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Magnesium-promoted Additions of Difluoroenolates to Unactivated Imines

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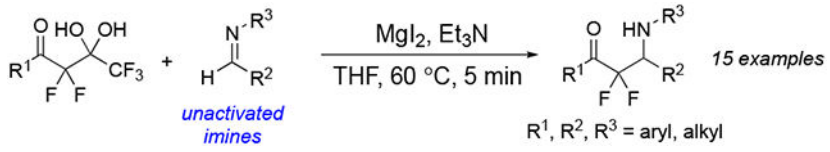
Abstract

Although there are many synthetic methods to produce fluorinated and trifluoromethylated organic structures, the construction of difluoromethylated compounds remains a synthetic challenge. We have discovered that using magnesium salts and organic bases, unactivated imines will react with difluoroenolates, generated under exceedingly mild conditions. We have applied this approach to the iminoaldol reaction to produce difluoromethylene groups as α,α-difluoro-β-amino-carbonyl groups. This method provides synthetically useful quantities of difficult to access α,α-difluoro-β-aminoketones without the need of protecting groups or the use of activated imines. Moreover, we have applied this strategy to create analogues of the dual orexin receptor antagonist, almorexant, in only two synthetic steps.

Graphical Abstract



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Author Contributions

A.L.N., H.R.K., J.R.W., and C.S.B. conducted the synthetic experiments and acquired analytical data. F.R.F. acquired the X-ray data. D.A.C., A.L.N., and J.R.W. wrote the manuscript and designed the experimental approach.

Supporting Information.

Spectroscopic data from ^{1}H, ^{13}C and ^{19}F NMR, and X-ray experimental and data. The Supporting Information is available free of charge on the ACS Publications website.

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INTRODUCTION

Organic compounds displaying fluorine are particularly valuable in the pharmaceutical, chemical, and agrochemical industries, because the presence of fluorine on a molecule can drastically improve its chemical and biological properties.[1–3] Specifically in drug development, nearly 25% of all marketed drugs contain at least one fluorine atom.[4–6] Numerous efforts for the synthesis of fluorine-containing organic compounds have been reported, yet it is challenging to create some complex fluorinated structures.[7,8] For example, there are vastly more methods for the synthesis of molecules displaying a trifluoromethyl group or a single fluorine than a difluoromethylene group. A primary reason is the difluoromethyl group is not a terminal group; and therefore, newer strategies such as late-stage fluorination cannot be readily applied. A uniquely appealing type of difluorinated compound is a difluoro-β-amino acid, and the typical synthetic target is an α,α-difluoro-β-amino-carbonyl group. These building blocks have found potential use as difluorinated drug leads[9,10] and enzyme inhibitors (Figure 1).[11–13]

The synthesis of α,α-difluoro-β-amino-carbonyl groups relies heavily on the addition of difluoroenolates to imines that are activated with protecting groups on nitrogen. Although the protecting groups assist in enhancing the reactivity (i.e., electrophilicity) of the imine, the utility of protecting groups continues to decline as two protection/deprotection steps must be added into the overall synthetic plan. The addition of difluoroenolates to unprotected, hence unactivated imines, is quite desirable but remains synthetically challenging. Currently, there are only two strategies to unite a difluoroenolate with an unactivated imine: 1) Reformatsky additions of bromodifluoroethyl acetate[14–19] and bromodifluormethyl ketones[20,21] 2) Mukaiyama additions of difluoroenoxy silanes (Figure 2). Typically, Reformatsky reactions with bromodifluoroethyl acetate are vigorous and therefore provide the cyclized lactam.[14,15] A diastereoselective variants have been reported, [16–18] and an indium-promoted version of the Reformatsky process has been developed to favor the amino-adduct rather than the lactam.[19] This chemistry has been extended to bromodifluoromethyl ketones in which the unactivated imines react in the presence of copper and zinc.[20,21] Unfortunately, all of these reactions are restricted to a few esters or ketones that bear the requisite bromodifluoromethyl group. The traditional Mukaiyama addition of difluoroenoxysilanes to unactivated imines is limited to a single example in the literature,[22] because these imines easily hydrolyze under typical reaction conditions.[23] Although the addition of the Ruppert-Prakash reagent (i.e., CF_3SiMe_3) to acyl silanes followed by treatment of nucleophilic fluorine can generate reactive difluoroenoxysilanes *in situ* that add to unactivated imines,[24] more effective methods are clearly needed. In order to address these deficiencies, we have devised a method that unleashes difluoroenolates under mild conditions yet tunes the reactivity to the unactivated imine. Moreover, we have applied this strategy to produce an α,α-difluoro-β-amino-carbonyl analogue of a drug candidate in only two synthetic steps.

In 2011, we reported a mild approach for the generation of difluoroenolates from highly α-fluorinated *gem*-diols following the release of trifluoroacetate (Figure 3).[25] These difluoroenolates subsequently react with aldehydes,[25,26] halogenation reagents,[27,28] trifluoromethyl ketones,[29] and disulfides[30] and can be quenched with water[31] or D_2O.[32]

This approach has been expanded to monofluoroenolates.[33,34] The difluoroenolates also add to activated imines, such as *N*-sulfonyl,[35,36] *N*-tosyl,[36] *N*-Boc,[35] and *N*-sulfinyl imines,[37] using the originally reported conditions of LiBr/Et_3N.[25] These reactions provide the β-amino-α,α-difluoroketones, bearing the corresponding *N*-substituent, in high yields. Additional studies on the fragmentation of highly α-fluorinated *gem*-diols have described a novel photoredox-mediated addition to iminiums derived *in situ* from tetrahydroquinolines;[38] however, a general method to add difluoroenolates produced from highly α-fluorinated *gem*-diols to imines without the need of protecting/activating groups is not currently available.

Herein, we describe a simple and mild method to add difluoroenolates, produced from the release of trifluoroacetate from highly α-fluorinated *gem*-diols, to unactivated imines. This task is accomplished by using magnesium salts and base. Also, we have applied this methodology to synthesizing derivatives of tetrahydroisoquinolines, and particularly, we have produced an α,α-difluoro-β-amino-carbonyl derivative of the drug candidate, almorexant, using these iminoaldol reactions.

RESULTS AND DISCUSSION

Our initial studies began by examining the scope of reactivity of the fluorinated *gem*-diol **1**[25] with activated imines using the reported conditions of LiBr/Et_3N (Table 1).[35–37] Imines **2**–**4** displaying an *N*-Boc,[35] *N*-tosyl,[36] or *N*-sulfonyl[35,36] substituent participated in yields similar to the reported values. Moreover, the oxaziridine **5** also is a suitable electrophile for this process and provides the same product **9** as direct addition to the *N*-sulfonylimine **4**. This type of addition to an oxaziridine has not been reported from a fluorinated *gem*-diol, to our knowledge. Also, the diazodicarboxylate **6** reacts with the difluoroenolate in the presence of LiBr and Et_3N to produce hydrazine **10**. This reactivity with azodicarboxylates has been recently reported using difluoroenoxysilanes as the difluoroenolate source,[39] but it is not known in the literature from highly α-fluorinated *gem*-diols. Although these iminoaldol-type reactions demonstrate and expand the existing scope for the case of LiBr/Et_3N using activated imines, additional reactivity can be easily tuned by selecting different reagents.

The addition of the fluorinated *gem*-diol **1**[25] and *N*-benzylidenebenzylamine **11** in the presence of Et3N and LiBr or LiCl failed to provide any of the desired product **12** (Table 2, entries 1–2). This lack of reactivity using lithium salts and unactivated imines has been previously reported.[35] We hypothesized that these entries (i.e., 1–2, Table 2) and the results in Table 1 were due to the fact that lithium salts activate the lone pairs of electrons associated with oxygen atoms whereas magnesium salts activate lone pairs of electrons on nitrogen. Indeed, the advantages of magnesium salts have been demonstrated in similar carbon-carbon bond forming process.[40,41] Accordingly, exchanging lithium salts with $MgBr_2$, $MgCl_2$, and MgI_2 (i.e., entries 3–5, respectively) enabled addition to the unactivated imine **11** and production of the desired adduct **12** in 43–74% yields. Further optimizations revealed that 60 °C was the optimal temperature in the presence of MgI_2 and product **12** was produced in 95% yield as determined by ^{19}F NMR. Isopropyl magnesium chloride also

provided the product **12** (entry 10), as Grignard reagents are a functional class of bases for generating fluorinated nucleophiles.[42]

We have previously reported the preparation of many highly α-fluorinated *gem*-diols **1**, **13**–**17**.[25,27,28] The scope of the magnesium-promoted additions of unactivated imine **11** and difluoroenolates derived from these highly α-fluorinated gem-diols was characterized and is displayed in Table 3. A substantial range of isolated yields (15–85%) of the β-amino-α,α-difluoro ketones **12**, **18**–**22** was observed. Typically, aromatic groups (**1**, **13**, **15**, and **16**) were fully compatible with the imino-aldol process mediated by the release of trifluoroacetate and isolated yields were 49–85%; however, alkyl substrates **14** and **17** provided the lowest yields of 15% and 25%, respectively. This disparity demonstrates the scope of process when varying only the α-fluorinated *gem*-diol.

Next, the scope of reactivity of unactivated imines **23**–**29** with the gem-diol **1** was investigated using the magnesium-promoted aldol reaction (Table 4). The effects of both of the substituents on the imine were examined by varying alkyl groups as well as aryl groups with electron-donating and electron-withdrawing substituents. Flame-dried magnesium iodide was needed to obtain good yields in some examples.[40] In the case of imine **23**, with a phenyl groups at each substituent, the product **30** was obtained in 59% isolated yield. The presence of an electron-donating methoxy group on phenyl imine **24** enabled a higher yield of 79% whereas the presence of an electron-withdrawing fluorine on the phenyl imine **32** resulted in a similar yield of 64%. On the hand, the methoxylphenyl imine **26** bearing a *N*-fluorophenyl substituent gave a high yield of 78%, yet the *bis*-methoxylphenyl imine **27** resulted in a lower 38% yield. Imines bearing a *N*-*t*-butyl group (**28**, entry 6) or *N*-benzyl group (**29**, entry 7) produced yields of 30 and 61%, respectively. This method provides quick access to useful quantities of compounds bearing α,α-difluoro-β-amino-carbonyl groups, and thus, X-ray structures of **30**, **31**, and **32** were obtained.

