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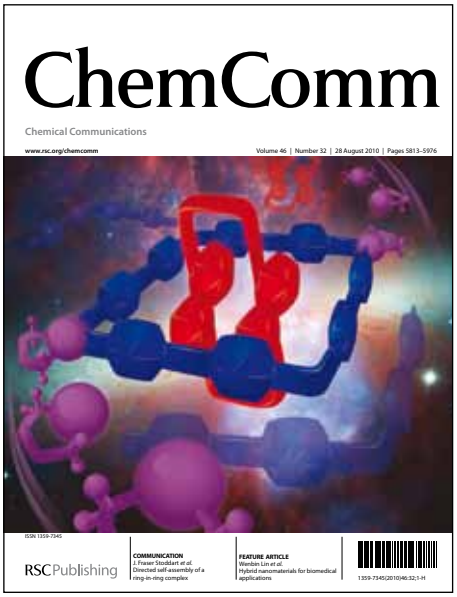

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Communication

Copper-Catalyzed *ortho*-Halogenation of Protected Anilines

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A practical Cu-catalyzed direct *ortho*-halogenation of anilines under aerobic conditions has been developed. The reaction shows typically excellent mono-substitution selectivity, high *ortho*-regiocontrol and large functional group tolerance.

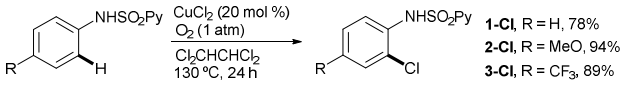
Oxidative coupling reactions under O_2 are extremely attractive from academic and industrial standpoints.[1-3] In this context, Cu has proven to be a versatile oxidant in coupling reactions, many of which can be rendered catalytic under aerobic conditions.[4] In spite of this, Cu-catalyzed aerobic aryl C–H functionalization[5] has only recently begun to draw attention. Most precedents deal with base-promoted reactions at acidic C–H bonds ($pK_a < 35$; polyfluoroarenes or 1,2-azoles),[6] whilst base-free activation of "inert" aryl C–H bonds has been seldom explored. In a pioneering work, Yu reported the Cu-catalyzed *o*-functionalization of 2-arylpyridines.[7] The aerobic Cu-catalyzed cyclization (hence intramolecular) of anilides has also been disclosed.[8,9] Cu-catalysis allows new activation modes that could result in novel patterns of reactivity or selectivity. For instance, Cu^{II} has been proposed to induce SET oxidations[10] involving cation-radical intermediates.

Halogenated anilines are versatile precursors for heterocyclic frameworks that have been historically accessed through electrophilic halogenation or *o*-directed-lithiation. Pd- or Rh-catalyzed C–H halogenation has recently provided useful alternative approaches.[11] However, limitations still remain in terms of scope, mono-/disubstitution selectivity, and enviromental impact (expensive/toxic metals, stoichiometric oxidant, chlorinated solvents and/or strong acids).

Cu-catalyzed/promoted *o-halogenation strategies*[12] *have been exclusively applied to arenes with a non-removable 2-pyridyl (or a related heteroaryl) directing group*. Yu *et al.* reported the *o*-halogenation of 2-arylpyridines using X_2CHCHX_2 (X = Cl, Br) as halogen source.[7] Chlorination of 2-arylpyridines with $PhCOCl/Li_2CO_3$[13] or LiCl[14] was also reported. In all cases, controlling mono- *vs* disubstitution was problematic.

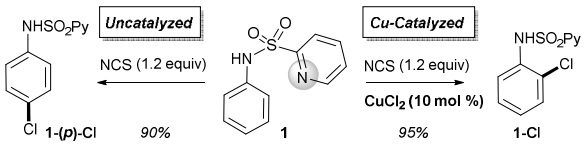
Paucity of Cu-catalyzed *o*-C–H functionalization methods arises from challenges in the activation mechanism (different from typical cyclometalation) and lack of suitable removable directing groups.[10b,15] Herein we disclose a Cu-catalyzed *o*-halogenation of anilines that relies on a readily removable *N*-sulfonyl directing group. This method uses convenient X^+ source, *N*-halosuccinimides (NXS, X = Cl, Br)/industrially friendly solvent (CH_3CN), operates under aerobic conditions, and displays high regio- and mono-halogenation selectivity.

