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Redox-Neutral Rh(III)-Catalyzed Olefination of Carboxamides with Trifluoromethyl Allylic Carbonate

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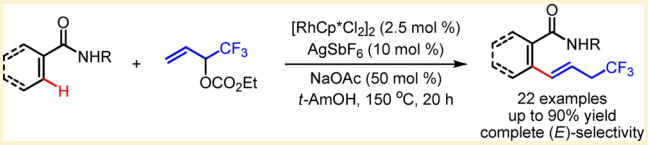
Supporting Information

ABSTRACT: The rhodium(III)-catalyzed olefination of various carboxamides with α-CF_3-substituted allylic carbonate is described. This reaction provides direct access to linear CF_3-allyl frameworks with complete trans-selectivity. In particular, a rhodium catalyst provided Heck-type γ-CF_3-allylation products via the β-O-elimination of rhodacycle intermediate and subsequent olefin migration process.



INTRODUCTION

With considerable advances in organic and medicinal chemistry, the introduction of the trifluoromethyl group into biologically active molecules is of great importance due to its unique physiochemical properties such as electronegativity, hydrophobicity, metabolic stability, bioavailability, and binding affinity.[1] Therefore, the incorporation of the CF_3 group for structural modulation has been intensively investigated for the development of new drugs and material candidates.[2] In this regard, most efforts have been focused on the construction of aromatic and vinylic $C(sp^2)-CF_3$ bonds.[3] Recently, the allylic trifluoromethylation of alkenes and their derivatives has been intensively studied because the allylic trifluoromethyl frameworks are found in various bioactive compounds and can be used as versatile building blocks for the synthesis of CF_3-containing molecules.[4] For example, Buchwald,[5] Liu,[6] and Wang[7] independently disclosed the efficient copper-catalyzed allylic trifluoromethylations of unactivated alkenes with electrophilic CF_3 reagents such as Togni's and Umemoto's reagents (Scheme 1). In addition, Qing reported the copper-catalyzed oxidative trifluoromethylation of terminal alkenes using nucleophilic CF_3SiMe_3 reagent to deliver an allylic trifluoromethyl moiety.[8] The trifluoromethylations of allylic halides[9] and allylic silanes[10] have been also established for the formation of compounds with a CF_3 group in an allylic position. In sharp contrast to allylic trifluoromethylation, the trifluoromethylations of olefins and alkynes under photoredox catalysis and a radical process also provided α-CF_3-allyl derivatives.[11]

With the development of catalytic C−H functionalization, direct $C(sp^2)-H$ allylations have been recently explored by using allylic halides, acetates, carbonates, phosphonates, allenes, and vinyl oxiranes as allyl surrogates.[12] Particularly, Loh reported the Rh(III)-catalyzed allylation of benzamides with allylic acetates to furnish Heck-type olefinated products via migration of terminal olefins by a trace amount of Rh−H species. However, allylic substrates containing a CF_3 group have rarely been investigated in the C−H allylation event. Krische described the elegant studies on iridium- and ruthenium-catalyzed carbonyl trifluoromethylallylations of alcohols and aldehydes using α-trifluoromethyl allyl benzoate and trifluoromethyl allenes.[13] To this end, we envisioned that readily available CF_3-containing allylic carbonates could provide direct access to the formation of γ-trifluoromethylallyl frameworks.[14] Very recently, our research group has reported the site-selective trifluoromethylallylation of indoles and indolines with CF_3-containing allylic carbonate under Rh(III) catalysis.[15] In this

Scheme 1. Trifluoromethylallylation Reactions

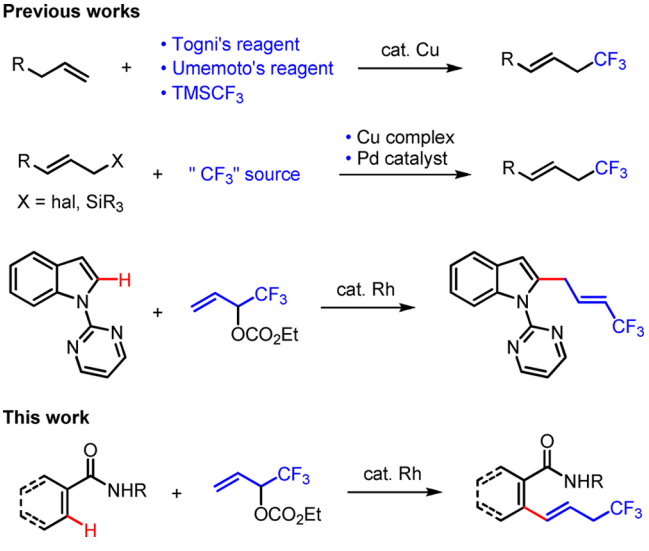


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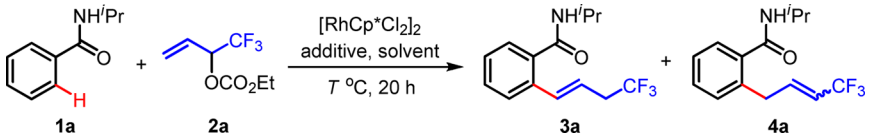
Table 1. Selected Optimization of Reaction Conditions[a]



1a 2a 3a 4a

entry	additive (mol %)	solvent	T (°C)	yield (%)[b,c]
1	$AgSbF_6$ (10)	*t*-AmOH	120	75 (1:1.2)
2	$AgSbF_6$ (10), $Cu(OAc)_2$ (50)	*t*-AmOH	120	87 (5.3:1)
3	$AgNTf_2$ (10), $Cu(OAc)_2$ (50)	*t*-AmOH	120	66 (4.5:1)
4	$AgBF_4$ (10), $Cu(OAc)_2$ (50)	*t*-AmOH	120	47 (4.0:1)
5	$AgSbF_6$ (10), $Cu(OAc)_2$ (50)	DCE	120	66 (2.3:1)
6	$AgSbF_6$ (10), $Cu(OAc)_2$ (50)	DMF	120	trace
7	$AgSbF_6$ (10), $Cu(OAc)_2$ (50)	EtOH	120	trace
8	$AgSbF_6$ (10), $Cu(OAc)_2$ (50)	CH_2Cl_2	120	79 (2.6:1)
9	$AgSbF_6$ (10), CsOAc (50)	*t*-AmOH	120	N.R.
10	$AgSbF_6$ (10), AgOAc (50)	*t*-AmOH	120	74 (2.7:1)
11	$AgSbF_6$ (10), NH_4OAc (50)	*t*-AmOH	120	N.R.
12	$AgSbF_6$ (10), NaOAc (50)	*t*-AmOH	120	73 (>50:1)
13	$AgSbF_6$ (10),NaOAc (50)	*t*-AmOH	150	90 (>50:1)
14[d]	$AgSbF_6$ (10), NaOAc (50)	*t*-AmOH	150	62 (>50:1)

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive (quantity noted), solvent (1 mL) under air at indicated temperature for 20 h in pressure tubes. [b]Yield by flash column chromatography. [c]Parentheses shows ratio between **3a** and **4a**, and the ratio was determined by ^{1}H NMR analysis of the crude mixture. [d]Scale-up experiment (2 mmol scale for 40 h).

work, no migration of olefin was observed, and only vinylic trifluoromethyl products were obtained. In sharp contrast, the present study describes the Rh(III)-catalyzed trifluoromethylallylation of various carboximides with α-trifluoromethyl allyl carbonate, providing allylic trifluoromethylated products with complete olefin migration and high trans-selectivity.