The trifluoroacetate-release mediated imino aldol reaction using unactivated imines has substantial potential in the creation of α,α-difluoro-β-amino-carbonyl groups on organic molecules. A previous report demonstrated the utility of the trifluoroacetate-release aldol reaction in adding difluoroenolates to iminiums derived *in situ* from *N*-substituted tetrahydroisoquinoline using visible light-induced photoredox catalysis.[38] We envisioned that the magnesium-initiated process could be analogously applied to dihydroisoquinolines to provide tetrahydroisoquinolines. Using this approach, the *gem*-diol **1** was added to dihydroisoquinoline **37** in the presence of MgI_2 and Et_3N to provide the corresponding tetrahydroisoquinoline α,α-difluoro ketones **38** in good 84% yield (Scheme 1). Suzuki–Miyaura cross-coupling of **38** with vinyltrifluoroborate[43] provided the tetrahydroisoquinoline **39** in 40% yield and demonstrates structural variants of tetrahydroquinolines can be quickly created.

Tetrahydroisoquinolines are a valuable class of heterocycle that appears in bioactive natural products, such as the ecteinascidins,[44] as well as drug discovery (Figure 4).[45] Notably, almorexant belongs to a class of drugs that act as dual orexin receptor antagonist for treatment of sleep disorders and displays a key tetrahydroisoquinoline.[46] There are few reported enantioselective syntheses of almorexant that involved key steps such as

asymmetric transfer hydrogenation,[47] asymmetric allylic amidation,[48] and asymmetric induction with *N*-*tert*-butanesulfinamide.[49] In addition, several almorexant analogues have been synthesized and reported.[50]

We envisioned a strategy to produce derivatives of almorexant using the magnesium-promoted reaction between a fluorinated *gem*-diol and a dihydroquinoline (Scheme 2). Furthermore, this approach would be short and not require any protecting groups. Accordingly, the known fluorinated *gem*-diol **40**[38] and 6,7-dimethoxy-3,4-dihydroisoquinoline **41** were treated with MgI_2 and Et_3N and gave the α,α-difluoro-β-aminoketone **42**. Next, **42** was coupled using the literature method[48] to amide **43**[50] to give a 2.2:1 mixture of diastereomers and the major isomer was purified in 28% isolated yield. Accessing the almorexant derivative **44** in two synthetic steps is a functional demonstration of this method and displays how the unique α,α-difluoro-β-amino-carbonyl group integrates into known bioactive structures.

CONCLUSIONS

In summary, we have reported a new protocol to synthesize β-amino-α,α-difluoro ketones using magnesium-promoted additions of difluoroenolates with unactivated imines. The difluoroenolates were unleashed from highly α-fluorinated *gem*-diols using only MgI_2 and Et_3N following the release of trifluoroacetate. This process eliminates the need of an imine with an activating *N*-substituent or a protecting group. This approach is compatible with many alkyl and aryl substituted imines and *gem*-diols. It can be easily integrated into drug discovery, and we have demonstrated its potential use in the synthesis of the analogues of almorexant in only two steps. These reactions further establish the role of releasing trifluoroacetate in the presence of mild reagents, such as a salt and an organic base, to generate valuable and reactive difluoroenolates.

EXPERIMENTIAL SECTION

N-(1-(4-Chlorophenyl)-2,2-difluoro-3-(naphthalen-2-yl)-3-oxopropyl)-4-methylbenzene-sulfonamide 8.[51]

To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **1**[25,27] (65.7 mg, 0.205 mmol), *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **3** (133 mg, 0.452 mmol) and LiBr (101 mg, 1.16 mmol) in THF (3 mL) was added was Et_3N (60 μL, 0.43 mmol) dropwise. After 5 min, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the resultant mixture was extracted with EtOAc (5 mL × 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash column chromatography (9:1–8:2 hexanes/EtOAc) afforded the title compound **8** as a yellow solid in 84% yield (86.1 mg): mp 143–145 °C; ^1H NMR (300 MHz, $CDCl_3$) 8.47 (s, 1H), 8.00–7.82 (m, 4H), 7.72–7.50 (m, 4H), 7.19 (s, 4H), 7.09 (d, J = 8.1 Hz, 2H), 5.66 (d, J = 9.5 Hz, 1H), 5.26 (td, J = 12.2, 9.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3 (t, J_{CF} = 29.1 Hz, 1C), 143.7, 136.9, 136.1, 134.9, 132.8, 132.1, 130.1, 130.0 (3C), 129.7, 129.4 (2C), 129.0, 128.6 (3C), 127.8, 127.0 (3C), 124.4, 116.1 (t, J_{CF} = 262.1 Hz, 1C), 59.6 (t, J_{CF} = 25.4 Hz, 1C), 21.4; ^{19}F NMR (282 MHz, $CDCl_3$) −103.87 (dd, J_{FF} = 284.0, J_{HF} = 11.8 Hz, 1F), −105.92 (dd, J_{FF} = 284.2, J_{HF} = 12.6 Hz, 1F); IR (film) ν_{max} 3584, 3234,

3055, 2974, 2920, 1702 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{20}O_3NSClF_2Na$ $(M+Na)^+$ 522.0718, found 522.0721.

N-(2,2-Difluoro-3-(naphthalen-2-yl)-3-oxo-1-phenylpropyl)benzenesulfonamide 9.[51]

To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (30 mg, 0.09 mmol) and *N*-benzylidenebenzenesulfonamide **4** (28 mg, 0.11 mmol) in THF (620 μL) was added LiBr (24 mg, 0.28 mmol), and the mixture was stirred for 10 min at rt. Next, Et_3N (26 μl, 0.19 mmol) was added dropwise, and after 5 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL). The resultant mixture was extracted with EtOAc (2 mL × 3). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (2:1:1 hexane/Et_2O/$CHCl_3$) afforded the title compound **9** as a colorless solid in 87 % yield (37 mg): mp 132–135 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.88–7.82 (m, 3H), 7.71–7.61 (m, 3H), 7.57 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.1 Hz, 1H), 7.31–7.18 (m, 7H), 5.73 (m, 1H), 5.32 (td, J = 12.2, 9.9 Hz, 1H); ^{13}C NMR (125 MHz $CDCl_3$) 188.6 (t, J_{CF} = 29.0 Hz, 1C), 140.1, 136.0, 132.7 (t, J_{CF} = 4.3 Hz, 1C), 132.5, 132.4, 132.1, 130.1, 129.6, 129.3, 128.8, 128.7 (2C), 128.6, 128.5 (2C), 128.4 (2C), 127.7, 127.1, 126.9 (2C), 124.4, 116.3 (t, J_{CF} = 261.9 Hz, 1C), 60.2 (t, J_{CF} = 25.0 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −103.77 (dd, J_{FF} = 280, J_{HF} = 12.0 Hz, 1F), −105.48 (dd, J_{FF} = 280, J_{HF} = 12.8 Hz, 1F); IR (film) ν_{max} 3272, 1696, 1331, 1284, 1166 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{25}H_{19}F_2NO_3SNa$ $[M+Na]^+$ 474.0951, found 474.0962.

N-(2,2-Difluoro-3-(naphthalen-2-yl)-3-oxo-1-phenylpropyl)benzenesulfonamide 9.

2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **1**[25,27] (8 mg, 0.02 mmol) was azeotroped with toluene (3 × 1 mL) and dissolved in THF (0.3 mL). Next, the solution was added to a flask containing LiBr (8.0 mg, 0.92 mmol) and cooled to −78 °C under an argon atmosphere. A solution of Davis oxaziridine D1 (14 mg, 0.054 mmol), that was azeotroped with toluene (3 × 1 mL) and dissolved in THF (0.20 mL), was added dropwise to the reaction mixture and stirred for 15 min at −78 °C. Next, Et_3N (5 μL, 0.04 mmol) was added, and the resultant mixture was allowed to warm slowly to rt and stirred for 24 h at rt. Then, the reaction mixture was quenched with saturated NH_4Cl solution (5 mL), extracted with EtOAc (3 × 10 mL), washed with brine (3 × 5 mL), and dried over Na_2SO_4. The organics were concentrated under reduced pressure and purified by preparative TLC using 30% EtOAc in hexanes to give the title compound **9** as a colorless solid (6 mg, 57%).

Diisopropyl 1-(1,1-difluoro-2-(naphthalen-2-yl)-2-oxoethyl)hydrazine-1,2-dicarboxylate 10.

To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **1**[25,27] (30 mg, 0.094 mmol) and LiBr (35 mg, 0.40 mmol) in THF (0.8 mL) at rt was added diisopropyl azodicarboxylate (40 μL, 0.20 mmol) followed by Et_3N (28 μL, 0.20 mmol). The reaction mixture was warmed to 60 °C for 30 min. Then, the reaction mixture was cooled to rt, quenched with 1 mL of saturated NH_4Cl solution (5 mL), extracted with EtOAc (3 × 10 mL), washed with brine (3 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by SiO_2 flash chromatography using 5–10% EtOAc in hexanes provided the title compound **10** as a colorless oil (35 mg, 91 %): ^1H NMR (500 MHz,

$CDCl_3$) δ 9.17 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 5.13 (qu, *J* = 6.2 Hz, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 1.34 (d, *J* = 4.6 Hz, 6H), 1.11 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.8 (t, J_{CF} = 29.4 Hz, 1C), 155.5, 152.1, 135.8, 132.7, 132.4, 130.3, 129.1, 129.0, 128.4, 127.6, 126.8, 124.5, 112.7 (t, J_{CF} = 259.6 Hz, 1C), 73.4, 70.8, 21.9, 21.8, 21.3, 21.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −86.96 (d, J_{FF}= 190.5 Hz, 2F); IR ν_{max} 3319, 2984, 2934, 1736, 1717, 1628, 1428, 1376, 1249, 1104, 1045 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{21}F_2N_2O_5$ $[M–H]^-$ 407.1419, found 407.1418.

Representative Reaction Procedure for Trifluoroacetate Release/Imino-Aldol Reaction.

To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (50 mg, 0.16 mmol) and *N*-benzylidinebenzylamine **11** (62 μL, 0.33 mmol) in THF (1.0 mL) was added MgI_2 (182 mg, 0.656 mmol). The resultant mixture was stirred for 2 min at rt. Then, the mixture was warmed to 60 °C for 1 min and then Et_3N (46 μL, 0.33 mmol) was added. After 5 min of stirring at 60 °C, the reaction was quenched with saturated aqueous NH_4Cl (1.5 mL) and the resultant mixture was extracted with EtOAc (10 mL × 3). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was then treated with saturated $NaHSO_3$ solution (15 mL) and stirred vigorously for 18 h. Next, the mixture was extracted with EtOAc (10 mL × 3). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (9:1:0.01 hexanes/EtOAc/Et_3N) afforded the product **12** as a colorless solid in 73% yield (45.8 mg).

