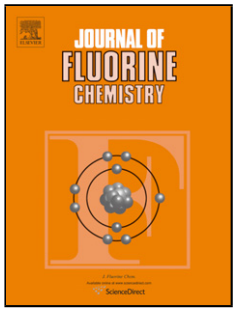

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Copper-catalyzed allylic difluoromethylation of allyl carbonates with (difluoromethyl)zinc reagent

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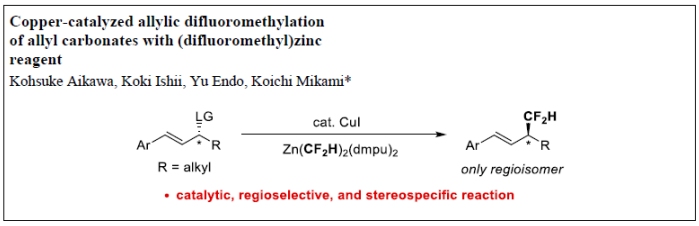
Graphical abstract



Highlights

- The catalytic allylic difluoromethylation of allyl carbonates with (difluoromethyl)zinc reagent in the presence of copper catalyst was achieved.
- (Difluoromethyl)zinc reagent can be readily prepared via iodine-zinc exchange reaction of difluoroiodomethane with diethylzinc.
- The catalytic reaction proceeded with not only good-to-high yields but also complete regioselectivity.
- The catalytic reaction was found to be stereospecific, and hence chiral allylic difluoromethylated compound can be obtained by treatment of chiral substrates.

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ABSTRACT
The catalytic allylic difluoromethylation of allyl carbonates with (difluoromethyl)zinc reagent, which can be readily prepared via iodine-zinc exchange reaction of difluoroiodomethane with diethylzinc, was achieved by employing copper salt as a catalyst. The difluoromethylation proceeded with not only good-to-high yields but also complete regioselectivity. Furthermore, the reaction was demonstrated to be stereospecific, and hence chiral allylic difluoromethylated compound can be obtained by treatment of chiral substrates which are synthesized through catalytic asymmetric hydrogenation of α,β-unsaturated carbonyl compounds

Keywords:organofluorine chemistry bioisosteric effect difluoromethyl group difluoromethylation allylic substitution

1. Introduction

Huge successes of fluorine-containing drugs continue to stimulate research on fluorine in medicinal chemistry directed toward drug discovery [1]. Therefore, various fluorinated functional groups are of great interest in the field of pharmaceuticals and agrichemicals [1-2]. Particularly, difluoromethyl (CF_2H) group as a lipophilic hydrogen-bonding donor has attracted quite recent attention, due to bioisosteric nature of alcohols [3]. As a conventional synthetic method, it is widely known that difluoromethylated compounds can be prepared by deoxofluorination of aldehydes by treatment of *N*,*N*-diethylaminosulfur trifluoride (DAST) or its derivatives [4]. However, there is a possibility that the reaction undergoes explosive decomposition upon heating in large scale operation. Therefore, the direct introduction of difluoromethyl group via carbon-carbon bond forming reaction has recently been desired instead of functional group transformation [3e]. As practical and reliable cross-coupling reactions, in particular, the development of transition metal-catalyzed direct difluoromethylations with (difluoromethyl)metal reagents (MCF_2H) is essential in the field of synthetic organofluorine chemistry. In fact, the first catalytic aromatic difluoromethylation with (difluoromethyl)silicone reagent ($TMSCF_2H$) as the cooperative dual palladium/silver catalyst system has been described by Shen group in 2014 [5-6]. Quite recently, Vicic group has succeeded in the nickel-catalyzed aromatic difluoromethylation with $Zn(CF_2H)_2(dmpu)_2$ as a (difluoromethyl)zinc reagent [7] (Scheme 1a). At the same time, our group has independently disclosed the copper- and palladium-catalyzed aromatic difluoromethylations by employment of $Zn(CF_2H)_2(dmpu)_2$ and $Zn(CF_2H)_2(tmeda)$ reagents, respectively [8] (Scheme 1a). On the other hand, the direct difluoromethylation on sp^3 carbon with (difluoromethyl)metal reagents has so far been limited. As a sole single report, Burton group clarified that $Zn(CF_2H)X$ or $Cd(CF_2H)X$ underwent the allylic difluoromethylation of allyl halides without a catalyst, but a mixture of regioisomer was obtained [9] (Scheme 1b). Furthermore, $CuCF_2H$ prepared *in situ* via transmetalation from $Cd(CF_2H)X$ was also found to facilitate the same reaction to give only liner product [9]. However, there is no report on the copper-catalyzed allylic difluoromethylation [10]. Herein, we describe the first copper-catalyzed allylic difluoromethylation of allyl carbonates with (difluoromethyl)zinc reagent which possesses the complete regioselectivity and stereospecificity [11] (Scheme 1c).

2. Results and discussion

Initially, the catalytic difluoromethylation of cinnamyl chloride **1a** with $Zn(CF_2H)_2(dmpu)_2$ [8] as a difluoromethyl source was examined in the presence of 10 mol% copper iodide (Table 1). The reaction in DMF at -20 °C proceeded to give the products **2a** and **2a'** as regioisomers in 81% and 19% yields, which can be obtained via substitution in the α- and γ-positions, respectively (entry 1). It was confirmed that no reaction without copper salt occurred at -20 °C (entry 2). With the aim of enhancing γ-regioselectivity, the effect of counteranion and ligand was investigated (entries 3-11). Although employment of $CuBr(SMe_2)$, CuCl, $CuOTf(toluene)_{1/2}$, CuTC, and CuCN instead of CuI led to increase α-regioselectivity, the reaction in the presence of CuOAc was found to enhance γ-regioselectivity to furnish the products **2a** and **2a'** in 31% and 33% yields, respectively (entries 3-7 vs. 8). Moreover, the addition of ligand to copper catalyst did not sufficiently produce a desired effect on γ-regioselectivity, but the branch product **2a'** (40% and 47% yields) was obtained preferentially by treatment of NHC liagnds (**L2-3**), compared to phosphoramidate (**L1**) (entries 9-11).

Encouraged by the efficient reactivity on the sp^3 carbon, we next attempted to develop the α-regioselective allylic difluoromethylation depending on the leaving group (Table 2). Fortunately, substrates **3a** and **4a** bearing phosphate ester and carbonate as leaving groups also underwent the reaction to give single regioisomer **2a** in about 60% yields, in spite of decreasing of the reactivity (entries 1 *vs*. 2-3). No reaction of **4a** without CuI proceeded at room temperature, and even at 40 °C (entries 4 and 9). The introduction of acetate as a leaving group extremely decreased the reactivity to give almost no product (entry 5). Furthermore, the use of DMPU instead of DMF and higher reaction temperature (40 °C) led to the best yield (90%) with shorter reaction time (24 h) (entry 8).

To extend the scope of substrates, the difluoromethylation of various allyl carbonates (**4**) was further examined under the optimized reaction conditions in hand (Table 3). Significantly, benzyl group instead of methyl group in **4b** exhibited the good

result (**2c**: 80% yield), while 3.4 equivalents of zinc reagent was necessary. Allyl carbonates (**4d-f**) bearing aromatic ring with chlorine in the *ortho*, *meta*, *para*-positions gave the excellent results without deleterious steric and electric effects (**2d-f**: 94-97% yields). Electron-withdrawing and -donating substituents in the *para*-position of the aromatic ring also underwent the desired reaction to provide the corresponding products in good-to-excellent yields (**2g-k**: 71-99% yields). Moreover, substrates (**4l-m**) with backbone such as pyridine and naphthyl groups gave good yields (**2l-m**: 74-79% yields). Importantly, the transformation of alphatic substrate (**4n**) with cyclohexyl group took place without deteriorating effect on the regioselectivity to afford **2n** as an only regioisomer in 84% yield. It is supposed that the complete regioselectivity originates from steric difference between cyclohexyl and methyl substituents.

