JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Stereoselective Organocatalytic Synthesis of α,α-Difluoro-γ,γ-Disubstituted Butenals

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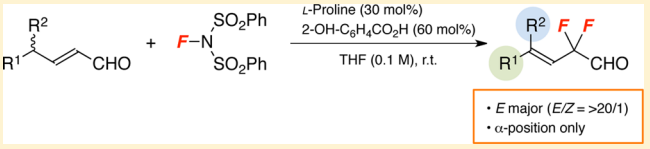
Supporting Information

ABSTRACT: A highly stereoselective reaction of α,α-difluoro-γ,γ-disubstituted butenals **2** bearing two different substituents at the γ position has been developed with an organocatalytic system of L-proline (30 mol %) and salicylic acid (60 mol %). This novel reaction demonstrated a wide substrate scope and excellent *E* stereoselectivity in most cases. The obtained difluorinated aldehyde **2a** was applied as a useful synthetic precursor for constructing 3,3-disubstituted allylic difluoride moieties.



INTRODUCTION

The allylic motif has been found in many bioactive compounds and medicines, and compounds with a fluorine atom at the α position of an allylic moiety, allylic fluorides, have exhibited excellent enhancement of the bioactivity of their parent compounds, as shown in Figure 1.[1] Furthermore, allyl fluorides

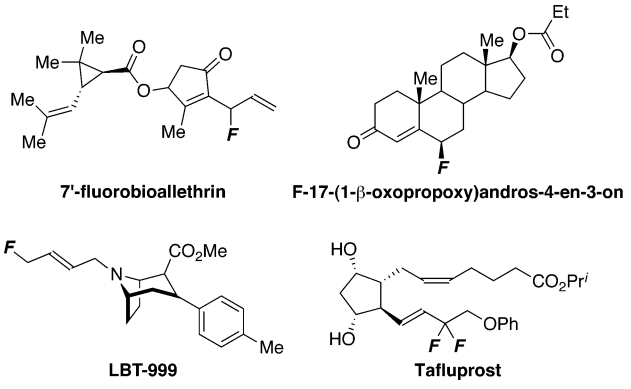
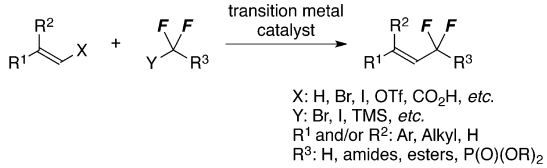


Figure 1. Examples of bioactive allylic fluorides.

have served as versatile intermediates in the synthesis of a large number of fluorinated compounds,[2] motivating the development of numerous synthesis methods with controlled regio- and stereoselectivity for allylic fluorides.[3]

The importance of allylic difluorides has been validated by the success of Tafluprost, a potent prostanoid FP receptor agonist that has been commercialized for the treatment of glaucoma.[4] The most common method of synthesizing allylic difluorides is the deoxygenative fluorination of allylic ketones with diethylaminosulfur trifluoride (DAST) or its derivatives used for manufacturing of Tafluprost and other medicinal compounds.[5] Recent extensive efforts focusing on the transition metal-catalyzed reaction of vinylic coupling units with CF_2-containing reagents have led to the emergence of an alternative protocol for the synthesis of allylic difluorides with high efficiency and high reliability (Scheme 1).[6]

Scheme 1. Recent Examples of Transition Metal-Catalyzed Reactions for the Synthesis of Allylic Difluorides



Among all possible substitutional patterns of allylic difluorides, 3-monosubstituted allylic difluorides have been more frequently reported than 3,3-disubstituted allylic difluorides;[7] to date, no general synthesis for 3,3-disubstituted allylic difluorides with nonequivalent substituents ($R^1 \neq R^2$)[8] has been described (Figure 2) because of the inaccessibility of vinylic compounds with highly controlled stereoconfigurations.

During the past several decades, organocatalysis has become the norm for environmentally friendly stereoselective reactions. Recently, electrophilic functionalization of dienamine intermediates generated from γ-enolizable α,β-unsaturated alde-

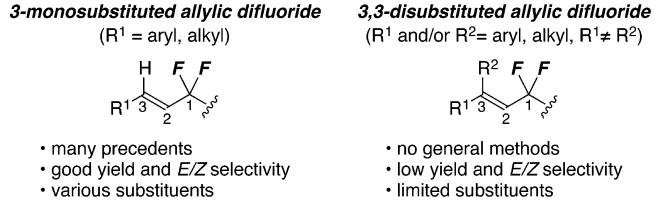
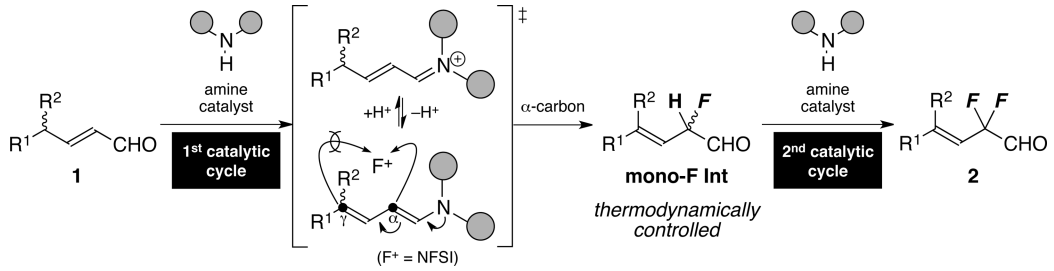


Figure 2. Summary of structural features of allylic difluorides.

Received: June 5, 2016
Published: July 6, 2016

DOI: 10.1021/acs.joc.6b01334
J. Org. Chem. 2016, 81, 6707−6713

Scheme 2. Our Strategy, Difluorination of Enolizable α,β-Unsaturated Aldehydes



hydes has gained attention as a new subject of organocatalysis.[9] Dienamine intermediates are known to react with electrophiles at the α or γ position;[10] therefore, if this vinylogous principle could be applied in an electrophilic fluorination, a wide variety of allylic fluorides could be prepared.

Here, we report the first highly regio- and stereoselective organocatalytic synthesis of α,α-difluoro-γ,γ-disubstituted butenals; these compounds are useful synthetic intermediates for many types of 3,3-disubstituted allylic difluorides.

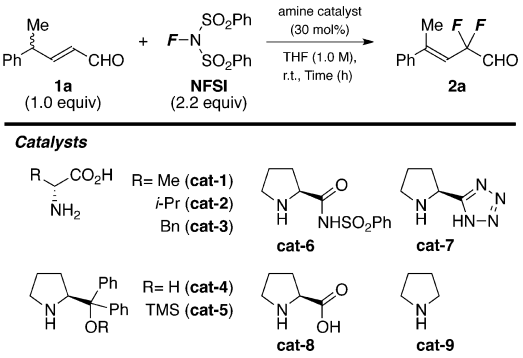
The details of our synthetic strategy are depicted in Scheme 2. Although a dienamine intermediate possesses ambident nucleophilicity at both α and γ positions, in the case of γ,γ-disubstituted α,β-unsaturated aldehydes **1**, the reaction at the γ position can be suppressed because of steric hindrance; therefore, the first fluorination can presumably be performed at only the α position to produce the monofluorinated aldehyde, **mono-F INT**, with the thermodynamically favored stereochemistry on the vinylic moiety. Furthermore, the second fluorination can occur smoothly to furnish allylic difluorides **2** because the presence of a fluorine at the α position will enhance the reactivity toward the amino catalyst.[11] Notably, stereocontrolled prefunctionalization of starting material **1** is not necessary for this strategy.

