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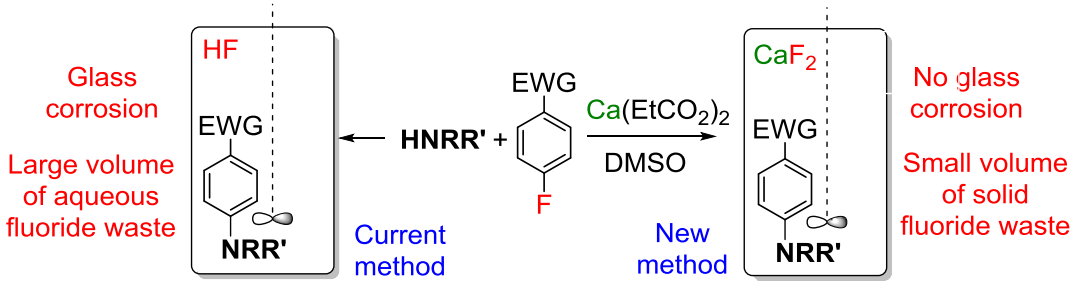
Blacker, AJ orcid.org/0000-0003-4898-2712, Moran Malagon, G, Powell, L et al. (3 more authors) (2018) Development of an SNAr Reaction: A Practical and Scalable Strategy to Sequester and Remove HF. Organic Process Research & Development, 22 (9). pp. 1086-1091. ISSN 1083-6160

https://doi.org/10.1021/acs.oprd.8b00090


Glass corrosion
Large volume of aqueous fluoride waste
HF
EWG
NRR'
HNRR' +
EWG
F
Ca(EtCO2)2
DMSO
Current method
New method
CaF2
EWG
NRR'
No glass corrosion
Small volume of solid fluoride waste

Development of an S_NAr Reaction: A Practical and Scalable Strategy to Sequester and Remove HF

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KEYWORDS: S_NAr reaction, calcium fluoride, aryl amines, fluoride sequestration, scale-up

ABSTRACT

A simple and operationally practical method to sequester and remove fluoride generated through the S_NAr reaction between amines and aryl fluorides is reported. Calcium propionate acts as an inexpensive and environmentally benign *in situ* scrubber of the hydrofluoric acid byproduct, which is simply precipitated and filtered from the reaction mixture during standard aqueous work-up. The method has been tested from 10 → 100 g scale of operation, showing > 99.5% decrease in fluoride content in each case. Full mass recovery of calcium fluoride is demonstrated

at both scales, proving this to be a general, efficient and robust method of fluoride abstraction to help prevent corrosion of glass-lined reactors.

INTRODUCTION

The formation of aryl C-N bonds is ubiquitous in organic chemistry, and the resulting *N*-arylamines are found in a multitude of natural products and drug molecules.[1-2] In particular, *N*-arylpiperazines are central to many pharmaceutical compounds, such as (i) AZM574670 PDK inhibitor,[3] (ii) AZD4547, a development Fibroblast growth factor receptor (FGFR) tyrosine kinase family inhibitor,[4] (iii) Levofloxacin, Ciprofloxacin and Sparfloxacin antibiotics,[5] (iv) tetrahydroquinazolinone derivatives such as poly ADP-ribose polymerase (PARP) inhibitors,[6-7] and (v) Prazosin, an off-patent anti-hypertensive[8-9] (Figure 1). It is therefore unsurprising that aryl piperazines are considered privileged structures in medicinal chemistry.

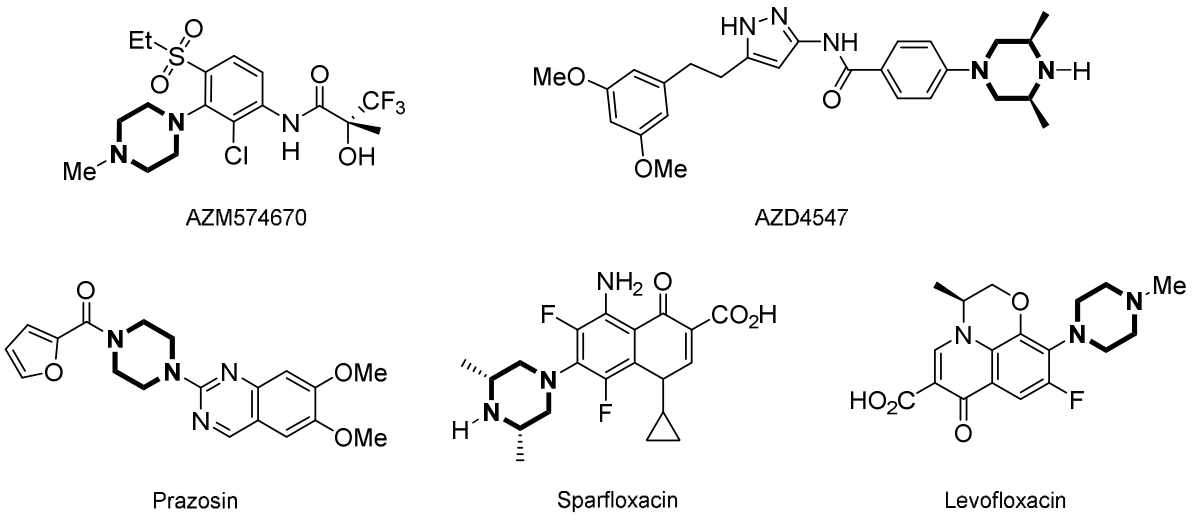
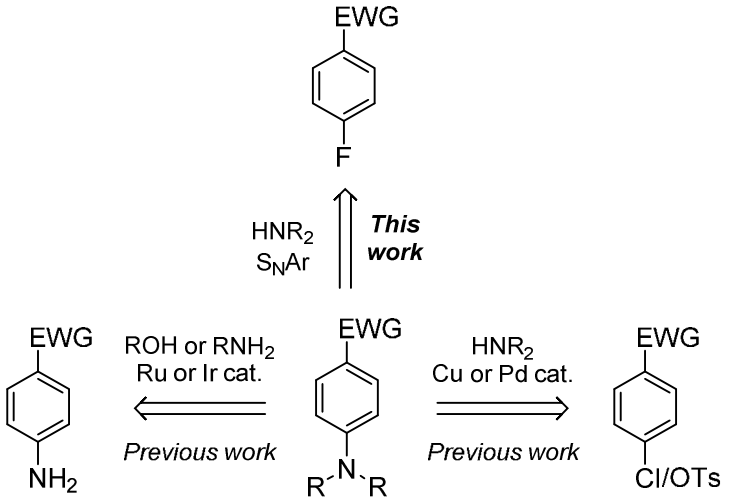


