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Nucleophilic Aromatic Substitution of Unactivated Aryl Fluorides with Primary Aliphatic Amines via Organic Photoredox Catalysis

Weimin Shi,[a] Jingjie Zhang,[a] Fengqian Zhao,[a] Wei Wei,[a] Fang Liang,[a] Yin Zhang,[a] Shaolin Zhou*[a,b]

Abstract: Here, we report a mild and transition-metal-free approach for the nucleophilic aromatic substitution (S_NAr) of unactivated fluoroarenes with primary aliphatic amines to form aromatic amines. This reaction is facilitated by the formation of cationic fluoroarene radical intermediates in the presence of an acridinium-based organic photocatalyst under blue light irradiation. Various electron-rich and electron-neutral fluoroarenes are competent electrophiles for this transformation. A wide range of primary aliphatic amines, including amino acid esters, dipeptides, and linear and branched amines are suitable nucleophiles. The synthetic utility of this protocol is demonstrated by the late-stage functionalization of several complex drug molecules.

Aromatic amines are ubiquitous in natural products, pharmaceuticals and pesticides;[1] hence, there is growing demand to develop mild and cost-effective protocols for their synthesis.[2] The classical nucleophilic aromatic substitution (S_NAr) of aryl halides (particularly aryl fluorides) with aliphatic amines is a straightforward and well-documented protocol for preparing aromatic amines.[3] This reaction commonly occurs by the addition of aliphatic amines to aryl fluorides to form a negatively charged Meisenheimer intermediate, and subsequent elimination of HF delivers the products. Because the stabilization of the Meisenheimer intermediate requires strongly electron-withdrawing groups at the positions para and/or ortho to the fluorine atom, the scope of this reaction is restricted to highly electron-deficient aryl fluorides.[4]

Recent advances have begun to address the limited substrate scope. The pioneering work by Shibata used Ru catalysis,[5] while Wang employed Ni catalysis to facilitate the amination of unactivated aryl fluorides with aliphatic amines at elevated temperatures.[6] Although significant advances have been made, both reactions rely on the use of transition-metal catalysts, and the trapping and removal of these species might be pose serious economic and environmental concerns for the pharmaceutical industry.[7] As such, several other reports have mainly focused on the use of alkali metal or other main group metal reagents, such as LiHMDS,[8] BuLi,[9] NaOH,[10] K_2CO_3,[11] and Mg(II)[12] and Pb(II)[13] amides. Despite these significant advances, however, either the strong basicities of these reagents or the harsh reaction conditions resulted in limited functional group tolerance. Therefore, there is still need for improvement with regard to mild and transition-metal-free conditions with broad functional group tolerance.

