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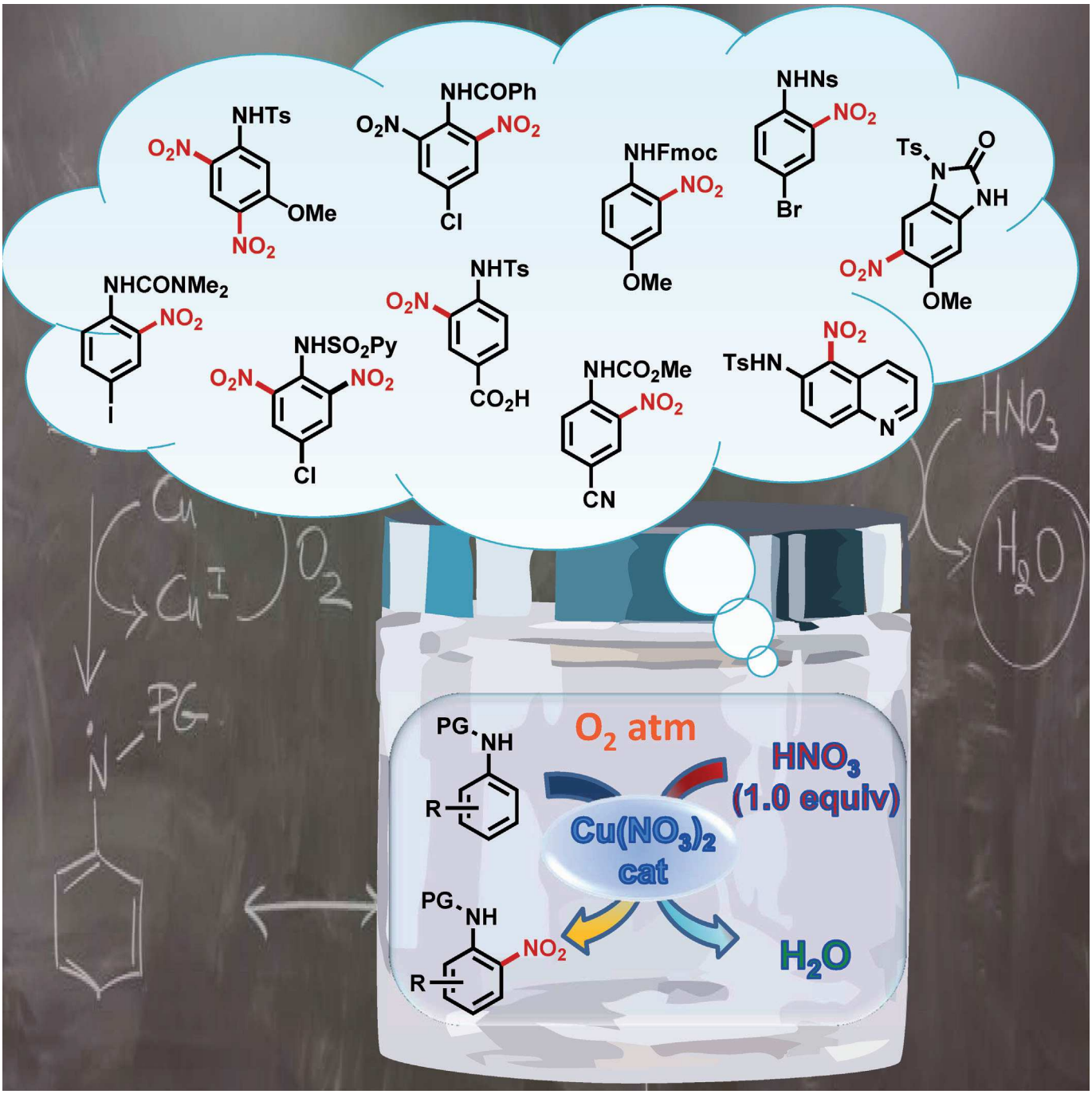
Copper-Catalyzed Mild Nitration of Protected Anilines

Elier Hernando, Rafael R. Castillo, Nuria Rodríguez,* Ramón Gómez Arrayás,* and Juan C. Carretero*[a]



Abstract: A practical copper-catalyzed direct nitration of protected anilines, by using one equivalent of nitric acid as the nitrating agent, has been developed. This procedure features mild reaction conditions, wide structural scope (with regard to both N-protecting group and arene substitution), and high functional-group tolerance. Dinitration with two equivalents of nitric acid is also feasible.