RESULTS AND DISCUSSION

Our study commenced by examining the coupling of *N*-isopropylbenzamide (**1a**) and ethyl 1,1,1-trifluorobut-3-en-2-yl carbonate (**2a**) under rhodium catalysis (Table 1). A cationic rhodium complex, derived from $[RhCp^*Cl_2]_2$ and $AgSbF_6$, was found to promote the coupling of **1a** and **2a** to give a mixture of allylic and vinylic CF_3-allylation products **3a** (*E*:*Z* > 50:1) and **4a** (*E*:*Z* = 12:1) in 75% yield with a ratio of 1:1.2 (Table 1, entry 1). To our delight, a cationic rhodium complex in the presence of $Cu(OAc)_2$ afforded allylic CF_3-containing product **3a** as a major product with a 5.3:1 ratio in high yield (Table 1, entry 2). After screening of silver additives, $AgSbF_6$ was found to be relatively more effective in both chemical yield and regioisomeric ratio (Table 1, entries 3 and 4). Screening of solvents showed that *t*-AmOH was the most effective solvent in this transformation (Table 1, entries 5−8). Other acetate additives such as CsOAc, AgOAc, and NH_4OAc were found to be less effective in this coupling reaction (Table 1, entries 9−11). Surprisingly, NaOAc additive showed remarkable regioselectivity for the formation of **3a** (Table 1, entry 12). Further elevation of reaction temperature to 150 °C was found to be highly crucial for the formation of γ-CF_3-allylation product **3a** in 90% yield with complete trans-selectivity (Table 1, entry 13). To show the robustness and practicality of this reaction, we successfully scaled the reaction to 2 mmol and obtained 0.337 g of **3a** in 62% yield (Table 1, entry 14).

To explore the substrate scope and limitations of γ-trifluoromethylallylation reaction, various directing groups on benzamides were screened to couple with **2a**, as shown in Table 2. Primary benzamide **1b** furnished no formation of allylation product **3b**. However, secondary and tertiary benzamides were reactive for this coupling reaction to give corresponding products **3c−e** in moderate yields with complete regioselectivity of olefin moiety. In addition, carboxamide **1f** containing a bidendate directing group did not undergo the coupling reaction. With either electron-rich or electron-deficient groups at the para-position of benzamides, α-trifluoromethyl allyl carbonate **2a** was coupled to give the corresponding CF_3-allylation products **3g−j**. It should be noted that all reactions exclusively afforded the monoallylated products, and trace amounts of bis-allylated products were observed by ^{1}H NMR or GC-MS analysis. In addition, this reaction was found to be tolerable with ortho-substituted benzamides **1k−m** furnishing the desired products **3k−m** with excellent (*E*)-selectivity. The meta-substituted benzamides **1n** and **1o** were smoothly coupled with **2a** to afford the desired products **3n** and **3o** at the less hindered C−H bond. However, benzamides **1p−r** with other meta-substitutents, such as OBn, Br, and Cl, furnished a regioisomeric mixture of products. Particularly noteworthy was the site-selectivity according to the electronic property of the substrate **1s**, which underwent the coupling reaction at less sterically accessible position to afford **3s** in 79% yield. Moreover, we were pleased to observe the C−H trifluoromethylallylation of heterocyclic and α,β-unsaturated carboxamides **1t** and **1u**, which provided the corresponding products **3t** and **3u**, albeit in low yields.

To show the synthetic utility of CF_3-allylated products, epoxidation of **3a** with *m*-CPBA in the presence of pH 7 buffer solution was first performed (Scheme 2). Interestingly, the phthalide **5a** was obtained in 71% yield presumably via epoxidation of olefin and subsequent O-cyclization reaction of the amido moiety followed by hydrolysis of the benzimido intermediate.[16] In addition, E1cB elimination of the allyl trifluoromethyl moiety was carried out by employing NaH in the presence of DMF to provide difluorodiene **5b** in 32% yield.[10a,17]

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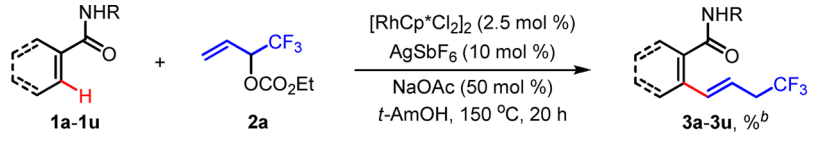
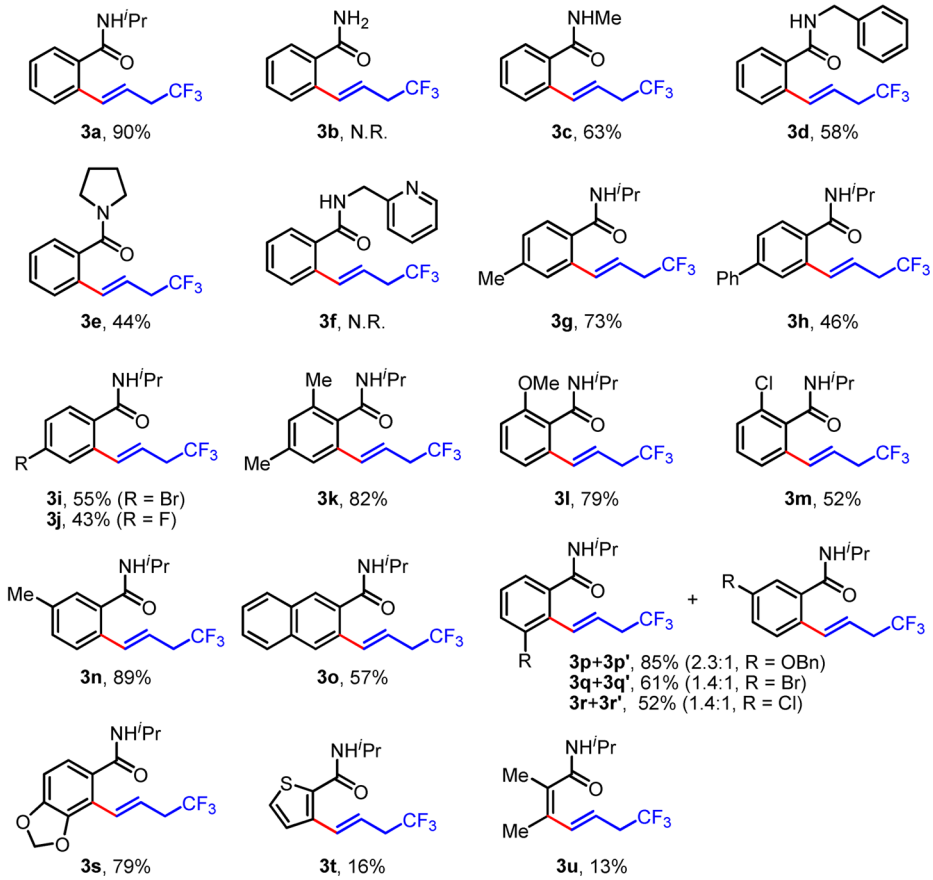
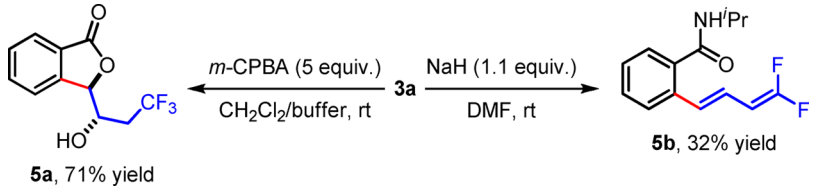
Table 2. Scope of Carboxamides[a]



