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Enantioselective Functionalization of Difluorocyclopropenes Catalyzed by Chiral Copper Complexes: Proposal for Chiral *gem*-Dimethyl and *tert*-Butyl Analogues

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Supporting Information Placeholder

ABSTRACT: The highly enantioselective copper/chiral phosphine-catalyzed hydro-, bora-, and carbo-metalations of difluorocyclopropenes with PHMS [H-Si], H-BPin, $(BPin)_2$ and $(CH_3)_2Zn$ [Zn-Me] are shown to regiodivergently afford highly enantioenriched and functionalized difluorocyclopropanes. These examples can be viewed as the first successful syntheses of "chiral" *gem*-dimethyl and *tert*-butyl analogues.

INTRODUCTION

gem-Difluorocyclopropanes particularly in optically active form have attracted current attention in pharmaceutical and material sciences,[1] because *gem*-difluorocyclopropane groups have metabolic stability, lipophilicity, and bioisostere to epoxides,[2] based on their unique chemical and biological properties.[3] Therefore, highly efficient synthetic methods for difluorocyclopropanation of olefinic compounds have intensively been developed (Figure 1).[4] Difluorocyclopropene analogues have been synthesized under a similar reaction condition using acetylenic compounds and hence can in turn be employed as synthetic intermediates for difluorocyclopronanes.[4] However, synthetic transformation of difluorocyclopropenes *via* hydro- or carbo-functionalization is quite limited, due to their instability under various reaction conditions. Recently, radical hydrostannylation reaction of difluorocyclopropene was reported (Scheme 1, Eq. 1) but subsequent treatment of the tin intermediates with methyllithium led only to cyclopropane ring opening products.[5] Obviously, development of transition metal-catalyzed hydrometalation reaction of difluorocyclopropenes affords formidable endeavour particularly in an enantioselective manner. Herein, we report the highly regio- and stereoselective copper-catalyzed functionalization of difluorocyclopropenes under mild reaction conditions even at ambient temperature (Scheme 1, Eq. 2). Enantio-enriched *gem*-difluorocyclopropane products can thus be employed as chiral

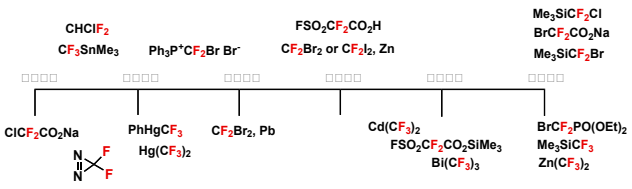
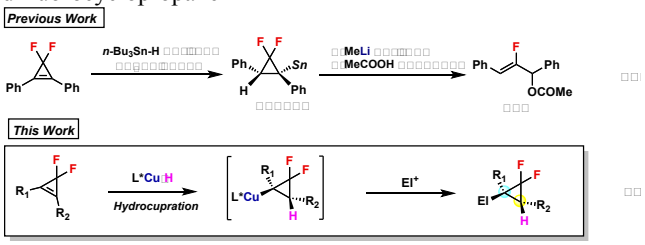
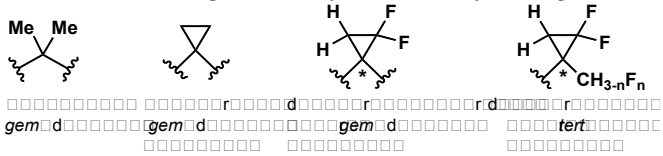


Figure 1. History of difluorocyclopropa(e)nes

Scheme 1. Catalytic asymmetric synthesis of difluorocyclopropane



Scheme 2. "Chiral" *gem*-dimethyl and *tert*-butyl analogues



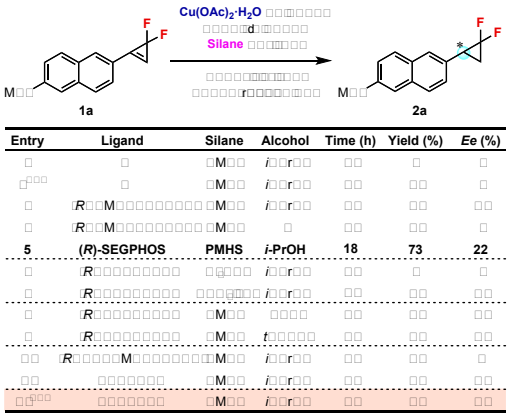
gem-dimethyl or *tert*-butyl analogues in close analogy to the well-accepted *gem*-dimethyl[6] or *tert*-butyl[7] analogues however in totally achiral form (Scheme 2).

RESULTS AND DISCUSSION

The enantioselective hydrometalation of difluorocyclopropenes was first executed with rhodium,[8] nickel,[9] and finally copper catalysts.[10] However, rhodium and nickel catalysts gave only ring opening products *via* M-F elimination even with silyl, boryl, and aluminum hydrides. In contrast, copper catalysis *via* copper hydrides easily prepared from copper salts and metal hydrides including hydro-silane and -borane afforded the desired hydrometalation product (Table 1); Hydrocupration of difluorocyclopropene **1a** was attempted initially with the Stryker reagent,[11] $[(Ph_3P)_3CuH]_6$ (20 mol%) and 4 eq. of polymethyl-hydrosilane (PMHS) to give

71% yield of the desired reduction product, difluorocyclopropane **2a** *via* retarding Cu–F elimination by sterically demanding and electron-donating phosphine ligands (entry 2). No reaction was confirmed to take place in the absence of either copper pre-catalyst or (di-)phosphine ligands (entry 1-3). When difluorocyclopropene **1a** was treated with $Cu(OAc)_2$ (10 mol%) and (*R*)-MeO-BIPHEP (12 mol%) in toluene at ambient temperature, the desired product **2a** was generated in 67% yield with 13% ee along with 1% recovery of difluorocyclopropene **1a** (entry 3). Extensive screening of solvents clarified that toluene, THF, and dioxane are the best solvent employed in term of high enantioselectivity. After screening copper pre-catalysts, $Cu(OAc)_2$ and CuO*t*-Bu are the best pre-catalysts in terms of enantioselectivity and chemical yield. CuCl, CuTC, $Cu(OTf)_2$, and $Cu[O(C{=}O)CF_3)_2$ turned out to be far inferior to $Cu(OAc)_2$ and CuO*t*-Bu in view of not only chemical yield but also enantioselectivity. Additional *sec*- and *prim*-alcohols rather than *tert*-alcohol are critical to attain not only higher chemical yield but also higher enantioselectivity (entry 5, 8, and 9). A significant improvement in enantioselectivity up to 86% ee along with 79% yield was attained by changing chiral ligands from BIPHEP, BINAP, and (DTBM)SEGPHOS to Walphos ligands (entry 11), fine-tuned by TADDOL-derived phosphoramidites and H_8-BINAP, depending on the substrates specified (Supporting Information). In combination of an elevated temperature with shortened reaction time, high enantioselectivity was recorded along with an increased yield (81%) (entry 12).

