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Platform for Ring-Fluorinated Benzoheterole Derivatives: Palladium-Catalyzed Regioselective 1,1-Difluoroallylation and Heck Cyclization

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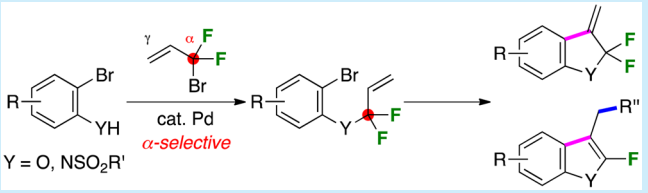
Supporting Information

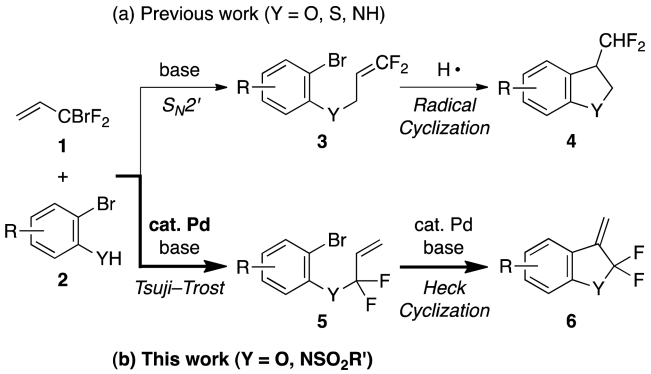
ABSTRACT: The synthesis of difluoromethylene-containing heterocycles was achieved via the palladium-catalyzed 1,1-difluoroallylation of heteronucleophiles followed by intramolecular Heck reaction. The allylic substitution of 3-bromo-3,3-difluoropropene was regioselectively accomplished by heteronucleophiles without rearrangement to give the corresponding 1,1-difluoroallylated compounds whose Heck cyclization proceeded in a 5-*exo* manner to afford ring-difluorinated indolines and dihydrobenzofurans. Their defluorinative allylic substitution further provided 2-fluoroindoles and 2-fluorobenzofurans.



Allylic substitutions including nucleophilic reactions (S_N2' and S_N2 reaction) and palladium-catalyzed reactions (the Tsuji–Trost reaction) have been applied in various synthetic processes as one of the most important organic reactions.[1] Despite the versatility of allylic substitution, it is often difficult to control the regioselectivity of unsymmetrically substituted allylic substrates. For example, *gem*-difluoroallylic electrophiles have served as two-fluorine-containing three-carbon building blocks; substitution on their carbon atoms α or γ to the fluorine substituents affords 1,1- or 3,3-difluoroallylic compounds, respectively.[2−4] The regioselectivity in such reactions has not been well controlled; however, it has been typically determined by the choice of substrate. Even worse for product selectivity, both of the difluoroallylated products are susceptible to further C−F substitution by nucleophiles.

In recent times, we developed a base-mediated selective S_N2' reaction of 3-bromo-3,3-difluoropropene (**1**) with brominated heteronucleophiles **2** (Scheme 1a).[5] In this previous report, the subsequent 5-*exo* radical cyclization of the obtained 3,3-difluoroallyl compounds **3** afforded 3-difluoromethylated 2,3-dihydrobenzoheteroles. In contrast, we herein disclose the complete switching of the regioselectivity in the reactions of **1** with heteronucleophiles **2** using a palladium catalyst (Scheme 1b). The α-selective substitution of **1** with 2-bromophenols **2a** and 2-bromoanilines **2b** selectively proceeded via the Tsuji–Trost reaction to afford *O*- and *N*-(1,1-difluoroallyl) compounds **5**.[6] Furthermore, their subsequent 5-*exo* Heck reaction[7] provided ring-difluorinated benzoheterole derivatives **6**.[8]

Scheme 1. Regioswitchable Allylic Substitution of 3-Bromo-3,3-difluoropropene (1)