Figure 1. Representative drug molecules comprising the piperazine substructure.

There are several synthetic options to make *N*-aryl amines. Alkylation of anilines with alkyl halides is widely used by industry at large scale and over-alkylation products can be separated

during work-up. An alternative method avoiding the use of Potential Genotoxic Impurities (PGIs) is catalytic hydrogen transfer using alcohols or alkyl amines though at present only with uneconomic quantities of precious metal-based catalyst.[10-13] Another option is the direct amination of aryl halides catalyzed by metals, with copper complexes showing much potential in place of palladium.[14-17] A commonly employed retrosynthetic option for making these subunits is the S_NAr reaction between an activated aryl fluoride and primary or secondary amine (Scheme 1).[18] A preference for this route has already been identified by Moody *et al.* who made a similar conclusion when comparing Pd-catalyzed amination and S_NAr with heteroaryl chlorides. The team also evaluated the use of green solvents in this reaction.[19]



Scheme 1. Approaches to *p*-electron withdrawing group (EWG) substituted anilines.

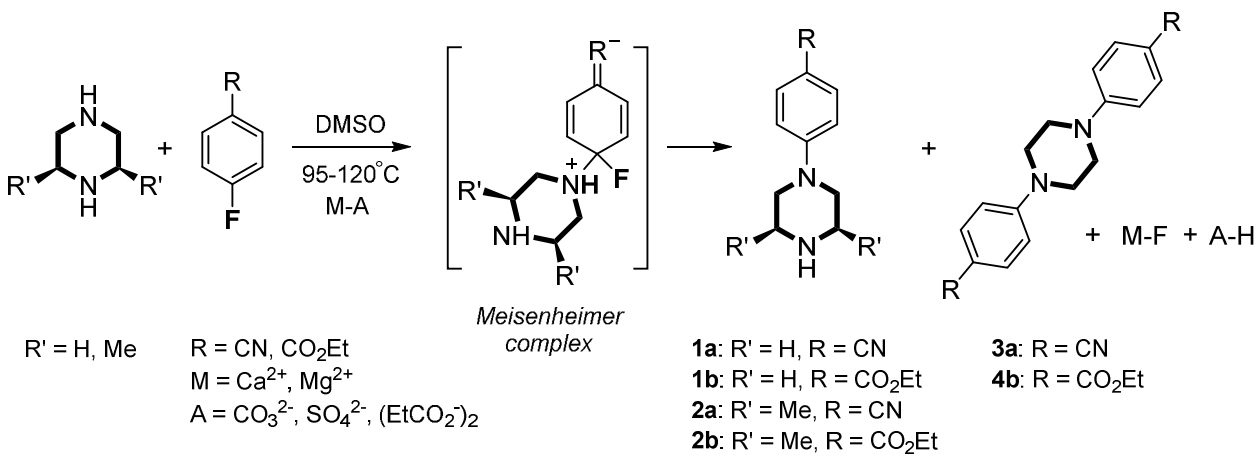
The S_NAr reaction of amines and activated aryl fluorides is used commonly in scaled-up processes but suffers long reaction times at high temperatures and use of dipolar aprotic solvents, which cause separation and waste problems during work-up. Moreover, the generation of fluoride salts as by-products can be detrimental to glass-lined reactors, especially with their repeated use, which occurs *via* the formation of low levels of hydrofluoric acid (HF) generated

through the intentional or unintentional presence of water.[20] The use of mild bases such as potassium carbonate are well known in S_NAr reactions to neutralize the HF generated, however the product KF can still react with moisture to cause glass etching; the potassium fluoride dihydrate is highly soluble in water. In this paper, we discuss a number of potential improvements to processes for making a variety of *N*-aryl piperazines which includes a screen of green solvents, overcoming the problem of hydrofluoric glass-etching, some scoping of amine and fluoroaromatic and an exemplar scale-up with an intermediate used in making Linezolid.[21]