Table 1. Optimization of reaction conditions[a]

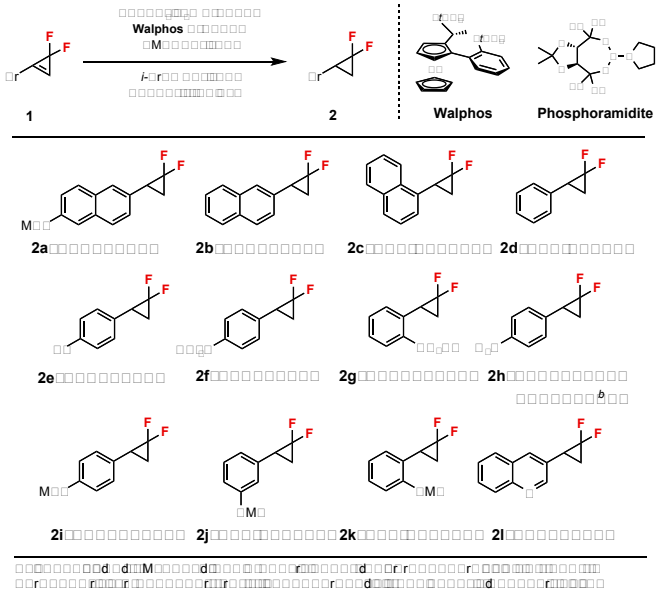


Entry	Ligand	Silane	Alcohol	Time (h)	Yield (%)	*Ee* (%)
5	(*R*)-SEGPHOS	PMHS	*i*-PrOH	18	73	22

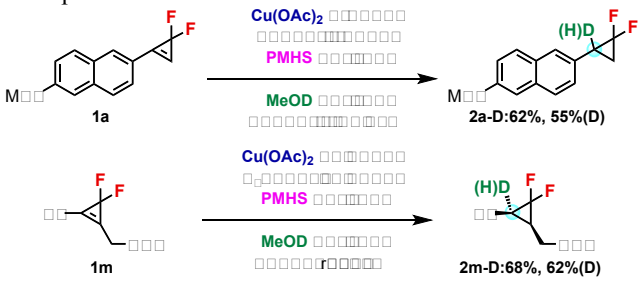
Substrate generality was then scrutinized under the optimal reaction conditions thus established (5 mol% of the Cu pre-catalyst, $Cu(OAc)_2$, Walphos ligands (6 mol%) and ambient reaction temperatures) (Table 2). Both electron-donating and -withdrawing substituents in either *para*- or *ortho*-positions showed good reactivity and enantioselectivity to give the desired products (**2e-k**). Moderate enantioselectivity (71:29) was fine-tuned by phosphoramidite ligand for *para*-nitro substrate (**1h**). Methoxy substituent at *meta*-position did also provide good yield (**2j**). Heterocyclic compounds such as **1l** gave, for example, quinolone derivative **2l** in an excellent yield of 80%.

Deuteration clarified the regioselectivity of Cu-C intermediates in hydrocupration to produce deuterated **2a-D** along with the formation of Walphos-Cu-H species (Scheme 3). MeOD gave solely the *cis*-diastereomeric product **2m-D** (Scheme 3) stabilized as the α-benzylic copper species, while the more sterically demanding DTBM-SEGPHOS-Cu-H species gave the opposite regioisomer (Table 3).

Table 2. Substrate scope[a]



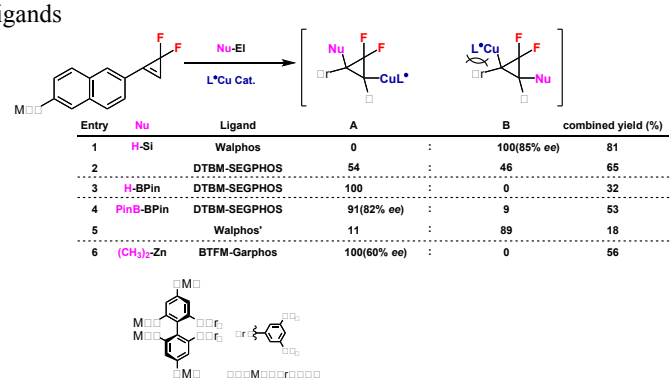
Scheme 3. Regio- and cis-selectivity of deuteration in hydrocupration



Regioselectivity was found to be dependent primarily on steric demand of ligands employed for copper complexes (Table 3).[12] Walphos-Cu-H species gave the α-benzylic copper species (**B**) (entry 1), while the sterically demanding DTBM-SEGPHOS-Cu-H species[13] provided the opposite regioisomer (**A**) (entry 2). Further hydroboration with pinacol borane, HBPin with DTBM-SEGPHOS-Cu complex also afforded the hydroboration regioisomer (**A**) (entry 3). Boracupration was then executed with bis(pinacolato)-diboron $(BPin)_2$, catalyzed by DTBM-SEGPHOS-Cu complex to show the same regiochemistry to give the borylated product in 82% *ee* with 91 : 9 regioisomeric ratio (entry 4). Significantly, $(CH_3)_2Zn$ afforded carbometalation product of difluorocyclopropenes with modified DTBM, namely bis(trifluoromethyl), BTFM-Garphos-Cu complex exhibited complete (100%) regioselectivity and 80 : 20 enantiomer ratio (60% *ee*) (entry 6).

Table 3. Regioselectivity depending on steric demand of

ligands



Entry	Nu	Ligand	A		B	combined yield (%)
1	H-Si	Walphos	0	:	100(85% ee)	81
2		DTBM-SEGPHOS	54	:	46	65
3	H-BPin	DTBM-SEGPHOS	100	:	0	32
4	PinB-BPin	DTBM-SEGPHOS	91(82% ee)	:	9	53
5		Walphos'	11	:	89	18
6	$(CH_3)_2$-Zn	BTFM-Garphos	100(60% ee)	:	0	56

The reaction mechanism of the present copper-catalyzed functionalization poses a challenge to clarify particularly the regioselectivity (Figure 2);[10,14] Based on the experimental results, the plausible catalytic reaction course can be visualized for *cis*-addition (Scheme 3) of the catalytically active CuNu species (**i**). The regioselectivity depends primarily on the steric demand of ligands employed, and secondary on the steric and electronic effects of the Cu-C intermediates (**A** and **B**). Generally, copper hydride species has been reported to be in the range of dimeric to hexameric, depending on the steric demand of ligands therewith.[11,13] The Walphos-copper species (**B**) is stabilized at α-benzylic position. In turn, the more sterically demanding DTBM-SEGPHOS[13] provides the less sterically demanding and hence terminal organo-copper species (**A**). The two initially formed cyclopropyl copper regioisomers (**A** and **B**) are likely in equilibrium and eventually lead to regioselective products (Figure 2).

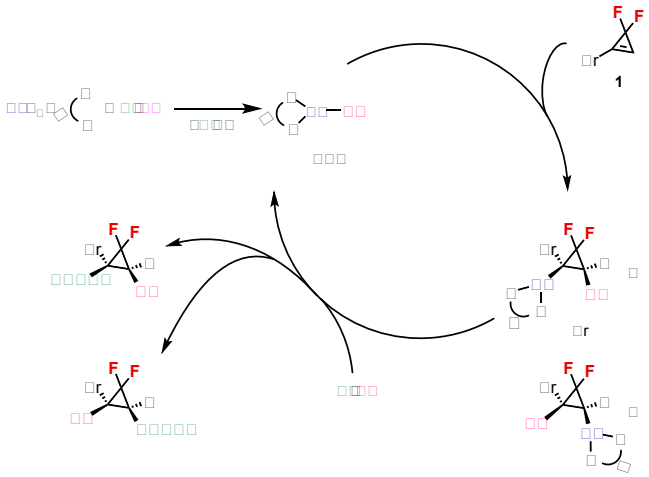


Figure 2. Proposed reaction course

Highly enantio-enriched difluorocyclopropane products can thus be employed as chiral *gem*-dimethyl or *tert*-butyl analogues in close analogy to the well-accepted *gem*-dimethyl[6] or *tert*-butyl[7] analogues of cyclopropanes but in totally achiral form.

CONCLUSION

In conclusion, we have succeeded in the development of highly enantioselective copper-catalyzed hydro-, bora-, and carbo-cupration reactions of difluorocyclopropanes. This is a new route to *gem*-difluorocyclopropyl analogues of *chiral* gem-dimethyl and *tert*-butyl with all carbon quaternary centers.

EXPERIMENTAL SECTION

General

^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were measured on a Bruker AV300M (300 MHz) spectrometer. Chemical shifts of ^{1}H NMR were expressed in parts per million relative to the singlet (δ = 7.26) for $CHCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million relative to the central line of the triplet (δ = 77.0) for $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million relative to the singlet (δ= -63.24) for BTF as an internal standard. Important NMR data were tabulated in following order: multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, sept: septet, m: multiplet, brs: broad singlet) and coupling constant (*J* (Hz)).

