EurJOC
European Journal of Organic Chemistry

Full Papers
doi.org/10.1002/ejoc.202100040

Chemistry Europe
European Chemical Societies Publishing

Rh(III)-Catalyzed C–H Activation/Annulation of Aryl Hydroxamates with CF_3-Containing α-Propargyl α-Amino Acid Derivatives

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A series of new orthogonally protected α-CF_3-substituted α-amino carboxylates, and α-amino phosphonates decorated with pharmacophore isoquinolone core has been elaborated through the Rh(III)-catalyzed C–H activation/annulation of aryl hydroxamates with propargyl-containing α-amino acid derivatives and their phosphorus analogues.

Introduction

Isoquinolone and its derivatives are important nitrogen heterocycles found in various natural products, biologically active molecules, and pharmaceuticals[1] with a broad spectrum of important properties, such as anti-inflammatory, antidiabetic, antiviral, and antitumor activities (Figure 1). They are also widely used as key intermediates in a variety of organic transformations to access more potent bioactive molecules.[2] Among synthetic routes to isoquinoline core,[3] metal-catalyzed tandem C–H activation/annulation of aromatic amides with alkynes under chelation control of appropriate directing group has become a powerful strategy for constructing isoquinolone skeletons from cheap starting materials in step- and atom-economical manner.[4] Particular attention has been focused on *O*-substituted aryl hydroxamates as the amide component, in which the hydroxamate moiety can act both as a directing group and an internal oxidant,[5] often displaying increased reactivity under mild conditions. This redox-neutral annulation of alkynes with the aryl hydroxamates has shown to proceed *via* the C–N bond reductive elimination of a 7-membered metallocycle intermediate and a subsequent N–O bond oxidative addition followed by protonolysis to afford free NH isoquinolones suitable for further derivatization.[6,7]

Over the last two decades, the fluorine chemistry has become a major area of multidisciplinary research modernizing healthcare, food, and energy industries. The remarkable reactivity, physicochemical and biological properties of fluorinated compounds are widely used today for the development of innovative technologies.[8]

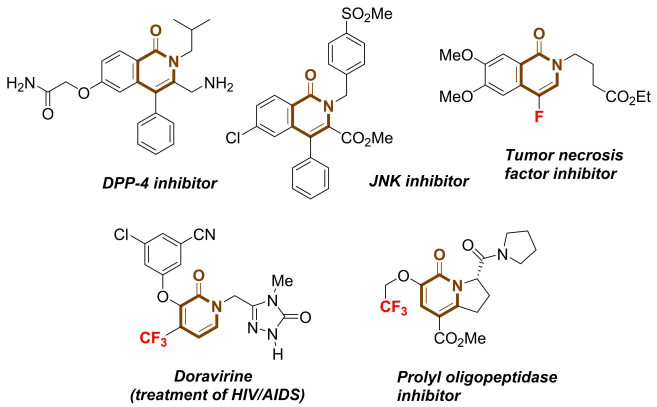

Figure 1. Pharmaceutically relevant isoquinolones and related heterocycles.

The most prominent area of fluorine application is the design of new pharmaceuticals *via* selective incorporation of fluorine functionalities into biologically relevant compounds. The main advantages of such a modification include enhanced solubility, bioavailability, and conformational and metabolic stability. Notably, more than 50% of extremely popular drugs or formulations contain at least one fluorine atom.[9] In addition, the exceptional NMR properties of fluorine nuclei are often used as an efficient technique for the elucidation of metabolic processes, mainly, due to the relatively large range of chemical shift values, which gives a possibility to detect even minor differences in the ^{19}F label environment. This phenomenon has found application in magnetic resonance imaging (MRI) and peptide/protein engineering.[10] In the field of amino acids and peptides, special attention is focused on α-amino acids with fluoromethyl groups in the α-position due to their ability to function as highly selective inhibitors of pyridoxal phosphate-dependent enzymes exhibiting a range of interesting biological properties.[11] Therefore, the development of new representa-

