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Mild Transition-Metal-Free Amination of Fluoroarenes Catalyzed by Fluoride Ions

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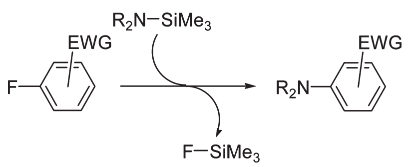

Trimethylsilyl-protected heterocycles undergo N−C bond formation with a variety of electron-deficient fluoroarenes catalyzed by fluoride ions. This reaction avoids stoichiometric amounts of base and thus makes *N*-arylheterocycles accessible in a very mild and transition-metal-free way.

N-Arylheterocycles are ubiquitous motifs in pharmaceuticals,[1] natural products,[2] *N*-heterocyclic carbenes,[3] and compounds of interest in material science.[4] Traditional methods for their preparation are the aromatic nucleophilic substitution (S_NAr) reaction[5] and the classical Ullmann coupling.[6] These methods suffer from several drawbacks including harsh reaction conditions such as high temperatures, the need for strong bases (K_2CO_3, K_3PO_4 ,or NaH), or the stoichiometric use of copper. During the last two decades, transition-metal-catalyzed *N*-arylation has received wide interest. Buchwald[7] and Hartwig[8] developed broadly applicable palladium-catalyzed aminations of haloarenes. Following this breakthrough, numerous publications on the palladium-catalyzed cross-coupling of aryl halides with amines have been reported. However, the use of stoichiometric amounts of a base is still mandatory, and elevated reaction temperatures are often required.[9] Using bidentate ligands, Buchwald[10] and Taillefer[11] accomplished the copper-catalyzed *N*-arylation of heterocycles with bromo- and iodoarenes. Since then, the Ullmann reaction has seen a resurgence due to the economic attractiveness of copper.[12] Instead of aryl halides, several other types of cross-coupling partners have also been employed, among them arylboronic acids,[13] potassium aryltrifluoroborates,[14] arylsiloxanes,[15] arylstannanes,[16] aryllead triacetates,[17] and arylbismuth reagents.[18] Quite mild conditions have been achieved with these substrates; however, these

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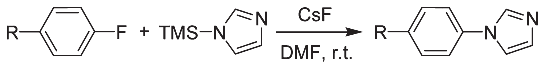
transformations are limited by the high cost and poor availability of functionalized substrates.

Since most of the common methods utilize at least a stoichiometric amount of base (K_2CO_3, K_3PO_4, or Cs_2CO_3) and often apply high temperatures, there is still a demand for procedures with mild conditions in case substrates are incompatible with these requirements. For our approach, we envisaged the S_NAr reaction as a viable alternative. However, we decided to employ a "masked" nucleophile instead of generating the nucleophile in situ through deprotonation. By this method, S_NAr reactions under mild conditions can be achieved. Here, we present N−C bond formations catalyzed by fluoride ions using fluoroarenes and silylamines as coupling partners.

Trimethylsilyl (TMS) groups are common protecting groups in organic chemistry.[19] Most commonly employed to protect hydroxyl moieties, they have also proven to be valuable for amines.[20] For example, in the first asymmetric synthesis of thienamycin, a dibenzyl aspartate was monosilylated in order to achieve a Grignard-mediated cyclization.[21] Silylamines are easily accessible using trimethylsilyl chloride or hexamethyldisilazane.[22] This class of compounds has already been used as precursor for the generation of new N−C bonds. Their addition to aldehydes,[23] alkynes,[24] thiolesters,[25] α,β-unsaturated ketones,[26] and a variety of cumulenes[27] is already known. Ring openings of lactones[28] and anhydrides[29] have also been reported.

