Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Copper-Catalyzed Olefinic C-H Difluoroacetylation of Enamides

Gilles Caillot, Jérémy Dufour, Marie-Charlotte Belhomme, Thomas Poisson, Laurence Grimaud, Xavier Pannecoucke, and Isabelle Gillaizeau**

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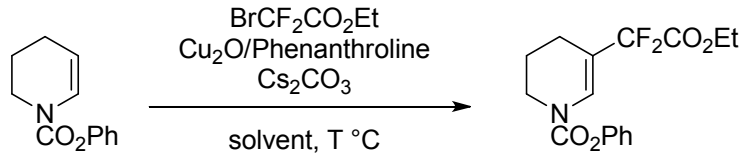
1. General Information

THF was purified with a dry station GT S100 immediately prior to use. Acetonitrile was distilled over CaH_2 prior to use. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation and/or spraying with a solution of potassium permanganate, followed by charring at 150 °C. Flash column chromatography was performed on silica gel 60 (230-400 mesh, 0.040-0.063 mm). The infrared spectra of compounds were recorded on a Thermo Scientific Nicolet iS10. Specific rotation was measured on a Model 341 Perkin-Elmer polarimeter at 589 nm in a 1 dm cell. ^{1}H and ^{13}C NMR spectra were recorded on an Avance II Bruker spectrometer at 250 MHz (^{13}C, 62.9 MHz) or an Avance III HD NanoBay Bruker at 400 MHz (^{13}C: 100 MHz; ^{19}F: 376 MHz CPD). 1,1,2,2-Tetrachloroethane was used as an internal standard on the ^{1}H NMR spectra for the determination of the crude yield of coupling. Chemical shifts (δ) are given in parts per million from tetramethylsilane (TMS) as internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, dd: doublet of doublets, dt: doublet of triplets, td: triplet of doublets. All ^{19}F NMR spectra are reported in ppm relative to a $CFCl_3$ external standard (0 ppm). Electronic ionspray methodology was used to record mass spectra. HRMS Spectra were recorded on a Maxis Bruker 4G. All reagents were obtained from commercial suppliers unless otherwise stated.

Solvent screening for the coupling reaction



1a **2a**

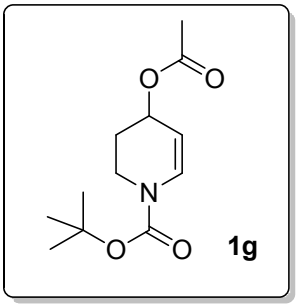
entry[a]	solvent	T (°C)	time (h)	yield[b] (%)
1	NMP	80	18	79
2	DMF	80	24	68
3	THF	80	18	44
4	1,4-Dioxane	80	18	56
5	Toluene	80	18	traces
6	DCE	80	18	traces
7	MeCN	80	18	88
8	**MeCN**	**80**	**6**	**85**
9	MeCN	40	28	0
10	MeCN	20	40	0

[a] Conditions: enamide **1a** (1 equiv), Cu_2O (0.10 equiv), 1,10-Phenanthroline (0.12 equiv), Cs_2CO_3 (2 equiv), $BrCF_2CO_2Et$ (4 equiv), solvent ($c \approx 0.33$ mol/L). [b] Isolated yield after flash chromatography.

2. Preparation of starting enamides

Enamides 1-(Phenyloxycarbonyl)-1,2,3,4-tetrahydropyridine **1a**,[1] 1-benzoyl-1,2,3,4,-tetrahydro-pyridine **1b**,[2] 1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine **1c**,[2] 1-(*tert*-butyloxycarbonyl)-2,3,4,5-tetrahydroazepine **1d**,[3] 1-benzyl-3,4-dihydro-1*H*-pyridin-2-one **1e**,[3] 1-allyl-3,4-dihydro-1*H*-pyridin-2-one **1f**,[4] 1-(phenyloxycarbonyl)-2,3-dehydro-4-piperidone **1i**,[5] 1,3-dibenzyluracil **1j**,[6] (*E*)-*N*-styryl-oxazolidinone **1n**,[7] *N*-(*tert*-butyloxycarbonyl)-*N*-(1-phenylvinyl)-aniline **1p**,[8] *N*-acetyl-*N*-benzyl-dehydroalanine methyl ester **1q**[9] and *N*-benzyl-*N*-isopropenylacetamide **1r**[10] were synthesized according to the literature procedures.

1-(*tert*-Butyloxycarbonyl)-4-acetyl-1,2,3,4-tetrahydropyridine (1g)



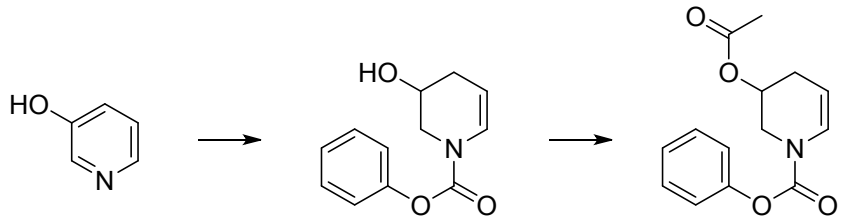
Following a procedure described in the literature,[11] 1-(*tert*-butyloxycarbonyl)-2-methoxy-1,2,5,6-tetrahydropyridine[12] (1.0 g, 4.65 mmol, 1.0 equiv) was placed in acetic acid under argon and the suspension was stirred at room temperature for 2h. Ethyl acetate and saturated aqueous ammonium chloride were added and the two layers were separated. The organic layer was washed three times with water and once with brine, dried over magnesium sulfate and evaporated to dryness. The residue was

[1] F. Lepifre, S. Clavier, P. Bouyssou, G. Coudert, *Tetrahedron* **2001**, *57*, 6969-6975.
[2] N. Gigant, L. Chausset-Boissarie, M.-C. Belhomme, T. Poisson, X. Pannecoucke, I. Gillaizeau, *Org. Lett.* **2013**, *15*, 816-819.
[3] J. Yu, V. Truc, P. Riebel, E. Hierl, B. Mudryk, *Tetrahedron Lett.* **2005**, *46*, 4011-4013.
[4] N. Gigant, I. Gillaizeau, *Org. Lett.* **2012**, *14*, 3304-3307.
[5] (a) R. Sebesta, M.G. Pizzuti, A.J. Boersma, A.J. Minnaard, B.L. Feringa, *Chem. Commun.* **2005**, 1711-1713; (b) S. Knapp, C. Yang, S. Pabbaraja, B. Rempel, S. Reid, S.G. Withers, *J. Org. Chem.* **2005**, *70*, 7715-7720.
[6] M. Cernova, I. Cerna, R. Pohl, M. Hocek, *J. Org. Chem.* **2011**, *76*, 5309-5319.
[7] F. Song, J.A. Snook, B.M. Foxman, B.B. Snider, *Tetrahedron* **1998**, *54*, 13035-13044.
[8] A. Bouet, M. Cieslikiewicz, K. Lewinski, G. Coudert, I. Gillaizeau, *Tetrahedron* **2010**, *66*, 498-503.
[9] D.T. Davies, K. Goodall, N. Kapur, M. O'Brien, A.F. Parsons, *Synth. Commun.* **1997**, *27*, 3815-3822.
[10] (a) K. Tanaka, M. Takahashi, H. Imase, T. Osaka, K. Noguchi, M. Hirano, *Tetrahedron Lett.* **2008**, *64*, 6289-6293; (b) M. Kobayashi, T. Suda, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.* **2011**, *50*, 1664-1667.
[11] (a) S. Furukubo, N. Moriyama, O. Onomura, Y. Matsumura, *Tetrahedron Lett.* **2004**, *45*, 8177-8181; (b) O. Onomura, N. Fujimura, T. Oda, Y. Matsumura, Y. Demizu, *Heterocycles* **2008**, *76*, 177-182.
[12] T. Shono, J. Terauchi, Y. Ohki, Y. Matsumura, *Tetrahedron Lett.* **1990**, *31*, 6385-6386.