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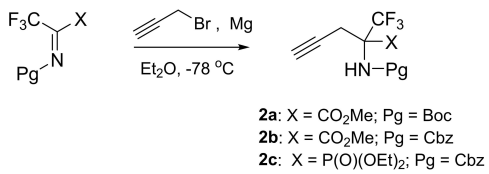
Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202100040

tives of α-fluoromethyl-α-amino acids is of great interest. Here we wish to disclose a convenient pathway to the novel α-CF_3-α-amino acid derivatives and their phosphorus analogues decorated with pharmacophore isoquinolone core *via* intermolecular Rh(III)-catalyzed C–H activation/annulation of aryl amides with α-CF_3-substituted α-propargyl-α-amino carboxylates and α-propargyl-α-amino phosphonates. To the best of our knowledge, any metal-catalyzed annulation reactions of acetylene-containing α-amino acid derivatives have not been reported before.

Results and discussion

Our continuous interest in the development of efficient metal-catalyzed methods for the preparation of diverse fluorinated compounds including amino acid derivatives[12] prompted us to explore feasibility of cyclization of N-OPiv benzamides with terminal alkynes under Rh(III)-catalysis. The choice of the pivalate derivatives was based on the fact that the pivalate group is one of the best directing and leaving groups in transformations of this type.[5a] The starting propargylic α-amino acid derivatives **2a–c** were easily synthesized *via* the previously described protocol,[13] that included an addition of corresponding Grignard reagent to the orthogonally protected α-imino carboxylates and α-imino phosphonate (Scheme 1).



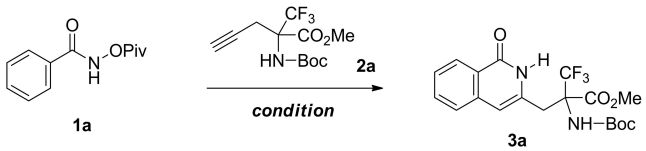
Scheme 1. Synthesis of starting CF_3-substituted α-propargyl-α-amino carboxylates **2a**,**b** and phosphonate **2c**.

At the beginning of our studies, phenyl hydroxamate **1a** was chosen as a model substrate to react with 1.0 equiv. of propargylic amino ester **2a** for the screening of optimal conditions for the annulation (Table 1). Initially $[Cp^*RhCl_2]_2$/CsOAc system was tested as has shown be competent catalyst for these transformations.[6] Thus, we found that the reaction performed in the presence of 1 mol% $[Cp^*RhCl_2]_2$ and 2.0 equiv. of cesium acetate in methanol at ambient temperature for 2 h to afford the desired amino acid derivative **3a** in 63% NMR-yield (Table 1, entry 1). The reaction revealed not the full conversion of the starting acetylene component. The prolonged reaction time did not result in a better yield of the product. The sequential increase of the catalyst loading up to 3 mol% and the change MeOH for trifluoroethanol (TFE) lead to full conversion of **2a** and quantitative formation of **3a** (entry 5). A further variation of the base and the solvent gave slightly worse results.

With these optimized conditions in hand, different aryl hydroxamates were involved in C–H activation/annulation reaction with Boc- and Cbz-protected propargylic amino ester **2a**,**b** (Scheme 2). As a result, a series of the corresponding isoquinolinone-containing α-CF_3-amino carboxylates were synthesized in good yields. The nature of the substituents in *para*-position of the hydroxamate component did not significantly affect the outcome of the reaction in all investigated cases. In the case of *meta*-methoxy substituted hydroxamate the reaction leads to formation of inseparable mixture of two corresponding regioisomers (**3ia** and **3ib**, **3ja** and **3jb**). It is noteworthy that the methyl group placed in *ortho*-position completely suppresses the C–H activation process (**3k** and **3l**). The similar phenomenon was previously found for the reaction with internal acetylenes.[2d]

