

# Microwave-assisted Synthesis of a 3-Aminoimidazo[1,2-*a*]-pyridine/pyrazine Library by Fluorous Multicomponent Reactions and Subsequent Cross-coupling Reactions

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## Full Paper

Microwave and fluorous technologies are employed to increase reaction speed and reduce separation time in solution-phase parallel synthesis of a substituted 3-aminoimidazo[1,2-*a*]pyridine and 3-aminoimidazo[1,2-*a*]pyrazine library. Multicomponent reactions of perfluorooctanesulfonyl-tagged benzaldehydes with 2-aminopyridines (or 2-

aminopyrazines) and isocyanides are followed by Pd-catalyzed cross-coupling reactions with boronic acids or thiols to form biaryls or aryl sulfides. Reaction mixtures are purified by fluorous solid-phase extraction (F-SPE) or crystallization.

## Introduction

Microwave irradiation has been widely used as a powerful and easily controllable heating source for organic reactions. Reactions conducted under microwave usually have short reaction times, high yields, and better selectivities [1]. The coupling of microwave-assisted reactions with phase-tag-based separations, such as solid-phase [2] or fluorous synthesis [3], has great potential to further improve the efficiency of organic synthesis. Fluorous synthesis is a new solution-phase technology that has favorable homogeneous reaction kinetics and solid-phase type separation [4]. Perfluoroalkyl groups employed in fluorous synthesis have good physical and chemical properties including high

stability at elevated temperature, low ability to absorb microwave, good solubility in many common organic solvents. Limitations associated with solid-phase synthesis such as slower heterogeneous reactions, resin swelling in different solvents, requirement of large excess reagents to complete the reaction, and difficulty to analyze resin-bound intermediates are not concerns in fluorous synthesis.

Multicomponent reactions (MCRs) are powerful tools to assemble molecules with high diversity [5]. Performing additional reactions after MCRs can increase the molecular complexity and improve drug-like characteristics of the initial products [6]. We recently reported the use of perfluorooctylsulfonates as an alternative to halogen atoms and triflate groups for Suzuki and other cross-coupling reactions in the formation C–C, C–S, and C–H bonds [7]. In this paper, perfluorooctanesulfonyl benzaldehydes are used for the synthesis of 3-aminoimidazo[1,2-*a*]pyridine and 3-aminoimidazo[1,2-*a*]pyrazine derivatives **4**.

Imidazo[1,2-*a*]pyridines/pyrazines are biologically interesting compounds which possess antifungal, antibacterial, cytoprotective, cardiac stimulating, and benzodiazepine receptor antagonistic properties [8]. The Blackburn and other groups have reported solution-phase syntheses of **4** by 3-component condensation reactions involving 2-aminopyridines/2-aminopyrazines, aldehydes, and isonitriles (Scheme 1A) [9]. The MCRs completed in 48–72 hours at ambient temperature and purifications were conducted by resin capture and release [9a]. The Blackburn group also developed a solid-phase synthesis with polymer-supported aldehydes to simplify the purification of condensation

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**Key words:** fluorous synthesis, microwave irradiation, multicomponent reaction, solid-phase extraction, parallel synthesis, Suzuki coupling, cross-coupling, perfluorooctylsulfonate, 3-aminoimidazo[1,2-*a*]pyridine, 3-aminoimidazo[1,2-*a*]pyrazine

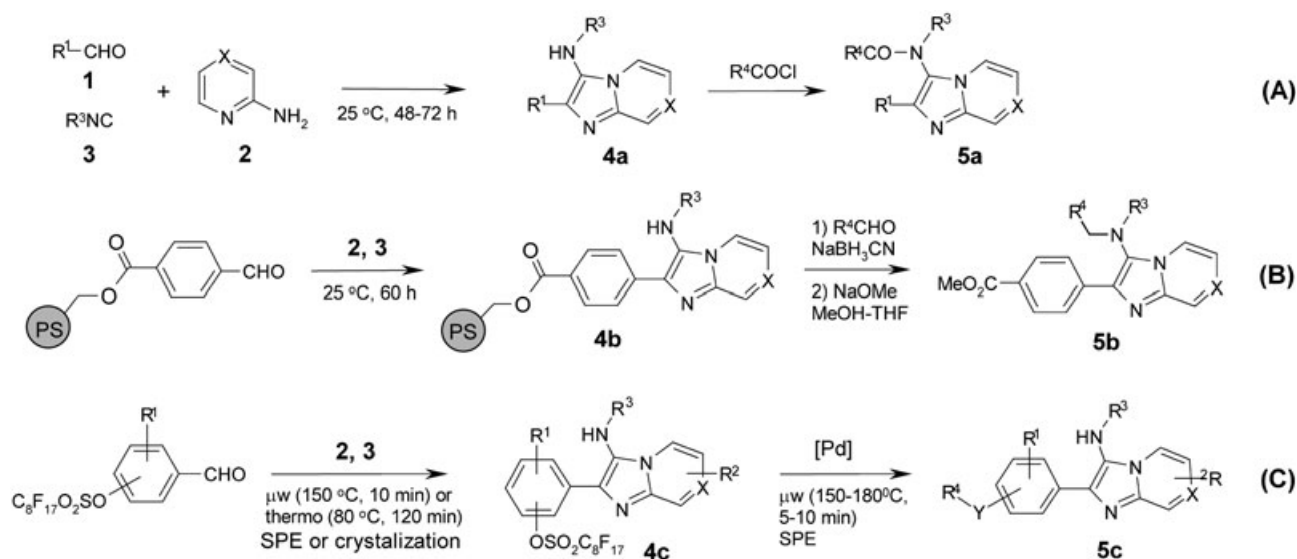
**Abbreviations:** MCR: multicomponent reaction; SPE: solid-phase extraction; F-SPE: fluorous solid-phase extraction; LC-MS: liquid chromatography-mass spectrometry, <sup>1</sup>H NMR: proton nuclear magnetic resonance, DMF: *N,N*-dimethylformamide; THF: tetrahydrofuran; DME: dimethyl ethylene glycol ether; dppe: 1,1'-bis(diphenylphosphino)ferrocene; OTf: trifluoromethanesulfonyl; DCM: dichloromethane; R<sub>f</sub>: C<sub>8</sub>F<sub>17</sub>.

products (Scheme 1B) [10]. We report here a new method that incorporates microwave irradiation and fluorous tagging strategy [11] to speed up reaction and separation processes (Scheme 1C). The post-condensation modification was carried out by Pd-catalyzed cross-coupling reactions to cleave the fluorous tag and introduce an additional diversity point (YR<sup>4</sup>). In the fluorous approach, the perfluoroalkanesulfonyl tag has three functions: as a phenol protecting group for the condensation reaction, as a phase tag for purification of reaction mixture, and as an activating group for the cross-coupling reaction. The final products have four diversity points (R<sup>1</sup> to R<sup>4</sup>) with additional variations of X (=N or CH) and Y (=nothing or S).