On the basis of our previous results on *N*-(2-pyridyl)sulfonyl-directed C–H functionalization,[16] we initially examined the prospective *o*-chlorination of *N*-(2-pyridyl)sulfonyl aniline (**1**) under Yu's conditions (20 mol% $CuCl_2$ in $Cl_2CHCHCl_2$, O_2 at 130 °C).[7] Gratifyingly, the *o*-chloroaniline **1-Cl** was isolated as the only product (78% yield, Scheme 1). Both electron-rich and electron-deficient derivatives performed well (products **2-Cl** and **3-Cl**, 94% and 89% yield, respectively). A striking feature of this reaction was that no di-*o*-chlorination occurred.



Scheme 1 Initial Cu-catalyzed aerobic *o*-chlorination of anilines.

Despite these encouraging results, the industrially disfavored solvent $Cl_2CHCHCl_2$ and heating at 130 °C for 24 h were important drawbacks. Therefore, it was deemed appropriate to develop a more efficient and environmentally benign protocol. After some investigation (see ESI), we were keen to find that selective *o*-chlorination of aniline **1** was cleanly achieved in the presence of 10 mol % $CuCl_2$ using NCS (1.2 equiv), upon heating for 4 h at 100 °C in MeCN under O_2 (Scheme 2).[17] The *o*-chloroaniline **1-Cl** was obtained in 95% isolated yield with excellent regiocontrol (only traces of the *p*-Cl derivative were detected by GC) and complete mono-substitution selectivity. An attempt to lower the amount of $CuCl_2$ to 5 mol % resulted in the competitive formation of the *p*-Cl aniline derivative **1-(*p*)-Cl** (*o*/*p* = 3:1), likely *via* an electrophilic substitution pathway. Consistent with this result, product **1-(*p*)-Cl** was formed in 90% isolated yield in the absence of Cu-catalyst, illustrating also the complementarity between the Cu-catalyzed and uncatalyzed reactions (Scheme 2).



Scheme 2 Cu-catalyzed *vs* uncatalyzed aerobic NCS-*o*-chlorination of **1**. Conditions: O_2 (1 atm), MeCN, 100 ºC, 4 h.

A screening of protecting groups revealed that the *NH*-(SO_2Py)- group was uniquely effective for the formation of **1-Cl** (Table 1). The *NH*-Ts aniline **4** led to the *p*-Cl product with very high selectivity (entry 2), suggesting that the lack of the

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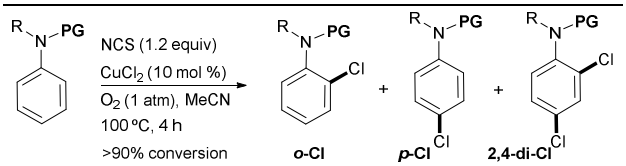
"directing" 2-Py unit caused the background electrophilic chlorination to dominate. The more activated acetanilide (**5**) led mainly to the 2,4-dichlorination product (entry 3), while the unprotected aniline resulted in very low *o*/*p*- and mono/di-selectivities (entry 4). Notably, the coordinating *NH*-CO(2-Py)-group (substrate **6**) provided the *p*-Cl regioisomer as the major product (entry 5), emphasizing the cooperative directing role of both SO_2 and 2-Py moieties in **1**. Finally, *N*-alkylation did not fit for this reaction, as the *N*-(Me)(SO_2Py)-aniline **7** provided only traces of the *o*-Cl product (entry 6).