First, we sought a suitable base for the α-selective Tsuji–Trost reaction using 2-bromophenol (**2aa**) in the presence of 4 mol % of $Pd(OAc)_2$ and 16 mol % of PPh_3 (Table 1). Weak bases ($NaHCO_3$ and $KHCO_3$) were found to be ineffective in this reaction (entries 2 and 3). The use of NaOMe promoted the selective formation of the α-substitution product **5aa**, albeit in low yield (entry 4). Both the yield of **5aa** and the **5aa**/**3aa** ratio were drastically improved by the use of *t*-BuOK or NaH without the loss of the C−Br bond of **2aa** (entries 5 and 6). When the amount of $Pd(OAc)_2$ was reduced to 1 mol % (entry 7), **5aa** was obtained in 97% isolated yield. Notably, the Pd catalysts switched the regioselectivity in the allylic substitution of **1** with **2aa** since γ-selective substitution proceeded with Cs_2CO_3 in the absence of Pd catalysts, as we have reported previously (entry 1).[5]

The α-selective Tsuji–Trost reaction of 2-bromophenols **2a** was then investigated with the optimal conditions obtained above (Table 2). Phenols **2ab** and **2ac** with electron-donating methyl and methoxy groups along with phenol **2ad** with an electron-withdrawing cyano group successfully underwent regioselective allylation with **1** in the presence of the Pd

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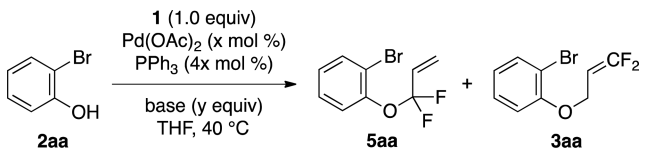
Org. Lett. XXXX, XXX, XXX−XXX

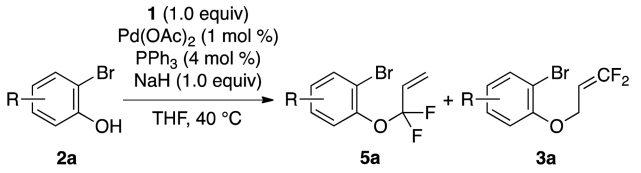
Table 1. Screening of Bases for the α-Selective Tsuji–Trost Reaction with Phenol 2aa



entry	x	base (y equiv)	time (min)	5aa[a] (%)	3aa[a] (%)
1[b]		Cs_2CO_3 (1.0)	30	16[c]	79[c]
2	4	$NaHCO_3$ (1.0)	60	2	2
3	4	$KHCO_3$ (1.0)	60	2	2
4	4	NaOMe (1.1)	30	27	2
5	4	*t*-BuOK (1.0)	30	92	3
6	4	NaH (1.0)	15	96	4
7	**1**	**NaH (1.0)**	**30**	**97**[c]	**3**

[a]Yield was determined by ^{19}F NMR measurements using $PhCF_3$ as an internal standard. [b]**1** (2.0 equiv), *N*-methyl-2-pyrrolidone (NMP), 90 °C. See ref 5. [c]Isolated yield.

Table 2. 1,1-Difluoroallylation of Phenols 2a



entry	2a	time (min)	5a (%)[a]	3a (%)[b]
1	**2aa** (R = H)	30	**5aa** 97	**3aa** 3
2	**2ab** (R = Me)	20	**5ab** 94	**3ab** 3
3	**2ac** (R = OMe)	20	**5ac** 93	**3ac** 4
4	**2ad** (R = CN)	30	**5ad** 95	**3ad** 1
5	**2ae** (R = Cl)	60	**5ae** 96	**3ae** 3
6	**2af**	10	**5af** 94	**3af** 1

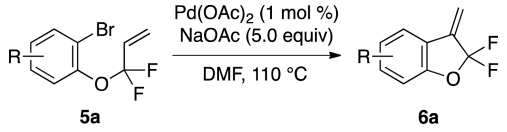
[a]Isolated yield. [b]Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard.

catalyst. The corresponding 1,1-difluoroallylated compounds **5ab–ad** were obtained in 94, 93, and 95% yields, respectively (entries 2–4). The 1,1-difluoroallylation of chlorine-substituted bromophenol **2ae** proceeded without the loss of its C–Cl and C–Br bonds, leading to the formation of **5ae** in 96% yield (entry 5). 1-Bromo-2-naphthol (**2af**) also participated in the reaction to give **5af** in 94% yield (entry 6).[9]

The obtained 1,1-difluoroallylated compounds **5a** underwent an intramolecular Heck reaction in a 5-*exo* manner to afford 2,2-difluorinated 3-methylene-2,3-dihydrobenzofuran **6a** (Table 3). Upon treatment of **5aa** with 1 mol % of $Pd(OAc)_2$ and 5.0 equiv of NaOAc, dihydrobenzofuran **6aa** was synthesized in 94% yield. Irrespective of the substituents on the aromatic rings, the 5-*exo* Heck reactions of **5ab–af** successfully proceeded to afford the corresponding difluorinated dihydrobenzofuran **6ab–af** in high to excellent yields (entries 2–6).