3-(Benzylamino)-2,2-difluoro-1-(naphthalen-2-yl)-3-phenylpropan-1-one 12.[51]

See representative reaction procedure: mp 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.91–7.86 (m, 3H), 7.64 (m, 1H), 7.56 (m, 1H), 7.46−7.36 (m, 5H), 7.09−7.03 (m, 5H), 4.48 (dd, *J* = 20.1, 7.7 Hz, 1H), 3.76 (d, *J* = 13.1 Hz, 1H), 3.49 (d, *J* = 13.1 Hz, 1H), 1.82 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3 (t, J_{CF} = 28.4 Hz, 1C), 138.6, 135.7, 134.4, 132.2, 132.1, 130.4, 130.0, 129.1 (2C), 129.0, 128.7, 128.6 (2C), 128.4, 128.2 (4C), 127.7, 127.0, 126.8, 124.8, 118.1 (t, J_{CF}= 258.5 Hz, 1C), 63.8 (t, J_{CF} = 24.3 Hz, 1C), 50.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −102.7 (dd, J_{FF} = 268.4, J_{HF} = 7.6 Hz, 1F), −115.3 (dd, J_{FF} = 268.4, J_{HF} = 20.1 Hz, 1F); IR (film) ν_{max} 1701, 1626, 1455, 1114, 698 cm^{-1}; HRMS (EI-BE) *m/z* calcd for $C_{26}H_{22}F_2NO$ $(M+H)^+$ 402.1669, found 402.1664.

3-(Benzylamino)-1-(4-chlorophenyl)-2,2-difluoro-3-phenylpropan-1-one 18.[51]

See representative reaction procedure. To a solution of 1-(4-chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **13**[25,27] (30.9 mg, 0.101 mmol) and *N*-benzylidinebenzylamine **11** (38 μL, 0.20 mmol) in THF (680 μL) was added MgI_2 (112 mg, 0.404 mmol). The mixture was warmed to 60 °C for 1 min and then Et_3N (30 μL, 0.20 mmol) was added. SiO_2 flash chromatography (9:1:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **18** as a colorless oil (33.1 mg) in 85% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.47−7.36 (m, 7H), 7.22−7.17 (m, 3H), 7.10−7.04 (m, 2H), 4.38 (dd, *J* = 20.7, 7.2 Hz, 1H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.49 (d, *J* = 13.1 Hz, 1H), 2.11 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3 (t, J_{CF} = 27.5 Hz, 1C), 140.4, 138.5, 134.2, 131.6 (2C), 131.1, 129.0 (2C), 128.9 (2C), 128.8, 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.2,

117.8 (t, J_{CF} = 255.0 Hz, 1C), 63.4 (t, J_{CF} = 22.5 Hz, 1C), 50.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −102.8 (dd, J_{FF} = 268.7, J_{HF} = 6.5 Hz, 1F), −116.4 (dd, J_{FF} = 268.5, J_{HF} = 18.6 Hz, 1F); IR (film) ν_{max} 1693, 1444, 1266, 1039, 699 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{19}ClF_2NO$ $(M+H)^+$ 386.1123, found 386.1131.

1-(Benzylamino)-2,2-difluoro-5-methyl-1-phenylhexan-3-one 19.

See representative reaction procedure. To a solution of 1,1,1,3,3-pentafluoro-2,2-dihydroxy-6-methylheptan-4-one **14**[25] (32.6 mg, 0.130 mmol) and *N*-benzylidinebenzylamine **11** (51 μL, 0.27 mmol) in THF (1.0 mL) was added MgI_2 (152 mg, 0.547 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (38 μL, 0.27 mmol) was added. SiO_2 flash chromatography (100% hexanes–5:5:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **19** as a colorless oil (6.3 mg) in 15% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.32–7.25 (m, 3H), 7.19 (d, *J* = 6.9 Hz, 2H), 4.22 (dd, *J* = 20.6, 7.6 Hz, 1H), 3.73 (d, *J* = 13.0 Hz, 1H), 3.52 (d, *J* = 13.0 Hz, 1H), 2.52 (dd, *J* = 18.1, 6.9 Hz, 1H), 2.39 (dd, *J* = 18.1, 6.4 Hz, 1H), 2.16 (septet, *J* = 6.6 Hz, 1H), 1.68 (br s, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5 (dd, J_{CF} = 31.1, 26.5 Hz, 1C), 139.0, 134.4, 128.9 (2C), 128.7, 128.6 (2C), 128.4 (2C), 128.3 (2C), 127.3, 116.4 (dd, J_{CF} = 260.0, 256.6 Hz, 1C), 62.8 (dd, J_{CF} = 26.4, 21.6 Hz, 1C), 51.0, 46.7, 23.4, 22.4 (2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.9 (dd, J_{FF} = 258.6, J_{HF} = 7.5 Hz, 1F), −123.6 (dd, J_{FF} = 258.8, J_{HF} = 20.5 Hz, 1F); IR (film) ν_{max} 2959, 1740, 1455, 1124 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{24}F_2NO$ $(M+H)^+$ 332.1826, found 332.1828.

1-(Benzo[b]thiophen-3-yl)-3-(benzylamino)-2,2-difluoro-3-phenylpropan-1-one 20.

See representative reaction procedure. To a solution of 1-(benzo[b]thiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **15**[27] (31 mg, 0.10 mmol) and *N*-benzylidinebenzylamine **11** (38 μL, 0.20 mmol) in THF (570 μL) was added MgI_2 (112 mg, 0.402 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (28 μL, 0.20 mmol) was added. SiO_2 flash chromatography (9:1:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **20** as a pale yellow solid (26.7 mg) in 69% yield: mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 8.2 Hz, 1H), 8.40 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.44–7.35 (m, 5H), 7.16–6.99 (m, 5H), 4.43 (dd, *J* = 19.8, 8.0 Hz, 1H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.51 (d, *J* = 13.2 Hz, 1H), 2.02 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7 (dd, J_{CF} = 29.0, 27.9 Hz, 1C), 140.0 (t, J_{CF} = 9.0 Hz, 1C), 138.9, 138.7, 137.2, 134.5, 129.8, 129.1 (2C), 128.7, 128.6 (2C), 128.1 (4C), 127.1, 126.1, 125.7, 125.3, 122.1, 117.7 (dd, J_{CF} = 260.4, 256.8 Hz, 1C), 63.7 (dd, J_{CF} = 26.2, 22.0 Hz, 1C), 50.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.8 (dd, J_{FF} = 263.0, J_{HF} = 7.5 Hz, 1F), −116.1 (dd, J_{FF} = 263.0, J_{HF} = 18.8 Hz, 1F); IR (film) ν_{max} 1675, 1458, 1106, 698 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{24}H_{20}F_2NOS$ $(M+H)^+$ 408.1234, found 408.1235.

1-(Benzo[*d*][1,3]dioxol-5-yl)-3-(benzylamino)-2,2-difluoro-3-phenylpropan-1-one 21.[51]

See representative reaction procedure. To a solution of 1-(benzo[*d*][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **16**[25] (16 mg, 0.05 mmol) and *N*-benzylidinebenzylamine **11** (20 μL, 0.105 mmol) in THF (800 μL) was added MgI_2 (57 mg, 0.205 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 5 min and then Et_3N (14 μL, 0.10 mmol) was added. Preparative TLC (8:2 hexanes/EtOAc) afforded the desired product **21** as a colorless solid (12 mg) in 61% yield: mp 89–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 7.40 (m, 5H), 7.24–7.19 (m, 3H), 7.14–7.09 (m, 2H), 6.82 (d, J = 8.3 Hz, 1H), 6.07 (dd, J = 5.7, 1.3 Hz, 2H), 4.39 (dd, J = 20.0, 7.6 Hz, 1H), 3.77 (d, J = 13.2 Hz, 1H), 3.50 (d, J = 13.2 Hz, 1H), 2.18 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1 (t, J_{CF} = 28.8 Hz, 1C), 152.5, 148.0, 138.8, 134.5, 129.1 (2C), 128.6, 128.5 (2C), 128.2 (4C), 127.5, 127.1, 126.7, 117.8 (t, J_{CF} = 258.4 Hz, 1C), 109.5, 108.0, 102.0, 63.7 (t, J_{CF} = 23.7 Hz, 1C), 50.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −102.5 (dd, J_{FF} = 269.1, J_{HF} = 7.3 Hz, 1F), −114.53 (dd, J_{FF} = 269.1, 20.0 Hz, 1F); IR (film) ν_{max} 1693, 1444, 1265, 1039, 699 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{20}F_2NO_3$ $(M+H)^+$ 396.1411, found 396.1405.

1-(Adamantan-1-yl)-3-(benzylamino)-2,2-difluoro-3-phenylpropan-1-one 22.

See representative reaction procedure. To a solution of 1-(adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **17**[25,27] (35 mg, 0.11 mmol) and *N*-benzylidinebenzylamine **11** (42 μL, 0.23 mmol) in THF (570 μL) was added MgI_2 (126 mg, 0.452 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (31 μL, 0.23 mmol) was added. SiO_2 flash chromatography (100% hexanes–5:5:0.01 hexanes/CH_2Cl_2/Et_3N) afforded the title compound **22** as a colorless solid (10.8 mg) in 25% yield: mp 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.16 (m, 10H), 4.39 (dd, J = 20.2, 8.4 Hz, 1H), 3.72 (d, J = 13.0 Hz, 1H), 3.54 (d, J = 13.0 Hz, 1H), 2.02 (s, 3H), 1.88 (q, J = 12.4 Hz, 6H), 1.79 (br s, 1H), 1.71 (q, J = 12.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6 (dd, J_{CF} = 28.4, 25.3 Hz, 1C), 139.3, 134.8, 129.1, 128.4 (4C), 128.3 (2C), 128.2 (2C), 127.1, 118.7 (dd, J_{CF} = 264.1, 259.9 Hz, 1C), 62.9 (dd, J_{CF} = 25.4, 21.1 Hz, 1C), 51.1, 46.5, 36.9 (3C), 36.4 (3C), 27.7 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.8 (dd, J_{FF} = 270.7, J_{HF} = 7.5 Hz, 1F), −116.9 (dd, J_{FF} = 268.8, J_{HF} = 20.7 Hz, 1F); IR (film) ν_{max} 2907, 2852, 1716, 1454, 1114 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{26}H_{30}F_2NO$ $(M+H)^+$ 410.2295, found 410.2279.

