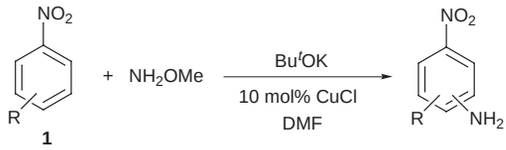
[a] Reactions were performed with nitrobenzene (1 equiv.), NH_2OMe (1.25 equiv.), Bu^{t}OK and CuCl in a solvent at room temperature for 3 h. [b] Determined by GC.

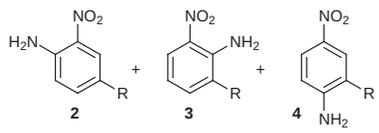
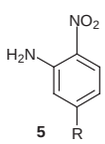
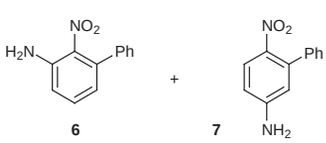
yield. Consequently copper catalysts were found to play a significant role in promoting the reaction. CuCl (10 mol%) improved the yield up to 93% (*o*:*p* = 71:29) (Table 1, Entry 1). A variety of copper compounds such as CuBr, CuI, $CuCl_2$, $Cu(acac)_2$, $Cu(OAc)_2$ and $Cu(NO_3)_2$ as well as CuCl showed the same effect, but CuCN and $CuSO_4$ were less effective. It is worth noting that both univalent and bivalent copper catalysts could be used equally well. Various *O*-alkylhydroxylamines could be found to aminate nitrobenzene to give *ortho*- and *para*-nitroanilines, as shown in Table 1. Among them, *O*-methylhydroxylamine was the best aminating agent in terms of yield of nitroanilines, which was higher than those in the previously reported VNS aminations of nitrobenzene.[7] *O*-Methylhydroxylamine could be used both as the free amine as well as its hydrochloride salt together with additional base to provide similar results. The use of *O*-ethylhydroxylamine, *O*-benzylhydroxylamine and *O*-*tert*-butylhydroxylamine gave somewhat lower yields (Entries 2–4). The reaction with *O*-*tert*-butylhydroxylamine gave *para*-rich nitroanilines because of its steric bulk (Entry 4). Methylamination using *N*,*O*-dimethylhydroxylamine also occurred with *para*-selectivity, although in low yield (Entry 5). Amination with an unsubstituted hydroxylamine, known to aminate 1,3-dinitrobenzene and bicyclic nitroarenes,[8] did not take place under these conditions, and the starting material was recovered quantitatively (Entry 6).

The theoretical amount of the base in the VNS reaction (Scheme 1) is 2 equivalents to the substrate. The present amination also required 2 equivalents of the base according to the VNS reaction (Table 2, Entries 1 and 2). Excess base (3 equiv.) further improved the yield of nitroanilines (Entry 3). Use of only 1 mol% of CuCl gave a somewhat lower yield than that of 10 mol% (Entry 4). The reaction proceeded even in low-polar hydrocarbon solvents such as toluene and hexane in spite of poor solubility of the base and catalyst (Entries 5 and 6). Such solvents influenced the *o*:*p* ratio of the products, which were slightly changed to 80:20 from 70:30.

Amination of a variety of mono-substituted nitrobenzenes with *O*-methylhydroxylamine in the presence of Bu^{t}OK and CuCl catalyst in DMF at room temperature afforded the corresponding substituted nitroanilines in excellent yields. The results are summarized in Table 3. A remarkable regioselectivity was observed in the amination of *meta*-substituted nitrobenzenes in which the substituent has a lone pair of electrons such as OMe, Cl, F and NMe_2. The most sterically congested 1,2,3-trisubstituted nitroanilines **3c**–**f** were predominantly produced (Entries 3–6).[12] In particular the reaction of *N*,*N*-dimethyl-3-nitroaniline afforded **3f** in 75% yield and selectivity (Entry 6). These compounds cannot easily be synthesized by conventional methods due to the steric hindrance. Addition of CuCl has no effect on the orientation of the aminations. Simple electron charge or orbital control, according to molecular calculations on the substrates, could not explain this regioselectivity. The reaction of *para*-substituted nitrobenzenes gave 5-substituted

Table 3 Direct amination of nitrobenzenes with *O*-methylhydroxylamine[a]

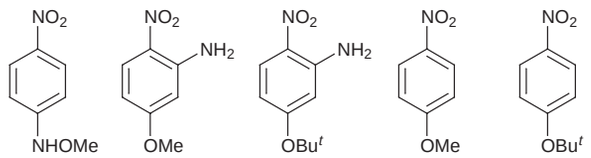


Entry		R	Ratio of products[b]			Yield (%)[c]
						
1[d]	**a**	H	71 (65)[e] :	na :	29 (35)[e]	93 (60)[e]
2	**b**	3-CF_3	50 (48)[e] :	26 (31)[e] :	24 (21)[e]	93 (25)[e]
3	**c**	3-OMe	15 (15)[e] :	61 (61)[e] :	24 (24)[e]	94 (57)[e]
4	**d**	3-Cl	18 :	48 :	34	85
5	**e**	3-F	15 :	55 :	30	88
6	**f**	3-NMe_2	10 (10)[e] :	75 (73)[e] :	15 (17)[e]	99 (65)[e]
						
7	**g**	4-OMe				69 (41)[e]
8	**h**	4-OPh				70 (42)[e]
9	**i**	4-SMe				92 (65)[e]
10	**j**	4-Bu^t				91
11	**k**	4-CF_3				76 (28)[e]
12	**l**	4-Cl				86 (39)[e]
13	**m**	4-Br				71
14	**n**	4-F				17
15	**o**	4-(1*H*-imidazol-1-yl)				70
						
16	**p**	2-Ph	70 (99)[e] :	30 (1)[e]		86 (31)[e]

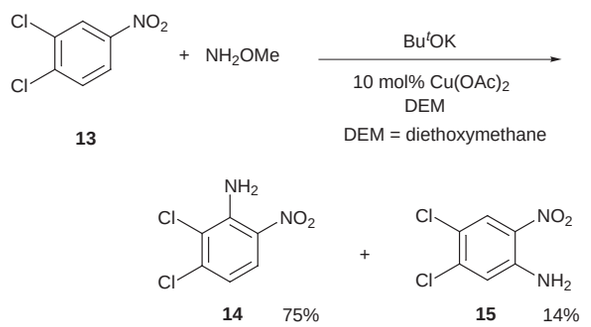
[a] Reactions were performed with NH_2OMe (1.25 equiv.), Bu^{t}OK (3 equiv.) and CuCl (0.1 equiv.) in DMF at room temperature for 10–60 min. [b] Unless otherwise noted, all isomers were isolated. [c] Total yield of all isomers. [d] Yield and ratio of the products were determined by GC. [e] Results when CuCl was not used are in parentheses.