Next, we sought suitable conditions for the 1,1-difluoroallylation of sulfonamides with 3-bromo-3,3-difluoropropene (**1**) using *N*-(2-bromophenyl)-4-methylbenzenesulfonamide (**2ba**) as a model substrate (Table 4). Although the

Table 3. Synthesis of Dihydrobenzofurans 6a



entry	5a	time (min)	6a (%)[a]
1	**5aa** (R = H)	30	**6aa** 94
2	**5ab** (R = Me)	20	**6ab** 85
3	**5ac** (R = OMe)	20	**6ac** 93
4[b]	**5ad** (R = CN)	20	**6ad** 96
5[b]	**5ae** (R = Cl)	30	**6ae** 88
6	**5af**	30	**6af** 96

[a]Isolated yield. [b]1,2,2,6,6-Pentamethylpiperidine was used instead of NaOAc.

reaction of **2ba** with **1** was conducted under the optimal conditions for phenols **2a**, both the 1,1-difluoroallylated compound **5ba** and 3,3-difluoroallylated compound **3ba** were obtained in an almost 1:1 ratio (entry 1). To improve the yield and the regioselectivity, several bidentate phosphine ligands were used with $Pd_2(dba)_3{\cdot}CHCl_3$ (entries 2–5). Among them, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), which was used with NaH, provided the highest total yield of **5ba** and **3ba** (entry 5), albeit with no selectivity. Other bases used with Xantphos were thus examined for α-selective substitution (entries 6–9). Although *t*-BuOK was comparable to NaH (entry 6), lithium bases (LiH, LDA, and LHMDS) improved the **5ba**/**3ba** ratios, providing excellent total yields of **5ba** and **3ba** (entries 7–9). Further screening of solvents and temperatures (entries 10–15) revealed that LHMDS exhibited the best efficiency in ether at 0 °C (entry 15).

Since the isolation of **5b** from **3b** proved troublesome, we attempted the direct synthesis of *N*-sulfonyl-2,2-difluoro-3-methyleneindolines **6b** via the 1,1-difluoroallylation of *N*-sulfonylanilines **2b** followed by Heck cyclization using the mixtures of **5b** and **3b** obtained immediately after aqueous workup (Table 5). When a crude mixture of **5ba** and **3ba** prepared with 1.1 equiv of **1** under the optimal conditions above was treated with 1 mol % of $Pd(OAc)_2$, 10 mol % of NEt_3, and 1.2 equiv of sodium benzoate, *N*-tosyl-2,2-difluoro-3-methyleneindoline (**6ba**) was obtained in 84% isolated yield from **2ba** (entry 1). Similarly, *N*-tosylanilines **2bb** and **2bc** bearing electron-donating groups (Me and OMe) and **2bd–bf** bearing halogen substituents (F, Cl, and Br) successfully underwent the sequence of 1,1-difluoroallylation and Heck cyclization to afford the corresponding indolines **6bb–bf** in high yields (entries 2–6). Notably, in each case, the selective and almost quantitative formation of **5b** in the 1,1-difluoroallylation step was confirmed by ^{19}F NMR measurement. 1,1-Difluoroallylation of *N*-mesylanilines **2bg** and **2bh** also proceeded at room temperature, leading to selective formation of **5bg** and **5bh**, whose Heck cyclization gave *N*-mesylindolines **6bg** and **6bh** in good yields (entries 7 and 8).