Analytical thin layer chromatography (TLC) was performed on a glass plates pre-coated with silica-gel (Merck Kieselgel 60 F_{254}, layer thickness 0.25 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde and $KMnO_4$. Column chromatography was performed on KANTO Silica Gel 60N (spherical, neutral).

Optical rotations were measured on JASCO P-1020.

Mass spectra were measured on JEOL JMS-T100CS (Accu-TOF) spectrometer.

IR spectra were measured on JASCO FT/IR-4200 spectrometer.

High performance liquid chromatography (HPLC) was conducted on JASCO PU-980, LG-980-02, DG-980-50, MD-2010, and CO-966 instrument equipped with model UV-975 spectrometers as an ultra violet light. Peak areas were calculated by JASCO chrom NAV (Windows 7) as an automatic integrator. DAICEL CHIRALCEL OD-3, DAICEL CHIRALCEL OD-H, DAICEL CHIRALCEL OJ-3, and DAICEL CHIRALCEL OJ-H were used as chiral columns.

Dichloromethane (dehydrate), toluene (dehydrate), tetrahydrofuran (dehydrate), diethyl ether (dehydrate), *N*,*N*-dimethylformamide (dehydrate), 2-propanol (dehydrate), ethanol (dehydrate), methanol (dehydrate) and acetonitrile (dehydrate) were purchased from Kanto Chemical Co., Inc. Triethylamine (dehydrate), copper(I) thiophene-2-carboxylate, copper(I) iodide, copper(I) acetate were purchased from Aldrich. Copper(I) trifluoromethanesulfonate was purchased from TCI. Copper(II) acetate monohydrate and copper(I) chloride were purchased from Wako Pure Chemical Industries. (*R*)-BINOL, (*S*)-BINAP, (*S*)-H_8-BINAP (*R*)-tol-BINAP, (*R*)-DM-BINAP, (*R*)-Cy-BINAP, (*R*)-SEGPHOS, (*R*)-DTBM-SEGPHOS, (*R*)-MeO-BIPHEP were provided from Takasago International Co. (*R*)-2-furyl-MeO-BIPHEP, (*R*)-DTBM-MeO-BIPHEP, Walphos and Joshiphos ligands were provided from Solvias AG. (*R*)-BTFM-Garphos was purchased from Strem Chemicals, Inc. (Trifluoromethyl)trimethylsilane (CF_3TMS) was gifted from TOSOHF-TECH. All other reagents were purchased from Sigma-Aldrich, Kanto Chemical, Tokyo Chemical Industries, and Wako Pure Chemical Industries and used without further purification. Phenylethyne **1d'** and *p*-chlorophenylethyne **1e'** were purchased from TCI.

2-Ethynyl-6-methoxynaphthalene **1a'**, 2-ethynylnaphthylene **1b'**, 1-ethynylnaphthylene **1c'** were synthesized by Corey-Fuchs alkyne synthesis[15]. Ethyl (*p*-ethynyl)benzoate **1f'**, ethyl (*o*-ethynyl)benzoate **1g'** (*p*-ethynyl)nitrobenzene **1h'**, (*p*-ethynyl)methoxybenzene **1i'**, (*m*-ethynyl)methoxybenzene **1j'**, (*o*-ethynyl)methoxybenzene **1k'**, 3-ethynylquinolone **1l'** were synthesized by Sonogashira coupling reaction[16].

All experiments were carried out under argon atmosphere unless otherwise noted.

Synthesis of ethyl 2-ethynylbenzoate (1f')

To a solution of $Pd(PPh_3)_2Cl_2$ (28.1 mg, 0.04 mmol) and CuI (15.2 mg, 0.08 mmol) in diethylamine (27 mL) were added ethyl 2-iodobenzoate (1.24 mL, 8.0 mmol) and trimethylsilylethyne (1.22 mL, 8.8 mmol) by Sonogashira coupling reaction[16]. The reaction mixture was stirred at room temperature for 12 h. During the reaction a second liquid phase formed. The solvent was removed in vacuo. Et_2O (20 mL) and water (20 mL) were added and the aqueous phase was extracted with Et_2O (20 mL). The combined organic phase was washed with aqueous 4N HCl solution (20 mL) and water (20 mL). After drying over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give ethyl 2-(2-trimethylsilylethynyl)benzoate. The compound was used for next step without further purification.

To a solution of ethyl 2-(2-trimethylsilylethynyl)benzoate in ethanol (24 mL) was added K_2CO_3 (1.11 g, 8.0 mmol). The reaction mixture was stirred at room temperature for 2 h, water (20 mL) was added and the aqueous phase was extracted with Et_2O (20 mL). The combined organic phase was washed with saturated aqueous NaCl (20 mL). After drying over anhydrous $MgSO_4$, filtered and solvent was removed. Resulting crude product was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) to give the ethyl 2-ethynylbenzoate (460 mg, 33%) as a brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, 1H, J = 7.7, 1.4 Hz), 7.62 (dd, 1H, J = 7.8, 1.4 Hz), 7.50-7.37 (m, 2H), 4.40 (q, 2H, J = 7.1 Hz), 3.38 (s, 1H), 1.40 (t, 3H, J = 7.1 Hz); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 166.0 (s), 134.9 (s), 132.8 (s), 131.5 (s), 130.2 (s), 128.4 (s), 122.5 (s), 82.2 (s), 82.0 (s), 61.3 (s), 14.2 (s); FT-IR (neat, cm^{-1}) 3287, 2982, 2939, 2904, 2107, 1725, 1483, 1445, 1366, 1292, 1273, 1254, 1134, 1077, 758; HRMS (APCI-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{11}O_2$ 175.0759; Found 175.0755.

Typical Procedure: Synthesis of *gem*-difluorocyclopropenes[4f]

Corresponding alkyne **1'** (8.0 mmol), $TMSCF_3$ (2.37 mL, 16 mmol), NaI (2.638 g, 17.6 mmol), and THF (24 mL) were mixed into a pressure tube at room temperature. Then the reaction mixture was heated in an oil bath at 110 °C for 2 h. The reaction mixture was quenched by adding saturated Na_2CO_3 solution (20 mL), followed by extraction with Et_2O (30 mL x3). The combined organic phase was dried over anhydrous K_2CO_3, filtered and concentrated under reduced pressure. Resulting crude product was purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/0/1 ~ 40/2/1) to give the corresponding difluorocyclopropane **1** (the column should be eluted previously with hexane/NEt_3 (10/1)).

2-(3,3-difluorocycloprop-1-en-1-yl)naphthalene (1b)

This compound was prepared from 2-ethynylnaphthylene **1b'** and purified by silica-gel column chromatography (hexane/NEt_3 = 40/1) as a yellow solid (79% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.94-7.86 (m, 3H), 7.71 (dd, 1H, J = 8.4, 1.5 Hz), 7.76-7.53 (m, 3H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 134.5 (s), 134.1 (t, J_{C-F} = 10.6 Hz), 132.9 (s), 131.2 (s), 129.0 (s), 128.7 (s), 128.1 (s), 127.9 (s), 127.0 (s), 125.8 (s), 120.6 (s), 113.6 (t, J_{C-F} = 12.3 Hz), 101.8 (t, J_{C-F} = 268.5 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.3 (s, 3F); FT-IR (neat, cm^{-1}) 3133, 3062, 1718, 1287, 1007, 831, 808, 783, 769, 748; HRMS (APCI-TOF) m/z: $[M]^-$ Calcd for $C_{13}H_8F_2^-$ 202.0594; Found 202.0595.