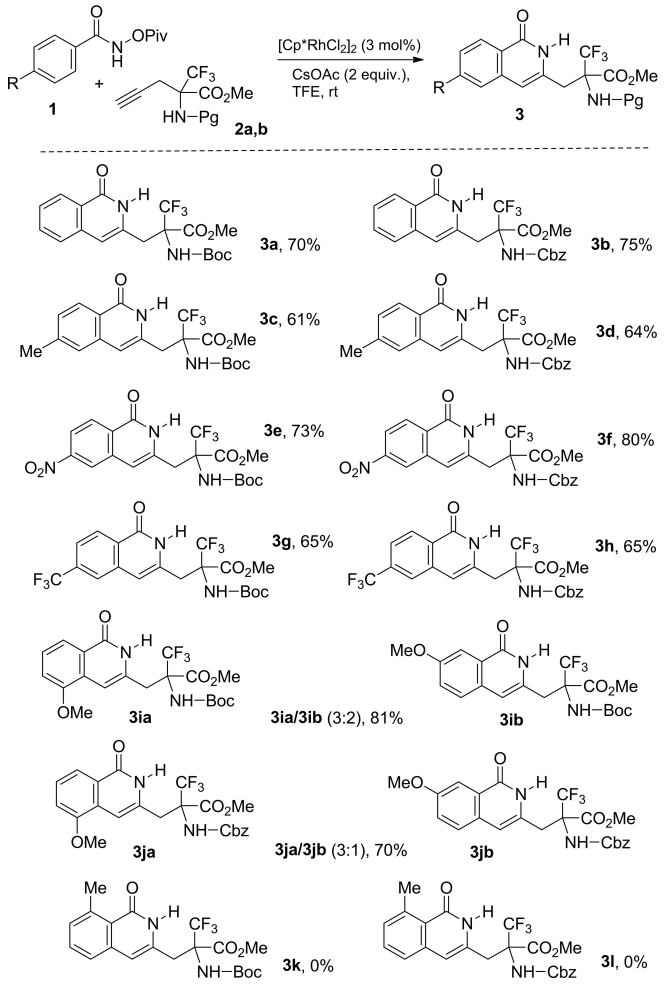
To get some insight into the mechanism we performed a series of experiments with deuterated compounds. The reversibility of the C–H activation stage is known from the results obtained if the reaction is carried out under the same

Table 1. Optimization of C–H activation/annulation reaction.[a]

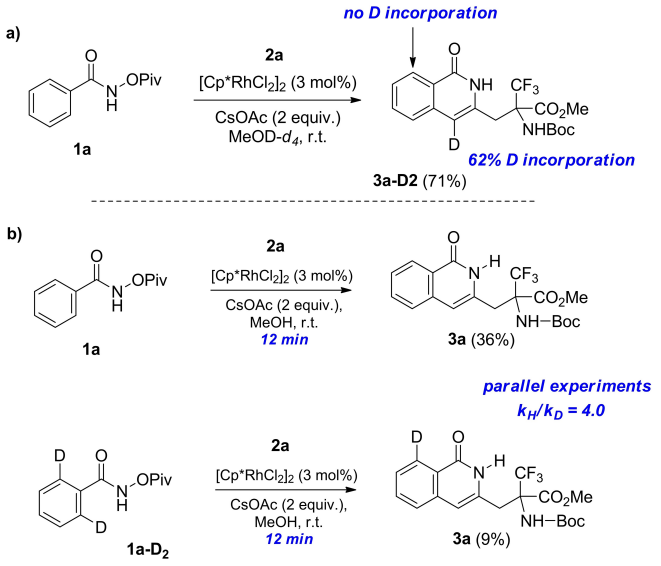


Entry	Catalyst [mol%]	Solvent	Base (equiv.)	Yield[b] [%]
1	$[Cp^*RhCl_2]_2$ (1)	MeOH	CsOAc (2)	63
2	$[Cp^*RhCl_2]_2$ (2)	MeOH	CsOAc (2)	78
3	$[Cp^*RhCl_2]_2$ (3)	MeOH	CsOAc (2)	90
4	$[Cp^*RhCl_2]_2$ (3)	MeOH	CsOAc (1)	65
5	$[Cp^*RhCl_2]_2$ (3)	TFE	CsOAc (2)	100 (70[c])
6	$[Cp^*RhCl_2]_2$ (3)	TFE	NaOAc (2)	68
7	$[Cp^*RhCl_2]_2$ (3)	TFE	KOAc (2)	91
8	$[Cp^*RhCl_2]_2$ (3)	TFE	CsOAc (1.5)	89
9	$[Cp^*RhCl_2]_2$ (3)	THF	CsOAc (2)	77
10	$[Cp^*RhCl_2]_2$ (3)	toluene	CsOAc (2)	62
11	–	TFE	CsOAc (2)	NR
12	$[Cp^*RhCl_2]_2$ (5)	TFE	–	NR