To get insight of regioselectivity on the reaction, **4a'** and **4b'** which possess the leaving group in benzyl position were employed under the same reaction conditions, and consequently **2a** and **2b** were obtained as single regioisomers in 97% yields, respectively (Scheme 2, Eq. 1). It was clarified that the reductive elimination of copper(III) species in the benzyl position cannot be caused under the same reaction conditions, because allyl carbonate **4o** did not undergo the reaction at all (Scheme 2, Eq. 2). Significantly, the allylic difluoromethylation was also found to proceed via the stereospecific manner. Treatment of optically active substrate (*R*)-**4b** (91% *ee*) thus led to the allylic difluoromethylated product (*S*)-**4b** (90% *ee*) in 87% yield through the total inversion of stereochemistry (Scheme 2, Eq. 3).

After hydrogenation of **2b** by treatment of Pd/C to provide alkylated product **10** (Scheme 3b), the absolute configuration at the created carbon center of **2b** were determined to be the *S* in comparison with the optical rotation of (*R*)-**10** obtained by the synthetic method in the previous report [12] (Scheme 3a). According to the previous report, the catalytic asymmetric hydrogenation of **6** in the presence of $[RuCl_2(p\text{-cymene})]_2$ and (*R*)-MeO-BIPHEP followed by reduction of the carboxylic acid (*R*)-**7** by $LiAlH_4$ provided the corresponding alcohol (*R*)-**8** [12]. Deoxofluorination of aldehyde (*R*)-**9**, which was obtained by treatment of DMP to (*R*)-**8**, with DAST led to difluoromethylated product (*R*)-**10** in a 70% *ee*.

Based on the above-mentioned results, the proposed catalytic cycle is visualized in Scheme 4 [10]. At first, transmetalation of the difluoromethyl group from $Zn(CF_2H)_2(dmpu)_2$ to copper salt triggers the catalytic reaction to generate the cuprate $[Cu(CF_2H)X]^-$ [8]. Oxidative addition of allyl carbonate (*R*)-**4b** to cuprate leads to the formation of π-allyl copper(III) species which occurs with inversion of configuration. It is proposed that zinc(II) cation as a Lewis acid facilitates oxidative addition via coordination to carbonate moiety. Finally, reductive elimination of copper(III) complex closes the catalytic cycle to afford the allylic difluoromethylated product (*S*)-**2b** with not only complete regioselectivity but also total inversion of configuration from the chiral substrate (*R*)-**4b**.

3. Conclusions

We have succeeded in the first copper-catalyzed allylic difluoromethylation of allyl carbonates with (difluoromethyl)zinc reagent to give the corresponding allylic difluoromethylated products in good-to-excellent yields. The reaction took place with complete regioselectivity and stereospecificity to afford chiral difluoromethyl product by employing chiral allyl carbonate, which can be readily prepared through catalytic asymmetric hydrogenation of α,β-unsaturated carbonyl compounds. Development of catalytic enantioselective allylic difluoromethylation is actively in progress in our laboratory.

4. Experimental

4.1. General

^{1}H, ^{13}C, and ^{19}F NMR spectra were measured with a Bruker AV300M (300 MHz) spectrometer. ^{1}H NMR spectra were calibrated using the singlet (δ = 7.26 ppm) for $CDCl_3$, and chemical shifts are expressed in parts per million. ^{13}C NMR spectra were calibrated using the central line of the triplet (δ = 77.0 ppm) for $CDCl_3$, and chemical shifts are expressed in parts per million. ^{19}F NMR data were calibrated using the singlet (δ = -63.24 ppm) for BTF (benzotrifluoride), used as an internal standard, and chemical shifts are expressed in parts per million. Important NMR spectroscopic data are tabulated in the following order: multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet) and coupling constant [*J* (Hz)]. Mass spectra were measured with a JEOL JMS-T100CS (Accu-TOF) spectrometer. IR spectra were measured with a JASCO FTIR-4200 spectrometer. Optical rotations were measured with a JASCO P-1020. High performance liquid chromatography (HPLC) was conducted with 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 CHIRALPAK AD-3 and DAICEL CHIRALCEL OD-3 were used as chiral columns. Column chromatography was carried out on KANTO Silica Gel 60N (spherical, neutral). Dichloromethane (dehydrate), THF (dehydrate), DMF(dehydrate), EtOH (dehydrate), and MeOH (dehydrate) were purchased from Kanto Chemical Co., Inc.. Copper salts and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU, dehydrate) were purchased from Aldrich. Ethyl chloroformate and **1a** were purchased form TCI. Substrates **3a** [13], **4a** [14], **4a'** [14], **4b'** [15], **4c** [16], **4o** [17], and **5a** [18] were synthesized employing published procedure. $Zn(CF_2H)_2(dmpu)_2$ was prepared employing published procedure [8a].

4.2. General procedure for synthesis of allyl carbonate (4)

General Procedure A: The corresponding allyl alcohol (5 mmol) was dissolved in CH_2Cl_2 (15 mL) and pyridine (1.2 mL, 15 mmol) under argon atmosphere. After the solution was cooled to 0 °C, ethyl chloroformate (0.95 mL, 10 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 24 h and quenched with water (15 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (15 mL × 2). The combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by silica-gel column chromatography to give the allyl carbonate **4**.

4.2.1. (*R,E*)-ethyl (4-phenylbut-3-en-2-yl) carbonate [(*R*)-4b]

The titled compound was synthesized from (*R,E*)-4-phenylbut-3-en-2-ol according to General Procedure A. The yield of the compound (90% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (30.9 mg, 85% yield) as a colorless oil. The product was known compound as (*S*)-isomer and ^{1}H NMR data were in good accordance with the previous data [19]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.47 (d, 3H, *J* = 6.5 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 5.32-5.42 (m, 1H), 6.20 (dd, 1H, *J* = 15.9, 7.0 Hz), 6.65 (d, 1H, *J* = 16.0 Hz), 7.22-7.40 (m, 5H); $[\alpha]_D^{23}$ +73.4 (*c* 1.25, $CHCl_3$), 91% *ee*; HPLC (column, CHIRALPAK AD-3, Hexane/2-Propanol = 98/2, flow rate 0.8 mL/min, 20 °C, detection UV 220 nm) t_R of major (*R*)-isomer 7.9 min, t_R of minor (*S*)-isomer 9.4 min.

4.2.2.(*E*)-4-(2-chlorophenyl)but-3-en-2-yl ethyl carbonate (4d)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (939.5 mg, 86% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* = 7.1 Hz), 1.49 (d, 3H, *J* = 6.5 Hz), 4.21 (q, 2H, *J* = 7.1 Hz), 5.36-5.45 (m, 1H), 6.20 (dd, 1H, *J* = 16.0, 6.8 Hz), 7.03 (d, 1H, *J* = 15.9 Hz), 7.25-7.12 (m, 2H), 7.33-7.37 (m, 1H), 7.50-7.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.3, 63.7, 74.5, 126.8, 126.9, 128.0, 128.9, 129.7, 131.1, 133.3, 134.3, 154.4; HRMS (ESI-TOF) calcd for $C_{13}H_{15}ClNaO_3Na$ $[M+Na]^+$: 277.0607, found: 277.0617; FT-IR (neat, cm^{-1}) 752, 1036, 1257, 13721471, 1591, 1743, 2935, 2983, 3063.