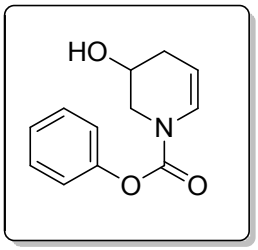
purified by flash chromatography using ethyl acetate/petroleum ether (1:9) as eluent. The product **1g** was obtained as colorless oil (460 mg, 41%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.93 (m, 2H), 2.07 (s, 3H), 3.32 (br m, 1H), 3.98 (br m, 1H), 5.00 (br m, 1H), 5.22 (dd, 1H, J_1 = 3.9 Hz, J_2 = 8.3 Hz), 7.05 (br m, 1H).

Synthesis of 1-(Phenyloxycarbonyl)-3-acetyl-1,2,3,4-tetrahydropyridine (1h)



1-(Phenyloxycarbonyl)-3-hydroxy-1,2,3,4-tetrahydropyridine

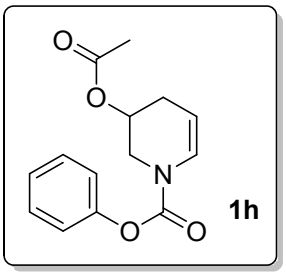


This compound was synthesized following a reported procedure[13]. A suspension of 3-hydroxypyridine (951 mg, 10 mmol, 1.0 equiv) in absolute ethanol (40 mL) was cooled at -78°C, and sodium borohydride (832 mg, 22 mmol, 2.2 equiv) was added followed by sodium hydrogenocarbonate (630 mg, 7.5 mmol, 0.75 equiv). Phenyl chloroformate (1.88 mL, 15 mmol, 1.5 equiv) was then added dropwise at -78°C, and the mixture was stirred at this temperature for 6h. Upon completion of the reaction, potassium carbonate (160 mg) was added and the mixture was filtered on a plug of celite. The filtrate was concentrated and brine (25 mL) and ethyl acetate were added to the residue. The aqueous layer was separated and further extracted twice with ethyl acetate. The organic layers were gathered, dried over magnesium sulfate and evaporated to dryness. The resulting yellow oil was purified by flash chromatography using ethyl acetate/petroleum ether (1:2 → 3:2) as eluent. The product was obtained as pale orange viscous oil (756 mg, 35%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.99 (br s, 1H), 2.18 (m, 1H), 2.46 (m, 1H), 3.65-3.95 (m, 2H), 4.25 (m, 1H), 4.97 (m, 1H), 7.02 (m, 1H), 7.17 (m, 2H), 7.25 (m, 1H), 7.41 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 31.7 (CH_2), 49.4/50.0 (CH_2-N, rotamers), 64.6 (CH-OH), 105.3 (CH), 123.0 ($C_{ar}H$), 126.2/126.7 (CH-N, rotamers), 127.1 ($C_{ar}H$), 130.8 ($C_{ar}H$), 152.4 (C), 153.5 (C).

[13] H. Sakagami, K. Ogasawara, *Synthesis* **2000**, 521-524.

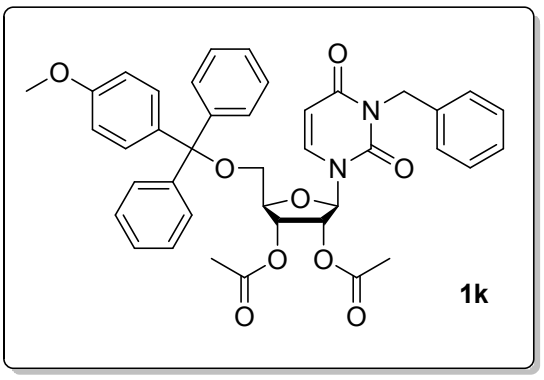
1-(Phenyloxycarbonyl)-3-acetyl-1,2,3,4-tetrahydropyridine 1h



To a solution of the above compound (548 mg, 2.5 mmol, 1.0 equiv) in dichloromethane (15 mL) were added triethylamine (0.84 mL, 6 mmol, 2.4 equiv) and DMAP (37 mg, 0.3 mmol, 0.12 equiv) followed by dropwise addition of acetic anhydride (0.43 mL, 4.5 mmol, 1.8 equiv). Upon completion of the reaction after 2.5h at room temperature, water (15 mL) and dichloromethane (15 mL) were added. The organic layer was separated, washed with saturated aqueous sodium hydrogenocarbonate (15 mL) and brine (15 mL), dried over magnesium sulfate and evaporated to dryness. The resulting yellowish oil was purified by flash chromatography using ethyl acetate/petroleum ether (1:7) as eluent. The product **1h** was obtained as colorless oil (533 mg, 82%). NMR indicated a probable mixture of rotamers.

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.12/2.13 (2x s, 3H), 2.20/2.28 (2x br m, 1H), 2.47/2.54 (2x br m, 1H), 3.72/3.88 (2x br dd, 1H, J_1 = 2.6 Hz, J_2 = 12.9 Hz), 3.90/4.00 (2x br dd, 1H, J_1 = 6.0 Hz, J_2 = 12.9 Hz), 4.99 (m, 1H), 5.27 (m, 1H), 6.98/7.04 (2x br dt, 1H, J_1 = 1.8 Hz, J_2 = 8.4 Hz), 7.17 (m, 2H), 7.25 (m, 1H), 7.40 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.6 (CH_3), 28.5/28.7 (CH_2), 46.5/46.9 (CH_2-N), 66.8/66.9 (CH-O), 105.0/105.4 (CH), 123.0 (2x $C_{ar}H$), 126.3/126.7 (CH-N), 127.1 ($C_{ar}H$), 130.8 ($C_{ar}H$), 152.2/152.4 (C), 153.3/153.6 (C), 171.7/171.8 (C(O)O).

***N*-Benzyl-2',3'-*O*-diacetyl-5'-*O*-(*p*-methoxy-α,α-diphenyl-benzyl)-uridine 1k**



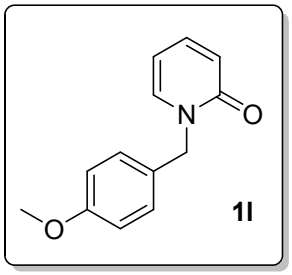
5'-*O*-(4-Methoxytrityl)uridine[14] (517 mg, 1 mmol, 1.0 equiv) was placed in distilled THF (8 mL), and DMAP (49 mg, 0.4 mmol, 0.4 equiv), triethylamine (0.56 mL, 4 mmol, 4 equiv) and acetic anhydride

[14]S.K. Choi, T. K. Vu, J. M. Jung, S. J. Kim, H. R. Jung, T. Chang, B. H. Kim, *ChemBioChem* **2005**, *6*, 432-439.