2-nitroanilines as sole products in good yields (Entries 7–13 and 15). It is noteworthy that *p*-chloro- or *p*-bromonitrobenzene can be aminated smoothly to provide 5-chloro- or 5-bromo-2-nitroaniline in good yields without formation of 4-(*N*-methoxyamino)nitrobenzene **8**, which is a conventional nucleophilic aromatic substitution (S_NAr) product, despite the fact that the chlorine or bromine atom was activated by the *p*-nitro group in the substrate (Entries 12 and 13). On the other hand, in the case of *p*-fluoronitrobenzene, the desired aminated product **5n** was obtained in only 17% yield along with **9** (37%), **10** (14%), **11** (25%) and **12** (7%), but without **8** (Entry 14). The *para*-fluorine atom, being more reactive than either the chlorine or bromine atom, was substituted by a *tert*-butoxy anion derived from the base or a methoxy anion generated *in situ* after the amination to give **9**, **10**, **11** and **12**. However, even though *p*-fluoronitrobenzene has such a high reactivity towards S_NAr, the compound **8**, which should be produced through S_NAr with NH_2OMe, was not detected. This fact suggests that the direct amination with NH_2OMe is much faster than S_NAr with NH_2OMe. The byproduct **9** is particularly intriguing as it arises from stepwise and regioselective introduction of both

NH_2 and MeO in NH_2OMe, although in low yield. In the reaction of 2-nitrobiphenyl **1p** preferential *ortho*-orientation was observed (Entry 16, Table 3).

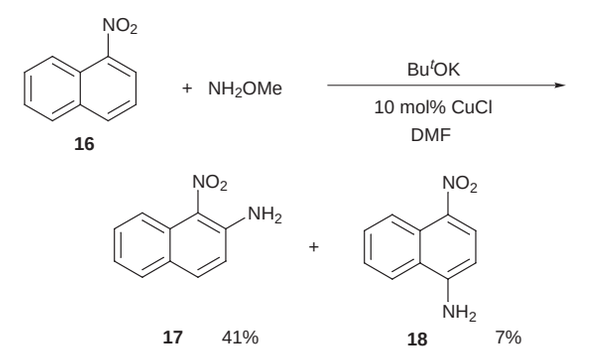


As an example of the amination of a disubstituted nitrobenzene, the amination of 3,4-dichloronitrobenzene **13** with *O*-methylhydroxylamine in the presence of Bu^{t}OK (3 equiv.) and $Cu(OAc)_2$ (0.1 equiv.) in diethoxymethane at room temperature for 2 h furnished the 2,3-dichloro-6-nitroaniline **14** (75%) and 4,5-dichloro-2-nitroaniline **15** (14%) (Scheme 2). The



Scheme 2

reaction in the presence of CuCl (0.1 equiv.) in DMF gave the products in only 34% yield. Also in this case the unusual regioselectivity was observed and 1,2,3,4-tetrasubstituted product **14**, which is a versatile intermediate for a herbicide,[13] was predominantly produced. The direct aminations of nitronaphthalenes have been extensively studied.[7a–c,8a,b] In the present case, the reaction of 1-nitronaphthalene **16** with *O*-methylhydroxylamine gave 2-amino-1-nitronaphthalene **17** and 1-amino-4-nitronaphthalene **18** in 41% and 7% yields, respectively (Scheme 3). On the other hand, unfortunately, the

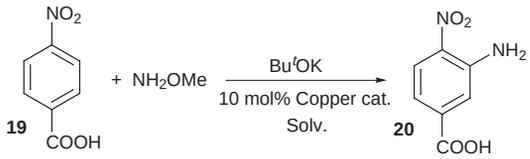


Scheme 3

amination of 1,3-dinitrobenzene, nitrothiophenes or nitropyridines[14] was unsuccessful under the present copper-catalyzed conditions, although these compounds could be aminated by the aminating agents previously reported.[7]

Our attention then turned to an amination of nitrobenzoic acids due to their significance as intermediates for pharmaceuticals.[15] An attempted amination of *p*-nitrobenzoic acid **19** with *O*-methylhydroxylamine under the same conditions as those in the amination of nitrobenzene [NH_2OMe (1.25 equiv.), Bu$'$OK (3 equiv.), CuCl (0.1 equiv.) in DMF] gave the expected

Table 4 Direct amination of *p*-nitrobenzoic acid with *O*-methylhydroxylamine[a]



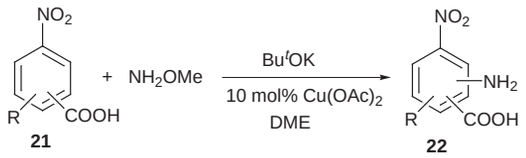
Entry	NH_2OMe (equiv.)	Bu$'$OK (equiv.)	Copper cat.	Solvent	Yield (%)[b]
1	1.25	3	CuCl	DMF	14
2	1.25	4	CuCl	DMF	28
3	1.25	4	$Cu(OAc)_2$	DMF	35
4	1.25	4	$Cu(OAc)_2$	DEM[c]	27
5	1.25	4	$Cu(OAc)_2$	DME[d]	36
6	2.00	7	$Cu(OAc)_2$	DMF	40
7	2.00	7	$Cu(OAc)_2$	DME[d]	51

[a] Reactions were performed with *p*-nitrobenzoic acid, NH_2OMe, Bu$'$OK and a copper catalyst in a solvent at room temperature for 3 h. [b] Isolated yield. [c] Diethoxymethane. [d] Dimethoxyethane.

