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Oxidative nucleophilic aromatic amination of nitrobenzenes†

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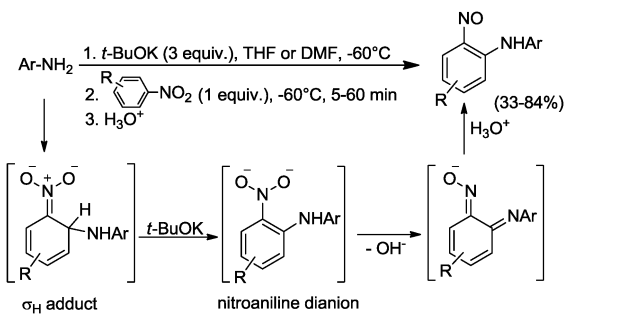
Nitrobenzenes substituted with electron-acceptor groups such as halogen, nitro, trifluoromethyl, pentafluorosulfanyl, or cyano underwent oxidative nucleophilic substitution with lithium salts of arylamines to afford *N*-aryl-2-nitroanilines.

Many agrochemicals, pharmaceuticals, pigments, electronic materials, and conducting polymers contain aromatic amines.[1] Their synthesis is based on nitration of aromatics followed by reduction,[1] transition-metal-catalysed[2] or transition-metal-free[3] amination of aryl halides or pseudohalides, addition to benzyne intermediates,[4] or nucleophilic substitution of electron-deficient aromatic halides.[5] In recent years, impressive achievements have been made in transition-metal-catalysed C–H amination of (hetero)aromatics.[6] Another route to the synthesis of arylamines from electron-poor aromatics is the nucleophilic substitution of hydrogen.[5,7] Certain requirements, however, must be met in order to achieve an efficient substitution reaction. The equilibrium must be shifted to the formation of a σ_H adduct. The σ_H adduct must be amenable to oxidation under conditions that do not affect the nitrogen nucleophile. This process is generally known as oxidative nucleophilic substitution of hydrogen (ONSH).[8] Alternatively, if the nucleophile contains a leaving group connected directly to the nitrogen atom, another reaction channel opens in the presence of excess base – vicarious nucleophilic substitution (VNS).[9] In rare cases, such as in the Chichibabin reaction of sodium amide with pyridine or nitrobenzene, the hydride ion of the σ_H adduct is eliminated in the form of H_2.[10]

Early ONSH amination reactions of nitroaromatics and heteroaromatics have relied on 'spontaneous' oxidation of the σ_H adduct by oxygen dissolved in the reaction solvent or an excess of nitrobenzene which gets reduced to nitrosobenzene.[5,11] This redox process can take place in an intramolecular fashion leading to the nitroso product or the intermediate is subsequently transformed into a fused heterocyclic product.[12] This is the case for the Wohl–Aue reaction of anilines with nitroarenes in the presence of a base leading to phenazine derivatives.[13] In 2010, Wróbel and Kwast have reported the reaction of anions of primary arylamines with nitrobenzenes affording *N*-aryl-2-nitrosoanilines (Scheme 1).[14] The authors rationalized the formation of nitroso products by the transformation of the initially formed σ_H adduct into the nitroaniline dianion (Scheme 1).

Aside from the abovementioned processes, along with the electrochemical oxidation of σ_H adducts formed from polynitroaromatics and *n*-butylamine,[15] there are only a few isolated examples of amination of nitrobenzenes and electron-deficient nitrogen aromatics by S_NAr or ONSH.[16] There is no general method for nucleophilic aromatic C–H amination. We hypothesized that electron-deficient aromatics might undergo ONSH with alkali metal salts of aromatic amines giving single-step transition metal-free access to aminated aromatic products.

Based on the report of Wróbel and Kwast[14] initial investigations on the nucleophilic substitution of hydrogen were carried out with 4-nitro-1-(pentafluorosulfanyl)benzene (**1**), aniline and *t*-BuOK in DMF (Table 1). The choice of this particular substrate for optimization was motivated by several factors. The SF_5



Scheme 1 Formation of *N*-aryl-2-nitrosoanilines by the reaction of anions of primary arylamines with nitrobenzenes.