2,2-Difluoro-1-(naphthalen-2-yl)-3-phenyl-3-(phenylamino)propan-1-one 30.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (24 mg, 0.075 mmol), 4Å molecular sieves (100 mg), and *N*-benzylideneaniline **23** (27 mg, 0.15 mmol) in THF (1.5 mL) was added flame-dried MgI_2 (84 mg, 0.302 mmol), and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (21 μL, 0.15 mmol) was added. The crude mixture was recrystallized from chloroform and hexanes to afford the title compound **30** as a yellow solid (17 mg) in 59% yield. Recrystallization from a solution of hexanes and CH_2Cl_2 (by slow evaporation) provided a crystalline solid suitable for X-ray structure analysis: mp 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.98–7.83

(m, 4H), 7.64 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.48 (d, J = 7.3 Hz, 2H), 7.38–7.28 (m, 3H), 7.10 (t, J = 7.9 Hz, 2H), 6.71 (t, J = 7.3 Hz, 1H), 6.62 (d, J = 7.8 Hz, 2H), 5.38 (dt, J = 17.4, 8.9 Hz, 1H), 4.60 (d, J = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9 (dd, J_{CF} = 29.5, 27.9 Hz, 1C), 145.5, 135.8, 134.5, 132.4 (dd, J_{CF} = 5.0, 4.4 Hz, 1C), 132.2, 130.1, 130.0, 129.3, 129.2 (2C), 128.7, 128.7 (2C), 128.6 (2C), 128.5, 127.7, 127.0, 124.6, 118.9, 117.5 (dd, J_{CF} = 260.8, 259.3 Hz, 1C), 114.2 (2C), 60.6 (dd, J_{CF} = 25.7, 22.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.6 (dd, J_{FF} = 272.0, J_{HF} = 8.8 Hz, 1F), −112.2 (dd, J_{FF} = 272.1, J_{HF} = 17.1 Hz, 1F); IR (film) ν_{max} 1694, 1455, 1285, 1105 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{25}H_{20}F_2NO$ $(M+H)^+$ 388.1513, found 388.1506.

2,2-Difluoro-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)-3-(phenylamino)propan-1-one 31.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (32 mg, 0.10 mmol) and *N*-(4-methoxybenzylidene)aniline **24** (44 mg, 0.21 mmol) in THF (1.0 mL) was added MgI_2 (115 mg, 0.414 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (29 μL, 0.21 mmol) was added. SiO_2 flash chromatography (9:1:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **31** as a dark orange solid (32.5 mg) in 79% yield. Recrystallization from a solution of hexanes and CH_2Cl_2 (by slow evaporation) provided a crystalline solid suitable for X-ray structure analysis: mp 126–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 5.7 Hz, 1H), 7.87 (d, J = 5.1 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.11 (t, J = 7.9 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.72 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 7.9 Hz, 2H), 5.34 (dt, J = 16.3, 8.0 Hz, 1H), 4.58 (d, J = 7.3 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9 (dd, J_{CF} = 29.2, 28.1 Hz, 1C), 159.8, 145.6, 135.8, 132.4 (t, J_{CF} = 4.5 Hz, 1C), 132.1, 130.1, 130.0, 129.7 (2C), 129.3, 129.2 (2C), 128.5, 127.7, 127.0, 126.3, 124.6, 118.8, 117.5 (t, J_{CF} = 259.8 Hz, 1C), 114.2 (2C), 114.1 (2C), 60.0 (dd, J_{CF} = 25.7, 22.9 Hz, 1C), 55.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −104.2 (dd, J_{FF} = 270.4, J_{HF} = 9.1 Hz, 1F), −112.1 (dd, J_{FF} = 270.4, J_{HF} = 16.6 Hz, 1F); IR (film) ν_{max} 1694, 1626, 1465, 1106, 692 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{26}H_{22}F_2NO_2$ $(M+H)^+$ 418.1619, found 418.1613.

3-((3,4-Dimethylphenyl)amino)-2,2-difluoro-3-(4-fluorophenyl)-1-(naphthalen-2-yl)propan-1-one 32.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (29 mg, 0.09 mmol), 4Å molecular sieves (100 mg), and 3,4-dimethyl-*N*-(4-fluorobenzylidene)aniline **25** (44 mg, 0.19 mmol) in THF (1.7 mL) was added flame-dried MgI_2 (107 mg, 0.385 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (25 μL, 0.19 mmol) was added. The crude mixture was recrystallized from chloroform and hexanes to afford the title compound **32** as a pale yellow solid (25 mg) in 64% yield. Recrystallization from a solution of hexanes and CH_2Cl_2 (by slow evaporation) provided a crystalline solid suitable for X-ray structure analysis: mp 141–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.96 (dd, J = 15.4, 8.6 Hz, 2H), 7.88 (t, J = 7.3 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 6.1 Hz, 2H), 7.04 (t, J = 8.6 Hz, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.41 (s, 1H), 6.32 (d, J = 8.1 Hz, 1H), 5.32 (dt, J = 17.7, 7.3 Hz, 1H), 4.36 (d, J = 7.7

Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6 (dd, J_{CF} = 29.3, 27.7 Hz, 1C), 162.8 (d, J_{CF} = 247.5 Hz, 1C), 143.3, 137.4, 135.9, 132.3 (t, J_{CF} = 4.5 Hz, 1C), 132.2, 130.5 (d, J_{CF} = 2.5 Hz, 1C), 130.2, 130.2 (d, J_{CF} = 8.0 Hz, 2C), 130.1, 130.0, 129.4, 128.6, 127.7, 127.2, 127.0, 124.6, 117.4 (t, J_{CF} = 248.5 Hz, 1C), 116.1, 115.6 (d, J_{CF} = 21.6 Hz, 2C), 111.5, 60.1 (dd, J_{CF} = 26.0, 22.7 Hz, 1C), 19.9, 18.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −103.0 (dd, J_{FF} = 272.9, 1F), −113.3 (dd, J_{FF} = 272.2, J_{HF} = 15.7 Hz, 1F), −114.4 (s, 1F); IR (film) ν_{max} 1692, 1507, 1212, 1063 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{27}H_{23}F_3NO$ $(M+H)^+$ 434.1732, found 434.1725.

2,2-Difluoro-3-((4-fluorophenyl)amino)-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)propan-1-one 33.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (32 mg, 0.10 mmol) and *N*-(4-methoxybenzylidene)-4-fluoroaniline **26** (48 mg, 0.21 mmol) in THF (570 μL) was added MgI_2 (115 mg, 0.414 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (29 μL, 0.21 mmol) was added. SiO_2 flash chromatography (9:1:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **33** as a dark orange oil (33.5 mg) in 78% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.89–7.81 (m, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 7.7 Hz, 2H), 6.80 (t, *J* = 8.7 Hz, 2H), 6.55 (m, 2H), 5.23 (dt, *J* = 17.0, 8.5 Hz, 1H), 4.44 (d, *J* = 8.6 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9 (t, J_{CF} = 28.9 Hz, 1C), 159.9, 156.5 (d, J_{CF} = 236.9 Hz, 1C), 141.9 (d, J_{CF} = 1.9 Hz, 1C), 135.8, 132.4 (dd, J_{CF} = 5.2, 4.3 Hz, 1C), 132.2, 132.0, 130.1, 130.0, 129.7 (2C), 128.5, 127.7, 127.0, 126.1, 124.6, 117.5 (t, J_{CF} = 259.9 Hz, 1C), 115.7 (d, J_{CF} = 22.5 Hz, 2C), 115.3 (d, J_{CF} = 7.5 Hz, 2C), 114.1 (2C), 61.0 (dd, J_{CF} = 25.9, 22.8 Hz, 1C), 55.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.9 (dd, J_{FF} = 271.8, J_{HF} = 8.6 Hz, 1F), −112.4 (dd, J_{FF} = 271.8, J_{HF} = 16.9 Hz, 1F), −127.1 (sept, *J* = 3.8 Hz, 1F); IR (film) ν_{max} 1692, 1626, 1114 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{26}H_{21}F_3NO_2$ $(M+H)^+$ 436.1524, found 436.1515.

2,2-Difluoro-3-(4-methoxyphenyl)-3-((4-methoxyphenyl)amino)-1-(naphthalen-2-yl)propan-1-one 34.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (35 mg, 0.11 mmol) and *N*-(4-methoxybenzylidene)-4-methoxyaniline **27** (55 mg, 0.23 mmol) in THF (570 μL) was added magnesium iodide (127 mg, 0.455 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (32 μL, 0.23 mmol) was added. SiO_2 flash chromatography (8:2:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **34** as a dark orange oil (12.3 mg) in 25% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 8.2, 5.5 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 5.21 (dd, *J* = 17.6, 8.6 Hz, 1H), 4.25 (d, *J* = 9.0 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0 (dd, J_{CF} = 29.5, 27.7 Hz, 1C), 159.8, 153.0, 139.5, 135.8, 132.3 (dd, J_{CF} = 5.3, 3.9 Hz, 1C), 132.2, 130.3, 130.0, 129.7 (2C), 129.3, 128.5, 127.7, 127.0, 126.5, 124.7, 117.7 (dd,

J_{CF} = 260.8, 258.2 Hz, 1C), 115.9 (2C), 114.7 (2C), 114.1 (2C), 61.2 (dd, J_{CF} = 26.0, 22.4 Hz, 1C), 55.6, 55.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −103.6 (dd, J_{FF} = 270.1, J_{HF} = 8.5 Hz, 1F), −113.3 (dd, J_{FF} = 270.0, J_{HF} = 17.6 Hz, 1F); IR (film) ν_{max} 1693, 1509, 1114 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{27}H_{24}F_2NO_3$ $(M+H)^+$ 448.1724, found 448.1721.

3-(*tert*-Butylamino)-2,2-difluoro-1-(naphthalen-2-yl)-3-phenylpropan-1-one 35.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (32 mg, 0.10 mmol) and *N*-benzylidene-*tert*-butylamine **28** (37 μL, 0.21 mmol) in THF (570 μL) was added MgI_2 (115 mg, 0.414 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for1 min and then Et_3N (29 μL, 0.21 mmol) was added. SiO_2 flash chromatography (9:1:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **35** as a colorless solid (10.7 mg) in 30% yield: mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.94–7.84 (m, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45–7.43 (m, 2H), 7.41–7.29 (m, 3H), 4.63 (dd, *J* = 22.0, 6.5 Hz, 1H), 1.83 (br s, 1H), 0.84 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0 (dd, J_{CF} = 30.5, 26.5 Hz, 1C), 138.3, 135.6, 132.2, 132.0 (t, J_{CF} = 2.9 Hz, 1C), 131.9, 131.4, 129.9, 128.9, 128.7 (2C), 128.4 (2C), 128.2, 127.7, 126.8, 125.1, 118.3 (dd, J_{CF} = 260.9, 257.3 Hz, 1C), 59.5 (dd, J_{CF} = 26.9, 21.2 Hz, 1C), 51.5, 30.0 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −100.9 (dd, J_{FF} = 258.8, J_{HF} = 6.4 Hz, 1F), −117.5 (dd, J_{FF} = 258.8, J_{HF} = 22.2 Hz, 1F); IR (film) ν_{max} 1698, 1456, 1108, 1077 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{24}F_2NO$ $(M+H)^+$ 368.1826, found 368.1825.