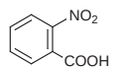
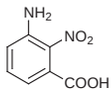
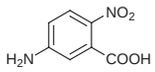
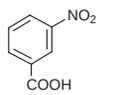
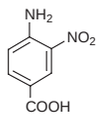
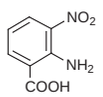
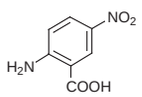
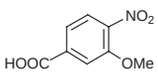
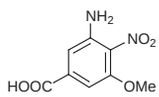
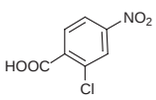
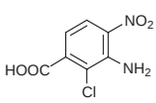
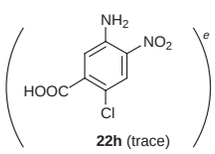
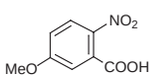
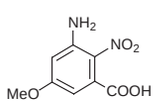
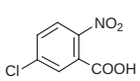
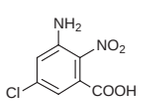
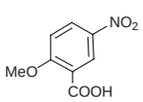
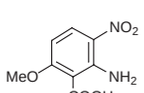
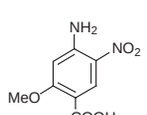
3-amino-4-nitrobenzoic acid **20** in only 14% yield, and 80% of the starting material was recovered (Table 4, Entry 1). However, by the use of 2 equivalents of *O*-methylhydroxylamine, 7 equivalents of Bu$'$OK and 0.1 equivalent of $Cu(OAc)_2$ in DME, the yield of the product was improved to 51% (Entry 7). The use of $Cu(OAc)_2$ provided a slightly better yield than that of CuCl (Entries 2 and 3). DME was the best choice of solvent, and a large excess of the base and *O*-methylhydroxylamine was effective for the amination of **19**. The results of the amination of *o*- and *m*-nitrobenzoic acid and nitrobenzoic acids bearing a chlorine or a methoxy group are summarized in Table 5. With *o*- or *m*-nitrobenzoic acid, no trends in regioselectivity could be observed (Entries 1 and 2). In the previous papers,[7] 1,2,3-trisubstituted isomer **22d** could not be detected by the aminations of *m*-nitrobenzoic acid. However, in our case, it was obtained in 21% yield accompanied with **22c** (30%) and **22e** (31%) (Entry 2). The amination of 2-chloro-4-nitrobenzoic acid **21d** gave 3-amino-2-chloro-4-nitrobenzoic acid **22g** with high regioselectivity (Entry 4), which is consistent with those observed in the amination of 3-chloronitrobenzene or 3,4-dichloronitrobenzene. Fairly good yields were indicated in the reactions of **21e** and **21f**, and a sole product was obtained in each case (Entries 5 and 6).

A proposed reaction mechanism, in principle, follows the general VNS reaction with a modification of the copper catalyzed system (Scheme 4). The copper salt should catalyze the addition of *O*-methylhydroxylamine to the nitroarene. The copper amide ate complex **24** might be generated and undergo oxidative addition to *ortho*- and *para*-positions of the nitroarene **25** to give **26** and **27**.[16] Examination of the NMR spectrum of *O*-methylhydroxylamine in the presence of a copper salt and a base suggests the generation of **24**. The ^{1}H-NMR spectrum (DMSO-d_6) of *O*-methylhydroxylamine in the presence of Bu$'$OK and CuCl showed two singlets at δ 3.35 and 3.22 ppm assignable as the methoxy groups of *O*-methylhydroxylamine itself and copper complexed *O*-methylhydroxylamine, while in the absence of CuCl only one singlet at δ 3.34 ppm was observed. This indicates the existence of some interaction between *O*-methylhydroxylamine and CuCl. Nilsson reported a copper salt mediated VNS alkylation of 1,3-dinitrobenzene, where the addition of a stoichiometric amount of copper salt changed the regioselectivity by chelation of the σ-adduct to the copper ion.[17] However, we assume that the copper catalyst does not activate the substrate or the σ-adduct in our amination because a catalytic amount of the copper salt is sufficient to promote the reaction and the addition of the copper catalyst does not affect the regioselectivity of the amin-

Table 5 Direct amination of nitrobenzoic acids with *O*-methylhydroxylamine[a]



21 **22**

Entry	Substrate	Products, Yields (%)[b]		
1	 **21a**	 **22a** (35)	 **22b** (34)	
2	 **21b**	 **22c** (30)[c]	 **22d** (21)	 **22e** (31)[c]
3	 **21c**	 **22f** (40 (78)[d])		
4	 **21d**	 **22g** (62)	 **22h** (trace)[e]	
5	 **21e**	 **22i** (85)		
6	 **21f**	 **22j** (78)		
7	 **21g**	 **22k** (21)	 **22l** (44)	

[a] Reactions were performed with NH_2OMe (2 equiv.), Bu^{t}OK (7 equiv.) and $Cu(OAc)_2$ (0.1 equiv.) in DME at room temperature for 2–4 h. [b] All isomers were isolated, unless otherwise noted. [c] **22c** and **22e** could not be separated. [d] Calculated on consumed substrate. [e] The structure could not be fully determined.

ation. The intermediates **26** and **27** should subsequently undergo reductive elimination to give the σ-adducts, Meisenheimer complexes **28** and **29**, respectively. Finally the reaction of **28** and **29** with a base provides the deep red intermediates **30** and **31** according to the usual VNS reaction mechanism[3] and a subsequent acidic work-up gives the corresponding *ortho*- and *para*-nitroanilines. In the competitive non-catalytic system, **23** directly adds to nitroarene **25** to give **28** and **29**, which are reversible reactions. However the non-catalytic system gave insufficient conversion of **25** and yields of nitroanilines. The regioselectivity would be governed by the irreversible steps (**28**→**30**, **29**→**31**), base-induced β-eliminations. This would be a reasonable explanation for the fact that the copper catalyst did not influence the orientation of the amination. The preferential *ortho*-orientation observed in some cases might be attributable to a contribution of a neighboring effect of the nitro group on the σ-adduct **28**. The neighboring nitro group may assist in elimination of the methoxy anion to form five-membered intermediate **32** (Scheme 5).

