JOC The Journal of Organic Chemistry

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Copper-Catalyzed C(sp^2)–H Difluoroalkylation of Aldehyde Derived Hydrazones with Diboron as Reductant

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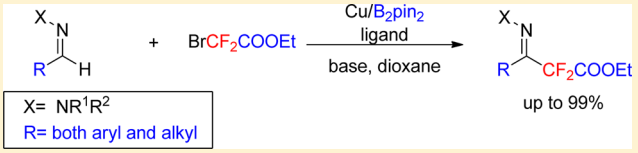
Supporting Information

ABSTRACT: An efficient and general method for C(sp^2)–H difluoroalkylation of aldehyde derived hydrazones via a Cu^{II}/B_2pin_2-catalyzed reaction between difluoroalkyl bromides and hydrazones was developed. In this reaction, both aromatic and aliphatic difluoroalkylated aldehyde derived hydrazones could be achieved in good to excellent yields. For some heteroaromatic aldehyde derived hydrazones, two fluoroacetates could be introduced onto the final products. A preliminary mechanism study manifested that a difluoroalkyl radical via SET pathway was involved in the reaction. In addition, the catalytic diboron reagent plays an indispensable role in this transformation.



INTRODUCTION

The incorporation of fluorinated functional groups into organic molecules has generated extraordinary research activity because of the enhanced metabolic stability, lipophilicity, and reactivity of the molecules in comparison to their nonfluorinated counterparts.[1−3] Although significant advances have been made in the functionalized fluoroalkylation of aromatic compounds,[4−6] efficient and general methods for the synthesis of hydrazones containing difluorinated functional groups with high stereoselectivity through copper-catalyzed transformations are relatively rare.[9e] Aldehyde derived hydrazones are important intermediates in organic synthesis.[7] Conceptually, introduction of the CF_2 group into such a structual motif would open a good possibility to discover some novel bioactive molecules.

Recently, the fluoroalkyl radical addition of aldehyde derived hydrazones has become an efficient tactic to synthesize α,α-difluoro-β-keto esters. There are two known methods to achieve fluoroalkylated aldehyde derived hydrazone compounds: (a) visible-light photoredox-catalyzed cross-coupling between aldehyde hydrazones and fluoroalkylating reagent (for example, with iridium or gold catalysts)[8] and (b) transition-metal-catalyzed cross-coupling of aldehyde derived hydrazones and fluoroalkyl halides.[9] In the latter case, Monteiro and coworkers reported an elegant Pd-catalyzed C–H alkylation of aldehyde derived hydrazones with functional difluoromethyl bromides.[9d] Very recently, they also reported a Cu-catalyzed difluoroalkylation of aldehyde derived hydrazones.[9e] However, in both cases aliphatic aldehyde derived hydrazones failed to provide difluoroacetated hydrazones, and expensive metals or ligands were essential to the success of the reactions. Inspired by our recent work on the Cu^{II}/B_2pin_2-catalyzed hydrodifluoroacetylation of alkynes or phenylpropiolic acids with bromodifluoroacetate, in which difluoroalkyl radicals were generated via a single-electron-transfer (SET) pathway (Scheme 1a),[10] we envisioned that C(sp^2)–H difluoroalkylation of aldehyde derived hydrazones might be synthesized via the same novel radical generation system, Cu/B_2pin_2. Undoubtedly and ideally, if a catalytic amount of B_2pin_2 were enough for the success of the transformation instead of a stoichiometric amount, this reaction would become more attractive. Most interestingly, we successfully obtained C(sp^2)–H difluoroalkylation of aldehyde derived hydrazones with our Cu^{II}/B_2pin_2 catalytic system in which only 30 mol % of B_2pin_2 was enough for this transformation and aliphatic aldehyde derived hydrazones could also be smoothly difluoroalkylated.

RESULTS AND DISCUSSION

In order to examine our hypothesis, our investigation commenced with aldehyde derived hydrazone **1** and ethyl bromodifluoroacetate **2** as the model substrates with 1 equiv of B_2pin_2 according to our previous work.[10] To our delight, the desired difluoroalkylated aldehyde hydrazone compound **3** was obtained in 52% isolated yield at 80 °C using 10% $CuBr_2$ as catalyst, 10% **L1** as ligand, 1 equiv of B_2pin_2 as additive, and 2 equiv of KOAc as base in 1,4-dioxane. Subsequently, other reaction parameters, such as base, loading of B_2pin_2, Cu salt, ligand, and reaction atmosphere were surveyed (Table 1, entries 1–24). Among the tested bases (Table 1, entries 1–7), $NaHCO_3$ showed activity superior to that of the others (KOAc, K_2CO_3, Na_2CO_3, NaOAc, KF, Cs_2CO_3), providing the desired product **3** in 93% isolated yield (Table 1, entries 1–7). Surprisingly, we found that the loading of B_2pin_2 could be dropped to 30 mol % without deterioration of the yield (Table 1, entries 9 and 10). However, further lowering the loading of B_2pin_2 significantly reduced the yield (Table 1, 83%, entry 8). As we can see, CuCl, CuBr, $CuCl_2$, and $Cu(OAc)_2$ were all good catalysts in combination with ligand L1, yet $CuBr_2$ was

Received: February 13, 2016
Published: March 29, 2016

DOI: 10.1021/acs.joc.6b00324
J. Org. Chem. 2016, 81, 3654–3664

Scheme 1. Synthetic Methods Involving $^{\bullet}CF_2COOEt$ Radical with Cu^{II}/B_2pin_2 Catalyst System

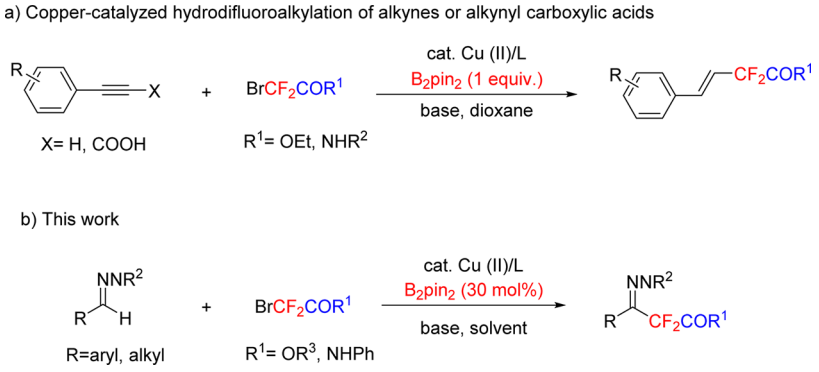
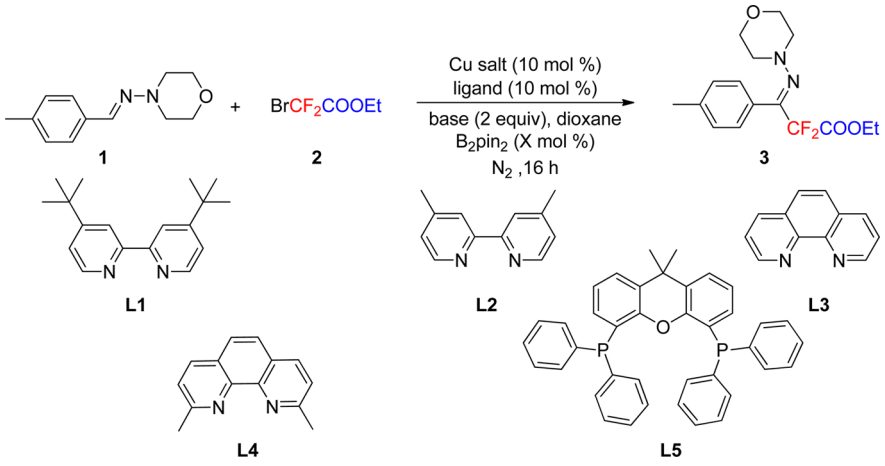


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (10 mol %)	ligand (10 mol %)	base (2 equiv)	yield (%)
1	$CuBr_2$	**L1**	KOAc	52
2	$CuBr_2$	**L1**	K_2CO_3	72
3	$CuBr_2$	**L1**	Na_2CO_3	78
4	$CuBr_2$	**L1**	NaOAc	77
5	$CuBr_2$	**L1**	$NaHCO_3$	96 (93)
6	$CuBr_2$	**L1**	KF	34
7	$CuBr_2$	**L1**	Cs_2CO_3	30
8[b]	$CuBr_2$	**L1**	$NaHCO_3$	83
9[c]	$CuBr_2$	**L1**	$NaHCO_3$	>99 (96)
10[d]	$CuBr_2$	**L1**	$NaHCO_3$	>99
11	CuCl	**L1**	$NaHCO_3$	95
12	CuBr	**L1**	$NaHCO_3$	89
13	$CuCl_2$	**L1**	$NaHCO_3$	93
14	$Cu(OAc)_2$	**L1**	$NaHCO_3$	91
15	$CuBr_2$	**L2**	$NaHCO_3$	75
16	$CuBr_2$	**L3**	$NaHCO_3$	18
17	$CuBr_2$	**L4**	$NaHCO_3$	8
18	$CuBr_2$	**L5**	$NaHCO_3$	NR
19		**L1**	$NaHCO_3$	NR
20	$CuBr_2$		$NaHCO_3$	NR
21	$CuBr_2$	**L1**		NR
22[e]	$CuBr_2$	**L1**	$NaHCO_3$	NR
23[f]	$CuBr_2$	**L1**	$NaHCO_3$	NR
24[g]	$CuBr_2$	**L1**	$NaHCO_3$	NR

[a]Reaction conditions unless specified otherwise: **1** (0.2 mmol), **2** (0.4 mmol), Cu salt (10 mol %), ligand (10 mol %), base (2 equiv), B_2pin_2 (entries 1−7, 1 equiv), B_2pin_2 (entries 11−23, 30 mol %), dioxane (1 mL), under N_2, 16 h. GC yields were obtained by using *n*-dodecane as an internal standard. The isolated yields are given in parentheses. [b]B_2pin_2 (20 mol %). [c]B_2pin_2 (30 mol %). [d]B_2pin_2 (40 mol %). [e]Under air. [f]Under O_2. [g]Absence of B_2pin_2.