1-(3,3-difluorocycloprop-1-en-1-yl)naphthalene (1c)

This compound was prepared from 1-ethynylnaphthylene **1c'** and purified by silica-gel column chromatography (hexane/NEt_3 = 40/1) as a brown liquid (59% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, 1H, J = 8.4 Hz), 8.02 (d, 1H, J = 8.2 Hz), 7.92 (t, 2H, J = 7.4 Hz), 7.71-7.55 (m, 4H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 133.6 (s), 132.5 (s), 132.4 (t, J_{C-F} = 11.9 Hz), 131.6 (s), 130.7 (s), 128.7 (s), 128.0 (s), 126.8 (s), 125.3 (s), 124.2 (s), 120.1 (s), 113.9 (t, J_{C-F} = 12.2 Hz), 101.2 (t, J_{C-F} = 268.5 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -104.5 (s, 2F); FT-IR (neat, cm^{-1}) 3126, 3057, 1705, 1508, 1341, 1299, 1238, 1216, 1186, 1020, 857, 843, 807, 777, 767, 593; HRMS (APCI-TOF) m/z: $[M]^{-\cdot}$ Calcd for $C_{13}H_8F_2$ 202.0594; Found 202.0591.

1-chloro-4-(3,3-difluorocycloprop-1-en-1-yl)benzene (1e)

This compound was prepared from *p*-chlorophenylethyne **1e'** and purified by silica-gel column chromatography (hexane/NEt_3 = 40/1) as a brown liquid (50% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2H), 7.50-7.45 (m, 3H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 133.9 (s), 133.0 (t, J_{C-F} = 10.6 Hz), 131.3 (s), 129.5 (s), 121.8 (s), 114.1 (t, J_{C-F} = 12.3 Hz), 101.3 (t, J_{C-F} = 268.7 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.6 (s, 2F); FT-IR (neat, cm^{-1}) 3134, 1721, 1593, 1486, 1310, 1291, 1486, 1310, 1291, 1274, 1092, 1018, 838, 820, 777; HRMS (APCI-TOF) m/z: $[M]^{-\cdot}$ Calcd for $C_9H_5ClF_2$ 186.0048; Found 186.0052.

Ethyl 4-(3,3-difluorocycloprop-1-en-1-yl)benzoate (1f)

This compound was prepared from ethyl 2-ethynylbenzoate **1f'** and purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/2/1) as a brown solid (40% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, 2H, J = 6.7, 1.7 Hz), 7.72 (d, 2H, J = 8.3 Hz), 7.62 (t, 1H, J = 1.4 Hz), 4.41 (q, 2H, J = 7.1 Hz), 1.42 (t, 3H, J = 7.1 Hz); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 165.6 (s), 133.3 (t, J_{C-F} = 10.7 Hz), 133.1 (s), 130.2 (s), 129.9 (s), 127.1 (s), 116.1 (t, J_{C-F} = 12.2 Hz), 101.1 (t, J_{C-F} = 269.2 Hz), 61.5 (s), 14.3 (s); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.5 (s, 2F); FT-IR (neat, cm^{-1}) 3126, 2985, 1718, 1410, 1368, 1311, 1277, 1233, 1176, 1110, 1021, 865, 818, 759, 694; HRMS (APCI-TOF) m/z: $[M]^{-\cdot}$ Calcd for $C_{12}H_{10}F_2O_2$ 224.0649; Found 224.0657.

Ethyl 2-(3,3-difluorocycloprop-1-en-1-yl)benzoate (1g)

This compound was prepared from ethyl (*o*-ethynyl)benzoate **1g'** and purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/2/1) as a brown solid (40% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, 1H, J = 7.7, 1.4 Hz), 7.75-7.72 (m, 1H), 7.67-7.54 (m, 3H), 4.44 (q, 2H, J = 7.1 Hz), 1.42 (t, 3H, J = 7.1 Hz); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 165.9 (s), 132.6(s), 132.6 (t, J_{C-F} = 10.2 Hz), 132.3 (s), 131.3 (s), 131.1 (s), 130.7 (s), 123.2 (s), 118.2 (t, J_{C-F} = 11.4 Hz), 102.0 (t, J_{C-F} = 270.3 Hz), 61.7 (s), 14.2 (s); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -105.5 (s, 2F); FT-IR (neat, cm^{-1}) 3131, 3071, 2983, 1724, 1596, 1447, 1368, 1311, 1263, 1133, 1111, 1074, 1021, 812, 753; HRMS (APCI-TOF) m/z: $[M]^{-\cdot}$ Calcd for $C_{12}H_{10}F_2O_2$ 224.0649; Found 224.0640.

1-(3,3-difluorocycloprop-1-en-1-yl)-4-nitrobenzene (1h)

This compound was prepared from (*p*-ethynyl)nitrobenzene **1h'** and purified by silica-gel column chromatography

(hexane/EtOAc/NEt_3 = 40/2/1) as a brown solid (20% yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, 2H, *J* = 8.8 Hz), 7.83 (d, 2H, *J* = 8.7 Hz), 7.77 (t, 1H, *J* = 1.3 Hz); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 149.4 (s), 132.5 (t, J_{C-F} = 11.1 Hz), 130.9 (s), 129.0 (s), 124.3 (s), 118.3 (t, J_{C-F} = 12.2 Hz), 100.5 (t, J_{C-F} = 270.1 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.5 (s, 2F); FT-IR (neat, cm^{-1}) 3115, 1717, 1601, 1520, 1347, 1319, 1305, 1286, 1022, 817, 745; HRMS (APCI-TOF) m/z: $[M]^{-\cdot}$ Calcd for $C_9H_5F_2N_1O_2$ 197.0288; Found 197.0279.

1-(3,3-difluorocycloprop-1-en-1-yl)-3-methoxybenzene (1j)
This compound was prepared from (*m*-ethynyl)methoxybenzene **1j'** and purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/1/1) as a yellow liquid (79% yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, 1H, *J* = 1.7 Hz), 7.39 (t, 1H, *J* = 7.9 Hz), 7.25 (d, 1H, *J* = 7.5 Hz), 7.15 (t, 1H, *J* = 1.9 Hz), 7.05 (ddd, 1H, *J* = 8.3, 2.6, 0.9 Hz), 3.85 (s, 3H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 159.9 (s), 134.0 (t, J_{C-F} = 10.5 Hz), 130.1 (s), 124.4 (s), 122.5 (s), 117.9 (s), 114.7 (s), 113.7 (t, J_{C-F} = 12.3 Hz), 101.7 (t, J_{C-F} = 268.4 Hz), 55.4 (s); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.3 (s, 2F); FT-IR (neat, cm^{-1}) 3131, 2965, 2944, 2840, 1720, 1598, 1582, 1484, 1304, 1273, 1212, 1181, 1019, 808, 785, 686; HRMS (APCI-TOF) m/z: $[M]^{-\cdot}$ Calcd for $C_{10}H_8F_2O_1$ 182.0543; Found 182.0548.

1-(3,3-difluorocycloprop-1-en-1-yl)-2-methoxybenzene (1k)
This compound was prepared from (*o*-ethynyl)methoxybenzene **1k'** and purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/1/1) as a yellow liquid (65% yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, 1H, *J* = 7.5, 1.7 Hz), 7.50-7.44 (m, 1H), 7.42 (t, 1H, *J* = 2.0 Hz), 7.03 (td, 1H, *J* = 7.5, 0.7 Hz), 6.98 (d, 1H, *J* = 8.4 Hz), 3.93 (s, 3H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 159.3 (s), 133.4 (s), 131.9 (s), 130.0 (s), 120.6 (s), 113.7 (t, J_{C-F} = 12.4 Hz), 112.4 (s), 111.1 (s), 101.2 (t, J_{C-F} = 267.8 Hz), 55.7 (s); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -105.3 (s, 2F); FT-IR (neat, cm^{-1}) 3135, 2944, 2842, 1724, 1598, 1489, 1466, 1306, 1273, 1164, 1023, 825, 784, 755, 729; HRMS (APCI-TOF) m/z: $[M]^{-\cdot}$ Calcd for $C_{10}H_8F_2O_1$ 182.0543; Found 182.0551.