Table 1 Optimization of the *N*-directing/protecting group



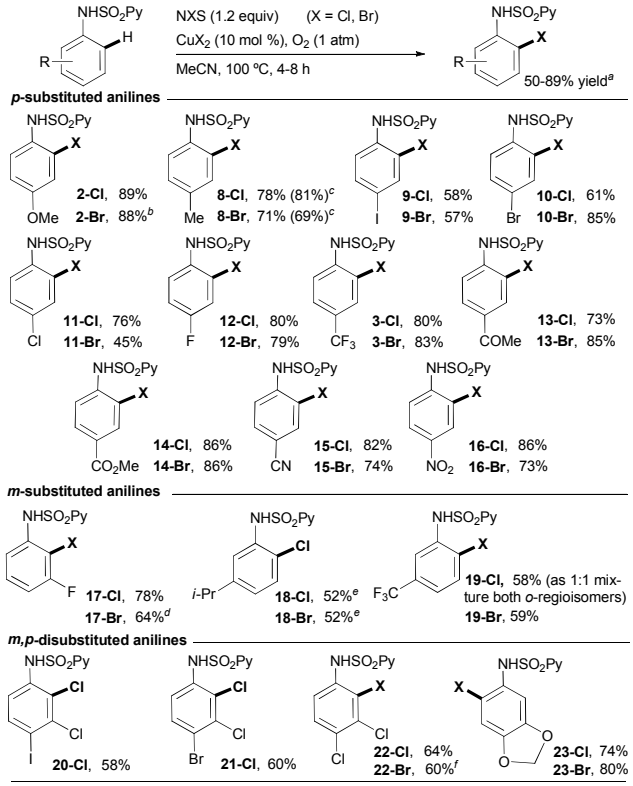
Entry	PG / R (substrate)	*o*-Cl[a]	*p*-Cl[a]	*di*-Cl[a]
1	SO_2(2-Py) / H (**1**)	79 (95)[b]	<5	–
2	Ts / H (**4**)	6	90	–4
3	Ac / H (**5**)	10	–	60
4	H / H	34	29	15
5	C(O)(2-Py) / H (**6**)	12	69	18
6	SO_2(2-Py) / Me (**7**)	10	87	–

Conditions: aniline (0.20 mmol), NCS (0.24 mmol), $CuCl_2$ (10 mol %), MeCN (0.2 M), 100 °C, 4 h, O_2 (1 atm). [a] GC yields (*n*-hexadecane as internal standard). [b] Isolated yield.

Examination of the scope revealed that a wide variety of *p*- and *m*-substituted anilines underwent *o*-chlorination in good yields (52−89%, Scheme 3). Selective mono-chlorination and *o*-selectivity with regard to the amino group was observed in *p*-substituted derivatives, regardless of the electron-rich (**2-**, **8-** and **23-Cl**) and electron-deficient [**3-** and (**9-16**)**-Cl**] nature of the substitution. The regioselectivity in *m*-substituted substrates proved to be sensitive to both electronic and steric issues. For example, chlorination of the *m*-F-derivative occurred with complete regiocontrol at the more acidic *o*-C–H flanked by the C–F bond [**17-Cl**; also (**20-22**)**-Cl**], whereas a bulky *m*-(*i*-Pr) group directed the chlorination to the less hindered *o*-position (**18-Cl**). A *m*-CF_3 group, however, was not effective in controlling the regioselectivity (**19-Cl**).

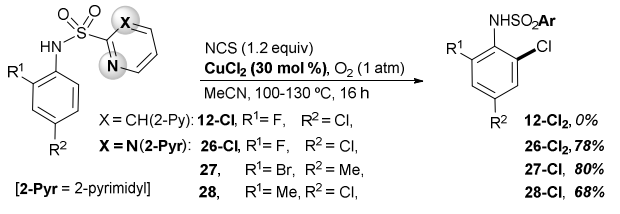
Substrates bearing strong electron-withdrawing groups (NO_2, CN, COMe, CF_3, CO_2Me) were equally effective than those with electron-donating groups (OMe, Me), which stands in contrast to most of Pd-catalyzed examples that are especially suited for electron-rich substrates.[11] Even a base-sensitive COMe group (**13**) was suitable. *N,N*-Dichloro-5,5-dimethylhydantoin (DCDMH) served as alternative reagent, as demonstrated for the *p*-toluidine derivative (**8-Cl**). The complete *o*-selectivity was particularly noteworthy in the *p*-OMe-aniline derivative, with two *o*-directing (electron releasing) groups (**2-Cl**). This selectivity in *p*-methoxyanilides typically requires *o*-lithiation strategies.[18]

We next studied the bromination using NBS/$CuBr_2$ under identical conditions. Interestingly, both *p*- and *m*-substituted anilines with either electron-donating or withdrawing groups were suitable substrates (Scheme 3). Anilines with *m*-substitution provided synthetically useful yields, particularly those with bulky or electron withdrawing substituents[19] [(**17-19**)**-Br**, 52-64%], although the *o*-regiocontrol proved to be less efficient than in the chlorination reaction. In fact, the $CuBr_2$-catalyzed NBS-bromination of the parent aniline **1** provided a 1:1 mixture of *o*- and *p*-substitution (in the absence of Cu only *p*-bromination was observed; see ESI).