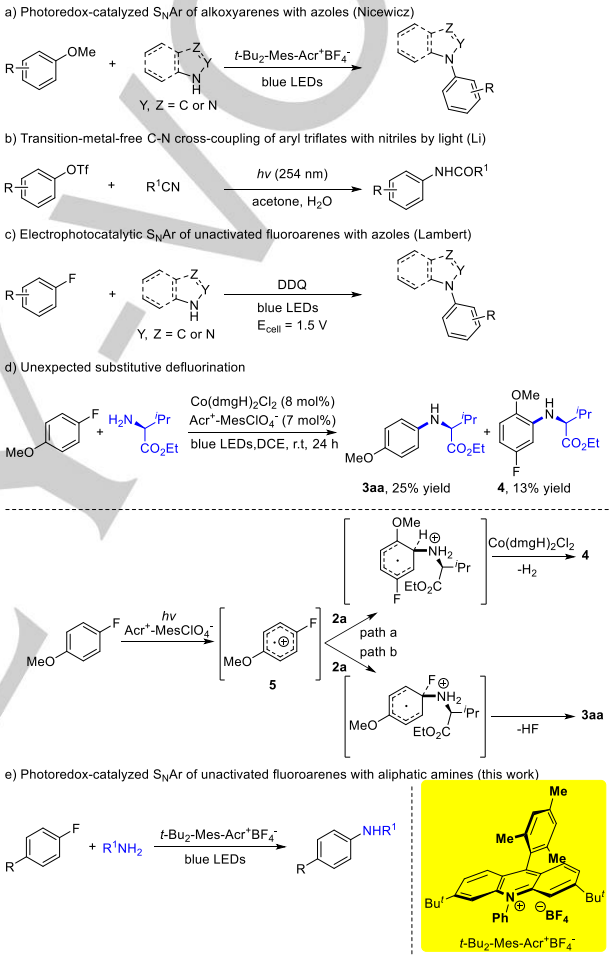

Figure 1. Photocatalytic and electrophotocatalytic SNAr amination reactions with unactivated aromatics.

Recently, Nicewicz and coworkers disclosed a visible light photocatalytic S_NAr of aryl ether using azoles and ammonia surrogates as nitrogen nucleophiles (Figure 1a).[14] This reaction is thought to be facilitated by the formation of arene cation radicals via photo-induced electron transfer. Very recently, Li and coworkers could further extend this strategy to aryl triflates using aliphatic nitriles as weaker nucleophiles under UV light irradiation in the absence of any transition-metal catalyst or photocatalyst (Figure 1b).[15] Remarkably, Lambert and coworker demonstrated an electrophotocatalytic S_NAr of unactivated aryl fluorides with azoles as nucleophiles to produce azolated arenes (Figure 1c).[16] In the course of our

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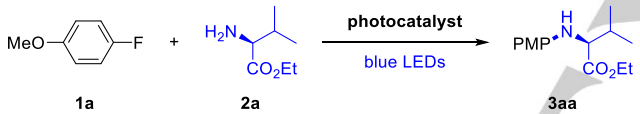
recent study on arene C-H amination with primary aliphatic amines in the presence of a photoredox catalyst (Acr^+-$MesClO_4^-$) and a proton-reduction catalyst ($Co(dmgH)_2Cl_2$),[17] we unexpectedly observed the reaction between 4-fluoroanisole (**1a**) and L-valine ethyl ester (**2a**) giving rise to substitutive defluorination product **3aa** (25% isolated yield) along with desired C-H amination product **4** (13% isolated yield) (Figure 1d). We hypothesize that both products may result from the competitive nucleophilic attack of the nitrogen atom of **2a** on the two possible electrophilic sites of fluoroarene radical cation intermediate **5**, which is formed by a photoinduced electron transfer from 1a to the excited state photocatalyst acr-Mes-Me^{+*}. Nucleophilic attack at the ortho-position relative to the methoxy group of radical cation **5** would produce C-H amination product **4** with the release of a molecule of hydrogen in the presence of the proton-reduction catalyst $Co(dmgH)_2Cl_2$ (Scheme 1d, path a), while nucleophilic ipso-attack of the fluorine atom on radical cation **5** would generate substitutive defluorination product 3aa with the loss of HF (Figure 1d, path b). We realized that if the proton-reduction catalyst is omitted from the catalyst system, the substitutive defluorination process would be the dominant pathway, and this reaction can be regarded as an S_NAr. With this in mind and inspired by the pioneering works,[18] we describe herein a mild and transition-metal-free approach for the S_NAr of (classically) unactivated fluoroarenes with primary aliphatic amines in the presence of an acridinium-based organic photocatalyst under blue light irradiation (Figure 1e).