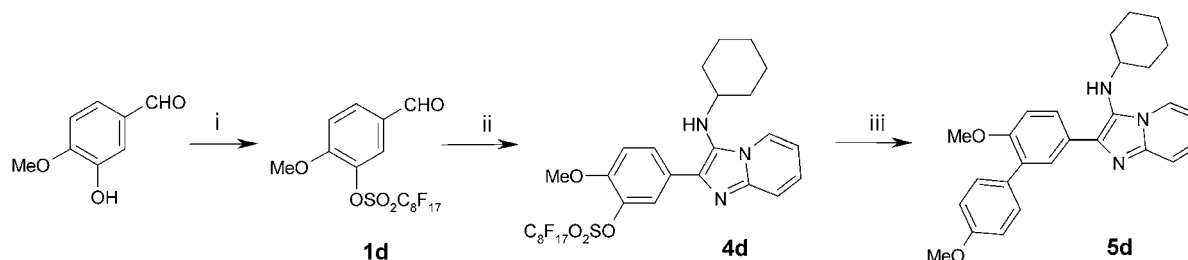
## Results and Discussion

**Method development.** Our initial effort was focused on testing the feasibility of MCR with fluorous aldehyde **1**.

Following our previous work on perfluoroalkylsulfonates [7], we made fluorous benzaldehyde **1** by a reaction of perfluorooctanesulfonyl fluoride with 3-hydroxy-4-methoxybenzaldehyde. The fluorous benzaldehyde **1** could be purified by flash chromatography or fluorous solid-phase extraction (F-SPE). It was then mixed with 2-aminopyridine and cyclohexylisocyanide for MCR (Scheme 2). The mixture was heated under microwave irradiation at 150 °C for 10 min in 3:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH. The desired product **4d** was purified by F-SPE or precipitation. Compound **4d** was subjected to the Suzuki coupling reaction with 4-methoxyphenylboronic acid under microwave irradiation at 130 °C for 20 min using Pd(dppf)Cl<sub>2</sub> (dppf = 1,1'-bis(diphenylphosphino)ferrocene) as a catalyst, K<sub>2</sub>CO<sub>3</sub> as a base, and 4:4:1 acetone/toluene/H<sub>2</sub>O as a co-solvent. The final product **5d** was isolated from the reaction mixture by F-SPE. After the development of a fluorous synthetic approach, we then explored the scope and limitations of this method by synthesizing a demonstration library.



**Scheme 1.** Solution-phase (A), solid-phase (B), and fluorous (C) syntheses of imidazo[1,2-a]pyridine/pyrazine derivatives by multicomponent and post-condensation reactions



**Scheme 2.** Microwave-assisted fluorous synthesis of imidazo[1,2-a]pyrazine **4d** followed by detagging with Suzuki coupling reaction for **5**. i) C<sub>8</sub>F<sub>17</sub>SO<sub>2</sub>F (0.9 equiv), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv), DMF, 70 °C, 5 h, 90% yield; ii) 2-aminopyridine (1.1 equiv), cyclohexylisocyanide (1.2 equiv), Sc(OTf)<sub>3</sub> (0.05 equiv), 3:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH, microwave (150 w, 150 °C, 10 min), 76%; iii) 4-methoxyphenylboronic acid (0.95 equiv), Pd(pddf)Cl<sub>2</sub> (0.1 equiv), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv), 4:4:1 acetone/toluene/H<sub>2</sub>O, microwave (150 w, 130 °C, 20 min), F-SPE eluted with 80:20 MeOH-H<sub>2</sub>O then MeOH, 75% yield (85% purity by LC-MS, 254 nm)

**3-Component condensation reactions.** An array of 60 ( $4 \times 5 \times 3$ ) MCRs were conducted through parallel synthesis by using five 2-aminopyridines/2-aminopyrazines, four aldehydes, and three isonitriles (Scheme 3). Since microwave reaction of 60 condensation reactions in sequential would take more than 15 h under the conditions described in Scheme 2, we decide to run parallel reactions by converting microwave heating to conventional heating. We found that at 60 °C using MeOH as the solvent, the MCR had 90% conversion after 6 h. When temperature increased to 80 °C with EtOH as the solvent, the reaction completed in 2 h. Products **4** could be precipitated out directly from the reaction mixture at room temperature with purities greater than 85%, F-SPE was not needed. The yields of sixty MCRs are summarized in Table 1. Due to their high solubility in EtOH four compounds **4**{2,1,3}, **4**{2,2,1}, **4**{3,2,1}, **4**{2,2,3} did not precipitate out from the reaction mixture.

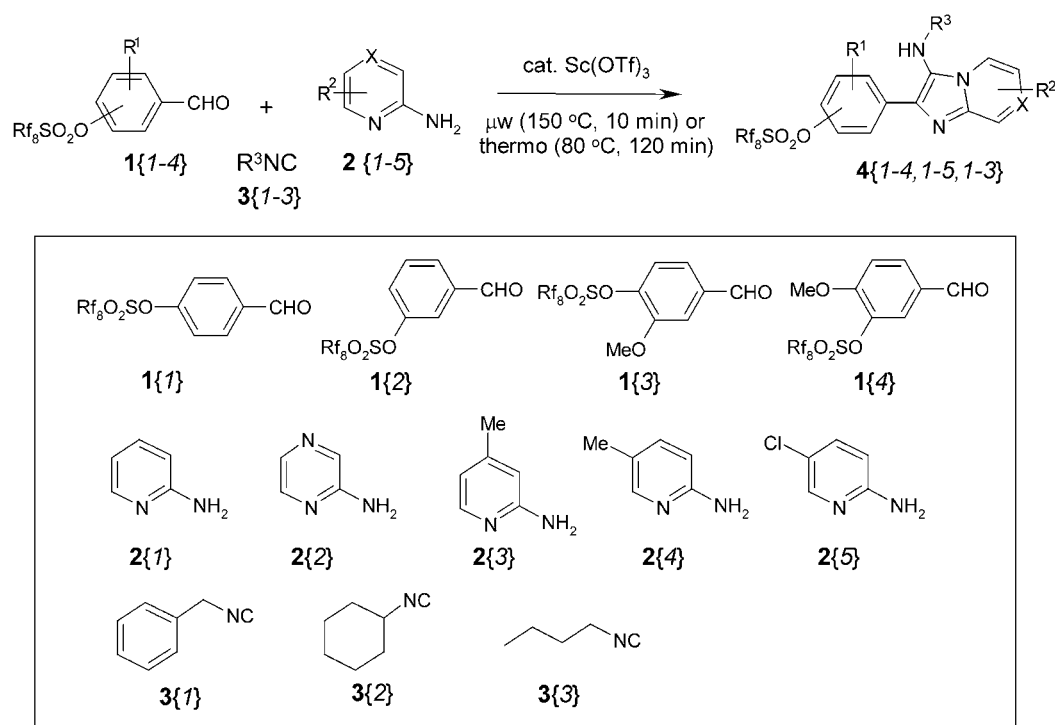
**Cross coupling reactions.** To evaluate cross-coupling reactions, some representative compounds **4**{1–4, 1–5, 1–3} were randomly selected for two kinds of cross-coupling reactions. Sixteen analogs of **4** were reacted with two boronic acids **6**{1–2} to form biaryl compounds **5** ( $R^4Y=R^4$ ), while another sixteen were coupled with two thiols **6**{3–4} to form aryl sulfides **5** ( $R^4Y=R^4S$ ) (Scheme 4).