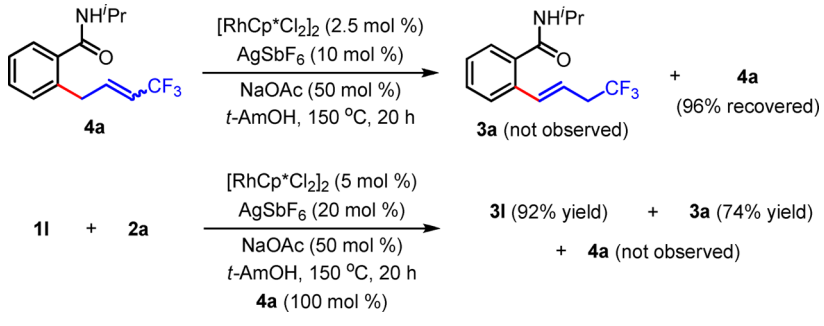


[a]Reaction conditions: **1a–u** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), NaOAc (50 mol %), *t*-AmOH (1 mL) under air at 150 °C for 20 h in pressure tubes. [b]Yield by flash column chromatography.

Scheme 2. Synthetic Transformation of Trifluoromethylallylated Product 3a



Scheme 3. Mechanistic Investigation for Olefin Migration



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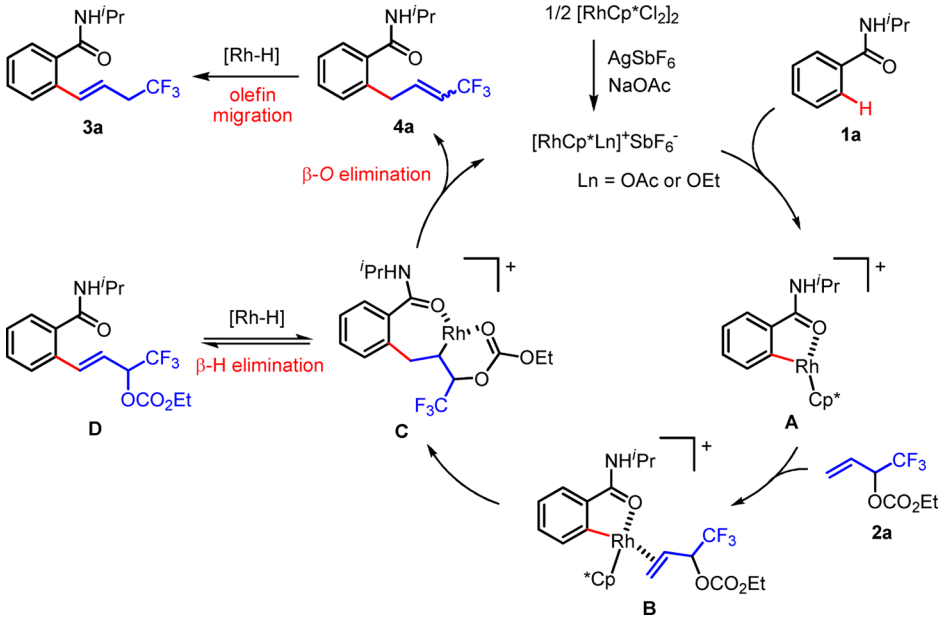
Scheme 4. Plausible Reaction Pathway



To investigate the olefin migration of this transformation, we performed the reaction of **4a** under the standard reaction conditions in the absence of allylic carbonate **2a** (Scheme 3). No formation of **3a** was observed, and **4a** was recovered in 96% yield suggesting that Rh(III) catalyst or other additives cannot promote the olefin migration process. Furthermore, to confirm the generation of Rh−H species in reaction media, we carried out the reaction of **1l** and **2a** under slightly modified reaction conditions in the presence of **4a**, affording the corresponding product **3l** and expected olefin migrated product **3a**. These results indicate that a trace amount of Rh−H species is responsible for the observation of olefin migration, which is in agreement with Loh's report[12c] on the olefination of carboxamides with allylic acetates.

Based on the precedent literatures on the Rh(III)-catalyzed C−H allylation reaction of aromatic compounds using allylic surrogates,[12,14] a plausible reaction pathway of this transformation was depicted in Scheme 4. First, the coordination of an amido directing group to a Rh(III) catalyst and subsequent C−H cleavage generate a five-membered rhodacycle intermediate **A**.[18] Then the olefin coordination of allylic carbonate **2a** and subsequent migratory insertion into Rh−C bond delivers a seven-membered Rh(III) species **C**. Subsequently, the β-oxygen elimination provides vinylic CF_3-containing compound **4a** and regenerates a Rh(III) catalyst. Finally, allylic CF_3-containing product **3a** might be formed through the migratory isomerization of the double bond by the Rh−H complex generated from intermediate **C**. The Rh−H species can be formed as a trace amount due to the conformational restriction of rhodacycle **C** by the coordination of both amido and carbonate groups.