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



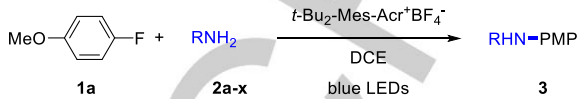
1a **2a** **3aa**

Entry	Catalyst	Solvent	Yield[b]
1	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	DCE	0%
2	Acr^+-Mes-$MeClO_4^-$	DCE	22%
3	Me_2-Mes-$Acr^+BF_4^-$	DCE	31%
4	*t*-Bu_2-Mes-$Acr^+BF_4^-$	DCE	62%
5	*t*-Bu_2-Mes-$Acr^+BF_4^-$	DCM	26%
6	*t*-Bu_2-Mes-$Acr^+BF_4^-$	CH_3CN	5%
7	*t*-Bu_2-Mes-$Acr^+BF_4^-$	EtOH	3%
8[c]	*t*-Bu_2-Mes-$Acr^+BF_4^-$	DCE	91%
9	--	DCE	0%
10[d]	*t*-Bu_2-Mes-$Acr^+BF_4^-$	DCE	0%

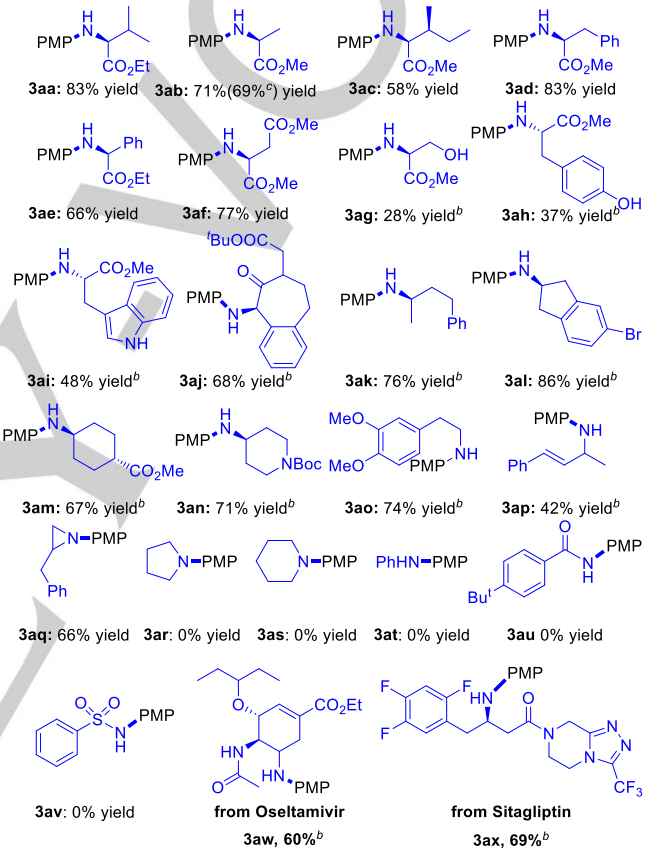
[a] Unless otherwise stated, the reaction of **1a** (0.1 mmol), **2a** (0.3 mmol), photocatalysts (5 mol%), and DCE (1 mL) was irradiated by blue LED lamps (6 W) under Ar atmosphere at room temperature for 24 h. [b] Yield was determined via GC using tetradecane as an internal standard. [c] **2a** (0.15 mmol) and reaction run for 48 h. [d] under darkness.

We commenced our study with **1a** (1 equiv) as the aromatic substrate and **2a** (3 equiv) as the nitrogen nucleophile in 1,2-dichloroethane (DCE) under argon atmosphere with blue LED irradiation (Table 1). Initially, several photocatalysts, including $Ir(dF(CF_3)ppy)_2(dtb\text{-}bpy)PF_6$, Acr^+-$MesClO_4^-$, Me_2-Mes-$Acr^+BF_4^-$ and *t*-Bu_2-Mes-$Acr^+BF_4^-$ (entries 1-4), were evaluated, and *t*-Bu_2-Mes-$Acr^+BF_4^-$ was the most active photocatalyst, resulting in desired product **3aa** in moderate yield with no erosion of enantiopurity (entry 4). Therefore, we chose *t*-Bu_2-Mes-$Acr^+BF_4^-$ as the photocatalyst for further studies. Next, other solvents were investigated. Other solvents, such as CH_2Cl_2, acetonitrile and ethanol, led to inferior results (entries 5-7). Gratifyingly, after appropriate optimization of the ratio of **1a** and **2a** (1/1.5) and the reaction times, an excellent yield was eventually obtained (entry 8). Finally, additional control reactions indicated that both the photocatalyst and light are crucial for this transformation (entries 9-10).