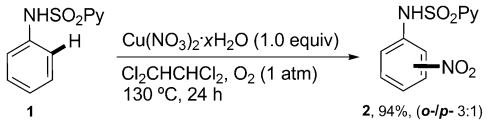
Nitroarenes are important intermediates for the synthesis of pharmaceuticals, dyes, and materials, among other valuable chemicals.[1] The synthetic versatility of the nitro group makes these compounds useful precursors for the construction of heterocyclic frameworks.[2] Most commonly, nitroarenes are prepared by means of the classical direct electrophilic nitration of arenes with excess nitric acid or mixed strong-acid systems, such as H_2SO_4/HNO_3. Although this method constitutes an important process in both academia and industry,[3–5] the harsh reaction conditions represent a limitation in terms of tolerance towards oxidation or to acid-sensitive functional groups. Moreover, from a bulk-scale standpoint, disposal of acidic waste after the reaction is often problematic.

In recent years, metal nitrate salts [e.g., $Ca(NO_3)_2$, $Bi(NO_3)_3{\cdot}6H_2O$, $AgNO_3$, or $Ni(NO_3)_2{\cdot}6H_2O$] have emerged as new nitrating agents.[4,6] These salts eliminate the need for strong acidic conditions, although the price for this improvement is the generation of significant amount of metal waste, which is derived from stoichiometric use of the metal nitrate salts. Additionally, these reagents are often expensive or difficult to prepare. Chelation-assisted *ortho*-nitration of aromatic C–H bonds under Pd,[7] Rh,[8] and Cu[9] catalysis has also been developed using $AgNO_2$, $NaNO_2$, or $AgNO_3$ as nitrating agents, but this strategy is limited in scope. In work by Liu and co-workers,[9] $Cu(NO_3)_2{\cdot}3H_2O$ (1.5 equiv) was found to be an efficient nitrating agent for the *ortho*-nitration of 2-phenylpyridines. An isolated example of *ortho*-nitration by using HNO_3 (2 equiv) in the presence of $Cu(OAc)_2$ (50 mol%) is also described.[9] Strong Lewis acids, such as lanthanide triflates, have been found to be efficient catalysts for the nitration of a range of simple aromatic compounds by using stoichiometric quantities of nitric acid.[10] However, generally these conditions are not compatible with aniline derivatives because they do not remain active in the presence of the basic nitrogen.

Very recently, Arns and co-workers have described the selective nitration of *N*-sulfonyl anilines with *tert*-butyl nitrite.[11] Although good yields are obtained with electron-neutral or electron-rich substrates, this protocol was not well-suited for aniline derivatives containing strong electron-withdrawing substituents, which generally provided incomplete conversions. Additionally, the use of common N-protecting groups different from sulfonamides, such as amides or carbamates, proved to be incompatible.

Despite these advances, there is a great need for more general, practical, safe, and green methods for the catalytic nitration of arenes. A method using one equivalent of inexpensive HNO_3 is ideal because the only stoichiometric byproduct of the reaction is water. Herein, we present a practical Cu-catalyzed nitration of anilines that uses one equivalent of HNO_3. This protocol expands the scope of the reaction in terms of N-derivatives (sulfonamides, carbamates, amides, and ureas) and arene substitution, including strongly electron-deactivated substrates with CF_3, CN, or NO_2 groups.