In conclusion, we have demonstrated that the novel copper-catalyzed direct amination of nitroarenes with *O*-alkylhydroxylamines, particularly *O*-methylhydroxylamine, provides the shortest synthesis of *ortho*- and *para*-nitroanilines. Commercially available *O*-methylhydroxylamine is a useful and effective aminating agent since it has only a methoxy group as the leaving group, and thus treatment after completion of the reaction is easier than for the other known VNS aminations,[7] in which the aminating agents have complicated and heavy leaving groups. The unusual regioselectivity observed in this amination allowed the synthesis of a new class of nitroanilines which are quite difficult to synthesize by conventional methods. In particular, *ortho*-nitroanilines obtained here are of extreme importance as intermediates of numerous pharmaceuticals containing benzimidazole or quinoxaline heterocycles.

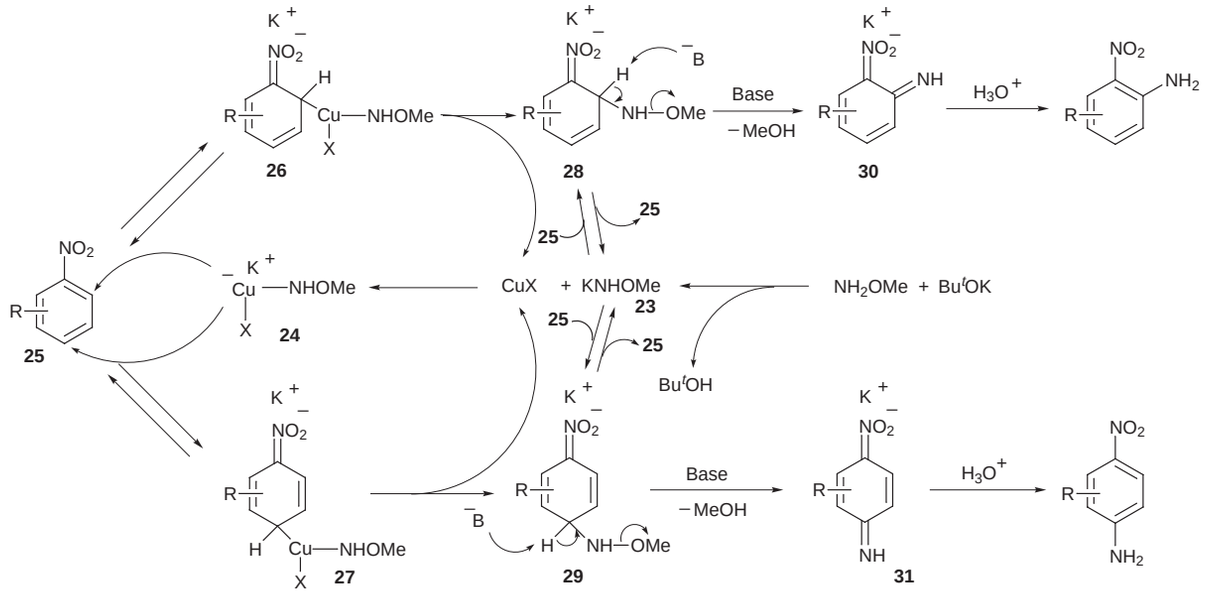
Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and Electrothermal IA9300 (Mitamura Riken), and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 as solvent on a JEOL JNM-EX270 spectrometer (at 270 and 67.8 MHz, respectively) and Varian UNITY-400P spectrometer (at 400 and 100 MHz, respectively), with tetramethylsilane for ^{1}H and $CDCl_3$ or DMSO-d_6 for ^{13}C as internal standards. Chemical shifts are quoted in parts per million (ppm). The following abbreviations are used for multiplicities: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, mutiplet. Coupling constants (*J*) are given in hertz (Hz). Mass spectra were recorded on a GC/MS HP 5971A and 5972A mass spectrometer. High resolution mass spectra were recorded on a JEOL JMS-SX-102A mass spectrometer. Elemental analyses were performed on a Elementar Vario EL analyzer. Analytical thin layer chromatography (TLC) was conducted on glass-backed 0.25 mm thick silica gel 60 F_{254} plates (Merck, No. 5719) and the chromatograms were visualized under a 254 nm UV lamp. Preparative thin layer chromatography (PLC) was carried out on 20 × 20 cm glass plates coated with silica gel 60 F_{254} (Merck, No. 13895) and eluted with the solvent system indicated. Flash column chromatography was carried out on silica gel 60 (Merck, No. 9385) and eluted with the solvent system indicated. Gas chromatography was carried out on a DB-1701 Megabore capillary column (J & W Scientific) in a Shimadzu GC-9A gas chromatograph, with dimethyl phthalate as an internal standard. Diethoxymethane (DEM) was obtained from Eastman Chemicals Co., Ltd.

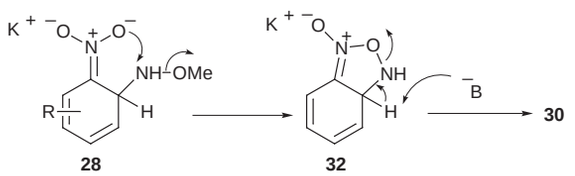
Typical procedure for the amination of nitrobenzene with *O*-alkylhydroxylamine

A solution of *O*-ethylhydroxylamine hydrochloride (244 mg, 2.5 mmol) and a nitrobenzene (246 mg, 2 mmol) in DMF (3 ml) was added dropwise to a stirred suspension of Bu^{t}OK (954 mg, 8.5 mmol) and CuCl (20 mg, 0.2 mmol) in DMF (7 ml) over 5 min at room temperature. After stirring for 60 min at room temperature, it was quenched with saturated aq. NH_4Cl and the products were extracted with CH_2Cl_2. The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product included 2-nitroaniline (127 mg, 46%), 4-nitroaniline (61 mg, 22%) and nitrobenzene (34 mg, 14%), which were determined by the GC-IS method.

