

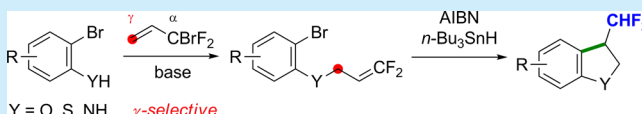
Two-Step Synthesis of Difluoromethyl-Substituted 2,3-Dihydrobenzoheteroles

Takeshi Fujita, Shohei Sanada, Yosuke Chiba, Kazuki Sugiyama, and Junji Ichikawa*

Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan

S Supporting Information

ABSTRACT: 3-Difluoromethylated 2,3-dihydrobenzoheteroles, 2,3-dihydrobenzofurans, 2,3-dihydrobenzothio-phenes, and indolines were readily synthesized from *ortho*-heterosubstituted bromobenzenes, 2-bromophenols, 2-bromobenzenethiols, and 2-bromoanilines, respectively, in two steps: (1) γ -selective allylic substitution of 3-bromo-3,3-difluoropropene with heteronucleophiles and (2) intramolecular radical cyclization of the resulting 3,3-difluoroallylic compounds.



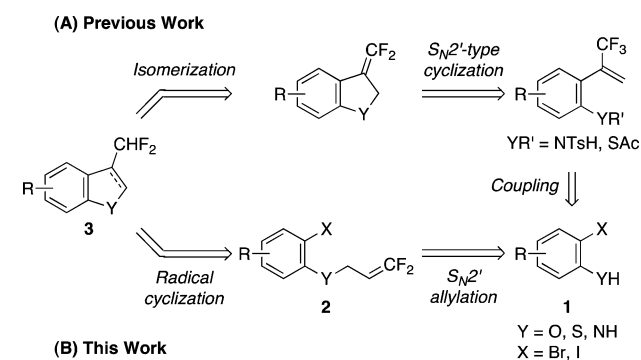
The difluoromethyl (CHF_2) group occupies a significant position among fluorinated functional groups, exhibiting unique properties derived from the steric and electronic characteristics of fluorine.¹ In particular, the CHF_2 group has been regarded as a bioisostere of the hydroxy group,² and indeed difluoromethylated compounds are increasingly found in bioactive substances, particularly agrochemicals.³ Furthermore, due to the electron-withdrawing effect of fluorine, the difluoromethyl group serves as a proton donor for hydrogen bonding, albeit with a hydrophobic nature.⁴

Despite the interesting potential of the CHF_2 group, conventional approaches to ring-difluoromethylated compounds have significant limitations; they require tedious reactions and toxic reagents such as diethylaminosulfur trifluoride (DAST).^{5–8} Thus, building block approaches to difluoromethylated compounds that include effective transformation of a fluorine-containing functional group into a CHF_2 group have attracted increasing attention.^{1c,9,10} Quite recently, a few methods for direct difluoromethylation have also been reported.¹¹

In our previous study on the building block approach, we developed an intramolecular $\text{S}_{\text{N}}2'$ reaction of 2-trifluoromethyl-1-alkenes bearing nucleophilic moieties for the regioselective synthesis of difluoromethylated heterocycles, such as indoles (Scheme 1A).⁹ Herein, we describe a two-step synthesis of 3-difluoromethylated 2,3-dihydrobenzoheteroles **3** (Scheme 1B). The reaction proceeds via (i) the $\text{S}_{\text{N}}2'$ allylic substitution of 3-bromo-3,3-difluoropropene with readily available 2-bromophenols **1a**, 2-bromobenzenethiols **1b**, and 2-bromoanilines **1c** under basic conditions¹² and (ii) the subsequent intramolecular radical cyclization of the intermediary 3,3-difluoroallylic compounds **2**.¹³ It is noteworthy that both the installation of the CHF_2 substituent and construction of the dihydrobenzoheterole framework are simultaneously achieved in this process. Thus, this methodology ensures regio-defined introduction of a CHF_2 group on the heterocyclic ring.