CONCLUSION

In conclusion, we described the rhodium(III)-catalyzed Heck-type olefination of various carboxamides with CF_3-substituted allylic carbonate to afford γ-CF_3-allylated carboxamides. The synthetic transformations revealed that this protocol can be readily applied to the formation of CF_3-containing phthalides and difluorodienes. Further applications of this method for the preparation of bioactive compounds and a detailed mechanistic study are currently underway.

EXPERIMENTAL SECTION

General Procedure and Characterization Data for the Synthesis of 2a. To an oven-dried flask charged with H_2SO_4 (8 mL) and P_2O_5 (1.2 g) was added dropwise trifluoroacetaldehyde hydrate (3 mL, 36 mmol, 1 equiv) by syringe at 100 °C. Trifluoroacetaldehyde gas was trapped in THF (20 mL) by using dry ice/acetone bath. Subsequently, vinylmagnesium bromide (42 mL, 42 mmol, 1.16 equiv., 1.0 M solution in THF) was added dropwise to flask charged with trifluoroacetaldehyde solution. The resulting mixture was stirred for 30 min at 0 °C under N_2 atmosphere. After stirring for 0.5 h, the reaction mixture was stirred for 5 h at room temperature and quenched with saturated aq NH_4Cl (8 mL) at 0 °C. The quenched solution was filtered to remove salt impurities by washing with Et_2O (30 mL), and the organic layer was separated. Et_3N (10 mL, 72 mmol, 1 equiv) was added dropwise to the organic layer at room temperature with the addition of ethyl chloroformate (5.2 mL, 54 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred for 24 h at room temperature. After completion of reaction, the mixture was diluted with saturated $NaHCO_3$ (4 mL). The combined layer was extracted with ether, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 9:1) to afford **2a** (3.42 g, 17.26 mmol) in 48% yield.

*Ethyl 1,1,1-Trifluorobut-3-en-2-yl Carbonate (**2a**).* Yield 3.42 g (48%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.80 (m, 1H), 5.62 (d, J= 17.0 Hz, 1H), 5.54 (d, J= 10.5 Hz, 1H), 5.49−5.42 (m, 1H), 4.25 (q, J= 7.1 Hz, 2H), 1.32 (t, J= 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.8, 126.8 (q, J_{C-F} = 1.3 Hz), 124.0, 122.9 (q, J_{C-F} = 278.7 Hz), 74.6 (q, J_{C-F} = 33.5 Hz), 65.4, 14.2; IR (KBr) ν 2923, 1715, 1432, 1362, 1221, 1092, 1006, 905, 757 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_7H_9F_3O_3$ $[M]^+$ 198.0504, found 198.0508.

General Procedure for the Trifluoromethylallylation of Carboxamides with 2a (3a−u and 4a). To an oven-dried sealed tube charged with *N*-isopropylbenzamide (**1a**) (32.6 mg, 0.2 mmol, 100 mol %), $[RhCp^*Cl_2]_2$ (3.1 mg, 0.005 mmol, 2.5 mol %), NaOAc (8.2 mg, 0.1 mmol, 50 mol %), and ethyl (1,1,1-trifluorobut-3-en-2-yl) carbonate (**2a**) (79.3 mg, 0.4 mmol, 200 mol %) was added $AgSbF_6$ (6.9 mg, 0.02 mmol, 10 mol %) and *tert*-amyl alcohol (1 mL) under air at room temperature. The reaction mixture was stirred at 150 °C for 20 h, and cooled to room temperature. The reaction mixture was

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diluted with EtOAc (3 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 1:1) to afford 49.0 mg of **3a** in 90% yield.

*(E)-N-Isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)benzamide (**3a**).* Yield 49.0 mg (90%); white solid; mp = 96.0−98.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J*= 7.7 Hz, 1H), 7.42−7.35 (m, 2H), 7.28 (t, *J*= 7.4 Hz, 1H), 6.94 (d, *J*= 15.7 Hz, 1H), 6.08−6.01 (m, 1H), 5.66 (br s, 1H), 4.29−4.21 (m, 1H), 3.03−2.94 (m, 2H), 1.22 (d, *J*= 6.5 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5, 135.9, 134.6, 134.4, 130.3, 128.2, 127.6, 126.7, 126.1 (q, J_{C-F} = 274.9 Hz), 120.1 (q, J_{C-F} = 3.5 Hz), 42.1, 38.1 (q, J_{C-F} = 29.7 Hz), 22.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ 49.6 (t, J_{F-H} = 9.3 Hz); IR (KBr) ν 3281, 2923, 2853, 1629, 1531, 1366, 1247, 1136, 1116, 1041, 966, 742, 698 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{17}F_3NO$ [M + H]$^+$ 272.1262, found 272.1260.

*(Z)-N-Isopropyl-2-(4,4,4-trifluorobut-2-en-1-yl)benzamide (**4a**).* Yield 22.2 mg (41%, *E*:*Z* = 12:1); white solid; mp = 70.3−73.0 °C; (*E*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.35 (m, 2H), 7.29 (d, *J*= 7.4 Hz, 1H), 7.21 (d, *J*= 7.6 Hz, 1H), 6.59−6.51 (m, 1H), 5.70−5.51 (m, 2H), 4.27−4.18 (m, 1H), 3.72−3.69 (m, 2H), 1.23 (d, *J*= 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.9, 139.6 (q, J_{C-F} = 6.5 Hz), 136.8, 136.1, 130.9, 130.5, 127.3, 127.0, 123.2 (q, J_{C-F} = 267.7 Hz), 119.6 (q, J_{C-F} = 33.1 Hz), 42.1, 35.3, 22.9; IR (KBr) ν 3262, 2974, 1629, 1537, 1459, 1342, 1251, 1112, 1051, 975, 743 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{17}F_3NO$ [M + H]$^+$ 272.1262, found 272.1267.

*(E)-N-Methyl-2-(4,4,4-trifluorobut-1-en-1-yl)benzamide (**3c**).* Yield 30.6 mg (63%); white solid; mp = 116.0−118.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J*= 7.8 Hz, 1H), 7.42−7.36 (m, 2H), 7.28 (d, *J*= 7.5 Hz, 1H), 6.96 (d, *J*= 15.8 Hz, 1H), 6.08−6.01 (m, 1H), 5.87 (br s, 1H), 3.05−2.93 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.1, 135.6, 134.7, 134.6, 130.4, 128.2, 127.6, 126.8, 126.0 (q, J_{C-F} = 274.9 Hz), 120.1 (q, J_{C-F} = 3.6 Hz), 37.9 (q, J_{C-F} = 29.7 Hz), 26.9; IR (KBr) ν 3304, 2936, 1631, 1541, 1403, 1256, 1131, 1118, 1041, 971, 747, 671 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{12}H_{13}F_3NO$ [M + H]$^+$ 244.0949, found 244.0948.

