Cu-Catalyzed Aminodifluoroalkylation of Alkynes and α-Bromodifluoroacetamides

Yunhe Lv,*† Yunhe Lv,‡ Weiya Pu,‡ Qian Chen,‡ Qingqing Wang,‡ Jiejie Niu,‡ and Qian Zhang*‡

College of Chemistry and Chemical Engineering, Anyang Normal University, Anyang 455000, P. R. China
‡Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, Changchun 130024, P. R. China

ABSTRACT: The copper-catalyzed highly regioselective aminodifluoroalkylation of alkynes and α-bromodifluoroacetamides was realized for the first time. With this method, 3,3-difluoro-1H-pyrrol-2(3H)-ones were constructed in a single step from various alkynes and α-bromodifluoroacetamides substrates without using any extra oxidant.

Scheme 1. Aminodifluoroalkylation of Alkynes and Our Strategy

We discovered that 1,10-phenanthroline (Phen) was an extremely efficient difluoromethylene group (CF2) not only acts as lipophilic hydrogen bond donors and as bioisosteres of alcohols and thiols but also may significantly improve the biological stability.6 Very recently, via reductive cleavage of C=Br bond, α-bromodifluoroacetamides were successfully utilized as a fluoroalkyl radical reagent which can be trapped by a series of unsaturated compounds. On the other hand, in the presence of transition metal, oxidant, and base, α-bromodifluoroacetamides may also be used as a suitable reagent for amination via cleavage of N–H bond in N-aryl amides. Therefore, we reasoned that in the presence of one suitable catalyst, the above two processes could be consequentially realized to fulfill a catalytic cycle. Thus, the gem-difluoro group and nitrogen atom can be simultaneously installed into an unsaturated C=C bond, which will lead to the gem-difluorinated aza-heterocycle (Scheme 1).

In contrast to the recent significant progress in the difluoroalkylation of arenes and difluoroalkylation of alkenes, efficient difluoralkylation of less reactive alkynes is less abundant. Recently, examples of metal-catalyzed difluoroalkylation of alkynes such as halodifluoroalkylation, aryldifluoroalkylation, cyanodifluoroalkylation, and carbodifluoroalkylation was realized to provide molecules with important difluoroalkyl units (C==CCF2R).10 However, to our knowledge, aminodifluoroalkylation of simple alkynes has never been reported. Herein, we report the first example of a copper-catalyzed highly regioselective aminodifluoroalkylation of alkynes with α-bromodifluoroacetamides as both fluorine and nitrogen sources for facile access to a series of fluorinated aza-heterocycles 3,3-difluoro-1H-pyrrol-2(3H)-ones11 (Scheme 1).

We began our investigation utilizing the reaction between ethynylbenzene 1a and 2-bromo-2,2-difluoro-N-(p-tolyl)acetamide 2a as the model reaction (Table 1). With Cu as the catalyst in the presence of K2CO3 in MeCN, the model reaction was performed at 110 °C for 2 h under air, and no desired aminodifluoroalkylation product was observed (Table 1, entry 1). When 10 mol % pyridine was added to the above reaction, intermolecular aminodifluoroalkylation product 3a was obtained in 18% yield (Table 1, entry 2). We were pleased to discover that 1,10-phenanthroline (Phen) was an extremely...
efficient ligand for promoting the reaction, affording product 3a in 92% yield (Table 1, entries 3−5). Control reactions demonstrated that base and catalyst were essential to the reaction (Table 1, entries 6 and 7). Other bases such as KOtBu and Et3N were not as effective as K2CO3 (Table 1, entries 8 and 9). Further investigation on different copper salts revealed that CuBr and CuCl were also efficient catalysts for this transformation, affording product 3a in satisfying 86 and 90% yields, respectively (Table 1, entries 10 and 11). With Cu(OTf)2 and Cu(OAc)2 as catalysts, 3a was provided in 41 and 45% yields, respectively (Table 1, entries 12 and 13). Other solvents (e.g., EtOH, DMF, and EtOAc) were examined but did not lead to any significant improvement (Table 1, entries 14−16). When the reaction was performed at 90 °C, 3a was isolated in 24% yield (Table 1, entry 17). It should be noted that the transformation from 1a into 3a represents the first direct aminodifluoroalkylation from alkynes.