(*4E*,*6E*)-3-(Benzylamino)-2,2-difluoro-1-(naphthalen-2-yl)octa-4,6-dien-1-one 36.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (20 mg, 0.06 mmol) and *N*-(hexa-2,4-dien-1-ylidene)-1-phenylmethanamine **29** (30 mg, 0.16 mmol, 5:1 (2*E*,4*E*)-isomer/(2*E*,4*Z*)-isomer mixture*) in THF (1 mL) was added flame-dried MgI_2 (56 mg, 0.20 mmol) and the mixture was stirred for 2 min at rt. The resultant mixture was warmed to 60 °C for 1 min and then Et_3N (14 μL, 0.10 mmol) was added. SiO_2 flash chromatography (9:1:0.01 hexanes/Et_2O/Et_3N) afforded the title compound **36** as a yellow oil in 61% yield (12 mg, 5:1 mixture of isomers*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57* (s, 1H), 8.55 (s, 1H), 8.03 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.65 (td, *J* = 7.5, 1.1 Hz, 1H), 7.57 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13–7.03 (m, 5H), 6.56* (dd, *J* = 15.2, 11.0 Hz, 1H), 6.24 (dd, *J* = 15.1, 10.4 Hz, 1H), 6.15 (qd, *J* = 12.5, 1.3 Hz, 1H), 5.79 (dq, *J* = 13.2, 6.6 Hz, 1H), 5.54 (dd, *J* = 14.7, 8.8 Hz, 1H), 3.86 (d, *J* = 13.4 Hz, 1H), 3.83 (m, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 1.80 (d, *J* = 6.6 Hz, 3H), 1.61 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1 (t, J_{CF} = 28.2 Hz, 1C), 138.9, 136.8, 135.7, 132.2, 132.0, 131.5, 130.5, 130.0, 129.1, 128.4, 128.1 (2C), 128.1 (2C), 127.7, 126.9, 126.8, 124.8, 123.0, 118.1 (t, J_{CF} = 257.4 Hz, 1C), 62.2 (dd, J_{CF} = 26.3, 22.4 Hz, 1C), 50.5, 18.2, 13.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −103.2 (dd, J_{FF} = 268.9, J_{HF} = 7.5 Hz, 1F), −115.5 (dd, J_{FF} = 268.9, J_{HF} = 18.8 Hz, 1F); IR (film) ν_{max} 1700, 1454, 1116, 990, 699 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{25}H_{24}F_2NO$ $(M+H)^+$ 392.1826, found 392.1841. * denotes minor isomer.

2-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-1-yl)-2,2-difluoro-1-(naphthalen-2-yl)ethenone 38.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalene-2-yl)butan-1-one **1**[25,27] (92.6 mg, 0.289 mmol) and 5-bromo-3,4-dihydroisoquinoline **37** (127 mg, 0.605 mmol) in THF (1.7 mL) was added MgI_2 (340 mg, 1.22 mmol) and the mixture was stirred for 5 min at rt. The resultant mixture was warmed to 60 °C for 5 min and then Et_3N (85 μL, 0.61 mmol) was added. SiO_2 flash chromatography (5:5:0.01 hexanes/CH_2Cl_2/Et_3N) afforded the title compound **38** as a pale yellow solid (101.7 mg) in 84% yield: mp 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.41 (dd, J = 7.7, 2.7 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 4.89 (dd, J = 21.0, 8.2 Hz, 1H), 3.26 (m, 1H), 3.02 (m, 1H), 2.85–2.66 (m, 2H), 1.89 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (dd, J_{CF} = 29.8, 27.8 Hz, 1C), 136.8, 135.8, 132.2 (t, J_{CF} = 8.3 Hz, 1C), 132.1, 131.9, 130.6, 130.0, 129.2, 128.5, 127.7 (2C), 127.6, 126.9 (2C), 125.7, 124.8, 118.9 (dd, J_{CF} = 265.1, 258.5 Hz, 1C), 57.1 (t, J_{CF} = 23.4 Hz, 1C), 39.5, 29.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −96.0 (dd, J_{FF} = 270.5, J_{HF} = 7.2 Hz, 1F), −110.4 (dd, J_{FF} = 270.5, J_{HF} = 21.0 Hz, 1F); IR (film) ν_{max} 1698, 1440, 1173, 754 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{17}BrF_2NO$ $(M+H)^+$ 416.0462, found 416.0448.

2,2-Difluoro-1-(naphthalen-2-yl)-2-(5-vinyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one 39.

To a solution of 2-(5-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl)-2,2-difluoro-1-(naphthalen-2-yl)ethenone **38** (23.5 mg, 0.056 mmol) in THF (0.3 mL) and water (40 μL), $PdCl_2$ (4.1 mg, 0.023 mmol), PPh_3 (5.8 mg, 0.02 mmol), Cs_2CO_3 (67.6 mg, 0.207 mmol), and potassium vinyltrifluoroborate (9.7 mg, 0.07 mmol) were added, and the resultant mixture was allowed to stir for 23 h at 85 °C in a sealed tube. The reaction mixture was warmed to rt, quenched with water (2 mL), and extracted with CH_2Cl_2 (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 mL × 3). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (100:0.01 CH_2Cl_2/Et_3N) afforded the title compound **39** as a pale yellow oil (8.3 mg) in 40% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 6.90 (dd, J = 17.3, 11.0 Hz, 1H), 5.62 (d, J = 17.3 Hz, 1H), 5.32 (d, J = 10.9 Hz, 1H), 4.93 (dd, J = 20.6, 8.3 Hz, 1H), 3.26 (m, 1H), 3.00 (m, 1H), 2.79–2.70 (m, 2H), 1.89 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (dd, J_{CF} = 29.7, 27.7 Hz, 1C), 137.2, 135.7, 134.7, 134.1, 132.2, 132.1 (dd, J_{CF} = 5.1, 4.0 Hz, 1C), 130.8, 130.0, 129.7, 129.1, 128.4, 128.2, 128.1, 127.7, 126.9, 125.7, 125.3, 124.9, 116.3 (dd, J_{CF} = 264.6, 258.5 Hz, 1C), 57.4 (t, J_{CF} = 23.6 Hz, 1C), 39.6, 26.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −96.6 (dd, J_{FF} = 268.8, J_{HF} = 5.6 Hz, 1F), −110.6 (dd, J_{FF} = 268.8, J_{HF} = 20.5 Hz, 1F); IR (film) ν_{max} 2923, 1698, 1627, 1466, 1074, 736 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{20}F_2NO$ $(M+H)^+$ 364.1513, found 364.1510.

2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-2,2-difluoro-1-(4-(trifluoromethyl)-phenyl)ethan-1-one 42.

See representative reaction procedure. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(4-(trifluoromethyl)phenyl)butan-1-one **40**[38] (117 mg, 0.345 mmol) and 6,7-dimethoxy-3,4-dihydroisoquinoline **41** (139 mg, 0.728 mmol) in THF (2.5 mL) was added MgI_2 (469.5 mg, 1.688 mmol) and the mixture was stirred for 5 min at rt. The resultant mixture was warmed to 60 °C for 5 min and then Et_3N (101 μL, 0.723 mmol) was added. SiO_2 flash chromatography (5:5:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **42** as a pale yellow solid (49.2 mg) in 34% yield: mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 2.4 Hz, 1H), 6.62 (s, 1H), 4.74 (dd, J = 21.2, 7.6 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.12 (m, 1H), 2.95 (dt, J = 3.2, 1.3 Hz, 1H), 2.63 (dt, J = 1.1, 1.0 Hz, 2H), 1.62 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2 (dd, J_{CF} = 31.6, 27.8 Hz, 1C), 148.7, 147.2, 136.8, 134.6 (d, J = 32.9 Hz, 1C), 130.0 (td, J_{CF} = 2.5, 1.2 Hz, 2C), 129.6, 125.4 (td, J_{CF} = 3.7, 3.6 Hz, 2C), 124.8 (t, J_{CF} = 287.7 Hz, 1C), 120.7, 118.9 (dd, J_{CF} = 264.7, 256.9 Hz, 1C), 111.7, 111.1 (d, J = 5.6 Hz, 1C), 56.5 (t, J_{CF} = 23.8 Hz, 1C), 56.0, 55.8, 39.8, 28.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4 (s, 3F), −97.2 (dd, J_{FF} = 265.9, J_{HF} = 6.2 Hz, 1F), −113.3 (dd, J_{FF} = 265.9, J_{HF} = 21.1 Hz, 1F); IR (film) ν_{max} 2927, 1714, 1518, 1465, 1129, 732 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{19}F_5NO_3$ $(M+H)^+$ 416.1285, found 416.1281.

(*2R*)-2-(1-(1,1-Difluoro-2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-*N*-methyl-2-phenylacetamide 44.