RESULTS AND DISCUSSION

The initial investigation commenced with the screening of the amine catalyst. Thus, treatment of (*E*)-4-phenyl-2-enal **1a**[12] and *N*-fluorobenzenesulfonimide (NFSI) with a catalytic amount of an amine catalyst (30 mol %) in THF at room temperature produced the corresponding α,α-difluorobutenal **2a** with excellent regio- and stereoselectivity; only α fluorination and the *E* isomer were observed in all cases (Table 1). In general, primary amine catalysts gave low yields because of the formation of many nonfluorinated byproducts (entries 1−3). By contrast, secondary amine catalysts gave cleaner reaction profiles (entries 4−8); in particular, the use of L-proline resulted in a good yield of the corresponding product **2a** in just 3 h (entry 8). Interestingly, the presence of acidic functional groups in secondary amines can play a critical role in smooth reaction (entries 6−8), and the possibility of hydrogen bonding between the dienamine intermediate and NFSI is indicated by a comparison of catalyst efficacy for L-proline and pyrrolidine (entries 8 and 9, respectively).[13] It is important to mention that all efforts to isolate **2a** failed because of the volatile and unstable nature of **2a**; therefore, a reduction of **2a** to corresponding alcohol **3a** was necessary for successful purification and characterization.[14]

We next screened solvents and additives; the results are listed in Table 2. The reactions were performed in various solvents, and substantial solvent effects were observed. The use of cyclic ethers such as 1,4-dioxane and THF resulted in good yields

Table 1. Catalyst Screening



entry	amine catalyst	time (h)[a]	*E*/*Z* of **2a**[b]	yield of **2a** (%)[c]
1	**cat-1**	8	>20/1	28
2	**cat-2**	8	>20/1	32
3	**cat-3**	5	>20/1	23
4	**cat-4**	24	>20/1	24[d]
5	**cat-5**	24	>20/1	45[d]
6	**cat-6**	6	>20/1	50
7	**cat-7**	6	>20/1	68
8	**cat-8**	3	>20/1	80
9	**cat-9**	24	>20/1	41[d]

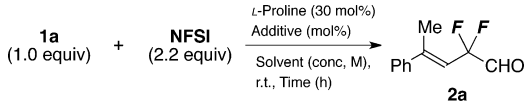
[a]The reaction time was determined by monitoring consumption of the starting material **1a** by TLC. [b]The stereoselectivity was determined by ^{1}H NMR of the reaction mixture after reduction to its alcohol **3a** by $NaBH_4$. [c]The yield of **2a** was determined by ^{19}F NMR. [d]The starting material **1a** remained after 24 h.

(entries 4 and 5, respectively), whereas other solvents gave a sluggish reaction (entries 1−3, 6, and 7) or a complex reaction mixture (entry 8). Among all of the tested solvents, THF was observed to be optimal, and the yield was dramatically improved by lowering the concentration despite the longer reaction time (entry 9). To shorten the reaction time, we next surveyed the effect of Brønsted acid additives (entries 10−16). When relatively stronger Brønsted acids were utilized, the *E*/*Z* isomer ratio decreased (entries 10 and 11); however, benzoic acid and its analogues allowed for a shorter reaction time, with excellent *E*/*Z* ratios (entries 12−15), where salicylic acid was observed to be the best additive.[15] Finally, increasing the amount of salicylic acid (60 mol %) dramatically accelerated the reaction speed and produced target compound **2** with excellent selectivity and yield (entry 16).

After determining the optimal conditions, we examined the scope of the substrates with regard to γ-enolizable α,β-unsaturated aldehydes **1** (Table 3). Aldehydes with *para*-substituted aromatics on R^1 possessing either electron-withdrawing (entries 2−4) or electron-donating (entries 5 and 6) functional groups gave only the *E* isomer (*E*/*Z* = >20/1) in

DOI: 10.1021/acs.joc.6b01334
J. Org. Chem. 2016, 81, 6707−6713

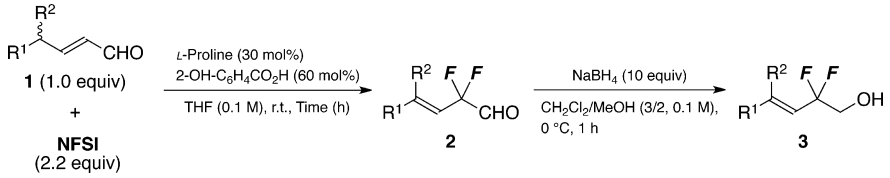
Table 2. Optimization of the Reaction



entry	solvent (conc, M)	additive (mol %)	time (h)[a]	E/Z of **2a**[b]	yield of **2a** (%)[c]
1	toluene (1.0)	–	24	>20/1	8
2	CH_2Cl_2 (1.0)	–	24	>20/1	28
3	Et_2O (1.0)	–	24	>20/1	57
4	1,4-dioxane (1.0)	–	8	>20/1	72
5	THF (1.0)	–	3	>20/1	80
6	MeCN (1.0)	–	24	>20/1	53
7	DMF (1.0)	–	24	>20/1	60
8	*i*-PrOH (1.0)	–	12	–	no reaction
9	THF (0.1)	–	24	>20/1	94
10	THF (0.1)	TFA (30)	5	11/1	83
11	THF (0.1)	*p*-TsOH (30)	24	18/1	69
12	THF (0.1)	$PhCO_2H$ (30)	15	>20/1	79
13	THF (0.1)	4-MeO-$C_6H_4CO_2H$ (30)	15	>20/1	82
14	THF (0.1)	4-CF_3-$C_6H_4CO_2H$ (30)	15	>20/1	84
15	THF (0.1)	2-OH-$C_6H_4CO_2H$ (30)	15	>20/1	94
16	THF (0.1)	2-OH-$C_6H_4CO_2H$ (60)	3	>20/1	98 (79)[d]

[a]The reaction time was determined by monitoring consumption of the starting material **1a** by TLC. [b]The stereoselectivity was determined by ^{1}H NMR of the reaction mixture after reduction to its alcohol **3a** by $NaBH_4$. [c]The yield of **2a** was determined by ^{19}F NMR. [d]The value in parentheses is the isolated yield of its alcohol **3a**.