First, we sought a base that was suitable for the $\text{S}_{\text{N}}2'$ allylation with 3-bromo-3,3-difluoropropene using 2-bromophenol (**1aa**) as a model substrate (Table 1). While an amine

Scheme 1. Synthetic Routes to Difluoromethylated Benzoheterole Derivatives

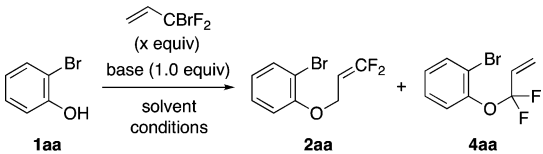


and an organolithium reagent were practically ineffective (entries 1 and 2), alkali metal hydrides enhanced the formation of the allylation products **2aa** and **4aa** (entries 3 and 4). In comparison with sodium hydride, potassium hydride highly improved the **2aa/4aa** ratio. A similar trend was observed using carbonate salts (entries 5–7). In terms of both efficiency and selectivity, cesium carbonate was found to be the best among the bases examined (entry 7). The efficiency and selectivity of the formation of **2aa** in the reaction with cesium carbonate in *N,N*-dimethylformamide (DMF) was improved when 3-bromo-3,3-difluoropropene was increased to 2 equiv, affording a 56% yield of **2aa** with a 2:1 ratio of **2aa/4aa** (entry 8).¹⁴ Moreover, this reaction was sensitive to the solvent used (entries 9–13). Thus, *N*-methyl-2-pyrrolidone provided better results than DMF (entries 12 and 7, respectively), and ultimately **2aa** was obtained in 79% yield with an approximately 5:1 ratio of **2aa/4aa** in the reaction using 2 equiv of 3-bromo-3,3-difluoropropene (entry 13).^{14,15}

We believe that the size of the counteranion may affect the selectivity because the **2aa/4aa** ratio was generally improved as

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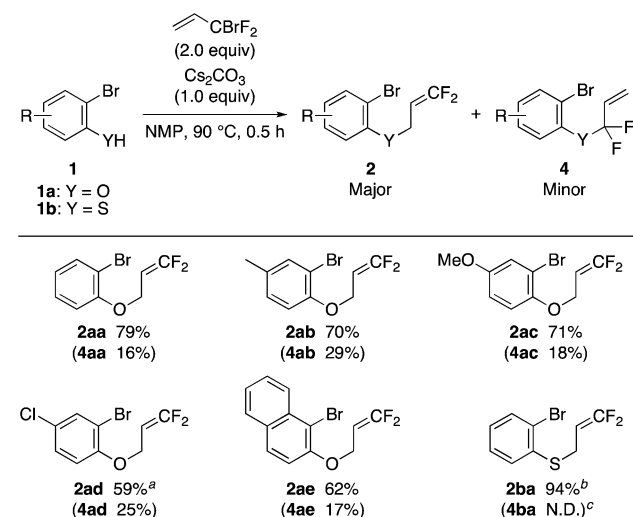
Table 1. Screening of Conditions for the S_N2' -Selective Reaction with Phenol **1aa**


entry	<i>x</i>	base	solvent	conditions	2aa (%) ^a	4aa (%) ^a
1	1.0	DMAP	DMF	90 °C, 1.5 h	6	16
2	1.0	<i>n</i> -BuLi	THF	−78 to 80 °C, 4 h	1	1
3	1.0	NaH	DMF	100 °C, 1.5 h	29	48
4	1.0	KH	DMF	100 °C, 4 h	41	13
5	1.0	Na ₂ CO ₃	DMF	100 °C, 2 h	16	27
6	1.0	K ₂ CO ₃	DMF	100 °C, 2 h	37	37
7	1.0	Cs ₂ CO ₃	DMF	100 °C, 17 h	42	28
8	2.0	Cs ₂ CO ₃	DMF	100 °C, 4 h	56	28
9	1.0	Cs ₂ CO ₃	EtOH	90 °C, 2 h	trace	trace
10	1.0	Cs ₂ CO ₃	MeCN	90 °C, 2 h	55	23
11	1.0	Cs ₂ CO ₃	DMSO	100 °C, 3 h	49	21
12	1.0	Cs ₂ CO ₃	NMP	100 °C, 3 h	62	21
13	2.0	Cs ₂ CO ₃	NMP	90 °C, 0.5 h	79	16

^aIsolated yield.

the diameter of the counteraction increased (Table 1, entries 3 and 4; entries 5–7). In the case of cesium carbonate, the intermediary cesium phenoxide formed in equilibrium could attack the carbon atom α or γ to the fluorine substituents of 3-bromo-3,3-difluoropropene. Under the optimal conditions, cesium phenoxide appears to predominantly attack the less hindered γ -carbon atom, avoiding the steric hindrance between the cesium core and the fluorine substituents on the α -carbon atom.