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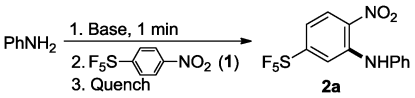
Table 1 Optimization of addition of phenylanilide to 4-nitro-1-(pentafluorosulfanyl)benzene (**1**)



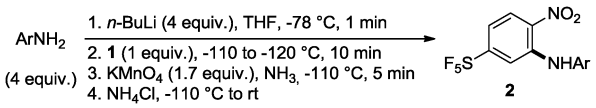
Entry	$PhNH_2$ (equiv.)	Base (equiv.)	Solvent	Temp. (°C)	Time (min)	Quenching method[a]	**2a** yield[b] (%)
1	1	*t*-BuOK (3)	DMF	−65	3	AcOH	36
2	1.5	*t*-BuOK (3)	DMF	−60	2	AcOH	28
3	1.2	*n*-BuLi (1.2)	THF	−70	5	$KMnO_4/NH_3/NH_4Cl$	41
4	2	*n*-BuLi (2)	THF	−70	5	$KMnO_4/NH_3/NH_4Cl$	55
5	4	*n*-BuLi (4)	THF	−70	5	$KMnO_4/NH_3/NH_4Cl$	64
6	8	*n*-BuLi (8)	THF	−70	5	$KMnO_4/NH_3/NH_4Cl$	51
7	4	*n*-BuLi (4)	THF	−110 to −120	10	$KMnO_4/NH_3/NH_4Cl$	83 (73)
8	4	*n*-BuLi (4)	THF	−110 to −120	10	NH_4Cl	46
9	4	*n*-BuLi (4)	THF	−110 to −120	30	$KMnO_4/NH_4Cl$	42
10	4	*n*-BuLi (4)	THF	−110 to −120	15	$AgOAc/NH_3/NH_4Cl$	36
11	4	*n*-BuLi (4)	THF	−110 to −120	15	$CAN/NH_3/NH_4Cl$	52
12	4	*n*-BuLi (4)	THF	−110 to −120	15	$Pb(OAc)_4/NH_3/NH_4Cl$	65

[a] Quenching methods: AcOH – addition of AcOH (excess) and warming to rt; oxidant – addition of oxidant [$KMnO_4$, AgOAc, CAN, or $Pb(OAc)_4$] (1.7 equiv.) at −110 °C; NH_3 – addition of liquid NH_3 at −110 °C, 5 min; NH_4Cl – addition of solid NH_4Cl and warming to rt. [b] ^{19}F NMR yields using 4-(pentafluorosulfanyl)anisole as an internal standard; isolated yield in parentheses.

group is a strongly electron withdrawing group with remarkable stability, high dipole moment and lipophilicity. SF_5-substituted compounds are being intensively investigated as drug candidates, agrochemicals, in materials sciences (polymers, ionic liquids, liquid crystals, explosives), and also in catalysis.[17] Compound **1** and the corresponding *meta*-isomer are produced by fluorination of nitrophenyl disulfides using elemental fluorine.[18] In recent years, investigations into nucleophilic aromatic substitutions of **1** (and the *meta*-isomer) provided routes to the synthesis of a variety of SF_5-(hetero)aromatic compounds.[19–23] In contrast to the literature,[14] the use of **1** did not provide any nitroso product. Instead, **2a** was formed in low yields (Table 1, entries 1 and 2). Yields of **2a** improved when *n*-BuLi in THF and $KMnO_4$ in liquid ammonia were used as oxidants (entry 3) – similar conditions to ONSH of **1** with carbon nucleophiles.[23] Further improvement was observed upon increasing the amount of PhNHLi and decreasing the temperature. Under optimized conditions (entry 7), **2a** was isolated in 73% yield as an orange solid and fully characterized including NMR spectroscopy and X-ray structure analysis (CCDC 1438933). Without $KMnO_4/NH_3$ (entry 8) the reaction was considerably less efficient but still took place and again, no nitroso product was observed. Upon using $KMnO_4$ in the absence of liquid ammonia (entry 9) a very similar result was obtained, indicating unavailability of the oxidant – perhaps due to its low solubility. Other oxidants were tested (entries 10–12) but none of them outperformed $KMnO_4$.