With the optimized reaction conditions in hand (Table 1, entry 5), the scope of the aminodifluoroalkylation of alkynes was examined, and the results are shown in Table 2. The reaction of 2a and a variety of alkynes derivatives afforded the desired aminodifluoroalkylation products 3 in 55−92% yields. Halo-substituted phenylacetylenes (1b−1d, 1k, 1l, 1s, and 1t) were tolerated in the aminodifluoroalkylation reaction and could be very useful for further transformations. Phenylacetylene substrates bearing electron-withdrawing substituents such as F, Cl, Br, and nitro were effectively converted into the corresponding products in moderate to excellent yields. Substrates with electron-donating substituents on the aromatic ring underwent aminodifluoroalkylation smoothly to afford the desired products (3e−3j and 3n−3r) in good yields. In addition, heteroaromatic alkynes such as 3-ethynylthiophene (1u) were also effective to provide 3u in 72% yield. Internal alkynes were subsequently examined. Starting from prop-1-yn-1-ylbenzene (1v) and but-1-yn-1-ylbenzene (1w), 3v and 3w were obtained in 85 and 82% yields, respectively. However, from the substrates hex-1-yne (1x) and diphenylacetylene (1y), no reactions occurred, and the substrate 2a was completely recovered.

Remarkably, in all cases, the reactions proceeded smoothly under air, and high regioselectivities were observed.

To further explore the potential of this efficient aminodifluoroalkylation reaction, a variety of α-bromodifluoroacetamides was investigated. As shown in Table 3, a-bromodi-
fluoroacetamides with different substituents at the aromatic ring could be converted to the desired products 4b−4k in moderate to good yields. Slightly decreased but acceptable yields were also achieved for reactions starting from ortho-substituted aryl amides (2i and 2j). Remarkably, we found that not only N-aryl substrates but also N-alkyl substrates worked well, affording 4l and 4m in 68 and 63% yields, respectively. However, the desired annulation product was not observed between the reaction of ethynylbenzene with mono-fluoroacetamide 2-bromo-2-fluoro-N-(p-tolyl)acetamide 2n.12

To gain insight into the mechanism of this transformation, a radical trapping experiment was performed. When the radical scavenger 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO, 2.0 equiv) was added to the aminodi-fluoroalkylation reaction of 1a under the optimal conditions, no desired products were isolated, and 80% 2a was recovered (eq 1). The results indicate that a radical pathway may be involved under the catalytic system. On the basis of the present experimental results and literature precedent, a possible mechanism was proposed as described in Scheme 2. Initially, the reaction of CuI and 2b gave a radical intermediate A and CuII species via a single electron transfer (SET) process. Subsequently, addition of the in situ generated fluoroalkyl radical A to the C=C triple bond of alkyne leads to the formation of vinyl radical which, with CuII species, gave the intermediate B in the presence of K2CO3. Nitrogen atom transfer from CuII to the adduct radical produces the aminodi-fluoroalkylation product and regenerates CuI,13 which enters into the next catalytic circle. On the other hand, we could not exclude another pathway: CuII-amido species reacts with vinyl radicals to form vinyl-CuIII-amido species C, which then undergoes the final reductive elimination to give the desired annulation product.7a,10c,e,14

In summary, we developed the first example of copper-catalyzed radical aminodi-fluoroalkylation reaction of alkynes for the synthesis of 3,3-di-fluoro-1H-pyrrol-2(3H)-ones. The high regioselectivity, broad substrate scope, no extra oxidant, and low loading of the copper catalyst make the aminodi-fluoroalkylation reactions very attractive. We believe that it should prompt further research in the area of transition-metal catalyzed aminodi-fluoroalkylation reactions and related chemistry using α-bromodifluoroacetamides as both difluoroalkyl and nitrogen sources.

### EXPERIMENTAL SECTION

All reagents were purchased from commercial sources and used without further treatment unless otherwise indicated. All reactions were run under air with no precautions taken to exclude moisture.1H NMR, 13C NMR, and 19F NMR spectra were recorded at 25 °C on a Varian instrument (400, 100, and 376 MHz). Melting points were obtained with a micro melting point XT4A Beijing Keyi electrooptic apparatus and are uncorrected. High resolution mass spectra were recorded on Bruck microTof. All reactions were monitored by TLC with Taizhou GF254 silica gel coated plates. Flash column chromatography was carried out using 200−300 mesh silica gel at increased pressure.

