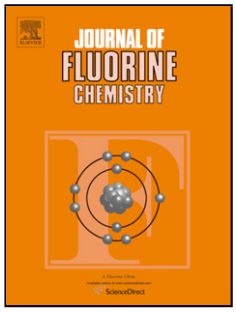

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Highly regioselective 4-hydroxy-1-methylpiperidine mediated aromatic nucleophilic substitution on a perfluorinated phthalimide core

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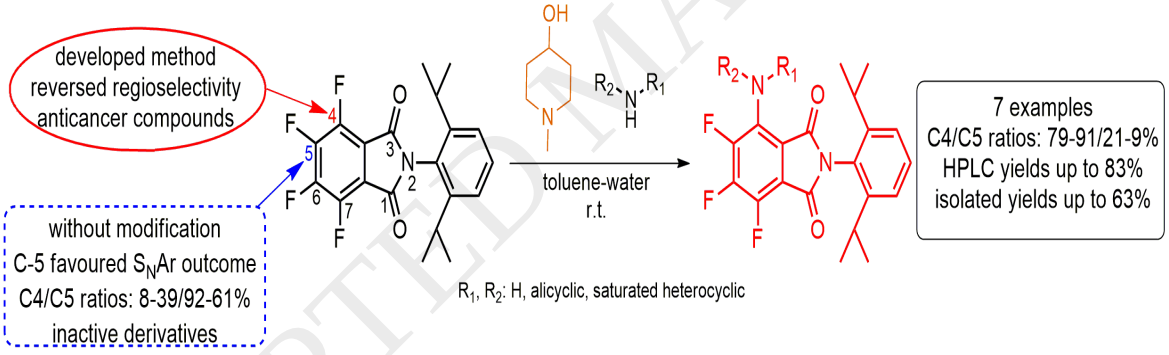

Highlights

- 1-methyl-4-hydroxypiperidine mediated highly regioselective S_NAr protocol was developed.
- The inherent regioselectivities were modified towards the less favoured bioactive regioisomer.
- The optimal condition could be utilized for gram scale synthesis.

Abstract

A tertiary amine-mediated highly regioselective aromatic nucleophilic substitution (S_NAr) protocol was developed in the assemblies of perfluorinated phtalimide with primary or secondary amines as inputs. Application of 1-methyl-4-hydroxypiperidine as additive, formation of the less favoured, bioactive regioisomer was facilitated, modifying their ratios from the initial 8-36% to 81-91%. After optimization, a facile gram scale syntheses were accomplished and isolated the desired analogues in up to 63% yield.

Keywords: aromatic nucleophilic substitution, S_NAr, phtalimide, regioselective, tertiary amine

1. Introduction

The selective decoration of (hetero)aromatic scaffolds is an undoubtedly essential synthetic tool in medicinal chemistry in order to generate a diverse set of compounds having the best balance of pharmacological properties. The most commonly used techniques for this purpose include either the transition metal-catalyzed, or the aromatic nucleophilic substitution (S_NAr) reactions [1,2].

The outcome of S_NAr transformations strongly depends on the simultaneous interplay between several parameters, such as, for instance, the overall electronics of the (hetero)arene affected by the substitution pattern, the influence and mobility of the leaving group, the nature of the nucleophile applied, solvent and medium effects, stability of the intermediate σ-complex, etc [3].

It should be emphasized, that hydrogen bonding between an S_NAr donor and acceptor may account for specific solvent effect on the regioselectivity [3,4]. For instance, *ortho* selectivity was observed in the reaction of 2,4-difluoroacetophenone with secondary amines in non-polar solvents (toluene, dioxane, etc.) [5]. In this case, precoordination of the amine to the carbonyl function via *H*-bond formation may occur, and intramolecular hydrogen bond stabilization (inverted built-in solvation) may operate in the transition state, preferring the *ortho*-displacement supported by the solvent. In contrast, solvents having high solvent hydrogen bond basicity (SHBB) (e.g. DMSO) result in *para*-displacement. The reversed selectivity can be interpreted by the lack of a transition

state stabilized by *H*-bond and a relatively strong *H*-bond interaction between the polar solvent and the nucleophile applied.

There are certain S_NAr synthetic 'tricks' described in the literature, which, in contrast to the general considerations, led to either improved conversion or regioselectivity [6-8]. For instance, a regioselective DABCO-catalyzed two-stage sequential S_NAr reaction of methyl 2,6-dichloronicotinate with phenols was first introduced by Merck Research Laboratories [6]. Besides the remarkable solvent effect observed, the reaction proceeds through the regioselective generation of an unprecedented DABCO–pyridine reactive intermediate. As disclosed by Amgen Inc., certain *ortho*-heteroaryl substituents, relative to the leaving group, exert moderate electron-withdrawing effects. As a result, they are able to facilitate the S_NAr reactions *via* preferential hydrogen bond formation between the directing group and the amine nucleophile, thereby stabilizing the transition state [7]. Furthermore, O'Reilly and co-workers have demonstrated the potential of metal ions such as Rh^{3+} to increase the electrophilicity of electron-rich fluoroarenes and allow the initiation S_NAr for even weak nucleophiles [8]. The nucleophile and 'host' fluoroarene are coordinated to the metal prior to nucleophilic attack.

In a recent medicinal chemistry program, we have synthesized and evaluated a large set of 4- and 5-amino-substituted perfluorophthalimide derivatives *via* S_NAr reactions [9-11]. In most cases, regioisomer **a** exerted excellent cytotoxicity in different cell lines including melanoma, leukemia, hepatocellular carcinoma, glioblastoma at micromolar concentrations. Unfortunately, the reaction mixtures contained predominantly the less or non-active isomer **b**. This required a relatively expensive, difficult and long isolation process resulting in low isolated yields. Therefore, our goal was to develop a regioselective and cost-efficient S_NAr reaction between the privileged C4-C7 perfluorinated phatlimide core and various amines towards the active C-4 (*ortho*) substituted isomers (**Figure 1**).

2. Results and discussion

Selected primary and secondary amines were reacted with **1** under general conditions we applied earlier. That is, two equivalents of the corresponding amine in DCM at room temperature were reacted to obtain preliminary data in terms of yields and isomer ratios (**Scheme 1** and **Table 1**).

As expected, the desired analogues **2a**–**8a** were detected as minor components (up to 39% conversion by HPLC), and poor HPLC yields (6–34%) were obtained.

Compounds were characterized by means of ^{1}H- ^{19}F- ^{13}C-NMR and mass-spectrometry. In addition, the exact structures of regioisomers **4a** and **4b** were defined by XRD analysis (*See* detailed X-Ray crystallographic data and molecular structure in the Supporting Information).