Table 2. Scope of amines.[a]



1a **2a-x** **3**



[a] Unless otherwise stated, the reaction of **1a** (0.1 mmol), amines **2** (0.15 mmol), *t*-Bu_2-Mes-$Acr^+BF_4^-$ (5 mol%), and DCE (2.0 mL) was irradiated by blue LED lamps (6 W) under Ar atmosphere at room temperature for 48 h. Isolated yields. [b] 8 mol% of *t*-Bu_2-Mes-$Acr^+BF_4^-$ was used and reaction run for 72 h. [c] 5-mmol scale.

Under the optimized conditions, the amine scope of this reaction was examined by employing 1a as the aromatic substrate (Table 2). A series of amino acid esters were successfully employed as nitrogen nucleophiles. Amino acid esters with normal alky and aryl side chains reacted smoothly and delivered the arylated products in good to moderate yields (**3aa**-**3af**). Benefiting from the mild and base-free reaction conditions, this reaction was compatible with several sensitive functional groups, including alcohol (**3ag**), phenol (**3ah**) and indole (**3ai**) moieties. We were also pleased to find that a cyclic dipeptide afforded arylated product **3aj** in moderate yield, highlighting the potential utility of our method in peptide chemistry. α-Branched and cyclic aliphatic amines were suitable desired product (**3ao**), and an allylamine afforded a modest yield

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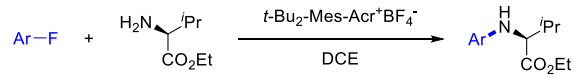
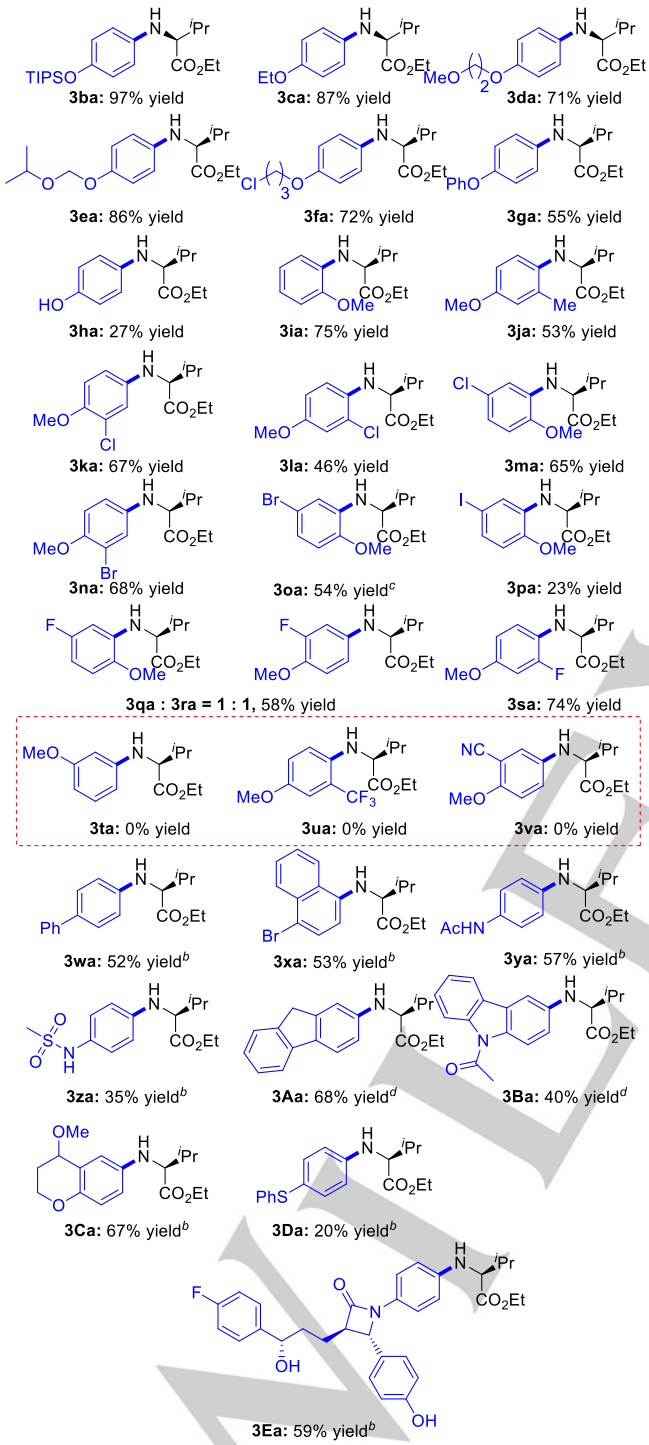
Table 3. Scope of fluoroarenes.[a]