**General Procedure for the Preparation of 1o−1r.** Substrates 1o−1q were prepared by the reaction of corresponding anilines (1 mmol) and acyl chlorides (1.1 mmol) in CH3Cl at room temperature. Substrates 1r was prepared according to literature procedure.15
General Procedure for the Preparation of 2 (2a as Example). In a nitrogen-filled glovebox, p-toluidine (533.8 mg, 5.0 mmol), ethyl bromodifluoroacetate (781.1 µL, 6.0 mmol), and La(OtBu)₃ (146.5 mg, 0.25 mmol) were combined in screw-cap test tube. The reaction mixture was stirred at 50 °C and monitored by TLC. After the amine was exhausted, the mixture was purified by silica gel column chromatography to give the corresponding products 2a (1.21 g, 92%).

General Procedure for the Preparation of 3 and 4 (3a as Example). To a solution of the 2-bromo-2,2-difluoro-N-(p-tolyl)-acetamide 2a (79.2 mg, 0.3 mmol) in CH₂CN (3.0 mL) was added the ethynylbenzylene 1a (49 µL, 0.45 mmol), Phen (5.4 mg, 0.03 mmol), Cul (5.7 mg, 0.03 mmol), and K₂CO₃ (82.9 mg, 0.6 mmol) in screw-cap test tube. The reaction mixture was stirred at 110 °C for 2 h. After the reaction finished, the reaction mixture was cooled to room temperature and quenched by water. The mixture was extracted with EtOAc (5.0 mL x 3); the combined organic phases were dried over anhydrous Na₂SO₄ and the solvent was evaporated under vacuum. The residue was purified by column chromatography to give the corresponding products 3a (78.7 mg, 92%).

N-(3-Ethynylphenyl)acetamide 1a. White solid (149.5 mg, 94%). Petroleum ether/ethyl acetate = 40/1 as eluent for column chromatography. Mp: 86–88 °C.¹ H NMR (400 MHz, CDCl₃): δ 2.13 (s, 3H), 3.04 (s, 1H), 7.20 (d, J = 6.8 Hz, 2H), 7.48–7.49 (m, 1H), 7.67 (t, J = 8.4 Hz, 2H), 7.80 (s, 1H).¹³C NMR (100 MHz, CDCl₃): δ 24.2, 77.4, 83.1, 120.7, 122.5, 123.6, 127.8, 128.8, 138.0, 169.4. HRMS (ESI-TOF) calcd for C₉H₇NO, [M + H]⁺ m/z 160.0762, found 160.0764.

N-(3-Ethynylphenyl)pivalamide 1b. White solid (180.9 mg, 94%). Petroleum ether/ethyl acetate = 40/1 as eluent for column chromatography. Mp: 144–146 °C.¹ H NMR (400 MHz, CDCl₃): δ 1.27 (s, 9H), 3.03 (s, 1H), 7.17–7.20 (m, 2H), 7.50–7.53 (m, 1H), 7.56 (s, 1H), 7.64 (s, 1H).¹³C NMR (100 MHz, CDCl₃): δ 27.4, 39.5, 77.3, 83.1, 120.8, 122.5, 123.7, 127.7, 128.7, 138.0, 176.6. HRMS (ESI-TOF) calcd for C₉H₇NO, [M + H]⁺ m/z 202.1232, found 202.1230.

N-(3-Ethynylphenyl)benzamide 1q. White solid (198.9 mg, 90%). Petroleum ether/ethyl acetate = 40/1 as eluent for column chromatography. Mp: 122–124 °C.¹ H NMR (400 MHz, CDCl₃): δ 3.08 (s, 1H), 7.26–7.31 (m, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.53 (t, J = 7.2 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.77 (s, 1H), 7.84 (d, J = 7.6 Hz, 2H), 8.12 (s, 1H).¹³C NMR (100 MHz, CDCl₃): δ 77.7, 83.1, 120.9, 122.8, 123.8, 127.0, 128.2, 128.7, 139.0, 131.9, 134.6, 138.0, 166.0. HRMS (ESI-TOF) calcd for C₃H₂N₂O₃, [M + H]⁺ m/z 222.0919, found 222.0922.

tert-Butyl (3-Ethynylphenyl)carbamate 1r. White solid (173.7 g, 80%). Petroleum ether/ethyl acetate = 40/1 as eluent for column chromatography. Mp: 70–72 °C.¹ H NMR (400 MHz, CDCl₃): δ 1.50 (s, 9H), 3.04 (s, 1H), 6.75 (s, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.53 (s, 1H).¹³C NMR (100 MHz, CDCl₃): δ 28.2, 77.1, 80.6, 83.3, 119.0, 121.9, 122.6, 122.6, 128.8, 138.4, 152.6. HRMS (ESI-TOF) calcd for C₃H₂N₂O₃, [M + H]⁺ m/z 218.1181, found 218.1171.