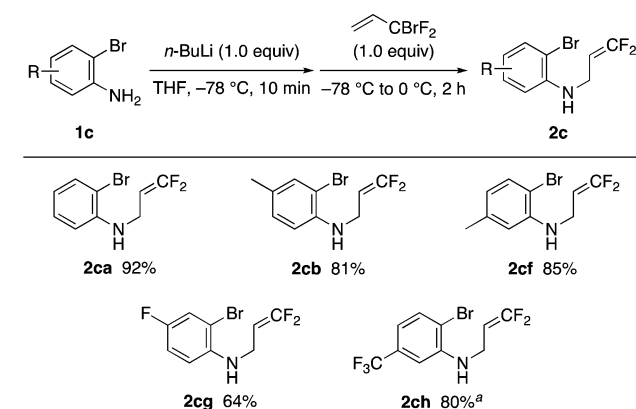
With the optimal conditions in hand, the substrate scope was then investigated (Scheme 2). Several functionalized (Me-, MeO-, and Cl-bearing) 2-bromophenols **1ab–1ad** and 1-bromo-2-naphthol (**1ae**) successfully underwent the S_N2' -

Scheme 2. 3,3-Difluoroallylation of Phenols **1a** and Benzenethiols **1b** via S_N2' -Selective Reaction

^a3-Bromo-3,3-difluoropropene (5.0 equiv), DMF, 100 °C, 2 h. ^b 3-Bromo-3,3-difluoropropene (1.0 equiv), DMF, rt, 3 h. ^c N.D. = Not detected.

selective reaction to afford the corresponding 3,3-difluoroallyl compounds **2ab–2ae** in good yields, whereas electron-withdrawing groups (e.g., CN) induced the selective formation of the undesired 1,1-difluoroallyl products **4a**.¹⁶ Intriguingly, the reaction of 2-bromothiophenol (**1ba**) smoothly proceeded at room temperature to afford a high yield (94%) of the 3,3-difluoroallylated product **2ba** with exclusive selectivity, even when only 1 equiv of 3-bromo-3,3-difluoropropene was used.¹⁷ This perfect selectivity may be the result of the ionic size effect of both sulfur and cesium.

In contrast to phenols **1a**, the S_N2' -selective allylation of 2-bromoanilines **1c** with 3-bromo-3,3-difluoropropene was effectively promoted using butyllithium as the base, which resulted in the exclusive formation of 3,3-difluoroallyl products **2c** in good to high yields (Scheme 3). In addition, 2-

Scheme 3. 3,3-Difluoroallylation of Anilines **1c** via S_N2' -Selective Reaction^a−78 to 80 °C, 8 h.

bromoanilines bearing not only a methyl or fluorine substituent but also an electron-withdrawing substituent (CF₃) successfully participated in the S_N2' reaction. The exclusive formation of **2c** may be attributed to the steric hindrance caused by the N–H and N–Ar bonds on the nitrogen atom of the intermediary lithium amides, which leads to exclusive attack of lithium amide on the carbon atom γ to the fluorine substituents in 3-bromo-3,3-difluoropropene.

Next, the intramolecular radical cyclization was investigated with tributyltin hydride using **2aa** as a model substrate (Table 2). The choice of radical initiator and solvent was found to be critical for efficient cyclization. Triethylborane with oxygen (entry 1) and 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V70, entry 2) were inappropriate as initiators for this reaction. In contrast, 2,2'-azobis(isobutyronitrile) in hexane effectively promoted the radical cyclization in the 5-*exo* fashion to give the desired 3-difluoromethyl-2,3-dihydrobenzofuran (**3aa**) in 92% isolated yield (entry 7) without the formation of the 6-*endo* cyclization product.