DOI: 10.1021/acs.joc.6b00324
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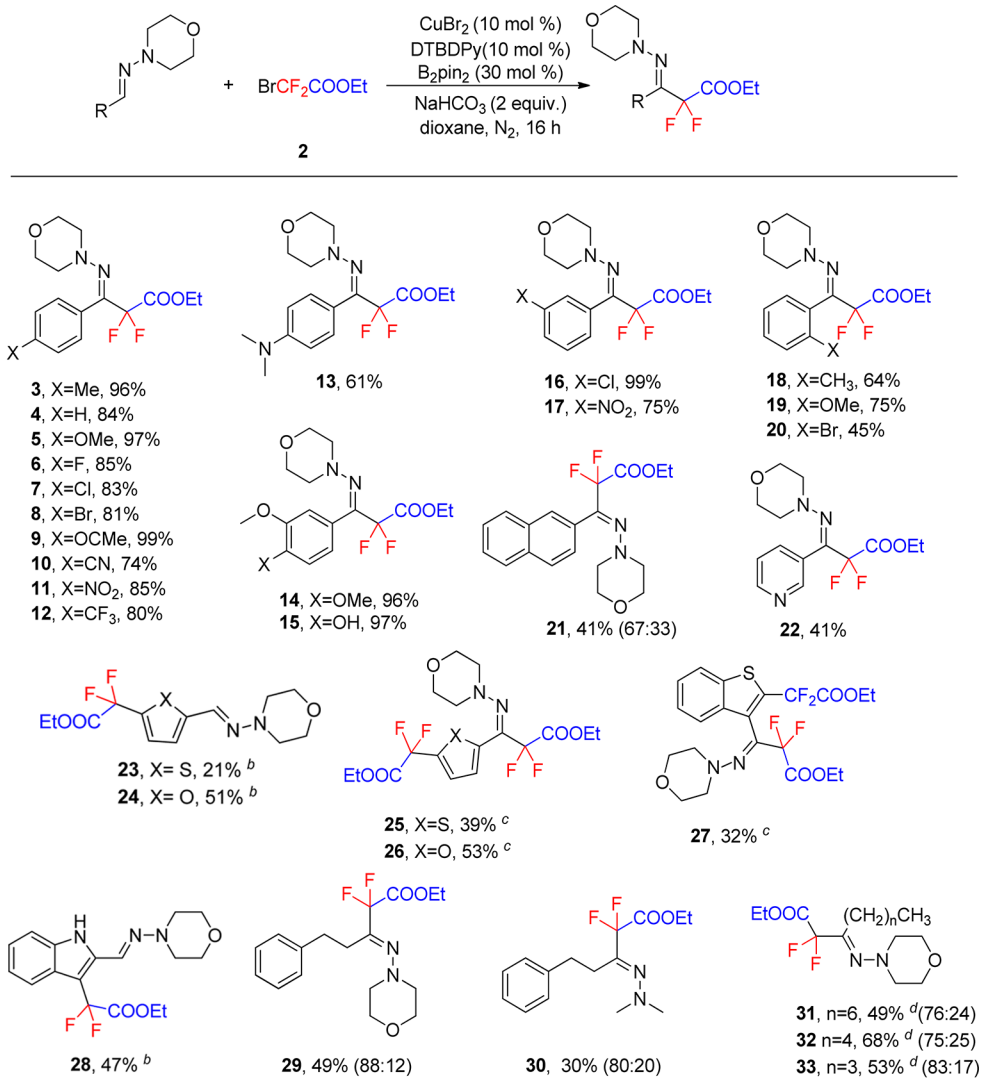
Scheme 2. Substrate Scope of Aldehyde Derived Hydrazones for Difluoroacetylation[a]



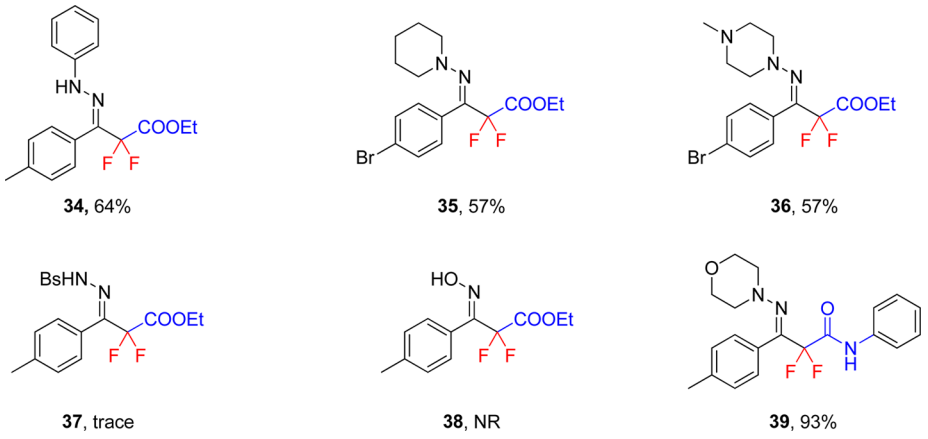
[a]Reaction conditions unless specified otherwise: aldehyde derived hydrazones (0.3 mmol), $BrCF_2COOEt$ (**2**; 0.6 mmol), $CuBr_2$ (10 mol %), **L1** (10 mol %), $NaHCO_3$ (2 equiv), B_2pin_2 (30 mol %), dioxane (1 mL), 80 °C, 16 h, under N_2 in a Schlenk tube. All yields are those of isolated product. [b]Using 1 equiv of $BrCF_2COOEt$. [c]Using 2.5 equiv of $BrCF_2COOEt$. [d]Using $CuCl_2$ instead of $CuBr_2$. The ratios in parentheses is the *E*/*Z* ratio.

the best among them (Table 1, entries 11−14). In terms of other ligands, the yields of the desired product dropped dramatically, and no desired product was observed when P ligand **L5** was used in the transformation (Table 1, entries 15−18). Control experiments suggested that the additive B_2pin_2 is indispensable to the reaction, since no reaction occurred in its absence (Table 1, entry 22). In addition, no desired product **3** was observed in the absence of copper catalyst, ligand, or base (Table 1, entries 19−21), demonstrating that the copper salt, ligand, and base play essential roles in the promotion of the reaction. This reaction is anaerobic and could not proceed under air or molecular oxygen (Table 1, entries 23 and 24).

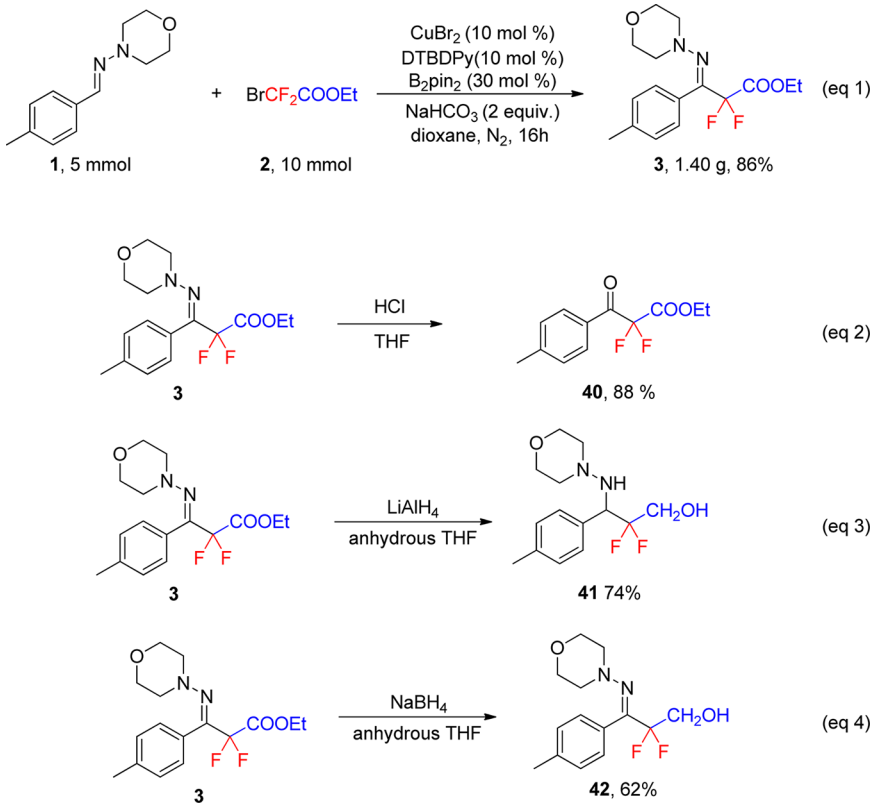
In order to test the scope of the method, a variety of aldehyde derived hydrazones was surveyed (Scheme 2). A series of difluoroacetylated aldehyde hydrazones was obtained in good to excellent yields with versatile substituents on the aromatic rings regardless of the electron-donating or electron-withdrawing nature (**3**−**12**). Notably, the 4-*N*,*N*-dimethyl product **13** was obtained in good yield under our standard conditions. Moreover, the position of substituents on the aromatic ring has less impact on the reactions, although *ortho* subsituents give relatively lower yields (**16**−**20**). With multiple substituents on the aromatic rings, the corresponding products were also obtained in good yields (**14** and **15**). However, the reaction of naphthylaldehyde hydrazone gave a surprisingly low yield (**21**). Heteroaromatic aldehyde derived hydrazones were also compatible under the standard conditions (**22**−**28**); interestingly, some bis-fluoroacetates were selectively synthesized from thiophene, furanyl, or benzothiophene aldehyde derived hydrazones (**23**−**27**). Importantly, aliphatic aldehyde hydrazones were good substrates in this transformation and the corresponding desired products were obtained in decent yields, albeit with relatively low stereoselectivities (**29**−**33**), which makes our method an alternative to the reported Pd- or Cu-catalyzed difluoroalkylation of aldehyde derived hydrazones, in which aliphatic aldehyde derived hydrazones only rendered a trace amount of the desired products.[9d,e] It needs to be pointed out that our conditions were also applicable to the *N*,*N*-dimethyl aliphatic aldehyde derived hydrazone and 30% of the corresponding product **30** was obtained. However, when (*E*)-

DOI: 10.1021/acs.joc.6b00324
J. Org. Chem. 2016, 81, 3654−3664

Scheme 3. Investigation of the Effect of the N Substituents and Bromodifluoroacetamide



Scheme 4. Application of Difluoroalkylation of Aldehyde-Derived Hydrazones



N-hexylidenemorpholin-4-amine was subjected to Monteiro's conditions[9e] in the presence of B_2Pin_2, the corresponding desired product was only obtained in 14% yield, much lower than that obtained under our current standard conditions (49% yield).