2-Bromo-2,2-difluoro-N-(p-tolyl)acetamide 2a. White solid (1.21 g, 92%). Petroleum ether/ethyl acetate = 90/1 as eluent for column chromatography. Mp: 118–120 °C.¹ H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H), 1.87 (d, J = 4.8 Hz, 2H), 2.74 (d, J = 4.8 Hz, 2H), 7.27 (s, 1H).¹³C NMR (100 MHz, CDCl₃): δ 20.9, 111.6 (t, J = 315.0 Hz), 120.5, 129.8, 132.7, 157.6 (t, J = 280.0 Hz).¹⁹F NMR (376 MHz, CDCl₃): δ −60.4. HRMS (ESI-TOF) calcd for C₃H₂BrF₂NO, [M + H]⁺ m/z 263.9836, found 263.9828.

2-Bromo-2,2-difluoro-N-(o-tolyl)acetamide 2b. White solid (1.12 g, 90%). Petroleum ether/ethyl acetate = 90/1 as eluent for column chromatography. Mp: 72–74 °C.¹ H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H), 7.06 (d, J = 7.6 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 8.29 (s, 1H).¹³C NMR (100 MHz, CDCl₃): δ 21.2, 111.5 (t, J = 315.0 Hz), 117.8, 121.3, 127.0, 129.0, 135.1, 139.3, 157.6 (t, J = 280.0 Hz).¹⁹F NMR (376 MHz, CDCl₃): δ −60.4. HRMS (ESI-TOF) calcd for C₃H₂BrF₂NO₂, [M + H]⁺ m/z 297.9785, found 297.9782.

2-Bromo-2,2-difluoro-N-(m-tolyl)acetamide 2h. White solid (1.08 g, 95%). Petroleum ether/ethyl acetate = 90/1 as eluent for column chromatography. Mp: 74–76 °C.¹ H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H), 2.72 (d, J = 7.8 Hz, 2H), 7.71 (s, J = 8.0 Hz, 1H).¹³C NMR (100 MHz, CDCl₃): δ 36.9, 59.4, 111.2, 120.5, 129.8, 132.7, 148.4, 157.0 (t, J = 27.0 Hz).¹⁹F NMR (376 MHz, CDCl₃): δ −60.4. HRMS (ESI-TOF) calcd for C₃H₂BrF₂NO₂, [M + H]⁺ m/z 329.8774, found 329.8770.
111.6 (t, J = 31.0 Hz), 112.8, 128.7, 147.2, 149.2, 157.4 (t, J = 28.0 Hz); 13C NMR (376 MHz, CDCl3): δ 60.3. HRMS (ESI-TOF) calcd for \text{C}_{21}\text{H}_{22}\text{F}_2\text{NO}_3, \text{[M+H]}^+ m/z 328.1513, found 328.1506.

5-(4-Ethylphenyl)-3,3-difluoro-1-(p-tolyl)-1H-pyrrol-2(3H)-one 3f. Colorless oil (76.1 mg, 81%). Petroleum ether/ethyl acetate = 70/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 0.91 (t, J = 7.2 Hz, 3H), 1.57–1.63 (m, 2H), 2.33 (t, J = 7.6 Hz, 2H), 5.99 (s, 1H), 6.92 (d, J = 8.0 Hz, 2H), 7.08–7.13 (m, 6H); 13C NMR (100 MHz, CDCl3): δ 15.0, 21.1, 28.6, 99.1 (t, J = 23.0 Hz), 111.0 (t, J = 244.0 Hz), 126.1, 126.6, 127.9, 128.0, 129.6, 131.1, 137.8, 147.2, 154.6 (t, J = 11.0 Hz), 167.0 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ –109.7. HRMS (ESI-TOF) calcd for \text{C}_{21}\text{H}_{22}\text{F}_3\text{NO}, \text{[M+H]}^+ m/z 367.1862, found 368.1821.