Scheme 3 Scope of the Cu-catalyzed *o*-halogenation. [a] Isolated yields. [b] DMF, 150 ºC (20 mol% of $CuBr_2$). [c] Using hydantoin derivatives (0.6 equiv). [d] The other *o*-regiosiomer was detected (10% by GC). [e] Minor unidentified halogenated products were detected. [f] The other *o*-regiosiomer was detected (14% by GC).

While *p*- and *m*-substitution were well tolerated, *o*-substituted anilines were not applicable, as evidenced in the chlorination of **12-Cl** (Scheme 4). To circumvent this problem we found inspiration in Gevorgian's Si-tethered 2-pyrimidyl (2-PyrSi) directing group, which enabled Pd-catalyzed double *o*-C–H oxygenation in cases where the 2-PySi group failed.[20] Indeed, a critical reactivity improvement was found in the chlorination of *N*-(2-Pyr)SO_2-aniline **26-Cl**, providing the *o*-chlorinated product **26-Cl$_2$** in 78% yield, yet requiring higher $CuCl_2$ loading (30 mol %) and longer time (16 h).[21] The 2-PyrSO_2 group also allowed the access to the anilines **27-Cl** and **28-Cl**.



Scheme 4 Chlorination of *o*-substituted *NH*-(2-PyrSO_2)-anilines.

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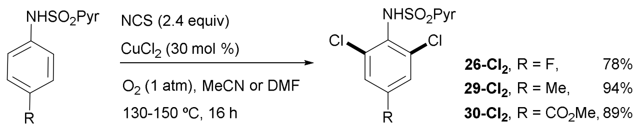
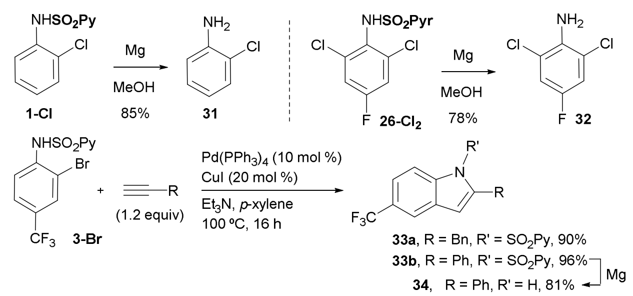
Notably, smooth di-*o*-chlorination was observed in anilines with the two *o*-positions unsubstituted (Scheme 5).[21]



Scheme 5 Di-*o*-chlorination.

The lack of NCS-chlorination of **1** in the presence of radical scavengers such as TEMPO or Galvinoxyl (1.0 equiv) suggested that a SET pathway might operate.[22] Finally, both Py- and Pyr-based directing groups could be removed under mild conditions to generate the free NH_2-anilines (**31** and **32**, Scheme 6). The versatility of the halogenated products as building blocks was illustrated in the conversion of the derivative **3-Br** into the functionalized indoles **33** and **34**.[23]



Scheme 6 Deprotection and synthetic applications.

In summary, a highly regioselective *N*-SO_2Py-directed Cu-catalyzed *o*-C–H monohalogenation of anilines leading to *o*-Cl and *o*-Br aniline derivatives has been developed. The directing 2-pyridylsulfonyl and 2-pyrimidylsulfonyl groups can be easily cleaved in the final products.

Acknowledgements

This work was supported by the Spanish Government (*MINECO*, CTQ2009-07791; CTQ2012-35790), and Madrid regional government (*AVANCAT*, S2009/PPQ-1634). N.R. and B.U. thank the *MICINN* for a Ramón y Cajal contract and a predoctoral fellowship. N.R. thanks the Marie Curie Foundation (CIG: CHAAS-304085) and B.U. thanks the MC for a contract. We thank Lim Jia Hui for optimization studies.

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