In order to investigate the effect of additives on the regioselectivity, first the possible role of Lewis acid activators was tested. For this purpose, several salts were examined in a model S_NAr reaction between **1** and morpholine in DCM (*see* Supplementary Information, Table S1, Entries 1–39). Unfortunately, most of the additives did not lead to either improved isomer ratios or yields in favour of isomer **2b**. However, using iron(III)-based Lewis acids, such as $FeCl_3 \cdot 6H_2O$ or $Fe(NO_3)_3 \cdot 6H_2O$, moderately altered ratios (**2a**:**2b**= 30:70 to 53:47) were observed. Therefore, $FeCl_3 \cdot 6H_2O$ was selected for further investigations in the Lewis acid-mediated S_NAr optimization phase.

As a continuation of our study, the optimal equivalent of amine and $FeCl_3 \cdot 6H_2O$ were identified (*see* Supplementary Information, Table S2 and S3, Entries 40–48). Employing one equivalent of morpholine along with 50 mol% of $FeCl_3 \cdot 6H_2O$ in DCM gave improved selectivity for isomer **2a** (**2a**:**2b**= 68:32%). Next, we investigated the solvent effects in the model reaction in terms of selectivity and conversion (*see* Supplementary Information, Table S4). Some polar-aprotic solvents (DMSO, CH_3CN and THF) and non-polar–aprotic toluene were tested besides DCM. To our delight, toluene as solvent was proved to be an excellent reaction medium to gain good *ortho* selectivity (**2a**:**2b** = 84:16%) and high conversion in favour of isomer **2a**.

Then we attempted to extend these conditions by means of different amine sources (**Scheme2** and **Table 2**). For *N*-methylethanolamine, a rather meager regioselectivity was detected (**6a**:**6b**= 48:52%). Moreover, no conversions were observed using 4-piperidinol (**3**) and thiomorpholine (**7**). Presumably, the formation of **3a**,**3b** or **7a**,**7b** is hindered due to a unsoluble metal salt–amine complex formed in the reaction, since the addition of few drops of water into the reaction mixture induced the reactions (data not shown). Hence, further experiments were focused on reactions performed in toluene–water reaction medium.

The synthesis of **3**, **6**, **7** and **8** were repeated in a toluene-water (1:1) solvent mixture without using any additives in the first instance (**Scheme 3** and **Table 3**). Interestingly, the toluene–water system increased the conversion in cases of **3**, **6** and **7**. Surprisingly and more importantly, the reaction of 4-piperidinol and **1** led to the exclusive formation of isomer **3a**. Presumably, a hydrogen bond is formed between the host (–C=O) and the guest (–OH), resulting in a sort of kinetic control favouring the *ortho* S_NAr selectivity. This observation gave a completely new direction for the synthetic development of regioselective S_NAr reactions in our model system. We hypothesized, that if the tertiary 1,3-aminoalcohol, which is converted to a quaternary ammonium cation after the first displacement, can serve as the leaving group, we might have control over the selectivity through a two-stage sequential S_NAr. Therefore, we turned our attention to select suitable tertiary amines as potential leaving groups. Besides, further studies for revealing the synthetic and theoretical aspects and background of a regioselective Fe(III)-mediated S_NAr reactions are ongoing in our laboratory.

As regards the tertiary amine-promoted selective S_NAr strategy, we assumed that 1-methyl-4-piperidinol as an 1,3-aminoalcohol promoter might be a suitable additive for influencing the favourable regioselectivity based on our observation described earlier. Other 1,2- and 1,3-aminoalcohols with tertiary amine moieties were also tested besides DABCO and DBU for having a full scope. In addition, the less selective S_NAr reaction, namely, the reaction of *N*-ethylaminoethanol and phthalimide derivative **1** was selected for these studies (**Scheme 4** and **Table 4**).

The reaction of **1** with 1-methyl-4-hydroxypiperidine followed by subsequent treatment with *N*-ethylethanolamine gave regioisomer **8a** with 88% conversion (total conversion: 95% by HPLC). Based on these findings, additional amines have been applied without any further optimization in the presence of 1-methyl-4-hydroxy piperidine, and in all cases the desired **2a**–**8a** isomers were detected as major components with excellent regioselectivity up to 91% (**Scheme 5** and **Table 5**).

Finally, the well-established regioselective S_NAr protocol was repeated on a gram scale, affording the desired isomers **2a**–**8a** with isolated yields up to 63% (**Figure 2**).

3. Conclusion

In this study we presented a novel, tertiary amine-mediated highly regioselective S_NAr method. The formation of the less favoured regioisomer was facilitated in the presence of equimolar *tert*-1,3-aminoalcohol. This facile protocol gave a simple and selective access to pharmacologically relevant compounds even on a gram scale.

4. Experimental section

^{1}H-NMR spectra were recorded on a Bruker Spectrospin 500 spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0$ ppm) in $CDCl_3$-d_1 as an internal standard. ^{13}C-NMR spectra were obtained by using the same NMR spectrometer and were calibrated with $CDCl_3$-d_1 ($\delta = 76.6$ ppm). ^{19}F-NMR spectra were obtained by using the same NMR spectrometer. Mass spectra were recorded by Micromass ZMD spectrometer. IR spectra were recorded by Jasco FT/IR-4700 spectrometer (ATR PRO ONE; ZnSe). Elemental analyses were performed using a Perkin Elmer 2400 elementary analyzer. Melting points were determined by a Stuart SMP10 device, and they are uncorrected. All chemicals and solvents were of commercial grade and used without further purification. For X-ray diffraction measurement see Supplementary Information CCDC 1843621-1843622.

*4.1. General procedure for the syntheses of compounds **2**–**8** for HPLC:*

To a solution of 50 mg (0.13 mmol) **1** in toluene–water (1:1) (0.5 mL) was added 15 mg (0.13 mmol, 1 equiv) 1-methyl-4-hydroxypiperidine, and the reaction mixture was stirred at room temperature for 36 hours. Then one equivalent of the corresponding amine was added, and the reaction mixture was stirred for an additional 24 hours at room temperature. The reaction was monitored by TLC (eluent: *n*-hexane:EtOAc). The mixture after complete reaction was evaporated to dryness and prepared for the HPLC measurements for detecting regioisomeric ratios.

*4.2. Gram-scale synthetic procedure for compounds **2a**-**8a**:*

To a solution of 3.0g (7.8 mmol) **1** in toluene–water mixture (1:1) (30 mL) was added 911 mg (7.8 mmol, 1 equiv) 1-methyl-4-hydroxypiperidine, and the reaction mixture was stirred at room temperature for 36 hours. Then one equivalent amine was added slowly, and the reaction mixture was stirred for an additional 24 hours at room temperature. The reaction was monitored by TLC

(eluent: *n*-hexane:EtOAc 6:1). Once the reaction was completed, the mixture was diluted with ethyl acetate (100 mL), and the organic phase was extracted with water (2 x 100 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated. The crude products were purified by flash chromatography (CombiFlash, R_f Gold column).