N-Methyl-4-nitroaniline was isolated and purified by silica gel thin layer chromatography (AcOEt–hexane = 1 : 1). Products, 2-nitroaniline, 4-nitroaniline and *N*-methyl-4-nitroaniline were identical with commercially available authentic samples.



Scheme 4



Scheme 5

4-*tert*-Butylnitrobenzene 1j. To a mixture of 96% sulfuric acid (12.6 g, 123 mmol) and 60% nitric acid (12.6 g, 120 mmol) was added *tert*-butylbenzene (5.37 g, 40 mmol) at 5–10 °C. After stirring for 60 min at room temperature, it was quenched with ice-water and the product was extracted with CH_2Cl_2. The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc–hexane = 1 : 10) afforded 4-*tert*-butylnitrobenzene **1j**[18] (2.30 g, 32%) as a pale yellow oil; R_f 0.62; δ_H (270 MHz; $CDCl_3$) 1.36 (9H, s), 7.54 (2H, dm, *J* 8.57), 8.15 (2H, dm, *J* 8.57).

1-(4-Nitrophenyl)-1*H*-imidazole 1o. A mixture of *p*-fluoronitrobenzene (1.41 g, 10 mmol), imidazole (748 mg, 11 mmol), K_2CO_3 (690 mg, 5 mmol) and DMF (5 ml) was stirred for 3 h at 100–120 °C. The reaction mixture was quenched with water and the product was extracted with CH_2Cl_2. The organic extract was washed twice with water and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by recrystallization (EtOAc, hexane, MeOH) afforded 1-(4-nitrophenyl)-1*H*-imidazole **1o**[19] (1.03 g, 54%) as a brown crystalline solid; δ_H (270 MHz; $CDCl_3$) 7.28 (1H, s), 7.40 (1H, s), 7.61 (2H, d, *J* 9.90), 8.00 (1H, s), 8.38 (2H, d, *J* 9.90).

General procedure for the amination of nitroarenes 1

A solution of *O*-methylhydroxylamine (118 mg, 2.5 mmol) and a nitroarene **1** (2 mmol) in DMF (3 ml) was added dropwise to a stirred suspension of Bu^{t}OK (672 mg, 6 mmol) and CuCl (20 mg, 0.2 mmol) in DMF (7 ml) over 5 min at room temperature. After stirring for 10–60 min at room temperature, it was quenched with saturated aq. NH_4Cl and the products were extracted with CH_2Cl_2. The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel thin layer chromatography (EtOAc–hexane) afforded the nitroanilines **2**–**7**. Products, 2-nitro-4-(trifluoromethyl)-aniline **2b**, 4-methoxy-2-nitroaniline **2c**, 4-chloro-2-nitroaniline **2d**, 4-fluoro-2-nitroaniline **2e**, 4-nitro-2-(trifluoromethyl)aniline **4b**, 2-methoxy-4-nitroaniline **4c**, 2-chloro-4-nitroaniline **4d**, 5-chloro-2-nitroaniline **5l** and 4-nitroanisole **11** were identical with commercially available authentic samples.

***N*^{4},*N*^{4}-Dimethyl-2-nitro-1,4-phenylenediamine 2f.**[20] R_f 0.10 (EtOAc–hexane = 1 : 5); δ_H (270 MHz; $CDCl_3$) 2.87 (6H, s), 5.78 (2H, br s), 6.77 (1H, d, *J* 9.23), 7.06 (1H, dd, *J* 2.97 and 9.23), 7.36 (1H, d, *J* 2.97).

2-Nitro-6-(trifluoromethyl)aniline 3b.[21] R_f 0.61 (EtOAc–hexane = 1 : 5); δ_H (270 MHz; $CDCl_3$) 6.67 (2H, br s), 6.75–6.81 (1H, m), 7.74 (1H, d, *J* 7.59), 8.35 (1H, d, *J* 8.58).

2-Methoxy-6-nitroaniline 3c.[7c] R_f 0.37 (EtOAc–hexane = 1 : 5); δ_H (270 MHz; $CDCl_3$) 3.91 (3H, s), 6.42 (2H, br s), 6.60 (1H, dd, *J* 7.92 and 8.91), 6.88 (1H, dd, *J* 1.32 and 7.92), 7.72 (1H, dd, *J* 1.32 and 8.91).

2-Chloro-6-nitroaniline 3d.[7c] R_f 0.50 (EtOAc–hexane = 1 : 5); δ_H (270 MHz; $CDCl_3$) 6.56 (2H, br s), 6.66 (1H, dd, *J* 7.91 and 8.91), 7.52 (1H, dd, *J* 1.65 and 7.91), 8.09 (1H, dd, *J* 1.65 and 8.91).

2-Fluoro-6-nitroaniline 3e.[7d] R_f 0.49 (EtOAc–hexane = 1 : 5); δ_H (270 MHz; $CDCl_3$) 6.41 (2H, br s), 6.63 (1H, ddd, *J* 5.28, 7.91 and 8.58), 7.23 (1H, ddd, *J* 1.32, 7.91 and 10.56), 7.92 (1H, td, *J* 1.32 and 8.58).

***N*^{1},*N*^{1}-Dimethyl-3-nitro-1,2-phenylenediamine 3f.** R_f 0.49 (EtOAc–hexane = 1 : 5); δ_H (270 MHz; $CDCl_3$) 2.66 (6H, s), 6.61 (1H, dd, *J* 7.59 and 8.91), 6.69 (2H, br s), 7.21 (1H, dd, *J* 1.32 and 7.59), 7.88 (1H, dd, *J* 1.32 and 8.91); δ_C (67.8 MHz; $CDCl_3$) 43.92, 115.08, 121.17, 125.41, 132.15, 141.40, 143.13; *m*/*z* (EI) 181(M^+), 162, 147, 145, 133, 119, 105, 92, 78, 65, 52, 42; HRMS(FAB) Found: $(M + H)^+$, 182.0948. $C_8H_{12}N_3O_2$ requires *M*, 182.0930.