In addition, the 2,2-difluorinated 3-methylene-2,3-dihydrobenzoheteroles obtained via the aforementioned sequence were further transformed into 2-fluorobenzoheteroles (eqs 1–3).[8a,10] 2,2-Difluorinated dihydronaphthofuran **6af** under-

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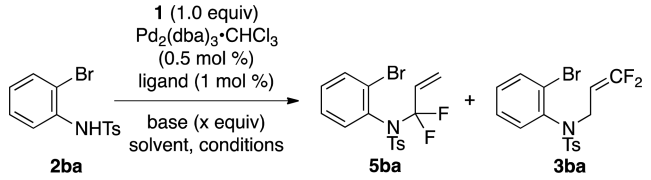
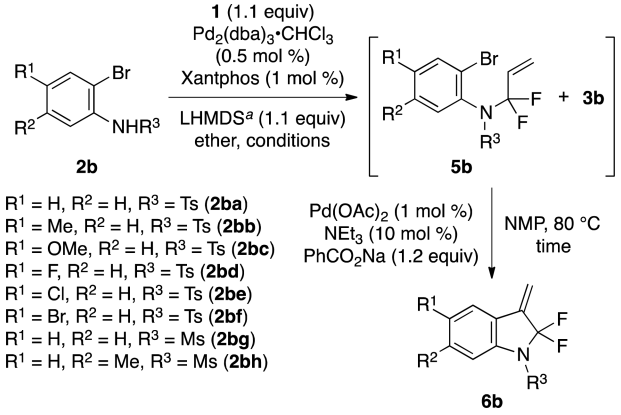
Table 4. Screening of Conditions for the α-Selective Tsuji–Trost Reaction with Aniline 2ba



entry	ligand	base (*x* equiv)	solvent	conditions	**5ba**[a] (%)	**3ba**[a] (%)
1[b]	PPh_3	NaH (1.0)	THF	40 °C, 4 h	36	39
2	dppe	NaH (1.0)	THF	40 °C, 2 h	ND[c]	3
3	dppb	NaH (1.0)	THF	40 °C, 2 h	ND[c]	3
4	dppf	NaH (1.0)	THF	40 °C, 2 h	25	28
5	Xantphos	NaH (1.0)	THF	40 °C, 2 h	49	48
6	Xantphos	*t*-BuOK (1.0)	THF	40 °C, 1 h	47	49
7	Xantphos	LiH (1.0)	THF	40 °C, 3 h	62	36
8	Xantphos	LDA (1.2)	THF	40 °C, 0.5 h	55	31
9	Xantphos	LHMDS (1.2)[d]	THF	40 °C, 0.5 h	63	37
10	Xantphos	LHMDS (1.2)[d]	DMF	40 °C, 1 h	54	46
11	Xantphos	LHMDS (1.2)[d]	hexane	40 °C, 4 h	13	5
12	Xantphos	LHMDS (1.2)[d]	ether	40 °C, 4 h	50	10
13	Xantphos	LHMDS (1.2)[d]	ether	rt, 0.5 h	86	14
14	Xantphos	LHMDS (1.2)[e]	ether	rt, 0.5 h	91	9
15	**Xantphos**	**LHMDS (1.2)[e]**	**ether**	**0 °C, 1 h**	**92**	**8**

[a]Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard. [b]$Pd(OAc)_2$ (1 mol %), PPh_3 (4 mol %). [c]ND = not detected. [d]THF solution. [e]Ether solution.

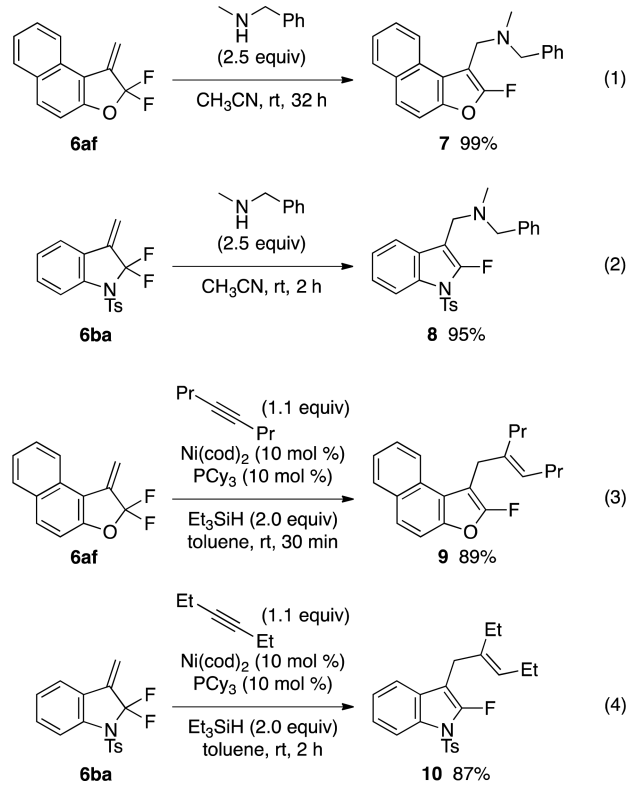
Table 5. Synthesis of Indolines 6b from Anilines 2b