4.2.1. 2-(2,6-Diisopropylphenyl)-4,5,6-trifluoro-7-morpholinoisoindoline-1,3-dione ***(2a)***

Yellow solid. m.p.: 146–148°C. TLC: R_f=0.31 (hexane:EtOAc=6:1). $C_{24}H_{25}F_3N_2O_3$. Elemental analysis: Calcd.: C 64.56, H 5.64, N 6.27. Found: C 67.56, H 5.64, N 6.28. IR (ATR PRO ONE; ZnSe) ν = 1401, 1499, 1503, 1630, 1723, 1778, 2878, 2932, 2972 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (t, *J* = 6.9 Hz, 4 CH_3), 2.67 (h, *J* = 7.3 Hz, 2 CH), 3.39–3.48 (m, 2 CH_2), 3.80–3.88 (m, 2 CH_2), 7.28 (d, *J* = 7.4 Hz, 2 ArH), 7.44 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 23.5, 23.6, 29.0, 51.7, 51.8, 66.9, 114.2–114.4 (m), 114.6–114.9 (m), 123.7, 126.0, 130.0, 135.9 (d, *J* = 8.0 Hz), 140.2 (d, *J* = 11.6 Hz), 142.3 (d, *J* = 11.0 Hz), 143.3–143.7 (m), 145.4–145.8 (m), 146.2, 148.5 (dd, *J* = 261.1 Hz, 10.7 Hz), 162.8, 164.3. ^{19}F NMR (471 MHz, DMSO) δ (ppm): -133.00 (d, *J* = 14.1 Hz), -143.81 (dd, *J* = 22.6, 6.1 Hz), -147.75 (dd, *J* = 22.1, 16.8 Hz). MS (ESI) m/z =447 $[(M+H)^+]$.

4.2.2. 2-(2,6-Diisopropylphenyl)-4,5,7-trifluoro-6-morpholinoisoindoline-1,3-dione ***(2b)***

Yellow solid. m.p.: 105–107°C. TLC: R_f=0.22 (hexane:EtOAc=6:1). $C_{24}H_{25}F_3N_2O_3$. Elemental analysis: Calcd.: C 64.56, H 5.64, N 6.27. Found: C 67.57, H 5.66, N 6.26. IR (ATR PRO ONE; ZnSe) ν = 1361, 1407, 1486, 1498, 1628, 1716, 1770, 2845, 2867, 2920, 2963 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (t, *J* = 6.5 Hz, 4 CH_3), 2.68 (h, *J* = 7.2 Hz, 2 CH), 3.42–3.48 (m, 2 CH_2), 3.81–3.88 (m, 2 CH_2), 7.28 (d, *J* = 7.8 Hz, 2 ArH), 7.46 (t, *J* = 7.6 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 23.6, 29.0, 29.3, 50.6, 66.7, 112.9–113.3 (m), 123.6, 125.7, 130.0, 135.4–135.6 (m), 144.6–145.0 (m), 146.8, 162.7, 163.7. ^{19}F NMR (471 MHz, DMSO) δ (ppm): -124.12 (t, *J* = 14.9 Hz), -135.15–-135.88 (m), -139.79 (dd, *J* = 20.5, 16.1 Hz). MS (ESI) m/z =447 $[(M+H)^+]$.

4.2.3. 2-(2,6-Diisopropylphenyl)-4,5,6-trifluoro-7-(4-hydroxypiperidin-1-yl)isoindoline-1,3-dione ***(3a)***

Yelllow solid. m.p.: 153–155°C. TLC: R_f=0.10 (hexane:EtOAc=4:1). $C_{25}H_{27}F_3N_2O_3$. Elemental analysis: Calcd.: C 65.21, H 5.91, N 6.08. Found: C 65.22, H 5.90, N 6.08. IR (ATR PRO ONE; ZnSe) ν = 1456, 1504, 1713, 1766, 2870, 2928, 2960, 3268 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (t, *J* = 7.1 Hz, 4 CH_3), 1.70–1.82 (m, CH_2), 1.98–2.08 (m, CH_2), 2.67 (h, 2 CH), 3.31 (t, *J* = 10.9 Hz, CH_2), 3.49–3.60 (m, CH_2), 3.85–3.94 (m, CH), 7.28 (d, *J* = 9.7 Hz, 2 ArH), 7.44 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 23.5, 23.6, 28.9, 34.4, 49.2, 49.3, 66.7, 114.1, 114.6 (d, *J* = 8.0 Hz), 123.6, 126.1, 129.9, 136.6 (d, *J* = 8.0 Hz), 141.1 (dd, *J* = 265.4 Hz, 12.5 Hz), 143.2–145.8 (m), 146.8, 149.7 (dd, *J* = 259.2 Hz, 10.7 Hz), 162.9, 164.4. ^{19}F NMR (471 MHz, DMSO) δ(ppm): -132.65 (d, *J* = 14.5 Hz), -144.55 (dd, *J* = 22.6, 5.6 Hz), -148.03 (dd, *J* = 22.1, 17.1 Hz). MS (ESI) m/z =461 [$(M+H)^+$].

*4.2.4. 2-(2,6-Diisopropylphenyl)-4,5,7-trifluoro-6-(4-hydroxypiperidin-1-yl)isoindoline-1,3-dione (**3b**)*

Pale yellow solid. m.p.: 177–179°C. TLC: R_f=0.06 (hexane:EtOAc=4:1). $C_{25}H_{27}F_3N_2O_3$. Elemental analysis: Calcd.: C 65.21, H 5.91, N 6.08. Found: C 65.23, H 5.90, N 6.08. IR (ATR PRO ONE; ZnSe) ν = 1483, 1701, 1758, 2853, 2910, 2960, 3236 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.16 (d, *J* = 6.9 Hz, 4 CH_3), 1.66–1.75 (m, CH_2), 1.98–2.05 (m, CH_2), 2.68 (h, 2 CH), 3.28 (t, *J* = 10.6 Hz, CH_2), 3.57–3.65 (m, CH_2), 3.89–3.98 (m, CH), 7.27 (d, *J* = 7.9 Hz, 2 ArH), 7.45 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 23.6, 28.9, 34.3, 48.0, 66.4, 108.4 (d, *J* = 10.7 Hz), 112.9 (d, *J* = 11.8 Hz), 123.6, 125.8, 130.0, 136.3–136.8 (m), 143.8 (dd, *J* = 266.4 Hz, 5.9 Hz), 146.6–146.8 (m), 146.9, 147.0–147.4 (m), 148.7–148.9 (m), 149.0–149.9 (m), 162.9, 163.4. ^{19}F NMR (471 MHz, DMSO) δ(ppm): -124.18 (t, *J* = 15.2 Hz), -136.05 (dd, *J* = 18.6, 17.6 Hz), -139.82 (dd, *J* = 20.6, 15.9 Hz). MS (ESI) m/z =461 [$(M+H)^+$].