4.2.3.(*E*)-4-(3-chlorophenyl)but-3-en-2-yl ethyl carbonate (4e)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (913.1 mg, 87% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* = 7.1 Hz), 1.47 (d, 3H, *J* = 6.5 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 5.31-5.40 (m, 1H), 6.21 (dd, 1H, *J* = 15.6, 6.8 Hz), 6.58 (d, 1H, *J* = 15.9 Hz), 7.21-7.25 (m, 3H), 7.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.3, 63.7, 74.4, 124.8, 126.5, 127.8, 129.7, 129.8, 130.5, 134.4, 133.1, 154.4; HRMS (ESI-TOF) calcd for $C_{13}H_{15}ClNaO_3Na$ $[M+Na]^+$: 277.0607, found: 277.0604; FT-IR (neat, cm^{-1}) 789, 846, 1037, 1258, 1372, 1567, 1742, 2931, 2983.

4.2.4.(*E*)-4-(4-chlorophenyl)but-3-en-2-yl ethyl carbonate (4f)

The titled compound was synthesized according to General Procedure A. urification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (760.5 mg, 88% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.46 (d, 3H, *J* = 6.5 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 5.30-5.38 (m, 1H), 6.17 (dd, 1H, *J* = 16.0, 6.9 Hz), 6.60 (d, 1H, *J* = 16.0 Hz), 7.27-7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.3, 63.7, 74.6, 127.8, 128.7, 128.9, 130.7, 133.5, 134.7, 154.4; HRMS (ESI-TOF) calcd for $C_{13}H_{15}ClNaO_3Na$ $[M+Na]^+$: 277.0607, found: 277.0614; FT-IR (neat, cm^{-1}) 829, 1091, 1258, 1372, 1492, 1593, 1742, 2935, 2983.

4.2.5.(*E*)-4-(4-bromophenyl)but-3-en-2-yl ethyl carbonate (4g)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (686.9 mg, 88% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.46 (d, 3H, *J* = 6.5 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 5.30-5.37 (m, 1H), 6.19 (dd, 1H, *J* = 16.0, 6.9 Hz), 6.58 (d, 1H, *J* = 16.0 Hz), 7.23-7.26 (m, 2H), 7.42-7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 20.3, 63.7, 74.5, 121.7, 128.1, 129.0, 130.7, 131.6, 135.1, 154.4; HRMS (ESI-TOF) calcd for $C_{14}H_{19}BrO_4Na$ $[M+MeOH+Na]^+$: 353.0364, found: 353.0355; FT-IR (neat, cm^{-1}) 733, 1037, 1257, 1372, 1487, 1588, 1741, 2871, 2934, 2982.

4.2.6. (*E*)-ethyl (4-(4-(trifluoromethyl)phenyl)but-3-en-2-yl) carbonate (4h)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (406.2 mg, 74% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* = 7.1 Hz), 1.48 (d, 3H, *J* = 6.5 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 5.34-5.43 (m, 1H), 6.29 (dd, 1H, *J* = 16.0, 6.7 Hz), 6.67 (d, 1H, *J* = 16.0 Hz), 7.47 (d, 2H, *J* = 8.2 Hz), 7.57 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.1, 63.8, 74.3, 124.1 (q, J_{C-F} = 270.0 Hz), 125.4 (q, J_{C-F} = 3.7 Hz), 126.7, 129.6 (q, J_{C-F} = 32.3 Hz), 130.3, 130.9, 139.7, 154.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.7 (s, 3F); HRMS (ESI-TOF) calcd for $C_{14}H_{15}F_3O_3Na$ $[M+Na]^+$: 311.0871, found: 311.0885; FT-IR (neat, cm^{-1}) 833, 1124, 1165, 1259, 1325, 1373, 1616, 1742, 2937, 2985.

4.2.7. (*E*)-ethyl (4-(*p*-tolyl)but-3-en-2-yl) carbonate (4i)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (428 mg, 79% yield) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.46 (d, 3H, *J* = 6.4 Hz), 2.33 (s, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 5.31-5.40 (m, 1H), 6.15 (dd, 1H, *J* = 15.9, 7.1 Hz), 6.62 (d, 1H, *J* = 15.9 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 20.5, 21.2, 63.7, 75.1, 126.6, 127.1, 129.3, 132.2, 133.5, 137.8, 154.5; HRMS (ESI-TOF) calcd for $C_{14}H_{18}O_3Na$ $[M+Na]^+$: 257.1154, found: 257.1160; FT-IR (neat, cm^{-1}) 800, 1036, 1256, 1372, 1514, 1741, 2872, 2933, 2982.

4.2.8. (*E*)-ethyl (4-(4-methoxyphenyl)but-3-en-2-yl) carbonate (4j)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (441 mg, 63% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, *J* = 7.2 Hz), 1.46 (d, 3H, *J* = 6.5 Hz), 3.81 (s, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 5.35 (m, 1H), 6.06 (dd, 1H, *J* = 15.9, 7.2 Hz), 6.60 (d, 1H, *J* = 15.9 Hz), 6.85 (dt, 2H, *J* = 9.6, 2.7 Hz), 7.32 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.5, 55.1, 63.6, 75.2, 114.0, 125.9, 127.9, 128.9, 131.8, 154.5, 159.6; HRMS (ESI-TOF) calcd for $C_{14}H_{18}O_4Na$ $[M+Na]^+$: 273.1103, found: 273.1104; FT-IR (neat, cm^{-1}) 834, 1035, 1252, 1512, 1607, 1740, 2837, 2935, 2982.

4.2.9. (*E*)-4-(benzo[d][1,3]dioxol-5-yl)but-3-en-2-yl ethyl carbonate (4k)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 5/1, 1% Et_3N) gave the desired product (366.6 mg, 53% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.45 (d, 3H, *J* = 6.5 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 5.29-5.38 (m, 1H), 5.95 (s, 2H), 6.02 (dd, 1H, *J* = 15.9, 7.1 Hz), 6.56 (d, 1H, *J* = 15.8 Hz), 6.75 (d, 1H, *J* = 8.0 Hz), 6.82 (dd, 1H, *J* = 8.0, 1.6 Hz), 6.92 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.4, 63.7, 75.0, 101.1, 105.7, 108.2, 121.5, 126.3, 130.6, 131.9, 147.6, 148.0, 154.5; HRMS (ESI-TOF) calcd for $C_{14}H_{16}O_5Na$ $[M+Na]^+$: 287.0895, found: 287.0887; FT-IR (neat, cm^{-1}) 801, 1037, 1251, 1504, 1606, 1739, 2779, 2899, 2982.

4.2.10. (*E*)-ethyl (4-(pyridin-3-yl)but-3-en-2-yl) carbonate (4l)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 2/1, 2% Et_3N) gave the desired product (558.1 mg, 62% yield) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* = 7.1 Hz), 1.48 (d, 3H, *J* = 6.5 Hz), 4.21 (q, 2H, *J* = 7.1 Hz), 5.30-5.43 (m, 1H), 6.29 (dd, 1H, *J* = 16.1, 6.6 Hz), 6.64 (d, 1H, *J* = 16.1 Hz), 7.27-7.31 (m, 1H), 7.73-7.76 (m, 1H), 8.48-8.50 (m, 1H), 8.61-8.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.0, 63.5, 74.0, 123.1, 128.0, 130.3, 131.5, 1323.6, 148.3, 148.7, 154.1; HRMS (ESI-TOF) calcd for $C_{12}H_{16}NO_3$ $[M+H]^+$: 222.1130, found: 222.1140; FT-IR (neat, cm^{-1}) 708, 791, 1037, 1257, 1372, 1479, 1569, 1741, 2935, 2983.