3-(3,3-difluorocycloprop-1-en-1-yl)quinolone (1l)
This compound was prepared from 3-ethynylquinolone **1l'** and purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/2/1) as a yellow solid (28% yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (d, 1H, *J* = 2.1 Hz), 8.44 (d, 1H, *J* = 1.8 Hz), 8.16 (d, 1H, *J* = 8.5 Hz), 7.91 (d, 1H, *J* = 8.2 Hz), 7.86-7.80 (m, 1H), 7.71 (t, 1H, *J* = 1.5 Hz), 7.67-7.61 (m, 1H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 149.9 (s), 148.9 (s), 138.0 (s), 131.7 (t, J_{C-F} = 11.0 Hz), 131.7 (s), 129.6 (s), 128.6 (s), 127.8 (s), 127.2 (s), 116.7 (s), 115.6 (t, J_{C-F} = 12.3 Hz), 100.8 (t, J_{C-F} = 269.5 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.5 (s, 2F); FT-IR (neat, cm^{-1}) 3140, 1720, 1570, 1495, 1286, 995, 982, 914, 802, 789, 771, 752, 583; HRMS (APCI-TOF) m/z: $[M]^{-\cdot}$ Calcd for $C_{12}H_7F_2N_1$ 203.0547; Found 203.0553.

2-(3,3-difluorocycloprop-1-en-1-yl)-6-methoxynaphthalene (1a)[41]
This compound was prepared from 2-ethynyl-6-methoxynaphthalene **1a'** and purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/1/1) as a yellow solid (74% yield). The following data are identical to those in the literature.[41]
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.82 (d, 2H, *J* = 8.7 Hz), 7.65 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.46 (t, 1H, *J* = 1.8 Hz), 7.22 (dd, 1H, *J* = 8.9, 2.5 Hz), 7.16 (d, 1H, *J* = 2.4 Hz), 3.95 (s, 1H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.3 (s, 2F).

(3,3-difluorocycloprop-1-en-1-yl)benzene (1d)[41]
This compound was prepared from phenylethyne **1d'** and purified by silica-gel column chromatography (hexane/NEt_3 = 40/1) as a brown liquid (61% yield). The following data are identical to those in the literature.[41]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.65 (m, 2H), 7.51-7.46 (m, 4H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.5 (s, 2F).

1-(3,3-difluorocycloprop-1-en-1-yl)-4-methoxybenzene (1i)[4g]
This compound was prepared from (*p*-ethynyl)methoxybenzene **1i'** and purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/1/1) as a yellow liquid (65% yield). The following data are identical to those in the literature.[4g]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* = 8.8 Hz), 7.28 (t, 1H, *J* = 1.9 Hz), 6.99 (d, 2H, *J* = 8.8 Hz), 3.87 (s, 3H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -106.4 (s, 2F).

(3,3-difluoro-2-phenylcycloprop-1-en-1-yl)methyl acetate (1m)[41]
This compound was prepared from 3-phenyl-2-propyl acetate **1m'**[17] and purified by silica-gel column chromatography (hexane/EtOAc/NEt_3 = 40/1/1) as a yellow solid (88% yield). The following data are identical to those in the literature.[41]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.49-7.47 (m, 3H), 5.19 (t, 2H, *J* = 2.7 Hz), 2.22 (s, 3H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -108.0 (s, 2F).

General Procedure for Hydrocupration of Difluorocyclopropene
Procedure A
To a mixture of $Cu(OAc)_2 \cdot H_2O$ (1.0 mg, 0.005 mmol) and Walphos (3.5 mg, 0.006 mmol) was added toluene (1.0 mL) at room temperature in a test tube, and the solution was stirred for 2 h. Difluorocyclopropene **1** (0.1 mmol), PMHS (26 μL, 0.4 mmol) and *i*-PrOH (15 μL, 0.2 mmol) were added to the reaction mixture at room temperature. The solution was warmed up to 60 °C in an oil bath and stirred for 40 h. The solvent was removed under reduced pressure, and the yield of crude product was determined by ^{19}F NMR analysis using BTF as an internal standard. The crude product was purified by silica-gel column chromatography to give corresponding difluorocyclopropane **2**. Enantiomer ratio was determined by chiral HPLC analysis.
Procedure B
To a mixture of $Cu(OAc)_2 \cdot H_2O$ (1.0 mg, 0.005 mmol) and phosphoramidite **L** (5.7 mg, 0.010 mmol) was added toluene (1.0 mL) at room temperature in a test tube, and the solution was stirred for 2 h. Difluorocyclopropene **1** (0.1 mmol), PMHS (26 μL, 0.4 mmol) and *i*-PrOH (15 μL, 0.2 mmol) were added to the reaction mixture at room temperature. The solution was stirred for at room temperature. The solvent was removed under reduced pressure, and the yield of crude product was determined by ^{19}F NMR analysis using BTF as an internal standard. The crude product was purified by silica-gel column chromatography to give corresponding difluorocyclopropane **2**. Enantiomer ratio was determined by chiral HPLC analysis.

2-(2,2-difluorocyclopropyl)-6-methoxynaphthalene (2a)
Procedure A
This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a white solid (18.7 mg, 81% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 (dd, 2H, J = 8.5, 2.6 Hz), 7.61 (s, 1H), 7.31 (dd, 1H, J = 8.5, 1.6 Hz), 7.17-7.12 (m, 2H), 3.92 (s, 3H), 2.89 (td, 1H, $J_{H\text{-}F}$ = 12.3 Hz, J = 8.2 Hz), 1.93-1.81 (m, 1H), 1.77-1.68 (m, 1H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 157.7 (s), 133.7 (s), 129.1 (s), 128.8 (s), 128.7 (s), 127.0 (s), 126.7 (s), 119.1 (s), 112.8 (dd, $J_{C\text{-}F}$ = 285.1, 285.1 Hz), 105.6 (s), 55.3 (s), 27.2 (t, $J_{C\text{-}F}$ = 11.4 Hz), 17.0 (t, $J_{C\text{-}F}$ = 10.4 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -125.7 (dt, 1F, $J_{F\text{-}F}$ = 153.4 Hz, $J_{F\text{-}H}$ = 12.8 Hz), -142.1 (d, 1F, $J_{F\text{-}F}$ = 151.6 Hz); FT-IR (neat, cm^{-1}) 2968, 1606, 1465, 1305, 1268, 1209, 1160, 1032, 932, 904, 856, 818, 708; HRMS (APCI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}F_2O_1$ 235.0935; Found 235.0934. $[\alpha]_D^{21}$ -37.3 (*c* 1.00, $CHCl_3$), 84% *ee*. HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 90/10, flow rate 1.0 mL/min, 22 °C detection UV 230 nm) t_R of major isomer 29.3 min, t_R of minor isomer 48.3 min.

2-(2,2-difluorocyclopropyl)naphthalene (2b)[4j]
Procedure A
This compound was purified by silica-gel column chromatography (hexane only) as a white solid (14.9 mg, 73% yield). The following data are identical to those in the literature.[4j] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85-7.80 (m, 3H), 7.70 (s, 1H), 7.53-7.44 (m, 2H), 7.36 (dd, 1H, J = 8.5, 1.5 Hz), 2.92 (td, 1H, $J_{H\text{-}F}$ = 12.3 Hz, J = 8.2 Hz), 1.96-1.84 (m, 1H), 1.82-1.71 (m, 1H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -125.6 (dt, 1F, $J_{F\text{-}F}$ = 153.8 Hz, $J_{F\text{-}H}$ = 12.7 Hz), -142.0 (dd, 1F, $J_{F\text{-}F}$ = 156.7 Hz, $J_{F\text{-}H}$ = 13.8 Hz). $[\alpha]_D^{20}$ -32.8 (*c* 1.00, $CHCl_3$), 86% *ee*. HPLC (column, CHIRALCEL OD-3, Hexane/2-Propanol = 99/1, flow rate 1.0 mL/min, 23 °C detection UV 230 nm) t_R of major isomer 7.4 min, t_R of minor isomer 6.6 min.