3.3-Difluoro-5-(4-propylphenyl)-1-(p-tolyl)-1H-pyrrol-2(3H)-one 3g. Colorless oil (81.4 mg, 83%). Petroleum ether/ethyl acetate = 70/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 0.91 (t, J = 7.2 Hz, 3H), 1.57–1.63 (m, 2H), 2.33 (t, J = 7.6 Hz, 2H), 5.99 (s, 1H), 6.92 (d, J = 8.0 Hz, 2H), 7.08–7.13 (m, 6H); 13C NMR (100 MHz, CDCl3): δ 15.0, 21.1, 28.6, 99.1 (t, J = 23.0 Hz), 111.0 (t, J = 244.0 Hz), 126.1, 126.6, 127.9, 128.0, 131.1, 137.8, 145.8, 154.6 (t, J = 11.0 Hz), 167.0 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ –109.8. HRMS (ESI-TOF) calcd for \text{C}_{21}\text{H}_{22}\text{F}_3\text{NO}, \text{[M+H]}^+ m/z 367.1862, found 368.1821.

3.3-Difluoro-5-(4-tert-Butylphenyl)-1-(p-tolyl)-1H-pyrrol-2(3H)-one 3j. Yellow oil (85.9 mg, 84%). Petroleum ether/ethyl acetate = 70/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 1.28 (s, 9H), 2.34 (s, 3H), 5.59 (s, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.11 (t, J = 8.4 Hz, 4H), 7.29 (d, J = 8.4 Hz, 2H); 13C NMR (100 MHz, CDCl3): δ 21.1, 31.1, 34.9, 99.2 (t, J = 23.0 Hz), 111.0 (t, J = 244.0 Hz), 125.4, 125.8, 126.6, 127.7, 129.6, 131.1, 137.8, 145.4, 154.5 (t, J = 11.0 Hz), 167.0 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ –109.8. HRMS (ESI-TOF) calcd for \text{C}_{21}\text{H}_{22}\text{F}_3\text{NO}, \text{[M+H]}^+ m/z 342.1669, found 342.1677.

3.3-Difluoro-5-(4-pentylphenyl)-1-(p-tolyl)-1H-pyrrol-2(3H)-one 3k. White solid (81.8 mg, 80%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 0.89 (t, J = 6.8 Hz, 3H), 1.28–1.35 (m, 4H), 1.55–1.62 (m, 2H), 2.33 (s, 3H), 2.58 (t, J = 7.6 Hz, 2H), 5.60 (s, 1H), 6.93 (d, J = 8.0 Hz, 2H), 7.09–7.19 (m, 6H); 13C NMR (100 MHz, CDCl3): δ 13.9, 21.1, 22.4, 30.6, 31.4, 35.7, 99.1 (t, J = 23.0 Hz), 111.0 (t, J = 244.0 Hz), 126.0, 126.5, 127.8, 128.5, 129.6, 131.1, 137.8, 146.0, 154.6 (t, J = 11.0 Hz), 167.0 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ –109.7. HRMS (ESI-TOF) calcd for \text{C}_{21}\text{H}_{22}\text{F}_3\text{NO}, \text{[M+H]}^+ m/z 364.1851, found 364.1821.

3.3-Difluoro-5-(3-fluorophenyl)-1-(p-tolyl)-1H-pyrrol-2(3H)-one 3l. Colorless oil (72.7 mg, 76%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 2.32 (s, 3H), 5.65 (s, 1H), 6.91 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 7.16–7.20 (m, 6H); 13C NMR (100 MHz, CDCl3): δ 21.1, 21.4, 99.1 (t, J = 23.0 Hz), 111.0 (t, J = 244.0 Hz), 125.9, 126.6, 127.9, 129.2, 129.6, 131.1, 137.8, 141.0, 154.6 (t, J = 11.0 Hz), 167.0 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ –110.9. HRMS (ESI-TOF) calcd for \text{C}_{21}\text{H}_{22}\text{F}_3\text{NO}, \text{[M+H]}^+ m/z 364.1851, found 364.1821.
ethyl acetate = 40/1 as eluent for column chromatography. Mp: 170.126.4, 129.0, 129.4, 129.7, 130.8, 138.0, 138.5, 154.2 (t, 1H), 10.39 (s, 1H); 13C NMR (376 MHz, CDCl3): δ = −110.4. HRMS (ESI-TOF) calc for C12H10F2NO, [M + H]+ m/z 201.1677, found 201.1676.