4.2.11. (*E*)-ethyl (4-(naphthalen-1-yl)but-3-en-2-yl) carbonate (4m)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (722.4 mg, 76% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, 3H, *J* = 7.1 Hz), 1.55 (d, 3H, *J* = 6.5 Hz), 4.23 (q, 2H, *J* = 7.1 Hz), 5.45-5.54 (m, 1H), 6.23 (dd, 1H, *J* = 15.7, 6.9 Hz), 7.39-7.60 (m, 5H), 7.78-7.86 (m, 2H), 8.08-8.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 20.5, 63.7, 75.0, 123.8, 124.0, 125.6, 125.9, 126.2, 128.4, 128.6, 129.4, 131.3, 131.6, 133.7, 134.0, 154.7; HRMS (ESI-TOF) calcd for $C_{17}H_{18}O_3Na$ $[M+Na]^+$: 293.1154, found: 293.1155; FT-IR (neat, cm^{-1}) 734, 792, 1038, 1151, 1257, 1371, 1446, 1590, 1740, 2934, 2981, 3059.

4.2.12. (*E*)-4-cyclohexylbut-3-en-2-yl ethyl carbonate (4n)

The titled compound was synthesized according to General Procedure A. Purification by silica-gel column chromatography (Hexane/EtOAc = 7/1, 1% Et_3N) gave the desired product (436.7 mg, 84% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.98-1.35 (m, 10H), 1.58-1.72 (m, 6H), 1.93 (br, 1H), 4.17 (q, 2H, *J* = 7.1 Hz), 5.10-5.18 (m, 1H), 5.38-5.46 (m, 1H), 5.69 (dd, 1H, *J* = 15.6, 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.2, 25.8, 25.9, 32.4, 40.0, 63.1, 75.8, 126.5, 139.1, 154.2; HRMS (ESI-TOF) calcd for $C_{13}H_{22}O_3Na$ $[M+Na]^+$: 249.1467, found: 249.1471; FT-IR (neat, cm^{-1}) 790, 846, 1036, 1256, 1371, 1449, 1742, 2852, 2925, 2982.

4.3. General procedure for catalytic allylic difluoromethylation of allyl carbonate (Table 3)

General Procedure B: To a test tube equipped with a magnetic stir bar were added the corresponding allyl carbonate **4** (0.2 mmol), CuI (3.8 mg, 0.02 mmol, 10 mol%), and $Zn(CF_2H)_2(dmpu)_2$ (0.17-0.18 M in DMPU, 1.9-2.1 mL, 0.34 mmol) [8a] at room temperature under argon atmosphere. The reaction mixture was stirred at 40 °C for 24 h and quenched with 1M HCl aq. (10 mL). The mixture was extracted with pentane (10 mL × 3) and the combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, the yield was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. The crude product was purified by silica-gel column chromatography to give the difluoromethylated product **2**.

4.3.1. (*E*)-(4,4-difluorobut-1-en-1-yl)benzene (2a)

The titled compound was synthesized according to General Procedure B. The yield of the compound (95% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (24.2 mg, 72% yield) as a colorless oil. The product was known compound and NMR data were in good accordance with the previous data [9]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69-2.84 (m, 2H), 5.87 (tt, 1H, J_{H-F} = 56.7, J = 4.5 Hz), 6.14 (dt, 1H, J = 15.7, 7.3 Hz), 6.57 (d, 1H, J = 15.9 Hz), 7.23-7.40 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.6 (dt, 2F, J = 57.6, 17.5 Hz). **2a'**: ^{19}F NMR (282 MHz, DMF) δ -122.2 (ddd, 1F, J_{F-F} = 275.1, J_{F-H} = 54.8, 13.8 Hz), -120.7 (ddd, 1F, J_{F-F} = 275.6, J_{F-H} = 55.4, 13.8 Hz).

4.3.2. (*S*,*E*)-(4,4-difluoro-3-methylbut-1-en-1-yl)benzene [(*S*)-2b] (Scheme 2, Eq. 3)

The titled compound was synthesized according to General Procedure B. The yield of the compound (90% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (Pentane/ Et_2O = 20/1) gave the desired product (30.9 mg, 85% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 7.0 Hz), 2.71-2.91 (m, 1H), 5.73 (td, 1H, J_{H-F} = 56.8, J = 3.9 Hz), 6.16 (dd, 1H, J = 16.0, 7.8 Hz), 6.56 (d, 1H, J = 16.0 Hz), 7.25-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.5 Hz), 41.4 (t, J_{C-F} = 20.2 Hz), 118.1 (t, J_{C-F} = 242.3 Hz), 126.3 (t, J_{C-F} = 5.3 Hz), 126.3, 127.7, 128.6, 132.9, 136.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.2 (ddd, 1F, J_{F-F} = 276.2, J_{F-H} = 56.3, 15.0 Hz), -121.2 (ddd, 1F, J_{F-F} = 275.5, J_{F-H} = 55.3, 13.8 Hz); FT-IR (neat, cm^{-1}) 693, 748, 967, 1067, 1125, 326, 1461, 2854, 2925; $[\alpha]_D^{21}$ +0.63 (*c* 0.58, $CHCl_3$), 90% *ee*; HPLC (column, CHIRALCEL OD-3, Hexane/2-Propanol = 96/4, flow rate 0.8 mL/min, 20 °C, detection UV 220 nm) t_R of minor (*R*)-isomer 6.2 min, t_R of major (*S*)-isomer 6.7 min.

4.3.3.(*E*)-(3-(difluoromethyl)but-1-ene-1,4-diyl)dibenzene (2c)

The titled compound was synthesized according to General Procedure B (use of 3.4 equiv of zinc reagent). The yield of the compound (80% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (41.3 mg, 80% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80-3.10 (m, 3H), 5.79 (td, 1H, J_{H-F} = 56.4, J = 3.0 Hz), 6.10 (dd, 1H, J = 15.9, 8.4 Hz), 6.40 (d, 1H, J = 15.9 Hz), 7.20-7.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.8 (t, J_{C-F} = 4.1 Hz), 48.9 (t, J_{C-F} = 19.5 Hz), 117.1 (t, J_{C-F} = 243.9 Hz), 124.1 (t, J_{C-F} = 4.5 Hz), 126.4, 126.5, 127.7, 128.5, 128.6, 129.3, 134.7, 136.7, 138.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.7 (ddd, 1F, J_{F-F} = 278.6, J_{F-H} = 56.5, 15.2 Hz), -122.4 (ddd, 1F, J_{F-F} = 277.7, J_{F-H} = 56.9, 13.6 Hz); FT-IR (neat, cm^{-1}) 695, 745, 966, 1049, 1129, 1381, 1454, 1603, 2857, 2933, 2964, 3028.