1-(2,2-difluorocyclopropyl)naphthalene (2c)
Procedure A
NMR yield (60%) was determined by using BTF as an internal standard. This compound was purified by silica-gel column chromatography (hexane only) as a colorless liquid (6.9 mg, 34% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 8.3 Hz), 7.89 (d, 1H, J = 8.5 Hz), 7.82 (d, 1H, J = 7.9 Hz), 7.63-7.51 (m, 2H), 7.48-7.39 (m, 2H), 3.14 (td, 1H, $J_{H\text{-}F}$ = 12.4 Hz, J = 8.3 Hz), 2.07-1.95 (m, 1H), 1.84-1.73 (m, 1H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 133.5 (s), 133.1 (s), 129.9 (s), 128.6 (s), 128.2 (s), 126.5 (s), 126.0 (s), 125.8 (d, $J_{C\text{-}F}$ = 3.5 Hz), 125.3 (s), 124.1 (s), 113.0 (dd, $J_{C\text{-}F}$ = 283.1, 281.5 Hz), 25.1 (t, $J_{C\text{-}F}$ = 11.3 Hz), 16.3 (t, $J_{C\text{-}F}$ = 10.7 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -126.6 (dt, 1F, $J_{F\text{-}F}$ = 152.0 Hz, $J_{F\text{-}H}$ = 12.6 Hz), -140.2 (dd, 1F, $J_{F\text{-}F}$ = 152.4 Hz, $J_{F\text{-}H}$ = 8.8 Hz); FT-IR (neat, cm^{-1}) 3063, 3016, 1472, 1371, 1304, 1241, 1209, 1095, 1022 954, 930, 800, 777; HRMS (APCI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{11}F_2$ 205.0837; Found 205.0829. $[\alpha]_D^{21}$ -19.9 (*c* 0.59, $CHCl_3$), 74% *ee*. HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 98/2, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 6.6 min, t_R of minor isomer 7.7 min.

(2,2-difluorocyclopropyl)benzene (2d)[4f]
Procedure A
NMR yield (88%) was determined by using BTF as an internal standard. This compound was purified by silica-gel column chromatography (pentane only) as a colorless liquid (7.6 mg, 49% yield). The following data are identical to those in the literature.[4f] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42-7.26 (m, 5H), 2.85-2.74 (m, 1H), 1.92-1.80 (m, 1H), 1.72-1.64 (m, 1H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -125.8 (dt, 1F, $J_{F\text{-}F}$ = 154.0 Hz, $J_{F\text{-}H}$ = 12.9 Hz), -142.4 (dd, 1F, $J_{F\text{-}F}$ = 156.6 Hz, $J_{F\text{-}H}$ = 13.7 Hz). $[\alpha]_D^{21}$ -26.0 (*c* 0.77, $CHCl_3$), 82% *ee*. HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 99/1, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 7.1 min, t_R of minor isomer 7.5 min.

1-chloro-4-(2,2-difluorocyclopropyl)benzene (2e)[20]
Procedure A
This compound was purified by silica-gel column chromatography (hexane only) as a colorless liquid (16.8 mg, 89% yield). The following data are identical to the literature data.[20] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (d, 2H, J = 8.5 Hz), 7.16 (d, 2H, J = 8.6 Hz), 2.72 (td, 1H, $J_{H\text{-}F}$ = 12.2 Hz, J = 8.0 Hz), 1.90-1.78 (m, 1H), 1.64-1.53 (m, 1H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -126.1 (dt, 1F, $J_{F\text{-}F}$ = 154.3 Hz, $J_{F\text{-}H}$ = 12.7 Hz), -142.2 (d, 1F, $J_{F\text{-}F}$ = 152.1 Hz). $[\alpha]_D^{21}$ -21.9 (*c* 0.46, $CHCl_3$), 90% *ee*. HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 99/1, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 7.6 min, t_R of minor isomer 7.1 min.

Ethyl 4-(2,2-difluorocyclopropyl)benzoate (2f)
Procedure A
This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a colorless liquid (18.1 mg, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00 (d, 2H, J = 8.4 Hz), 7.28 (d, 2H, J = 8.5 Hz), 4.37 (q, 2H, J = 7.1 Hz), 2.79 (td, 1H, $J_{H\text{-}F}$ = 12.1 Hz, J = 8.2 Hz), 1.95-1.83 (m, 1H), 1.74-1.63 (m, 1H), 1.39 (t, 3H, J = 7.1 Hz); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 166.3 (s), 138.9 (s), 129.7 (s), 129.5 (s), 127.9 (s), 112.2 (dd, $J_{C\text{-}F}$ = 285.2, 282.5 Hz), 61.0 (s), 27.3 (t, $J_{C\text{-}F}$ = 11.5 Hz), 17.5 (t, $J_{C\text{-}F}$ = 10.5 Hz), 14.3 (s); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -125.6 (dt, 1F, $J_{F\text{-}F}$ = 154.8 Hz, $J_{F\text{-}H}$ = 12.8 Hz), -142.2 (dd, 1F, $J_{F\text{-}F}$ = 150.6 Hz, $J_{F\text{-}H}$ = 9.2 Hz); FT-IR (neat, cm^{-1}) 2978, 1718, 1614, 1468, 1277, 1234, 1186, 1107, 1041, 935, 755, 709; HRMS (APCI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{13}F_2O_2$ 227.0884; Found 227.0873. $[\alpha]_D^{21}$ -16.4 (*c* 1.57, $CHCl_3$), 88% *ee*. HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 98/2, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 14.3 min, t_R of minor isomer 12.4 min.

Ethyl 2-(2,2-difluorocyclopropyl)benzoate (2g)
Procedure A
This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a colorless liquid (14.5 mg, 64% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99 (dd, 1H, J = 7.7, 1.3 Hz), 7.52-7.47 (m, 1H), 7.39-7.30 (m, 2H), 4.46-4.36 (m, 2H), 3.27 (td, 1H, $J_{H\text{-}F}$ = 11.5 Hz, J = 8.6 Hz), 1.90-1.78 (m, 1H), 1.64-1.53 (m, 1H), 1.41 (t, 3H, J = 7.1 Hz); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 167.1 (s), 134.4 (s), 132.1 (s), 131.7 (s), 130.7 (s), 129.5 (d, $J_{C\text{-}F}$ = 3.0 Hz), 127.5 (s), 112.4 (dd, $J_{C\text{-}F}$ = 284.9 Hz, 280.0 Hz), 61.3 (s), 26.9 (t, $J_{C\text{-}F}$ = 11.2 Hz), 16.4 (t, $J_{C\text{-}F}$ = 10.6 Hz), 14.2 (s); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -126.7 (td, 1F, $J_{F\text{-}F}$ = 154.1 Hz, $J_{F\text{-}H}$ = 12.4 Hz), -140.3 (dd, 1F, $J_{F\text{-}F}$ = 150.1 Hz, $J_{F\text{-}H}$ = 11.9 Hz); FT-IR (neat, cm^{-1}) 2981, 2934, 1466, 1291, 1262, 1229, 1134, 1081, 1024, 725; HRMS (APCI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{13}F_2O_2$ 227.0884; Found 227.0894. $[\alpha]_D^{21}$ -0.67 (*c* 1.19, $CHCl_3$), 68% *ee*. HPLC (column,

CHIRALCEL OD-3 and OD-H, Hexane/2-Propanol = 99/1, flow rate 0.6 mL/min, 20 °C detection UV 220 nm) t_R of major isomer 16.8 min, t_R of minor isomer 17.5 min.