2-Fluoro-4-nitroaniline 4e.[7] R_f 0.15 (EtOAc–hexane = 1 : 5); δ_H (270 MHz; $CDCl_3$) 5.20 (2H, br s), 6.81 (1H, t, *J* 8.58), 7.85–7.92 (2H, m).

***N*^{2},*N*^{2}-Dimethyl-4-nitro-1,2-phenylenediamine 4f.**[22] R_f 0.15 (EtOAc–hexane = 1 : 5); δ_H (270 MHz; $CDCl_3$) 2.68 (6H, s), 4.74 (2H, br s), 6.66 (1H, d, *J* 8.58), 7.87 (1H, dd, *J* 2.64 and 8.58), 7.91 (1H, d, *J* 2.64).

5-Methoxy-2-nitroaniline 5g, 9.[7c] R_f 0.14 (EtOAc–hexane =

1:5); δ_H (270 MHz; $CDCl_3$) 3.83 (3H, s), 6.17 (1H, d, *J* 2.64), 6.28 (1H, dd, *J* 2.64 and 9.57), 6.25 (2H, br s), 8.07 (1H, d, *J* 9.57).

2-Nitro-5-phenoxyaniline 5h.[23] R_f 0.29 (EtOAc–hexane = 1:5); δ_H (270 MHz; $CDCl_3$) 6.14 (2H, br s), 6.16 (1H, d, *J* 2.63), 6.33 (1H, dd, *J* 2.63 and 9.57), 7.07–7.45 (5H, m), 8.10 (1H, d, *J* 9.57).

5-Methylthio-2-nitroaniline 5i.[24] R_f 0.17 (EtOAc–hexane = 1:5); δ_H (270 MHz; $CDCl_3$) 2.48 (3H, s), 6.20 (2H, br s), 6.51 (1H, d, *J* 1.98), 6.51 (1H, dd, *J* 1.98 and 9.56), 7.99 (1H, d, *J* 9.56).

5-*tert*-Butyl-2-nitroaniline 5j.[7c] R_f 0.26 (EtOAc–hexane = 1:5); δ_H (270 MHz; $CDCl_3$) 1.29 (9H, s), 6.12 (2H, br s), 6.72–6.76 (2H, m), 8.00 (1H, d, *J* 8.91).

5-(Trifluoromethyl)-2-nitroaniline 5k.[7c] R_f 0.49 (EtOAc–hexane = 1:5); δ_H (270 MHz; $CDCl_3$) 6.31 (2H, br s), 6.90 (1H, dd, *J* 1.65 and 8.91), 7.13 (1H, d, *J* 1.65), 8.22 (1H, d, *J* 8.91).

5-Bromo-2-nitroaniline 5m.[25] R_f 0.52 (EtOAc–hexane = 1:5); δ_H (270 MHz; $CDCl_3$) 6.12 (2H, br s), 6.82 (1H, dd, *J* 1.98 and 9.24), 7.02 (1H, d, *J* 1.98), 7.98 (1H, d, *J* 9.24).

5-Fluoro-2-nitroaniline 5n.[7c] R_f 0.35 (EtOAc–hexane = 1:5); δ_H (270 MHz; $CDCl_3$) 6.23 (2H, br s), 6.40–6.51 (2H, m), 8.16 (1H, dd, *J* 5.94 and 9.57).

5-(1*H*-Imidazol-1-yl)-2-nitroaniline 5o.[26] R_f 0.26 (EtOAc); δ_H (270 MHz; $CDCl_3$) 6.30 (2H, br s), 6.76 (1H, dd, *J* 2.31 and 9.24), 6.82 (1H, d, *J* 2.31), 7.24 (1H, s), 7.26 (1H, s), 7.92 (1H, s), 8.27 (1H, d, *J* 9.24).

3-Amino-2-nitrobiphenyl 6. R_f 0.11 (EtOAc–hexane = 1:5); mp 77–78 °C; δ_H (270 MHz; $CDCl_3$) 5.03 (2H, br s), 6.65 (1H, dd, *J* 1.32 and 7.59), 6.76 (1H, dd, *J* 1.32 and 8.24), 7.21–7.41 (6H, m); δ_C (67.8 MHz; $CDCl_3$) 117.07, 120.45, 127.35, 127.71, 128.52, 132.36, 135.54, 138.33, 138.71, 141.80; *m*/*z* (EI) 214(M^+), 197, 185, 167, 157, 139, 130, 115, 91, 77, 63, 51, 39; Found: C, 67.01; H, 4.81; N, 12.99. $C_{12}H_{10}N_2O_2$ requires C, 67.28; H, 4.71; N, 13.08%.

5-Amino-2-nitrobiphenyl 7. R_f 0.06 (EtOAc–hexane = 1:5); mp 115–116 °C; δ_H (270 MHz; $CDCl_3$) 4.64 (2H, br s), 6.49 (1H, d, *J* 2.64), 6.60 (1H, dd, *J* 2.64 and 8.91), 7.23–7.39 (5H, m), 7.91 (1H, d, *J* 8.91); δ_C (67.8 MHz; $CDCl_3$) 112.90, 117.07, 127.82, 127.98, 128.05, 128.39, 128.61, 139.37, 140.45, 151.09; *m*/*z* (EI) 214(M^+), 197, 185, 167, 158, 139, 130, 63; Found: C, 66.89; H, 4.86; N, 12.94. $C_{12}H_{10}N_2O_2$ requires C, 67.28; H, 4.71; N, 13.08%.

5-*tert*-Butoxy-2-nitroaniline 10. R_f 0.31 (EtOAc–hexane = 1:5); mp 90–92 °C; δ_H (270 MHz; $CDCl_3$) 1.45 (9H, s), 6.11 (2H, br s), 6.31 (1H, s), 6.33 (1H, d, *J* 8.25), 8.03 (1H, d, *J* 8.25); δ_C (67.8 MHz; $CDCl_3$) 28.81, 80.25, 107.91, 112.11, 127.40, 127.53, 146.52, 162.70; *m*/*z* (EI) 210(M^+), 195, 154, 138, 124, 108, 96, 81, 68, 57; Found: C, 57.05; H, 6.60; N, 13.37. $C_{10}H_{14}N_2O_3$ requires C, 57.13; H, 6.71; N, 13.32%.