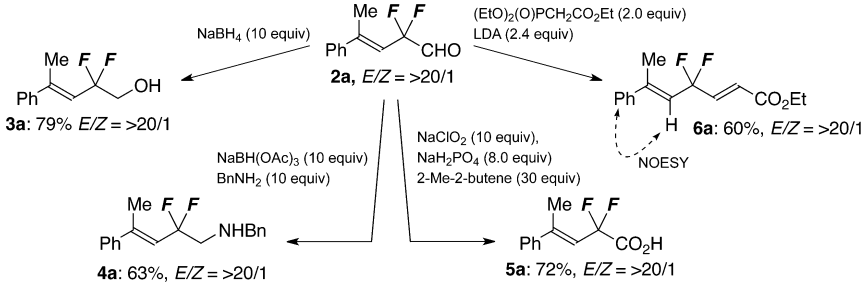
Table 3. Scope of Substrates



entry	R^1	R^2	time (h)[a]	E/Z of **2**[b]	yield of **2** (%)[c]	yield of **3** (%)[d]
1	Ph	Me	3	>20/1	**2a**, 98	**3a**, 79
2	4-F-C_6H_4	Me	3	>20/1	**2b**, 93	**3b**, 74
3	4-Cl-C_6H_4	Me	5	>20/1	**2c**, 80	**3c**, 70
4	4-Br-C_6H_4	Me	3	>20/1	**2d**, 96	**3d**, 75
5	4-Me-C_6H_4	Me	5	>20/1	**2e**, 99	**3e**, 79
6	4-MeO-C_6H_4	Me	5	>20/1	**2f**, 98	**3f**, 72
7	3-MeO-C_6H_4	Me	3	>20/1	**2g**, 96	**3g**, 70
8	2-MeO-C_6H_4	Me	12	5/1	**2h**, 86	**3h**, 77
9	Ph	Et	7	>20/1	**2i**, 82	**3i**, 66
10	Ph	H	5	>20/1	**2j**, 99	**3j**, 72
11	$PhCH_2$	Me	5	3/1	**2k**, 82	**3k**, 77
12	*n*-Hex	H	5	1.8/1	**2l**, 90	**3l**, 60

[a]The reaction time was determined by monitoring consumption of the starting material **1** by TLC. [b]The stereochemistry was determined by ^{1}H NMR of the reaction mixture after reduction to its alcohol **3** by $NaBH_4$. [c]The yield of **2** was determined by ^{19}F NMR. [d]Isolated yield.

Scheme 3. Synthetic Application of 2a



DOI: 10.1021/acs.joc.6b01334
J. Org. Chem. 2016, 81, 6707–6713

good yields. The influence of the steric hindrance was apparent in the case of *ortho* substitution on R^1 and gave rise to a longer reaction time with diminished *E*/*Z* selectivity (entry 8); however, *meta* substitution on R^1 still afforded an excellent result (entry 7). The other substituents on R^2, such as Et and H instead of Me, also gave excellent selectivity and good yields as long as a phenyl group was present on R^1 (entries 9 and 10). By contrast, the *E* selectivity was drastically decreased in the case of aliphatic groups on R^1 (entries 11 and 12). Although the comprehensive reaction mechanism and the origin of excellent regio- and stereoselectivity are still under investigation, it is apparent that the steroisomers of dienamine intermediates with an aliphatic group can be close in energy,[16] and this could be one of the reasons for poor *E* selectivity. Notably, in all cases, the corresponding monofluorinated intermediates were not observed under our optimal reaction conditions.

The obtained α,α-difluoro butenal **2a** was demonstrated to be a useful synthetic precursor for constructing various 3,3-disubstituted allylic difluorides, including homoallylic alcohol **3a** and amine **4a**, carboxylic acid **5a**, and 1,4-diene **6a**, without touching the excellent *E*/*Z* ratio of **2a** (Scheme 3). The *E* configuration of all products was determined by comparison of the chemical shifts and coupling constants with those of **6a**, for which the stereochemistry was revealed by NOESY experiments (see the Supporting Information).

CONCLUSION

In summary, we developed the first stereoselective organocatalytic synthesis of α,α-difluoro-γ,γ-disubstituted butenal bearing two different substituents at the γ position, with high *E* selectivity in most cases. Thus, the combination of L-proline (30 mol %) and salicylic acid (60 mol %) in THF (0.1 M) facilitated the smooth difluorination of γ-enolizable α,β-unsaturated aldehyde **1** at room temperature and gave the desired difluorinated aldehyde **2** with excellent *E* selectivity and good yield as long as R^1 was the aromatic group. Under these optimal reaction conditions, monofluorinated aldehydes were not observed. Investigations of the enantioselective synthesis of α-monofluorinated butenals are continuing in our laboratory. Difluorinated aldehyde **2a** has been demonstrated to be a useful synthetic unit for constructing 3,3-disubstituted allylic difluorides maintaining the *E* configuration.

EXPERIMENTAL SECTION

General Information. All commercially available reagents were used without further purification. All solvents were dried on MS 3A or by the reported procedure. ^{1}H NMR spectra were recorded using a 400 or 500 MHz NMR spectrometer. Data were reported as follows: chemical shifts in parts per million from tetramethylsilane as an internal standard in $CDCl_3$, integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet doublet; m, multiplet; br, broad), coupling constants (hertz), and assignment. ^{13}C NMR spectra were recorded using a 100 or 125 MHz NMR spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million from the residual solvent as an internal standard. ^{19}F NMR spectra were recorded using a 376 or 470 MHz NMR spectrometer. The ^{19}F NMR yield in the mixture was obtained using (trifluoromethoxy)benzene as an internal reference. High-resolution mass spectroscopy (HRMS) was performed using an LTQ Orbitrap ESI ion trap or FAB. For thin-layer chromatography (TLC) analysis, TLC plates (silica gel 60 F_{254}) were used. The products were purified by flash column chromatography on silica gel 60 (spherical, neutral, 40−50 μm). *trans*-2-Decenal (**1l**) was purchased and used without purification.

General Procedure for γ-Enolizable α,β-Unsaturated Aldehydes 1.[12] *Step i: Wittig reaction.* To a stirred solution of the branched aldehyde[17] (1.0 equiv) in anhydrous DCM (2.0 M) was added methyl(triphenylphosphoranyliden)acetate (1.1 equiv) in one portion at 0 °C. The reaction mixture was stirred at room temperature for 3 days until aldehyde was consumed. Then, the solvent was removed under reduced pressure, and a hexane/Et_2O mixture (1/1) was added to the residue at 0 °C. The precipitated solid was removed by Celite filtration and washed several times with a cold hexane/Et_2O mixture (1/1). The solvent of a filtrate was removed under reduced pressure. The residue was purified by flash chromatography to afford the ester.

Step ii: Reduction by DIBAL-H. To a stirred solution of the obtained ester (1.0 equiv) in anhydrous DCM (0.2 M) was added dropwise DIBAL-H (2.5 equiv, 1.0 M in Hexane) under an argon atmosphere at −78 °C. After being stirred for 2 h at −78 °C, the mixture was allowed to warm to 0 °C, and the reaction was quenched by MeOH. After addition of a saturated aqueous solution of potassium sodium tartrate at room temperature and stirring for 1 h, the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure after filtration. The residue was purified by flash chromatography to afford the alcohol.