(0.38 mL, 4 mmol, 4 equiv) were slowly added at room temperature. The mixture was stirred for 3 hours then partitioned between dichloromethane and 5% aqueous sodium hydrogenocarbonate. The organic layer was dried over magnesium sulfate and evaporated to dryness. The resulting white foam was dissolved in acetone (6 mL) and potassium carbonate (207 mg, 1.5 mmol, 1.5 equiv) was introduced, followed by dropwise addition of benzyl bromide (178 µL, 1.5 mmol, 1.5 equiv) at room temperature. After 17h, the solids were filtered off and washed with acetone, and the filtrate was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water; the aqueous phase was reextracted with ethyl acetate, then the organic layers were gathered, washed with brine, dried over magnesium sulfate and evaporated to dryness. The resulting yellow oil was purified by flash chromatography using ethyl acetate/petroleum ether (1:3 to 1:2) as eluent. The product **1k** was obtained as white foam (507 mg, 73%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.05 (s, 3H), 3.45 (m, 2H), 3.77 (s, 3H), 4.19 (m, 1H), 5.00 (d, 1H, J = 13.8 Hz), 5.10 (d, 1H, J = 13.8 Hz), 5.40 (d, 1H, J = 8.1 Hz), 5.54 (m, 2H), 6.21 (br d, 1H, J = 5.2 Hz), 6.82 (m, 2H), 7.20-7.45 (m, 17H), 7.64 (d, 1H, J = 8.1 Hz); HRMS (ESI) m/z calcd for $C_{40}H_{39}N_2O_9$ $[M+H]^+$: 691.265007, found: 691.264706.

_N_-(4-methoxybenzyl)-2-pyridone 1l[15]

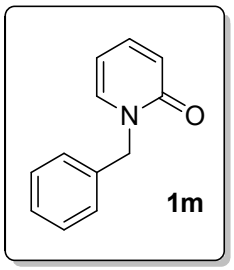


This compound was prepared following a reported procedure.[16] To a mixture of 2-hydroxypyridine (476 mg, 5 mmol, 1 equiv) and potassium carbonate (2.07 g, 15 mmol, 3 equiv) in acetone was added dropwise 4-methoxybenzyl chloride (1.0 mL, 7.5 mmol, 1.5 equiv), and the mixture was heated at reflux for 20h. It was then cooled to room temperature and the solids were filtered off and washed with acetone. The filtrate was concentrated *in vacuo*, and the residue was partitioned between water and chloroform. The aqueous layer was further extracted with chloroform, and the organic layers were gathered, dried over magnesium sulfate and evaporated to dryness. The resulting yellow oil was purified by flash chromatography using ethyl acetate/petroleum ether (1:2 to 1:1) as eluent. The product **1l** was obtained as a white solid (0.76 g, 71%).

[15] E. L. Lanni, M. A. Bosscher, B. D. Ooms, C. A. Shandro, B. A. Ellsworth, C. E. Anderson, *J. Org. Chem.* **2008**, *73*, 6425-6428.
[16] F. Mohr, A. Mendia, M. Laguna, *Eur. J. Inorg. Chem.* **2007**, 3115-3123.

^{1}H NMR (250 MHz, $CDCl_3$): δ 3.81 (s, 3H), 5.09 (s, 2H), 6.13 (td, 1H, J_1 = 1.1 Hz, J_2 = 6.7 Hz), 6.61 (br d, 1H, J = 9.2 Hz), 6.88 (m, 2H), 7.26 (m, 3H), 7.31 (ddd, 1H, J_1 = 2.0 Hz, J_2 = 2.1 Hz, J_3 = 6.7 Hz).

***N*-benzyl-2-pyridone 1m[15]**



This compound was prepared similarly to compound **1l** using 2-hydroxypyridine (761 mg, 8 mmol, 1 equiv), potassium carbonate (2.76 g, 20 mmol, 2.5 equiv) and benzyl bromide (1.19 mL, 10 mmol, 1.25 equiv). After flash chromatography using ethyl acetate/petroleum ether (1:2 to 2:1) as eluent, the product **1m** was obtained as a yellowish solid (1.30 g, 88%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.12 (s, 2H), 6.10 (td, 1H, J_1 = 1.3 Hz, J_2 = 6.7 Hz), 6.58 (ddd, 1H, J_1 = 0.8 Hz, J_2 = 1.2 Hz, J_3 = 9.1 Hz), 7.20-7.36 (m, 7H).

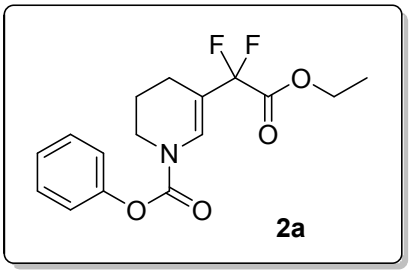
3. Experimental and characterization of coupling products

General procedure

In a flame-dried, argon-filled tube were successively placed the starting enamide **1** (0.5 mmol, 1.0 equiv), Cu_2O (7.2 mg, 0.05 mmol, 0.10 equiv), 1,10-phenanthroline (10.8 mg, 0.06 mmol, 0.12 equiv) and oven-dried potassium carbonate (138.2 mg, 1 mmol, 2 equiv). Freshly distilled acetonitrile (2.4 mL) was added, the mixture was stirred under argon for a few seconds and distilled ethyl bromodifluoroacetate (128-256 µL, 1-2 mmol, 2-4 equiv) was added. The tube was sealed and placed in an oil bath at 80 °C, and the mixture was stirred at this temperature until completion of the reaction as indicated by TLC. The mixture was then cooled at room temperature. Ethyl acetate and water were added; the aqueous layer was separated and extracted with ethyl acetate. The organic layers were gathered, dried over magnesium sulfate and the solvents were evaporated at room temperature. The residue was then purified by flash chromatography using diethyl ether/pentane to afford the corresponding fluorine-containing enamide **2**.

Phenyl 5-(2-ethoxy-1,1-difluoro-2-oxo-ethyl)-3,4-dihydro-2*H*-pyridine-1-carboxylate (2a)

Colorless oil, 91% (6h, 2 equiv of bromodifluoroester).

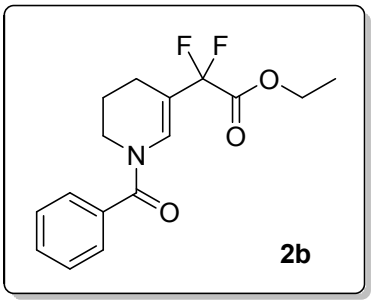


2a

^{1}H NMR (rotamers) (400 MHz, $CDCl_3$): δ 1.40 (t, 3H, J = 7.1 Hz), 1.99 (m, 2H), 2.27 (m, 2H), 3.80 (m, 2H), 4.39 (q, 2H, J = 7.0 Hz), 7.15 (m, 1H), 7.18 (m, 1H), 7.23-7.31 (m, 1H), 7.38-7.46 (m, 2H), 7.48/7.55 (2x br s, 1H); ^{13}C NMR (rotamers) (100 MHz, $CDCl_3$): δ 14.1/14.1, 19.6/20.0, 20.6/20.8, 42.4/42.9, 63.2/63.3, 110.4, 121.6/121.7, 126.1, 127.1/127.6 (t, J = 11Hz), 129.6/129.6, 150.9/151.6, 158.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.2, -104.8; HRMS (ESI) m/z calcd for $C_{16}H_{18}F_2NO_4$ $[M+H]^+$: 326.119841, found: 326.119854.