With the optimal set of reaction conditions the scope of the new amination process was explored using a range of aromatic amines (Table 2). Both aromatic amines with electron donating and withdrawing groups reacted equally well affording products **2** in good to high yields. Functional groups such as halogen or ethynyl were tolerated. In the case of 4-iodoaniline (entry 8) partial deiodination was observed while the yield of **2k** (entry 11) was reduced due to competing amide formation. Some arylamines proved to be unreactive such as 2- or 4-nitroaniline, 2-aminopyridine, and 2,6-dimethylaniline, presumably due to low stability, nucleophilicity, or high steric hindrance of their lithium salts.

Table 2 Scope of the reaction of lithium salts of arylamines with 4-nitro-1-(pentafluorosulfanyl)benzene (**1**)

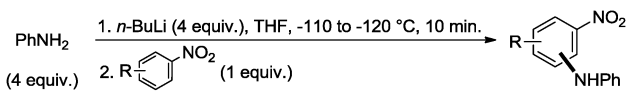


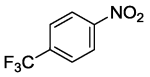
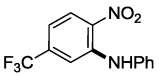
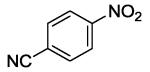
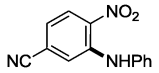
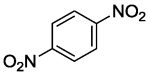
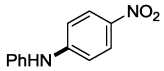
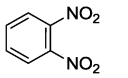
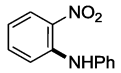
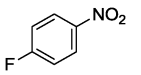
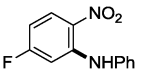
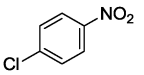
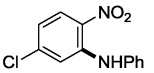
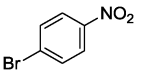
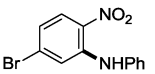
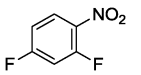
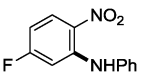
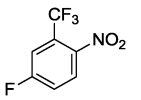
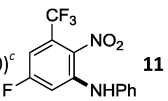
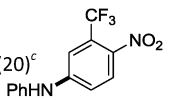
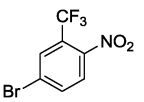
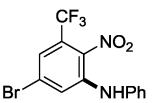
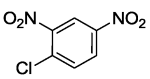
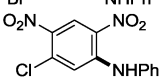
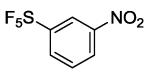
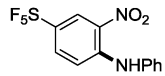
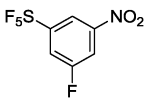
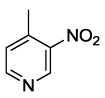
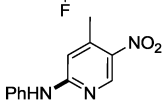
Entry	Ar	**2**	Yield[a] (%)
1	Ph	**2a**	73
2	$4\text{-}MeC_6H_4$	**2b**	73
3	$4\text{-}(MeO)C_6H_4$	**2c**	70
4	$2,4\text{-}(MeO)_2C_6H_3$	**2d**	59
5	$4\text{-}FC_6H_4$	**2e**	66
6	$4\text{-}ClC_6H_4$	**2f**	72
7	$3\text{-}BrC_6H_4$	**2g**	58
8	$4\text{-}IC_6H_4$	**2h**	68[b]
9	$3\text{-}(CF_3)C_6H_4$	**2i**	60
10	$4\text{-}(HC{\equiv}C)C_6H_4$	**2j**	78
11	$4\text{-}(i\text{-}PrO_2C)C_6H_4$	**2k**	35
12	1-Naphthyl	**2l**	55

[a] Isolated yield. [b] Along with side-product **2a** (16% yield).