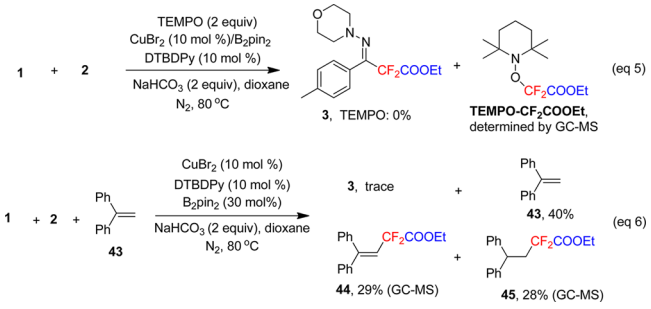
Next, we investigated the scope of N-substituent aldehyde hydrazones and the scope of difluoro reagents (Scheme 3). Delightedly, the reactions were not just restricted to morpholine-derived hydrazones; phenylamine, piperidinyl, and 4-methylpiperazinyl derived hydrazones were also suitable candidates for this transformation, with the corresponding desired products obtained in reasonable yields (**34**–**36**). However, the N-Bs (Bs = benzenesulfonyl) hydrazones (**37**) and oxime hydrazones (**38**) failed to furnish the desired product, probably due to their low HOMO level. Gratifyingly, the corresponding difluorinated hydrazone (**39**) was obtained in excellent yield using bromodifluoroacetamide, which was prepared from the reaction of bromodifluoroacetate **2** with phenylamine.[11]

Satisfyingly, this reaction could be easily scaled up to 5 mmol, and the desired product **3** was achieved in a high isolated yield of 86% (1.4 g) (Scheme 4, eq 1), which illustrated the practicality and robustness of our transformation. Aldehyde derived hydrazones are facile, important intermediates in organic chemistry which could be easily subjected to further structural manipulation. For instance, compound **3** could be hydrolyzed into the α,α-difluoro-β-keto ester **40** in 88% yield (Scheme 4, eq 2). Also, difluorinated hydrazine **41** was readily generated when compound **3** was reacted with lithium aluminum hydride in anhydrous THF (Scheme 4, eq 3), in

DOI: 10.1021/acs.joc.6b00324
J. Org. Chem. 2016, 81, 3654−3664

which the ester group was also reduced simultaneously along with the C═N bond to render an alcohol. It is worth noting that the ester group in compound **3** was transformed into a hydroxyl group while the C═N double bond was untouched in compound **42** when compound **3** was treated with sodium borohydride (Scheme 4, eq 4).

Radical trapping experiments were subsequently performed in order to understand the mechanism of this Cu^{II}/B_2pin_2-catalyzed C(sp^2)−H difluoroalkylation of aldehyde derived hydrazones. The desired product **3** was not obtained when the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added; instead, TEMPO-CF_2COOEt was generated in ca. 20% yield, implying that a radical pathway was involved in this reaction (eq 5). Furthermore, when 1-



phenylstyrene (**43**) was added to a mixture of compound **1** and **2** under the standard conditions, the desired product **3** was only formed in a trace amount with 40% of compound **43** remaining along with the formation of compounds **44** and **45**. This result further confirmed the involvement of a free radical pathway in this transformation (eq 6).

On the basis of the above control experiments, our previous work,[10] and preceding reports,[9e] a plausible mechanism is postulated (Figure 1). Initially, interaction between the Cu(II) salt **A** and B_2pin_2 generates the Cu^I/Bpin species **B**.[10,12,14] Subsequently, an electrophilic fluoroalkyl radical from bromodifluoro reagent is formed via bromide abstraction by the copper(I) complex **B** with concomitant generation of copper(II) **C**.[10,12b] The radical can be trapped by aldehyde derived hydrazone to form the aminyl radical **D**, which further converts into intermediate **E** via an SET process.[8,13] Then the removal of a proton eventually produces the desired product **3**.

In summary, we described a novel, efficient C(sp^2)−H difluoroalkylation of aldehyde derived hydrazones via a Cu^{II}/B_2pin_2-catalyzed reaction between difluoroalkyl bromides and hydrazones. A broad range of functional groups was tolerated well under standard conditions with good to excellent yields. In addition, aliphatic aldehyde derived hydrazones are good candidates in this method to render the corresponding products, which makes our method a complementary protocol to the existing methods. Further applications of this transformation are under investigation in our laboratory.

EXPERIMENTAL SECTION

General Information. All reactions were accomplished in Schlenk tubes or round flasks under an atmosphere of N_2. Column chromatography was performed over silica gel (200−300 mesh). ^1H NMR spectra were recorded on a 500 MHz spectrometer, and chemical shifts (in ppm) were referenced to $CDCl_3$ (δ 7.26 ppm) as an internal standard. ^{13}C NMR spectra were obtained by using the same NMR spectrometer and were calibrated with $CDCl_3$ (δ 77.0 ppm). ^{19}F NMR spectra were obtained on the same NMR spectrometer with $CFCl_3$ as an external standard and low field being positive. The following abbreviations are used to illuminate the diversities: δ, chemical shift; *J*, coupling constant; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HRMS (EI) measurements were obtained with quadrupole and TOF mass spectrometers. CH_2Cl_2 was distilled from CaH_2. All reagents and solvents were obtained from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography (TLC), GC, or GC-MS analysis. The products were purified by column chromatography on silica gel using petroleum ether and ethyl acetate as the eluent.

Synthesis of Aldehyde-Derived Hydrazones 1a−1ah.[15] Morpholin-4-amine (2.2 mmol), aldehyde (2.0 mmol), and anhydrous $MgSO_4$ (0.5 g) in CH_2Cl_2 (10 mL) was stirred overnight at room temperature until consumption of the raw material aldehyde (TLC tracking). After filtration of $MgSO_4$, the solvent was removed under reduced pressure and the residue was subjected to column chromatography to give the aldehyde derived hydrazone (**1a−1ah**) in good yield.

General Procedure for the Difluoroalkylation of Aldehyde-Derived Hydrazones. The aldehyde hydrazone (0.3 mmol), bis(pinacolato)diboron (30 mol %, 22.9 mg), $CuBr_2$ (10 mol %, 6.7 mg), 4,4′-dibutyl-2,2′-bipyridyl (10 mol %, 8.1 mg), and $NaHCO_3$ (0.6 mmol, 50.5 mg) were placed in a 25 mL Schlenk tube in air. Then the mixture was evacuated and back-filled with N_2 (three times). Ethyl bromodifluoroacetate (0.6 mmol, 77 μL) and dioxane (1 mL) were added subsequently. The Schlenk tube was screw-capped and put into a preheated oil bath (80 °C). The reaction mixture was cooled to room temperature after being stirred for 16 h. After the reaction was finished, the mixture was concentrated under vacuum to remove dioxane, and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate 10/1 to 1/2) to afford the product.

*(E)-N-(4-Methylbenzylidene)morpholin-4-amine (**1a**).*[16] The general procedure afforded **1a** (390 mg, 96%) as a white solid, mp 92−93 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 3.89 (t, *J* = 5.0 Hz, 4H), 3.16 (t, *J* = 5.0

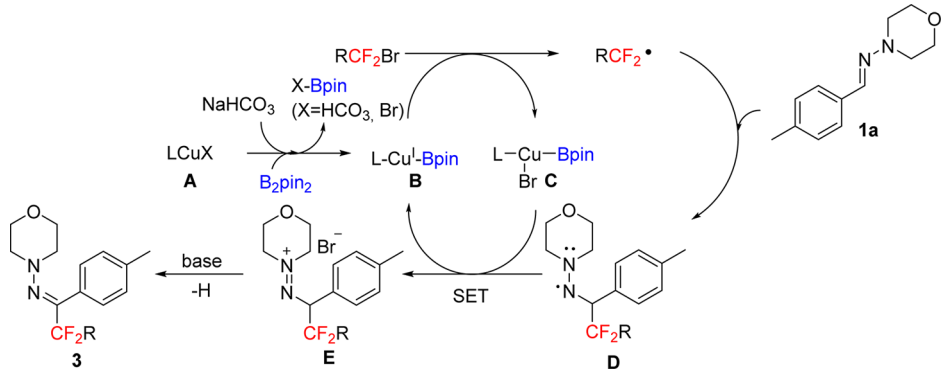


Figure 1. Plausible mechanistic pathway.

DOI: 10.1021/acs.joc.6b00324
J. Org. Chem. 2016, 81, 3654−3664

Hz, 4H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 138.3, 136.7, 133.2, 129.2, 126.2, 66.5, 52.0, 21.3.

*(E)-N-Benzylidenemorpholin-4-amine (**1b**).*[17] The general procedure afforded **1b** (360 mg, 95%) as a white solid, mp 68−69 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.65−7.58 (m, 3H), 7.35 (t, J = 7.5 Hz, 2H), 7.29 (ddd, J = 7.3, 3.8, 1.2 Hz, 1H), 3.89 (t, J = 5.0 Hz, 4H), 3.18 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.2, 135.9, 128.5, 128.3, 126.2, 66.4, 51.8.

*(E)-N-(4-Methoxybenzylidene)morpholin-4-amine (**1c**).*[18] The general procedure afforded **1c** (396 mg, 90%) as a white solid, mp 74−75 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 3.88 (t, J = 5.0 Hz, 4H), 3.81 (s, 3H), 3.13 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 159.9, 136.7, 128.7, 127.5, 114.0, 66.4, 55.2, 52.1.

*(E)-N-(4-Fluorobenzylidene)morpholin-4-amine (**1d**).*[8a] The general procedure afforded **1d** (408 mg, 98%) as a white solid, mp 77−78 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.61−7.53 (m, 3H), 7.03 (t, J = 8.7 Hz, 2H), 3.88 (t, J = 5.0 Hz, 4H), 3.15 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 162.8 (d, J = 246.3 Hz), 135.0, 132.1 (d, J = 2.5 Hz), 127.7 (d, J = 5.0 Hz), 115.4 (d, J = 8.8 Hz), 66.4, 51.8.