Ethyl 2-(1-benzoyl-3,4-dihydro-2*H*-pyridin-5-yl)-2,2-difluoro-acetate (2b)

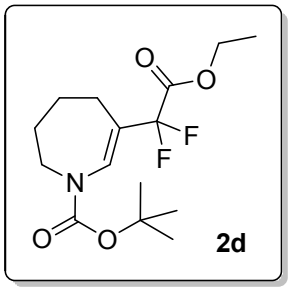
Yellow oil, 77% (6h, 2 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, DMSO-d_6, 80°C): δ 1.17 (t, 3H, J = 7.1 Hz), 1.85 (m, 2H), 2.15 (tq, 2H, J_1 = 1.7 Hz, J_2 = 6.2 Hz), 3.60 (m, 2H), 4.21 (d, 2H, J = 7.1 Hz), 7.01 (br s, 1H), 7.40-7.54 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6, 80°C): δ 14.0, 20.1 (t, J = 2 Hz), 20.7, 25.6, 63.5, 67.5, 114.6 (t, J = 248 Hz), 128.0, 128.8, 129.0, 131.0, 134.7, 163.3 (t, J = 35 Hz), 169.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -104.8; HRMS (ESI) m/z calcd for $C_{16}H_{18}F_2NO_3$ $[M+H]^+$: 310.124926, found: 310.125331.

***tert*-Butyl 6-(2-ethoxy-1,1-difluoro-2-oxo-ethyl)-2,3,4,5-tetrahydroazepine-1-carboxylate (2d)**

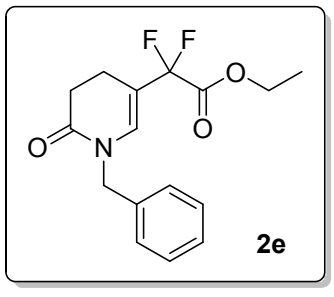
Pale yellow oil, 89% (14h, 2 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, 3H, J = 7.2 Hz), 1.51 (s, 9H), 1.83 (m, 4H), 2.33 (m, 2H), 3.75 (m, 2H), 4.36 (q, 2H, J = 7.2 Hz), 7.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 23.7 (br), 24.3, 27.1, 28.2, 29.8, 62.9, 83.0, 116.0 (t, J = 248 Hz), 117.5 (t, J = 20 Hz), 133.3, 134.6 (t, J = 11 Hz), 154.6, 165.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ -104.2 (brs), -103.8 (brs); HRMS (ESI) m/z calcd for $C_{15}H_{24}F_2NO_4$ $[M+H]^+$: 320.166791, found: 320.166692.

Ethyl 2-(1-benzyl-2-oxo-3,4-dihydropyridin-5-yl)-2,2-difluoro-acetate (2e)

Yellow oil, 82% (6h, 2 equiv of bromodifluoroester).

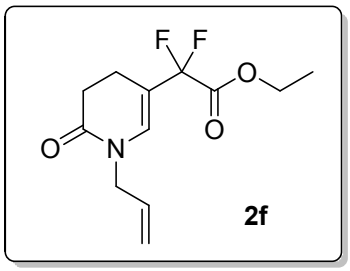


^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.2 Hz), 2.51 (m, 2H), 2.67 (m, 2H), 4.31 (q, 2H, J = 7.1 Hz), 4.74 (s, 2H), 6.57 (m, 1H), 7.24 (m, 2H), 7.28-7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

13.9, 19.1 (t, J = 2.6 Hz), 30.6, 49.5, 63.1, 109.9 (t, J = 25 Hz), 113.1 (t, J = 250 Hz), 127.7, 127.9, 128.8, 131.4 (t, J = 10 Hz), 136.4, 163.4 (t, J = 36 Hz), 168.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.3; HRMS (ESI) m/z calcd for $C_{16}H_{18}F_2NO_3$ $[M+H]^+$: 310.124926, found: 310.125126.

Ethyl 2-(1-allyl-2-oxo-3,4-dihydropyridin-5-yl)-2,2-difluoro-acetate (2f)

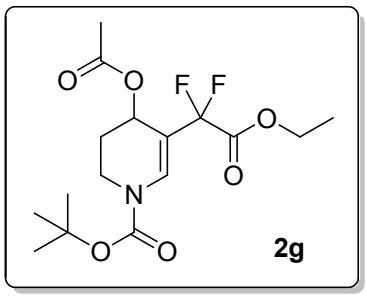
Colorless oil, 22% (6h, 2 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 3H, J = 7.2 Hz), 2.50 (m, 2H), 2.63 (m, 2H), 4.16 (br d, 2H, J = 5.7 Hz), 4.36 (q, 2H, J = 7.2 Hz), 5.16-5.25 (m, 2H), 5.79 (m, 1H), 6.55 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.1 (t, J = 3 Hz), 30.5, 48.3, 63.1, 109.6 (t, J = 25 Hz), 113.1 (t, J = 251 Hz), 118.0, 131.2 (t, J = 10 Hz), 132.3, 163.5 (t, J = 36 Hz), 168.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.3; HRMS (ESI) m/z calcd for $C_{12}H_{16}F_2NO_3$ $[M+H]^+$: 260.109276, found: 260.109495.

***t*-Butyl 4-acetoxy-5-(2-ethoxy-1,1-difluoro-2-oxo-ethyl)-3,4-dihydro-2*H*-pyridine-1-carboxylate (2g)**

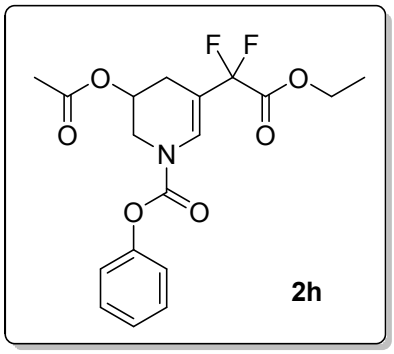
Colorless oil, 51% (6h, 2 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 3H, J = 7.1 Hz), 1.53 (s, 9H), 1.81 (br tt, 1H, J_1 = 3.8 Hz, J_2 = 14.2 Hz), 2.04 (s, 3H), 2.10 (br d, 1H, J = 14.2 Hz), 3.23 (br s, 1H), 4.05 (br m, 1H), 4.33 (m, 2H), 5.60 (t, 1H, J = 2.9 Hz), 7.65 (br m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.1, 27.0, 28.1, 36.7 (br m), 61.3 (m), 63.0, 82.9 (br), 113.3 (t, J = 251 Hz), 132.7 (t, J = 10 Hz), 146.3, 163.9 (t, J = 36 Hz), 169.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -104.6 (br d, J = 256 Hz), -101.9 (d, J = 256 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{23}F_2NNaO_6$ $[M+Na]^+$: 386.138565, found: 386.138443.

Phenyl 3-acetoxy-5-(2-ethoxy-1,1-difluoro-2-oxo-ethyl)-3,4-dihydro-2*H*-pyridine-1-carboxylate (2h)

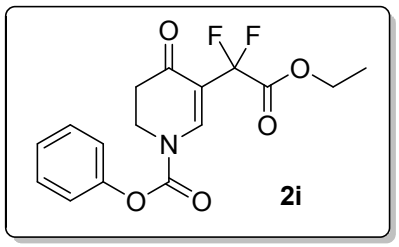
Colorless oil, 53% (23h, 2 equiv of bromodifluoroester).