Step iii: Oxidation by IBX. To a stirred solution of the obtained allylic alcohol (1.0 equiv) in anhydrous DMSO (0.2 M) was added a solution of IBX (2.0 equiv) in DMSO (0.4 M), and the whole solution was stirred for 30 min at room temperature. Then H_2O was added to the reaction mixture, and the resulting cloudy suspension was filtered through Celite and washed with EtOAc. The filtrate was extracted with EtOAc, and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure after filtration. The residue was purified by flash chromatography to afford α,β-unsaturated aldehyde **1**.

*(2E)-4-Phenylpent-2-enal (**1a**).*[12] Purification by flash chromatography (SiO_2, 20/1 hexane/EtOAc) afforded **1a** (1.30 g, 8.10 mmol, 81% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (3H, d, *J* = 7.0 Hz), 3.73 (1H, quint, *J* = 6.6 Hz), 6.11 (1H, ddd, *J* = 15.6, 7.8, 1.4 Hz), 6.96 (1H, dd, *J* = 15.6, 6.4 Hz), 7.18−7.35 (5H, m), 9.53 (1H, d, *J* = 7.8 Hz).

*(2E)-4-(4-Fluorophenyl)pent-2-enal (**1b**).* Purification by flash chromatography (SiO_2, 20/1 hexane/EtOAc) afforded **1b** (0.46 g, 2.60 mmol, 87% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, d, *J* = 7.0 Hz), 3.73 (1H, quint, *J* = 6.8 Hz), 6.08 (1H, dd, *J* = 15.6, 7.7 Hz), 6.91 (1H, dd, *J* = 15.6, 6.3 Hz), 7.00−7.04 (2H, m), 7.15−7.26 (2H, m), 9.54 (1H, d, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 41.7, 115.6 (d, *J* = 21.2 Hz), 128.7 (d, *J* = 7.9 Hz), 131.3, 138.3 (d, *J* = 3.3 Hz), 161.2, 161.8 (d, *J* = 245.4 Hz), 193.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.6 (1F, m); HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{11}H_{12}FO$) *m*/*z* 179.0872, found *m*/*z* 179.0863.

*(2E)-4-(4-Chlorophenyl)pent-2-enal (**1c**).* Purification by flash chromatography (SiO_2, 20/1 hexane/EtOAc) afforded **1c** (0.36 g, 1.86 mmol, 62% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, d, *J* = 7.0 Hz), 3.72 (1H, quint, *J* = 6.8 Hz), 6.09 (1H, dd, *J* = 15.6, 7.7 Hz), 6.91 (1H, dd, *J* = 15.6, 6.3 Hz), 7.13 (2H, *J* = 8.2 Hz), 7.30 (2H, *J* = 8.2 Hz), 9.53 (1H, d, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 41.8, 128.7, 129.0, 131.4, 132.8, 141.1, 160.7, 193.7; HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{11}H_{12}ClO$) *m*/*z* 195.0577, found *m*/*z* 195.0575.

*(2E)-4-(4-Bromophenyl)pent-2-enal (**1d**).* Purification by flash chromatography (SiO_2, 40/1 hexane/EtOAc) afforded **1d** (0.51 g, 2.14 mmol, 71% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, d, *J* = 7.0 Hz), 3.71 (1H, quint, *J* = 6.7 Hz), 6.09 (1H, dd, *J* = 15.6, 7.7 Hz), 6.91 (1H, dd, *J* = 15.6, 6.3 Hz), 7.07 (2H, d, *J* = 8.28 Hz), 7.46 (2H, d, *J* = 8.3 Hz), 9.53 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 41.9, 120.9, 129.0, 131.5, 132.0, 141.6, 160.6, 193.7; HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{11}H_{12}BrO$) *m*/*z* 239.0072, found *m*/*z* 239.0081.

*(2E)-4-(4-Methylphenyl)pent-2-enal (**1e**).* Purification by flash chromatography (SiO_2, 40/1 hexane/EtOAc) afforded **1e** (0.42 g, 2.42 mmol, 80% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$)

DOI: 10.1021/acs.joc.6b01334
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δ 1.46 (3H, d, J = 7.0 Hz), 2.33 (3H, s), 3.70 (1H, quint, J = 6.8 Hz), 6.10 (1H, dd, J = 15.6, 7.7 Hz), 6.94 (1H, dd, J = 15.6, 6.4 Hz), 7.09 (2H, d, J = 7.0 Hz), 7.15 (2H, d, J = 7.9 Hz), 9.52 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 21.0, 42.1, 127.1, 129.5, 131.0, 136.7, 139.6, 162.0, 194.1; HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{12}H_{14}O$) m/z 175.1123, found m/z 175.1113.

*(2E)-4-(4-Methoxyphenyl)pent-2-enal (**1f**).* Purification by flash chromatography (SiO_2, 20/1 hexane/EtOAc) afforded **1f** (0.30 g, 1.57 mmol, 66% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, d, J = 7.0 Hz), 3.69 (1H, quint, J = 6.8 Hz), 3.78 (3H, s), 6.08 (1H, dd, J = 15.6, 7.8 Hz), 6.87 (2H, d, J = 8.5 Hz), 6.93 (1H, dd, J = 15.6, 7.8 Hz), 7.11 (2H, d, J = 8.5 Hz), 9.52 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 41.7, 55.2, 114.2, 128.2, 130.9, 134.7, 158.6, 162.1, 194.0; HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{12}H_{15}O_2$) m/z 191.1072, found m/z 191.1076.

*(2E)-4-(3-Methoxyphenyl)pent-2-enal (**1g**).* Purification by flash chromatography (SiO_2, 40/1 hexane/EtOAc) afforded **1g** (0.17 g, 0.88 mmol, 88% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, d, J = 7.0 Hz), 3.70 (1H, quint, J = 6.8 Hz), 3.79 (3H, s), 6.11 (1H, dd, J = 15.6, 7.8 Hz), 6.74 (1H, s), 6.79 (2H, d, J = 7.8 Hz), 6.94 (dd, 1H, J = 15.6, 6.4 Hz), 7.25 (1H, t, J = 7.8 Hz), 9.53 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 42.5, 55.2, 112.0, 113.4, 119.6, 129.8, 131.2, 144.3, 159.9, 161.4, 193.9; HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{12}H_{14}O_2$) m/z 190.0994, found m/z 190.0989.

*(2E)-4-(2-Methoxyphenyl)pent-2-enal (**1h**).* Purification by flash chromatography (SiO_2, 40/1 hexane/EtOAc) afforded **1h** (0.39 g, 2.07 mmol, 69% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, d, J = 7.0 Hz), 3.82 (3H, s), 4.17 (1H, quint, J = 7.2 Hz), 6.10 (1H, dd, J = 15.6, 7.8 Hz), 6.87−7.02 (m, 3H), 7.11 (1H, d, J = 7.2 Hz), 7.23 (1H, t, J = 7.5 Hz), 9.52 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 35.5, 55.3, 110.7, 120.8, 127.4, 128.0, 130.9, 131.0, 156.7, 162.2, 194.3 (CHO); HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{12}H_{14}O_2$) m/z 190.0994, found m/z 190.0999.