4.3.4. (*E*)-1-chloro-2-(4,4-difluoro-3-methylbut-1-en-1-yl)benzene (2d)

The titled compound was synthesized according to General Procedure B. The yield of the compound (94% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (37.6 mg, 87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 7.0 Hz), 2.77-2.93 (m, 1H), 5.73 (td, 1H, J_{H-F} = 56.7, J = 3.8 Hz), 6.13 (dd, 1H, J = 16.0, 7.8 Hz), 6.93 (d, 1H, J = 15.9 Hz), 7.16-7.25 (m, 2H), 7.36 (dd, 1H, J = 7.3, 1.4 Hz), 7.53 (dd, 1H, J = 7.4, 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8 (t, J_{C-F} = 4.9 Hz), 41.5 (t, J_{C-F} = 20.2 Hz), 117.9 (t, J_{C-F} = 242.2 Hz), 126.8, 126.9, 128.7, 129.1 (t, J_{C-F} = 5.3 Hz), 129.2, 129.7, 133.0, 134.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.1 (ddd, 1F, J_{F-F} = 276.5, J_{F-H} = 56.4, 15.0 Hz), -121.5 (ddd, 1F, J_{F-F} = 278.4, J_{F-H} = 55.3, 15.4 Hz); FT-IR (neat, cm^{-1}) 751, 995, 1054, 1120, 1390, 1471, 2885, 2977, 3063.

4.3.5. (*E*)-1-chloro-3-(4,4-difluoro-3-methylbut-1-en-1-yl)benzene (2e)

The titled compound was synthesized according to General Procedure B. The yield of the compound (96% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (36.9 mg, 85% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, 3H, J = 7.0 Hz), 2.68-2.89 (m, 1H), 5.71 (td, 1H, J_{H-F} = 56.7, J_{H-F} = 3.9 Hz), 6.15 (dd, 1H, J = 16.0, 7.8 Hz), 6.48 (d, 1H, J = 16.0 Hz), 7.19-7.28 (m, 3H), 7.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.9 Hz), 41.3 (t, J_{C-F} = 20.2 Hz), 117.9 (t, J_{C-F} = 242.2 Hz), 124.6, 126.3, 127.7, 127.9 (t, J_{C-F} = 4.9 Hz), 129.8, 131.7, 134.6, 138.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -122.9 (ddd, 1F, J_{F-F} = 276.5, J_{F-H} = 56.2, 14.8 Hz), -121.5 (ddd, 1F, J_{F-F} = 277.4, J_{F-H} 57.3, 14.0 Hz); FT-IR (neat, cm^{-1}) 684, 779, 966, 1059, 1125, 1390, 1595, 2885, 2977, 3029.

4.3.6. (*E*)-1-chloro-4-(4,4-difluoro-3-methylbut-1-en-1-yl)benzene (2f)

The titled compound was synthesized according to General Procedure B. The yield of the compound (97% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (34.3 mg, 79% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, 3H, J = 7.0 Hz), 2.67-2.88 (m, 1H), 5.70 (td, 1H, J_{H-F} = 56.7, J = 3.9 Hz), 6.11 (dd, 1H, J = 16.0, 7.8 Hz), 6.48 (dd, 1H, J = 16.0, 0.8 Hz), 7.29 (br, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.5 Hz), 41.3 (t, J_{C-F} = 20.2 Hz), 117.9 (t, J_{C-F} = 242.2 Hz), 127.0 (t, J_{C-F} = 5.3 Hz), 127.5, 128.7, 131.7, 133.3, 135.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -122.9 (ddd, 1F, J_{F-F} = 276.5, J_{F-H} = 56.6, 15.1 Hz), -121.5 (ddd, 1F, J_{F-F} = 276.7, J_{F-H} = 56.6, 14.3 Hz); FT-IR (neat, cm^{-1}) 701, 806, 968, 1057, 1390, 1492, 2855, 2962, 3032.

4.3.7. (*E*)-1-bromo-4-(4,4-difluoro-3-methylbut-1-en-1-yl)benzene (2g)

The titled compound was synthesized according to General Procedure B. The yield of the compound (>99% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (40.6 mg, 78% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, 3H, J = 7.0 Hz), 2.69-2.89 (m, 1H), 5.72 (td, 1H, J_{H-F} = 56.8, J = 3.9 Hz), 6.14 (dd, 1H, J = 16.0, 7.8 Hz), 6.49 (d, 1H, J = 16.0 Hz), 7.24-7.28 (m, 2H), 7.44-7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.5 Hz), 41.4 (t, J_{C-F} = 20.2 Hz), 117.9 (t, J_{C-F} = 242.2 Hz), 121.5, 127.1 (t, J_{C-F} = 5.3 Hz), 127.9, 131.7, 131.8, 135.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -122.9 (ddd, 1F, J_{F-F} = 276.1, J_{F-H} = 56.3, 15.2 Hz), -121.5 (ddd, 1F, J_{F-F} = 275.8, J_{F-H} = 55.5, 13.8 Hz); FT-IR (neat, cm^{-1}) 804, 994, 1072, 1124, 1390, 1487, 1588, 2976, 3030.

4.3.8. (*E*)-1-(4,4-difluoro-3-methylbut-1-en-1-yl)-4-(trifluoromethyl)benzene (2h)

The titled compound was synthesized according to General Procedure B. The yield of the compound (78% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (39.6 mg, 79% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 7.0 Hz), 2.71-2.92 (m, 1H), 5.72 (td, 1H, J_{H-F} = 56.7, J = 3.8 Hz), 6.24 (dd, 1H, J = 16.1, 7.7 Hz), 6.57 (d, 1H, J = 16.0 Hz), 7.47 (d, 2H, J = 8.2 Hz), 7.57 (d, 2H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8 (t, J_{C-F} = 4.5 Hz), 41.4 (t, J_{C-F} = 20.2 Hz), 117.8 (t, J_{C-F} = 242.6 Hz), 124.2 (q, J_{C-F} = 270.0 Hz), 125.5 (q, J_{C-F} = 3.7 Hz), 126.5, 129.0 (t, J_{C-F} = 5.3 Hz), 129.5 (q, J_{C-F} = 32.2 Hz), 131.7, 140.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -122.6 (ddd, 1F, J_{F-F} = 275.9, J_{F-H} = 44.6, 17.2 Hz), -121.6 (ddd, 1F, J_{F-F} = 269.0, J_{F-H} = 48.7, 14.1 Hz), -62.5 (s, 3F); FT-IR (neat, cm^{-1}) 818, 1067, 1125, 1326, 1462, 1617, 2889, 2981, 3044.

4.3.9. (*E*)-1-(4,4-difluoro-3-methylbut-1-en-1-yl)-4-methylbenzene (2i)

The titled compound was synthesized according to General Procedure B. The yield of the compound (73% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (26.8 mg, 68% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, 3H, J = 7.0 Hz), 2.35 (s, 3H), 2.69-2.85 (m, 1H), 5.70 (td, 1H, J_{H-F} = 56.8, J = 3.9 Hz), 6.07 (dd, 1H, J = 16.0, 7.8 Hz), 6.50 (d, 1H, J = 16.0 Hz), 7.13 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.9 Hz), 21.2, 41.4 (t, J_{C-F} = 19.9 Hz), 118.1 (t, J_{C-F} = 242.2 Hz), 125.3 (t, J_{C-F} = 4.9 Hz), 126.2, 129.3, 132.7, 134.0, 137.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.4 (ddd, 1F, J_{F-F} = 275.5, J_{F-H} = 57.2, 16.0 Hz), -121.1 (ddd, 1F, J_{F-F} = 275.5, J_{F-F} = 59.1, 13.6 Hz); FT-IR (neat, cm^{-1}) 799, 995, 1058, 1126, 1389, 1515, 2856, 2925, 2972.