RESULTS AND DISCUSSION

Evaluation of a Selected S_NAr Reaction

We began our study by evaluating published methods for making *N*-aryl piperazines (Scheme 2). It is well known that the S_NAr reaction is particularly intolerant of solvents other than dipolar aprotics. One report of the reaction of 4-fluorobenzonitrile with piperazine employed 2-butanone solvent at reflux over 4 days to achieve a 90% conversion.[22] The same reaction in DMSO gave 93% conversion of the aromatic using 3 equivalents (eq.) of piperazine, and 1.5 eq. K_2CO_3 at 95°C for 20 hours. Repeating this experiment, we found that only 40% of the product was *N*-piperazinyl-4-cyanobenzene (**1a**), with 60% being the double addition product, *N,N'*-di-(4-cyanophenyl)piperazine (**3a**). Other reports have used a 3- and 4-fold excess of piperazine in DMSO at 120°C with 92% and 93% conversion of ethyl-4-fluorobenzoate starting material, respectively.[23-25] Repeating this with 2 eq. piperazine, we found the yield of ethyl *N*-piperazinyl-4-benzoate (**1b**) was 51%, with the *N*,*N*-diarylated product (**4b**) the remaining 49%. The use an excess of the amine was needed to obtain high yields.



Scheme 2. S_NAr reaction of piperazine and aryl fluoride to form *mono*- and *di*-aryl piperazines.

Changing to the hindered, unsymmetrical *cis*-2,6-dimethyl piperazine, the reaction with ethyl-4-fluorobenzoate and 4-fluorobenzonitrile was regiospecific to the less hindered amine, with the flanking methyl groups providing an effective steric block (Scheme 2). With 1.5 – 4 eq. piperazine, the *N*-arylated piperazine (**2a**) were produced over several experiments with yields varying between 82-97% during the present study (Table 1).

General comments and observations from repeating these reactions:

- DMSO provides solubility for all the materials and possibly stabilises the intermediate Meisenheimer complex.
- Heating is required to increase the reaction rate; despite this, long reaction times of 18-24 hours are required, and at higher temperatures some decomposition of DMSO is observed, as evidenced by an increasingly dark solution.
- Reactions with piperazine (>4 eq. excess) still lead to mixtures of *mono*- and *di*-arylated products, and reported reactions quote conversion of aromatic rather than yield of product.

- Above 110°C, both *N*-(1,4)-piperazinyl-4-benzonitrile (**1a**) and ethyl *N*-(1,4)-piperazinyl-4-benzoate (**1b**) sublime from the reaction forming a solid above the stirred level.
- Whilst no specific etching of the glassware was observed, a glass test piece added to the reaction lost 0.1% of its mass.
- Substantial amounts of water (10 – 15 volume equivalents) are added at the end of reaction along with a water immiscible solvent such as dichloromethane or ethyl acetate to assist in separating the product from DMSO and by-products. This results in a sizeable waste stream.
- Repeated washings of the solid product are required to remove the DMSO, further lowering the reaction mass efficiency and increasing the waste.

These problems combine to diminish the efficiency of larger scale S_NAr processes.

Process Improvements

Rather than a multi-parallel study, we opted to investigate single parameters with overhead-stirred split-necked flasks, as this can assist in evaluating more complex issues such as mixing, glass-etching, hetereogeneous sampling and sublimation. The concentration of aromatic used was 0.7 M, and typically 1.5 eq. of the amine was employed in a total solvent volume of 10 – 1000 mL. Unless stated otherwise, the reaction time was 24 hours which gave full conversion of starting material in every case.

(a) Solvent Screen

It was decided to evaluate a series of green solvents, with a view to find a dipolar aprotic alternative for the S_NAr reaction.

Table 1. Isolated yield (%) of **2a** from various alternative solvents.[a]

Entry	Solvent	Yield (%)[b]
1	Water	0
2	Butyl methyl imidazolium chloride [BMIM][Cl]	89
3	[BMIM][PF_6]	0
4	Dimethylsulfoxide [DMSO]	82-94
5	DMSO/H_2O, 2:1	76
6	DMSO/H_2O, 1:1	86
7	DMSO/H_2O, 1:2	61
8	DMSO/pyridine, 9:1	90
9	DMSO/MeCN, 9:1	64
10	Methanol, ethanol, *iso*-propanol, or *tert*-butanol	2-3
11	Ethylene glycol	19
12	Methyl ethyl ketone [MEK]	5
13	EtOAc	0
14	Diethyl carbonate	0
15	Ethylene carbonate	0
16	THF/toluene, 1:1	35
17	Anisole	0
18	Pyridine	<5

[a] The experimental conditions used were those described in the general lab-scale procedure replacing DMSO with the solvents indicated. [b] Isolated mass of **2a**.