*(2E)-4-Phenylhex-2-enal (**1i**).* Purification by flash chromatography (SiO_2, 40/1 hexane/EtOAc) afforded **1i** (0.37 g, 2.11 mmol, 14% yield for three steps) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.4 Hz), 1.87 (2H, m), 3.43 (1H, q, J = 7.4 Hz), 6.10 (1H, dddd, J = 15.6, 7.8, 1.2 Hz), 6.93 (1H, dd, J = 7.5 Hz), 7.17−7.36 (5H, m), 9.52 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 27.7, 50.6, 127.1, 127.8, 128.8, 131.6, 141.4, 160.9, 194.0; HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{12}H_{14}O$) m/z 174.1045, found m/z 174.1053.

*(2E)-4-Phenylbut-2-enal (**1j**).* Purification by flash chromatography (SiO_2, 20/1 hexane/EtOAc) afforded **1j** (1.18 g, 8.10 mmol, 8% yield for three steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (2H, d, J = 6.7 Hz), 6.11 (1H, dd, J = 15.5, 7.9 Hz), 6.96 (1H, dt, J = 15.5, 6.7 Hz), 7.17−7.35 (5H, m), 9.53 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0, 127.0, 128.8, 128.9, 133.6, 137.0, 156.3, 193.7; HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{10}H_{10}O$) m/z 146.0732, found m/z 146.0741.

*(2E)-4-Methyl-5-phenylpent-2-enal (**1k**).* Purification by flash chromatography (SiO_2, 20/1 hexane/EtOAc) afforded **1k** (68 mg, 0.39 mmol, 66% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, J = 6.2 Hz), 2.73 (3H, m), 6.05 (1H, dd, J = 15.7, 7.8 Hz), 6.79 (1H, dd, J = 15.7, 6.4 Hz), 7.13−7.31 (5H, m), 9.48 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 38.6, 42.3, 126.4, 128.4, 129.1, 131.5, 139.1, 162.7, 194.1; HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{12}H_{15}O$) m/z 175.1123, found m/z 175.1116.

General Procedure for α,α-Difluoro-γ,γ-Disubstituted Butenals 2 and Reduction to the Corresponding Alcohols 3. Aldehyde **1** (1.0 equiv) and NFSI (2.2 equiv) were added at room temperature to a suspension of L-proline (30 mol %) and salicylic acid (60 mol %) in THF (0.1 M), and the entire solution was stirred until TLC showed that aldehyde **1** was totally consumed. After Me_2S was added to quench the reaction, the solution was stirred for 30 min. The resulting mixture was mixed with saturated $NaHCO_3$ and extracted with Et_2O. The combined organic phase was washed with brine and dried over $MgSO_4$. The organic solvents were filtered and concentrated under moderately reduced pressure at 450 mbar and 35 °C (note that some difluorinated aldehydes **2** were very volatile). The resulting difluorinated aldehyde **2** was dissolved in a 3/2 CH_2Cl_2/EtOH mixture (0.1 M), and $NaBH_4$ (10 equiv) was added at 0 °C. After 1 h, the reaction was quenched with saturated NH_4Cl and the mixture extracted EtOAc. The organic phase was dried over $MgSO_4$ and concentrated, and the residue was subsequently purified by silica-gel chromatography to afford the corresponding alcohols **3**.

*(3E)-2,2-Difluoro-4-phenylpent-3-en-1-ol (**3a**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3a** as a colorless oil (E/Z = >20/1, 15.2 mg, 0.077 mmol, 77% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (1H, brs), 2.28 (3H, s), 3.89 (2H, t, J = 13.1 Hz), 5.80 (1H, t, J = 14.3 Hz), 7.32−7.41 (5H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.14 (2F, q, J = 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (t, J = 2.1 Hz), 65.5 (t, J = 31.4 Hz), 119.5 (t, J = 25.1 Hz), 120.3 (t, J = 239.0 Hz), 126.1, 128.4, 128.5, 142.2, 146.5 (t, J = 5.7 Hz); HRMS (FAB) exact mass calcd for $[M - H]^+$ ($C_{11}H_{11}F_2O$) requires m/z 197.0778, found m/z 197.0781.

*(3E)-2,2-Difluoro-4-(4-fluorophenyl)pent-3-en-1-ol (**3b**).* Purification by flash chromatography (SiO_2, 5/1 hexane/EtOAc) afforded **3b** as a colorless oil (E/Z = >20/1, 16.1 mg, 0.074 mmol, 74% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (1H, brs), 2.26 (3H, s), 3.88 (2H, t, J = 13.2 Hz), 5.78 (1H, t, J = 14.2 Hz), 7.03 (2H, t, J = 8.6 Hz), 7.38 (2H, dd, J = 8.4, 5.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.64 (1F, m), −101.28 (2F, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (t, J = 2.4 Hz), 65.4 (t, J = 31.6 Hz), 115.3 (t, J = 21.3 Hz), 119.4 (t, J = 24.6 Hz), 120.1 (t, J = 239.0 Hz), 127.8 (t, J = 8.3 Hz), 138.2 (d, J = 3.0 Hz), 145.4 (t, J = 5.5 Hz), 162.8 (d, J = 246.3 Hz); HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{11}H_{11}F_3O$) m/z 216.0762, found m/z 216.0772.

*(3E)-4-(4-Chlorophenyl)-2,2-difluoropent-3-en-1-ol (**3c**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3c** as a pale yellow oil (E/Z = >20/1, 16.3 mg, 0.070 mmol, 70% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (1H, brs), 2.25 (3H, s), 3.89 (2H, dt, J = 13.0, 3.7 Hz), 5.82 (1H, t, J = 14.2 Hz), 7.33−7.36 (4H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.38 (2F, q, J = 2.5, 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (t, J = 2.2 Hz), 65.5 (t, J = 31.6 Hz), 119.9 (t, J = 25.0 Hz), 120.1 (t, J = 239.1 Hz), 127.4, 128.6, 134.4, 140.6, 145.3 (t, J = 5.5 Hz); HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{11}H_{11}ClF_2O$) m/z 232.0466, found m/z 232.0466.

*(3E)-4-(4-Bromophenyl)-2,2-difluoropent-3-en-1-ol (**3d**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3d** as a pale yellow oil (E/Z = >20/1, 20.9 mg, 0.075 mmol, 75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (1H, brs), 2.25 (3H, s), 3.88 (2H, t, J = 13.1 Hz), 5.82 (1H, t, J = 14.2 Hz), 7.27 (2H, d, J = 8.5 Hz), 7.47 (2H, d, J = 8.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.39 (2F, dq, J = 2.5, 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (t, J = 2.3 Hz), 65.4 (t, J = 31.7 Hz), 119.9 (t, J = 25.1 Hz), 120.1 (t, J = 240.2 Hz), 122.5, 127.7, 131.6, 141.0, 145.3 (t, J = 5.5 Hz); HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{11}H_{11}BrF_2O$) m/z 275.9961, found m/z 275.9954.