entry	2b	conditions	**5b** + **3b**[b] (%)	**5b**:**3b**[c]	time (h)	**6b**[d] (%)
1	**2ba**	0 °C, 1 h	99	93:7	1	**6ba**, 84
2	**2bb**	0 °C, 2 h	quant	92:8	2	**6bb**, 82
3	**2bc**	0 °C, 2 h	quant	92:8	2	**6bc**, 88
4[e]	**2bd**	0 °C, 2 h	quant	93:7	0.5	**6bd**, 78
5	**2be**	0 °C, 0.5 h	98	94:6	0.5	**6be**, 78
6	**2bf**	0 °C, 0.5 h	quant	95:5	0.5	**6bf**, 82
7	**2bg**	rt, 0.5 h	94	91:9	1	**6bg**, 60
8	**2bh**	rt, 0.5 h	97	93:7	1	**6bh**, 60

[a]Ether solution. [b]Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard. [c]Ratio was determined by ^{19}F NMR measurement. [d]Isolated yield. [e]NEt_3 (4 mol %).

went S_N2' substitution with benzylmethylamine to afford 3-(aminomethyl)-2-fluoronaphthofuran **7** in 99% yield, requiring neither catalysts nor additives (eq 1).[3] In the case of indoline derivative **6ba**, the S_N2' reaction was completed more quickly to give the corresponding *N*-tosylated 2-fluoroindole **8** in 95% yield (eq 2). The nickel-catalyzed defluorinative coupling of



6af with 4-octyne via *β*-fluorine elimination also proceeded in the presence of Et_3SiH to afford the 3-allylated 2-fluoronaphthofuran **9** in 89% yield (eq 3).[11] Similarly, indoline **6ba** underwent nickel-catalyzed coupling with 3-hexyne to give the corresponding 2-fluoroindole **10** in 87% yield (eq 4).

In summary, we have disclosed that (i) 1,1-difluoroallylation of phenols and *N*-sulfonylanilines with 3-bromo-3,3-difluor-

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opropene (**1**) was accomplished by a palladium catalyst and (ii) its practical use provided a facile synthetic platform for ring-fluorinated benzoheterole derivatives. In light of our previously reported synthesis of difluoromethylated dihydrobenzoheteroles via the base-mediated 3,3-difluoroallylation with **1**,[5] the current method serves as a complementary approach to fluorine-containing benzoheterole derivatives, which are promising for pharmaceutical and agrochemical uses.[12]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03390.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected recent reviews on allylic substitution, see: (a) Diéguez, M.; Pàmies, O. *Acc. Chem. Res.* **2010**, *43*, 312−322. (b) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461−1475. (c) Bandini, M.; Cera, G.; Chiarucci, M. *Synthesis* **2012**, *2012*, 504−512. (d) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467−4483. (e) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339−2372. (f) Liu, W.; Zhao, X. *Synthesis* **2013**, *45*, 2051−2069. (g) Oliver, S.; Evans, P. A. *Synthesis* **2013**, *45*, 3179−3198. (h) Baeza, A.; Nájera, C. *Synthesis* **2013**, *46*, 25−34. (i) Arnold, J. S.; Zhang, Q.; Nguyen, H. M. *Eur. J. Org. Chem.* **2014**, *2014*, 4925−4948.

(2) For S_N2' and S_N2 reactions of difluoroallylic electrophiles, see: (a) Capuzzi, L.; Bettarini, F.; Meazza, G.; Massardo, P. *Gazz. Chim. Ital.* **1991**, *121*, 53−54. (b) Shi, G.-q.; Cai, W.-l. *Synlett* **1996**, *1996*, 371−372. (c) Tellier, F.; Baudry, M.; Sauvêtre, R. *Tetrahedron Lett.* **1997**, *38*, 5989−5992.