*4.2.5. 2-(2,6-Diisopropylphenyl)-4-(ethylamino)-5,6,7-trifluoroisoindoline-1,3-dione (**4a**)*

Orange solid. m.p.: 147–149°C. TLC: R_f=0.57 (hexane:EtOAc=6:1). $C_{22}H_{23}F_3N_2O_2$. Elemental analysis: Calcd.: C 65.34, H 5.73, N 6.93. Found: C 65.35, H 5.72, N 6.92. IR (ATR PRO ONE; ZnSe) ν = 1460, 1496, 1512, 1702, 1720, 1766, 1779, 2872, 2932, 2971, 3370 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (d, *J* = 6.8 Hz, 4 CH_3), 1.32 (t, *J* = 7.2 Hz, CH_3), 2.69 (h, *J* = 6.8 Hz, 2 CH), 3.55–3.63 (m, CH_2), 6.35–6.40 (m, NH), 7.28 (d, *J* = 7.8 Hz, 2 ArH), 7.45 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 15.7, 23.5, 23.6, 28.9, 39.4, 39.5, 104.9 (d,

J = 10.0 Hz), 112.7–113.0 (m), 123.6, 125.7, 129.9, 134.9 (d, *J* = 10.0 Hz), 137.9 (dd, *J* = 263.0 Hz, 15.0 Hz), 142.6–142.9 (m), 144.2–145.0 (m), 146.3–146.8 (m), 147.0, 163.1, 168.0. ^{19}F NMR (471 MHz, DMSO) δ (ppm): -142.16 (d, *J* = 15.1 Hz), -148.55 (dd, *J* = 22.0, 15.7 Hz), -149.74 (t, *J* = 30.6 Hz). MS (ESI) m/z =405 [(M+H)$^+$]. The structure of the molecule was verified using single crystal X-ray diffraction measurement.

4.2.6. 2-(2,6-Diisopropylphenyl)-5-(ethylamino)-4,6,7-trifluoroisoindoline-1,3-dione ***(4b)***

Pale yellow solid. m.p.: 169–171°C. TLC: R_f=0.33 (hexane:EtOAc=6:1). $C_{22}H_{23}F_3N_2O_2$. Elemental analysis: Calcd.: C 65.34, H 5.73, N 6.93. Found: C 65.34, H 5.71, N 6.92. IR (ATR PRO ONE; ZnSe) ν = 1501, 1701, 1753, 2836, 2930, 2972, 3368 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (d, *J* = 6.8 Hz, 4 CH_3), 1.32 (t, *J* = 7.2 Hz, CH_3), 2.71 (m, 2 CH), 3.48–3.83 (m, CH_2), 4.39–4.58 (m, NH), 7.27 (d, *J* = 7.8 Hz, 2 ArH), 7.45 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 15.8, 23.6, 28.9, 39.9, 103.4 (d, *J* = 11.0 Hz), 113.0 (d, *J* = 12.0 Hz), 123.5, 125.9, 129.9, 133.7–134.1 (m), 141.2–141.8 (m), 143.8 (dd, *J* = 264.0 Hz, 13.5 Hz), 143.3–143.8 (m), 146.9, 163.2, 163.5. ^{19}F NMR (471 MHz, DMSO) δ (ppm): -133.29 (dd, *J* = 18.7, 15.1 Hz), -141.01 (dd, *J* = 20.2, 14.0 Hz), -148.82 (t, *J* = 20.3 Hz). MS (ESI) m/z =405 [(M+H)$^+$]. The structure of the molecule was verified using single crystal X-ray diffraction measurement.

4.2.7. 4-(Cyclopentylamino)-2-(2,6-diisopropylphenyl)-5,6,7-trifluoroisoindoline-1,3-dione ***(5a)***

Yellow solid. m.p.: 118–120°C. TLC: R_f=0.69 (hexane:EtOAc=6:1). $C_{25}H_{27}F_3N_2O_2$. Elemental analysis: Calcd.: C 67.55, H 6.12, N 6.30. Found: C 67.52, H 6.12, N 6.31. IR (ATR PRO ONE; ZnSe) ν= 1467, 1483, 1504, 1613, 1650, 1700, 1768, 2870, 2929, 2962, 3350 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ1.17 (dd, *J* = 6.8 Hz, 2.2 Hz, 4 CH_3), 1.54–1.71 (m, 2 CH_2), 1.72–1.83 (m, CH_2), 1.98–2.10 (m, CH_2), 2.69 (h, 2 CH), 4.23–4.34 (m, CH), 6.43 (d, *J* = 7.4 Hz, NH), 7.27 (d, *J* = 7.9 Hz, 2 ArH), 7.45 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ(ppm): 23.0, 23.5, 23.6, 28.9, 34.2, 55.9, 56.0, 105.1 (d, *J* = 8.0 Hz), 112.7–113.1 (m), 123.6, 125.7, 129.9, 134.5 (d, *J* = 9.0 Hz), 137.9 (dd, *J* = 263.0 Hz, 15.0 Hz), 142.3–142.8 (m), 144.1–144.8 (m), 146.2–146.7 (m), 146.9, 163.1, 168.0. ^{19}F NMR (471 MHz, DMSO) δ(ppm): -140.64 (d, *J* = 15.3 Hz), -148.18 (dd, *J* = 22.0, 16.0 Hz), -148.59 (d, *J* = 22.2 Hz). MS (ESI) m/z =445 [(M+H)$^+$].