*(E)-N-(4-Chlorobenzylidene)morpholin-4-amine (**1e**).*[8a] The general procedure afforded **1e** (426 mg, 95%) as a white solid, mp 94−95 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.56−7.46 (m, 3H), 7.30 (d, J = 8.5 Hz, 2H), 3.86 (t, J = 5.0 Hz, 4H), 3.15 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 134.5, 134.4, 133.8, 128.6, 127.2, 66.3, 51.6.

*(E)-N-(4-Bromobenzylidene)morpholin-4-amine (**1f**).*[8b] The general procedure afforded **1f** (472 mg, 88%) as a white solid, mp 128−129 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.47−7.44 (m, 4H), 3.88 (t, J = 5.0 Hz, 4H), 3.17 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 134.9, 134.5, 131.6, 127.6, 122.4, 66.4, 51.7.

*(E)-1-(4-(((Morpholinoimino)methyl)phenyl)ethanone (**1g**).* The general procedure afforded **1g** (418 mg, 90%) as a yellow solid, mp 97−98 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.55 (s, 1H), 3.88 (t, J = 5.0 Hz, 4H), 3.22 (t, J = 5.0 Hz, 4H), 2.58 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 197.5, 140.5, 136.3, 133.6, 128.7, 125.9, 66.3, 51.4, 26.6. HRMS: m/z (EI-TOF) calculated [M], 232.1212; found, 232.1208.

*(E)-4-((Morpholinoimino)methyl)benzonitrile (**1h**).*[19] The general procedure afforded **1h** (357 mg, 83%) as a white solid, mp 124−125 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.49 (s, 1H), 3.88 (t, J = 5.0 Hz, 4H), 3.22 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 140.4, 132.4, 132.3, 126.2, 119.0, 110.8, 66.2, 51.3.

*(E)-N-(4-Nitrobenzylidene)morpholin-4-amine (**1i**).*[9a] The general procedure afforded **1i** (423 mg, 90%) as a yellow solid, mp 145−146 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.50 (s, 1H), 3.87 (t, J = 5.0 Hz, 4H), 3.24 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 146.8, 142.4, 131.4, 126.1, 123.8, 66.1, 51.1.

*(E)-N-(4-(Trifluoromethyl)benzylidene)morpholin-4-amine (**1j**).*[8a] The general procedure afforded **1j** (475 mg, 92%) as a white solid, mp 75−76 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.55 (s, 1H), 3.89 (t, J = 5.0 Hz, 4H), 3.21 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.4, 133.5, 129.7 (t, J = 31.3 Hz), 125.1, 125.4 (t, J = 3.8 Hz), 124.2 (t, J = 270 Hz), 66.3, 51.5.

*(E)-N-(4-(Dimethylamino)benzylidene)morpholin-4-amine (**1k**).*[20] The general procedure afforded **1k** (419 mg, 90%) as a pale yellow solid, mp 154−155 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 3.88 (t, J = 5.0 Hz, 4H), 3.11(t, J = 5.0 Hz, 4H), 2.98 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 150.7, 138.7, 127.5, 124.1, 112.0, 66.5, 52.5, 40.3.

*(E)-N-(3,4-Dimethoxybenzylidene)morpholin-4-amine (**1l**).*[21] The general procedure afforded **1l** (490 mg, 95%) as a white solid, mp 68−69 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.31 (d, J = 1.8 Hz, 1H), 6.99 (dd, J = 8.2, 1.8 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.87 (t, J = 5.0 Hz, 4H), 3.14 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 149.5, 149.1, 136.7, 128.9, 120.4, 110.5, 107.2, 66.4, 55.8, 55.7, 52.0.

*(E)-2-Methoxy-4-((morpholinoimino)methyl)phenol (**1m**).*[20] The general procedure afforded **1m** (420 mg, 89%) as a brown solid, mp 152−153 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.30 (d, J = 1.5 Hz, 1H), 6.96 (dd, J = 8.1, 1.4 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 3.91 (s, 3H), 3.88 (t, J = 5.0 Hz, 4H), 3.14 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 146.9, 146.4, 137.2, 128.5, 121.2, 114.1, 107.0, 66.5, 55.8, 52.1.

*(E)-N-(3-Chlorobenzylidene)morpholin-4-amine (**1n**).*[8a] The general procedure afforded **1n** (430 mg, 96%) as a white solid, mp 43−44 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (t, J = 1.6 Hz, 1H), 7.48 (s, 1H), 7.42 (dt, J = 7.4, 1.4 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.25−7.21 (m, 1H), 3.88 (t, J = 5.0 Hz, 4H), 3.18 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 137.9, 134.6, 133.9, 129.7, 128.0, 125.7, 124.4, 66.3, 51.6.

*(E)-N-(3-Nitrobenzylidene)morpholin-4-amine (**1o**).*[22] The general procedure afforded **1o** (428 mg, 91%) as a yellow solid, mp 145−146 °C. 1H NMR (500 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.07 (dd, J = 8.1, 2.3 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.48 (t, J = 8.0 Hz, 1H), 3.88 (t, J = 5.0 Hz, 4H), 3.22 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.6, 138.0, 132.0, 131.4, 129.3, 122.3, 120.6, 66.3, 51.4.

*(E)-N-(2-Methylbenzylidene)morpholin-4-amine (**1p**).*[8b] The general procedure afforded **1p** (384 mg, 94%) as a brown solid, mp 64−65 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.81−7.77 (m, 1H), 7.21−7.18 (m, 2H), 7.17−7.12 (m, 1H), 3.91 (t, J = 5.0 Hz, 4H), 3.19 (t, J = 5.0 Hz, 4H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 135.4, 134.9, 133.7, 130.5, 128.1, 126.1, 125.5, 66.4, 51.9, 19.5.

*(E)-N-(2-Methoxybenzylidene)morpholin-4-amine (**1q**).*[8a] The general procedure afforded **1q** (722 mg, 96%) as a pale yellow solid, mp 76−77 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.87 (dd, J = 7.7, 1.7 Hz, 1H), 7.26 (dt, J = 7.5, 5.0 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 3.89 (t, J = 5.0 Hz, 4H), 3.85 (s, 3H), 3.18 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 157.0, 132.3, 129.4, 125.4, 124.4, 120.8, 110.7, 66.4, 55.4, 52.0.

*(E)-N-(2-Bromobenzylidene)morpholin-4-amine (**1r**).* The general procedure afforded **1r** (509 mg, 95%) as a white solid, mp 77−78 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (dd, J = 7.9, 1.7 Hz, 1H), 7.87 (s, 1H), 7.52 (dd, J = 8.0, 1.1 Hz, 1H), 7.28 (t, J = 5.0 Hz, 1H), 7.12 (td, J = 7.9, 1.7 Hz, 1H), 3.89 (t, J = 5.0 Hz, 4H), 3.22 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 134.6, 34.6, 132.8, 129.3, 127.4, 126.7, 123.2, 66.3, 51.7. HRMS: m/z (EI-TOF) calculated [M], 268.0211; found, 268.0203.

*(E)-N-(Naphthalen-2-ylmethylene)morpholin-4-amine (**1s**).*[18] The general procedure afforded **1s** (432 mg, 92%) as a white solid, mp 125−127 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (dd, J = 8.6, 1.4 Hz, 1H), 7.86 (s, 1H), 7.85−7.80 (m, 3H), 7.75 (s, 1H), 7.46- 7.45 (m, 2H), 3.92 (t, J = 5.0 Hz, 4H), 3.24 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.2, 133.7, 133.5, 133.4, 128.3, 128.0, 127.8, 126.6, 126.2, 126.0, 123.0, 66.4, 51.8.

*(E)-N-(Pyridin-3-ylmethylene)morpholin-4-amine (**1t**).* The general procedure afforded **1t** (330 mg, 86%) as a brown solid, mp 31−32 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.70 (d, J = 1.8 Hz, 1H), 8.47 (dd, J = 4.8, 1.6 Hz, 1H), 7.96 (dt, J = 8.0, 1.8 Hz, 1H), 7.52 (s, 1H), 7.25 (dd, J = 7.9, 4.8 Hz, 1H), 3.87 (t, J = 5.0 Hz, 4H), 3.19 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 149.0, 148.2, 132.3, 131.9, 131.8, 123.5, 66.3, 51.5. HRMS: m/z (EI-TOF) calculated [M], 191.1059; found, 191.1057.

*(E)-N-(Thiophen-2-ylmethylene)morpholin-4-amine (**1u**).*[23] The general procedure afforded **1u** (345 mg, 88%) as a brown solid, mp 92−93 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.2 (d, J = 5.0 Hz, 1H), 7.07 (dd, J = 3.6, 0.8 Hz, 1H), 6.99 (dd, J = 5.1, 3.6 Hz, 1H), 3.86 (t, J = 5.0 Hz, 4H), 3.13 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.5, 131.2, 127.1, 126.3, 125.5, 66.3, 51.8.

*(E)-N-(Furan-2-ylmethylene)morpholin-4-amine (**1v**).* The general procedure afforded **1v** (299 mg, 83%) as a pale yellow solid, mp 53−54 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.41 (d, J = 0.8 Hz, 1H), 6.46 (d, J = 3.4 Hz, 1H), 6.43−6.38 (m, 1H), 3.85 (t, J = 5.0 Hz, 4H), 3.13 (t, J = 5.0 Hz, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.1, 142.7, 126.6, 111.3, 109.2, 66.2, 51.6. HRMS: m/z (EI-TOF) calculated [M], 180.0899; found, 180.0894.

DOI: 10.1021/acs.joc.6b00324
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*(E)-N-(Benzo[b]thiophen-3-ylmethylene)morpholin-4-amine (**1w**).* The general procedure afforded **1w** (423 mg, 86%) as a brown solid, mp 73−74 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (dd, J = 7.4, 0.7 Hz, 1H), 7.93 (s, 1H), 7.87−7.83 (m, 1H), 7.51 (s, 1H), 7.41 (dtd, J = 14.9, 7.2, 1.2 Hz, 2H), 3.92 (t, J = 5.0 Hz, 4H), 3.22 (t, J = 5.0 Hz, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.7, 136.3, 132.7, 132.4, 126.6, 124.9, 124.9, 124.6, 122.5, 66.4, 51.8. HRMS: m/z (EI-TOF) calculated [M], 342.0827; found,246.0826.