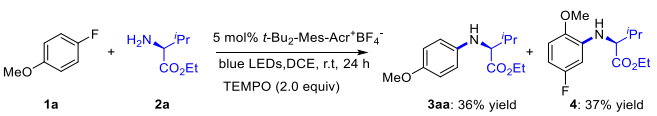
1b-E 2a 3



[a] Unless otherwise stated, the reaction of fluoroarene **1** (0.1 mmol), **2a** (0.15 mmol), *t*-Bu2-Mes-Acr$^+$BF$_4^-$ (5 mol%), and DCE (2.0 mL) was irradiated by blue LED lamps (6 W) under Ar atmosphere at room temperature for 48 h. Isolated yield. [b] Reaction run at 50 °C for 72 h. [c] 8 mol% of *t*-Bu2-Mes-Acr$^+$BF$_4^-$ was used and reaction run for 72 h. [d] 20 mol% of *t*-Bu2-Mes-Acr$^+$BF$_4^-$ was used and reaction run for 72 h.

(**3ap**). Notably, a secondary amine nucleophile derived from azridine was arylated to give the corresponding arylated product and delivered the arylated products in good to moderate yields (**3ak**-**3an**). A linear amine reacted efficiently and produced (**3aq**). However, no reactivity of other secondary amines, such as pyrrolidine and piperidine (**3ar** and **3as**), was observed, which may be a result of steric. Other weaker nitrogen nucleophiles, such as aniline, benzamide, benzosulfonamide, didn't lead to the desired products under the optimal reaction conditions (**3at**-**3av**). A 5-mmol scale reaction of **1a** with **2a** successfully afforded (**3aa**) in 69% yield. Finally, the utility of this protocol was demonstrated by the late-stage arylation of two primary amine-containing drugs. Oseltamivir, an anti-influenza virus drug, can be arylated with **1a** in 60% yield (**3aw**). Sitagliptin, a dipeptidyl peptidase-4 inhibitor, afforded arylated product (**3ax**) in 69% yield.