4.3.10. (*E*)-1-(4,4-difluoro-3-methylbut-1-en-1-yl)-4-methoxybenzene (2j)

The titled compound was synthesized according to General Procedure B. The yield of the compound (71% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (30.1 mg, 71% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3H, J = 5.0 Hz), 2.65-2.85 (m, 1H), 3.81 (s, 3H), 5.69 (td, 1H, J_{H-F} = 56.9, J = 3.9 Hz), 5.98 (dd, 1H, J = 16.0, 7.8 Hz), 6.47 (d, 1H, J = 16.0 Hz), 6.84-6.88 (m, 2H), 7.29-7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.9 Hz), 41.4 (t, J_{C-F} = 20.2 Hz), 55.3, 114.0, 118.2 (t, J_{C-F} = 242.3 Hz), 124.1 (t, J_{C-F} = 4.9 Hz), 127.5, 129.6, 132.3, 159.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.3 (ddd, 1F, J_{F-F} = 275.5, J_{F-H} = 57.2, 15.7 Hz), -121.1 (ddd, 1F, J_{F-F} = 275.4, J_{F-H} = 55.1, 13.6 Hz); HRMS (APCI-TOF) calcd for $C_{12}H_{15}OF_2$ $[M+H]^+$: 213.1091, found: 213.1100; FT-IR (neat, cm^{-1}) 814, 993, 1037, 1176, 1253, 1513, 1607, 2838, 2971.

4.3.11. (*E*)-5-(4,4-difluoro-3-methylbut-1-en-1-yl)benzo[d][1,3]dioxole (2k)

The titled compound was synthesized according to General Procedure B. The yield of the compound (90% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 20/1) gave the desired product (42.9 mg, 95% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3H, J = 7.0 Hz), 2.64-2.84 (m, 1H), 5.68 (td, 1H, J_{H-F} = 56.8, J = 3.9 Hz), 5.94 (dd, 1H, J = 15.9, 7.9 Hz), 5.95 (s, 2H), 6.44 (d, 1H, J = 15.9 Hz), 6.75 (d, 1H, J = 8.0 Hz), 6.80 (dd, 1H, J = 8.0, 1.5 Hz), 6.92 (d, 1H, J = 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.5 Hz), 41.3 (t, J_{C-F} = 20.2 Hz), 101.1, 105.6, 108.3, 118.0 (t, J_{C-F} = 244.6 Hz), 121.0, 124.5 (t, J_{C-F} = 5.3 Hz), 131.3, 132.4, 147.3, 148.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.2 (ddd, 1F, J_{F-F} = 276.0, J_{F-H} = 57.3, 16.2 Hz), -121.2 (ddd, 1F, J_{F-F} = 276.0, J_{F-H} = 59.4, 13.5 Hz); HRMS (APCI-TOF) calcd for $C_{12}H_{13}F_2O_2$ $[M+H]^+$: 227.0884, found: 227.0894; FT-IR (neat, cm^{-1}) 800, 1040, 1251, 1357, 1446, 1492, 1606, 2780, 2902, 2976.

4.3.12. (*E*)-3-(4,4-difluoro-3-methylbut-1-en-1-yl)pyridine (2l) The titled compound was synthesized according to General Procedure B. The yield of the compound (74% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 2/1, 1% Et_3N) gave the desired product (26.7 mg, 73% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, 3H, J = 7.2 Hz), 2.73-2.88 (m, 1H), 5.71 (td, 1H, J_{H-F} = 56.6, J = 3.8 Hz), 6.20 (dd, 1H, J = 16.1, 7.7 Hz), 6.52 (d, 1H, J = 16.1 Hz), 7.26 (s, 1H), 7.71 (d, 1H, J = 7.8 Hz), 8.49 (br, 1H), 8.60 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.9 Hz), 41.4 (t, J_{C-F} = 20.2 Hz), 117.7 (t, J_{C-F} = 242.2 Hz), 123.6, 128.8 (t, J_{C-F} = 5.3 Hz), 129.4, 132.5, 132.9, 148.1, 148.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -122.7 (ddd, 1F, J_{F-F} = 276.6, J_{F-H} = 56.3, 14.7 Hz), -121.7 (ddd, 1F, J_{F-F} = 277.7, J_{F-H} = 57.2, 15.1 Hz); HRMS (ESI-TOF) calcd for $C_{10}H_{12}NF_2$ $[M+H]^+$: 184.0938, found: 184.0947; FT-IR (neat, cm^{-1}) 709, 793, 1060, 1377, 1462, 1570, 2853, 2924.

4.3.13. (*E*)-1-(4,4-difluoro-3-methylbut-1-en-1-yl)naphthalene (2m)

The titled compound was synthesized according to General Procedure B. The yield of the compound (79% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (38.1 mg, 82% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, 3H, J = 7.0 Hz), 2.83-3.03 (m, 1H), 5.79 (td, 1H, J_{H-F} = 56.8, J = 4.0 Hz), 6.16 (dd, 1H, J = 15.7, 7.8 Hz), 7.30 (d, 1H, J = 15.9 Hz), 7.43-7.61 (m, 4H), 7.79-7.89 (m, 2H), 8.09-8.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1 (t, J_{C-F} = 12.4 Hz), 41.7 (t, J_{C-F} = 20.2 Hz), 118.1 (t, J_{C-F} = 242.2 Hz), 123.7, 124.0, 125.6, 125.8, 126.1, 128.1, 128.6, 129.7 (t, J_{C-F} = 4.9 Hz), 130.3, 131.1, 133.6, 134.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.0 (ddd, 1F, J_{F-F} = 275.8, J_{F-H} = 57.0, 15.6 Hz), -121.2 (ddd, 1F, J_{F-F} = 276.7, J_{F-H} = 56.7, 14.0 Hz); FT-IR (neat, cm^{-1}) 775, 795, 969, 993, 1056, 1392, 1460, 1509, 1591, 2977, 3047, 3061.

4.3.14. (*E*)-(4,4-difluoro-3-methylbut-1-en-1-yl)cyclohexane (2n)

The titled compound was synthesized according to General Procedure B. The yield of the compound (84% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the desired product (32.3 mg, 86% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.34 (m, 5H), 1.10 (d, 3H, J = 6.5 Hz), 1.62-1.72 (m, 5H), 1.90-1.99 (m, 1H), 2.42-2.62 (m, 1H), 5.29 (ddd, 1H, J = 15.6, 7.6, 1.2 Hz), 5.54 (dd, 1H, J = 15.9, 6.6 Hz), 5.57 (td, 1H, J_{H-F} = 57.1, J = 4.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (t, J_{C-F} = 4.9 Hz), 26.0, 26.1, 32.9, 40.7, 40.9 (t, J_{C-F} = 20.2 Hz), 118.5 (t, J_{C-}

$_F$ = 241.9 Hz), 124.0 (t, J_{C-F} = 5.3 Hz), 140.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -124.1 (ddd, 1F, J_{F-F} = 274.8, J_{F-H} = 56.8, 16.7 Hz), -121.0 (ddd, 1F, J_{F-F} = 274.1, J_{F-H} = 57.1, 12.9 Hz); FT-IR (neat, cm^{-1}) 968, 995, 1057, 1123, 1365, 1390, 1450, 2853, 2926.