Under the conditions described in Scheme 2, byproducts imine **7** and subsequent hydrolyzed product **8** were observed from some of the reaction mixtures (Scheme 5). The

formation of imine **7** was indicated by the color change from orange (imine) to light purple (aniline) when the imine was treated with  $\text{NaBH}(\text{OAc})_3$  and acetic acid in  $\text{CH}_2\text{Cl}_2$ . LC-MS analysis also suggested the formation of **7** and **8** [12].

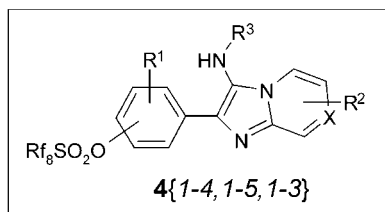
We found the formation of **7** and **8** could be suppressed in the absence of water. However, the conversion of **4** was low because the Suzuki coupling requires  $\text{OH}^-$  to generate the trihydroxyborate anion [13]. Better results were obtained by using dimethyl ethylene glycol ether (DME) as the solvent with 2–3 drops of water under microwave irradiation at 150 °C for 10 min. The reaction mixtures were purified by F-SPE to remove the fluorous components followed by silica gel SPE with 20:80 EtOAc/hexane to remove the less polar byproducts. The product was collected by elution with 50:50 EtOAc/hexane, while polar impurities remained on the cartridge. The yields and purities of the Suzuki coupling products are summarized in Table 2. Reactions with 3-chlorobenzeneboronic acid **6**{1} gave better yield than those with the more electron-deficient 4-acetylbenzeneboronic acid **6**{2}.

The cross-coupling reactions of **4** with thiols were conducted under microwave irradiation at 180 °C for 5 min using  $\text{Pd}(\text{dppf})\text{Cl}_2$  as a catalyst,  $\text{Cs}_2\text{CO}_3$  as a base, and anhydrous DMF as a solvent. The reaction mixtures were purified by F-SPE followed by silica gel SPE (Table 3). Structures of some representative cross-coupling products **5** are listed in Scheme 6.

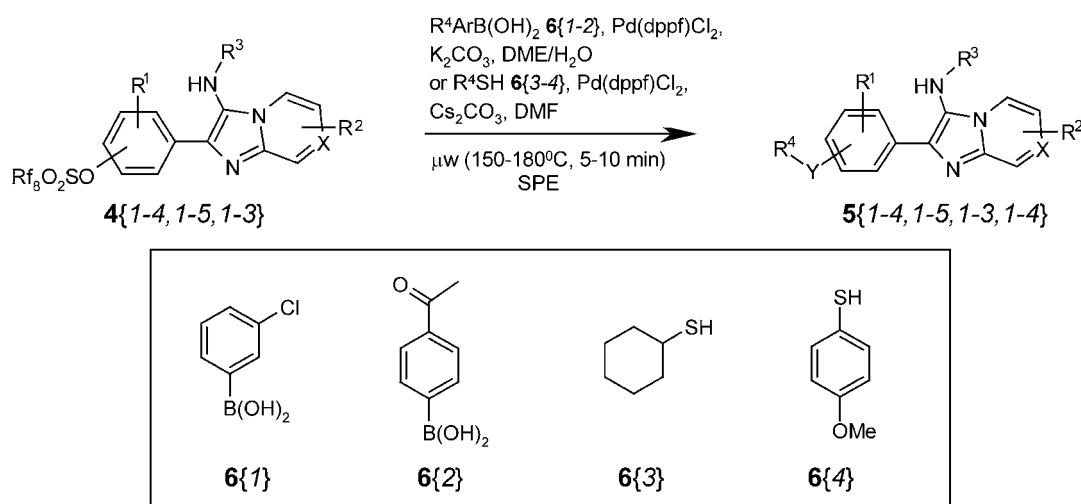


**Scheme 3.** Parallel synthesis of 60 imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrazine analogs

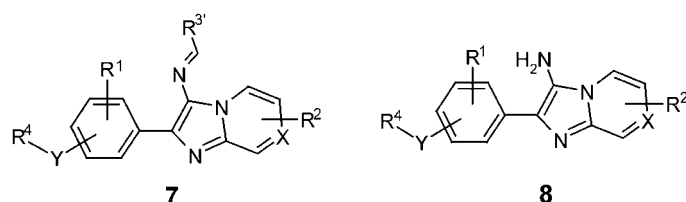
**Table 1.** Yields of compounds **4**{1–4, 1–5, 1–3}



<b>4</b>	yield	<b>4</b>	yield	<b>4</b>	yield	<b>4</b>	yield	<b>4</b>	yield
{1, 1, 1}	38%	{1, 2, 1}	40%	{1, 3, 1}	53%	{1, 4, 1}	103%	{1, 5, 1}	58%
{2, 1, 1}	29%	{2, 2, 1}	0%	{2, 3, 1}	58%	{2, 4, 1}	70%	{2, 5, 1}	55%
{3, 1, 1}	40%	{3, 2, 1}	0%	{3, 3, 1}	48%	{3, 4, 1}	66%	{3, 5, 1}	31%
{4, 1, 1}	39%	{4, 2, 1}	22%	{4, 3, 1}	69%	{4, 4, 1}	48%	{4, 5, 1}	26%
{1, 1, 2}	48%	{1, 2, 2}	26%	{1, 3, 2}	68%	{1, 4, 2}	48%	{1, 5, 2}	56%
{2, 1, 2}	34%	{2, 2, 2}	32%	{2, 3, 2}	31%	{2, 4, 2}	82%	{2, 5, 2}	75%
{3, 1, 2}	66%	{3, 2, 2}	39%	{3, 3, 2}	49%	{3, 4, 2}	36%	{3, 5, 2}	35%
{4, 1, 2}	63%	{4, 2, 2}	54%	{4, 3, 2}	43%	{4, 4, 2}	53%	{4, 5, 2}	51%
{1, 1, 3}	35%	{1, 2, 3}	27%	{1, 3, 3}	36%	{1, 4, 3}	65%	{1, 5, 3}	49%
{2, 1, 3}	0%	{2, 2, 3}	0%	{2, 3, 3}	51%	{2, 4, 3}	73%	{2, 5, 3}	55%
{3, 1, 3}	39%	{3, 2, 3}	47%	{3, 3, 3}	38%	{3, 4, 3}	61%	{3, 5, 3}	34%
{4, 1, 3}	30%	{4, 2, 3}	41%	{4, 3, 3}	33%	{4, 4, 3}	36%	{4, 5, 3}	56%