4.2.8. 5-(Cyclopentylamino)-2-(2,6-diisopropylphenyl)-4,6,7-trifluoroisoindoline-1,3-dione ***(5b)***

Pale yellow solid. m.p.: 164–167°C. TLC: R_f=0.45 (hexane:EtOAc=6:1). $C_{25}H_{27}F_3N_2O_2$. Elemental analysis: Calcd.: C 67.55, H 6.12, N 6.30. Found: C 67.54, H 6.11, N 6.29. IR (ATR PRO ONE; ZnSe) ν= 1432, 1474, 1630, 1689, 2868, 2912, 2953, 3420 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ1.17 (d, *J* = 6.8 Hz, 4 CH_3), 1.51–1.63 (m, CH_2), 1.64–1.85 (m, 2 CH_2), 2.04–2.15 (m, CH_2), 2.71 (h, 2 CH), 4.30–4.43 (m, NH, CH), 7.27 (d, *J* = 7.8 Hz, 2 ArH), 7.45 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ(ppm): 23.2, 23.6, 28.9, 34.3, 56.2, 113.1 (d, *J* = 12.0 Hz), 123.5, 126.0, 133.4–133.7 (m), 141.1–141.4 (m), 143.1–143.5 (m), 144.7–145.0 (m), 146.9, 163.2, 163.5. ^{19}F NMR (471 MHz, DMSO) δ(ppm): -131.74 (dd, *J* = 17.2, 16.2 Hz), -140.87 (dd, *J* = 20.4, 14.0 Hz), -147.02 (t, *J* = 20.2 Hz).MS (ESI) m/z =445 [$(M+H)^+$].

*4.2.9. 2-(2,6-Diisopropylphenyl)-4,5,6-trifluoro-7-((2-hydroxyethyl)(methyl)amino)isoindoline-1,3-dione (**6a**)*

Yelllow solid. m.p.: 127-130°C. TLC: R_f=0.18 (hexane:EtOAc=4:1). $C_{23}H_{25}F_3N_2O_3$. Elemental analysis: Calcd.: C 63.59, H 5.80, N 6.45. Found: C 63.57, H 5.81, N 6.46. IR (ATR PRO ONE; ZnSe) ν = 1465, 1490, 1632, 1643, 1698, 1722, 1758, 1782, 2871, 2929, 2972, 3360 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.15 (d, *J* = 6.8 Hz, 2 CH_3), 1.18 (d, *J* = 6.8 Hz, 2 CH_3), 2.65 (h, *J* = 6.7 Hz, 2 CH), 2.71–2.79 (m, OH), 3.06 (d, *J* = 1.6 Hz, CH_3), 3.47 (t, *J* = 4.8 Hz, CH_2), 3.72–3.79 (m, CH_2), 7.29 (d, *J* = 7.7 Hz, 2 ArH), 7.46 (t, *J* = 7.9 Hz, ArH), ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 23.5, 29.0, 40.2, 40.9, 56.9, 57.0, 58.6, 123.7, 125.8, 130.1, 142.4 (dd, *J* = 264.0 Hz, 15.0 Hz), 144.5 (dd, *J* = 261.0 Hz, 15.0 Hz), 146.7, 151.4 (dd, *J* = 264.0 Hz, 11.0 Hz), 162.7, 165.3. MS (ESI) m/z =435 [$(M+H)^+$].

*4.2.10. 2-(2,6-Diisopropylphenyl)-4,5,7-trifluoro-6-((2-hydroxyethyl)(methyl)amino)isoindoline-1,3-dione (**6b**)*

Pale yellow solid. m.p.: 80-83°C. TLC: R_f=0.08 (hexane:EtOAc=4:1). $C_{23}H_{25}F_3N_2O_3$. Elemental analysis: Calcd.: C 63.59, H 5.80, N 6.45. Found: C 63.56, H 5.80, N 6.43. IR (ATR PRO ONE; ZnSe) ν = 1450, 1462, 1620, 1713, 1765, 2870, 2925, 2968, 3349 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (d, *J* = 6.9 Hz, 4 CH_3), 2.22–2.51 (m, OH), 2.69 (h, *J* = 6.8 Hz, 2 CH), 3.13–3.16 (m, CH_3), 3.51 (t, *J* = 5.3 Hz, CH_2), 3.86 (t, *J* = 5.3 Hz, CH_2), 7.28 (d, *J* = 7.8 Hz, 2 ArH), 7.46 (t, *J* = 7.5 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 23.6, 28.9, 40.4, 56.6, 59.7, 109.1 (d, *J* = 10.9 Hz), 112.9 (d, *J* = 13.2 Hz), 115.5, 123.1, 123.6, 125.6, 130.0, 136.9 (t, *J*

= 11.3 Hz), 143.7 (dd, *J* = 267.4 Hz, 14.7 Hz), 146.9, 148.2 (dd, *J* = 263.8 Hz, 5.0 Hz), 148.8 (ddd, *J* = 255.2 Hz, 13.6 Hz, 5.4 Hz), 162.8, 163.4. ^{19}F NMR (471 MHz, DMSO) δ(ppm): -123.30 (t, *J* = 15.0 Hz), -135.91 (t, *J* = 17.8 Hz), -140.18 (dd, *J* = 20.0, 15.6 Hz). MS (ESI) m/z =435 [(M+H)$^+$].

*4.2.11. 2-(2,6-Diisopropylphenyl)-4,5,6-trifluoro-7-thiomorpholinoisoindoline-1,3-dione (**7a**)*

Yellow solid. m.p.: 181–183°C. TLC: R_f=0.55 (hexane:EtOAc=6:1). $C_{24}H_{25}F_3N_2O_2S$. Elemental analysis: Calcd.: C 62.32, H 5.45, N 6.06. Found: C 62.34, H 5.44, N 6.08. IR (ATR PRO ONE; ZnSe) ν = 1478, 1495, 1630, 1722, 1781, 2880, 2940, 2973 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (t, *J* = 6.2 Hz, 4 CH_3), 2.66 (h, *J* = 6.7 Hz, 2 CH), 2.78–2.84 (m, 2 CH_2), 3.60–3.66 (m, 2 CH_2), 7.28 (d, *J* = 7.9 Hz, 2 ArH), 7.46 (t, *J* = 7.6 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 23.5, 23.6, 27.6, 29.0, 53.9, 54.0, 114.7 (d, *J* = 6.2 Hz), 115.1, 123.7, 126.0, 126.8, 129.7, 130.0, 136.7 (d, *J* = 6.7 Hz), 141.6 (dd, *J* = 265.7 Hz, 12.9 Hz), 144.5 (dt, *J* = 262.7 Hz, 15.6 Hz), 146.7, 150.0 (dd, *J* = 259.2 Hz, 10.8 Hz), 162.7, 164.2. ^{19}F NMR (471 MHz, DMSO) δ(ppm): -131.50 (d, *J* = 12.4 Hz), -143.16 (dd, *J* = 22.6, 7.0 Hz), -147.80 (dd, *J* = 21.9, 18.0 Hz). MS (ESI) m/z =463 [(M+H)$^+$].