*(E)-N-((1H-Indol-3-yl)methylene)morpholin-4-amine (**1x**).*[24] The general procedure afforded **1x** (357 mg, 78%) as a pale white solid, mp 128−129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.32 (d, J = 7.4 Hz, 1H), 7.99 (s, 1H), 7.34 (dd, J = 7.1, 1.1 Hz, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.25−7.23 (m, 1H), 7.22−7.17 (m, 1H), 3.93 (t, J = 5.0 Hz, 4H), 3.18 (t, J = 5.0 Hz, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 136.7, 135.2, 125.5, 124.8, 123.0, 122.0, 120.7, 114.0, 111.1, 66.5, 52.6.

*(E)-N-(3-Phenylpropylidene)morpholin-4-amine (**1y**).*[8a] The general procedure afforded **1y** (392 mg, 90%) as a clear colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, J = 10.1, 4.9 Hz, 2H), 7.24−7.17 (m, 3H), 6.97 (t, J = 5.3 Hz, 1H), 3.82 (t, J = 5.0 Hz, 4H), 2.94 (t, J = 5.0 Hz, 4H), 2.83(t, J = 7.5 Hz, 2H), 2.62−2.54 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 141.1, 140.6, 128.4, 128.3, 126.0, 66.4, 52.3, 34.6, 33.6.

*(E)-Ethyl 3-(2,2-Dimethylhydrazono)-2,2-difluoro-5-phenylpentanoate (**1z**).*[9a] The general procedure afforded **1z** (290 mg, 48%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.27 (m, 2H), 7.24−7.20 (m, 3H), 6.67 (t, J = 5.4 Hz, 1H), 2.84−2.79 (m, 2H), 2.73 (s, 6H), 2.60−2.52 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 141.4, 138.0, 128.4, 128.3, 125.9, 43.3, 34.7, 34.1.

*(E)-N-Octylidenemorpholin-4-amine (**1aa**).*[25] The general procedure afforded **1aa** (352 mg, 83%) as a clear colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (t, J = 5.6 Hz, 1H), 3.80 (t, J = 5.0 Hz, 4H), 2.92 (t, J = 5.0 Hz, 4H), 2.25−2.19 (m, 2H), 1.46 (dt, J = 15.1, 7.4 Hz, 2H), 1.31−1.23 (m, 8H), 0.85 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 142.4, 67.0, 66.4, 52.5, 33.0, 31.7, 29.1, 29.0, 27.4, 22.6, 14.0.

*(E)-N-Hexylidenemorpholin-4-amine (**1ab**).* The general procedure afforded **1ab** (302 mg, 82%) as a clear colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (t, J = 5.6 Hz, 1H), 3.80 (t, J = 5.0 Hz, 4H), 2.92 (t, J = 5.0 Hz, 4H), 2.26−2.18 (m, 2H), 1.52−1.40 (m, 2H), 1.33−1.26 (m, 4H), 0.87 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 142.4, 66.4, 52.5, 33.0, 31.3, 27.0, 22.4, 13.9. HRMS: m/z (EI-TOF) calculated [M], 184.1576; found, 184.1570.

*(E)-N-Pentylidenemorpholin-4-amine (**1ac**).* The general procedure afforded **1ac** (296 mg, 87%) as a clear colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (t, J = 5.6 Hz, 1H), 3.80 (t, J = 5.0 Hz, 4H), 2.92 (t, J = 5.0 Hz, 4H), 2.27−2.18 (m, 2H), 1.48−1.40 (m, 2H), 1.38−1.29 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H). ^{113}C{1H}NMR (125 MHz, $CDCl_3$): δ 142.4, 66.4, 52.4, 32.7, 29.5, 22.2, 13.9. HRMS: m/z (EI-TOF) calculated [M], 170.1419; found, 170.1415.

*(E)-1-(4-Methylbenzylidene)-2-phenylhydrazine (**1ad**).*[26] The general procedure afforded **1ad** (412 mg, 98%) as a brown solid, mp 108−109 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.53 (s, 1H), 7.33−7.27 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.12 (dd, J = 8.5, 0.9 Hz, 2H), 6.92−6.85 (m, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.8, 138.4, 137.5, 132.5, 129.3, 129.2, 126.1, 119.9, 112.7, 21.4.

*(E)-N-(4-Bromobenzylidene)piperidin-1-amine (**1ae**).* The general procedure afforded **1ae** (495 mg, 93%) as a white solid, mp 51−52 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54−7.37 (m, 5H), 3.16 (t, J = 5.0 Hz, 4H), 1.74 (dt, J = 11.6, 5.8 Hz, 4H), 1.57−1.52 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.7, 132.7, 131.5, 127.3, 121.3, 51.9, 25.1, 24.1. HRMS: m/z (EI-TOF) calculated [M], 266.0419; found, 266.0417.

*(E)-N-(4-Bromobenzylidene)-4-methylpiperazin-1-amine (**1af**).* The general procedure afforded **1af** (489 mg, 87%) as a white solid, m.p.140−141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49−7.45 (m, 5H), 3.20 (t, J = 5.0 Hz, 4H), 2.60 (t, J = 5.0 Hz, 4H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 135.2, 134.0, 131.5, 127.4, 121.7, 54.4, 50.8, 45.9. HRMS: m/z (EI-TOF) calculated [M], 281.0528; found, 281.0525.

*(E)-4-Methylbenzaldehyde Oxime (**1ag**).*[27] The general procedure afforded **1ag** (182 mg, 75%) as a white solid, mp 70−71 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.17 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 150.3, 140.3, 129.5, 129.0, 127.0, 21.4.

*(E)-N′-(4-Methylbenzylidene)benzenesulfonohydrazide (**1ah**).*[8a] The general procedure afforded **1ah** (507 mg, 88%) as a white solid, mp 116−117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.02 (s, 1H), 8.00 (d, J = 1.4 Hz, 1H), 7.77 (s, 1H), 7.61−7.55 (m, 1H), 7.50 (dd, J = 10.5, 4.7 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.4, 140.8, 138.1, 133.2, 130.3, 129.3, 129.0, 127.8, 127.3, 21.4.

*2-Bromo-2,2-difluoro-N-phenylacetamide (**2b**).*[9d] The general procedure afforded **2b** (488 mg, 98%) as a white solid, mp 83−84 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 157.5 (t, J = 27.5 Hz), 135.3, 129.4, 126.24, 114.00, 111.5 (t, J = 315.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ −60.6.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-3-(p-tolyl)-propanoate (**3**).*[8a] The general procedure was used. The reaction gave 63 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-(*p*-tolyl)propanoate in 96% isolated yield as a pale yellow solid (PE/EA = 10/1), mp 68−69 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H), 2.37 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.7 (t, J = 31.3 Hz), 141.1 (t, J = 31.3 Hz), 139.7, 129.4, 128.5, 128.2, 114.32 (t, J = 248.6 Hz), 65.98, 62.5, 54.1, 21.4, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.54.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-3-phenylpropanoate (**4**).*[8a] The general procedure was used. The reaction gave 79 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-phenylpropanoate in 87% isolated yield as a clear yellow liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (dd, J = 6.1, 2.6 Hz, 2H), 7.43−7.38 (m, 3H), 4.37 (q, J = 7.1 Hz, 2H), 3.58 (t, J = 5.0 Hz, 4H), 2.92 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.64(t, J = 31.3 Hz), 140.63 (t, J = 30.0 Hz), 131.2, 129.7, 128.6, 128.6, 114.3 (t, J = 247.5 Hz), 65.9, 62.5, 54.1, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.49.

*(E)-Ethyl 2,2-Difluoro-3-(4-methoxyphenyl)-3-(morpholinoimino)propanoate (**5**).* The general procedure was used. The reaction gave 99 mg of (*E*)-ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-(morpholinoimino)propanoate in 97% isolated yield as a pale yellow liquid (PE/EA = 5/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.60 (t, J = 5.0 Hz, 4H), 2.92 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.7 (t, J = 31.3 Hz), 160.46, 141.5 (t, J = 31.3 Hz), 129.9, 123.0, 116.33, 114.35 (t, J = 247.5 Hz), 114.1, 66.0, 62.5, 55.2, 54.0, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.52. HRMS: m/z (EI-TOF) calculated [M], 342.1391; found, 342.1388.

*(E)-Ethyl 2,2-Difluoro-3-(4-fluorophenyl)-3-(morpholinoimino)-propanoate (**6**).*[8a] The general procedure was used. The reaction gave 84 mg of (*E*)-ethyl 2,2-difluoro-3-(4-fluorophenyl)-3-(morpholinoimino)propanoate in 85% isolated yield as a clear colorless liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, J = 8.6, 5.4 Hz, 2H), 7.11 (t, J = 8.7 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 2.91 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.45 (t, J = 31.3 Hz), 163.2 (d, J = 248.8 Hz), 140.0 (t, J = 31.3 Hz), 130.7 (t, J = 7.5 Hz), 127.1 (t, J = 2.5 Hz) 115.9 (t, J = 21.3 Hz), 114.2 (t, J = 247.5 Hz), 65.9, 62.6, 54.1, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.5, −109.8.

*(E)-Ethyl 3-(4-Chlorophenyl)-2,2-difluoro-3-(morpholinoimino)-propanoate (**7**).*[8a] The general procedure was used. The reaction gave 86 mg of (*E*)-ethyl 2,2-difluoro-3-(4-chlorophenyl)-3-(morpholinoimino)propanoate in 83% isolated yield as a pale yellow liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46−7.36

DOI: 10.1021/acs.joc.6b00324
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(m, 4H), 4.37 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.64, 163.38 (t, J = 32.5 Hz), 139.46 (t, J = 31.3 Hz), 135.9, 130.09, 129.59, 129.09, 114.1 (t, J = 247.5 Hz), 65.9, 62.6, 54.1, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.3.

*(E)-Ethyl 3-(4-Bromophenyl)-2,2-difluoro-3-(morpholinoimino)-propanoate (**8**).* The general procedure was used. The reaction gave 95 mg of (*E*)-ethyl 2,2-difluoro-3-(4-bromophenyl)-3-(morpholinoimino)propanoate in 81% isolated yield as a pale yellow liquid (PE/EA = 10/1).^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.36 (t, J = 31.3 Hz), 139.35 (t, J = 32.5 Hz), 132.0, 130.2, 130.0, 124.2, 114.1 (t, J = 251.3 Hz), 65.9, 62.6, 54.1, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.3. HRMS: m/z (EI-TOF) calculated [M], 390.0391; found, 390.0386.