*(E)-N-Benzyl-2-(4,4,4-trifluorobut-1-en-1-yl)benzamide (**3d**).* Yield 37.1 mg (58%); white solid; mp = 120.1−122.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J*= 7.8 Hz, 1H), 7.43 (d, *J*= 7.6 Hz, 1H), 7.40−7.26 (m, 7H), 6.93 (d, *J*= 15.8 Hz, 1H), 6.21 (br s, 1H), 6.06−5.99 (m, 1H), 4.59 (d, *J*= 5.7 Hz, 2H), 2.96−2.86 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.2, 138.2, 135.3, 134.7, 134.4, 130.5, 128.9, 128.2, 128.1, 127.9, 127.6, 126.8, 125.9 (q, J_{C-F} = 274.9 Hz), 120.2 (q, J_{C-F} = 3.6 Hz), 44.2, 37.9 (q, J_{C-F} = 29.7 Hz); IR (KBr) ν 3285, 2924, 1633, 1526, 1310, 1250, 1124, 1116, 1047, 969, 736, 697 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{18}H_{17}F_3NO$ [M + H]$^+$ 320.1262, found 320.1262.

*(E)-Pyrrolidin-1-yl(2-(4,4,4-trifluorobut-1-en-1-yl)phenyl)-methanone (**3e**).* Yield 25.0 mg (44%); white sticky solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J*= 7.4 Hz, 1H), 7.35−7.23 (m, 3H), 6.66 (d, *J*= 15.8 Hz, 1H), 6.13−6.05 (m, 1H), 3.63 (t, *J*= 6.9 Hz, 2H), 3.06 (t, *J*= 6.8 Hz, 2H), 3.01−2.91 (m, 2H), 1.95−1.78 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 136.9, 134.0, 132.7, 129.3, 128.4, 126.5, 126.4, 125.9 (q, J_{C-F} = 275.0 Hz), 120.2 (q, J_{C-F} = 3.5 Hz), 48.4, 45.7, 38.1 (q, J_{C-F} = 29.7 Hz), 26.0, 24.7; IR (KBr) ν 2923, 1622, 1451, 1420, 1340, 1248, 1132, 1050, 969, 923, 862, 750 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{15}H_{17}F_3NO$ [M + H]$^+$ 284.1262, found 284.1262.

*(E)-N-Isopropyl-4-methyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3g**).* Yield 41.8 mg (73%); white solid; mp = 98.7−100.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J*= 7.8 Hz, 1H), 7.30 (s, 1H), 7.10 (d, *J*= 7.8 Hz, 1H), 6.96 (d, *J*= 15.8 Hz, 1H), 6.07−6.00 (m, 1H), 5.58 (br s, 1H), 4.30−4.21 (m, 1H), 3.04−2.94 (m, 2H), 2.37 (s, 3H), 1.23 (d, *J*= 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5, 140.4, 134.9, 134.6, 133.2, 128.9, 127.7, 127.4, 126.1 (q, J_{C-F} = 275.1 Hz), 119.8 (q, J_{C-F} = 3.6 Hz), 42.2, 38.1 (q, J_{C-F} = 29.8 Hz), 22.9, 21.5; IR (KBr) ν 3281, 2923, 1626, 1536, 1505, 1456, 1327, 1249, 1132, 1115, 1046, 966, 752 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{15}H_{19}F_3NO$ [M + H]$^+$ 286.1419, found 286.1424.

*(E)-N-Isopropyl-3-(4,4,4-trifluorobut-1-en-1-yl)-[1,1′-biphenyl]-4-carboxamide (**3h**).* Yield 32.2 mg (46%); white solid; mp = 176.1−179.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.58 (d, *J*= 7.2 Hz, 2H), 7.52 (br s, 2H), 7.47 (t, *J*= 7.7 Hz, 2H), 7.40−7.37 (m, 1H), 7.03 (d, *J*= 15.8 Hz, 1H), 6.17−6.10 (m, 1H), 5.68 (d, *J*= 7.5 Hz, 1H), 4.34−4.25 (m, 1H), 3.08−2.98 (m, 2H), 1.26 (d, *J*= 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.3, 143.4, 140.3, 135.1, 134.8, 134.6, 129.1, 128.3, 128.2, 127.3, 126.1 (q, J_{C-F} = 278.3 Hz), 120.5 (q, J_{C-F} = 3.5 Hz), 42.3, 38.2 (q, J_{C-F} = 29.8 Hz), 22.9; IR (KBr) ν 3282, 2977, 1626, 1533, 1267, 1253, 1135, 1045, 968, 742, 700, 656 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{21}F_3NO$ [M + H]$^+$ 348.1575, found 348.1577.

*(E)-4-Bromo-N-isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3i**).* Yield 38.7 mg (55%); white solid; mp = 162.7−165.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.40 (dd, *J*= 8.2, 1.9 Hz, 1H), 7.27 (d, *J*= 8.2 Hz, 1H), 6.88 (d, *J*= 15.8 Hz, 1H), 6.09−6.02 (m, 1H), 5.68 (d, *J*= 7.0 Hz, 1H), 4.27−4.18 (m, 1H), 3.04−2.94 (m, 2H), 1.22 (d, *J*= 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.6, 136.5, 134.6, 133.4, 131.1, 129.7, 129.2, 125.8 (q, J_{C-F} = 275.1 Hz), 124.6, 121.6 (q, J_{C-F} = 3.6 Hz), 42.3, 38.1 (q, J_{C-F} = 29.9 Hz), 22.8; IR (KBr) ν 3278, 2977, 1628, 1539, 1467, 1305, 1268, 1249, 1137, 1041, 968, 850, 741 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{16}BrF_3NO$ [M + H]$^+$ 350.0367, found 350.0372.

*(E)-4-Fluoro-N-isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3j**).* Yield 25.0 mg (43%); white solid; mp =137.4−139.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J*= 8.5, 5.7 Hz, 1H), 7.19 (dd, *J*= 9.9, 2.5 Hz, 1H), 7.01−6.93 (m, 2H), 6.10−6.03 (m, 1H), 5.58 (br s, 1H), 4.30−4.21 (m, 1H), 3.06−2.96 (m, 2H), 1.24 (d, *J*= 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.6, 163.7 (d, J_{C-F} = 248.0 Hz), 137.3 (d, J_{C-F} = 8.3 Hz), 133.8 (d, J_{C-F} = 2.0 Hz), 132.1 (d, J_{C-F} = 3.0 Hz), 129.9 (d, J_{C-F} = 8.8 Hz), 125.9 (q, J_{C-F} = 274.9 Hz), 121.5 (q, J_{C-F} = 3.5 Hz), 115.3 (d, J_{C-F} = 21.5 Hz), 113.6 (q, J_{C-F} = 22.5 Hz), 42.4, 38.1 (q, J_{C-F} = 29.9 Hz), 22.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ 49.7 (t, J_{F-H} = 9.4 Hz), 5.5; IR (KBr) ν 3283, 2981, 1627, 1536, 1309, 1271, 1247, 1140, 1114, 1043, 968, 857, 739 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{16}F_4NO$ [M + H]$^+$ 290.1168, found 290.1165.