The S_NAr reaction in water was unsuccessful because the fluoroaromatic was insoluble (entry 1). Interestingly the ionic liquid [BMIM][Cl] proved a good solvent for the reaction of ethyl-4-fluorobenzoate and 2,6-dimethylpiperazine with 89% isolated yield (entry 2). Surprisingly, the [PF_6] analogue was ineffective (entry 3) and the reason for this is unknown. The cost, separation and potential toxicity issues of ionic liquids precluded their further evaluation. The aromatics investigated, and piperazine, are completely soluble in DMSO, whilst 2,6-dimethyl piperazine required some heating to fully dissolve. All of the reactions conducted in DMSO (and mixtures thereof) performed well (entries 4 – 9). With 2:1 ($^v/_v$) water/DMSO the yield of product was ~ 20% lower, and this might reflect destabilisation of the Meisenheimer intermediate. The addition of 10% pyridine in DMSO gave a 90% yield, possibly because it assists in deprotonation of this intermediate (entry 8). Since it had been observed that product

sublimed from the reaction, a lower boiling co-solvent was needed that would reflux, dissolve the amine, and return-it to the reaction mass. A 1:9 combination of MeCN in DMSO ($^{v}/_{v}$) at 100°C had the desired effect, though the lower temperature slowed the overall rate and resulted in a lower yield (64%, entry 9). Except for ethylene glycol (entry 11), the alcoholic solvents gave trace yields (2 – 3%, entry 10). The ketones, esters and carbonates also performed poorly (≤ 5%, entries 12 – 15). The poor performance of ethylene and diethyl carbonate was disappointing as these are said to have properties similar to dipolar aprotics. Toluene gave only poor yields, whilst reaction rates in THF were low. An equal volume of both toluene and THF at 100°C gave 35% yield of **2b** over 24 hours (entry 16). Both anisole and pyridine were unsuccessful solvents (entries 19 and 20).

DMSO was selected as the preferred solvent, giving consistently higher yields than all other solvents tested. Furthermore, it is on the list of solvents preferred by the pharma industry for its low biological toxicity.[26] Nevertheless, this is a problematic solvent since its high boiling point makes it difficult to separate from products. Moreover, its miscibility with water prevents disposal to drain, hence requiring incineration, and associated problems of cost and odour abatement. The use of DMSO translated well to produce the derivative **2b** as an alternative example (94-97%, see ESI).

(b) Fluoride Sequestration

One of the problems with the use of aryl fluorides in the S_NAr reaction is the fluoride salt by-product that can cause damage to glass-lined vessels during repeated batch manufacture.[11] The use of an amine base, or excess amine reactant is often used to neutralize the HF generated, however the conjugate acid is strong (pKa ~9 in DMSO) and leads to a significant solution concentration of HF (pKa = 3.2 in water). The reaction of HF with silica is well known and since

even neutral or mildly acidic conditions can generate sufficient concentrations to cause glass-etching. The use of calcium salts to sequester fluoride is an approach that is widely known in dentistry/medicine, and calcium gluconate is used as an antidote for accidental contact in fluorochemical producing industries,[27] but appears not to have been used within a fluoride-generating process, and might be especially useful for protecting standard glass-lined assets used in repeat manufacture. The solubility product (K_{sp}) of calcium fluoride is 3.9×10^{-11} in water, whilst salts such as calcium carbonate and calcium sulfate are higher with K_{sp} of 4.8×10^{-9} and 4.9×10^{-5} respectively;[28] whereas the solubility of calcium fluoride in dipolar aprotic solvents is much lower. Calcium propionate is much more soluble in water: 49% and 56% ($^{w}/_{v}$) at 0°C and at 100°C respectively, with slight solubility in lower alcohols.

Several calcium salts were initially tested to effectively sequester the fluoride generated in the reaction. The experiments employed an equimolar stoichiometry of finely divided anhydrous calcium salt, based on the fluoroaromatic added to the stirred DMSO, amine and aromatic, which is twice that required if the product is CaF_2. The amine in the process may neutralise the acid released from the reaction of the calcium salt with hydrogen fluoride. Following the reaction, methyl *tert*-butyl ether (MTBE) was charged to the reaction vessel, the mixture stirred and emptied *via* the bottom run-off to a vacuum filter (optionally coated with filter-aid). A further MTBE wash of the reactor and screened solid ensured full product recovery. The combined filtrates were washed repeatedly with water, the lower aqueous phase containing DMSO and other impurities. The level of fluoride in the effluent aqueous washings was measured. The MTBE solution was concentrated by distillation, before cooling to crystallize the product.

Anhydrous calcium carbonate showed no advantage over calcium sulfate, whilst use of the more soluble calcium propionate showed similar rates and levels of fluoride sequestration. Calcium propionate was preferred to the other salts, being more easily charged, dispersed in the reaction, and recovered. The difference in cost of calcium propionate over other salts is minor. The S_NAr reaction rates with any of the calcium salts tested were identical to that without, and this indicates the absence of a thermodynamic equilibrium between fluoride, product and the Meisenheimer complex. Fluoride analysis of the organic-aqueous work-up solution, using an ion selective electrode, showed minimum detectable levels compared to the theory amounts, or control reactions without $Ca(EtCO_2)_2$ (Table 2). The mass balance of CaF_2 was based on the product yield from fluoroaromatic, and compared to the dried solid CaF_2 recovered from the filter, and the fluoride measured in the work-up liquors. The remaining mass may be due to physical losses at this small scale.