After demonstrating the good performance of this protocol towards a wide range of amine nucleophiles, we further explored the scope of fluoroarenes using **2a** as the nitrogen nucleophile (Table 3). Silyl and aliphatic protected para-fluorophenolic ethers can be efficiently converted to the desired aminated products (**3ba**-**3fa**). Notably, this reaction is tolerant of alkyl chlorides (**3fa**). *para*-Fluorinated diphenyl ether led to a moderate yield (**3ga**). Interestingly, unprotected *para*-fluorophenol could also undergo amination, albeit with lower reactivity (**3ha**). *ortho*-Fluoroanisole afforded the corresponding aminated product in good yield (**3ia**), while *meta*-fluoroanisole showed no reactivity (**3ta**). The *para*- and *ortho*-monofluorinated anisole derivatives containing functionalities such as methyl, chloride, bromide and iodide can be converted to the desired aminated products in modest to good yields (**3ja**-**3pa**), while 4-fluoroanisole bearing mildly electron-withdrawing (trifluoromethyl, **3ua**) and strongly electron-withdrawing group (cyano, **3va**), gave no product at all (**3ua** and **3va**). To probe the regioselectivity of the reaction, two difluorinated anisole derivatives were chosen. Although no selectivity was found with 2,4-difluoroanisole (1:1 **3qa**/**3ra**), excellent para-selectivity was observed with 3,4-difluoroanisole (**3sa**). The scope of fluoroarenes is not restricted to phenolic ethers but extends to other electron-neutral and electron-rich fluorinated aromatic compounds. Fluorinated diphenyl, naphthalene, acetylaniline, methylsulfonylaniline, fluorene, *N*-acetylcarbazole, 4-chromanol and phenyl sulphide delivered the desired amination products in modest to moderate yields (**3wa**-**3Da**). Finally, the utility of this protocol is highlighted by the late-stage defluorinative amination of a pharmaceutical compound. Ezetimibe, an inhibitor of tumor angiogenesis, can be aminated with **3Ea** in 59% yield.



1a 2a **3aa**: 36% yield **4**: 37% yield

Figure 2. Mechanistic study.

To obtain a better understanding of the reaction pathway, we conducted the model reaction of **1a** and **2a** with two equivalent of TEMPO as additive. The result showed that the yield of substitutive defluorination product **3aa** was significantly decreased (36%), while the significant amount of C-H/N-H coupled product **4** (37%) was obtained (Figure 2). The role of

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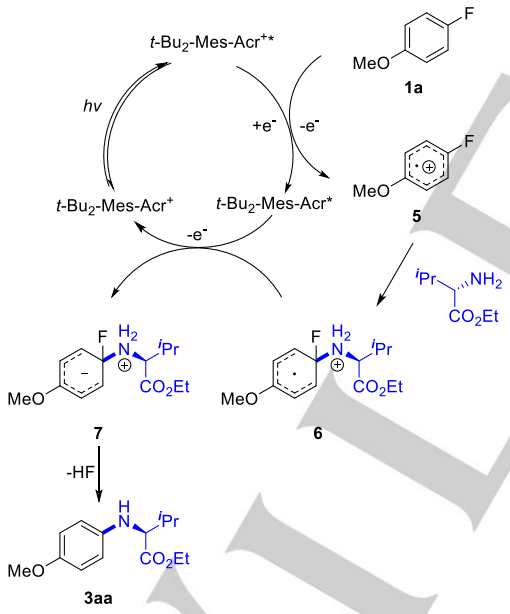
TEMPO is to be believed to aromatize a radical intermediate (As shown in Figure 1d, path a) by hydrogen atom abstraction, which is in line with previous Nicewice's report.[18a] This result implies that a fluoroarene radical cation **5** may be involved in the reaction pathway. Furthermore, Stern-Volmer quenching experiments were performed to identify the primary radical species involved in the reaction process. The results indicate that both **1a** (a comparable arene, anisole, has an oxidation potential, $E_{p/2}$ = +1.87 V vs. SCE)[18a] and **2a** (a comparable amine, isopropylamine, has an oxidation potential, $E_{p/2}$ = +1.16 V vs. SCE) can act as reductive quenchers for the excited state of the photocatalyst *t*-Bu_2-Mes-Acr^{+}* ($E_{1/2}$ red = +2.15 V vs. SCE);[18a] however, **1a** is more effective than **2a** (see the Supporting Information, Figure S1). These results suggest that a fluoroarene radical cation and/or an aminium radical cation may be involved in the reaction pathway. As we have shown, the use of a weaker oxidizing photocatalyst such as $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ ($E_{1/2}$*III/II = +1.21 V vs SCE in MeCN)[19] resulted in no product formation (table 1, entry 1), which indicates that a fluoroarene radical cation is most likely involved in the reaction mechanism and that the aminium radical cation is unlikely. Additionally, we noted that the reaction of **1a** with **2a** gives rise to product **3aa** upon irradiation, while no product was formed under darkness (ESI, Figure S2). Moreover, the quantum yield of the model reaction of **1a** and **2a** was determined to be 0.56 (see ESI). These results suggest that this reaction should undergo a non-chain radical pathway.