3.3-Difluoro-5-(3-nitrophenyl)-1-(p-tolyl)-1H-pyrrolo[2,3-h]one 3c. Colorless oil (53.6 mg, 59%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ = 2.29 (3H, s), 5.70 (1H, s), 6.91 (d, J = 8.0 Hz, 2H), 7.00 (t, J = 9.2 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 6.8 Hz, 1H), 7.35–7.40 (m, 1H); 13C NMR (100 MHz, CDCl3): δ = 21.1, 102.5 (d, J = 3.0 Hz, 2H), 112.5 (t, J = 245.0 Hz), 116.2 (d, J = 21.0 Hz), 117.3 (d, J = 14.0 Hz), 124.3 (d, J = 3.0 Hz), 126.1, 129.5, 130.2 (d, J = 2.0 Hz), 130.7, 132.6 (d, J = 8.0 Hz), 137.9, 149.7 (t, J = 11.0 Hz), 159.5 (d, J = 251.0 Hz), 166.1 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ = −111.2, −111.0. HRMS (ESI-TOF) calc for C12H10F2NO3 [M + H]+ m/z 331.0894, found 331.0893.

5-(2-Chlorophenyl)-3,3-difluoro-5-(p-tolyl)-1H-pyrrolo[2,3-h]one 3d. Colorless oil (52.6 mg, 55%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ = 2.26 (3H, s), 5.64 (d, J = 1.2 Hz, 1H), 6.90 (d, J = 6.8 Hz, 2H), 7.03 (d, J = 7.6 Hz, 2H), 7.24–7.32 (m, 4H); 13C NMR (100 MHz, CDCl3): δ = 21.0, 102.5 (t, J = 23.0 Hz), 112.6 (t, J = 245.0 Hz), 126.3, 126.9, 128.5, 129.0, 130.4, 130.7, 131.6, 133.1, 137.9, 152.4 (t, J = 14.0 Hz), 165.9 (t, J = 10.0 Hz), 169.9 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ = −111.7. HRMS (ESI-TOF) calc for C12H10F2ClNO, [M + H]+ m/z 320.0654, found 320.0652.

3.3-Difluoro-5-(thiophen-3-yl)-1-(p-tolyl)-1H-pyrrolo[2,3-h]one 3e. White solid (76.3 mg, 85%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ = 2.53 (3H, s), 2.60 (3H, s), 2.66 (3H, s), 2.72 (3H, s), 2.75 (3H, s), 2.79 (s, 3H), 2.84 (s, 3H), 4.51 (s, 2H), 7.20 (t, J = 8.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 7.55 (t, J = 7.6 Hz, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H), 10.36 (s, 1H); 13C NMR (100 MHz, CDCl3): δ = 25.8, 32.3, 44.4, 104.5 (t, J = 23.0 Hz), 118.5 (t, J = 243.0 Hz), 124.8, 127.2, 127.7, 133.2, 133.6, 134.3, 134.7, 142.9, 145.0, 160.0 (t, J = 11.0 Hz), 171.6 (t, J = 30.0 Hz); 181.8; 19F NMR (376 MHz, CDCl3): δ = −108.9. HRMS (ESI-TOF) calc for C12H16F2NO3 [M + H]+ m/z 343.1258, found 343.1251.
as eluent for column chromatography. Mp: 142 °C. 1H NMR (400 MHz, CDCl3): δ 5.66 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.6 Hz, 2H), 7.27–7.34 (m, 4H), 7.41 (d, J = 7.6 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 100.4 (t, J = 24.0 Hz), 112.7 (t, J = 244.0 Hz), 127.8, 127.9, 128.4, 128.7, 129.2, 130.9, 132.1, 133.6, 154.0 (t, J = 110. Hz), 166.5 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ −109.7. HRMS (ESI-TOF) calcd for C8H12BrF3NO, [M + H]+ m/z 306.0497, found 306.0487.