The cleavage of the TMS group can be achieved by fluoride ions. Liu and Larock used this approach to generate arynes from *o*-silylaryl triflates, which then undergo reaction with a variety of nucleophiles.[30] Lam generated hypervalent siloxane species with TBAF in order to promote *N*-arylation.[15] A number of reactions catalyzed by fluoride ions have been reported, taking advantage of the great affinity between silicon and fluorine.[31] Only a handful of examples have been reported for fluoride-catalyzed S_NAr reactions generally using silyl ethers and silylacetylenes as the nucleophile precursors.[32]

TABLE 1. Effect of Different EWGs on the *N*-Arylation of Trimethylsilylimidazole with Fluoroarenes at rt[a]



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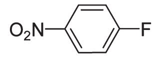
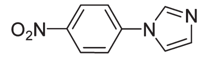
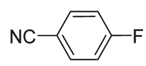
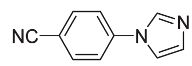
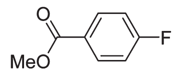
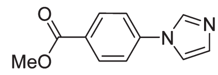
1		5		94
2		60		33
3		60		0

[a]Reaction conditions: fluoroarene (9.7 mmol), trimethylsilylimidazole (10.2 mmol), CsF (24 mol % relative to the fluoroarene), DMF (5 mL), rt, N_2. [b]Isolated yields.

We recently developed a fluoride-catalyzed method for the formation of P−C bonds between fluoroarenes and silylphosphines.[33] To the best of our knowledge, there is only one publication on the usage of silylamines in this type of reaction: in 1994, Miller and Furin reported the reaction of bis(trimethylsilyl)amine with perfluorinated arenes yielding a mixture of arylamines, diarylamines, and triarylamines.[34]

For our initial studies on the fluoride-catalyzed N−C coupling, we used the conditions we had already optimized for the P−C coupling. Trimethylsilylimidazole was first used as the nucleophile precursor due to its commercial availability and the great importance of imidazole arenes.[2a] All kinds of fluoroarenes bearing electron-withdrawing groups can be used as coupling partners, the only exception being arenes with acidic protons, for example, carboxylic acids. First tests with three fluoroarenes substituted with electron-withdrawing groups in the *para* position showed mixed results (Table 1).

In case the electron-withdrawing effect is sufficiently strong, as for the nitro group, the reaction proceeds rapidly (Table 1, entry 1). The nitrile and the ester derivative showed a much lower reactivity (Table 1, entries 2 and 3), giving the order $NO_2 > CN \gg COOMe$. This corresponds well with the Hammett substituent constants σ_p (NO_2: 0.78, CN: 0.66, COOMe: 0.45) for these electron-withdrawing groups (EWGs),[35] which are a measure of the electron-withdrawing capacity of a substituent. Generally, the reactivity of fluoroarenes for S_NAr reaction increases if the arene is more electron-deficient. After a brief optimization, we found that 20 h at 60 °C are sufficient for the coupling of TMS-imidazole with a series of fluoroarenes (Table 2).

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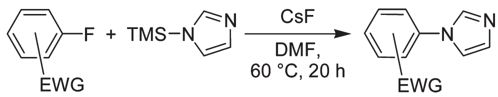
TABLE 2. ***N*-Arylation of Trimethylsilylimidazole with Fluoroarenes**[a]



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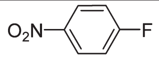
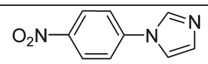
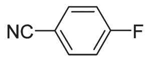
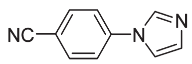
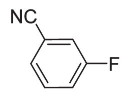
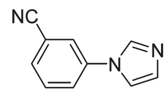
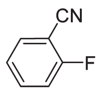
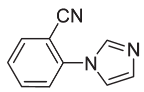
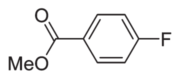
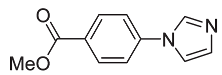
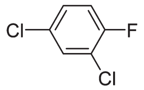
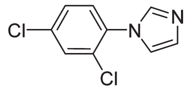
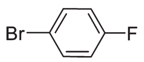
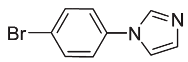
1			97
2			96
3			57
4			93
5			77
6			80
7			2

[a]Reaction conditions: fluoroarene (9.7 mmol), trimethylsilylimidazole (10.2 mmol), CsF (24 mol % relative to the fluoroarene), DMF (5 mL), 60 °C, 20 h, N_2. [b]Isolated yields.