To a solution of 2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-2,2-difluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one **42** (12.1 mg, 0.029 mmol) and (*S*)-2-(methylamino)-2-oxo-1-phenylethyl 4-methylbenzenesulfonate **43**[48] (10.2 mg, 0.032 mmol) in CH_3CN (1.0 mL) was added *i*-Pr_2NEt (10 μL, 0.06 mmol). The resultant mixture was stirred for 26 h at 85 °C. Then, reaction mixture was cooled to rt and concentrated under reduced pressure. The mixture was washed with saturated aqueous Na_2CO_3 (5 mL) and extracted with EtOAc (5 mL). The organics were dried over Na_2SO_4 and concentrated under reduced pressure to give a 2.2:1 mixture of diastereomers. SiO_2 flash chromatography (5:5:0.01 hexanes/EtOAc/Et_3N) afforded the title compound **44** as a colorless oil (4.6 mg, major isomer) in 28% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.02 (t, J = 7.7 Hz, 2H), 6.69 (s, 1H), 6.52 (m, 1H), 6.45 (d, J = 7.5 Hz, 2H), 6.37 (d, J = 2.4 Hz, 1H), 4.19 (s, 1H), 3.91 (s, 3H), 3.89 (m, 1H), 3.79 (s, 3H), 3.52 (m, 1H), 3.12 (m, 1H), 2.92 (dd, J = 14.8, 7.0 Hz, 1H), 2.79 (d, J = 4.9 Hz, 3H), 2.58 (dd, J = 17.4, 5.6 Hz, 1H), 2.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (t, J_{CF} = 27.5 Hz, 1C), 171.2, 149.5, 147.4, 135.6, 135.5 (d, J_{CF} = 32.9 Hz, 1C), 134.8, 129.4 (dt, J_{CF} = 2.6, 2.3 Hz, 2C), 129.1 (2C), 128.9, 128.6 (2C), 128.5, 127.8, 126.2 (dt, J_{CF} = 3.7, 3.6 Hz, 2C), 124.7 (t, J_{CF} = 283.3 Hz, 1C), 118.3 (t, J_{CF} = 263.3 Hz, 1C), 111.5, 111.1 (d, J_{CF} = 3.3 Hz, 1C), 69.7, 60.5 (dd, J_{CF} = 28.0, 23.1 Hz, 1C), 56.1, 55.8, 42.3, 29.7, 25.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.3 (s, 3F), −95.4 (dd, J_{FF} = 259.9, J_{HF} = 10.2 Hz, 1F), −106.6 (dd, J_{FF} = 259.5, J_{HF} = 20.9 Hz, 1F); IR (film) ν_{max} 2922, 1712, 1664, 1466, 1116, 701 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{29}H_{28}F_5N_2O_4$ $(M+H)^+$ 563.1969, found 563.1968.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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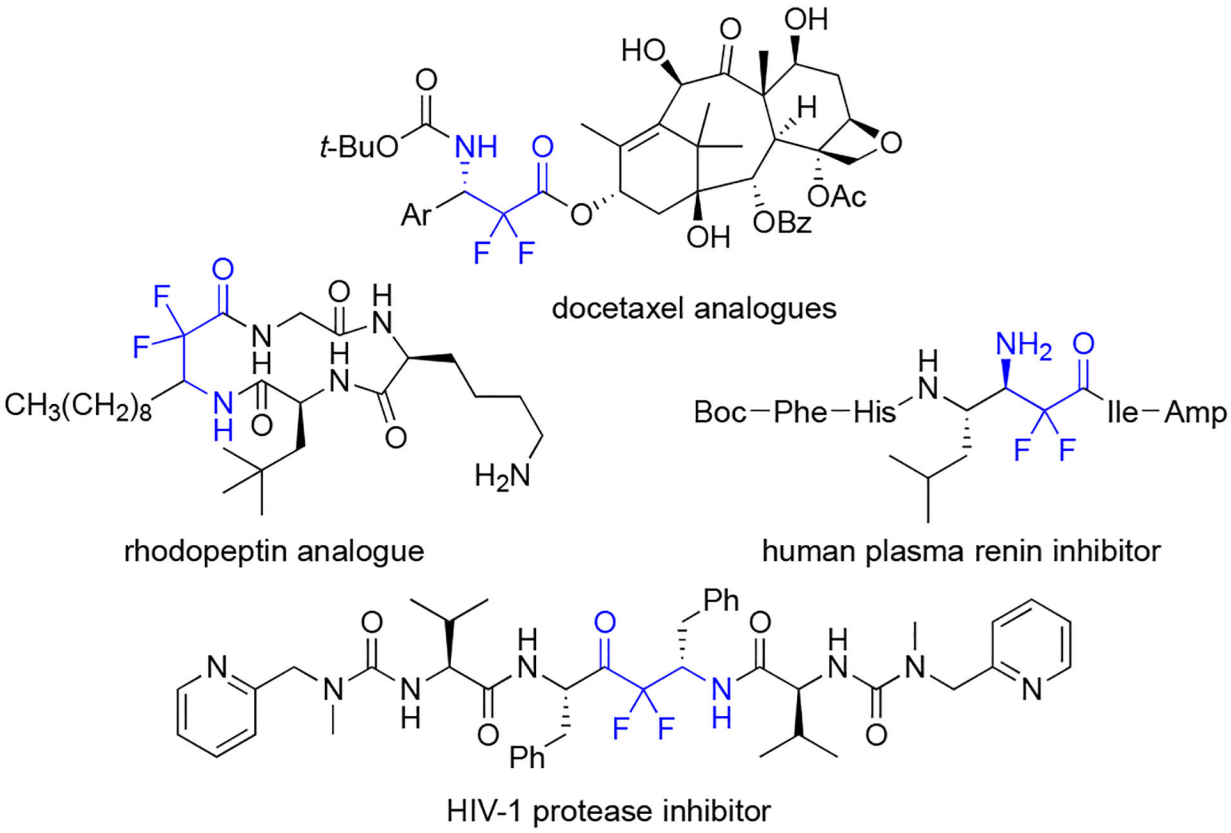


Figure 1.
Examples of compounds displaying α,α-difluoro-β-amino-carbonyl groups.

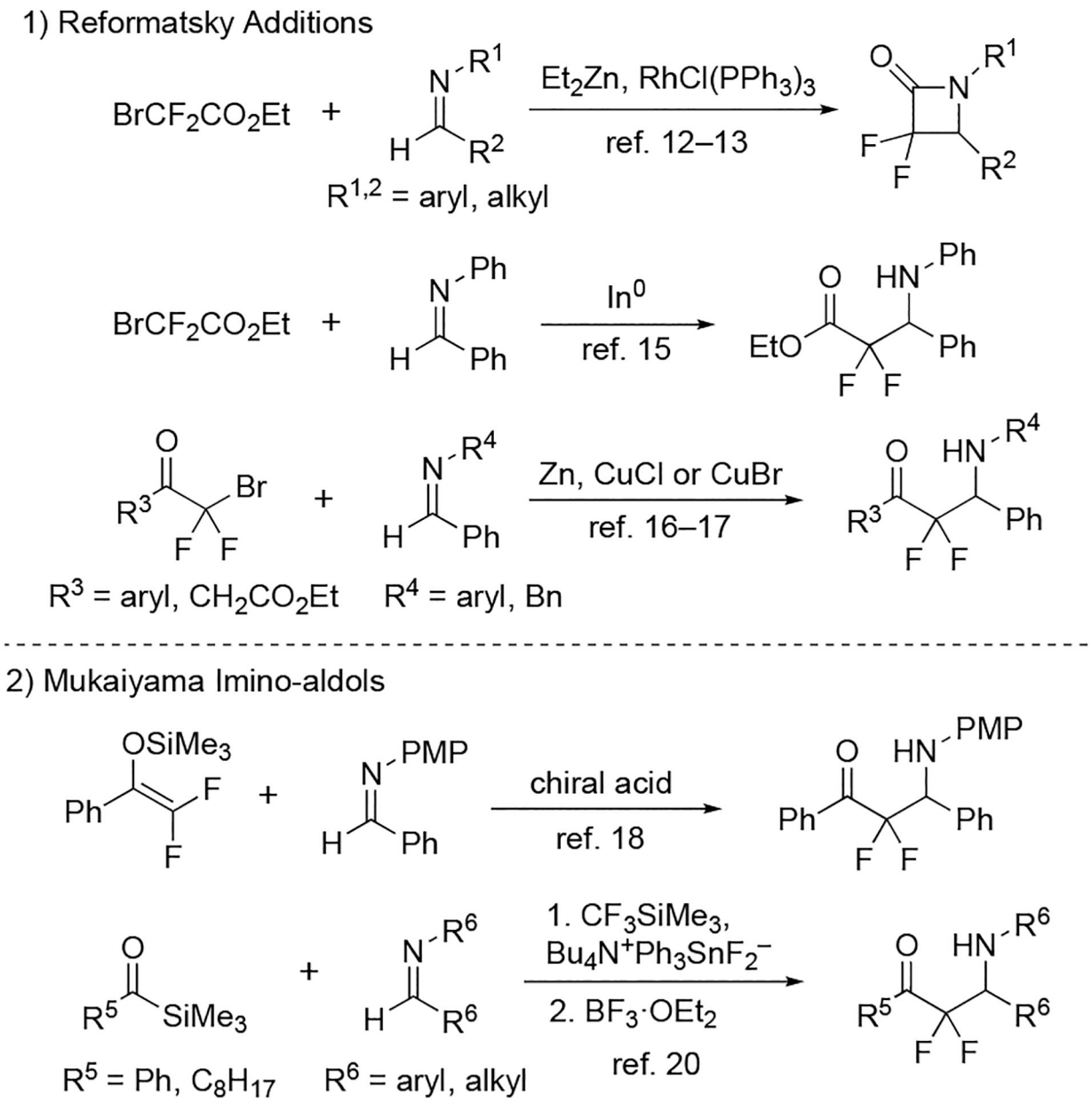


Figure 2.

Two existing methods to prepare α,α-difluoro-β-amino-carbonyl groups from unactivated imines.