*4.2.12. 2-(2,6-Diisopropylphenyl)-4,5,7-trifluoro-6-thiomorpholinoisoindoline-1,3-dione (**7b**)*

Pale yellow solid. m.p.: 145–147°C. TLC: R_f=0.43 (hexane:EtOAc=6:1). $C_{24}H_{25}F_3N_2O_2S$. Elemental analysis: Calcd.: C 62.32, H 5.45, N 6.06. Found: C 62.33, H 5.43, N 6.07. IR (ATR PRO ONE; ZnSe) ν = 1467, 1486, 1628, 1716, 1771, 2870, 2918, 2963 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (t, *J* = 7.4 Hz, 4 CH_3), 2.67 (h, *J* = 7.1 Hz, 2 CH), 2.75–2.82 (m, 2 CH_2), 3.60–3.66 (m, 2 CH_2), 7.28 (d, *J* = 8.2 Hz, 2 ArH), 7.45 (t, *J* = 7.5 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 23.6, 27.6, 29.0, 29.2, 29.3, 52.7, 109.2–109.9 (m), 112.5–114.4 (m), 116.4–117.7 (m), 123.6, 125.7, 130.0, 136.0–136.6 (m), 142.6 (d, *J* = 12.7 Hz), 144.6–144.9 (m), 146.8, 147.1–147.7 (m), 148.8–149.1 (m), 149.4–149.8 (m), 162.6, 163.1. ^{19}F NMR (471 MHz, DMSO) δ(ppm): -123.49 (t, *J* = 14.6 Hz), -134.54 (dd, *J* = 20.6, 14.3 Hz), -139.68 (dd, *J* = 20.8, 16.5 Hz). MS (ESI) m/z =463 [(M+H)$^+$].

*4.2.13. 2-(2,6-Diisopropylphenyl)-4-(ethyl(2-hydroxyethyl)amino)-5,6,7-trifluoroisoindoline-1,3-dione (**8a**)*

Yellow semisolid. TLC: R_f=0.36 (hexane:EtOAc=4:1). $C_{24}H_{27}F_3N_2O_3$. Elemental analysis: Calcd.: C 64.27, H 6.07, N 6.25. Found: C 64.30, H 6.08, N 6.25. IR (ATR PRO ONE; ZnSe) ν = 1460, 1496, 1512, 1641, 1655, 1703, 1720, 1766, 1780, 2852, 2872, 2930, 2971, 3369 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.09 (t, *J* = 7.1 Hz, CH_3), 1.14 (d, *J* = 6.8 Hz, $2CH_3$), 1.18 (d, *J* = 6.8 Hz, 2 CH_3), 2.58–2.69 (m, 2 CH), 2.92 (t, *J* = 6.4 Hz, OH), 3.34 (q, *J* = 7.1 Hz, CH_2), 3.45 (t, *J* = 4.7, CH_2), 3.59–3.69 (m, CH_2), 7.28 (d, *J* = 7.8 Hz, 2 ArH), 7.46 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 12.8, 23.4, 23.5, 29.1, 47.3, 54.3, 58.8, 114.1, 119.6, 123.7, 125.7, 130.1, 135.6 (d, *J* = 8.3 Hz), 143.2 (dd, *J* = 270.0 Hz, 12.3 Hz), 144.4 (d, *J* = 264.1 Hz), 146.7, 153.0 (dd, *J* = 261.4 Hz, 8.6 Hz), 162.6, 165.4. MS (ESI) m/z =449 $[(M+H)^+]$.

*4.2.14. 2-(2,6-Diisopropylphenyl)-5-(ethyl(2-hydroxyethyl)amino)-4,6,7-trifluoroisoindoline-1,3-dione (**8b**)*

Pale yellow semisolid. TLC: R_f=0.20 (hexane:EtOAc=4:1). $C_{24}H_{27}F_3N_2O_3$. Elemental analysis: Calcd.: C 64.27, H 6.07, N 6.25. Found: C 64.29, H 6.07, N 6.22. IR (ATR PRO ONE; ZnSe) ν = 1466, 1487, 1620, 1714, 1768, 2870, 2928, 2963, 3348 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ with 0.03 % TMS) δ 1.17 (d, *J* = 6.9 Hz, 4 CH_3), 1.20 (t, *J* = 7.1 Hz, CH_3), 1.78–1.98 (m, OH), 2.61–2.76 (m, 2 CH), 3.38–3.45 (m, CH_2), 3.51 (t, *J* = 5.1, CH_2), 3.76 (t, *J* = 5.1 Hz, CH_2), 7.28 (d, *J* = 7.8 Hz, 2 ArH), 7.46 (t, *J* = 7.8 Hz, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 13.0, 23.6, 28.9, 47.5, 53.8, 59.9, 110.4 (d, *J* = 10.6 Hz), 112.8 (d, *J* = 13.7 Hz), 123.6, 125.7, 130.0, 135.4 (t, *J* = 11.7 Hz), 143.5 (dd, *J* = 266.1 Hz, 15.8 Hz), 146.8, 149.5 (dd, *J* = 264.3 Hz, 4.3 Hz), 150.2 (ddd, *J* = 257.1 Hz, 12.8 Hz, 5.5 Hz), 162.7, 163.3. ^{19}F NMR (471 MHz, DMSO) δ(ppm): -122.59 (t, *J* = 14.8 Hz), -134.58 (dd, *J* = 19.3, 15.7 Hz), -140.16 (dd, *J* = 20.2, 16.0 Hz). MS (ESI) m/z =449 $[(M+H)^+]$.

*4.3. Representative gram-scale isolation method for compound **7a**:*

To a solution of 5.0g (13.2 mmol) **1** in toluene–water mixture (1:1) (50 mL) was added 1.52 g (13.2 mmol, 1 equiv) 1-methyl-4-hydroxypiperidine, and the reaction mixture was stirred at room temperature for 36 hours. Then one equivalent amine was added slowly, and the reaction mixture was stirred for an additional 24 hours at room temperature. The reaction was monitored by TLC (eluent: *n*-hexane:EtOAc 6:1). Once the reaction was completed, the mixture was diluted with ethyl acetate (100 mL), and the organic phase was extracted with water (2 x 100 mL). The organic

phase was dried over Na_2SO_4, filtered and evaporated. The crude products were isolated by crystallization with heptane:EtOAc mixture (5:1) to yield pure compound **7a** (2.31 g, 38%)