In previous studies on Cu-catalyzed C–H halogenation of aniline derivatives,[12] we accidentally observed partial nitration of aniline when using $Cu(NO_3)_2{\cdot}xH_2O$ as the catalyst. In fact, full conversion of *N*-(2-pyridyl)sulfonyl aniline (**1**) was achieved when using one equivalent of $Cu(NO_3)_2{\cdot}xH_2O$ under otherwise similar conditions. Unfortunately, the reaction was not regioselective and a mixture 3:1 of *o*-/*p*- regioisomers **2** was obtained (Scheme 1).[13]



Scheme 1. Cu-promoted nitration of aniline derivative **1**. Py = 2-pyridyl.

Therefore, *N*-(2-pyridyl)sulfonyl *p*-toluidine (**3**) was chosen as a model substrate for optimization studies aiming to develop a catalytic, rather than stoichiometric (with respect to copper), version of this process (Table 1). Firstly, it was deemed appropriate to find a solvent that would be more attractive to industry. We found that the Cu-promoted nitration of **3** occurs smoothly in MeCN[14] to afford the desired product **5** with >99% yield (entry 1). Next, we focused on developing a Cu-catalyzed protocol. In an initial attempt, we used NH_4NO_3 as an stoichiometric NO_2 source and 10% of $Cu(NO_3)_2{\cdot}xH_2O$ in the presence of O_2 as an external oxidant, but only 13% yield of the desired product **5** was achieved (entry 2). However, changing the nitro source to one equivalent of HNO_3 (entry 3) or *i*AmONO (entry 4) afforded desired product **5** in excellent yield (>99% and 94% by NMR spectroscopy, respectively). Based on these results, HNO_3 was chosen for further studies. Control experiments determined that nitroaniline derivative **5** is not produced in the absence of a Cu catalyst[15] (entry 5), and that the reaction requires aerobic conditions (1 atm O_2) to achieve reactivity under catalytic conditions (entry 6), thus highlighting the crucial role of catalyst and oxidant in this reaction.

From a synthetic standpoint, it is remarkable that this protocol allows for simultaneous scale-up, lower catalyst loading, and lower temperature. For example, a one-gram-scale nitra-

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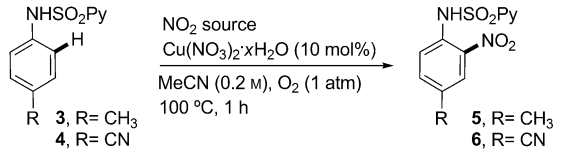
Table 1. Optimization of the reaction conditions.[a]



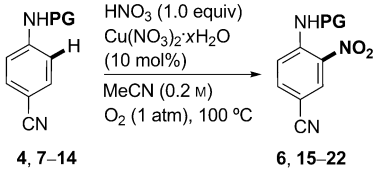
Entry	R [(substrate)]	Nitrating agent	Product	Yield [%][b]
1[c]	CH_3 (**3**)	$Cu(NO_3)_2{\cdot}xH_2O$	**5**	>99
2	CH_3 (**3**)	$(NH_4)NO_3$	**5**	13
3	CH_3 (**3**)	HNO_3	**5**	>99 (95)[d]
4	CH_3 (**3**)	*i*AmONO	**5**	94
5[e]	CH_3 (**3**)	HNO_3	**5**	<5
6[f]	CH_3 (**3**)	HNO_3	**5**	<5
7[g]	CH_3 (**3**)	HNO_3	**5**	94 (93)[d]
8	CN (**4**)	HNO_3	**6**	>99 (94)[d]
9[h]	CN (**4**)	HNO_3	**6**	<5

[a] Conditions: **3** or **4** (0.20 mmol), nitrating agent (0.20 mmol), $Cu(NO_3)_2{\cdot}xH_2O$ (10 mol%), MeCN (0.2 M), O_2 (1 atm), 100 °C, 1 h. [b] Conversion yields by ^{1}H NMR spectroscopy. [c] Under Ar with a stoichiometric amount of Cu. [d] Isolated yield. [e] Without Cu. [f] Under Ar atmosphere. [g] 1 gram scale, 1 mol% Cu catalyst, 40 °C. [h] 1 mol% Cu catalyst. *i*AmONO = *iso*-amyl nitrite.

tion of **3** was performed with 1 mol% of Cu catalyst at 40 °C for 1.5 h. Simple addition of water and removal of MeCN under vacuum caused precipitation of product **5**, which was isolated in 93% yield upon filtration (entry 7).