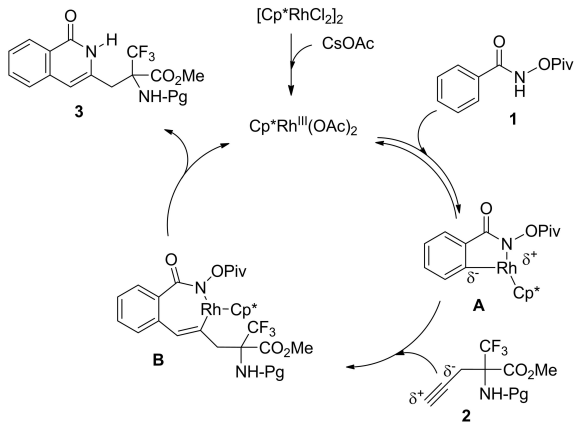
[a] Reagents and conditions: phenyl hydroxamate **1a** (0.2 mmol), acetylene **2a** (0.2 mmol), solvent (3 ml), r.t. [b] Determined by ^{19}F NMR spectroscopy. [c] Isolated yield.



Scheme 2. C–H activation/annulation of aryl hydroxamates with α-propargyl-α-amino carboxylates **2a,b**.



Scheme 3. Kinetic isotope effect studies.



Scheme 4. Plausible mechanism.

conditions but in deuterated solvent and without the acetylene component.[14] In the presence of the acetylene **2a** we have found no deuterium incorporation in the position 8 of the isoquinolone product that may suggest either the fast insertion of acetylene in C–H activated hydroxamate or irreversibility of the C–H activation step in the presence of **2a** (Scheme 3a). The incorporation of deuterium at position 4 may be rationalized by the fact that acetylene **2a** undergoes deuterium exchange on the course of the reaction that was confirmed by independent experiment (see Supporting Information). After that, a kinetic isotope effect was measured on the basis of the reaction of *ortho*-deuterated phenyl hydroxamate **1a-D$_2$**[14a,15] with **2a** (Scheme 3b).

The observed KIE value ($k_H/k_D = 4.0$) indicates that cleavage of the C–H bond is probably involved in the rate-limiting step (for details see Supporting Information).

Following the literature precedents[6] and above mechanistic experiments, a plausible reaction mechanism of this transformation is depicted in Scheme 4. After dissociation of the rhodium dimer, ligand exchange of the monomer with the present cesium salts provides a rhodium(III)-carboxylate species. Precomplexation to the directing N-pivaloyloxy amide moiety is followed by C–H activation to form rhodacyle **A**; C–H activation is a slow step in the catalytic cycle and is reversible in the absence and irreversible in the presence of acetylene **2**. The regioselective insertion of the alkyne triple bond into the C–Rh bond provides a seven-membered rhodacycle intermediate **B**. The observed selectivity can be probably explained by the coordination of Rh with the donor atom of alkyne. Next, a concerted or stepwise C–N bond forming/N–O bond cleaving event occurs, affording the annulation product **3**, and releasing the Rh(III) catalyst.

All synthesized compounds were fully characterized by physicochemical methods. In addition, a single crystal of good quality for X-ray analysis from **3f** was obtained (Figure 2).