*(E)-N-Isopropyl-2,4-dimethyl-6-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3k**).* Yield 49.1 mg (82%); white solid; mp =103.1−106.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.93 (s, 1H), 6.67 (d, *J*= 15.7 Hz, 1H), 6.07−6.00 (m, 1H), 5.50 (d, *J*= 7.8 Hz, 1H), 4.34−4.26 (m, 1H), 2.99−2.90 (m, 2H), 2.29 (d, *J*= 6.6 Hz, 6H), 1.22 (d, *J*= 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.9, 138.9, 134.9, 134.4, 134.2, 133.3, 130.9, 126.1 (q, J_{C-F} = 275.1 Hz), 123.8, 119.6 (q, J_{C-F} = 3.6 Hz), 41.9, 38.1 (q, J_{C-F} = 29.7 Hz), 22.9, 21.4, 19.1; IR (KBr) ν 3283, 2981, 1627, 1536, 1309, 1271, 1247, 1140, 1114, 1043, 968, 857, 739 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{16}H_{21}F_3NO$ [M + H]$^+$ 300.1575, found 300.1574.

*(E)-N-Isopropyl-2-methoxy-6-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3l**).* Yield 47.7 mg (79%); white solid; mp =102.2−105.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J*= 8.0 Hz, 1H), 7.10 (d, *J*= 7.8 Hz, 1H), 6.81 (d, *J*= 8.2 Hz, 1H), 6.72 (d, *J*= 15.8 Hz, 1H), 6.10−6.03 (m, 1H), 5.62 (d, *J*= 7.8 Hz, 1H), 4.34−4.26 (m, 1H), 3.79 (s, 3H), 3.00−2.90 (m, 2H), 1.22 (d, *J*= 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5, 156.4, 135.4, 133.9, 130.2, 126.1, 125.9 (q, J_{C-F} = 273.2 Hz), 120.1 (q, J_{C-F} = 3.5 Hz), 118.2, 110.6, 56.1, 41.9, 38.1 (q, J_{C-F} = 29.6 Hz), 22.8; IR (KBr) ν 3276, 2971, 1636, 1577, 1469, 1250, 1132, 1113, 1083, 1045, 966, 739, 654 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{15}H_{19}F_3NO_2$ [M + H]$^+$ 302.1368, found 302.1371.

*(E)-2-Chloro-N-isopropyl-6-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3m**).* Yield 32.1 mg (52%); white solid; mp =94.2−96.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J*= 6.9 Hz, 1H), 7.29−7.23 (m, 2H), 6.67 (d, *J*= 15.8 Hz, 1H), 6.14−6.06 (m, 1H), 5.62 (d, *J*= 7.5 Hz, 1H), 4.36−4.27 (m, 1H), 3.02−2.92 (m, 2H), 1.25 (d, *J*= 6.5 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.7, 135.8, 135.7, 133.1, 131.3, 130.2, 129.1, 125.9 (q, J_{C-F} = 279.4 Hz), 124.3, 121.5 (q, J_{C-F} = 3.6 Hz), 42.3, 38.1 (q, J_{C-F} = 29.8 Hz), 22.7; IR (KBr) ν 3255, 2973, 1635, 1545, 1453, 1255, 1132, 1111, 1051, 963, 882, 743, 706

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cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{16}ClF_3NO$ $[M + H]^+$ 306.0873, found 306.0877.

*(E)-N-Isopropyl-5-methyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3n**).* Yield 50.8 mg (89%); white solid; mp =133.2−135.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J= 7.9 Hz, 1H), 7.23 (s, 1H), 7.18 (d, J= 8.0 Hz, 1H), 6.89 (d, J= 15.8 Hz, 1H), 6.04−5.97 (m, 1H), 5.62 (d, J= 6.9 Hz, 1H), 4.30−4.21 (m, 1H), 3.02−2.93 (m, 2H), 2.34 (s, 3H), 1.23 (d, J= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 138.3, 135.8, 134.5, 131.6, 131.1, 128.1, 126.7, 126.1 (q, J_{C-F} = 275.0 Hz), 119.2 (q, J_{C-F} = 3.6 Hz), 42.2, 38.2 (q, J_{C-F} = 29.5 Hz), 22.9, 21.2; IR (KBr) ν 3280, 2924, 1631, 1536, 1457, 1367, 1254, 1138, 1115, 1042, 966, 827, 739 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{15}H_{19}F_3NO$ $[M + H]^+$ 286.1419, found 286.1419.

*(E)-N-Isopropyl-3-(4,4,4-trifluorobut-1-en-1-yl)-2-naphthamide (**3o**).* Yield 36.8 mg (57%); white solid; mp =171.2−174.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 2H), 7.80 (t, J= 6.6 Hz, 2H), 7.53−7.45 (m, 2H), 7.03 (d, J= 15.7 Hz, 1H), 6.17−6.10 (m, 1H), 5.85 (d, J= 7.4 Hz, 1H), 4.36−4.24 (m, 1H), 3.08−2.98 (m, 2H), 1.27 (d, J= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.5, 134.9, 134.0, 133.9, 132.4, 132.1, 128.2, 128.1, 127.7, 127.4, 127.0, 126.2, 126.1 (q, J_{C-F} = 274.9 Hz), 120.1 (q, J_{C-F} = 3.5 Hz), 42.3, 38.2 (q, J_{C-F} = 29.6 Hz), 22.9; IR (KBr) ν 3278, 2979, 1632, 1541, 1450, 1348, 1247, 1140, 1113, 1041, 966, 897, 745 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{18}H_{19}F_3NO$ $[M + H]^+$ 322.1419, found 322.1421.