In light of the above-mentioned limitations of the nitration of anilines related to their sensitivity to electronic properties,[11] we were eager to test whether this protocol is compatible with electron-deficient anilines. We chose *p*-aminobenzonitrile derivative **4**, which is an especially challenging substrate owing to the additional metal-coordinating ability of the nitrile group. Gratifyingly, nitration of **4** by using 10 mol% of the catalyst at 100 °C was completed after 1 h, providing the desired nitroaniline derivative **6** in 94% yield (entry 8). In contrast, negligible conversion was observed with 1 mol% of the Cu catalyst (entry 9).

A broad range of common protecting groups (PG) were next examined in the nitration reaction of 4-aminobenzonitrile (derivatives **4** and **7–14** in Scheme 2) with HNO_3 (1.0 equiv) under our optimized conditions (10 mol% of Cu, 100 °C). Additionally, Figure 1 shows the reaction profile for each case from a measure of conversion (%) versus time (min). All of the sulfonamide



6, PG = SO_2Py, 98% (30 min)
15, PG = Ts, 97% (30 min)
16, PG = Ns, 94% (30 min)
17, PG = $CONMe_2$, 99% (10 min)
18, PG = COPh, 86% (12 h)
19, PG = CO_2Me, 89% (12 h)
20, PG = Fmoc, 57% (12 h)
21, PG = CO-*p*NO_2Ph, 23% (16 h)
22, PG = COC_6F_5, 12% (16 h)

Scheme 2. Evaluation of N-protecting groups in the nitration of 4-aminobenzonitrile.

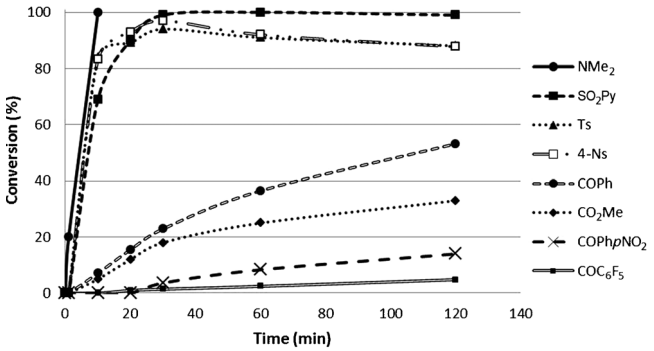
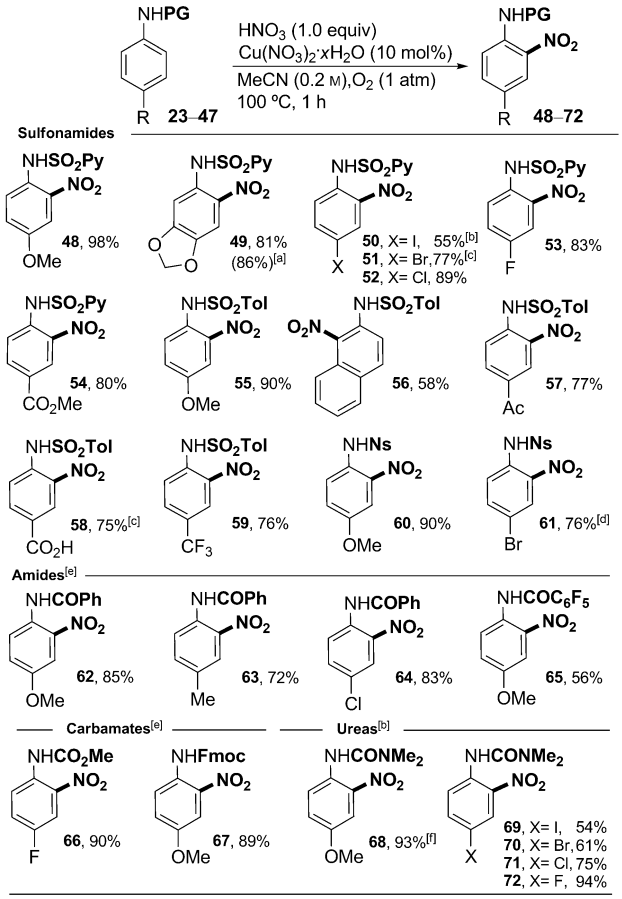