Table 2. The effect of calcium propionate sequestration of fluoride

Entry	Product	Theory level of fluoride in wash[a]	Fluoride level in wash (no $Ca(EtCO_2)_2$)/ppm	Fluoride level in wash (with $Ca(EtCO_2)_2$)/ppm	Mass recovery CaF_2/%[a]
1	**2a**	1414	1349[b]	9[b]	74
2	**2b**	1248	1473	7	70
3	**3a**	1201	1053	3	69
4	**4b**	1260	1752	4	87[c]

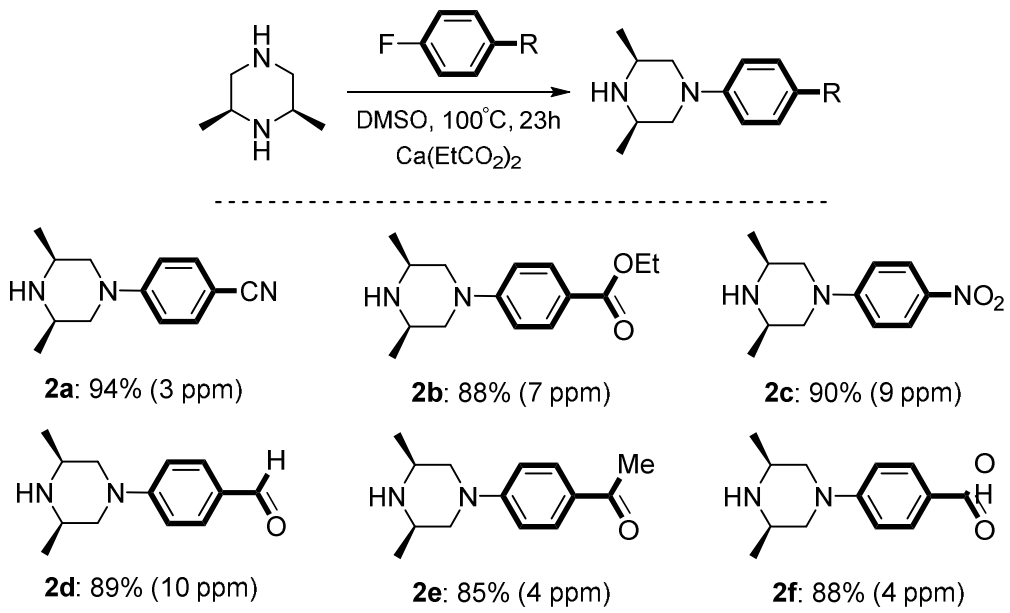
[a] Based on 100% reaction of aromatic charged. [b] Average of 3 experiments. [c] Average of 2 experiments.

The ion selective electrode cannot be used in organic solvent, so to assess the effect of calcium sequestration of fluoride in the reaction mass prior to work-up, careful observation of the glass was done under the microscope and showed no etching. Using $Ca(EtCO_2)_2$, the pH of both the reaction mass and MTBE wash were neutral.