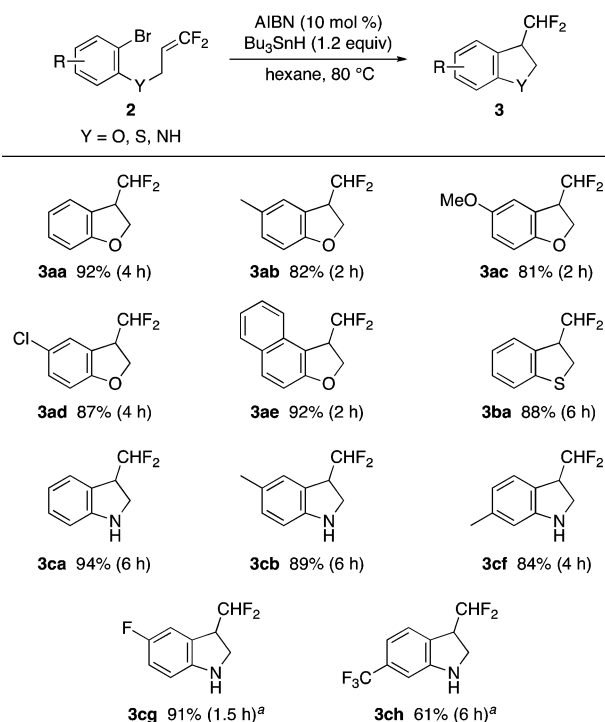
The synthesis of 3-difluoromethylated 2,3-dihydrobenzoheteroles **3** was investigated under the conditions described above (Scheme 4). Regardless of the heteroatoms and substituents attached to the aromatic rings, the 3,3-difluoroallyl compounds **2** successfully underwent intramolecular radical cyclization to afford 3-difluoromethyl-2,3-dihydrobenzofurans **3a**, 3-difluoromethyl-2,3-dihydrobenzothiophenes **3b**, and 3-difluoromethylindolines **3c** in good to high yields (61%–96%).

Table 2. Effect of Reaction Conditions on the Radical Cyclization of 3,3-Difluoroallyl Compound 2aa

entry	initiator (mol %)	solvent	conditions	3aa (%) ^a
1	Et ₃ B(200) + O ₂ (1 atm)	toluene	−78 °C, 9 h	35
2	V70 (20)	benzene	rt, 8 h	2
3	AIBN (50)	benzene	80 °C, 24 h	20
4	AIBN (20)	toluene	100 °C, 8 h	8
5	AIBN (10)	MeCN	80 °C, 12 h	trace
6	AIBN (10)	DCE	80 °C, 12 h	30
7	AIBN (10)	hexane	80 °C, 4 h	92 ^b

^a¹⁹F NMR yield using PhCF₃ as an internal standard. ^bIsolated yield.

Scheme 4. Synthesis of 3-Difluoromethylated Dihydrobenzoheteroles 3 via Radical Cyclization of 3,3-Difluoroallyl Compounds 2



^aBu₃SnH (1.0 equiv).

In summary, we disclosed a facile approach to the synthesis of difluoromethyl-substituted dihydrobenzoheteroles starting from readily available bromoarenes and 3-bromo-3,3-difluoropropene. This sequence provides a powerful protocol for the regioselective introduction of CHF₂ substituents, which has attracted increasing attention.¹⁸

The 2,3-dihydrobenzoheterole frameworks thus formed have been recognized as enormously important structures in pharmaceutical science; e.g., this structure can be found in a diuretic¹⁹ and a putative entactogen drug.²⁰ Because difluoromethylated dihydrobenzoheteroles are hybrids of two pharmaceutically important components, the CHF₂ group and the dihydrobenzoheterole framework, they are expected to serve as new bioactive compounds.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedures and ¹H, ¹³C, and ¹⁹F NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: junji@chem.tsukuba.ac.jp.

Notes

The authors declare no competing financial interest.

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(14) Unreacted **1aa** assisted the 1,3-allylic rearrangement of **2aa** to **4aa**. To suppress this undesired process, the reaction time should be shortened by the addition of an excess of 3-bromo-3,3-difluoropropene.

(15) When the reaction of 2-bromophenol **1aa** was quenched at an early stage (1 min), a 16% yield of the desired product **2aa** and a 4% yield of the side product **4aa** were obtained. The **2aa/4aa** ratio of this reaction (80/20) was similar to that of the reaction quenched after 30 min (83/17). This result suggests that the side product **4aa** can be formed directly via the reaction of bromophenol **1aa** with 3-bromo-3,3-difluoropropene.

(16) Reactions of 3-bromo-4-hydroxybenzonitrile with 3-bromo-3,3-difluoropropene afforded a 79% yield of the corresponding 1,1-difluoroallyl product with exclusive selectivity.

(17) Alternatively, thioethers **2b** were also prepared via the reaction with 1,1-difluoroallene. Treatment of **1ba** with 5 equiv of 1,1-difluoropropa-1,2-diene in the presence of 0.5 equiv of KOH (THF, 60 °C, 12 h) exclusively afforded **2ba** in 79% yield. In contrast, the reaction of bromophenols **1a** with 1,1-difluoropropa-1,2-diene selectively provided undesirably allylated products **4a**.

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