Figure 1. Reactivity profile [conversion (%) versus time (min)] of different protecting groups (PG) in the nitration of 4-aminobenzonitrile derivatives. Conversions determined by ^{1}H NMR spectroscopy.

groups evaluated enabled a very fast nitration reaction (≥90% conversion in 20 min). Among the sulfonyl groups tested, the *N*-SO_2Py showed the best reactivity–selectivity balance, affording **6** as the only product (no dinitration was detected by ^{1}H NMR spectroscopy), which was isolated in 98% yield. For the other two sulfonamides tested (PG = Ts (4-toluenesulfonyl), 4-Ns (4-nitrobenzenesulfonyl)), reaction times longer than 30 min resulted in a small amount (5–12%) of competitive dinitration at the positions *ortho* to the amino group. Nevertheless, high yields of the corresponding nitro derivatives can be achieved if the reaction is stopped after 30 min [97% for **15** (PG = Ts) and 94% for **16** (PG = Ns)].

The *N*,*N*-dimethyl urea **9** was even more reactive, reaching full conversion to mononitrated product **17** after just 10 min. The product was isolated in 99% yield by simple precipitation. This protocol also proved to be compatible with carbamates and amides. Although conversions below 55% were observed in the nitration of benzamide **10** and methyl carbamate **11** after 2 h, the reaction occurred cleanly and good yields of the corresponding mononitrated products, **18** and **19**, were obtained after 12 h (86 and 89%, respectively). In the case of the Fmoc-protected derivative, partial decomposition of the starting material prevented an accurate measure of its kinetic profile (substrate **12**, not recorded in Figure 1). Despite this shortcoming, the corresponding nitro derivative **20** was obtained in synthetically useful yield (12 h, 57%). In contrast, more electrophilic benzamides **13** and **14** showed very poor reactivity (products **21** and **22** were obtained in 23 and 12% yield, respectively, after 16 h).

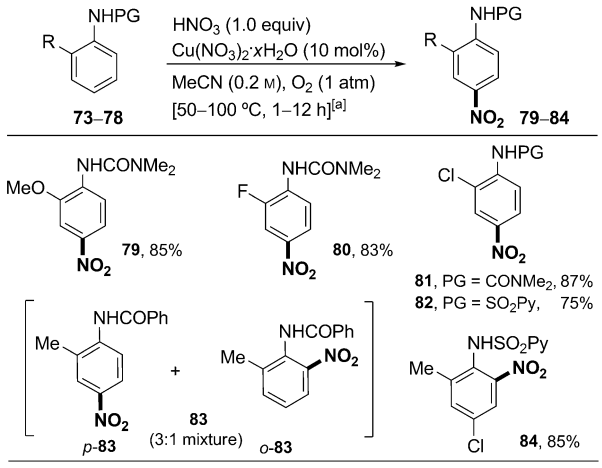
Once the compatibility of the catalyst system with standard nitrogen protecting groups was demonstrated, we examined the scope in terms of arene substitution. As shown in Scheme 3, a wide range of protected *p*-substituted anilines underwent nitration at the *ortho*-position in acceptable to good yields (25 examples, 54–98%). Substrates bearing strong electron-withdrawing groups (CF_3, CN, CO_2Me, and COMe) showed a similar reactivity to those with electron-donating groups (OMe, Me) in terms of reaction yield. It is also important to stress the high functional-group tolerance (ether, ketone, ester, nitro, cyano, or acetal), especially to halogen substitution (F, Cl, Br, or I, products **50–53**, **61**, **64**, **66**, and **69–72**), thus providing



Scheme 3. Nitration of *para*-substituted aniline derivatives. Isolated yields. [a] 1 h, 40 °C, 1% of Cu catalyst. [b] 2 h, 50 °C. [c] 2 h, 80 °C. [d] 4 h, 50 °C. [e] 12 h, 100 °C. [f] 10 min, RT.