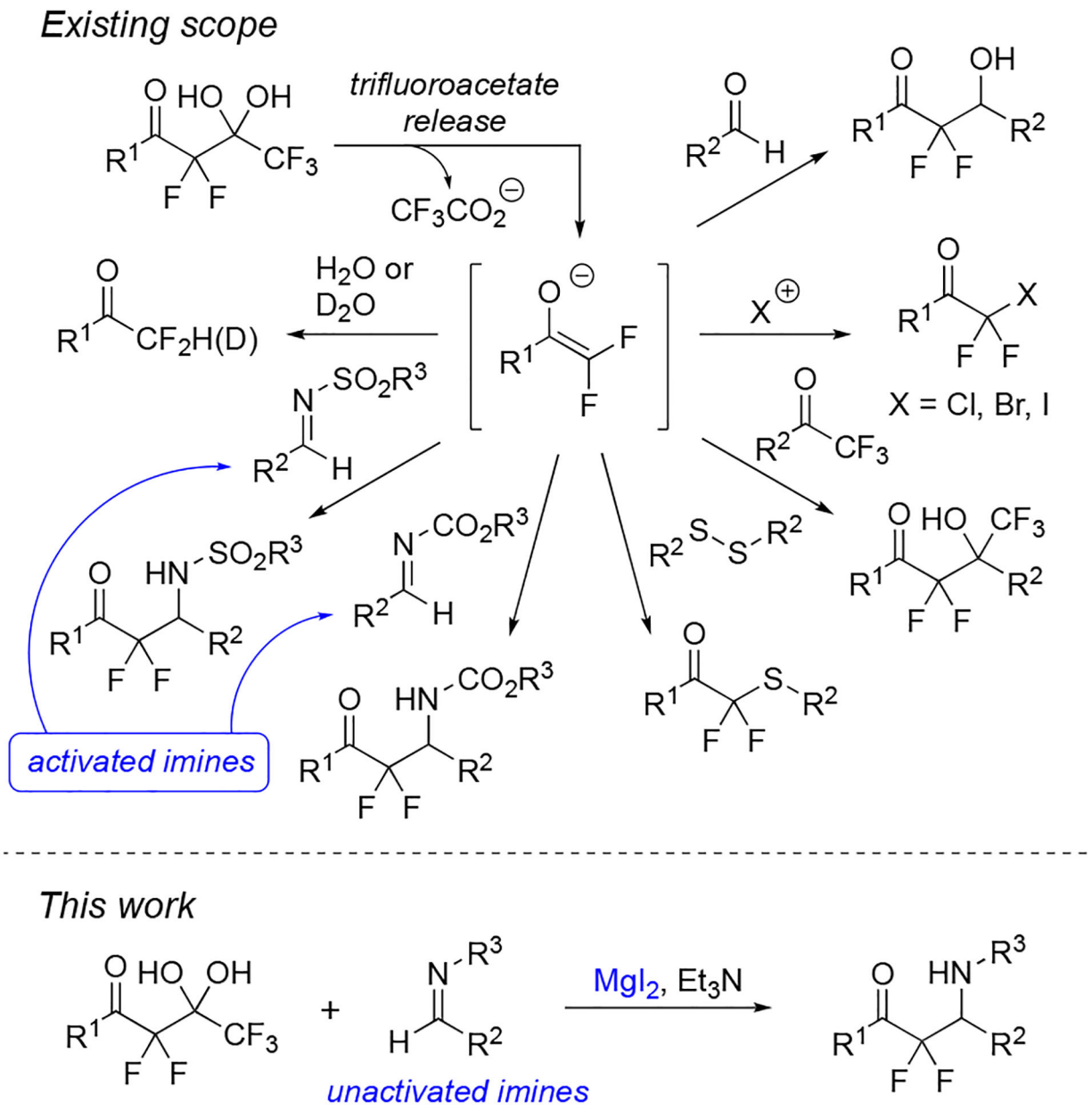


Figure 3.
Preparation of α,α-difluoro-β-aminocarbonyl groups from highly α-fluorinated *gem*-diols.

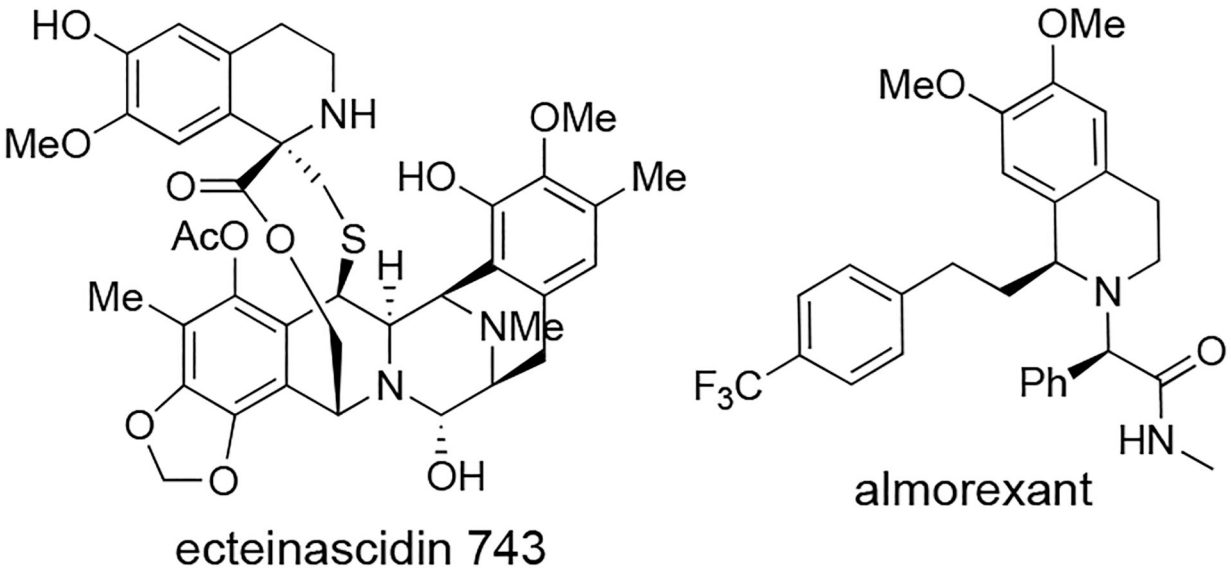
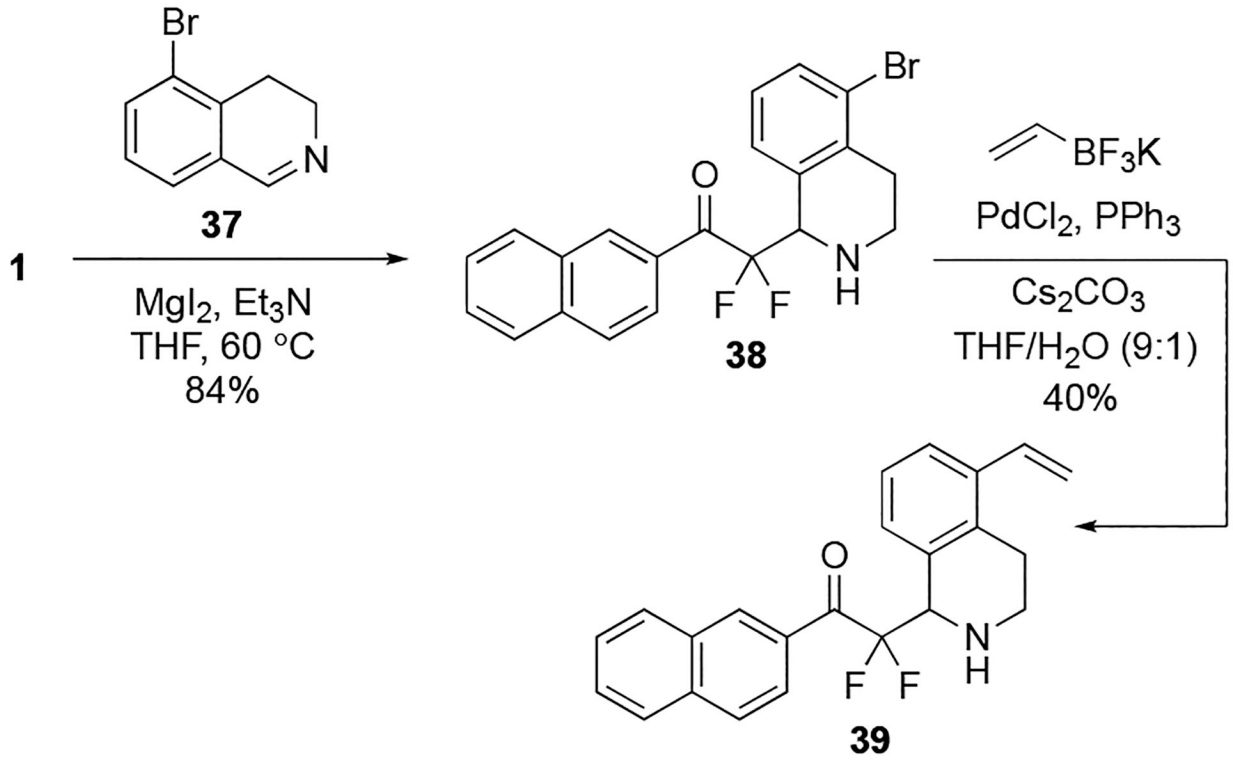
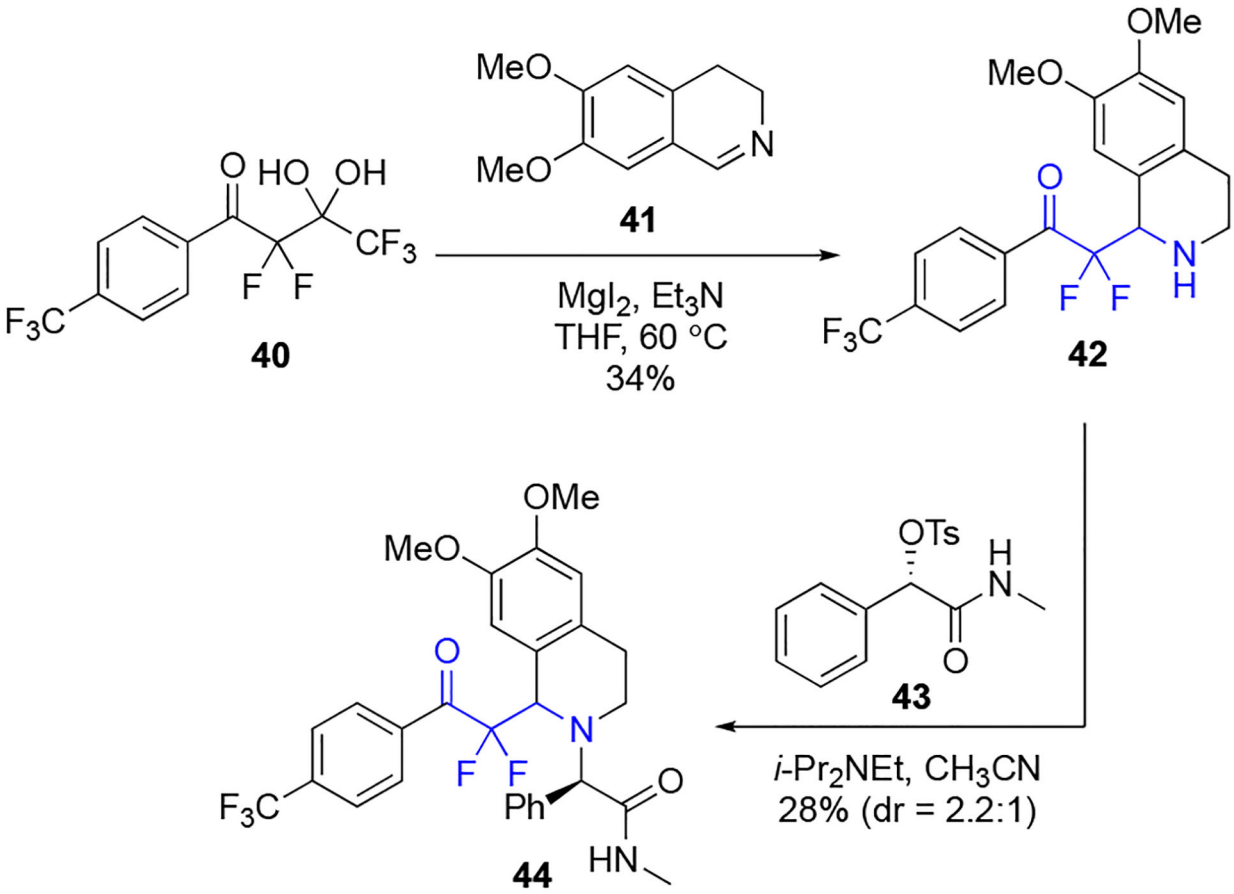


Figure 4.
Structure of biologically active molecules displaying a tetrahydroisoquinoline.