The nitro and nitrile derivatives gave excellent yields, the only exception being the *meta*-functionalized arene which still gave a satisfactory result (Table 2, entry 3). This difference in reactivity is explained by the fact that a substituent in the *meta* position will not stabilize the intermediate in the addition−elimination mechanism by a resonance effect. Due to steric reasons, the reactivity of *ortho*-functionalized arenes is slightly lower than that of the *para* derivatives (Table 2, entries 2 and 4). This is consistent with the general order of reactivity in S_NAr reactions being *para* > *ortho* ≫ *meta*. Since a fluoro substituent accelerates the addition step to the *ipso* position in S_NAr reactions by its enormous inductive effect, the halide-substituted fluoroarenes (Table 2, entries 6 and 7) showed exclusive displacement of fluoride, which was confirmed by NMR and high-resolution mass spectroscopy. Only traces of product could be isolated when 1-bromo-4-fluorobenzene was used as the coupling partner (Table 2, entry 7). This shows that activation of the arene by one bromine group is not sufficient, whereas two chloro groups in the *ortho* and *para* positions are activating enough to achieve a acceptable yield (Table 2, entry 6).

The proposed catalytic cycle can be explained as follows: a fluoride ion cleaves the TMS group from the amine generating a nucleophile. This nucleophile undergoes S_NAr with a fluoroarene yielding the product and regenerates the fluoride ion (Scheme 1).

To gain a deeper insight into the coupling reaction, we set up a series of control experiments which are summarized in

SCHEME 1. Fluoride-Catalyzed N−C Coupling

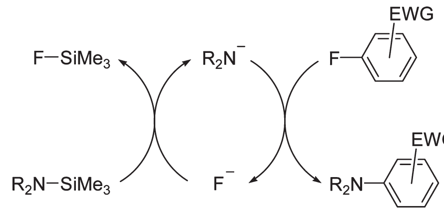
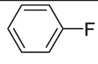
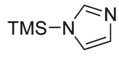
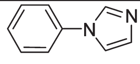
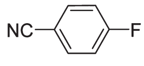
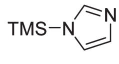
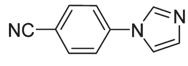
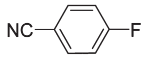
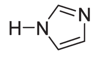
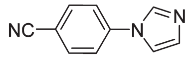
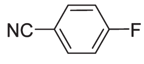
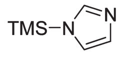
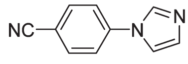
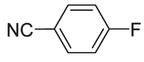
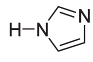
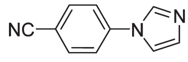
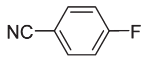
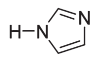
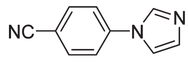
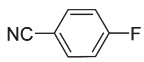
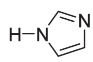
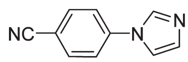


Table 3. First, we investigated the reaction between fluorobenzene and trimethylsilylimidazole. The functionalization of the fluoroarene with an EWG is an absolute necessity. Without an EWG present, not even traces of product can be detected (Table 3, entry 1). The fluoride source also plays an important role. From our studies on the P−C coupling it can be concluded that CsF is superior compared to KF or TBAF. We also noticed that different batches of CsF showed different reactivity. A huge increase in reactivity could be achieved by dissolving CsF in deionized water followed by removal of the solvent and drying under vacuum at 150 °C for several days. A possible reason for the increased reactivity may be a change in the morphology of the treated CsF. When the reaction was carried out in the absence of CsF no reaction occurred (Table 3, entry 2). Instead of CsF, *catalytic* amounts of bases, for example, K_2CO_3, are also able to start the reaction; however, the yields are lower in this case. We suppose that under these basic conditions traces of water in the solvent will initially cleave the TMS group from the imidazole, which then will liberate the catalyst fluoride by N−C coupling. There have been several reports on the usage of CsF as a base in transition-metal-catalyzed N−C bond formations.[9a,36] We therefore wanted to rule out this role for CsF. If 1*H*-imidazole is applied instead of trimethylsilylimidazole only traces of product are formed at rt (Table 3, entry 3), compared to 94% at rt with the silylated reagent (Table 3, entry 4). Even at 60 °C, just 9% of the product are formed (Table 3, entry 5), proving that the noncatalyzed S_NAr reaction with CsF acting as base only has a minor impact on the overall rate. With potassium acetate as base, which is comparable to CsF in terms of its basicity,[37] only traces of the product were detected (Table 3, entry 6); with K_2CO_3, a much stronger base, only 1 equiv of product according to the amount of base is generated (Table 3, entry 7). These results clearly prove that the reaction takes place due to the special capability of fluoride ions to cleave TMS groups and not because of their basicity.