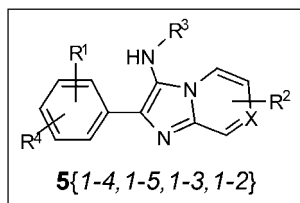
**Scheme 4.** Parallel cross-coupling reactions for **5**{1–4, 1–5, 1–3, 1–2}



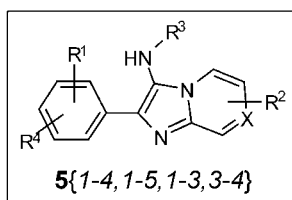
**Scheme 5.** Possible byproducts **7** and **8** found in the mixture of coupling reactions

## Conclusions

A fluororous synthetic route to 3-aminoimidazo[1,2-*a*]pyridines and 3-aminoimidazo[1,2-*a*]pyrazines derivatives has been developed by conducting MCRs followed by post-condensation reactions. The microwave heating has been applied to both steps. The MCRs were established under microwave heating and later converted to conventional heating for quick parallel library synthesis. The post-condensation reactions were conducted by microwave-

**Table 2.** Yields and purities for Suzuki coupling products **5**{1-4, 1-5, 1-3, 1-2}

<b>5</b>	yield	purity	<b>5</b>	yield	purity
{1, 1, 1, 1}	49%	58%	{2, 1, 2, 2}	34%	86%
{1, 1, 3, 1}	41%	89%	{3, 2, 3, 2}	17%	45%
{4, 2, 2, 1}	27%	88%	{1, 3, 1, 2}	12%	20%
{2, 3, 2, 1}	58%	91%	{3, 3, 2, 2}	25%	75%
{1, 4, 1, 1}	24%	75%	{3, 3, 3, 2}	16%	68%
{2, 4, 1, 1}	41%	86%	{4, 4, 2, 2}	26%	79%
{3, 4, 1, 1}	42%	76%	{1, 5, 2, 2}	10%	21%
{1, 5, 3, 1}	18%	81%	{3, 5, 2, 2}	8%	35%

**Table 3.** Yields and purities for aryl sulfide products **5**{1-4, 1-5, 1-3, 3-4}

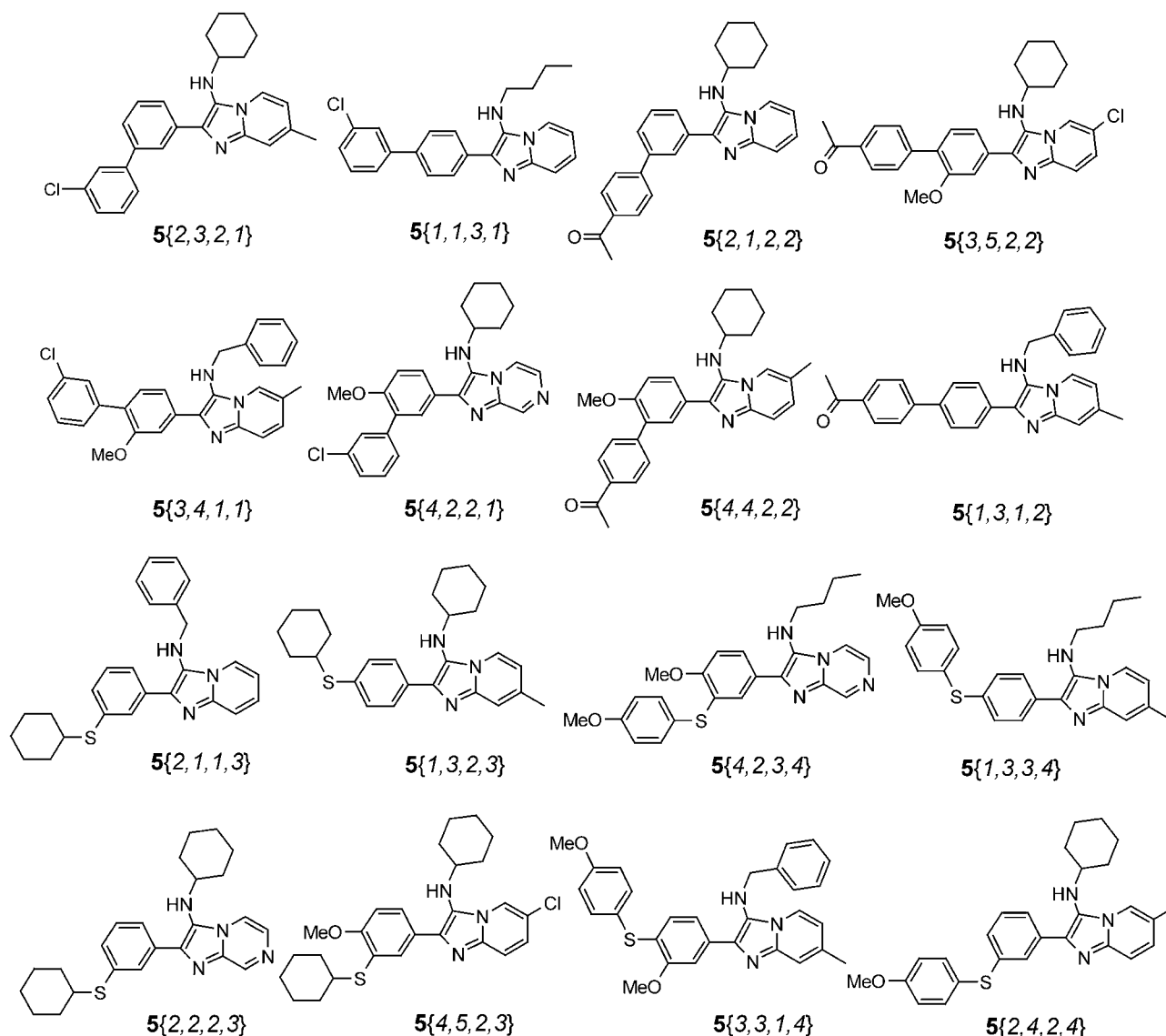
<b>5</b>	Yield	purity	<b>5</b>	yield	purity
{2, 1, 1, 3}	30%	86%	{3, 2, 2, 4}	30%	46%
{2, 2, 2, 3}	28%	93%	{4, 2, 3, 4}	41%	77%
{1, 3, 2, 3}	8%	80%	{2, 1, 3, 4}	29%	88%
{4, 3, 3, 3}	65%	73%	{1, 3, 3, 4}	22%	75%
{1, 4, 2, 3}	4%	73%	{4, 4, 1, 4}	45%	54%
{1, 5, 1, 3}	8%	42%	{2, 4, 2, 4}	17%	64%
{4, 5, 2, 3}	37%	52%	{4, 1, 3, 4}	15%	76%
{2, 5, 3, 3}	16%	75%	{4, 5, 3, 4}	48%	52%