*(3E)-2,2-Difluoro-4-(4-methylphenyl)pent-3-en-1-ol (**3e**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3e** as a colorless oil (E/Z = >20/1, 16.7 mg, 0.078 mmol, 79% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (1H, brs), 2.25 (3H, s), 2.35 (3H, s), 3.88 (2H, t, J = 12.9 Hz), 5.82 (1H, t, J = 14.3 Hz), 7.96 (2H, d, J = 7.2 Hz), 8.04 (2H, d, J = 7.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.39 (2F, q, J = 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (t, J = 2.3 Hz), 21.1, 65.5 (t, J = 31.4 Hz), 118.6 (t, J = 24.9 Hz), 120.4 (t, J = 238.8 Hz), 125.9, 129.1, 138.4, 139.2, 146.3 (t, J = 5.6 Hz); HRMS (FAB) exact mass calcd for $[M - H]^+$ ($C_{12}H_{13}F_2O$) m/z 211.0935, found m/z 211.0936.

*(3E)-2,2-Difluoro-4-(4-methoxyphenyl)pent-3-en-1-ol (**3f**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3f** as a colorless oil (E/Z = >20/1, 16.4 mg, 0.072 mmol, 72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (1H, brs), 2.25 (3H, s), 3.81 (3H, s), 3.88 (2H, t, J = 14.5 Hz), 5.77 (1H, t, J = 14.3 Hz), 6.87 (2H, d, J = 8.7 Hz), 7.36 (2H, d, J = 8.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −100.85 (2F, q, J = 13.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (t, J = 2.1 Hz), 55.3, 65.5 (t, J = 31.6 Hz), 113.8, 117.7 (t, J = 25.0 Hz), 120.4 (t, J = 239.0 Hz), 127.2, 134.3, 145.7 (t, J = 5.6 Hz), 159.9;

DOI: 10.1021/acs.joc.6b01334
J. Org. Chem. 2016, 81, 6707−6713

HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{12}H_{15}F_2O_2$) requires m/z 229.1040, found m/z 229.1040.

*(3E)-2,2-Difluoro-4-(3-methoxyphenyl)pent-3-en-1-ol (**3g**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3g** as a colorless oil (E/Z = >20/1, 15.9 mg, 0.070 mmol, 70% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (1H, brs), 2.26 (3H, s), 3.82 (3H, s), 3.88 (2H, t, J = 13.3 Hz), 5.82 (1H, t, J = 14.4 Hz), 6.87 (1H, d, J = 8.8 Hz), 6.92 (1H, s), 7.00 (1H, d, J = 7.9 Hz), 7.26 (1H, t, J = 8.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.41 (2F, q, J = 13.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (t, J = 2.3 Hz), 55.2, 65.4 (t, J = 31.5 Hz), 112.0, 113.6, 118.5, 119.6 (t, J = 25.0 Hz), 120.2 (t, J = 240.3 Hz), 129.3, 143.7, 146.3 (t, J = 5.7 Hz), 159.6; HRMS (EI+) exact mass calcd for $[M + H]^+$ ($C_{12}H_{15}F_2O_2$) m/z 229.1040, found m/z 229.1037.

*(3E)-2,2-Difluoro-4-(2-methoxyphenyl)pent-3-en-1-ol (**3h**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3h** as a colorless oil (E/Z = 5/1, 17.6 mg, 0.077 mmol, 77% yield). The assignments were made for a mixture of E and Z isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (0.6H, s), 2.20 (3H, s), 3.44 (3H, t, J = 12.4 Hz), 3.82 (3H, s), 3.83 (0.6H, s), 3.88 (2H, t, J = 13.4 Hz), 5.56 (1H, t, J = 14.4 Hz), 5.72 (1H, t, J = 12.0 Hz), 6.87−6.96 (2.4H, m), 7.07 (0.2H, d, J = 4.0 Hz), 7.13 (1H, d, J = 8.0 Hz), 7.25−7.30 (1.2H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −97.50 (Z isomer, 2F, brs), −101.90 (E isomer, 2F, q, J = 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7 (t, J = 2.0 Hz), 26.2, 55.4, 55.5, 64.7 (t, J = 33.2 Hz), 65.4 (t, J = 31.2 Hz), 117.8 (t, J = 239.4 Hz), 120.2 (t, J = 241.4 Hz), 120.6, 120.7, 121.1 (t, J = 28.2 Hz), 121.3 (t, J = 25.2 Hz), 125.6, 127.3, 129.0, 129.05, 129.10, 129.3, 132.9 137.0, 145.1 (t, J = 10.1 Hz), 146.7 (t, J = 6.0 Hz), 155.3, 156.2; HRMS (EI+) exact mass calcd for $[M + H]^+$ ($C_{12}H_{15}F_2O_2$) m/z 229.1040, found m/z 229.1039.

*(3E)-2,2-Difluoro-4-phenylhex-3-en-1-ol (**3i**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3i** as a pale yellow oil (E/Z = >20/1, 13.9 mg, 0.065 mmol, 66% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.5 Hz), 2.01 (1H, brs), 2.73 (2H, q, J = 7.5 Hz), 3.88 (2H, dt, J = 13.2, 5.9 Hz), 5.67 (1H, t, J = 14.6 Hz), 7.26−7.38 (5H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.21 (2F, q, J = 13.7 Hz, CF_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 24.3 (t, J = 1.7 Hz), 65.7 (t, J = 31.4 Hz), 119.1 (t, J = 25.3 Hz), 120.2 (t, J = 239.2 Hz), 126.7, 128.3, 128.5, 141.9, 153.3 (t, J = 5.6 Hz); HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{12}H_{14}F_2O$) m/z 212.1013, found m/z 212.1010.

*(3E)-2,2-Difluoro-4-phenylbut-3-en-1-ol (**3j**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3j** as a colorless oil (E/Z = >20/1, 40 mg, 0.217 mmol, 72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (1H, brs), 3.89 (2H, t, J = 12.7 Hz), 6.25 (1H, dt, J = 16.3, 12.7 Hz), 7.01 (1H, d, J = 16.3 Hz), 7.25−7.45 (5H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.00 (2F, q, J = 12.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.2 (t, J = 32.6 Hz), 119.8 (t, J = 240.1 Hz), 120.4 (t, J = 25.2 Hz), 127.2, 128.8, 129.2, 134.6, 135.7 (t, J = 9.4 Hz); HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{10}H_{10}F_2O$) m/z 184.0700, found m/z 184.0694.