^{1}H NMR (rotamers) (400 MHz, $CDCl_3$): δ 1.39 (t, 2H, J = 7.1 Hz), 2.12/2.11 (2x s, 3H), 2.42/2.47 (2x br m, 1H), 2.55/2.60 (2x br m, 1H), 3.63/3.79 (2x br d, 1H, J = 13.0 Hz), 4.01/4.10 (2x dd, 1H, J_1 = 4.6 Hz, J_2 = 13.1 Hz), 4.38 (m, 2H), 5.36 (m, 1H), 7.17 (m, 2H), 7.28 (m, 1H), 7.42 (m, 2H), 7.52/7.59 (2x br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.0, 25.3/25.6, 45.0/45.5, 63.2, 63.7/63.9, 106.9 (t, J = 249 Hz), 121.3/121.4, 126.1, 126.9 (t, J = 12 Hz), 129.5, 150.6, 151.6, 170.1/170.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.7 (d, J = 254.6 Hz), -104.8 (d, J = 254.6 Hz); HRMS (ESI) m/z calcd for $C_{18}H_{20}F_2NO_6$ $[M+H]^+$: 384.125320, found: 384.125033.

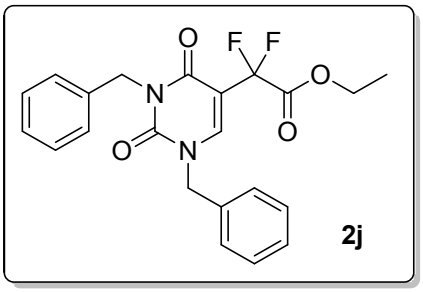
Phenyl 5-(2-ethoxy-1,1-difluoro-2-oxo-ethyl)-4-oxo-2,3-dihydropyridine-1-carboxylate (2i)

Slightly yellow oil, 22% (46h, 4 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 1H, J = 7.2 Hz), 2.73 (t, 2H, J = 7.5 Hz), 4.25 (m, 2H), 4.37 (q, 2H, J = 7.2 Hz), 7.20 (m, 2H), 7.33 (m, 1H), 7.46 (m, 2H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 35.0, 42.8 (brs), 63.2, 111.4 (t, J = 249 Hz), 121.1, 126.0, 126.8, 129.5, 129.8, 143.4 (brs), 150.2, 163.1 (t, J = 33 Hz), 189.3 (t, J = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -104.6; HRMS (ESI) m/z calcd for $C_{16}H_{16}F_2NO_5$ $[M+H]^+$: 340.099105, found: 340.099387.

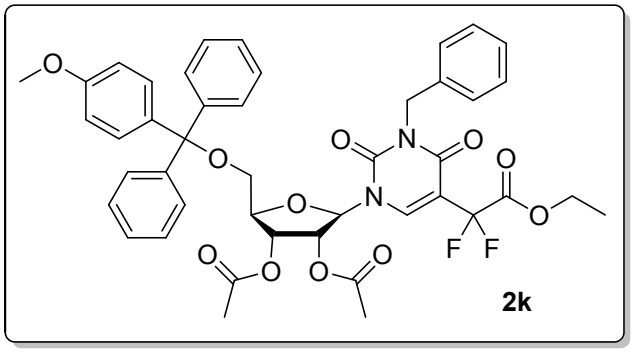
Ethyl 2-(1,3-dibenzyl-2,4-dioxo-pyrimidin-5-yl)-2,2-difluoro-acetate (2j)
Slightly yellow oil, 51% (80h, 4 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, 3H, J = 7.2 Hz), 4.38 (q, 2H, J = 7.2 Hz), 4.99 (s, 2H), 5.13 (s, 2H), 7.32 (m, 5H), 7.41 (m, 3H), 7.48 (m, 2H), 7.64 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 44.7, 53.2, 63.4, 107.8 (t, J = 25 Hz), 111.0 (t, J = 250 Hz), 127.9, 128.3, 128.5, 128.9, 129.2, 129.3, 134.3, 136.0, 141.5 (t, J = 8 Hz), 150.9, 160.0 (t, J = 4 Hz), 162.5 (t, J = 33 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -104.7; HRMS (ESI) m/z calcd for $C_{22}H_{21}F_2N_2O_4$ $[M+H]^+$: 415.146390, found: 415.146241.

***N*-Benzyl-2',3'-*O*-diacetyl-5-(2-ethoxy-1,1-difluoro-2-oxo-ethyl)-5'-*O*-(*p*-methoxy-α,α-diphenyl-benzyl)-uridine (2k)**

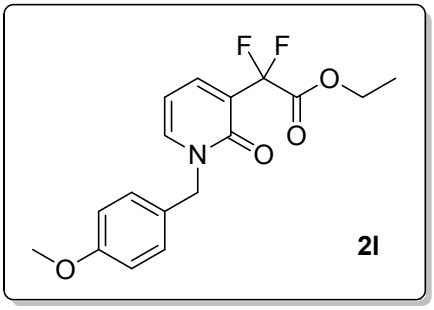
Yellow oil, 32% (72h, 4 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, 3H, J = 7.2 Hz), 2.03 (s, 3H), 2.07 (s, 3H), 3.38 (dd, 1H, J_1 = 3.1 Hz, J_2 = 11.1 Hz), 3.51 (dd, 1H, J_1 = 2.4 Hz, J_2 = 11.1 Hz), 3.77 (s, 3H), 4.22 (q, 1H, J = 3.1 Hz), 4.32 (q, 2H, J = 7.2 Hz), 5.03 (d, 1H, J = 13.9 Hz), 5.10 (d, 1H, J = 13.8 Hz), 5.44 (dd, 1H, J_1 = 3.6 Hz, J_2 = 5.4 Hz), 5.55 (dd, 1H, J_1 = 5.4 Hz, J_2 = 6.3 Hz), 6.21 (d, 1H, J = 6.3 Hz), 6.83 (m, 2H), 7.18-7.24 (m, 2H), 7.25-7.34 (m, 9H), 7.38-7.44 (m, 6H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 20.4, 20.6, 44.6, 55.2, 62.6, 63.3, 71.0, 73.1, 82.2, 87.0, 87.6, 108.9 (t, J = 26 Hz), 110.7 (t, J = 250 Hz), 113.4, 127.2, 127.2, 127.9, 128.0, 128.3, 128.3, 128.5, 129.1, 130.3, 134.6, 135.8, 137.2 (t, J = 8 Hz), 143.5, 150.3, 158.8, 159.6 (t, J = 4 Hz), 162.4 (t, J = 33 Hz), 169.5, 169.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.2 (d, J = 276.8 Hz), -104.1 (d, J = 276.8 Hz); HRMS (ESI) m/z calcd for $C_{44}H_{43}F_2N_2O_{11}$ $[M+H]^+$: 813.282943, found: 813.282233.