Reaction Scope

(a) Varying the fluoroaromatic

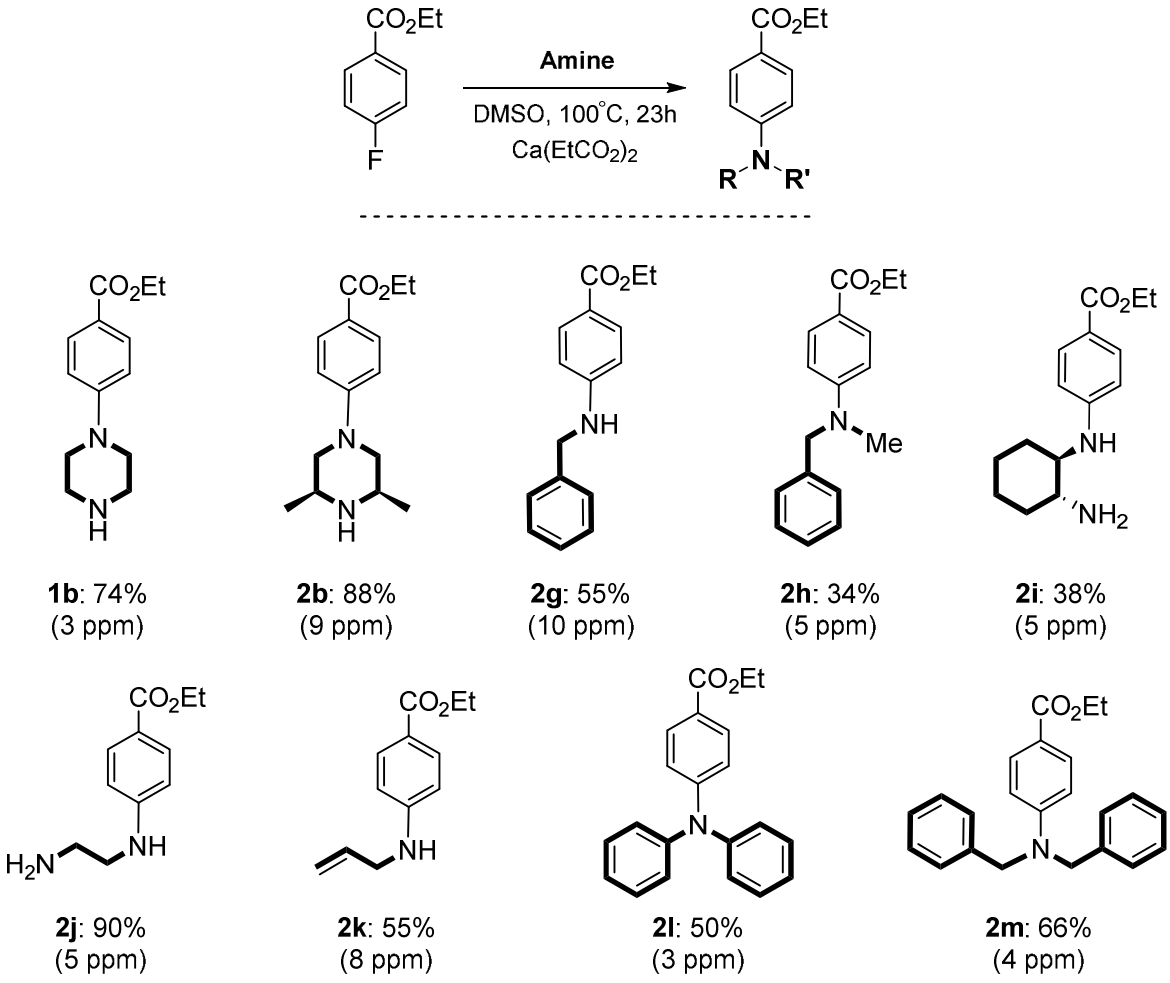
With a method to remove fluoride in hand, we set out to investigate the scope of the process using a range of fluoroaromatics and amine substrates. Initially, 2,6-dimethylpiperazine was reacted with various 4-substituted fluoroaromatic compounds in the presence of calcium propionate (Scheme 3). Good isolated yields of carboxylate-based aromatics (**2c**-**2f**, 85-90%) were obtained under the standard reaction conditions, with excellent yields of 94 and 90% observed for cyano- and nitro- substituted aromatics, **2a** and **2c**, respectively. For all examples, fluoride content was measured to be ≤ 10 ppm, with no apparent change in reaction rate.



Scheme 3. A fluoroaromatic scoping study with isolated yields of amine. The fluoride content is given in parentheses.

(b) Varying the amine

To complement our scope study, the amine coupling partner was varied under otherwise analogous conditions to those outlined above. Primary and secondary amines were employed, and reaction conversion was monitored by ^{1}H NMR spectroscopy. In general, less hindered primary amines were converted in moderate to good yields of 38 – 90%, whilst more encumbered secondary amines (**2h, 2i, 2m**) afforded low conversion to product (34 – 66%). However, only trace levels of fluoride were detected for each example post-reaction (≤ 10 ppm), demonstrating the generality of calcium propionate as a sequestering agent.



Scheme 4. Scoping study with isolated yields of amine. The fluoride content given in parentheses.

Process Scale-up

To finalize our study, we next evaluated the scalability of fluoride sequestration by conducting two parallel S_NAr reactions at 10 and 100 g scales. Reaction between 4-fluorobenzonitrile and piperazine was selected as model system. Carrying out the process on a 0.1 L scale with 11.5 g piperazine, 5.5 g CaF_2 was precipitated from the reaction mixture during work-up. Linearly scaling the reaction by an order of magnitude, 115 g piperazine yielded 55 g of CaF_2 during work-up, highlighting the robustness of our method. Following removal of solvent, the small and large-scale reaction mixtures showed 8 and 2 ppm fluoride content, respectively (Table 3), with quantitative conversion of piperazine in both cases. Importantly, a full mass recovery of CaF_2 was obtained to allow simple removal of fluoride by filtration.

Table 3. Fluoride mass balance for scale-up of **1a**.

Entry	Scale/mL	Theory level of fluoride in wash[a]	Fluoride level in wash (with $Ca(EtCO_2)_2$)/ppm	Mass recovery CaF_2/%[a]
1	100	1273	8	105
2	1000	1273	2	104

[a]Based on 100% reaction of aromatic charged.

CONCLUSIONS

We report a systematic study of the factors which impact the process development of the S_NAr reaction between amines and aryl fluorides. This is a useful strategy to generate anilines, though is compromised by the generation of stoichiometric equivalents of hydrofluoric acid by-product which often leads to glass-etching of industrial reactor vessels. In this study, we employ calcium propionate as an effective *in-situ* HF scrubber, generating calcium fluoride by-product which is simply removed by precipitation/filtration post-reaction. This method appears to avoid hydrofluoric glass-etching, showing trace ppm levels of fluoride content on both 10 and 100 g

reaction scale. Full mass recovery of CaF_2 is observed at both reaction scales, suggesting that this strategy translates linearly and efficiently to kilogram scale.