*(E)-Ethyl 3-(4-Acetylphenyl)-2,2-difluoro-3-(morpholinoimino)-propanoate (**9**).* The general procedure was used. The reaction gave 86 mg of (*E*)-ethyl 2,2-difluoro-3-(4-acetylhenyl)-3-(morpholinoimino)propanoate in 83% isolated yield as a yellow liquid (PE/EA = 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.58 (t, J = 5.0 Hz, 4H), 2.92 (t, J = 5.0 Hz, 4H), 2.61 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 197.2, 163.30 (t, J = 31.3 Hz), 138.8 (t, J = 31.3 Hz), 137.7, 136.0, 129.0, 128.4, 114.08 (t, J = 248.8 Hz), 65.8, 62.7, 54.2, 26.6, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.1. HRMS: m/z (EI-TOF) calculated [M], 354.1391; found, 354.1385.

*(E)-Ethyl 3-(4-Cyanophenyl)-2,2-difluoro-3-(morpholinoimino)-propanoate (**10**).* The general procedure was used. The reaction gave 75 mg of (*E*)-ethyl 2,2-difluoro-3-(4-acetylphenyl)-3-(morpholinoimino)propanoate in 74% isolated yield as a yellow solid (PE/EA = 10/1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 3.92 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.0 (t, J = 31.3 Hz), 137.7 (t, J = 31.3 Hz), 136.0, 132.3, 129.5, 117.9, 114.0 (t, J = 31.3 Hz), 113.6, 65.8, 62.8, 54.3, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −100.8. HRMS: m/z (EI-TOF) calculated [M], 377.1238; found, 337.1240.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-3-(4-nitrophenyl)-propanoate (**11**).*[9d] The general procedure was used. The reaction gave 91 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-(4-nitrophenyl)propanoate in 85% isolated yield as a yellow solid (PE/EA = 10/1), mp 119−120 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 2.94 (t, J = 5.0 Hz, 4H), 1.38 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.0 (t, J = 30.0 Hz), 148.3, 137.9, 137.2 (t, J = 32.5 Hz), 129.9, 123.8, 113.93 (t, J = 248.8 Hz), 65.8, 62.8, 54.3, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −100.7.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-3-(4-(trifluoromethyl)phenyl)propanoate (**12**).*[8a] The general procedure was used. The reaction gave 92 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-(4-trifluoromethylphenyl)propanoate in 80% isolated yield as a yellow solid (PE/EA = 10/1), mp 78−79 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H), 1.38 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.3 (t, J = 31.3 Hz), 138.5 (t, J = 31.3 Hz), 135.0, 131.7 (q, J = 32.5 Hz), 129.2, 125.6 (q, J = 3.8 Hz), 123.6 (q, J = 271.3 Hz), 114.1 (t, J = 248.8 Hz), 65.9, 62.7, 54.2, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −63.0, −101.1.

*(E)-Ethyl 3-(4-(Dimethylamino)phenyl)-2,2-difluoro-3-(morpholinoimino)propanoate (**13**).* The general procedure was used. The reaction gave 65 mg of (*E*)-ethyl 3-(4-(dimethylamino)phenyl)-2,2-difluoro-3-(morpholinoimino)propanoate in 61% isolated yield as a clear colorless liquid (PE/EA = 1/1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.63 (t, J = 5.0 Hz, 4H), 3.00 (s, 6H), 2.94 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.95 (t, J = 31.9 Hz), 150.9, 143.38 (t, J = 30.0 Hz), 129.4, 117.4, 114.67 (t, J = 248.8 Hz), 111.40, 66.1, 62.4, 54.0, 40.0, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.3. HRMS: m/z (EI-TOF) calculated [M], 355.1707; found, 355.1706.

*(E)-Ethyl 3-(3,4-Dimethoxyphenyl)-2,2-difluoro-3-(morpholino-imino)propanoate (**14**).* The general procedure was used. The reaction gave 107 mg of (*E*)-ethyl 3-(3,4-dimethoxyphenyl)-2,2-difluoro-3-(morpholinoimino)propanoate in 96% isolated yield as a clear colorless liquid (PE/EA = 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.07 (d, J = 8.1 Hz, 1H), 7.03 (s, 1H), 6.88 (d, J = 8.3 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.60 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.7 (t, J = 31.3 Hz), 150.1, 148.9, 141.0 (t, J = 31.9 Hz), 123.0, 121.6, 114.4 (t, J = 248.1 Hz), 111.3, 111.0, 66.1, 62.5, 56.0, 55.8, 54.0, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.4. HRMS: m/z (EI-TOF) calculated [M], 372.1497; found, 372.1500.

*(E)-Ethyl 2,2-Difluoro-3-(4-hydroxy-3-methoxyphenyl)-3-(morpholinoimino)propanoate (**15**).* The general procedure was used. The reaction gave 100 mg of (*E*)-ethyl 3-(4-hydroxy-3-methoxyphenyl)-2,2-difluoro-3-(morpholinoimino)propanoate in 97% isolated yield as a clear colorless liquid (PE/EA = 3/1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.05−7.00 (m, 2H), 6.93 (d, J = 8.2 Hz, 1H), 5.95 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.61 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.7 (t, J = 31.3 Hz), 146.9, 146.5, 141.1 (t, J = 31.3 Hz), 122.4, 114.7, 114.4 (t, J = 253.4 Hz), 110.7, 66.1, 62.5, 56.1, 54.0, 24.8, 14.1. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.4. HRMS: m/z (EI-TOF) calculated [M], 358.1340; found, 358.1342.

*(E)-Ethyl 3-(3-Chlorophenyl)-2,2-difluoro-3-(morpholinoimino)-propanoate (**16**).*[8a] The general procedure was used. The reaction gave 103 mg of (*E*)-ethyl 2,2-difluoro-3-(3-chlorophenyl)-3-(morpholinoimino)propanoate in 99% isolated yield as a pale yellow liquid (PE/EA = 10/1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.41−7.33 (m, 3H), 4.37 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 2.94 (t, J = 5.0 Hz, 4H), 1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.3 (t, J = 31.9 Hz), 138.5 (t, J = 31.9 Hz), 134.7, 132.9, 129.9, 129.9, 128.7, 126.9, 114.1 (t, J = 248.8 Hz), 65.9, 62.6, 54.2, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.2.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-3-(3-nitrophenyl)-propanoate (**17**).* The general procedure was used. The reaction gave 81 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-(3-nitrophenyl) propanoate in 75% isolated yield as a yellow solid (PE/EA = 10/1). ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.28 (ddd, J = 8.3, 2.2, 1.0 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.61 (t, J = 5.0 Hz, 4H), 2.95 (t, J = 5.0 Hz, 4H), 1.39 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.0 (t, J = 31.9 Hz), 148.2, 137.0 (t, J = 31.2 Hz), 134.6, 132.8, 129.8, 124.5, 123.8, 113.9 (t, J = 250.0 Hz), 65.8, 62.8, 54.3, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −100.84 (d, J = 9.4 Hz). HRMS: m/z (EI-TOF) calculated [M], 357.1136; found, 357.1131.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-3-(o-tolyl)-propanoate (**18**).* The general procedure was used. The reaction gave 63 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-(*o*-tolyl)propanoate in 64% isolated yield as a clear colorless liquid (PE/EA = 10/1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.34−7.28 (m, 2H), 7.21 (t, J = 8.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.62−3.52 (m, 4H), 2.97−2.84 (m, 4H), 2.28 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.90 (t, J = 32.5 Hz), 138.8 (t, J = 31.3 Hz), 138.1, 131.2, 130.0, 129.7, 128.8, 125.7, 114.4 (t, J = 247.5 Hz), 66.3, 62.5, 53.8, 19.7, 14.1. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.0 (d, J = 273.2 Hz), −103.3 (d, J = 273.2 Hz). HRMS: m/z (EI-TOF) calculated [M], 326.1442; found, 326.1441.

*(E)-Ethyl 2,2-Difluoro-3-(2-methoxyphenyl)-3-(morpholino-imino)propanoate (**19**).*[8a] The general procedure was used. The reaction gave 77 mg of (*E*)-ethyl 2,2-difluoro-3-(2-methoxyphenyl)-3-(morpholinoimino)propanoate in 75% isolated yield as a clear colorless liquid (PE/EA = 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (t, J = 7.9 Hz, 1H), 7.24 (s, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.57 (t, J = 5.0 Hz, 4H), 2.97 (t, J = 5.0 Hz, 4H), 1.36 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 164.1 (t, J = 33.1 Hz), 157.6, 135.0 (t, J = 31.1 Hz), 131.2, 130.5, 120.5, 114.2 (t, J = 248.1 Hz), 111.12, 66.2,

DOI: 10.1021/acs.joc.6b00324
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62.4, 55.8, 53.4, 14.1. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.6, −103.2.