1-(2,2-difluorocyclopropyl)-4-nitrobenzene (2h)[18]
Procedure B
This compound was purified by silica-gel column chromatography (hexane/EtOAc = 10/1) as a white solid (13.7 mg, 69% yield). The following data are identical to those in the literature.[18] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.20 (dt, 2H, J = 9.3, 2.4 Hz), 7.38 (d, 2H, J = 8.8 Hz), 2.84 (td, 1H, J_{H-F} = 12.1 Hz, J = 8.2 Hz), 2.04-1.91 (m, 1H), 1.78-1.67 (m, 1H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 147.1 (s), 141.4 (s), 128.8 (s), 123.7 (s), 111.8 (dd, J_{C-F} = 286.4, 282.0 Hz), 27.1 (t, J_{C-F} = 11.7 Hz), 18.0 (t, J_{C-F} = 10.5 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -125.5 (dt, 1F, J_{F-F} = 155.5 Hz, J_{F-H} = 12.2 Hz), -141.9 (dd, 1F, J_{F-F} = 155.6 Hz, J_{F-H} = 13.3 Hz). $[\alpha]_D^{21}$ -6.16 (*c* 1.29, $CHCl_3$), 42% *ee.* HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 99/1, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 30.3 min, t_R of minor isomer 28.1 min.

1-(2,2-difluorocyclopropyl)-4-methoxybenzene (2i)[4f]
Procedure A
This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a colorless liquid (5.6 mg, 31% yield). The following data are identical to those in the literature.[4f] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.16 (d, 2H, J = 8.8 Hz), 6.87 (dt, 2H, J = 9.6, 2.9 Hz), 3.80 (s, 3H), 2.71 (td, 1H, J_{H-F} = 11.9 Hz, J = 8.1 Hz), 1.84-1.72 (m, 1H), 1.60-1.49 (m, 1H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -126.2 (dt, 1F, J_{F-F} = 153.0 Hz, J_{F-H} = 12.7 Hz), -142.4 (dd, 1F, J_{F-F} = 150.3 Hz, J_{F-H} = 12.5 Hz). $[\alpha]_D^{21}$ -20.5 (*c* 0.27, $CHCl_3$), 64% *ee.* HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 98/2, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 12.5 min, t_R of minor isomer 11.1 min.

1-(2,2-difluorocyclopropyl)-3-methoxybenzene (2j)
Procedure A
NMR yield (83%) was determined by using BTF as an internal standard. This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27-7.25 (m, 1H), 6.84-6.77 (m, 3H), 3.81 (s, 3H), 2.73 (td, 1H, J_{H-F} = 13.1 Hz, J = 8.2 Hz), 1.87-1.75 (m, 1H), 1.67-1.59 (m, 1H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 159.7 (s), 135.2 (s), 129.4 (s), 120.4 (s), 114.0 (s), 112.5 (t, J_{C-F} = 283.7 Hz), 112.5 (s), 55.2 (s), 27.2 (t, J_{C-F} = 11.4 Hz), 17.0 (t, J_{C-F} = 10.5 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -125.7 (dt, 1F, J_{F-F} = 153.6 Hz, J_{F-H} = 12.6 Hz), -142.2 (dd, 1F, J_{F-F} = 151.4 Hz, J_{F-H} = 8.4 Hz); FT-IR (neat, cm^{-1}) 2972, 2937, 1604, 1494, 1469, 1268, 1219, 1158, 1136, 1091, 1041, 905, 847, 778; HRMS (APCI-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{11}F_2O_1$ 185.0778; Found 185.0780. $[\alpha]_D^{21}$ -23.4 (*c* 0.88, $CHCl_3$), 70% *ee.* HPLC (column, CHIRALCEL OD-3, Hexane/2-Propanol = 99/1, flow rate 0.8 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 12.6 min, t_R of minor isomer 13.2 min.

1-(2,2-difluorocyclopropyl)-2-methoxybenzene (2k)[20]
Procedure A
NMR yield (67%) was determined by using BTF as an internal standard. This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a colorless liquid. The following data are identical to those in the literature.[20] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29-7.23 (m, 1H), 7.11-7.09 (m, 1H), 6.95-6.88 (m, 2H), 3.87 (s, 3H), 2.92-2.81 (m, 1H), 1.84-1.72 (m, 1H), 1.62-1.52 (m, 1H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -126.9 (dt, 1F, J_{F-F} = 151.9 Hz, J_{F-H} = 12.9 Hz), -142.1 (d, 1F, J_{F-F} = 150.0 Hz). $[\alpha]_D^{21}$ -20.1 (*c* 0.58, $CHCl_3$), 80% *ee.* HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 98/2, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 5.9 min, t_R of minor isomer 6.6 min.

3-(2,2-difluorocyclopropyl)quinolone (2l)
Procedure A
This compound was purified by silica-gel column chromatography (hexane/EtOAc = 5/1) as a brown solid (16.5 mg, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.10 (d, 1H, J = 8.5 Hz), 7.96 (s, 1H), 7.79 (dd, 1H, J = 8.1, 1.1 Hz), 7.73-7.68 (m, 1H), 7.58-7.53 (m, 1H), 2.92 (td, 1H, J_{H-F} = 12.1 Hz, J = 8.1 Hz), 2.05-1.93 (m, 1H), 1.82-1.71 (m, 1H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 151.0 (s), 147.3 (s), 134.2 (t, J_{C-F} = 1.8 Hz), 129.4 (s), 129.3 (s), 127.6 (s), 127.5 (s), 127.0 (s), 126.9 (s), 112.1 (dd, J_{C-F} = 285.9, 282.0 Hz), 24.9 (t, J_{C-F} = 11.7 Hz), 17.3 (t, J_{C-F} = 10.6 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -126.2 (dt, 1F, J_{F-F} = 154.5 Hz, J_{F-H} = 11.9 Hz), -141.5 (d, 1F, J_{F-F} = 155.1 Hz); FT-IR (neat, cm^{-1}) 3063, 3016, 1495, 1473, 1366, 1305, 1222, 1018, 955, 910, 787, 754; HRMS (APCI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{10}F_2N_1$ 206.0788; Found 206.0781. $[\alpha]_D^{21}$ -27.2 (*c* 1.25, $CHCl_3$), 90% *ee.* HPLC (column, CHIRALCEL OD-3, Hexane/2-Propanol = 98/2, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 33.7 min, t_R of minor isomer 37.4 min.

(2,2-difluoro-3-phenylcyclopropyl)methyl acetate (2m)[21]
Procedure B
Use of H_8-BINAP as a ligand. The reaction mixture was warmed up to 60 °C in an oil bath. This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a colorless liquid (16.7 mg, 74% yield). The following data are identical to those in the literature.[21] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 (br, 5H), 4.15-4.07 (m, 1H), 3.89-3.82 (m, 1H), 3.01 (t, 1H, J_{H-F} = 12.9 Hz), 2.36-2.22 (m, 1H), 2.04 (s, 3H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -121.8 (dt, 1F, J_{F-F} = 160.8, J_{F-H} = 13.4 Hz), -147.6 (d, 1F, J_{F-F} = 162.1 Hz). $[\alpha]_D^{21}$ -24.1 (*c* 1.43, $CHCl_3$). HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 95/5, flow rate 1.0 mL/min, 20 °C detection UV 210 nm) t_R of major isomer 9.4 min, t_R of minor isomer 8.8 min, 72% *ee*.

2-(2,2-difluorocyclopropyl-1-d)-6-methoxynaphthalene (2a-D)
Procedure A
Use of $Cu(OAc)_2$ as a catalyst and MeOD instead of *i*-PrOH. NMR yield (62%, 55% D) was determined by using BTF as an internal standard. This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 (dd, 2H, J = 8.4, 2.5 Hz), 7.61 (s, 1H), 7.31 (dd, 1H, J = 8.4, 1.1 Hz), 7.17-7.12 (m, 2H), 3.92 (s, 3H), 1.93-1.81 (m, 1H), 1.78-1.68 (m, 1H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -126.0 (dd, 1F, J_{F-F} = 154.0, J_{F-H} = 12.2 Hz), -142.3 (dd, 1F, J_{F-F} =151.9, J_{F-H} = 10.5 Hz).