4.4. Determination of absolute configuration of 2b (Scheme 3)

4.4.1. Synthetic procedure of (*R*)-2-methyl-4-phenylbutan-1-ol [(*R*)-8] [12]

To a test tube equipped with a magnetic stir bar were added $[RuCl_2(p\text{-cymene})]_2$ (11 mg, 0.018 mmol, 0.6 mol%) and (*R*)-MeO-BIPHEP (21 mg, 0.036 mmol, 1.2 mol%) in methanol (1 mL) at room temperature under argon atmosphere. The solution was stirred at room temperature for 3 h. To a stainless steel autoclave equipped with a magnetic stir bar were added 2-phenethylacrylic acid **6** (500 mg, 2.84 mmol) and triethylamine (363 μL, 2.84 mmol) in methanol (9 mL) and then the solution of ruthenium complex was added at room temperature under argon atmosphere. It was pressurized with H_2 (ca. 50 atm) and stirred at room temperature for 48 h. The solvent was evapolated and the residue was dissolved in CH_2Cl_2 (20 mL). The suspension was treated by 10% Na_2CO_3 aq. until the aqueous phase was at pH = 11 and washed with Et_2O. The aqueous phase was acidified until pH = 1 and extracted with CH_2Cl_2 (15 mL × 3), and the combined organic phases were dried with anhydrous $MgSO_4$. After filtration and concentration under vacuum, (*R*)-2-methyl-4-phenylbutyric acid (*R*)-**7** (435 mg, 86% yield) was obtained as a colourless liquid. The product was known compound and the following data were in good accordance with the previous data [12,20]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, 3H, *J* = 7.0 Hz), 1.69-1.81 (m, 1H), 1.99-2.09 (m, 1H), 2.48-2.55 (m, 1H), 2.65-2.73 (m, 2H), 7.17-7.21 (m, 3H), 7.28-7.31 (m, 2H); $[\alpha]_D^{22}$ -18.7 (*c* 1.50, $CHCl_3$), (*R*)-isomer in ref 12: $[\alpha]_D^{25}$ -28.0 (neat), 96% *ee*.

To a suspention of $LiAlH_4$ (185 mg, 4.88 mmol) in THF (2 mL) was added (*R*)-**7** (435 mg, 2.44 mmol) in THF (3 mL) at 0 °C. The resulting mixture was refluxed for 2 h. To a mixture, in order of water (0.18 mL), 15% NaOH aq. (0.18 mL), and water (0.4 mL) were added. After the mixture was stirred for several minutes, the precipitation was generated. The reaction mixture was filtered through a pad of celite with the aid of Et_2O. After concentration under vacuum, the crude product was purified by silica-gel column chromatography to give the product (*R*)-**8** as a colourless liquid. The product was known compound and the following data were in good accordance with the previous data [12,21]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, 3H, *J* = 6.6 Hz), 1.28-1.40 (br s, 1H), 1.40-1.52 (m, 1H), 1.64-1.83 (m, 2H), 2.55-2.76 (m, 2H), 3.44-3.57 (m, 2H), 7.15-7.30 (m, 5H); $[\alpha]_D^{22}$ +10.4 (*c* 2.47, $CHCl_3$), (*R*)-isomer in ref 12: $[\alpha]_D^{25}$ +19.1 (*c* 5.0, $CHCl_3$), 96% *ee*.

4.4.2. Synthetic procedure of (*R*)-2-methyl-4-phenylbutanal [(*R*)-9]

To a test tube equipped with a magnetic stir bar were added alcohol (*R*)-**8** (164 mg, 1.0 mmol), Dess-Martin periodinane (636 mg, 1.5 mmol), and dry CH_2Cl_2 (3 mL) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for 2.5 h and then quenched with sat. $NaHCO_3$ aq. (3 mL) and sat. Na_2SO_3 aq. (3 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 2). The combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by silica-gel column chromatography (Hexane/EtOAc = 15/1) to give chiral aldehyde (*R*)-**9** (105 mg, 65% yield). The product was known compound as racemate and ^{1}H NMR data were in good accordance with the previous data [22]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, 3H, *J* = 7.0 Hz), 1.62-1.74 (m, 1H), 2.01-2.13 (m, 1H), 2.32-2.44 (m, 1H), 2.64-2.71 (m, 2H), 7.18-7.23 (m, 3H), 7.28-7.33 (m, 2H), 9.63 (d, 1H, *J* = 1.8 Hz).

4.4.3. Synthetic procedure of (*R*)-(4,4-difluoro-3-methylbutyl)benzene [(*R*)-10] (Scheme 3a)

To a test tube equipped with a magnetic stir bar was added aldehyde (*R*)-**9** (105 mg, 0.65 mmol) in CH_2Cl_2 (1.5 mL) at room temperature under argon atmosphere. After the solution was cooled to 0 °C, *N*,*N*-diethylaminosulfur trifluoride (94 μL, 0.72 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 24 h and then quenched with sat. $NaHCO_3$ aq. (10 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3) and the combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by silica-gel column chromatography (pentane only) to give difluorinated product (*R*)-**10** (35.4 mg, 30% yield) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, 3H, *J* = 6.7 Hz), 1.49-1.60 (m, 1H), 1.84-2.00 (m, 2H), 2.57-2.67 (m, 1H), 2.71-2.80 (m, 1H), 5.64 (td, 1H, J_{H-F} = 56.9, *J* = 3.7 Hz), 7.17-7.22 (m, 3H), 7.27-7.32 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -124.2 (ddd, 1F, J_{F-F} = 277.0, J_{F-H} = 57.2, 16.0 Hz), -122.5 (ddd, 1F, J_{F-F} = 275.8, J_{F-H} = 55.7, 13.6 Hz); $[\alpha]_D^{21}$ +8.2 (*c* 1.79, $CHCl_3$), 70% *ee*.

4.4.4. Synthetic procedure of (*S*)-(4,4-difluoro-3-methylbutyl)benzene [(*S*)-10] (Scheme 3b)

To a test tube equipped with a rubber septum and a magnetic stir bar were added the difluoromethylated product (*S*)-**2b** (36.4 mg, 0.2 mmol, 90% *ee*), palladium (10% on carbon, wetted with ca. 55% water) (33 mg, 0.02 mmol, 10 mol%), and ethanol (1 mL) at room temperature under argon atmosphere. Then H_2 balloon was attached to the test tube and the suspension was stirred at room temperature for 2.5 h. The resulting mixture was directly passed through short silica-gel column (pentane only) to isolate the reducted product (*S*)-**10** (29.4 mg, 94% yield) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, 3H, *J* = 6.7 Hz), 1.50-1.62 (m, 1H), 1.84-2.00 (m, 2H), 2.57-2.67 (m, 1H), 2.71-2.81 (m, 1H), 5.64 (td, 1H, J_{H-F} = 56.9, *J* = 3.6 Hz), 7.18-7.23 (m, 3H), 7.28-7.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3 (t, J_{C-F} = 5.6 Hz), 31.4 (t, J_{C-F} = 4.5 Hz), 32.8, 36.7 (t, J_{C-F} = 19.5 Hz), 119.2 (t, J_{C-F} = 240.4 Hz), 126.0, 128.3, 128.5, 141.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -124.2 (ddd, 1F, J_{F-F} = 276.7, J_{F-H} = 56.7, 16.4 Hz), -122.5 (ddd, 1F, J_{F-F} = 277.1, J_{F-H} = 57.8, 13.5 Hz); FT-IR (neat, cm^{-1}) 699, 747, 990, 1057, 1396, 1455, 1496, 1604, 2865, 2945, 3029; $[\alpha]_D^{21}$ -8.4 (*c* 2.90, $CHCl_3$), 80% *ee*; HPLC (column, CHIRALCEL OD-3, Hexane/2-Propanol = 99/1, flow rate 0.8 mL/min, 20 °C, detection UV 220 nm) t_R of minor (*R*)-isomer 9.1 min, t_R of major (*S*)-isomer 10.5 min.