*(3E)-2,2-Difluoro-4-methyl-5-phenylpent-3-en-1-ol (**3k**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3k** as a pale yellow oil (E/Z = 3/1, 49.0 mg, 0.231 mmol, 77% yield). The assignments were made as a mixture of E and Z isomers: ^{1}H NMR (400 MHz, $CDCl_3$) of the E isomer δ 1.70 (0.9H, s), 1.82 (3H, s), 1.86 (1H, brs), 3.37 (2H, s), 3.61 (0.6H, s), 3.79 (2.6H, dt, J = 13.2, 3.3 Hz), 5.38 (1H, t, J = 14.1 Hz), 5.51 (0.3H, t, J = 14.2 Hz), 7.16−7.32 (6.5H, m); ^{1}H NMR (400 MHz, $CDCl_3$) of the Z isomer δ 1.70 (3H, s), 3.61 (2H, s), 3.79 (2H, dt, J = 3.3, 13.2 Hz, overlapping with the E isomer), 5.51 (1H, t, J = 14.2 Hz), 7.16−7.32 (5H, m, overlapping with the E isomer); ^{19}F NMR (376 MHz, $CDCl_3$) δ −99.69 (Z isomer, 2F, q, J = 13.8 Hz), −101.41 (E isomer, 2F, dq, J = 2.3, 22.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) of the E isomer δ 17.6 (t, J = 2.1 Hz), 23.8, 39.0, 46.5, 65.4 (t, J = 31.5 Hz), 65.7 (t, J = 31.5 Hz), 119.0 (t, J = 25.4 Hz, overlapping with two isomers), 119.8 (t, J = 240.0 Hz), 120.1 (t, J = 239.0 Hz), 126.4, 126.6, 128.48, 128.54, 128.9, 129.0, 138.1, 138.4, 146.9 (t, J = 5.2 Hz), 147.5 (t, J = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) of the Z isomer δ 23.8, 39.0, 65.7 (t, J = 31.5 Hz), 119.0 (t, J = 25.4 Hz, overlapping with the E isomer), 119.8 (t, J = 240.0 Hz), 126.4, 128.5, 128.9, 138.4, 146.9 (t, J = 5.2 Hz); HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{12}H_{14}F_2O$) m/z 212.1013, found m/z 212.1003.

*(3E)-2,2-Difluorodec-3-en-1-ol (**3l**).* Purification by flash chromatography (SiO_2, 10/1 hexane/EtOAc) afforded **3l** as a colorless oil (E/Z = 1.8/1, 11.6 mg, 0.060 mmol, 60% yield) (as a mixture of E and Z isomers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (8.4H, t, J = 7.0 Hz), 1.26−1.37 (17H, m), 1.39−1.44 (5H, m), 1.86 (2.8H, brs), 2.09−2.15 (4H, m), 2.24−2.30 (2H, m), 3.78 (5.6H, t, J = 12.8 Hz), 5.43−5.70 (2.8H, m), 5.83−5.90 (1H, m), 6.14−6.23 (1.8H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.23 (Z isomer, 2F, q, J = 13.9 Hz), − 105.48 (E isomer, 2F, dq, J = 2.7, 12.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.55, 22.57, 28.3, 28.6, 28.8, 28.9, 29.1, 29.4, 29.7, 31.6, 32.0, 65.1 (t, J = 33.2 Hz), 65.4 (t, J = 33.2 Hz), 119.4 (t, J = 239.4 Hz), 120.3 (t, J = 240.0 Hz), 121.5 (t, J = 26.2 Hz), 122.1 (t, J = 25.1 Hz), 138.6 (t, J = 9.1 Hz), 140.9 (t, J = 6.0 Hz); HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{10}H_{19}F_2O$) m/z 193.1402, found m/z 193.1404.

General Procedure for the Reductive Amination of 2a. The resulting difluorinated aldehyde **2a** (1.0 equiv) and benzylamine (10 equiv) were mixed in DCM (0.2 M), and then to the solution were added sodium triacetoxyborohydride (10 equiv) and AcOH (10 equiv). The mixture was stirred at room temperature under an argon atmosphere for 15 h. The reaction was quenched with saturated Na_2CO_3, and the product was extracted with EtOAc and dried over $MgSO_4$. The organic layer was filtered and concentrated *in vacuo*. The residue was purified by a silica-gel chromatography (20/1 hexane/EtOAc) that afforded **4a** as a colorless oil (E/Z = >20/1, 18 mg, 0.063 mmol, 63% yield).

*(3E)-N-Benzyl-2,2-difluoro-4-phenylpent-3-en-1-amine (**4a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (1H, s), 3.11 (2H, t, J = 14.1 Hz), 3.92 (2H, s), 5.87 (1H, t, J = 13.7 Hz), 7.31−7.41 (10H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −95.22 (2F, q, J = 13.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (t, J = 2.1 Hz), 53.5, 54.1 (t, J = 28.7 Hz), 121.3 (t, J = 25.1 Hz), 121.5 (t, J = 240.63 Hz), 126.0, 127.1, 128.0, 128.1, 128.3, 128.4, 139.8, 142.2, 144.9 (t, J = 5.65 Hz); HRMS (FAB) exact mass calcd for $[M]^+$ ($C_{18}H_{19}F_2N$) m/z 287.1486, found m/z 287.1492.

General Procedure for Pinnick Reaction of 2a. Sodium phosphate monobasic (8.0 equiv) was added at 0 °C to a solution of difluorinated aldehyde **2a** (1.0 equiv) in a 2/1 *t*-BuOH/H_2O mixture (0.05 M). The resulting suspension was treated with 2-methyl-2-butene (30 equiv) and sodium chlorite (80%, 10 equiv) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 3 h. After the reaction had reached completion, the reaction was quenched with saturated NH_4Cl; the product was subsequently extracted with EtOAc and dried over $MgSO_4$. The organic layer was filtered and concentrated *in vacuo*. The residue was purified by silica-gel chromatography (5/1 DCM/MeOH) to afford **5a** as a colorless oil (E/Z = >20/1, 15.1 mg, 0.072 mmol, 72% yield).

*(3E)-2,2-Difluoro-4-phenylpent-3-enoic acid (**5a**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19 (3H, s), 6.00 (1H, t, J = 13.8), 7.32−7.47 (5H, m); ^{19}F NMR (376 MHz, DMSO-d_6) δ −93.81 (2F, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.2, 115.1 (t, J = 246.1 Hz), 122.8 (t, J = 26.4 Hz), 126.2, 128.1, 128.9, 141.9, 143.3, 166.2 (t, J = 29.9 Hz); HRMS (FAB) exact mass calcd for $[M - H]^-$ ($C_{11}H_9F_2O_2$) m/z 211.0571, found m/z 211.0572.

General Procedure for Horner−Wadsworth−Emmons Reaction of 2a. A solution of diisopropylamine (2.52 equiv) in THF (0.2 M) was carefully treated with *n*-BuLi (2.4 equiv) at 0 °C under an argon atmosphere, and the resulting solution was stirred for 15 min at 0 °C. Triethyl phosphonoacetate (2.0 equiv) was added to a prepared LDA solution at 0 °C. After 30 min, the reaction mixture was cooled to −40 °C and difluorinated aldehyde **2a** (1.0 equiv) was added to the solution at this temperature. After the mixture had been stirred for 1 h at −40 °C, the reaction was quenched with saturated NH_4Cl; the product was then extracted with EtOAc and dried over $MgSO_4$. The organic layer was filtered and concentrated *in vacuo*. The residue was purified by silica-gel chromatography (40/1 hexane/Et_2O) to afford **6a** as a colorless oil (E/Z = >20/1, 15.6 mg, 0.059 mmol, 60% yield).