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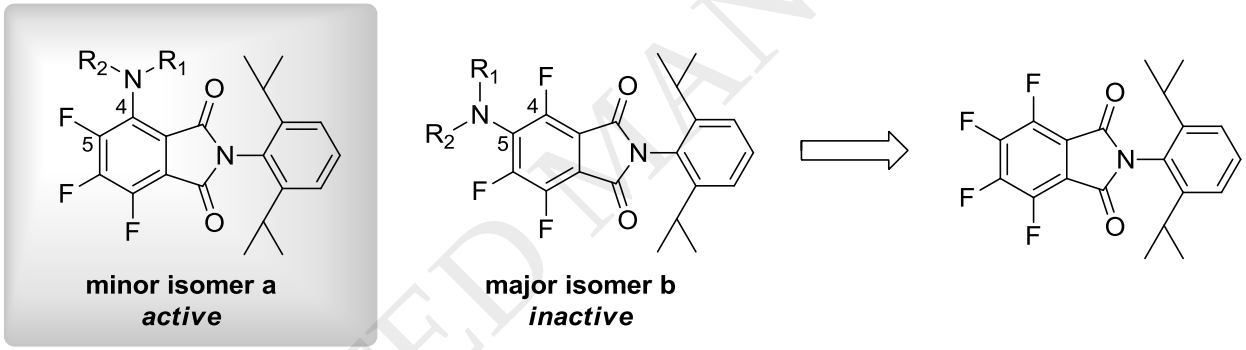


Figure 1. The regioselective outcomes of the S_NAr transformation of the perfluorinated phthalimide

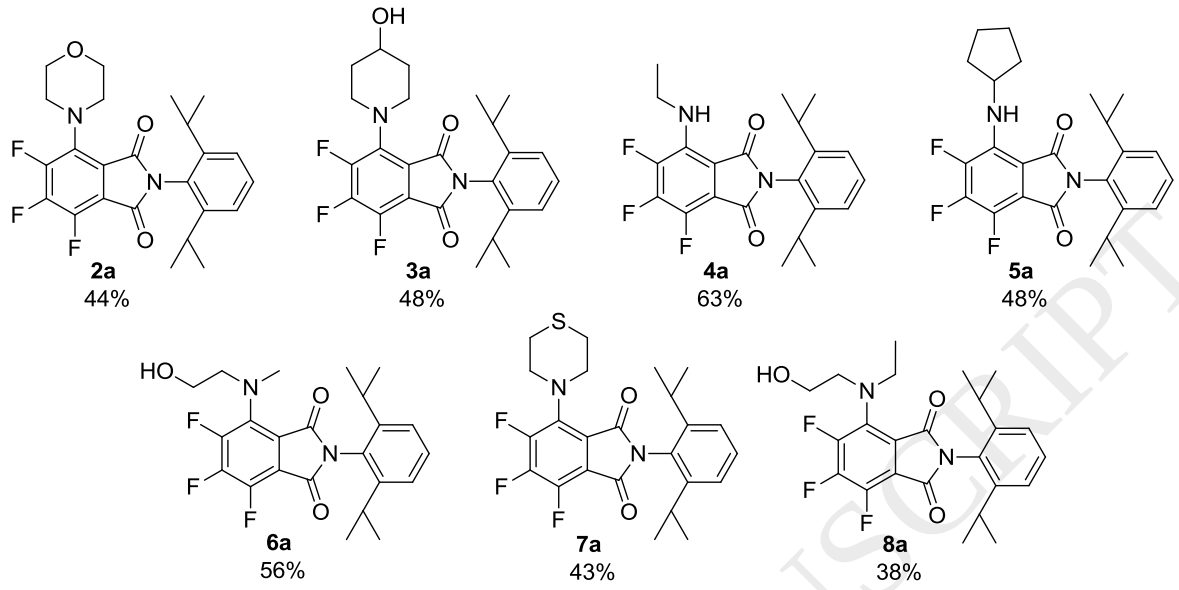
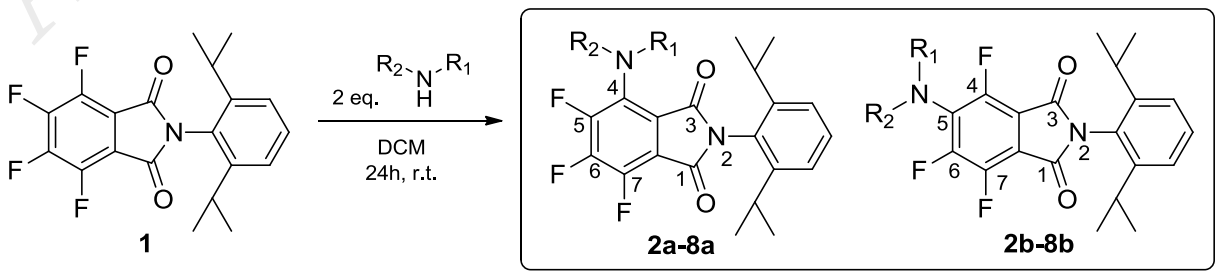
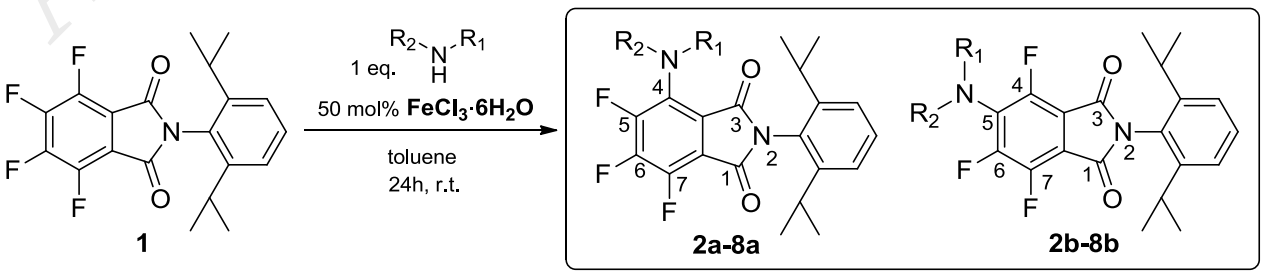


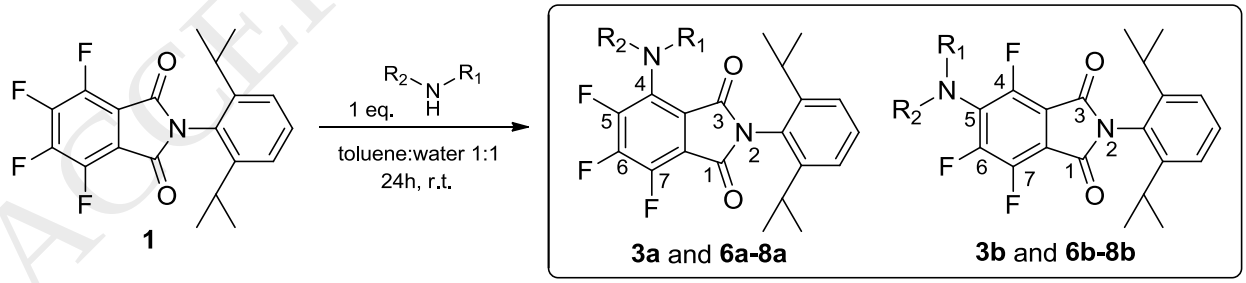
Figure 2. The isolated bioactive *ortho* substituted regioisomers **2a**–**8a**.