Ethyl 2,2-difluoro-2-[1-[(4-methoxyphenyl)methyl]-2-oxo-3-pyridyl]acetate (2l)

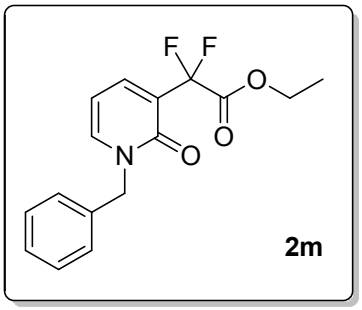
Yellow oil, 77% (21h, 2 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, 3H, J = 7.1 Hz), 3.81 (s, 3H), 4.39 (q, 2H, J = 7.1 Hz), 5.08 (s, 2H), 6.27 (t, 1H, J = 7.0 Hz), 6.89 (m, 2H), 7.26 (m, 2H), 7.41 (m, 1H), 7.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 51.3, 55.3, 62.9, 105.1, 111.6 (t, J = 248 Hz), 114.4, 124.7 (t, J = 24 Hz), 127.5, 130.0, 137.3 (t, J = 7 Hz), 139.4, 159.6 (t, J = 5 Hz), 159.6, 163.3 (t, J = 33 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.8; HRMS (ESI) m/z calcd for $C_{17}H_{18}F_2NO_4$ $[M+H]^+$: 338.119841, found: 338.119950.

Ethyl 2-(1-benzyl-2-oxo-3-pyridyl)-2,2-difluoro-acetate (2m)

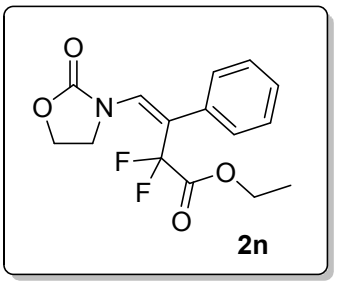
Amorphous yellow solid, 79% (22h, 4 equiv of bromodifluoroester).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, 3H, J = 7.1 Hz), 4.35 (q, 2H, J = 7.1 Hz), 5.13 (s, 2H), 6.26 (t, 1H, J = 7.0 Hz), 7.27 (m, 2H), 7.29-7.37 (m, 3H), 7.41 (br d, 1H, J = 6.8 Hz), 7.76 (br d, 1H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 51.8, 62.9, 105.2, 115.2 (t, J = 248 Hz), 124.8 (t, J = 24 Hz), 128.3, 128.3, 129.0, 135.6, 137.4 (t, J = 7 Hz), 139.7 (t, J = 1 Hz), 159.6 (t, J = 5 Hz), 163.2 (t, J = 33 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.8; HRMS (ESI) m/z calcd for $C_{16}H_{16}F_2NO_3$ $[M+H]^+$: 308.109276, found: 308.109525.

Ethyl 2,2-difluoro-4-(2-oxo-oxazolidin-3-yl)-3-phenyl-but-3-enoate (2n)

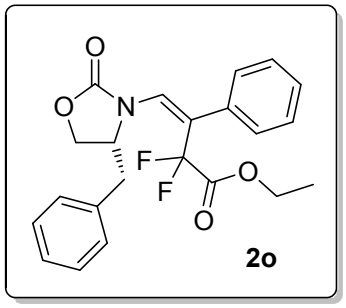
Yellow oil, 61% (7h, 4 equiv of bromodifluoroester). **2n** was isolated as a single Z-stereoisomer.



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, 3H, J = 7.2 Hz), 3.08 (t, 2H, J = 8.1 Hz), 4.20 (t, 2H, J = 8.0 Hz), 4.25 (q, 2H, J = 7.2 Hz), 7.29 (m, 2H), 7.33-7.41 (m, 3H), 7.43 (t, 1H, J = 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 44.2, 62.6, 63.0, 113.8 (t, J = 253 Hz), 114.1 (t, J = 23 Hz), 125.5, 127.3 (t, J = 11 Hz), 128.0, 128.8, 129.1, 130.8 (t, J = 2 Hz), 131.7, 132.0, 156.2, 163.5 (t, J = 35 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -101.4; HRMS (ESI) m/z calcd for $C_{15}H_{16}F_2NO_4$ $[M+H]^+$: 312.104191, found: 312.104265.

Ethyl 4-[(4R)-4-benzyl-2-oxo-oxazolidin-3-yl]-2,2-difluoro-3-phenyl-but-3-enoate (2o)

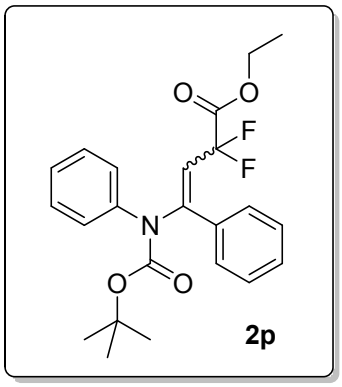
Yellow oil, 56% (72h, 4 equiv of bromodifluoroester). **2o** was isolated as a single Z-stereoisomer.



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 3H, J = 7.2 Hz), 2.34 (dd, 1H, J_1 = 10.5 Hz, J_2 = 13.7 Hz), 2.85 (dd, 1H, J_1 = 3.5 Hz, J_2 = 13.6 Hz), 3.69 (m, 1H), 3.98 (m, 2H), 4.24 (q, 2H, J = 7.1 Hz), 6.55 (m, 2H), 7.19 (m, 3H), 7.48 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 36.8, 54.9, 63.0, 65.7, 113.8 (t, J = 253 Hz), 115.5 (t, J = 22 Hz), 126.1 (dd, J_1 = 9 Hz, J_2 = 13 Hz), 127.2, 128.6, 128.8, 128.8, 129.1, 129.3, 131.1, 131.4 (d, J = 3 Hz), 134.4, 156.0, 163.4 (t, J = 35 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -103.9 (d, J = 254 Hz), -96.9 (d, J = 254 Hz); HRMS (ESI) m/z calcd for $C_{22}H_{22}F_2NO_4$ $[M+H]^+$: 402.151141, found: 402.151016; α_D(20°C) = +38.8° (c=0.6, CH_3CN).

Ethyl 4-(*N-tert*-butoxycarbonylanilino)-2,2-difluoro-4-phenyl-but-3-enoate (2p)

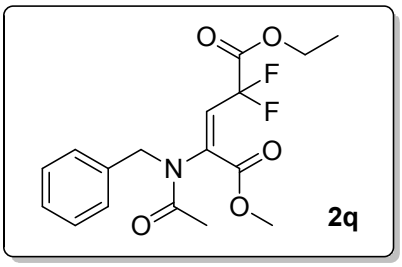
Amorphous yellowish solid, 67% (6h, 2 equiv of bromodifluoroester). **2p** was isolated as a single diastereoisomer.



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, 3H, J = 7.2 Hz), 1.22 (s, 9H), 3.86 (q, 2H, J = 7.2 Hz), 5.63 (t, 3H, J = 12.1 Hz), 7.23 (m, 1H), 7.38 (m, 7H), 7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 27.7, 62.7, 82.1, 112.6 (t, J = 244 Hz), 117.4 (t, J = 30 Hz), 126.2, 126.3, 128.1, 128.9 (t, J = 2 Hz), 129.1, 129.6, 136.1, 142.7, 150.7 (t, J = 10 Hz), 153.2, 162.9 (t, J = 34 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -89.3; HRMS (ESI) m/z calcd for $C_{23}H_{25}F_2NNaO_4$ $[M+Na]^+$: 440.164385, found: 440.164068.