Scheme 1. A proposed mechanism.

On the basis of these observations, a plausible mechanism was proposed for this reaction by using la as the aromatic substrate and **2a** as the nitrogen nucleophile (Scheme 1). Irradiation of *t*-Bu_2-Mes-Acr^{+} forms an excited state photocatalyst, *t*-Bu_2-Mes-Acr^{+}*, which could be reduced by **1a** to generate a *t*-Bu_2-Mes-Acr radical and radical cation **5**. Owing to the higher positive charge on the *ipso* carbon in fluoroarene radical cation relative to anisole radical cation,[14, 16, 20] the regioselective nucleophilic attack of **5** by **2a** at the carbon atom bearing the fluorine would lead to **6**. Then **6** is reduced by the *t*-Bu_2-Mes-Acr radical to regenerate the photocatalyst and produce anion **7**. Finally, anion **7** eliminates HF to give the desired product **3aa**.

In summary, we have developed a S_NAr of unactivated fluoroarenes with primary aliphatic amines in the presence of an organic photocatalyst under blue light irradiation. The notable features of this protocol include mild reaction conditions, wide substrate scope, and excellently functional group tolerance. In addition, the utility of this protocol has been demonstrated by the late-stage functionalization of several complex drug molecules. Further applications of this strategy towards other synthetically important nitrogen-containing compounds are currently being explored in our laboratory.

Acknowledgements

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Keywords: nucleophilic aromatic substitution • unactivated aryl fluorides • primary aliphatic amines • visible light photocatalysis

[1] Modern Amination Methods (Ed.: A. Ricci), Wiley-VCH, Weinheim, 2008
[2] For selected reviews, see: a) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 19, 12564–12649; b) J. F. Hartwig, *Nature* **2008**, *455*, 314–322; c) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450–1460.
[3] a) D G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458; b) J. Boström, D G. Brown, R. J. Young, G. M. Keserü, *Nat. Rev. Drug Discov.* **2018**, *17*, 709–727.
[4] March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Ed, Smith, M. B.; March, J. Wiley, Hoboken, 2007, pp. 853-932.
[5] M. Otsuka, K. Endo, T. Shibata, *Chem. Comm.* **2010**, *46*, 336–338.
[6] F. Zhu, Z.-X. Wang, *Adv. Synth. Catal.* **2013**, *355*, 3694–3702.
[7] a) Transition Metal-Catalyzed Couplings in Process Chemistry: Case Studies from the Pharmaceutical Industry; Magano, J. and Dunetz, J., Eds.; Wiley-VCH: Weinheim, 2013, pp. 313-354; b) C. J. Welch, J. Albaneze-Walker, W. R. Leonard, M. Biba, J. DaSilva, D. Henderson, B. Laing, D. J. Mathre, S. Spencer, X. Bu, T. Wang, *Org. Process Res. Dev.* **2005**, *9*, 198–205.
[8] C. B. Jacobsen, M. Meldal, F. Diness, *Chem. Eur. J.* **2017**, *23*, 846–851.
[9] a) J.-P. Chen, D.-Y. Huang, Y.-Q. Ding, *Eur. J. Org. Chem.* **2017**, 4300–4304; b) Y.-Y. Lin, M. Li, X.-F. Ji, J.-J. Wu, S. Cao, *Tetrahedron* **2017**, *73*, 1466–1472.
[10] S. Van Brandt, F. J. R. Rombouts, C. Martínez-Lamenca, J. Leenaerts, T. R. M. Rauws, A. A. Trabanco, *Eur. J. Org. Chem.* **2012**, 7048–7052.
[11] X.-G. Meng, Z.-Y. Cai, S. Xiong, W.-C. Zhou, *J. Flu. Chem.* 2013, 146, 70–75.
[12] L. J. Bole, L. Davin, A. R. Kennedy, R. Mclellan, E. Hevia, *Chem. Commun.* **2019**, *55*, 4339–4342.
[13] A. Jana, S. P. Sarish, H. W. Roesky, D. Leusser, I. Objartel, D. Stalke, *Chem. Commun.* **2011**, *47*, 5434–5436.
[14] K. A. Margrey, J. B. McManus, S. Bonazzi, F. Zecri, D. A. Nicewicz, *J. Am. Chem. Soc.* **2017**, *139*, 11288–11299.