*(E)-Ethyl 3-(2-Bromophenyl)-2,2-difluoro-3-(morpholinoimino)-propanoate (**20**).* The general procedure was used. The reaction gave 53 mg of (*E*)-ethyl 2,2-difluoro-3-(2-bromophenyl)-3-(morpholinoimino)propanoate in 45% isolated yield as a pale yellow liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.36 (dt, *J* = 14.8, 7.5 Hz, 2H), 7.31−7.26 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.61 (t, *J* = 4.9 Hz, 4H), 3.01 (dtd, *J* = 17.0, 11.9, 4.7 Hz, 4H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.7 (t, *J* = 33.9 Hz), 133.5, 132.7, 131.3, 131.0, 127.2, 127.0, 124.3, 114.2 (t, *J* = 248.8 Hz), 66.3, 62.5, 53.4, 14.1. ^{19}F NMR (471 MHz, $CDCl_3$): δ −99.6 (d, *J* = 268.5 Hz), −102.8 (d, *J* = 268.5 Hz). HRMS: *m*/*z* (EI-TOF) calculated [M], 390.0391; found, 390.0392.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-3-(naphthalen-2-yl)-propanoate (**21**, E/Z = 67/33).* The general procedure was used. The reaction gave 56 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-(naphthalen-2-yl)propanoate in 51% isolated yield as a pale yellow liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37−8.26 (m, 1H), 7.99 (s, 1H), 7.92−7.86 (m, 2H), 7.63−7.45 (m, 3H), 4.41 (q, *J* = 7.1 Hz, 3H), 3.60 (t, *J* = 5.0 Hz, 4H), 2.96 (t, *J* = 5.0 Hz, 4H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.7 (t, *J* = 35.0 Hz), 140.7 (t, *J* = 32.5 Hz), 133.5, 132.8, 131.3, 128.5, 128.4, 128.4, 127.8, 127.3, 126.8, 125.4, 114.4 (t, *J* = 211.3 Hz), 66.0, 62.6, 54.3, 14.1. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.1. HRMS: *m*/*z* (EI-TOF) calculated [M], 362.1442; found, 362.1439.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-3-(pyridin-3-yl)-propanoate (**22**).* The general procedure was used. The reaction gave 38 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-(pyridin-3-yl)propanoate in 41% isolated yield as a pale yellow liquid (PE/EA = 5/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.65 (d, *J* = 4.2 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.38 (dd, *J* = 7.8, 4.9 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.60 (t, *J* = 5.0 Hz, 4H), 2.94 (t, *J* = 5.0 Hz, 4H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.2 (t, *J* = 31.3 Hz), 150.6, 149.4, 136.2, 127.7, 123.5, 114.00 (t, *J* = 248.1 Hz), 65.8, 62.7, 54.2, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.3. HRMS: *m*/*z* (EI-TOF) calculated [M], 313.1238; found, 326.1237.

*(E)-Ethyl 2,2-Difluoro-2-(5-((morpholinoimino)methyl)thiophen-2-yl)acetate (**23**).* The general procedure was used. The reaction gave 21 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-3-(pyridin-3-yl)propanoate in 21% isolated yield as a pale yellow liquid (PE/EA = 7:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.26−7.23 (m, 1H), 6.96 (d, *J* = 3.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.86 (t, *J* = 5.0 Hz, 4H), 3.16 (t, *J* = 5.0 Hz, 4H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.2 (t, *J* = 35.0 Hz), 145.63, 132.6 (t, *J* = 30.0 Hz), 129.0, 128.4 (t, *J* = 5.6 Hz), 125.1, 111.6 (t, *J* = 248.7 Hz), 66.2, 63.4, 51.4, 13.9. ^{19}F NMR (471 MHz, $CDCl_3$): δ −93.9. HRMS: *m*/*z* (EI-TOF) calculated [M], 318.0850; found, 318.0848.

*(E)-Ethyl 2,2-Difluoro-2-(5-((morpholinoimino)methyl)furan-2-yl)acetate (**24**).* The general procedure was used. The reaction gave 46 mg of (*E*)-ethyl 2,2-difluoro-3-(furan-2-yl)-3-(morpholinoimino) propanoate in 51% isolated yield as a pale yellow liquid (PE/EA = 7/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (s, 1H), 6.77 (dd, *J* = 3.4, 1.6 Hz, 1H), 6.57 (d, *J* = 3.5 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.86 (t, *J* = 5.0 Hz, 4H), 3.16 (t, *J* = 5.0 Hz, 4H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.3 (t, *J* = 33.8 Hz), 154.3, 143.5 (t, *J* = 33.1 Hz), 124.8, 113.5, 108.59 (t, *J* = 246.9 Hz), 107.18, 66.2, 63.5, 51.2, 13.9. ^{19}F NMR (471 MHz, $CDCl_3$): δ −102.2. HRMS: *m*/*z* (EI-TOF) calculated [M], 302.1078; found, 302.1076.

*(E)-Ethyl 3-(5-(2-Ethoxy-1,1-difluoro-2-oxoethyl)thiophen-2-yl)-2,2-difluoro-3-(morpholinoimino)propanoate (**25**).* The general procedure was used. The reaction gave 45 mg of (*E*)-ethyl 3-(5-(2-ethoxy-1,1-difluoro-2-oxoethyl)thiophen-2-yl)-2,2-difluoro-3-(morpholinoimino)propanoate in 39% isolated yield as a pale yellow liquid (PE/EA = 7/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63−7.57 (m, 1H), 7.38−7.33 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 4H), 3.84 (t, *J* = 5.0 Hz, 4H), 2.91 (t, *J* = 5.0 Hz, 4H), 1.37 (t, *J* = 7.1, 3H), 1.36 (t, *J* = 7.1, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.76 (t, *J* = 34.4 Hz), 162.3 (t, *J* = 30.0 Hz), 147.72 (t, *J* = 31.3 Hz), 138.9 (t, *J* = 33.8 Hz), 132.0 (t, *J* = 3.1 Hz), 130.2 (t, *J* = 1.9 Hz), 127.5 (t, *J* = 5.6 Hz), 113.8 (t, *J* = 252.5 Hz), 111.4 (t, *J* = 250.0 Hz), 65.8, 63.7, 63.0, 54.5, 13.9, 13.9. ^{19}F NMR (471 MHz, $CDCl_3$): δ −94.2, −102.5. HRMS: *m*/*z* (EI-TOF) calculated [M], 440.1029; found, 440.1033.

*(E)-Ethyl 3-(5-(2-Ethoxy-1,1-difluoro-2-oxoethyl)furan-2-yl)-2,2-difluoro-3-(morpholinoimino)propanoate (**26**).* The general procedure was used. The reaction gave 68 mg of (*E*)-ethyl 3-(5-(2-ethoxy-1,1-difluoro-2-oxoethyl)furan-2-yl)-2,2-difluoro-3-(morpholinoimino)-propanoate in 53% isolated yield as a yellow liquid (PE/EA = 7/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (dd, *J* = 3.4, 1.3 Hz, 1H), 6.81 (d, *J* = 3.5 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 4H), 3.73 (t, *J* = 5.0 Hz, 4H), 3.07 (t, *J* = 5.0 Hz, 4H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.0 (t, *J* = 31.9 Hz), 161.9 (t, *J* = 33.1 Hz), 145.7 (t, *J* = 34.4 Hz), 144.3, 127.5 (t, *J* = 32.5 Hz), 114.8, 112.9, 112.9 (t, *J* = 124.4 Hz), 108.3 (t, *J* = 248.1 Hz), 66.1, 63.8, 62.8, 53.9, 14.0, 13.8. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.9, −102.8. HRMS: *m*/*z* (EI-TOF) calculated [M], 424.1257; found, 424.1258.

*(E)-Ethyl 3-(Benzo[b]thiophen-3-yl)-2,2-difluoro-3-(morpholino-imino)propanoate (**27**).* The general procedure was used. The reaction gave 47 mg of (*E*)-ethyl 3-(benzo[*b*]thiophen-3-yl)-2,2-difluoro-3-(morpholinoimino)propanoate in 32% isolated yield as a yellow liquid (PE/EA = 7/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91−7.84 (m, 1H), 7.80−7.73 (m, 1H), 7.52−7.46 (m, 2H), 4.48−4.32 (m, 4H), 3.59−3.47 (m, 4H), 3.20−2.80 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.6 (t, *J* = 31.9 Hz), 162.2 (t, *J* = 33.7 Hz), 138.5, 138.3, 134.1 (t, *J* = 27.5 Hz), 127.6 (t, *J* = 3.8 Hz), 127.0, 125.7, 124.8, 124.8, 122.4, 114.1 (t, *J* = 247.5 Hz), 111.7 (t, *J* = 250.0 Hz), 66.2, 63.8, 62.7, 53.1, 14.1, 13.8. ^{19}F NMR (471 MHz, $CDCl_3$): δ −89.6 (dd, *J* = 9.4, 277.9 Hz), −95.6 (dd, *J* = 4.7, 273.2 Hz), −99.4 (d, *J* = 9.4, 268.5 Hz), −101.6 (dt, *J* = 9.4, 263.8 Hz). HRMS: *m*/*z* (EI-TOF) calculated [M], 490.1186; found, 490.1190.

*(E)-Ethyl 2,2-Difluoro-2-(2-((morpholinoimino)methyl)-1H-indol-3-yl)acetate (**28**).* The general procedure was used. The reaction gave 58 mg of (*E*)-ethyl 2,2-difluoro-3-(1*H*-indol-3-yl)-3-(morpholino-imino)propanoate in 47% isolated yield as a yellow liquid (PE/EA = 7/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.42 (d, *J* = 8.1 Hz, 1H), 8.06 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.93 (t, *J* = 5.0 Hz, 4H), 3.22 (t, *J* = 5.0 Hz, 4H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.9 (t, *J* = 35.6 Hz), 135.7, 131.3, 125.55, 125.31 (t, *J* = 30.0 Hz), 125.2, 124.9, 123.8, 121.6, 114.6, 111.4, 111.12 (t, *J* = 250.0 Hz), 66.5, 63.7, 51.9, 13.9. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.0. HRMS: *m*/*z* (EI-TOF) calculated [M], 351.1397; found, 351.1394.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)-5-phenylpentanoate (**29**, E/Z = 88/12).* The general procedure was used. This compound is known.[8a] The reaction gave 50 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)-5-phenylpentanoate in 49% isolated yield as a clear colorless liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (q, *J* = 7.3 Hz, 2H), 7.25−7.19 (m, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.76 (t, *J* = 5.0 Hz, 4H), 2.98- 2.94 (m, 2H), 2.84- 2.81 (m, 2H), 2.77 (t, *J* = 5.0 Hz, 4H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.87 (t, *J* = 31.3 Hz), 158.1 (t, *J* = 29.4 Hz), 140.5, 128.6, 128.3, 126.4, 113.78 (t, *J* = 250.6 Hz), 65.9, 62.7, 54.9, 31.7, 28.8, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −105.9.