assisted Pd-catalyzed cross-coupling reactions of fluorous sulfonates with boronic acids to form biaryls or with thiols to form aryl sulfides. At each reaction step, the reaction mixtures were analyzed by LC-MS or TLC, which is important for the reactions which have low conversion or producing byproducts. The F-SPE purification of the reaction mixtures from MCRs was unnecessary because recrystallization of the product proved to be an easier choice. This modification reflects the compatibility of fluorous technology with other purification techniques. Because of competitive reactions and different reactivity of substrates, the yields for both MCRs and coupling

reactions were relatively low, which also affected the purities of intermediates **4** and products **5** after F-SPE and recrystallization.

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**Scheme 6.** Representative structures of cross-coupling products **5**

## Experimental Section

**General.** Perfluorooctanesulfonyl fluoride, building blocks **1**, **2**, **3**, and reagents were obtained from commercial sources. FluoroFlash® SPE cartridges were obtained from Fluorous Technologies, Inc. SPE purification was conducted in parallel on a 2 × 12 SPE manifold available from Supelco and Fisher. Microwave reactions were conducted sequentially on a CEM Explorer® single mode microwave reactor. NMR spectra were obtained on a Bruker AC-270 spectrometer (270 MHz). CDCl<sub>3</sub> was used as the solvent unless otherwise specified. LC-MS spectra were obtained on an Agilent 1100 system. Purities were calculated based on UV254 absorption. APCI was used as ion source for all MS.

**General SPE procedures for F-SPE** [14]: A mixture containing fluorous and non-fluorous compounds in a

minimum amount of solvent (< 20% of cartridge volume) was loaded onto a FluoroFlash® cartridge preconditioned with 80:20 MeOH/H<sub>2</sub>O. The cartridge was eluted with 80:20 MeOH/H<sub>2</sub>O (2–5 cartridge volume) for the non-fluorous fraction followed by same amount of MeOH for the fluorous fraction. The loading of a SPE cartridge was around 1–5%. The SPE was conducted on a standard 2 × 2 SPE manifold. The vacuum was controlled to allow the solvent level moves about 1 inch/min. The cartridge can be reused by washing thoroughly with acetone or THF.

**General procedure for the preparation of fluorous benzaldehyde 1{1–4}.** To a solution of a hydroxy-benzaldehyde (110 mmol) in DMF (30 mL) was added K<sub>2</sub>CO<sub>3</sub> powder (135 mmol) at room temperature. The reaction mixture was stirred for 10 minutes before perfluorooctanesulfonyl fluoride (91 mmol) was added neat. The

mixture was heated at 70 °C for 2–8 hours. The cooled reaction mixture was filtered and the solid was rinsed with EtOAc. The filtrate was washed with water, dried over MgSO<sub>4</sub> and concentrated. The residue was dissolved in DCM (10 mL), loaded onto Si gel (500 g) and eluted with EtOAc/hexane (20%, 2 × 500 mL; 30%, 500 mL). The fractions were combined and concentrated to give the product as a white solid.

Analytical data for **1**[1]: <sup>1</sup>H NMR (ppm) δ 7.48 (d, *J* = 8.6 Hz, 2H), 8.01 (d, *J* = 8.6 Hz, 2H), 10.05 (s, 1H).

Analytical data for **1**[2]: <sup>1</sup>H NMR (ppm) δ 7.57 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.68 (t, *J* = 8.1 Hz, 1H), 7.81, (s, 1H), 7.94 (dd, *J* = 7.7, 1.0 Hz, 1H), 10.05 (s, 1H).

Analytical data for **1**[3]: <sup>1</sup>H NMR (ppm) δ 4.02 (s, 3H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 10.00 (s, 1H).

Analytical data for **1**[4]: <sup>1</sup>H NMR (ppm) δ 4.01 (s, 3H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.76 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 9.88 (s, 1H).

**General Procedure for preparation of 4**[*I*–4, *I*–5, *I*–3]. Method A, microwave conditions: Fluorous benzaldehyde **1** (1.0 equiv.), 2-aminopyridine or pyrazine (1.1 equiv.), isonitrile (1.2 equiv.) and Sc(OTf)<sub>3</sub> (0.05 equiv.) in 3:1 DCM/MeOH were heated under microwaves to 150 °C in 2 min ramp time. The reaction was maintained at this temperature for 10 min. After cooling to room temperature, the white precipitate was filtered, washed with cold MeOH and dried under vacuum to afford **4**.

Method B, thermo conditions: Fluorous benzaldehyde **1** (1.0 equiv.), 2-aminopyridine or pyrazine (1.1 equiv.), isonitrile (1.2 equiv.) and Sc(OTf)<sub>3</sub> (0.05 equiv.) in EtOH were heated to 80 °C for 2 h. The cooled reaction mixture was diluted with hexane and filtered. The solid was washed with hexane and dried to afford **4**.

Analytical data for **4**[*I*,*I*,*I*]: <sup>1</sup>H NMR (ppm) δ 3.42 (t, *J* = 5.9 Hz, 1H), 4.21 (d, *J* = 5.9 Hz, 2H), 6.79 (t, *J* = 6.7 Hz, 1H), 7.18 (dd, *J* = 6.8, 6.6 Hz, 1H), 7.22–7.40 (m, 7H), 7.57 (d, *J* = 6.8 Hz, 1H), 7.95 (d, *J* = 6.6 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 2H); MS 798 (M + H).

Analytical data for **4**[*I*,*I*,2] (**4d**): <sup>1</sup>H NMR (ppm) δ 1.04–1.16 (m, 5H), 1.52–1.90 (m, 5H), 2.90–3.10 (m, 2H), 3.98 (s, 3H), 6.83 (t, *J* = 6.7 Hz, 1H), 7.08–7.26 (m, 2H), 7.56 (d, *J* = 9.0 Hz, 1H), 8.01–8.20 (m, 3H); MS 820 (M + H).