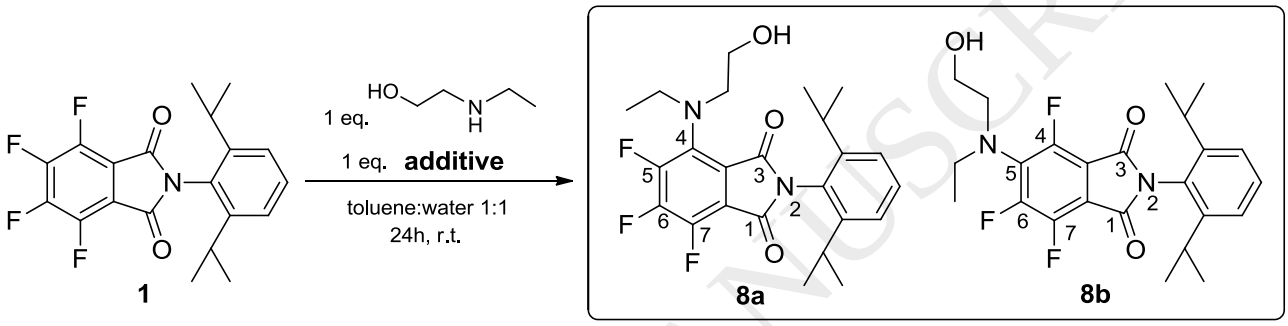
Scheme 1. The initial regioselective S_NAr outcomes of **1** with primary and secondary amines



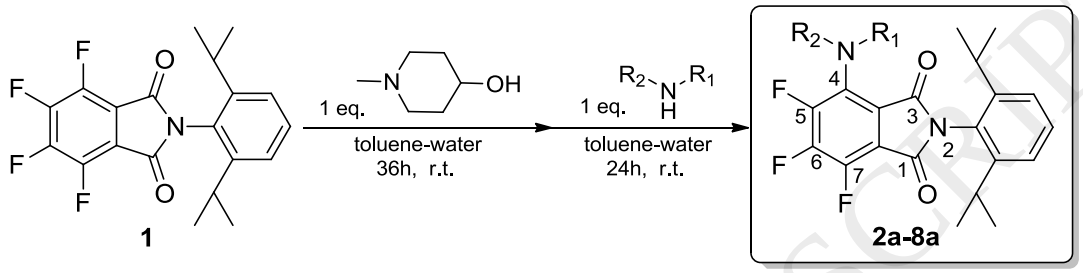
Scheme 2. Regioselective S_NAr efforts with application of 50 mol% $FeCl_3 \cdot 6H_2O$ as catalyst



Scheme 3. S_NAr study in toluene/water mixture with the unsoluble/unreactive amines



Scheme 4. The S_NAr outcomes of **1** with *N*-ethylethanolamine in the presence of additives



Scheme 5. Utilization of 1-methyl-4-hydroxypiperidine additive in the S_NAr treatments of **1**

Table 1. S_NAr transformations of **1**

Compound[a]	Amine	Conversion[b] (%)	Isomer ratio[c] (%) a	b
2	morpholine	98	30	70
3	4-piperidinol	87	34	66
4	ethylamine	95	39	61
5	cyclopentylamine	93	17	83
6	*N*-methylethanolamine	100	33	67
7	thiomorpholine	85	8	92
8	*N*-ethylethanolamine	99	28	72

[a]: reaction conditions: amine (2 equiv), CH_2Cl_2, 24 h, r.t.; [b]: total conversion calculated by HPLC; [c]: calculated by HPLC.

Table 2. The influence of 50 mol% $FeCl_3 \cdot 6H_2O$ for the S_NAr outcomes

Compounds	Amine	Conversion[a] (%)	Isomer ratio[b] (%)	
			a	b
2	morpholine	83	84	16
3	4-piperidinol	0	0	0
4	ethylamine	65	80	20
5	cyclopentylamine	75	71	29
6	*N*-methylethanolamine	64	48	52
7	thiomorpholine	0	0	0
8	*N*-ethylethanolamine	54	66	34

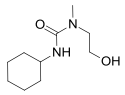
[a]: reaction conditions: amine (1 equiv), 50 mol% $FeCl_3 \cdot 6H_2O$, toluene, 24 h, r.t.; [b]: total conversion calculated by HPLC; [c]: calculated by HPLC

Table 3. The solvent effect (toluene/water mixture) for the S_NAr outcomes; without additive

Compounds	Amine	Conversion[a] (%)	Isomer ratio[b] (%)	
			a	b
3	4-piperidinol	77	100	0
6	*N*-methylethanolamine	68	81	19
7	thiomorpholine	72	80	20
8	*N*-ethylethanolamine	91	51	49

[a]: reaction conditions: amine (1 equiv), toluene:water 1:1, 24 h, r.t.; [b]: total conversion calculated by HPLC; [c]: calculated by HPLC

Table 4. The effect of tertiary 1,2- and 1,3-aminoalcohols on the ratios of **8a** and **8b**

Additive[a]	**Conversion**[b] **(%)**	**Isomer ratio**[c] **(%)**	
		8a	**8b**
-	90	51	49
1-methyl-4-hydroxypiperidine	95	88	12
2-diethylaminoethanol	82	58	42
2-dimethylaminoethanol	63	67	33
N,*N*-dimethylethylamine	66	65	35
4-methylmorpholin	65	72	28
DABCO	71	45	55
DBU	95	33	67
	61	61	39

[a]: using one equivalent of the corresponding additive; [b]: total conversion calculated by HPLC; [c]: calculated by HPLC

Table 5. S_NAr outcomes in the presence of 1-methyl-4-hydroxypiperidine

Compounds	Amine	Conversion[a] (%)	Isomer ratios[b] (%) a	b
2	morpholine	86	81	19
3	4-piperidinol	100	83	17
4	ethylamine	100	79	21
5	cyclopentylamine	89	80	20
6	*N*-methylethanolamine	91	89	11
7	thiomorpholine	87	91	9
8	*N*-ethylethanolamine	91	88	12

[a]: reaction conditions: 1-methyl-4-hydroxypiperidine (1 equiv), amine (1 equiv), toluene:water 1:1, 60 h, r.t.; [b]: total conversion calculated by HPLC; [c]: calculated by HPLC