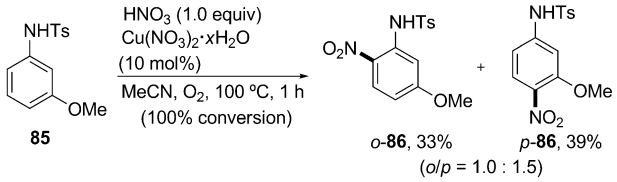
products suitable for further elaboration. Even an iodo substituent was tolerated on the aniline coupling partner, however, substantial protodehalogenation was observed and was responsible for the lowest yields of this series (**50** and **69** were obtained in 55 and 54%, respectively). A CO_2H group also proved to be suitable (**58**, 75%), with only a small amount of nitrodecarboxylated product being detected in the reaction mixture.[16] The Fmoc protecting group, which provided a modest yield in the case of the 4-aminobenzonitrile derivative, was compatible with anilines bearing an electron-donating substituent (**67**, 89% yield). The dramatic increase in the reactivity of electron-rich aniline derivatives allowed the use of the previously unreactive pentafluorobenzamide protecting group (**65**, 56%).

Complete *ortho* regioselectivity, with regard to the amino group, was observed in substrates in which the *para*-position was blocked, even in those cases where the blocking substituent has a strong *ortho*-directing effect, such as the OMe group (**48**, **55**, **60**, **62**, **65**, **67**, and **68**; 56–98% yield). Gratifyingly, *ortho*-substituted aniline derivatives underwent nitration at the *para*-position with complete regiocontrol and no apparent sensitivity to electronic properties of the substituent (Scheme 4, **79–82**, 75–87%). The only exception to this trend was found in the nitration of an *o*-toluidine derivative, which

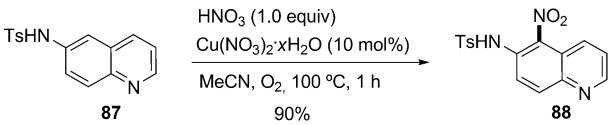


Scheme 4. Nitration of *ortho*-substituted aniline derivatives. [a] See the Supporting Information for details.

led to a 3:1 mixture of *para* and *ortho* regioisomers (**83**). When one *ortho*-position and the *para*-position were blocked, nitration occurred at the free *ortho*-position in good yield (**84**, 85%). Unfortunately, *meta*-substitution was not effective in controlling the regioselectivity, as exemplified in the nitration of *m*-methoxy *N*-tosyl aniline **85**, which afforded a 1.0:1.5 mixture of mono-nitrated regioisomers at the C2 and C4 positions (*o*-**86** and *p*-**86**) in good overall yield (Scheme 5, see the Supporting Information for an additional example). Heteroaromatic substrates were also amenable to the reaction, as demonstrated in the nitration of 6-aminoquinoline derivative **87**, which occurred cleanly at C5 to give **88** in 84% yield (no other regioisomer was detected by NMR spectroscopy in the crude mixture). Importantly, the reaction in the absence of Cu catalysis provided a complex mixture of products (Scheme 6).