Analytical data for **4**[*I*,*I*,3]: <sup>1</sup>H NMR (ppm) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.35–1.55 (m, 2H), 1.55–1.70 (m, 2H), 3.06 (q, *J* = 6.7 Hz, 2H), 3.22–3.48 (m, 1H), 6.92 (t, *J* = 6.7 Hz, 1H), 7.22–7.33 (m, 1H), 7.37 (d, *J* = 8.9 Hz, 2H), 7.66 (d, *J* = 8.9 Hz, 1H), 8.13 (d, *J* = 6.7 Hz, 1H), 8.17 (d, *J* = 8.9 Hz, 2H); MS 764 (M + H).

Analytical data for **4**[*I*,3,2]: <sup>1</sup>H NMR (ppm) δ 1.00–1.38 (m, 5H), 1.50–1.90 (m, 5H), 2.43 (s, 3H), 2.85–3.05 (m, 1H), 3.30–3.60 (m, 1H), 6.78 (d, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.47–7.59 (br, 1H), 8.08 (d, *J* = 7.0 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 2H); MS 804 (M + H).

Analytical data for **4**[*I*,3,3]: <sup>1</sup>H NMR (ppm) δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.35–1.55 (m, 2H), 1.55–1.70 (m, 2H), 2.41 (s,

3H), 3.04 (q, *J* = 6.7 Hz, 2H), 3.11–3.18 (m, 1H), 6.70 (dd, *J* = 6.7, 1.3 Hz, 1H), 7.34 (s, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.95 (d, *J* = 7.0 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 2H); MS 778 (M + H).

Analytical data for **4**[2,*I*,*I*]: <sup>1</sup>H NMR (ppm) δ 3.85–4.15 (br, 1H), 4.21 (d, *J* = 5.7 Hz, 2H), 6.92 (t, *J* = 6.7 Hz, 1H), 7.18–7.33 (m, 6H), 7.33–7.44 (m, 1H), 7.57 (t, *J* = 8.1 Hz, 1H), 7.78–7.95 (m, 1H), 7.98–8.08 (m, 2H), 8.18 (d, *J* = 8.1 Hz, 1H); MS 798 (M + H).

Analytical data for **4**[2,*I*,2]: <sup>1</sup>H NMR (ppm) δ 1.05–1.38 (m, 5H), 1.52–1.92 (m, 5H), 2.90–3.08 (m, 1H), 3.15–3.30 (m, 1H), 6.91 (t, *J* = 6.7 Hz, 1H), 7.20–7.35 (m, 2H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 8.12–8.32 (m, 2H), 8.23 (d, *J* = 8.1 Hz, 1H); MS 790 (M + H).

Analytical data for **4**[2,3,2]: <sup>1</sup>H NMR (ppm) δ 1.07–1.38 (m, 5H), 1.52–1.90 (m, 5H), 2.42 (s, 3H), 2.90–3.08 (m, 1H), 3.08–3.17 (m, 1H), 6.71 (dd, *J* = 6.9, 1.1 Hz, 1H), 7.21 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.39 (s, 1H), 7.53 (t, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 6.9 Hz, 1H), 8.13 (d, *J* = 2.2 Hz, 1H), 8.20 (d, *J* = 8.1 Hz, 1H); MS 804 (M + H).

Analytical data for **4**[4,2,3]: <sup>1</sup>H NMR (ppm) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.35–1.53 (m, 2H), 1.53–1.70 (m, 2H), 3.10–3.30 (m, 3H), 4.00 (s, 3H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.86 (d, *J* = 4.6 Hz, 1H), 7.94 (d, *J* = 1.8 Hz, 1H), 8.05 (dd, *J* = 8.7, 1.9 Hz, 1H), 8.20–8.32 (m, 1H), 8.97 (s, 1H); MS 795 (M + H).

Analytical data for **4**[4,4,2]: <sup>1</sup>H NMR (ppm) δ 1.05–1.38 (m, 5H), 1.52–1.90 (m, 5H), 2.39 (s, 3H), 2.98–3.08 (m, 1H), 3.20–3.40 (m, 1H), 3.98 (s, 3H), 7.09–7.22 (m, 2H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.94 (s, 1H), 8.11 (d, *J* = 1.8 Hz, 1H), 8.20 (dd, *J* = 8.7, 1.8 Hz, 1H); MS 834 (M + H).

**General procedure for preparation of biaryls 5**[*I*–4, *I*–5, *I*–3, *I*–2]. Method A: A mixture of **4** (0.2 mmol), boronic acid (0.19 mmol), K<sub>2</sub>CO<sub>3</sub> (0.4 mmol), Pd(dppf)Cl<sub>2</sub> (10 mol%) in 4:4:1 acetone/toluene/H<sub>2</sub>O (2 mL) was heated to 130 °C in 5 min under microwave irradiation. The reaction was maintained at this temperature for 20 min and cooled to room temperature. The mixture was loaded onto a FluoroFlash® SPE cartridge (5 g) and the cartridge was eluted with 80:20 MeOH/H<sub>2</sub>O (3 × 10 mL) and then acetone (2 × 10 mL). The MeOH/H<sub>2</sub>O fractions were combined and concentrated to afford the desired product.

Analytical data for **5d**: <sup>1</sup>H NMR (ppm) δ 1.05–1.38 (m, 5H), 1.51–1.94 (m, 5H), 2.98–3.15 (m, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 6.78 (t, *J* = 6.8 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.02–7.20 (m, 2H), 7.49–7.62 (m, 3H), 7.98–8.04 (m, 2H), 8.13 (d, *J* = 6.6 Hz, 1H); MS 428 (M + H).

Method B: To a mixture of **4** (0.2 mmol), boronic acid (0.19 mmol), K<sub>2</sub>CO<sub>3</sub> (0.4 mmol), Pd(dppf)Cl<sub>2</sub> (10 mol%) in DME (2 mL) was added 2 drops of water. The mixture was heated to 150 °C in 2 minutes under microwave irradiation. The reaction was maintained at this temperature for 10 minutes and cooled to room temperature. The mixture was diluted with 80:20 MeOH/H<sub>2</sub>O (5 mL) and loaded onto a FluoroFlash® SPE cartridge (5 g). The cartridge was eluted with 80:20 MeOH/H<sub>2</sub>O (3 × 10 mL) and then

acetone ( $2 \times 10$  mL). The MeOH/H<sub>2</sub>O fractions were combined and concentrated. The residue was dissolved in DCM (0.5 mL) and loaded onto a Si-SPE cartridge (2 g). The cartridge was eluted with EtOAc/hexane (20% 10 mL then 50%  $3 \times 10$  mL). The 50% fractions were combined and concentrated to afford the desired product. For pyrazines, the gradient was 50% (10 mL) followed by 100% ( $3 \times 10$  mL). The 100% fractions were combined and concentrated to give the desired product.