*(E)-3-(Benzyloxy)-N-isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3p**).* Yield 43.8 mg (58%); white solid; mp =120.2−123.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.30 (m, 5H), 7.20 (t, J= 7.9 Hz, 1H), 6.99 (t, J= 7.6 Hz, 2H), 6.75 (d, J= 16.1 Hz, 1H), 6.35−6.28 (m, 1H), 5.56 (d, J= 7.6 Hz, 1H), 5.11 (s, 2H), 4.28−4.19 (m, 1H), 2.99−2.89 (m, 2H), 1.22 (d, J= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.0, 156.9, 138.6, 136.7, 129.9, 128.8, 128.7, 128.2, 127.4, 126.1 (q, J_{C-F} = 275.1 Hz), 123.7 (q, J_{C-F} = 3.6 Hz), 123.2, 120.1, 113.9, 70.9, 42.1, 39.1 (q, J_{C-F} = 29.5 Hz), 22.8; IR (KBr) ν 3284, 2978, 1629, 1530, 1453, 1347, 1255, 1132, 1115, 1038, 965, 739, 697 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{21}H_{23}F_3NO_2$ $[M + H]^+$ 378.1681, found 378.1688.

*(E)-5-(Benzyloxy)-N-isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3p′**).* Yield 20.5 mg (27%); white solid; mp =143.7−147.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.33 (m, 6H), 7.04 (d, J= 2.7 Hz, 1H), 6.99 (dd, J= 8.6, 2.7 Hz, 1H), 6.86 (d, J= 15.8 Hz, 1H), 5.98−5.90 (m, 1H), 5.57 (d, J= 7.4 Hz, 1H), 5.08 (s, 2H), 4.30−4.22 (m, 1H), 3.02−2.92 (m, 2H), 1.23 (d, J= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.2, 158.6, 137.1, 136.6, 134.1, 128.9, 128.4, 128.3, 127.7, 127.3, 126.1 (q, J_{C-F} = 274.9 Hz), 118.3 (q, J_{C-F} = 3.5 Hz), 117.1, 113.7, 70.4, 42.2, 38.2 (q, J_{C-F} = 29.5 Hz), 22.9; IR (KBr) ν 3277, 2917, 1628, 1600, 1536, 1455, 1365, 1244, 1137, 1113, 1038, 967, 737, 698 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{21}H_{23}F_3NO_2$ $[M + H]^+$ 378.1681, found 378.1684.

*(E)-3-Bromo-N-isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3q**).* Yield 25.0 mg (36%); light yellow solid; mp =93.4−96.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J= 8.0 Hz, 1H), 7.33 (dd, J= 7.5 Hz, 1H), 7.13 (t, J= 7.8 Hz, 1H), 6.73 (d, J= 16.1 Hz, 1H), 5.96−5.88 (m, 1H), 5.58 (d, J= 6.6 Hz, 1H), 4.21−4.12 (m, 1H), 3.04−2.95 (m, 2H), 1.20 (d, J= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 138.7, 134.5, 134.1, 133.7, 129.9, 128.9, 126.9, 125.4 (q, J_{C-F} = 275.2 Hz), 124.7 (q, J_{C-F} = 3.6 Hz), 42.3, 38.2 (q, J_{C-F} = 29.9 Hz), 22.7; IR (KBr) ν 3262, 2973, 1631, 1537, 1428, 1348, 1250, 1133, 1103, 1048, 965, 893, 739, 699 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{16}BrF_3NO$ $[M + H]^+$ 350.0367, found 350.0375.

*(E)-5-Bromo-N-isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3q′**).* Yield 17.8 mg (25%); white solid; mp =134.8−137.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.49 (dd, J= 8.4, 2.0 Hz, 1H), 7.36 (d, J= 8.3 Hz, 1H), 6.85 (d, J= 15.8 Hz, 1H), 6.08−6.01 (m, 1H), 5.68 (d, J= 7.1 Hz, 1H), 4.28−4.19 (m, 1H), 3.03−2.93 (m, 2H), 1.23 (d, J= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 137.4, 133.6, 133.4, 133.3, 130.5, 128.3, 125.9 (q, J_{C-F} = 275.1 Hz), 121.9, 120.9 (q, J_{C-F} = 3.5 Hz), 42.4, 38.1 (q, J_{C-F} = 29.8 Hz), 22.8; IR (KBr) ν 3276, 2924, 1632, 1536, 1467, 1306, 1251, 1137, 1110, 1045, 969, 896, 830, 738 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{16}BrF_3NO$ $[M + H]^+$ 350.0367, found 350.0374.

*(E)-3-Chloro-N-isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3r**).* Yield 18.7 mg (31%); white solid; mp =115.6−118.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J= 7.8 Hz, 1H), 7.27 (d, J= 7.1 Hz, 1H), 7.19 (t, J= 7.8 Hz, 1H), 6.74 (d, J= 16.1 Hz, 1H), 6.02−5.94 (m, 1H), 5.68 (d, J= 6.7 Hz, 1H), 4.20−4.12 (m, 1H), 3.04−2.94 (m, 2H), 1.19 (d, J= 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 138.6, 134.1, 132.7, 131.4, 130.9, 128.7, 126.2, 125.8 (q, J_{C-F} = 275.1 Hz), 124.9 (q, J_{C-F} = 3.5 Hz), 42.3, 38.3 (q, J_{C-F} = 29.8 Hz), 22.6; IR (KBr) ν 3267, 2973, 1633, 1533, 1433, 1347, 1257, 1239, 1129, 1106, 1051, 959, 707, 658 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{16}ClF_3NO$ $[M + H]^+$ 306.0873, found 306.0876.

*(E)-5-Chloro-N-isopropyl-2-(4,4,4-trifluorobut-1-en-1-yl)-benzamide (**3r′**).* Yield 13.1 mg (21%); white solid; mp =126.3−128.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J= 8.4 Hz, 1H), 7.38 (s, 1H), 7.32 (dd, J= 8.3, 2.1 Hz, 1H), 6.86 (d, J= 15.8 Hz, 1H), 6.07−5.99 (m, 1H), 5.71 (d, J= 7.1 Hz, 1H), 4.28−4.19 (m, 1H), 3.03−2.93 (m, 2H), 1.23 (d, J= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.1, 137.2, 134.0, 133.5, 132.9, 130.3, 128.1, 127.6, 125.9 (q, J_{C-F} = 275.1 Hz), 120.7 (q, J_{C-F} = 3.6 Hz), 42.4, 38.1 (q, J_{C-F} = 29.8 Hz), 22.8; IR (KBr) ν 3278, 2924, 1632, 1536, 1468, 1305, 1250, 1136, 1119, 1044, 969, 902, 831, 741 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{16}ClF_3NO$ $[M + H]^+$ 306.0873, found 306.0876.