[15] W.-B. Liu, J.-B. Li, P. Querard, C.-J. Li, *J. Am. Chem. Soc.* 2019, 141, 6755–6764.

[16] H. He, T. H. Lambert, *Angew. Chem. Int. Ed.* **2020**, *59*, 658–662; *Angew. Chem.* **2020**, *132*, 668–672.

[17] F. Zhao, Q. Yang, J. Zhang, W. Shi, H. Hu, F. Liang, W. Wei, S. Zhou, *Org. Lett.* **2018**, *20*, 7753–7757.

[18] a) N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, *Science* **2015**, *349*, 1326–1330; b) K. A. Margrey, A. Levens, D. A. Nicewicz, *Angew. Chem. Int. Ed.* **2017**, *56*, 15644–15648; *Angew. Chem.* **2017**, *129*, 15850–15854; c) N. E. S. Tay, D. A. Nicewicz, *J. Am. Chem. Soc.* **2017**, *139*, 16100–16104; d) N. Holmberg-Douglas, D. A. Nicewicz, *Org. Lett.* **2019**, *21*, 7114–7118; e) Y.-W. Zheng, B. Chen, P. Ye, K. Feng, W.-G. Wang, Q.-Y. Meng, L.-Z. Wu, C.-H. Tung, *J. Am. Chem. Soc.* **2016**, *138*, 10080–10083; f) L.-B. Niu, H. Yi, S.-C. Wang, T.-Y. Liu, J.-M. Liu, A.-W. Lei, *Nat. Commun.* **2017**, *8*, 14226; g) L. Zhang, L. Liardet, J.-S. Luo, D. Ren, M. Grätzel, X.-L. Hu, *Nat. Catal.* **2019**, *2*, 366–373; h) A. Wimmer, B. König, *Adv, Synth. Catal.* **2018**, *360*, 3277–3285.

[19] M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712–5719.

[20] K. Ohkubo, A. Fujimoto, S. Fukuzumi, *J. Am. Chem. Soc.* 2013, 135, 5368–5371.

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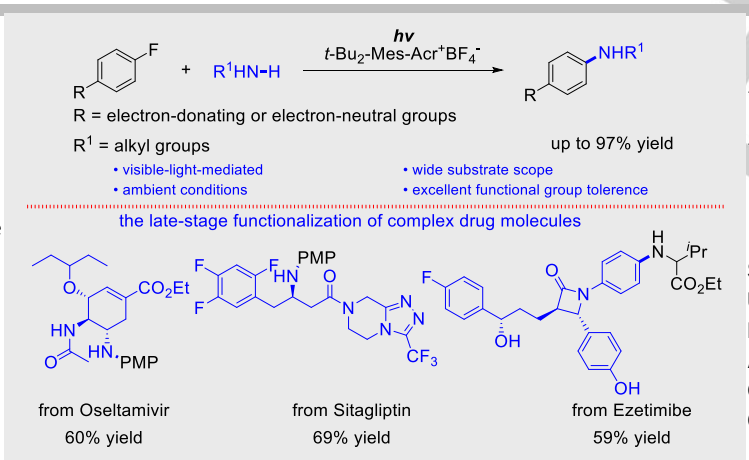

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