2,2-difluoro-3-phenylcyclopropyl-3-d)methyl acetate (2m-D)
Procedure B
Use of $Cu(OAc)_2$ as a catalyst and MeOD instead of *i*-PrOH.

NMR yield (68%, 62% D) was determined by using BTF as an internal standard. This compound was purified by silica-gel column chromatography (hexane/EtOAc = 20/1) as a colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 (s, 5H), 4.15-4.07 (m, 1H), 3.90-3.83 (m, 1H), 2.31-2.26 (m, 1H), 2.04 (s, 3H); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -121.9 (dd, 1F, J_{F-F} = 161.9, J_{F-H} = 12.2 Hz), -147.8 (d, 1F, J_{F-F} = 163.3 Hz).

Typical Procedure C : Hydroboration of Difluorocyclopropene

To a mixture of CuCl (1.0 mg, 0.01 mmol), ligand **L** (0.012 mmol) and NaO^{t}Bu (5.9 mg, 6.0 mmol) was added Et_2O (1.0 mL) at room temperature in a test tube, and the solution was stirred for 1 h. HBPin (17.3 μL, 0.12 mmol) were added to the reaction mixture at room temperature, and the solution was stirred for 10 min. Difluorocyclopropene **1a** (0.1 mmol) were added to the reaction mixture at room temperature. The solution was warmed up to 60 °C in an oil bath and stirred for 48 h. The solvent was removed under reduced pressure, and the yield of crude product was determined by ^{19}F NMR analysis using BTF as an internal standard. The crude product was purified by silica-gel column chromatography to give corresponding difluorocyclopropane**.**

Typical procedure D : Boracupration of difluorocyclopropene

To a mixture of CuCl (1.0 mg, 0.01 mmol), ligand **L** (0.01 mmol) and NaO^{t}Bu (2.0 mg, 2.0 mmol) was added toluene (1.0 mL) at room temperature in a test tube, and the solution was stirred for 30 min. Difluorocyclopropene **1a** (0.1 mmol), B_2Pin_2 (30.5 mg, 0.12 mmol) and MeOH (8.4 μL, 0.2 mmol) were added to the reaction mixture at room temperature, and the solution was stirred for 24 h at room temperature. The solvent was removed under reduced pressure, and the yield of crude product was determined by ^{19}F NMR analysis using BTF as an internal standard. The crude product was purified by silica-gel column chromatography to give corresponding difluorocyclopropane.

2-(2,2-difluoro-1-(6-methoxynaphthalen-2-yl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3a)

Procedure D

This compound was purified by silica-gel column chromatography (hexane/CH_2Cl_2 = 2/1) as a white solid (mp 139-143℃, 19.1 mg, 53%). **^{1}H NMR** (300 MHz, $CDCl_3$)) δ 7.70 (s, 1H), 7.67 (s, 1H), 7.63 (s, 1H), 7.40 (dd, 1H, J = 8.4, 1.8 Hz), 7.14-7.11 (m, 2H), 3.91 (s, 3H), 2.12 (ddd, 1H, J_{H-F} = 10.9, 4.9 Hz, J = 6.3 Hz), 1.79 (ddd, 1H, J_{H-F} = 11.9, 2.6 Hz, J = 6.7 Hz), 1.24 (s, 6H), 1.19 (s, 6H); **^{11}B NMR** (96 MHz, $CDCl_3$) δ 30.9 (brs.); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 157.5 (s), 133.4 (s), 131.5 (s), 129.2 (s), 128.9 (s), 128.5 (d, J = 1.8 Hz), 127.3 (d, J = 2.8 Hz), 126.7 (s), 118.7 (s), 105.6 (s), 84.4 (s), 77.2 (s), 55.3 (s), 24.7 (s), 24.4 (s), 20.7 (t, J = 9.9 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -125.1 (dd , J = 143.3, 9.5 Hz), -131.9~-132.5 (m); HRMS (APCI+) m/z: $[M+H]^+$ Calcd for $C_{20}H_{24}B_1F_2O_3$ 361.17866; Found 361.18214. HPLC (column, CHIRALCEL AS-H and AD-3, Hexane/2-Propanol = 97/3, flow rate 1.0 mL/min, 22 ℃ detection UV 230 nm) t_R of major isomer 9.307 min, t_R of minor isomer 98.720 min, 82% *ee*.

Typical Procedure E : Cu-catalyzed Methylation of Difluorocyclopropene

To a mixture of CuTC (1.0 mg, 0.005 mmol) and BTFM-Garphos (7.1 mg, 0.006 mmol) was added CH_2Cl_2 (1.0 mL) at room temperature in a test tube, and the solution was stirred for 2 h. The solvent was removed under reduced pressure, and the prepared catalyst was dissolved in THF (1.0 mL). Difluorocyclopropene **1** (23.2 mg, 0.1 mmol) was added to the solution. After the solution was cooled to 0 °C, $ZnMe_2$ (1.0 M in heptane, 150 μL, 0.15 mmol) was added in one portion. The reaction mixture was stirred at the same temperature for 2 h. The resulting mixture was quenched with 1N HCl (1 mL) at 0 °C. Et_2O (10 mL) and 1N HCl (10 mL) were added, the organic layer was separated and the aqueous layer was extracted with Et_2O (10 mL) twice. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The yield of crude product was determined by ^{19}F NMR analysis using BTF as an internal standard. The crude product was purified by silica-gel column chromatography (hexane/EtOAc = 30/1). Enantiomer ratio was determined by chiral HPLC analysis.

2-(2,2-difluoro-1-methylcyclopropyl)-6-methoxynaphthalene (5a)

Procedure E

This compound was purified by silica-gel column chromatography (hexane/EtOAc = 30/1) as a white solid (13.9 mg, 56% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74-7.69 (m, 3H), 7.40 (dd, 1H, J = 8.5, 1.8 Hz), 7.17-7.12 (m, 2H), 3.92 (s, 3H), 1.82-1.73 (m, 1H), 1.59-1.57 (m, 3H), 1.50-1.42 (m, 1H); **^{13}C{H} NMR** (75 MHz, $CDCl_3$) δ 157.7 (s), 134.2 (t, J_{C-F} = 2.2 Hz), 133.6 (s), 129.2 (s), 128.8 (s), 127.1 (s), 127.0 (d, J_{C-F} = 1.7 Hz), 126.8 (d, J_{C-F} = 2.4 Hz), 119.0 (s), 114.8 (dd, J_{C-F} = 287.7, 285.4 Hz), 105.6 (s), 55.3 (s), 31.2 (t, J_{C-F} = 10.2 Hz), 22.6 (t, J_{C-F} = 9.9 Hz), 21.4 (dd, J_{C-F} = 6.2, 1.7 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -132.5 (dd, 1F, J_{F-F} =150.0 Hz, J_{F-H} = 12.9 Hz), -137.3 (dd, 1F, J_{F-F} =128.8 Hz, J_{F-H} = 11.1 Hz); FT-IR (neat, cm^{-1}) 2966, 2940, 1608, 1469, 1448, 1256, 1201, 1163, 1029, 1004, 852, 821, 677; HRMS (APCI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{15}F_2O_1$ 249.1091; Found 249.1091. $[\alpha]_D^{20}$ +24.2 (*c* 0.90, $CHCl_3$), 60% *ee*. HPLC (column, CHIRALCEL OJ-3, Hexane/2-Propanol = 99/1, flow rate 1.0 mL/min, 20 °C detection UV 230 nm) t_R of major isomer 25.7 min, t_R of minor isomer 30.0 min.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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