1-(4-Bromophenyl)-3,3-difluoro-1H-pyrrol-2(3H)-one 4d. Colorless oil (71.0 mg, 68%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 5.66 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.40–7.45 (m, 3H); 13C NMR (100 MHz, CDCl3): δ 100.5 (t, J = 24.0 Hz), 112.7 (t, J = 244.0 Hz), 121.6, 127.9, 128.1, 128.7, 130.7, 133.2, 154.0 (t, J = 110. Hz), 165.5 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ −109.7. HRMS (ESI-TOF) calcd for C8H12BrF3NO, [M + H]+ m/z 306.0497, found 306.0487.

1-(4-Ethylphenyl)-3,3-difluoro-1H-pyrrol-2(3H)-one 4e. Colorless oil (73.5 mg, 84%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 1.21 (t, J = 7.6 Hz, 3H), 2.62 (q, J = 7.6 Hz, 2H), 5.63 (s, 1H), 6.94 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 15.2, 28.4, 99.8 (t, J = 23.0 Hz), 112.9 (t, J = 244.0 Hz), 126.5, 127.9, 128.4, 128.5, 128.8, 128.8, 131.4, 144.1, 154.6 (t, J = 110. Hz), 166.9 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ −110.0. HRMS (ESI-TOF) calcd for C9H12F3NO, [M + H]+ m/z 308.1200, found 308.1190.

1-(4-Tert-Butylphenyl)-3,3-difluoro-1H-pyrrol-2(3H)-one 4f. White solid (81.4 mg, 88%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. Mp: 121–123 °C. 1H NMR (400 MHz, CDCl3): δ 1.29 (s, 9H), 5.65 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 7.6 Hz, 2H), 7.28–7.34 (m, 4H), 7.39 (t, J = 7.6 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 31.2, 34.6, 99.8 (t, J = 23.0 Hz), 112.9 (t, J = 244.0 Hz), 125.9, 126.1, 127.9, 128.4, 128.8, 130.6, 130.8, 151.0, 154.6 (t, J = 110. Hz), 166.9 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ −110.0. HRMS (ESI-TOF) calcd for C10H12F3NO, [M + H]+ m/z 328.1513, found 328.1518.

3,3-Difluoro-1-(4-methoxyphenyl)-1H-pyrrol-2(3H)-one 4g. White solid (77.7 mg, 86%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. Mp: 142–143 °C. 1H NMR (400 MHz, CDCl3): δ 3.78 (s, 3H), 5.62 (s, 1H), 6.82 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 110.6. 13C NMR (100 MHz, CDCl3): δ 54.5, 99.6 (t, J = 23.0 Hz), 112.8 (t, J = 244.0 Hz), 114.3, 126.2, 126.8, 128.0, 128.5, 128.7, 130.6, 154.6 (t, J = 110. Hz), 159.0, 167.0 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ −110.2. HRMS (ESI-TOF) calcd for C10H12F3NO, [M + H]+ m/z 328.1504, found 328.1098.

3,3-Difluoro-1-(3-methylphenyl)-1H-pyrrol-2(3H)-one 4h. Colorless oil (71.9 mg, 84%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 2.30 (s, 3H), 5.65 (s, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.16–7.21 (m, 3H), 7.30 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.2 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 21.2, 99.8 (t, J = 23.0 Hz), 112.8 (t, J = 244.0 Hz), 123.7, 127.3, 129.7, 128.4, 128.7, 130.6, 133.5, 139.1, 154.6 (t, J = 110. Hz), 166.8 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ −110.0. HRMS (ESI-TOF) calcd for C7H12F3NO, [M + H]+ m/z 286.1034, found 286.1033.

3,3-Difluoro-1-(1-tolyl)-1H-pyrrol-2(3H)-one 4i. Colorless oil (62.4 mg, 73%). Petroleum ether/ethyl acetate = 60/1 as eluent for column chromatography. 1H NMR (400 MHz, CDCl3): δ 2.19 (s, 3H), 5.66 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 7.23–7.27 (m, 7H), 7.35 (s, J = 7.6 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 17.9, 99.3 (t, J = 23.0 Hz), 112.8 (t, J = 244.0 Hz), 126.8, 127.6, 128.5, 128.8, 129.1, 130.7, 131.3, 132.8, 136.3, 154.9 (t, J = 110. Hz), 166.7 (t, J = 30.0 Hz); 19F NMR (376 MHz, CDCl3): δ −110.6. HRMS (ESI-TOF) calcd for C7H12F3NO, [M + H]+ m/z 286.1045, found 286.1043.
REFERENCES


(12) The products were unidentifiable.