Analytical data for **5**{2,3,2,1}: <sup>1</sup>H NMR (ppm)  $\delta$  1.03–1.38 (m, 5H), 1.51–1.94 (m, 5H), 2.38 (s, 3H), 2.94–3.13 (m, 1H), 3.13–3.45 (m, 1H), 6.63 (dd,  $J$  = 6.9, 0.8 Hz, 1H), 7.27–7.45 (m, 3H), 7.50–7.63 (m, 3H), 7.67 (s, 1H), 8.00 (d,  $J$  = 7.6 Hz, 1H), 8.02–8.13 (m, 1H), 8.27 (t,  $J$  = 0.8 Hz, 1H); MS 416 (M + H), 418 (M + 2 + H).

Analytical data for **5**{1,1,3,1}: <sup>1</sup>H NMR (ppm)  $\delta$  0.95 (t,  $J$  = 7.2 Hz, 3H), 1.35–1.56 (m, 2H), 1.56–1.74 (m, 2H), 3.08 (t,  $J$  = 7.0 Hz, 2H), 3.15–3.38 (m, 1H), 6.84 (td,  $J$  = 7.0, 0.9 Hz, 1H), 7.14 (dd,  $J$  = 7.0, 1.2 Hz, 1H), 7.30–7.45 (m, 2H), 7.53 (dd,  $J$  = 4.9, 0.9 Hz, 1H), 7.56–7.72 (m, 4H), 8.05–8.15 (m, 3H); MS 376 (M + H), 378 (M + 2 + H).

Analytical data for **5**{2,1,2,2}: <sup>1</sup>H NMR (ppm)  $\delta$  1.03–1.38 (m, 5H), 1.51–1.94 (m, 5H), 2.65 (s, 3H), 2.94–3.09 (m, 1H), 3.09–3.30 (m, 1H), 6.82 (t,  $J$  = 6.7 Hz, 1H), 7.17 (td,  $J$  = 6.7, 1.0 Hz, 1H), 7.50–7.63 (m, 3H), 7.77 (d,  $J$  = 8.4 Hz, 2H), 8.03 (d,  $J$  = 8.4 Hz, 2H), 8.09–8.12 (m, 1H), 8.14 (d,  $J$  = 6.7 Hz, 1H) 8.37 (s, 1H); MS 410 (M + H).

Analytical data for **5**{4,4,2,2}: <sup>1</sup>H NMR (ppm)  $\delta$  1.05–1.38 (m, 5H), 1.51–1.94 (m, 5H), 2.35 (s, 3H), 2.65 (s, 3H), 2.85–3.15 (m, 2H), 3.88 (s, 3H), 7.00 (dd,  $J$  = 9.1, 1.4 Hz, 1H), 7.07 (d,  $J$  = 9.3 Hz, 1H), 7.46 (d,  $J$  = 9.1 Hz, 1H), 7.71 (d,  $J$  = 8.4 Hz, 2H), 7.88 (s, 1H), 8.01 (d,  $J$  = 8.4 Hz, 2H), 8.05–8.15 (m, 2H); MS 454 (M + H).

**General procedure for preparation of sulfides 5**{1–4, 1–5, 1–3, 3–4}. A mixture of **4** (0.2 mmol), thiol or thiophenol (0.19 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.4 mmol), and Pd(dppf)Cl<sub>2</sub> (10 mol%) in DMF (2 mL) was heated under microwaves to 180 °C in 2 min ramp time. The reaction was maintained at this temperature for 5 min and cooled to room temperature. The mixture was diluted with 80:20 MeOH/H<sub>2</sub>O (5 mL) and loaded onto a FluoroFlash® SPE cartridge (5 g). The cartridge was eluted with 80:20 MeOH/H<sub>2</sub>O ( $3 \times 10$  mL) and then acetone ( $2 \times 10$  mL). The MeOH/H<sub>2</sub>O fractions were combined and concentrated. The residue was dissolved in DCM (0.5 mL) and loaded on a Si-SPE cartridge (2 g). The cartridge was eluted with EtOAc/hexane (20%, 10 mL; 50%,  $3 \times 10$  mL). The 50% fractions were combined and concentrated to afford the desired product. For pyrazines, the gradient was 50% (10 mL) followed by 100% ( $3 \times 10$  mL). 100% fractions were combined and concentrated to afford the desired product.

Analytical data for **5**{2,1,1,3}: <sup>1</sup>H NMR (ppm)  $\delta$  1.03–1.38 (m, 5H), 1.51–1.94 (m, 5H), 3.10–3.28 (m, 1H), 3.50–4.10 (br, 1H), 4.20 (s, 2H), 6.79 (td,  $J$  = 6.7, 0.9 Hz, 1H), 7.10–7.25 (m, 1H), 7.28–7.45 (m, 7H), 7.62 (d,  $J$  = 9.1 Hz, 1H), 7.80–7.88 (m, 1H), 7.97–8.10 (m, 2H); MS 414 (M + H).

Analytical data for **5**{1,3,2,3}: <sup>1</sup>H NMR (ppm)  $\delta$  1.05–1.51 (m, 10H), 1.51–1.93 (m, 8H), 1.93–2.13 (m, 2H), 2.40 (s, 3H), 2.83–3.10 (m, 2H), 3.10–3.30 (m, 1H), 6.65 (dd,  $J$  = 7.0, 1.4 Hz, 1H), 7.30–7.40 (m, 1H), 7.44 (d,  $J$  = 8.4 Hz, 2H), 7.91–8.06 (m, 3H); MS 420 (M + H).

Analytical data for **5**{1,3,3,4}: <sup>1</sup>H NMR (ppm)  $\delta$  0.92 (t,  $J$  = 7.3 Hz, 3H), 1.33–1.51 (m, 2H), 1.51–1.70 (m, 2H), 2.38 (s, 3H), 2.85–3.08 (m, 3H), 3.83 (s, 3H), 6.64 (dd,  $J$  = 7.0, 1.3 Hz, 1H), 6.92 (d,  $J$  = 8.6 Hz, 2H), 7.23 (d,  $J$  = 8.4 Hz, 2H), 7.31 (s, 1H), 7.44 (d,  $J$  = 8.6 Hz, 2H), 7.86 (d,  $J$  = 8.4 Hz, 2H), 7.92 (d,  $J$  = 6.7 Hz, 1H); MS 418 (M + H).

Analytical data for **5**{4,2,3,4}: <sup>1</sup>H NMR (ppm)  $\delta$  0.90 (t,  $J$  = 7.3 Hz, 3H), 1.25–1.51 (m, 4H), 2.65–2.83 (m, 2H), 2.83–3.00 (m, 1H), 3.83 (s, 3H), 3.97 (s, 3H), 6.88–7.03 (m, 3H), 7.33 (d,  $J$  = 2.1 Hz, 1H), 7.50 (d,  $J$  = 8.6 Hz, 2H), 7.74–7.83 (m, 2H), 7.86 (d,  $J$  = 1.1 Hz, 1H), 8.91 (d,  $J$  = 1.3 Hz, 1H); MS 435 (M + H).