Acknowledgments

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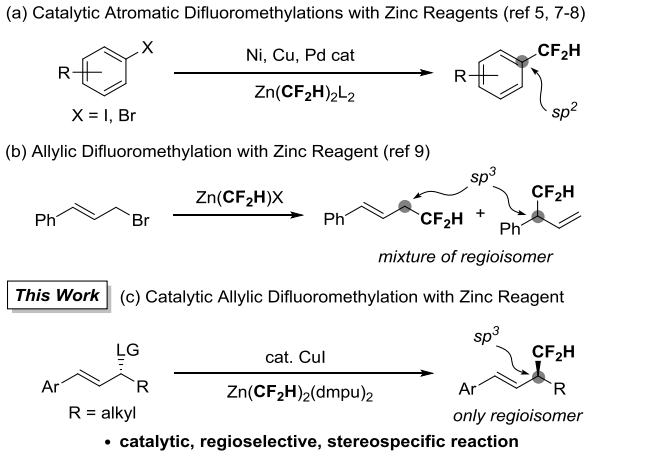
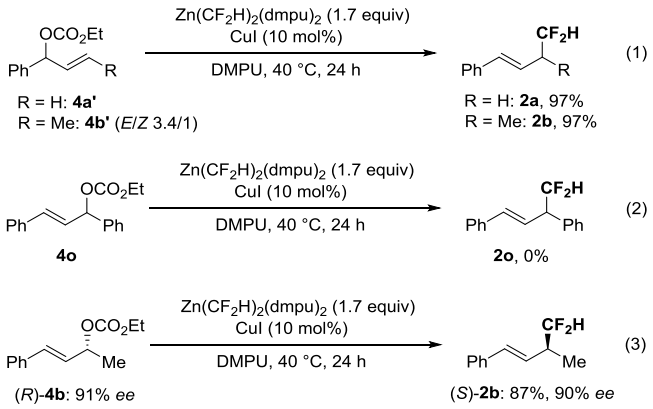
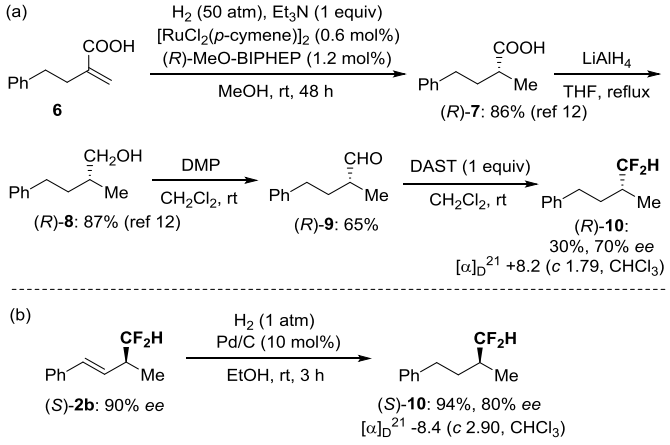


Scheme 1. Catalytic or non-catalytic direct difluoromethylations with (difluoromethyl)zinc reagents

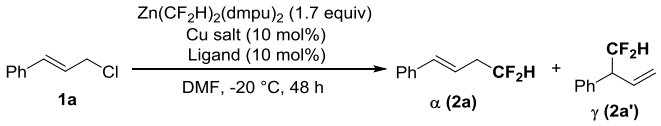


Scheme 2. Copper-catalyzed regioselective and stereospecific allylic difluoromethyations



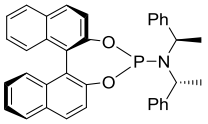
Scheme 3. Determination of absolute configuration of product **2b**

Table 1. Catalytic allylic difluoromethylation of cinnamyl chloride

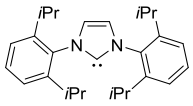


entry	Cu salt	Ligand	yield [%][a]
1	CuI	-	α: 81, γ: 19
2[b]	-	-	α: 0, γ: 0
3	$CuBr(SMe_2)$	-	α: 84, γ: trace
4	CuCl	-	α: 76, γ: tarce
5	$CuOTf(toluene)_{1/2}$	-	α: 93, γ: 1
6	CuTC	-	α: 89, γ: trace
7	CuCN	-	α: 54, γ: 5
8	CuOAc	-	α: 31, γ: 33
9	CuOAc	**L1**	α: 33, γ: 21
10	CuOAc	**L2**	α: 30, γ: 40
11	CuOAc	**L3**	α: 30, γ: 47

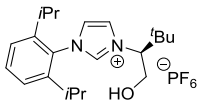
[a]Yields were determined by ^{19}F NMR analysis using BTF as an internal standard.
[b]Reaction was carried out without Cu salt.



L1

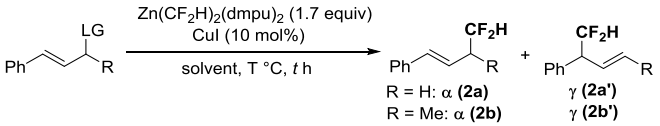


L2



L3

Table 2. Catalytic allylic difluoromethylation with α-regioselectivity

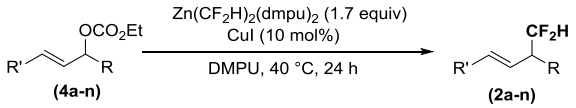


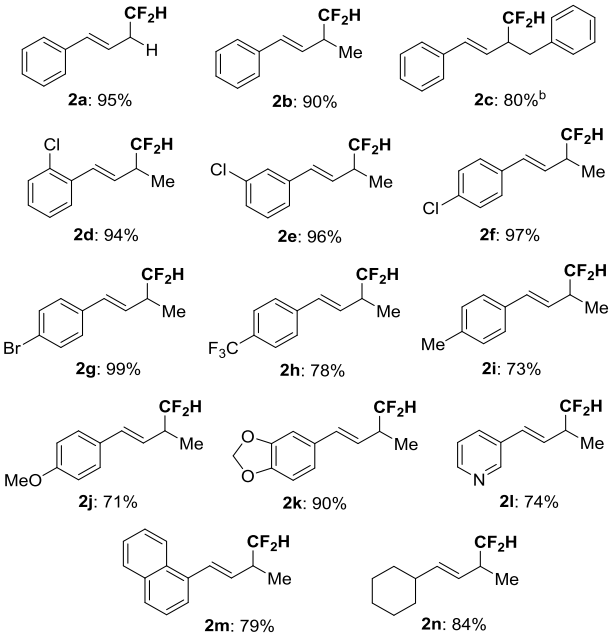
R = H: α **(2a)** γ **(2a')**
R = Me: α **(2b)** γ **(2b')**

entry	LG	R	solvent	T [°C]	*t* [h]	yield [%][a]
1	Cl	H (**1a**)	DMF	-20	48	α: 81, γ: 19
2	$OPO(OEt)_2$	H (**3a**)	DMF	rt	70	α: 64, γ: 0
3	OCO_2Et	H (**4a**)	DMF	rt	70	α: 62, γ: 0
4[b]	OCO_2Et	H (**4a**)	DMF	rt	70	α: 0, γ: 0
5	OAc	H (**5a**)	DMF	60	70	α: trace, γ: 0
6	OCO_2Et	Me (**4b**)	DMF	rt	70	α: 39, γ: 0
7	OCO_2Et	Me (**4b**)	DMPU	rt	70	α: 89, γ: 0
8	OCO_2Et	Me (**4b**)	DMPU	40	24	α: 90, γ: 0
9[b]	OCO_2Et	Me (**4b**)	DMPU	40	24	α: 0, γ: 0

[a]Yields were determined by ^{19}F NMR analysis using BTF as an internal standard.
[b]Reaction was carried out without Cu salt.

Table 3. Scope of allyl carbonates as substrates[a]





[a]Yields were determined by ^{19}F NMR analysis using BTF as an internal standard.
[b]3.4 equiv of $Zn(CF_2H)_2(dmpu)_2$ was used, and reaction time was 36 h.