Methyl (*E*)-2-(*N*-acetyl-benzylamino)-5-ethoxy-4,4-difluoro-5-oxo-pent-2-enoate (2q)

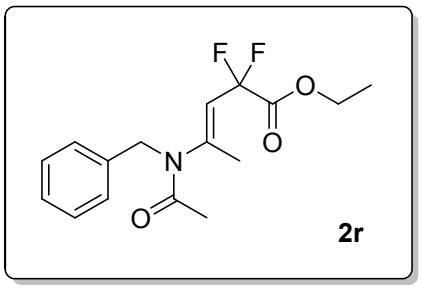
Yellow oil, 74% (22h, 2 equiv of bromodifluoroester). **2q** was isolated as a single diastereoisomer



^{1}H NMR (400 MHz, DMSO-d_6, 80°C): δ 1.17 (t, 3H, J = 7.1 Hz), 2.06 (s, 3H), 3.61 (s, 3H), 4.21 (q, 2H, J = 7.1 Hz), 4.78 (s, 2H), 6.17 (t, 1H, J = 12.8 Hz), 7.20-7.33 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 22.1, 22.5, 31.1, 52.6, 53.0 (br), 63.5, 63.6, 127.9, 127.9, 128.9, 129.0, 136.6, 137.2, 163.2, 170.2, 171.3, 207.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ -104.8; HRMS (ESI) m/z calcd for $C_{16}H_{18}F_2NO_3$ $[M+H]^+$: 310.124926, found: 310.125331.

Ethyl (*E*)-4-(*N*-acetylanilino)-2,2-difluoro-pent-3-enoate (2r)

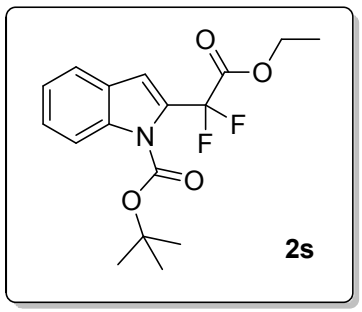
Yellow oil, 46% (24h, 2 equiv of bromodifluoroester). **2r** was isolated as a single Z-stereoisomer.



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.1 Hz), 2.00 (td, 3H, J_1 = 1.0 Hz, J_2 = 2.7 Hz), 2.12 (s, 3H), 4.30 (q, 2H, J = 7.1 Hz), 4.69 (s, 2H), 5.37 (tq, 1H, J_1 = 1.0 Hz, J_2 = 13.3 Hz), 7.23-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 18.2 (t, J = 2 Hz), 22.0, 49.3 (br), 63.3, 111.5 (t, J = 249 Hz), 122.8 (br t, J = 26 Hz), 127.7, 128.5, 128.7, 136.8, 147.4 (br), 163.2 (t, J = 34 Hz), 168.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -100.0; HRMS (ESI) m/z calcd for $C_{16}H_{20}F_2NO_3$ $[M+H]^+$: 312.140576, found: 312.140894.

***tert*-Butyl 2-(2-ethoxy-1,1-difluoro-2-oxo-ethyl)indole-1-carboxylate (2s)**

Colorless oil, 25% (23h, 2 equiv of bromodifluoroester).



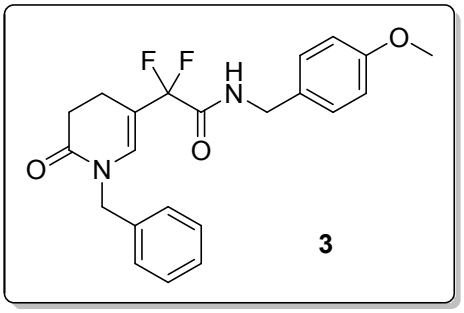
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.2 Hz), 1.68 (s, 9H), 4.34 (q, 2H, J = 7.1 Hz), 7.16 (s, 1H), 7.28 (m, 1H), 7.39 (m, 1H), 7.62 (br d, 1H, J = 7.8 Hz), 8.02 (dd, 1H, J_1 = 0.6 Hz, J_2 = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 28.1, 62.8, 85.8, 110.5 (t, J = 246 Hz), 112.0 (t, J = 7 Hz), 115.8, 122.0, 123.4, 127.9, 131.2 (t, J = 32 Hz), 136.4, 149.8, 162.7 (t, J = 33 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -97.8. HRMS (ESI) m/z calcd for $C_{17}H_{19}F_2NNaO_4$ $[M+Na]^+$: 362.117435, found: 362.117292.

4. Experimental and characterization of post-functionalization products

Aminolysis of fluorinated ester 2e

Ester **2e** (155 mg, 0.5 mmol, 1 equiv) was dissolved in methanol (5 mL) and 4-methoxybenzylamine (130 µL, 1 mmol, 2 equiv) was added dropwise at room temperature. After 5 hours, the mixture was diluted with dichloromethane (20 mL) and successively washed with 1N HCl (20 mL), water (20 mL) and brine (20 mL), then dried over magnesium sulfate and evaporated to dryness. The amide **3** was obtained sufficiently pure as an amorphous yellowish solid (186 mg, 93%).

2-(1-Benzyl-2-oxo-3,4-dihydropyridin-5-yl)-2,2-difluoro-*N*-[(4-methoxyphenyl)methyl]acetamide (3)



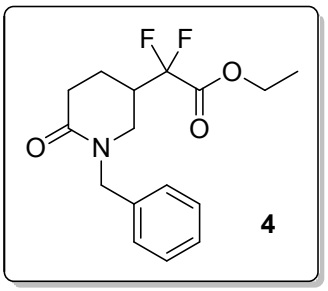
3

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (m, 2H), 2.68 (m, 2H), 3.83 (s, 3H), 4.44 (d, 2H, J = 5.8 Hz), 4.72 (s, 2H), 6.59 (br m, 2H), 6.89 (m, 2H), 7.16-7.27 (m, 4H), 7.30-7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (t, J = 2 Hz), 30.6, 43.2, 49.6, 55.3, 110.1 (t, J = 26 Hz), 114.3, 115.0 (t, J = 250 Hz), 127.7, 127.8, 128.7, 128.8, 129.3, 131.6 (t, J = 10 Hz), 136.4, 159.4, 163.0 (t, J = 31 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -104.2; HRMS (ESI) m/z calcd for $C_{22}H_{23}F_2N_2O_3$ $[M+H]^+$: 401.167125, found: 401.167294.

Hydrogenation of fluorinated ester 2e

Ester **2e** (155 mg, 0.5 mmol, 1 equiv) was dissolved in methanol (9 mL) in a hydrogenation vessel and palladium on carbon (5%; 80 mg) was added. The vessel was sealed, hydrogen (1 atm) was introduced and the mixture was stirred at room temperature for 5h. The hydrogen was then carefully evacuated and the suspension was filtered over celite and rinsed with methanol. The filtrate was evaporated and the crude residue was purified by flash chromatography using diethyl ether/pentane (1:3 to 1:1) as solvent of elution. The hydrogenated product **4** was obtained as colorless oil (96 mg, 62%).