(3) Defluorinative allylic substitutions via nucleophilic reactions proceed in an S_N2' manner. See: (a) Ichikawa, J. *Chim. Oggi* **2007**, *25* (4), 54−57 and references cited therein. (b) Ichikawa, J. *J. Synth. Org. Chem., Jpn.* **2010**, *68*, 1175−1184 and references cited therein. (c) Yanai, H.; Okada, H.; Sato, A.; Okada, M.; Taguchi, T. *Tetrahedron Lett.* **2011**, *52*, 2997−3000. (d) Bergeron, M.; Johnson, T.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2011**, *50*, 11112−11116. (e) Bergeron, M.; Guyader, D.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5888−5891.

(4) For the Tsuji−Trost reactions of fluoroallylic electrophiles, see: (a) Shi, G.-q.; Huang, X.-h.; Zhang, F.-J. *Tetrahedron Lett.* **1995**, *36*, 6305−6308. (b) Kirihara, M.; Takuwa, T.; Okumura, M.; Wakikawa, T.; Takahata, H.; Momose, T.; Takeuchi, Y.; Nemoto, H. *Chem. Pharm. Bull.* **2000**, *48*, 885−888. (c) Kawatsura, M.; Wada, S.; Hayase, S.; Itoh, T. *Synlett* **2006**, *2006*, 2483−2485. (d) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Org. Lett.* **2007**, *9*, 3465−3468. (e) Pigeon, X.; Bergeron, M.; Barabé, F.; Dubé, P.; Frost, H. N.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1123−1127. (f) Ref 2b.

(5) Fujita, T.; Sanada, S.; Chiba, Y.; Sugiyama, K.; Ichikawa, J. *Org. Lett.* **2014**, *16*, 1398−1401.

(6) Most recently, Zhang et al. reported the palladium-catalyzed regioselective 1,1-difluoroallylation of aromatic carbons by using arylboronic acids. See: (a) Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230−1233. (b) Zhang, B.; Zhang, X. *Chem. Commun.* **2016**, DOI: 10.1039/C5CC08394J.

(7) For recent reports on heterocycle construction via the 5-*exo* Heck cyclization, see: (a) Lubkoll, J.; Millemaggi, A.; Perry, A.; Taylor, R. J. K. *Tetrahedron* **2010**, *66*, 6606−6612. (b) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416−11417. (c) Zhong, Y.; Wang, L.; Ding, M.-W. *Tetrahedron* **2011**, *67*, 3714−3723. (d) Lei, M.; Tian, W.; Li, W.; Lu, P.; Wang, Y. *Tetrahedron* **2014**, *70*, 3665−3674. (e) Kröger, D.; Schlüter, T.; Fischer, M.; Geibel, I.; Martens, J. *ACS Comb. Sci.* **2015**, *17*, 202−207.

(8) For synthesis of 2,2-difluorinated dihydrobenzoheteroles, see: (a) Bailey, J.; Plevey, R. G.; Tatlow, J. C. *Tetrahedron Lett.* **1975**, *16*, 869−870. (b) Maksimov, A. M.; Platonov, V. E. *Heteroat. Chem.* **1992**, *3*, 373−384.

(9) Use of 2-bromobenzenethiol instead of 2-bromophenols afforded the corresponding *S*-3,3-difluoroallylated product exclusively, even in the presence of the Pd catalyst.

(10) For synthesis of 2-fluorobenzofurans and 2-fluoroindoles, see: (a) Nash, S. A.; Gammill, R. B. *Tetrahedron Lett.* **1987**, *28*, 4003−4006. (b) Hodson, H. F.; Madge, D. J.; Widdowson, D. A. *Synlett* **1992**, *1992*, 831−832. (c) Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899−1906. (d) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, 1537−1538. (e) Martín-Santamaría, S.; Carroll, M. A.; Carroll, C. M.; Carter, C. D.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A. *Chem. Commun.* **2000**, 649−650. (f) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, *2002*, 1917−1936. (g) Ichikawa, J.; Nadano, R.; Mori, T.; Wada, Y. *Org. Synth.* **2011**, *83*, 111−120. (h) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342−9345. (i) Shao, Q.; Huang, Y. *Chem. Commun.* **2015**, *51*, 6584−6586.

(11) Ichitsuka, T.; Fujita, T.; Ichikawa, J. *ACS Catal.* **2015**, *5*, 5947−5950.

(12) For the bioactivity of ring-(di)fluorinated heterocyclic compounds, see: Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529−2591 and references cited therein.

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