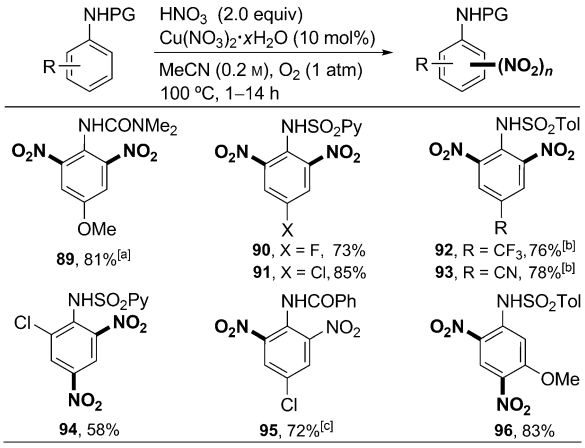


Scheme 5. Nitration of *meta*-substituted aniline derivative **85**.



Scheme 6. Nitration of 6-aminoquinoline derivative **87**.

Capitalizing on the high reactivity of our nitration protocol, especially in the case of strongly electronically deactivated aniline derivatives, we next evaluated the application of this pro-

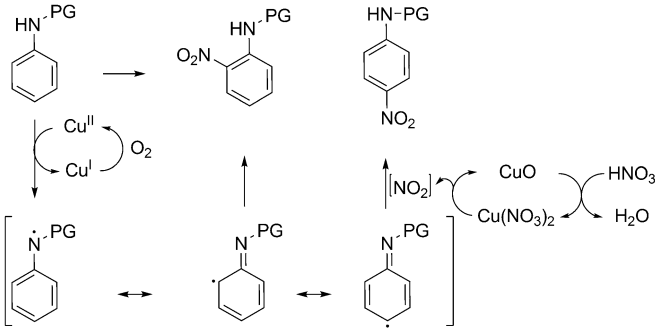


Scheme 7. Formation of dinitrated products. Isolated yields. [a] 2 h, 50 °C. [b] 30 mol% of the Cu catalyst, 24 h. [c] 1.0 equiv of HNO_3.

tocol to accessing dinitrated anilines by using two equivalents of HNO_3. To our delight, the efficiency of this catalytic system was also conserved when the aniline possessed a nitro substituent, enabling a mild dinitration procedure. Indeed, a representative set of protected *para*-substituted anilines underwent *ortho* dinitration in synthetically useful yields (**89–93**, 73–85% yield, Scheme 7), regardless of the electronic nature of the substituent or the identity of the protecting group at the nitrogen atom (sulfonamide or urea). Again, compatibility to halogen substitution (Cl; products **91**, **94**, and **95**, 58–85%) provides a useful handle for further derivatization. Even strong electron-withdrawing groups were tolerated at the aromatic ring (e.g., CF_3 or CN; **92** and **93**, 76 and 78%, respectively). The presence of a substituent at the *ortho*-position allowed dinitration at both the unsubstituted *ortho*- and *para*-positions (**94**, 58%), whereas the 4-chloro-2-nitro-disubstitution led to nitration at the available *ortho*-position (**95**, 72%, 1.0 equiv of HNO_3). The *m*-methoxy-substituted aniline derivative **85** underwent dinitration cleanly at the less hindered *ortho*-position and at the *para*-position (**96**, 83%).

Although the reaction mechanism remains unclear, some experiments are consistent with the hypothesis that the reaction proceeds through a radical pathway. For example, the model nitration of toluidine derivative **3** with HNO_3 was completely suppressed in the presence of one equivalent of galvinoxyl as a radical scavenger (see the Supporting Information for details). Also, N-alkylation resulted incompatible; no reaction was observed when using a *N*-Me-*N*-SO_2Py-protected aniline (see the Supporting Information). This N-substitution would prevent the formation of an amidyl radical intermediate[11] (that can be delocalized onto the aromatic ring) upon one-electron oxidation by the Cu^{II} species. This carbon-centered radical could react with $Cu(NO_3)_2$ or be intercepted by a nitrogen dioxide radical, which could be produced by thermal decomposition of $Cu(NO_3)_2$ (a plausible reaction pathway is outlined in Scheme 8).[17,18]

Taking advantage of the flexibility of this methodology with regard to the nature of the aniline protecting group, Scheme 9