EXPERIMENTAL SECTION

General S_NAr procedure (laboratory scale). Fluoroaromatic (6.7 mmol) was added to a suspension of amine (13.4 mmol) and calcium propionate (1.25 g, 6.7 mmol) in DMSO (10 mL). The mixture was heated to 100 °C for 23 hours. The reaction was allowed to cool to ambient temperature, and MTBE (30 mL) was added in a single portion. The resulting calcium precipitate was collected by vacuum filtration and oven-dried overnight. The filtrate was washed with water (3 × 30 mL) to remove the excess amine/propionic acid, and the organic phase dried over $MgSO_4$ and concentrated under reduced pressure to give the crude reaction product as the free-base. At this point, conversion was determined by ^{1}H NMR spectroscopy and/or the pure products isolated by recrystallization from a methanol/water combination (30:20 mL).

10 g scale S_NAr procedure. 4-Fluorobenzonitrile (8.1 g, 67 mmol) and piperazine (11.5 g, 134 mmol) were added to a suspension of calcium propionate (12.5 g, 67 mmol) in DMSO (100 mL), and heated to 100 °C for 23 hours. The reaction mixture was then cooled to room temperature and MTBE (300 mL) was added to cause precipitation of CaF_2. The precipitate was collected *via* vacuum filtration and dried in the oven overnight, to give a mass of 5.51 g. The filtrate was washed with water (3 × 300 mL) and the organic phase dried with $MgSO_4$, filtered and the solvent removed under vacuum to give 13.1 g of product. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed quantitative conversion to 40% **1a** and 60% **3a**, and residual fluoride in the aqueous phase was measured to be 8 ppm.

100 g scale S_NAr procedure. 4-Fluorobenzonitrile (81 g, 0.67 mol) and piperazine (115 g, 1.34 mol) were added to a suspension of calcium propionate (125 g, 0.67 mol) in DMSO (1000 mL), and heated to 100°C for 23 hours. The reaction mixture was then cooled to room temperature and MTBE (3000 mL) was added to cause precipitation of CaF_2. The precipitate was collected *via* vacuum filtration and dried in the oven overnight, to give a mass of 54.71 g. The filtrate was washed with water (3 × 3000 mL) and the organic phase dried with $MgSO_4$, filtered and the solvent removed under vacuum to give 130g of product. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed quantitative conversion to 40% **1a** and 60% **3a** and residual fluoride in the aqueous phase was measured as 2 ppm.

ACKNOWLEDGMENTS

The authors wish to thank AstraZeneca for support and the EPSRC Higher Educational Investment Funding for contributing to Dr Reynolds' position.

REFERENCES

1. Alessandro, M.; Gianna, R.; Massimo, C.; Lorenzo, Z., Stereoselective Synthesis of Polysubstituted Piperazines and Oxopiperazines. Useful Building Blocks in Medicinal Chemistry. *Current Topics in Medicinal Chemistry* **2014,** *14* (10), 1308-1316.
2. Vieth, M.; Siegel, M. G.; Higgs, R. E.; Watson, I. A.; Robertson, D. H.; Savin, K. A.; Durst, G. L.; Hipskind, P. A., Characteristic Physical Properties and Structural Fragments of Marketed Oral Drugs. *Journal of Medicinal Chemistry* **2004,** *47* (1), 224-232.
3. Parker, J. S.; Bower, J. F.; Murray, P. M.; Patel, B.; Talavera, P., Kepner-Tregoe Decision Analysis as a Tool To Aid Route Selection. Part 3. Application to a Back-Up Series of Compounds in the PDK Project. *Organic Process Research & Development* **2008,** *12* (6), 1060-1077.
4. Gavine, P. R.; Mooney, L.; Kilgour, E.; Thomas, A. P.; Al-Kadhimi, K.; Beck, S.; Rooney, C.; Coleman, T.; Baker, D.; Mellor, M. J.; Brooks, A. N.; Klinowska, T., AZD4547: An Orally Bioavailable, Potent, and Selective Inhibitor of the Fibroblast Growth Factor Receptor Tyrosine Kinase Family. *Cancer Research* **2012,** *72* (8), 2045-2056.