4-(*tert*-Butoxy)nitrobenzene 12.[27] R_f 0.65 (EtOAc–hexane = 1:5); δ_H (270 MHz; $CDCl_3$) 1.46 (9H, s), 7.05 (2H, d, *J* 9.23), 8.16 (2H, d, *J* 9.23).

Amination of 3,4-dichloro-1-nitrobenzene 13

A solution of *O*-methylhydroxylamine (59 mg, 1.25 mmol) and 3,4-dichloro-1-nitrobenzene **13** (192 mg, 1 mmol) in diethoxymethane (2 ml) was added dropwise to a stirred suspension of Bu^{t}OK (337 mg, 3 mmol) and $Cu(OAc)_2$ (18 mg, 0.1 mmol) in diethoxymethane (3 ml) over 5 min at room temperature. After stirring for 2 h at room temperature, it was quenched with saturated aq. NH_4Cl and the products were extracted with EtOAc. The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel thin layer chromatography (EtOAc–hexane = 1:5) afforded 2,3-dichloro-6-nitroaniline **14**[28] (156 mg, 75%) R_f 0.62; δ_H (270 MHz; $CDCl_3$) 6.83 (1H, d, *J* 9.24), 8.06 (1H, d, *J* 9.24) and 4,5-dichloro-2-nitroaniline **15**[29] (29 mg, 14%) R_f 0.52; δ_H (270 MHz; $CDCl_3$) 6.03 (2H, br s), 6.91 (1H, s), 8.17 (1H, s).

Amination of 1-nitronaphthalene 16

A solution of *O*-methylhydroxylamine (118 mg, 2.5 mmol) and 1-nitronaphthalene **16** (346 mg, 2 mmol) in DMF (3 ml) was added dropwise to a stirred suspension of Bu^{t}OK (673 mg, 6 mmol) and CuCl (20 mg, 0.2 mmol) in DMF (7 ml) over 5 min at room temperature. After stirring for 20 min at room temperature, it was quenched with saturated aq. NH_4Cl and the products were extracted with CH_2Cl_2. The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel thin layer chromatography (EtOAc–hexane = 1:5) afforded 2-amino-1-nitronaphthalene **17**[7c] (154 mg, 41%) R_f 0.32; δ_H (270 MHz; $CDCl_3$) 6.42 (2H, br s), 6.88 (1H, d, *J* 8.91), 7.32–7.38 (1H, m), 7.57–7.74 (3H, m), 8.68 (1H, d, *J* 9.57) and 1-amino-4-nitronaphthalene **18**[7c] (28 mg, 7%) R_f 0.14; δ_H (270 MHz; DMSO-d_6) 6.75 (1H, d, *J* 8.91), 7.55–7.81 (2H, m), 7.64 (2H, br s), 8.36 (1H, d, *J* 8.58), 8.45 (1H, d, *J* 8.91), 8.97 (1H, d, *J* 8.58).

Typical procedure for amination of *p*-nitrobenzoic acid 19

A solution of *O*-methylhydroxylamine (188 mg, 4 mmol) and *p*-nitrobenzoic acid **19** (334 mg, 2 mmol) in DME (12 ml) was added dropwise to a stirred suspension of Bu^{t}OK (1.57 g, 14 mmol) and $Cu(OAc)_2$ (36 mg, 0.2 mmol) in DME (8 ml) over 5 min at room temperature. After stirring for 3 h at room temperature, it was quenched with water and acidified by 2 M HCl. The products were extracted with EtOAc. The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel thin layer chromatography ($CHCl_3$–MeOH–AcOH = 10:1:0.1) afforded 3-amino-4-nitrobenzoic acid **20**[30] (186 mg, 51%) R_f 0.38; δ_H (270 MHz; DMSO-d_6) 7.07 (1H, dd, *J* 1.65 and 8.90), 7.56 (2H, br s), 7.68 (1H, d, *J* 1.65), 8.04 (1H, d, *J* 8.90), 13.47 (1H, br s) and 40% of the starting material was recovered.

2-Methoxy-5-nitrobenzoic acid 21g. To a mixture of 96% sulfuric acid (18.4 g, 180 mmol) and 60% nitric acid (13.8 g, 131 mmol) was added *o*-methoxybenzoic acid (7.61 g, 50 mmol) at 5–10 °C. After stirring for 2 h at the same temperature, it was quenched with ice-water and the product was extracted with EtOAc. The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by recrystallization (EtOH) afforded 2-methoxy-5-nitrobenzoic acid **21g**[31] (3.67 g, 59%) as a pale yellow crystalline solid; δ_H (270 MHz; $CDCl_3$) 4.04 (3H, s), 7.18 (1H, d, *J* 9.24), 8.36 (1H, dd, *J* 2.97 and 9.24), 8.66 (1H, d, *J* 2.97).

General procedure for amination of nitrobenzoic acids 21

A solution of *O*-methylhydroxylamine (188 mg, 4 mmol) and a nitrobenzoic acid **21** (2 mmol) in DME (12 ml) was added dropwise to a stirred suspension of Bu^{t}OK (1.57 g, 14 mmol) and $Cu(OAc)_2$ (36 mg, 0.2 mmol) in DME (8 ml) over 10 min at room temperature. After stirring for 2–4 h at room temperature, it was quenched with water and acidified by 2 M HCl. The products were extracted with EtOAc. The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

Purification by silica gel thin layer chromatography ($CHCl_3$–MeOH–AcOH) afforded the aminonitrobenzoic acids **22**.

3-Amino-2-nitrobenzoic acid 22a.[30] R_f 0.54 ($CHCl_3$–MeOH–AcOH = 10:10:0.1); δ_H (400 MHz; DMSO-d_6) 6.37 (2H, br s), 6.72 (1H, d, *J* 6.88), 6.92 (1H, d, *J* 8.39), 7.22 (1H, dd, *J* 6.88 and 8.39).