*(E)-N-Isopropyl-4-(4,4,4-trifluorobut-1-en-1-yl)benzo[d][1,3]-dioxole-5-carboxamide (**3s**).* Yield 49.9 mg (79%); white solid; mp = 147.0−150.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J= 8.0 Hz, 1H), 6.76 (d, J= 16.0 Hz, 1H), 6.68 (d, J= 8.0 Hz, 1H), 6.49−6.41 (m, 1H), 6.04 (s, 2H), 5.66 (d, J= 7.0 Hz, 1H), 4.26−4.18 (m, 1H), 3.04−2.94 (m, 2H), 1.22 (d, J= 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 149.0, 146.0, 130.6, 129.2, 126.1 (q, J_{C-F} = 275.0 Hz), 123.8 (q, J_{C-F} = 3.5 Hz), 121.7, 117.4, 107.3, 101.7, 42.2, 38.7 (q, J_{C-F} = 29.7 Hz), 22.9; IR (KBr) ν 3274, 2922, 1632, 1540, 1453, 1265, 1247, 1131, 1117, 1026, 971, 807, 741, 667 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{15}H_{17}F_3NO_3$ $[M + H]^+$ 316.1161, found 316.1161.

*(E)-N-Isopropyl-3-(4,4,4-trifluorobut-1-en-1-yl)thiophene-2-carboxamide (**3t**).* Yield 8.9 mg (16%); white solid; mp = 84.4−88.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J= 16.0 Hz, 1H), 7.27 (d, J= 5.5 Hz, 1H), 7.22 (d, J= 5.2 Hz, 1H), 6.09−6.01 (m, 1H), 5.64 (brs, 1H), 4.26−4.18 (m, 1H), 3.06−2.96 (m, 2H), 1.24 (d, J= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.9, 140.6, 132.3, 130.2, 127.1, 126.7, 127.4 (q, J_{C-F} = 275.0 Hz), 121.0 (q, J_{C-F} = 3.5 Hz), 42.4, 38.1 (q, J_{C-F} = 29.8 Hz), 23.0; IR (KBr) ν 3284, 2975, 1610, 1534, 1427, 1365, 1245, 1133, 1104, 1051, 970, 856, 740 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{12}H_{15}F_3NOS$ $[M + H]^+$ 278.0826, found 278.0826.

*(2Z,4E)-7,7,7-Trifluoro-N-isopropyl-2,3-dimethylhepta-2,4-dienamide (**3u**).* Yield 6.6 mg (13%); white solid; mp = 98.2−101.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, J= 16.0 Hz, 1H), 5.63−5.55 (m, 1H), 5.34 (d, J= 6.7 Hz, 1H), 4.22−4.09 (m, 1H), 2.90−2.80 (m, 2H), 1.94 (s, 3H), 1.79 (s, 3H), 1.18 (d, J= 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.9, 136.3, 133.8, 131.1, 127.4 (q, J_{C-F} = 275.0 Hz), 117.7 (q, J_{C-F} = 3.5 Hz), 41.7, 37.8 (q, J_{C-F} = 29.4 Hz), 22.9, 17.1, 14.0; IR (KBr) ν 3263, 2972, 1630, 1534, 1457, 1385, 1247, 1128, 1043, 963, 858, 740, 659 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{12}H_{19}F_3NO$ $[M + H]^+$ 250.1419, found 250.1418.

Experimental Procedure and Characterization Data for the Synthesis of Phthalide 5a. To a stirred solution of **3a** (54.3 mg, 0.2 mmol) in CH_2Cl_2/phosphate buffer (2 mL, 1:1, pH = 7.0) was added *m*-CPBA (172.6 mg, 1.0 mmol) at 0 °C. After stirring for 3 h, the mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 7:1) to afford phthalide **5a** (35.1 mg) in 71% yield as colorless oil.

*(R′)-3-((S′)-3,3,3-Trifluoro-1-hydroxypropyl)isobenzofuran-1(3H)-one (**5a**).* Yield 35.1 mg (71%); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J= 7.6 Hz, 1H), 7.73 (t, J= 7.6 Hz, 1H), 7.66 (d, J= 7.5 Hz, 1H), 7.60 (t, J= 7.5 Hz, 1H), 5.37 (d, J= 6.4 Hz, 1H), 4.23−4.17 (m, 1H), 2.60 (d, J= 5.6 Hz, 1H), 2.57−2.44 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 146.6, 134.7, 130.3, 126.4, 126.3 (q, J_{C-F} = 275.0 Hz), 126.2, 123.6, 81.6, 68.3 (q, J_{C-F} = 2.9 Hz), 37.7 (q, J_{C-F} = 27.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ 52.5 (t, J_{F-H} = 10.3

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Hz); IR (KBr) ν 2916, 2851, 1754, 1597, 1466, 1252, 1147, 1037, 995, 877, 747 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{11}H_{10}F_3O_3$ $[M]^+$ 247.0582, found 247.0590.

Experimental Procedure and Characterization Data for the Synthesis of Difluorodiene 5b. To a stirred solution of **3a** (54.3 mg, 0.2 mmol) in DMF (2 mL) was added NaH (5.3 mg, 0.22 mmol, 60% in mineral oil) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. The resulting solution was carefully quenched with *s*-NH_4Cl (1 mL), and the aqueous layer was extracted with EtOAc (2 mL × 2). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 8:1) to afford difluorodiene **5b** (16.2 mg) in 32% yield as a pale yellow solid.

*(E)-2-(4,4-Difluorobuta-1,3-dienyl)-N-isopropylbenzamide (**5b**).* Yield 16.2 mg (32%); pale yellow solid; mp = 128.7−130.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J*= 7.8 Hz, 1H), 7.39−7.35 (m, 2H), 7.25 (d, *J*= 7.8 Hz, 1H), 6.82 (d, *J*= 15.8 Hz, 1H), 6.62 (dd, *J*= 15.8, 10.9 Hz, 1H), 5.61 (br s, 1H), 5.15 (dd, *J*= 24.0, 10.9 Hz, 1H), 4.32−4.23 (m, 1H), 1.24 (d, *J*= 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.8, 157.2 (dd, J_{C-F} = 338.7, 290.6 Hz), 135.8, 135.1, 130.2, 128.3 (dd, J_{C-F} = 11.6, 3.2 Hz), 127.7, 127.5, 126.1, 120.4 (dd, J_{C-F} = 4.4, 2.2 Hz), 83.1 (dd, J_{C-F} = 27.5, 16.5 Hz), 42.1, 23.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ 31.0 (dd, J_{F-F} = 24.4 Hz, J_{F-H} = 24.0 Hz), 29.5 (d, J_{F-F} = 24.3 Hz); IR (KBr) ν 3284, 2850, 1715, 1625, 1529, 1349, 1286, 1180, 1037, 933, 746 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{14}H_{16}F_2NO$ $[M]^+$ 252.1200, found 252.1204.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02485.

Spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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