5. Foroumadi, A.; Emami, S.; Mansouri, S.; Javidnia, A.; Saeid-Adeli, N.; Shirazi, F. H.; Shafiee, A., Synthesis and antibacterial activity of levofloxacin derivatives with certain bulky residues on piperazine ring. *European Journal of Medicinal Chemistry* **2007,** *42* (7), 985-992.
6. Plummer, R., Poly(ADP-ribose)polymerase (PARP) inhibitors: from bench to bedside. *Clin Oncol (R Coll Radiol)* **2014,** *26* (5), 250-6.
7. Morales, J.; Li, L.; Fattah, F. J.; Dong, Y.; Bey, E. A.; Patel, M.; Gao, J.; Boothman, D. A., Review of Poly (ADP-ribose) Polymerase (PARP) Mechanisms of Action and Rationale for Targeting in Cancer and Other Diseases. **2014,** *24* (1), 15-28.
8. Desiniotis, A.; Kyprianou, N., Advances in the design and synthesis of prazosin derivatives over the last ten years. *Expert Opinion on Therapeutic Targets* **2011,** *15* (12), 1405-1418.
9. Antonello, A.; Hrelia, P.; Leonardi, A.; Marucci, G.; Rosini, M.; Tarozzi, A.; Tumiatti, V.; Melchiorre, C., Design, Synthesis, and Biological Evaluation of Prazosin-Related Derivatives as Multipotent Compounds. *Journal of Medicinal Chemistry* **2005,** *48* (1), 28-31.
10. Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M., Selective amine cross-coupling using iridium-catalyzed "borrowing hydrogen" methodology. *Angewandte Chemie* **2009,** *48* (40), 7375-8.
11. Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M., An Improved Ruthenium Catalyst for the Environmentally Benign Amination of Primary and Secondary Alcohols. *Chemistry – An Asian Journal* **2007,** *2* (3), 403-410.
12. Nordstrom, L. U.; Madsen, R., Iridium catalysed synthesis of piperazines from diols. *Chemical Communications* **2007,** (47), 5034-5036.
13. Leonard, J.; Blacker, A. J.; Marsden, S. P.; Jones, M. F.; Mulholland, K. R.; Newton, R., A Survey of the Borrowing Hydrogen Approach to the Synthesis of some Pharmaceutically Relevant Intermediates. *Org. Proc. Res. Dev.* **2015,** *19* (10), 1400-1410.
14. Surry, D. S.; Buchwald, S. L., Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide. *Chemical Science* **2011,** *2* (1), 27-50.
15. Hartwig, J. F.; Shekhar, S.; Shen, Q.; Barrios-landeros, F., Synthesis of Anilines. In *The Chemistry of Anilines*, 2007; pp 455-536.
16. Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C., Copper catalysed Ullmann type chemistry: From mechanistic aspects to modern development. *Chemical Society Reviews* **2014,** *43* (10), 3525-3550.
17. Ricci, A., *Modern amination methods*. Wiley-VCH, Weinheim: 2001; Vol. 15, p 267.
18. Bartoli, G.; Todesco, P. E., Nucleophilic substitution. Linear free energy relations between reactivity and physical properties of leaving groups and substrates. *Accounts of Chemical Research* **1977,** *10* (4), 125-132.
19. Walsh, K.; Sneddon, H. F.; Moody, C. J., Amination of Heteroaryl Chlorides: Palladium Catalysis or SNAr in Green Solvents? *ChemSusChem* **2013,** *6* (8), 1455-1460.
20. McGhie, S.; Strachan, C.; Aitken, S., A Review of the Use of Aqueous Hydrofluoric Acid in the Manufacture of Betamethasone. *Organic Process Research & Development* **2002,** *6* (6), 898-900.
21. Xu, G.; Zhou, Y.; Yang, C.; Xie, Y., A convenient synthesis of oxazolidinone derivatives linezolid and eperezolid from (S)□glyceraldehyde acetonide. *Heteroatom Chemistry* **2008,** *19* (3), 316-319.
22. Tahghighi, A.; Marznaki, F. R.; Kobarfard, F.; Dastmalchi, S.; Mojarrad, J. S.; Razmi, S.; Ardestani, S. K.; Emami, S.; Shafiee, A.; Foroumadi, A., Synthesis and antileishmanial activity

of novel 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazoles with piperazinyl-linked benzamidine substituents. *European Journal of Medicinal Chemistry* **2011,** *46* (6), 2602-2608.
23. Preti, D.; Baraldi, P. G.; Saponaro, G.; Romagnoli, R.; Aghazadeh Tabrizi, M.; Baraldi, S.; Cosconati, S.; Bruno, A.; Novellino, E.; Vincenzi, F.; Ravani, A.; Borea, P. A.; Varani, K., Design, Synthesis, and Biological Evaluation of Novel 2-((2-(4-(Substituted)phenylpiperazin-1-yl)ethyl)amino)-5′-N-ethylcarboxamidoadenosines as Potent and Selective Agonists of the A2A Adenosine Receptor. *Journal of Medicinal Chemistry* **2015,** *58* (7), 3253-3267.
24. Kubota, D.; Ishikawa, M.; Yamamoto, M.; Murakami, S.; Hachisu, M.; Katano, K.; Ajito, K., Tricyclic pharmacophore-based molecules as novel integrin αvβ3 antagonists. Part 1: Design and synthesis of a lead compound exhibiting αvβ3/αIIbβ3 dual antagonistic activity. *Bioorganic & Medicinal Chemistry* **2006,** *14* (7), 2089-2108.
25. Wang, G.; Zhang, H.; Zhou, J.; Ha, C.; Pei, D.; Ding, K., An Efficient Synthesis of ABT-263, a Novel Inhibitor of Antiapoptotic Bcl-2 Proteins. *Synthesis* **2008,** *2008* (15), 2398-2404.
26. Miller, J.; Parker, A. J., Dipolar Aprotic Solvents in Bimolecular Aromatic Nucleophilic Substitution Reactions1. *Journal of the American Chemical Society* **1961,** *83* (1), 117-123.
27. Roblin, I.; Urban, M.; Flicoteau, D.; Martin, C.; Pradeau, D., Topical Treatment of Experimental Hydrofluoric Acid Skin Burns by 2.5% Calcium Gluconate. *Journal of Burn Care & Research* **2006,** *27* (6), 889-894.
28. Patnaik, P., *Handbook of Inorganic Chemicals*. McGraw-Hill: 2002.