Ethyl 2-(1-benzyl-6-oxo-3-piperidyl)-2,2-difluoro-acetate (4)

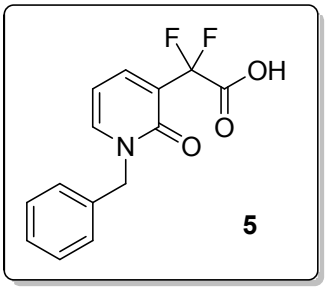


^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, 3H, J = 7.1 Hz), 1.80 (m, 1H), 2.01 (m, 1H), 2.47 (m, 1H), 2.55-2.71 (m, 2H), 3.31 (m, 2H), 4.31 (q, 2H, J = 7.1 Hz), 4.46 (d, 1H, J = 14.6 Hz), 4.77 (d, 1H, J = 14.7 Hz), 7.23-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 20.4 (t, J = 4 Hz), 30.8, 38.7 (t, J = 23 Hz), 45.0 (t, J = 5 Hz), 50.3, 63.3, 115.4 (t, J = 254 Hz), 127.6, 128.1, 128.7, 136.5, 163.1 (t, J = 32 Hz), 168.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -110.8 (d, J = 262 Hz), -113.7 (d, J = 262 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{20}F_2NO_3$ $[M+H]^+$: 312.140576, found: 312.140892.

Hydrolysis of fluorinated ester 2m

Ester **2m** (615 mg, 2 mmol, 1 equiv) was placed in methanol (6 mL) and 1M aqueous potassium carbonate (6 mL, 6 mmol, 3 equiv) was added. The reaction mixture was stirred at room temperature for 30 min then carefully poured in 1M HCl until pH reached 1. The mixture was then extracted three times with ethyl acetate; the organic layers were gathered, washed with brine, dried over magnesium sulphate and evaporated to dryness. The resulting solid was triturated in petroleum ether, filtered and dried. The carboxylic acid **5** was obtained as a yellow solid (469 mg, 84%).

2-(1-Benzyl-2-oxo-3-pyridyl)-2,2-difluoro-acetic acid (5)



^{1}H NMR (400 MHz, DMSO-d_6): δ 5.14 (s, 2H), 6.43 (t, 1H, J = 6.9 Hz), 7.26-7.39 (m, 5H), 7.84 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.0 Hz), 8.05 (dd, 1H, J_1 = 1.6 Hz, J_2 = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 51.7, 105.3, 112.3 (t, J = 246 Hz), 123.9 (t, J = 24 Hz), 128.2, 129.1, 137.1, 138.0 (t, J = 6 Hz), 142.3, 159.2 (t, J = 5 Hz), 164.2 (t, J = 32 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ -104.7; HRMS (ESI) m/z calcd for $C_{14}H_{12}F_2NO_3$ $[M+H]^+$: 280.077976, found: 280.077901.

5. Mechanistic studies (HRMS)

Figure 1: HRMS monitoring of the coupling reaction on enamide 1a

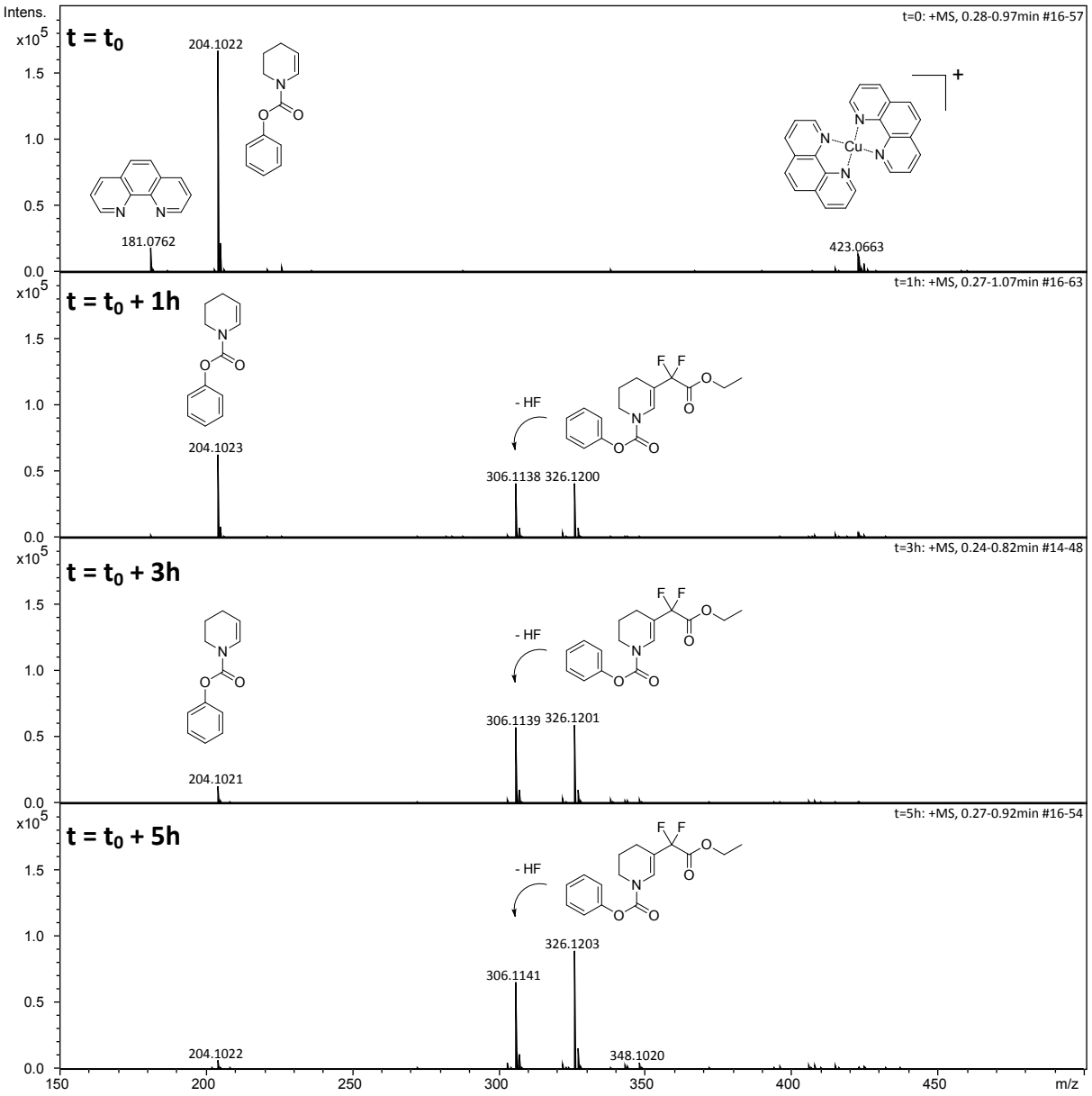
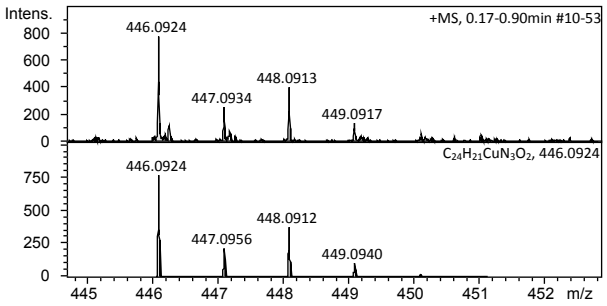
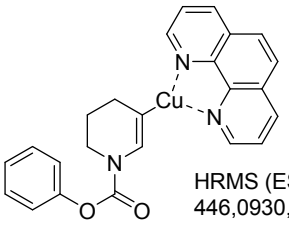


Figure 2: Intermediate III observed by HRMS (t = t_0 + 30 min)





HRMS (ESI) m/z calcd for $C_{24}H_{21}CuN_3O_2$ $[M+H]^+$: 446,0930, found: 446,0924.