Examining the scope of the electrophilic reaction partner (electron-deficient aromatic) in the reaction with lithium anilide revealed that the nitro group and an additional electron-acceptor group were necessary for the successful ONSH reaction (Table 3). The pentafluorosulfanyl group of **1** could be replaced by a trifluoromethyl or a cyano group while still affording the products of ONSH in good yields (entries 1 and 2). 1,4-Dinitrobenzene as well as 1,2-derivative reacted largely in S_NAr of the nitro group rather than in an ONSH fashion (entries 3 and 4). Remarkably, 1-fluoro-4-nitrobenzene provided solely the ONSH product **7** (entry 5) so did the other halo nitrobenzenes (entries 6 and 7). More activated 2,4-difluoro-1-nitrobenzene afforded the product of S_NAr of fluorine rather than substitution of hydrogen (entry 8). 4-Fluoro-1-nitro-2-(trifluoromethyl)benzene yielded a mixture of ONSH and S_NAr products (entry 9) while the 4-bromo derivative

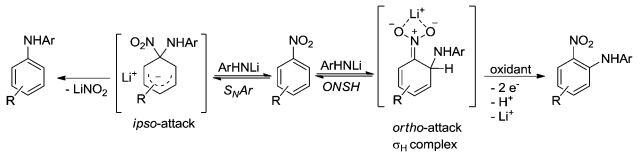
Table 3 Scope of the reaction of lithium anilide with electron-deficient aromatics



Entry	Substrate	Product and yield[a] (%)
1		**3** (64) 
2		**4** (72) 
3		**5** (85) 
4		**6** (90) 
5		**7** (61) 
6[b]		**8** (49) 
7[b]		**9** (42) 
8		**7** (59) 
9		**10** (10)[c]  **11** (20)[c] 
10		**12** (47) 
11[b]		**13** (51) 
12		**14** (71) 
13		**15** (70) 
14[b]		**16** (69) 

[a] Isolated yield. [b] Reaction performed at −78 °C. [c] Conversion determined by GC-MS.

provided the ONSH product (entry 10). Remarkably, 1-chloro-2,4-dinitrobenzene which is a prototypical, highly activated substrate for S_NAr of halogen afforded cleanly the product of ONSH under our conditions (entry 11). Some nitrobenzenes with the SF_5 group in the *meta*-position also gave ONSH products regiospecifically in the *ortho*-position to the nitro group since the *para*-position is hindered by the bulky SF_5 group (entries 12 and 13).



Scheme 2 Simplified mechanism of aromatic substitutions of substituted nitrobenzenes with lithium salts of anilines.

The only heterocyclic substrate tested 4-methyl-3-nitropyridine, on the other hand, provided the ONSH product substituted in the *para*-position (entry 14). Substrates such as nitrobenzene, 4-(cyanomethyl)nitrobenzene and 1,4-bis(trifluoromethyl)benzene (not shown in Table 3) were unreactive presumably as a result of their insufficient electron-acceptor character.

Generally accepted mechanisms of S_NAr and ONSH processes[5] applied to reactions of nitrobenzenes with lithium anilide are shown in Scheme 2. Reversible addition of lithium anilide to the *ortho*-position leads to the formation of a deep purple σ_H-complex. Hydride elimination from the σ_H adduct is not favourable and the rearomatization takes place by the action of an oxidant in an irreversible process eventually affording the ONSH product. In contrast, S_NAr of the nitro group favoured with polynitro aromatics and in polar solvents is initiated by reversible addition in the *ipso*-position, followed by nitrite elimination.

In conclusion, ONSH of electron-acceptor group substituted nitrobenzenes with lithium salts of arylamines afforded *N*-aryl-2-nitroanilines. This aromatic amination process showed a broad scope for arylamines in reactions with 4-nitro-1-(pentafluorosulfanyl)benzene. Similarly, nitrobenzenes substituted with halogen, nitro, CF_3, CN, and SF_5 groups as well as 4-methyl-3-nitropyridine underwent efficient substitution of hydrogen with lithium salt of aniline. *Ortho*- and *para*-dinitrobenzenes, however, reacted in S_NAr of a nitro group. Products of the ONSH process are attractive push–pull benzene derivatives with two electron-acceptor groups and one amino electron-donor group.

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Notes and references

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