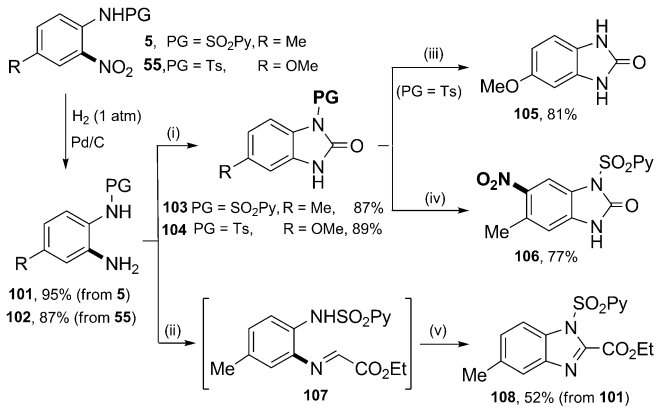
Scheme 8. Plausible mechanistic pathway.

PG	Conditions[a]	R	Product	Yield [%]
COPh	A	Me	**97**	97
COPh	A	Cl	**98**	99
$CONMe_2$	B	OMe	**99**	83
p-Ns	C	Br	**100**	96

[a] A: KOH, MeOH, RT; B: KOH (sat.), reflux; C: PhSH/K_2CO_3, DMSO, 100 °C

Scheme 9. Strategies for the amino deprotection.

shows varied possibilities for the amino deprotection without affecting the nitro-group functionality (products **97–100**, 83–99%). On the other hand, because the nitroaniline derivatives can be considered as orthogonally protected diamino benzenes, their versatility as valuable building blocks towards the construction of more complex heterocyclic ring systems was demonstrated (Scheme 10). Either of the two masked amino groups can be easily converted into the free NH_2 in a selective fashion. Thus, catalytic hydrogenation of the nitro group of **5** or **55** furnished the corresponding diamino benzene deriva-



Scheme 10. Synthetic application of the nitroaniline derivatives. i) $(Cl_3CO)_2CO$, CH_2Cl_2, RT; ii) ethyl glyoxalate, Na_2SO_4, toluene, RT; iii) Mg, MeOH, RT; iv) HNO_3 (1.0 equiv), $Cu(NO_3)_2{\cdot}xH_2O$ (10 mol%), O_2 (1 atm), MeCN, 100 °C; v) $PdCl_2$ (10 mol%), K_2CO_3 (2.0 equiv), $PhI(OAc)_2$ (2.0 equiv), toluene, RT.

tives **101** (PG = SO_2Py, 95%) and **102** (PG = Ts, 87%) in high yields.

These products can be further derivatized into the corresponding 1*H*-benzo[*d*]imidazol-2(3*H*)-ones **103** and **104** by using triphosgene (Scheme 10). Subsequent deprotection of the *N*-Ts protecting group afforded the unprotected heteroarene **105** in 81% yield. Interestingly, heterocyclic product **103** is well-suited for a subsequent nitration reaction under our Cu-catalyzed methodology, occurring selectively at the *para*-position with regard to the NH group, as illustrated in the preparation of product **106** (77% yield). Additionally, the Pd^{II}-catalyzed cyclization through the cascade sulfonamidation–oxidation of the glyoxalate-derived imine **107**,[19] obtained in situ from condensation of aniline **101** with ethyl glyoxalate, led to the formation of the benzimidazole derivative **108** in reasonable yield (52% over two steps).

In summary, we have developed a reliable Cu-catalyzed procedure for the selective nitration of *para*-substituted and *ortho*-substituted aniline derivatives by using one equivalent of HNO_3, which produces water as the only stoichiometric by-product. This protocol is compatible with a variety of N-protecting groups and features remarkable tolerance with regard to the arene substitution, including highly electron-deficient groups. This procedure can be extended to the preparation of dinitrated aniline derivatives by using two equivalents of HNO_3. The method is amenable to scale-up and enables the construction of relevant nitrogenated architectures, such as benzo[*d*]imidazol-2(3*H*)-ones and benzimidazoles.

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Keywords: anilines · benzimidazoles · copper · nitration · nitric acid

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