Scheme 1.
Imino-aldol addition of *gem*-diol **1** with dihydroisoquinoline **37**

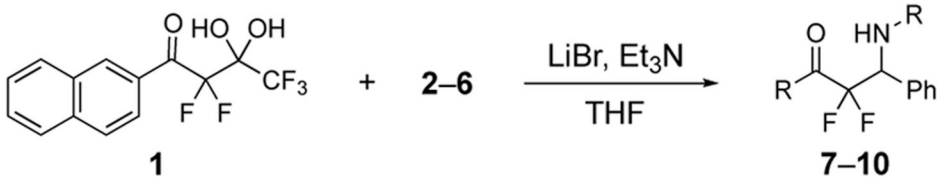


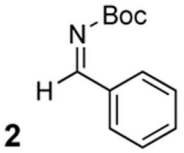
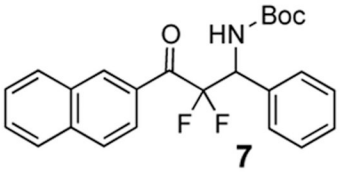
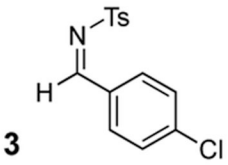
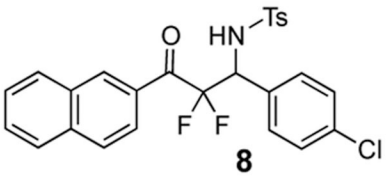
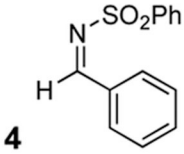
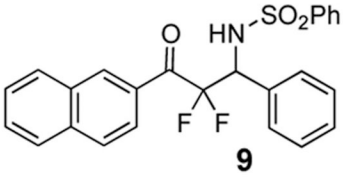
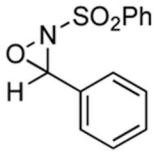
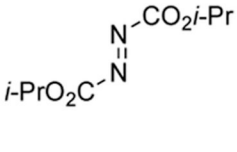
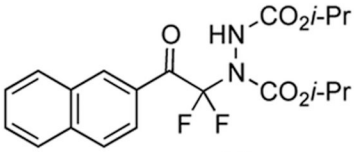
Scheme 2.

Two-step, protecting group-free synthesis of fluorinated almorexant analogue **44**.

Table 1.

LiBr/Et_3N Promoted Additions of Difluoroenolates Derived from Highly α-Fluorinated *gem*-Diols.

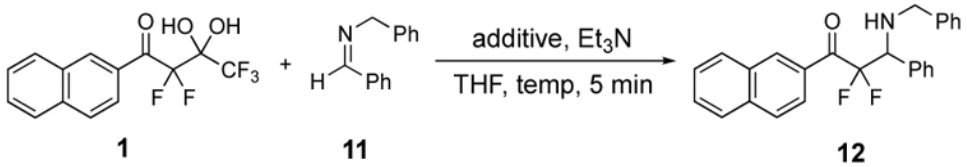


Entry	Reactant	Product	Yield[a]
1	 **2**	 **7**	88%
2	 **3**	 **8**	84%
3	 **4**	 **9**	87%
4	 **5**	**9**	57%
5	 **6**	 **10**	91%

[a]Yields determined by ^{19}F NMR using trifluorotoluene as the internal standard.

Table 2.

Optimization of Imino-aldol Process



1 **11** **12**

Entry	Additive	Imine (equiv.)	Temp	Yield[b]
1	LiBr	1.2	rt	0%
2	LiCl	1.2	rt	0%
3	$MgBr_2$	1.2	60 °C	50%[a]
4	$MgCl_2$	1.2	60 °C	74%[a]
5	MgI_2	1.2	rt	43%
6	MgI_2	2.0	rt	62%
7	MgI_2	2.0	40 °C	66%
8	MgI_2	2.0	60 °C	73% (95%)[a]
9	*i*-PrNMgCl·LiCl[c]	2.0	60 °C	4%
10	*i*-PrMgCl·LiBr[c]	2.0	rt	54%

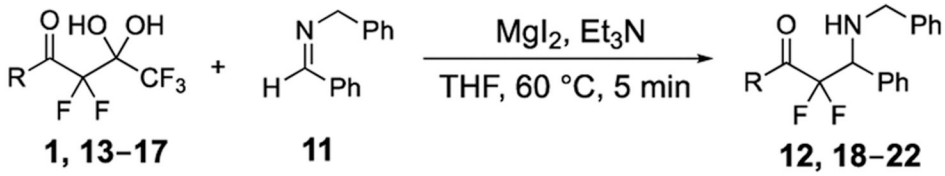
[a]Yields determined by ^{19}F NMR using trifluorotoluene as the internal standard.

[b]Isolated yields.

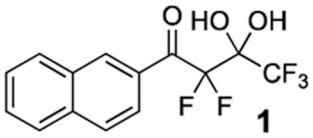
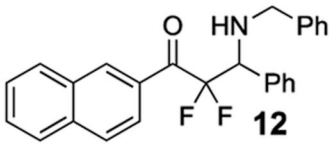
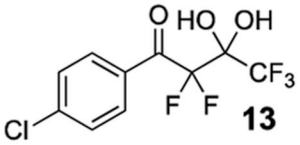
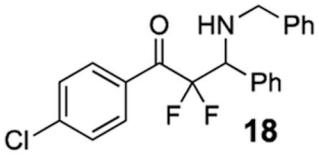
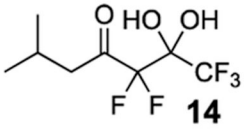
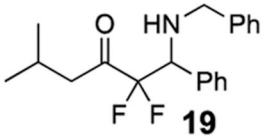
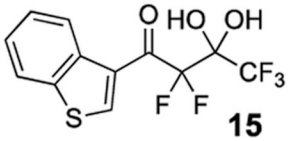
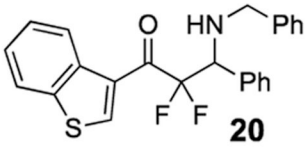
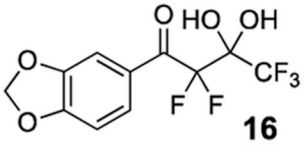
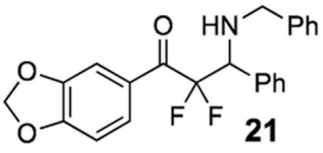
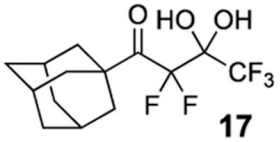
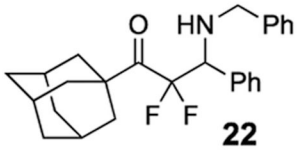
[c]Et_3N was not added.

Table 3.

Magnesium-promoted Addition of Highly α-Fluorinated *gem*-Diols to the Unactivated Imine 11[a]



1, 13–17 11 12, 18–22

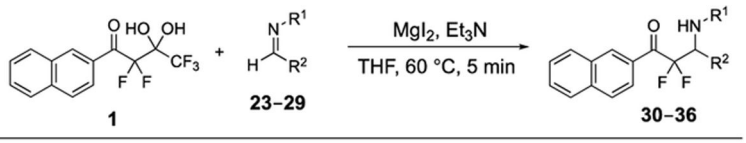
Entry	Substrate	Product	Yield[b]
1	 **1**	 **12**	73%
2	 **13**	 **18**	85%
3	 **14**	 **19**	15%
4	 **15**	 **20**	69%
5	 **16**	 **21**	49%
6	 **17**	 **22**	25%

[a]Reactions were typically performed with MgI_2 (4.2 equiv.) and Et_3N (2.1 equiv.), see Supporting Information for details.

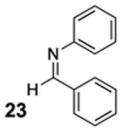
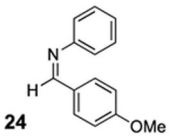
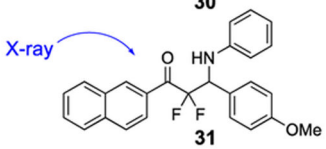
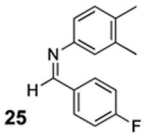
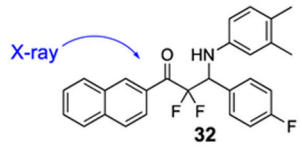
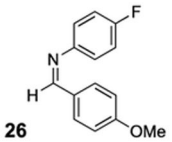
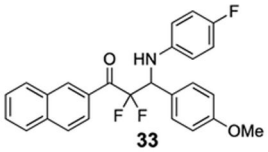
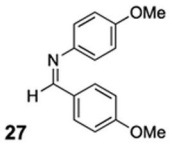
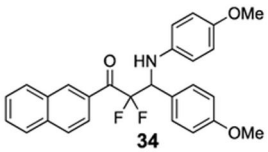
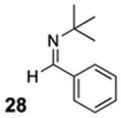
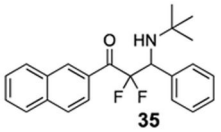
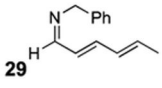
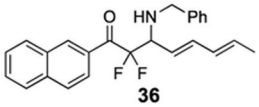
[b]Isolated yields.

Table 4.

Magnesium-promoted Addition of Highly α-Fluorinated *gem*-Diol 1 to the Unactivated Imines 23–29[a]



1 23–29 30–36

Entry	Imine	Product	Yield[b]
1	 23	 30	59%
2	 24	 31	79%
3	 25	 32	64%
4	 26	 33	78%
5	 27	 34	38%
6	 28	 35	30%
7	 29	 36	61%

[a] Reactions were typically performed with MgI_2 (4.2 equiv.) and Et_3N (2.1 equiv.), see Supporting Information for details.

[b] Isolated yields.