*(E)-Ethyl 3-(2,2-Dimethylhydrazono)-2,2-difluoro-5-phenylpentanoate (**30**, E/Z = 80/20).*[9d] The general procedure was used. The reaction gave 27 mg of (*E*)-ethyl 3-(2,2-dimethylhydrazono)-2,2-difluoro-5-phenylpentanoate in 30% isolated yield as a clear colorless liquid (PE/EA = 30/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.27 (m, 2H), 7.25−7.19 (m, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.00−2.89 (m, 2H), 2.83−2.76 (m, 2H), 2.74 (s, 6H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.5 (t, *J* = 31.3 Hz), 147.8 (t, *J* = 30.6 Hz), 140.8, 128.6, 128.25, 126.4, 114.8 (t, *J* = 247.5 Hz), 62.5, 46.9, 31.9, 28.6, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −104.6.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)decanoate (**31**, E/Z = 76/24).* The general procedure was used. The reaction gave 49 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)decanoate in 49% isolated

DOI: 10.1021/acs.joc.6b00324
J. Org. Chem. 2016, 81, 3654−3664

yield as a clear colorless liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.36 (q, J = 7.1 Hz, 1H), 3.80 (t, J = 5.0 Hz, 4H), 2.85 (t, J = 5.0 Hz, 4H), 2.55−2.47 (m, 2H), 1.67−1.63 (m, 3H), 1.42−1.26 (m, 11H), 0.90 (td, J = 6.9, 2.6 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.1 (t, J = 31.3 Hz), 161.81 (t, J = 31.3 Hz), 113.8 (t, J = 250 Hz), 65.9, 62.6, 55.0, 31.6, 29.8, 28.7, 26.9, 25.5, 22.6, 14.0, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −106.0. HRMS: m/z (EI-TOF) calculated [M], 334.2068; found, 324.2070.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)octanoate (**32**, E/Z = 75/25).* The general procedure was used. The reaction gave 62 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)decanoate in 68% isolated yield as a clear colorless liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.33 (q, J = 7.1 Hz, 2H), 3.78 (t, J = 5.0 Hz, 4H), 2.83 (t, J = 5.0 Hz, 4H), 2.52−2.45 (m, 2H), 1.68−1.58 (m, 2H), 1.38−1.29 (m, 7H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.1 (t, J = 31.3 Hz), 158.6 (t, J = 29.4 Hz), 113.8 (t, J = 250.0 Hz), 65.9, 62.6, 55.0, 32.0, 25.8, 25.2, 22.1, 14.0, 13.8. ^{19}F NMR (471 MHz, $CDCl_3$): δ −106.0. HRMS: m/z (EI-TOF) calculated [M], 306.1755; found, 306.1750.

*(E)-Ethyl 2,2-Difluoro-3-(morpholinoimino)heptanoate (**33**, E/Z = 83/17).* The general procedure was used. The reaction gave 47 mg of (*E*)-ethyl 2,2-difluoro-3-(morpholinoimino)decanoate in 53% isolated yield as a clear colorless liquid (PE/EA = 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.34 (q, J = 7.1 Hz, 2H), 3.78 (t, J = 5.0 Hz, 4H), 2.86−2.81 (t, J = 5.0 Hz, 4H), 2.53−2.46 (m, 2H), 1.65−1.57 (m, 2H), 1.42−1.35 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.1 (t, J = 31.3 Hz), 158.4 (t, J = 30.0 Hz), 113.8 (t, J = 250.0 Hz), 66.0, 62.6, 55.0, 27.6, 26.6, 23.0, 14.0, 13.6. ^{19}F NMR (471 MHz, $CDCl_3$): δ −106.0. HRMS: m/z (EI-TOF) calculated [M], 292.1598; found, 292.1601.

*(E)-Ethyl 2,2-Difluoro-3-(2-phenylhydrazono)-3-(p-tolyl)-propanoate (**34**).* The general procedure was used. The reaction gave 60 mg of (*E*)-ethyl 2,2-difluoro-3-(2-phenylhydrazono)-3-(*p*-tolyl)propanoate in 60% isolated yield as a clear colorless liquid (PE/EA = 4/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.36 (d, J = 3.5 Hz, 3H), 7.23 (dd, J = 8.5, 7.4 Hz, 2H), 6.94−6.87 (m, 3H), 4.49 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.6 (t, J = 32.5 Hz), 143.0, 140.6, 136.0 (t, J = 31.3 Hz), 130.4, 129.2, 129.1, 123.84, 121.53, 113.9 (t, J = 245 Hz), 113.3, 62.9, 21.5, 14.1. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.1. HRMS: m/z (EI-TOF) calculated [M], 362.1442; found, 362.1439.

*(E)-Ethyl 3-(4-Bromophenyl)-2,2-difluoro-3-(piperidin-1-ylimino)-propanoate (**35**).* The general procedure was used. The reaction gave 66 mg of (*E*)-ethyl 3-(4-bromophenyl)-2,2-difluoro-3-(piperidin-1-ylimino)propanoate in 57% isolated yield as a clear colorless liquid (PE/EA = 8/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.93 (t, J = 5.0 Hz, 4H), 1.50−1.41 (m, 6H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ163.8 (t, J = 31.9 Hz), 135.49 (t, J = 31.9 Hz), 131.7, 130.8, 130.4, 123.6, 114.8 (t, J = 246.9 Hz) 62.5, 54.8, 24.7, 23.8, 14.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −100.4. HRMS: m/z (EI-TOF) calculated [M], 388.0598; found, 388.0590.

*(E)-Ethyl 3-(4-Bromophenyl)-2,2-difluoro-3-((4-methylpiperazin-1-yl)imino)propanoate (**36**).* The general procedure was used. The reaction gave 69 mg of (*E*)-ethyl 3-(4-bromophenyl)-2,2-difluoro-3-((4-methylpiperazin-1-yl)imino)propanoate in 57% isolated yield as a clear yellow liquid (PE/EA = 1/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.99 (t, J = 5.0 Hz, 4H), 2.35 (t, J = 5.0 Hz, 4H), 2.23 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ163.6 (t, J = 31.3 Hz), 138.0 (t, J = 31.3 Hz), 131.9, 130.3, 127.7, 124.1, 114.4 (t, J = 248.1 Hz), 62.6, 53.8, 53.3, 45.6, 14.1. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.0. HRMS: m/z (EI-TOF) calculated [M], 403.0707; found, 407.0703.

*(E)-2,2-Difluoro-3-(morpholinoimino)-N-phenyl-3-(p-tolyl)-propanamide (**39**).*[8a] The general procedure was used. The reaction gave 105 mg of (*E*)-2,2-difluoro-3-(morpholinoimino)-*N*-phenyl-3-(*p*-tolyl)propanamide in 93% isolated yield as a white solid (PE/EA = 5/1), mp 131−132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.58 (d, J = 7.8 Hz, 2H), 7.37 (dt, J = 7.5, 3.8 Hz, 4H), 7.22 (d, J = 7.9 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 3.58 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ161.6 (t, J = 28.9 Hz), 141.2 (t, J = 30.6 Hz), 139.8, 136.5, 129.4, 129.1, 128.5, 128.5, 125.2, 120.2, 114.37 (t, J = 251.3 Hz), 66.0, 54.2, 21.4. ^{19}F NMR (471 MHz, $CDCl_3$): δ −101.2.

*Ethyl 2,2-Difluoro-3-oxo-3-(p-tolyl)propanoate (**40**).*[8a] Compound **3** was placed in a 25 mL round-bottom flask with 2 mL of THF and 2 mL of 0.6 M HCl. The reaction was stirred at room temperature and monitored by TLC. The crude product was diluted with ethyl acetate when the raw material **3** was consumed. Then scrubbed with saturated NaCl solution (three times). The organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography to give the pure product **40** (88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 184.9 (t, J = 27.5 Hz), 161.9 (t, J = 30.6 Hz), 146.5, 130.0 (t, J = 2.5 Hz), 129.7, 128.5, 109.8 (t, J = 263.1 Hz), 63.7, 21.9, 13.8. ^{19}F NMR (471 MHz, $CDCl_3$): δ −107.6.

*2,2-Difluoro-3-(morpholinoamino)-3-(p-tolyl)propan-1-ol (**41**).*[8a] **3** was placed in a 25 mL tube with 2 mL of anhydrous THF in an ice bath. $LiAlH_4$ (10 equiv) was gradually added to the mixture. Then the mixture was stirred at room temperature. The reaction was stirred at room temperature and monitored by TLC. The crude product was diluted with ethyl acetate when the raw material **3** was consumed. Then scrubbed with saturated NaCl solution (three times). The organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography to give the pure product **41** (PE/EA = 4/1, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J = 6.9 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 4.99 (s, 1H), 4.36 (dd, J = 22.5, 4.2 Hz, 1H), 4.00 (ddd, J = 29.6, 12.8, 3.9 Hz, 1H), 3.84−3.67 (m, 5H), 3.07−2.43 (m, 5H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 138.6, 131.8, 129.2, 128.6, 121.8 (t, J = 246.9 Hz), 66.7, 63.4−62.0 (m, 2C), 56.5, 21.1. ^{19}F NMR (471 MHz, $CDCl_3$): δ −107.3 (d, J = 254.3 Hz), −119.9 (d, J = 254.3 Hz).

*(E)-2,2-Difluoro-3-(morpholinoimino)-3-(p-tolyl)propan-1-ol (**42**).* **3** was placed in a 25 mL tube with 2 mL of anhydrous THF in an ice bath. $NaBH_4$ (10 equiv) was gradually added to the mixture. The reaction was stirred at room temperature and monitored by TLC. The crude product was diluted with ethyl acetate when the raw material 3 was consumed. Then scrubbed with saturated NaCl solution (three times). The organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography to give the pure product **42** (PE/EA = 4/1, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 4.08 (td, J = 11.8, 7.2 Hz, 2H), 3.62 (t, J = 5.0 Hz, 4H), 3.05 (t, J = 7.3 Hz, 1H), 2.90 (t, J = 5.0 Hz, 4H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 146.4 (t, J = 32.5 Hz), 139.7, 129.3, 128.6, 128.1, 118.2 (t, J = 240.6 Hz), 66.0, 64.2, 63.9, 63.7, 54.3, 21.4. ^{19}F NMR (471 MHz, $CDCl_3$): δ −103.7. HRMS: m/z (EI-TOF) calculated [M], 284.1336; found, 284.1339.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00324.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.joc.6b00324
J. Org. Chem. 2016, 81, 3654−3664

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21202049), the Recruitment Program of Global Experts (1000 Talents Plan), the Natural Science Foundation of Fujian Province (2016J01064), the Fujian Hundred Talents Program, the Program of Innovative Research Team of Huaqiao University (Z14X0047), and the Graduate Innovation Fund (for M.K.) of Huaqiao University is gratefully acknowledged. We also thank the Instrumental Analysis Center of Huaqiao University for analytical support.

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DOI: 10.1021/acs.joc.6b00324
J. Org. Chem. 2016, 81, 3654−3664