## References and Notes

- [1] Recent reviews on microwave synthesis: a) A. Loupy, Ed. *Microwaves in Organic Synthesis*; Wiley-VCH, Weinheim, 2002. b) B. L. Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. c) M. Larhed, C. Moberg, A. Hallberg, *Acc. Chem. Res.* **2002**, *35*, 717–727. d) B. Wathey, J. Tierney, P. Lidström, J. Westman, *Drug Discovery Today* **2002**, *7*, 373–380. e) C. O. Kappe, *Curr. Opin. Chem. Biol.* **2002**, *6*, 314–320. f) M. Larhed, A. Hallberg, *Drug Discovery Today* **2001**, *6*, 406–416. g) P. Lidström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron* **2001**, *57*, 9225–9283. h) R. S. Varma, *Pure Appl. Chem.* **2001**, *73*, 193–198.
- [2] a) P. Lidström, J. Westman, A. Lewis, *Comb. Chem. High Throughput Screening*, **2002**, *5*, 441–448. b) C. O. Kappe, *Am. Lab.* **2001**, *33*, 13–19. c) M. Larhed, G. Lindeberg, A. Hallberg, *Tetrahedron Lett.* **1996**, *37*, 8219–8222.
- [3] a) M. Larhed, M. Hoshino, S. Hadida, D. P. Curran, A. Hallberg, *J. Org. Chem.* **1997**, *62*, 5583–5587. b) K. Olofsson, S. Y. Kim, M. Larhed, D. P. Curran, A. Hallberg, *J. Org. Chem.* **1999**, *64*, 4539–4541.
- [4] a) *The Handbook of Fluorous Chemistry*; J. A. Gladysz, D. P. Curran, I. T. Horvath, Eds. Wiley-VCH: Weinheim, 2004. b) W. Zhang, *Chem. Rev.* **2004**, *104*, 2531–2556. c) W. Zhang, *Tetrahedron*, **2003**, *59*, 4475–4489. d) G. Pozzi, I. Shepperson, *Coord. Chem. Rev.* **2003**, *242*, 115–124. e) C. C. Tzschucke, C. Markert, W. Bannwarth, S. Roller, A. Hebel, *Angew. Chem. Int. Ed.* **2002**, *41*, 3964–4000. f) J. Yoshida, K. Itami, *Chem. Rev.* **2002**, *102*, 3693–3716. g) A. P. Dobbs, M. R. Kimberley, *J. Fluorine Chem.* **2002**, *118*, 3–17. h) D. P. Curran, *Synlett* **2001**, 1488–1496. i) D. P. Curran, in *Stimulating Concepts in Chemistry*; F. Stoddard, D. Reinhoudt and M. Shibasaki, Eds. Wiley-VCH: New York, 2000; pp 25–37. j) D. P. Curran, *Angew. Chem., Int. Ed. Eng.* **1998**, *37*, 1174–1196.
- [5] Recent reviews on MCRs: a) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144. b) M. Pulici, G. Cervi, K. Martina, F. Quartieri *Combin. Chem. High Throughput Syn.* **2003**, *6*, 693–727. c) A. J. von Wangelin, H. Neumann, D. Gordes, S. Kaus, D. Strubing, M. Beller, *Chem. Eur. J.* **2003**, *9*, 4286–4294. d) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S.



- Mathen, L. B. Balagopal, *Acc. Chem. Res.* **2003**, 36, 899–907.  
 e) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471–1499.  
 f) V. P. Litvinov, *Russian Chem. Rev.* **2003**, 72, 69–85. g) I. Ugi, *Pure Appl. Chem.* **2001**, 73, 187–191. h) I. Ugi, S. Hech, *Combin. Chem. High Throughput Syn.* **2001**, 4, 1–34. i) A. Domling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, 39, 3168–3210.  
 [6] a) C. Hulme, C. Gore, *Curr. Med. Chem.* **2003**, 10, 51–80. b) C. Hulme, T. Nixey, *Curr. Opin. Drug Discov. Dev.* **2003**, 6, 921–929. c) R. W. Armstrong, A. P. Combs, P. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, 29, 123–131.  
 [7] a) W. Zhang, C. H.-T. Chen, Y. Lu, T. Nagashima, *Org. Lett.* **2004**, 6, 1473–1476. b) W. Zhang, T. Nagashima, Y. Lu, C. H.-T. Chen, *Tetrahedron Lett.* **2004**, 45, 4611–4613. c) W. Zhang, Y. Lu, C. H.-T. Chen, *Mol. Diversity*, **2003**, 7, 199–202.  
 [8] a) G. Trapani, M. Franco, L. Ricciardi, A. Latrofa, G. Genchi, E. Sanna, F. Tuveri, E. Cagetti, G. Biggio, G. Liso, *J. Med. Chem.* **1997**, 40, 3109–3118. b) Y. Rival, G. Grassy, G. Michel, *Chem. Pharm. Bull.* **1992**, 40, 1170–1176. c) J. E. Starrett, T. A. Montzka, A. R. Crosswell, R. L. Cavanagh, *J. Med. Chem.* **1989**, 32, 2204–2210. d) C. Sabalayrolles, G. H. Cros, J. C. Milhavet, E. Rechenq, J. P. Chapat, M. Boucard, J. J. Serrano, J. H. McNeill, *J. Med. Chem.* **1984**, 27, 206–212. e) M. H. Fisher, A. Lusi, *J. Med. Chem.* **1972**, 15, 982–985.  
 [9] a) C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.* **1998**, 39, 3635–3638. b) C. Blackburn, *Tetrahedron Lett.* **1998**, 39, 5469–5299. see also c) K. Groebke, L. Weber, M. Fridolin, *Synlett* **1998**, 661–663. d) H. Bienayme, K. Bouzid, *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 2234–2237.  
 [10] C. Blackburn, B. Guan, *Tetrahedron Lett.* **2000**, 41, 1495–1500.  
 [11] Reviews of fluorous protecting groups and tags: a) W. Zhang, *Speciality Chem. Magazine* **2004**, 24 (5), 30–32. b) W. Zhang, in *The Handbook of Fluorous Chemistry*, J. A. Gladysz, D. P. Curran, I. T. Horvath, Eds. Wiley-VCH: Weinheim, 2004, pp 222–236.  
 [12] Isolation of compounds **7** and **8** as well as their structure characterization have not been attempted.  
 [13] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, 95, 2457–2483. b) V. Farina, V. Krishnamurthy, W. J. Scott, *Organic Reactions*, Wiley, New York, **1997**.  
 [14] For more information on F-SPE, log on to: [http://fluorous.com/download/an\\_spe.pdf](http://fluorous.com/download/an_spe.pdf).

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