*Ethyl (2E,5E)-4,4-Difluoro-6-phenylhepta-2,5-dienoate (**6a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, J = 7.1 Hz), 2.21−2.22 (3H,

DOI: 10.1021/acs.joc.6b01334
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m), 4.26 (2H, q, J = 7.1 Hz), 5.86 (1H, dt, J = 13.4, 1.2 Hz), 6.32 (1H, dt, J = 15.7, 2.4 Hz), 6.95 (1H, dt, J = 15.7, 10.0 Hz), 7.32−7.42 (5H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −89.18 (2F, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 17.5 (t, J = 1.5 Hz), 61.2, 118.0 (t, J = 235.9 Hz), 120.9 (t, J = 24.8 Hz), 124.5 (t, J = 8.0 Hz), 126.0, 128.50, 128.54, 139.4 (t, J = 30.7 Hz), 141.8, 145.9 (t, J = 7.2 Hz), 165.3; HRMS (FAB) exact mass calcd for $[M + H]^+$ ($C_{15}H_{17}F_2O_2$) m/z 267.1197, found m/z 267.1197.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01334.

NMR spectra of compounds **1**, **3**, **4a**, **5a**, and **6a** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors appreciate Dr. Michael C. Roy and Prof. Fujie Tanaka at Okinawa Institute of Science and Technology Graduate University for assistance with HRMS. Part of this research was financially supported by JSPS, Grant-in-Aid for Young Scientists (B), Grant 25810022.

■ REFERENCES

(1) (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, U.K., 2009. (b) Khan, M. O.; Lee, H. J. *Chem. Rev.* **2008**, *108*, 5131. (c) Herreros, E.; Almela, M. J.; Lozano, S.; Gomez De Las Heras, F.; Gargallo-Viola, D. *Antimicrob. Agents Chemother.* **2001**, *45*, 3132. (d) Hassan, A. E. A.; Shuto, S.; Matsuda, A. *Nucleosides Nucleotides* **1994**, *13*, 197. (e) Ando, T.; Koseki, N.; Yasuhara, I.; Kasuga, K.; Matsuo, N.; Ishiwatari, T. *Pestic. Sci.* **1994**, *40*, 307.

(2) For selected publications, see: (a) Combettes, L. E.; Schuler, M.; Patel, R.; Bonillo, B.; Odell, B.; Thompson, A. L.; Claridge, T. D. W.; Gouverneur, V. *Chem. - Eur. J.* **2012**, *18*, 13126. (b) Laurenson, J. A. B.; Meiries, S.; Percy, J. M.; Roig, R. *Tetrahedron Lett.* **2009**, *50*, 3571. (c) Tredwell, M.; Luft, J. A. R.; Schuler, M.; Tenza, K.; Houk, K. N.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 357. (d) Audouard, C.; Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Org. Biomol. Chem.* **2004**, *2*, 528. (e) Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 5741. (f) Audouard, C.; Barsukov, I.; Fawcett, J.; Griffith, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Chem. Commun.* **2004**, 1526. (g) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634. (h) Li, Q.; Wang, W.; Berst, K. B.; Claiborne, A.; Hasvold, L.; Raye, K.; Tufano, M.; Nilius, A.; Shen, L. L.; Flamm, R.; Alder, J.; Marsh, K.; Crowell, D.; Chu, D. T. W.; Plattner, J. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1953.

(3) For recent reviews on the synthesis of allylic fluorides, see: (a) Wu, J. *Tetrahedron Lett.* **2014**, *55*, 4289. (b) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929. (c) Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943.

(4) (a) Ref 1. (b) Klimko, P.; Hellberg, M.; McLaughlin, M.; Sharif, N.; Severns, B.; Williams, G.; Haggard, K.; Liao, J. *Bioorg. Med. Chem.* **2004**, *12*, 3451. (c) Matsumura, Y.; Mori, N.; Nakano, T.; Sasakura, H.; Matsugi, T.; Hara, H.; Morizawa, Y. *Tetrahedron Lett.* **2004**, *45*, 1527. (d) Nakajima, T.; Matsugi, T.; Goto, W.; Kageyama, M.; Mori, N.; Matsumura, Y.; Hara, H. *Biol. Pharm. Bull.* **2003**, *26*, 1691.

(5) (a) Ref 4. (b) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422. (c) Al-Maharik, N.; O'Hagan, D. *Aldrichimica Acta* **2011**, *44*, 65. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.

(6) (a) Chen, Q.; Wang, C.; Zhou, J.; Wang, Y.; Xu, Z.; Wang, R. *J. Org. Chem.* **2016**, *81*, 2639. (b) Li, G.; Wang, T.; Fei, F.; Su, Y.; Li, Y.; Lan, Q.; Wang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 3491. (c) Ivanova, M. V.; Bayle, A.; Besset, T.; Poisson, T.; Pannecoucke, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 13406. (d) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090. (e) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. (f) Zhu, J.; Zhang, W.; Zhang, L.; Liu, J.; Zheng, J.; Hu, J. *J. Org. Chem.* **2010**, *75*, 5505. (g) Schwaebe, M. K.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **2000**, *41*, 791. (h) Yokomatsu, T.; Suemune, K.; Murano, T.; Shibuya, S. *J. Org. Chem.* **1996**, *61*, 7207 and more references cited therein.

(7) (a) See ref 6. For other synthetic methods, see: (b) Omote, M.; Miake, T.; Tarui, A.; Sato, K.; Kumadaki, I.; Ando, A. *J. Fluorine Chem.* **2013**, *147*, 1. (c) Munemori, D.; Narita, K.; Nokami, T.; Itoh, T. *Org. Lett.* **2014**, *16*, 2638. (d) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem.* **1996**, *61*, 166.

(8) For a sporadic example, see: Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2004**, *69*, 7616.

(9) For recent reviews, see: (a) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287. (b) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869. (c) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748.

(10) See ref 9 and references cited therein.

(11) (a) Jones, J. H.; Appayee, C.; Brenner-Moyer, S. E. *Eur. J. Org. Chem.* **2014**, *2014*, 5273. (b) Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943. (c) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

(12) Starting material **1** was prepared according to a modified synthetic procedure from: Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, *13*, 70.

(13) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.

(14) The reduction step was not a straightforward reaction; that is, the nonfluorinated byproducts were observed. The experimental procedure is described in the Experimental Section.

(15) Salicylic acid was used in the primary amine-based emamine chemistry. See: Moteki, S. A.; Xu, S.; Arimitsu, S.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 17074.

(16) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

(17) Witten, M. R.; Jacobsen, E. N. *Org. Lett.* **2015**, *17*, 2772.

DOI: 10.1021/acs.joc.6b01334
J. Org. Chem. 2016, 81, 6707−6713