5-Amino-2-nitrobenzoic acid 22b.[32] R_f 0.25 ($CHCl_3$–MeOH–AcOH = 10:10:0.1); δ_H (400 MHz; DMSO-d_6) 6.35 (2H, br s), 6.40 (1H, d, *J* 9.23), 6.41 (1H, s), 7.67 (1H, d, *J* 9.23).

4-Amino-3-nitrobenzoic acid 22c.[7d] R_f 0.50 ($CHCl_3$–MeOH–AcOH = 10:1:0.1); δ_H (270 MHz; DMSO-d_6) 7.06 (1H, d, *J* 8.91), 7.86 (1H, dd, *J* 1.98 and 8.91), 7.95 (2H, br s), 8.56 (1H, d, *J* 1.98), 12.99 (1H, br s).

2-Amino-3-nitrobenzoic acid 22d.[33] R_f 0.63 ($CHCl_3$–MeOH–AcOH = 10:1:0.1); δ_H (270 MHz; DMSO-d_6) 6.72 (1H, dd, *J* 7.59 and 8.58), 8.23 (1H, dd, *J* 1.65 and 7.59), 8.32 (1H, dd, *J* 1.65 and 8.58), 8.51 (2H, br s), 13.45 (1H, br s).

2-Amino-5-nitrobenzoic acid 22e.[7c] R_f 0.50 ($CHCl_3$–MeOH–AcOH = 10:1:0.1); δ_H (270 MHz; DMSO-d_6) 6.88 (1H, d, *J* 9.24), 7.95 (2H, br s), 8.08 (1H, dd, *J* 2.64 and 9.24), 8.61 (1H, d, *J* 2.64), 12.99 (1H, br s).

3-Amino-5-methoxy-4-nitrobenzoic acid 22f. R_f 0.48 ($CHCl_3$–MeOH–AcOH = 10:1:0.1); mp 200–205 °C (dec.); δ_H (270 MHz; DMSO-d_6) 3.86 (3H, s), 6.78 (1H, s), 7.15 (1H, s); δ_C (67.8 MHz; DMSO-d_6) 56.37, 98.73, 111.02, 129.26, 133.75, 142.63, 152.62, 166.42; HRMS(FAB) Found: $(M + H)^+$, 213.0506. $C_8H_9N_2O_5$ requires *M*, 213.0512.

3-Amino-2-chloro-4-nitrobenzoic acid 22g. R_f 0.38 ($CHCl_3$–MeOH–AcOH = 10:5:0.1); mp 151–153 °C; δ_H (270 MHz; DMSO-d_6) 6.91 (1H, d, *J* 8.91), 7.47 (2H, br s), 8.08 (1H, d, *J* 8.91); δ_C (67.8 MHz; DMSO-d_6) 114.07, 118.46, 124.89, 132.31, 139.07, 142.32, 166.65; HRMS(FAB) Found: M^+, 215.9987. $C_7H_5ClN_2O_4$ requires *M*, 215.9938.

5-Amino-2-chloro-4-nitrobenzoic acid 22h. R_f 0.28 ($CHCl_3$–MeOH–AcOH = 10:5:0.1); δ_H (270 MHz; DMSO-d_6) 7.43 (1H, s), 7.45 (2H, br s), 8.03 (1H, s).

3-Amino-5-methoxy-2-nitrobenzoic acid 22i. R_f 0.46 ($CHCl_3$–MeOH–AcOH = 10:5:0.1); mp 188–190 °C (dec.); δ_H (270 MHz; DMSO-d_6) 3.81 (3H, s), 6.30 (1H, d, *J* 2.64), 6.53 (1H, d, *J* 2.64), 7.36 (2H, br s); δ_C (67.8 MHz; DMSO-d_6) 55.91, 100.11, 106.15, 123.29, 135.10, 148.05, 163.04, 167.91; HRMS(FAB) Found: $(M + H)^+$, 213.0528. $C_8H_9N_2O_5$ requires *M*, 213.0512.

3-Amino-5-chloro-2-nitrobenzoic acid 22j. R_f 0.50 ($CHCl_3$–MeOH–AcOH = 7:3:0.1); mp 178–180 °C; δ_H (270 MHz; DMSO-d_6) 6.79 (1H, d, *J* 1.98), 7.14 (2H, br s), 7.15 (1H, d, *J* 1.98); δ_C (67.8 MHz; DMSO-d_6) 115.38, 119.00, 129.22, 133.19, 137.92, 145.30, 166.33; HRMS(FAB) Found: $(M + H)^+$, 217.0056. $C_7H_6ClN_2O_4$ requires *M*, 217.0017.

2-Amino-6-methoxy-3-nitrobenzoic acid 22k. R_f 0.48 ($CHCl_3$–MeOH–AcOH = 10:1:0.1); mp 173–175 °C; δ_H (270 MHz; DMSO-d_6) 3.90 (3H, s), 6.56 (1H, d, *J* 9.57), 7.51 (2H, br s), 8.21 (1H, d, *J* 9.57); δ_C (67.8 MHz; DMSO-d_6) 56.66, 101.26, 107.42, 126.63, 130.53, 145.39, 163.65, 167.19; HRMS(FAB) Found: $(M + H)^+$, 213.0511. $C_8H_9N_2O_5$ requires *M*, 213.0512.

4-Amino-2-methoxy-5-nitrobenzoic acid 22l. R_f 0.33 ($CHCl_3$–MeOH–AcOH = 10:1:0.1); mp 207–209 °C (dec.); δ_H (270 MHz; DMSO-d_6) 3.82 (3H, s), 6.53 (1H, s), 7.83 (2H, br s), 8.51 (1H, s); δ_C (67.8 MHz; DMSO-d_6) 56.07, 98.67, 109.65, 124.21, 131.63, 150.08, 163.61, 164.92; HRMS(FAB) Found: $(M + H)^+$, 213.0559. $C_8H_9N_2O_5$ requires *M*, 213.0512.

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Paper 9/01537J