Fluorotrimethylsilane, the byproduct of the synthesis, has a boiling point of 16 °C and evaporates through a bubbler during the reaction. This offers an additional driving force to shift the equilibrium to the products. Monitoring the progress of the reaction is therefore quite simple: as soon as the evolution of fluorotrimethylsilane ceases, the reaction is finished. Typical workup consists of removing the solvent under reduced pressure and extraction with dichloromethane and washing with water. According to NMR and elemental analysis data the products are usually clean without further purification.

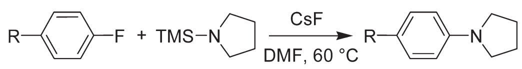
(36) Phillips, D. P.; Zhu, X. F.; Lau, T. L.; He, X.; Yang, K.; Liu, H. *Tetrahedron Lett*. **2009**, *50*, 7293–7296.
(37) Bordwell, F. G. *Acc. Chem. Res*. **1988**, *21*, 456–463.

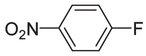
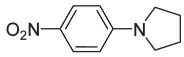
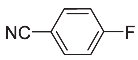
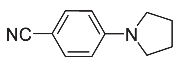
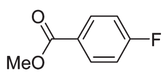
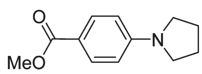
TABLE 3. Control Experiments[a]

entry	fluoroarene	nucleophile	CsF (mol%)	T (°C)	product	yield (%)[b]
1			24	60		0
2			0	60		0
3			24	r.t.		< 1
4			24	r.t.		94
5			24	60		9
6			0[c]	60		1
7			0[d]	60		20

[a]Reaction conditions: fluoroarene (9.7 mmol), nucleophile (10.2 mmol), DMF (5 mL), 20 h, N_2. [b]Isolated yields. [c]KOAc (24 mol % relative to the fluoroarene); [d]K_2CO_3 (24 mol % relative to the fluoroarene).

TABLE 4. Reaction of Fluoroarenes with Trimethylsilylpyrrolidine[a]



entry	fluoroarene	t (h)	product	yield (%)[b]
1		6		88
2		20		84
3		110		76

[a]Reaction conditions: fluoroarene (9.7 mmol), trimethylsilylpyrrolidine (10.2 mmol), CsF (24 mol % relative to the fluoroarene), DMF (5 mL), 60 °C, N_2. [b]Isolated yields.

For extension of this method to aliphatic amines, trimethylsilylpyrrolidine was investigated. Satisfactory results could be obtained (Table 4); however, the general reactivity is lower compared to imidazole since pyrrolidine lacks to stabilize the negative charge generated by the cleavage of the TMS group.

To summarize: fluoride-catalyzed N−C bond formation allows a mild and general access to *N*-arylated amines, which opens up new opportunities for the synthesis of pharmaceuticals and other valuable fine chemicals.

Experimental Section

All reactions were performed under nitrogen by using standard Schlenk techniques unless otherwise specified. CsF was obtained from Sigma-Aldrich and activated by dissolving in deionized water followed by removal of the solvent and drying under vacuum at 150 °C for several days. Trimethylsilylpyrrolidine was prepared according to ref 22a. All other reagents were purchased from commercial sources and used without further purification.

General Procedure for the Coupling Reactions. An oven-dried Schlenk tube was charged with CsF (2.3 mmol) and flame-dried under vacuum. After the tube had cooled to rt, dry DMF (5 mL) and a magnetic stirring bar were added under nitrogen. After the resulting suspension was stirred for 30 min, the fluoroarene (9.7 mmol) was added, and the mixture was stirred for 10 min followed by the addition of the nucleophile (10.2 mmol). The cap of the Schlenk tube was replaced by a bubbler, and the mixture was heated to the required temperature for the indicated time. For the workup, most of the solvent was removed under vacuum. Dichloromethane (20 mL) and water (20 mL) were added to the residue, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with water (15 mL) and a saturated NH_4Cl aqueous solution (15 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure.

Supporting Information Available: Compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org."