Taking into account that α-amino phosphonates are the structural mimics of α-amino acids exhibiting a broad spectrum of remarkable biological properties including antibacterial, antiviral, anticancer, and some other types of bioactivity,[16] we

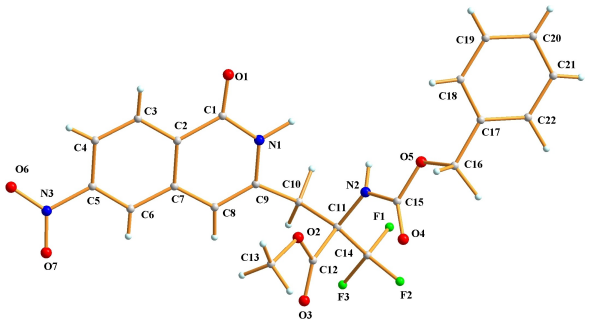
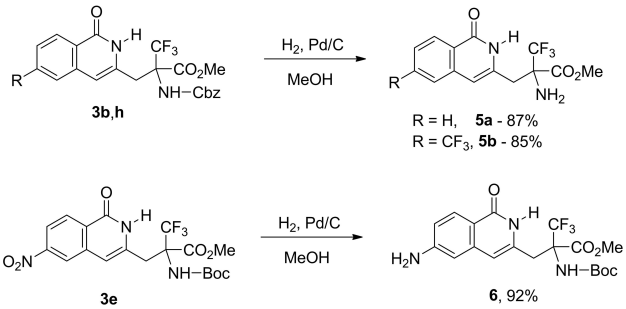


Figure 2. X-ray structure of **3 f** (CCDC 2039218).

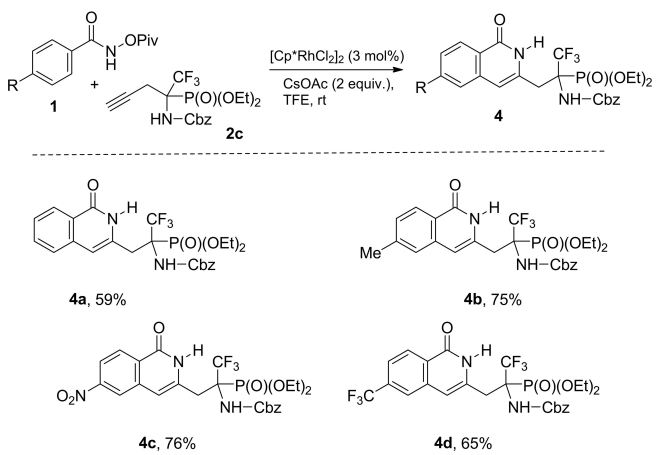


Scheme 6. Hydrogenation of **3 b**,**h and 3 e**.

checked the reactivity of α-CF_3-α-amino phosphonate **2 c** in the annulation process with the aryl hydroxamates. Phosphonate **2 c** turned out to demonstrate comparable to carboxylates **2 a**,**b** reactivity towards different aryl hydroxamates under found conditions yielding the corresponding α-amino phosphonates **4 a**–**d** in good yields (Scheme 5).

In general, the NMR yields of **3** and **4** exceeded 98% (determined by 19F NMR spectroscopy) in all studied reactions; however, moderate yields in some cases were caused by purification to get analytically pure samples using re-crystallization.

To demonstrate feasibility for the further synthetic application of the compounds obtained, *e.g.* in peptide synthesis or other useful derivatizations, we removed Cbz-protecting group of **3 b** and **3 h** and reduced nitro group of **3 e** by standard Pd-catalyzed hydrogenation. Both reactions proceeded smoothly in methanol at room temperature to afford the corresponding products **5 a**,**b** and **6** in high yields without any additional purification (Scheme 6).



Scheme 5. C–H activation/annulation of aryl hydroxamates with α-propargyl-α-amino phosphonate **2 c**.

Conclusion

A convenient synthetic approach to the novel α-CF_3-substituted α-amino carboxylic and α-amino phosphonic acid derivatives decorated with the pharmacophore isoquinolone core has been developed *via* the Rh(III)-catalyzed C–H activation/annulation of the aryl hydroxamates with the propargyl-containing α-amino acid derivatives and their phosphorus analogues. The reaction represents the first example of the metal-catalyzed annulation of acetylene amino acids derivatives with aryl amides. The compounds obtained can be regarded as promising drug candidates. Their biological activity is under current investigation and to be published somewhere in due course.

Experimental Section

General information

All solvents used in the reactions were freshly distilled from appropriate drying agents before use. All other reagents were distilled if necessary. Analytical TLC was performed with Merck silica gel 60 F 254 plates; visualization was accomplished with UV light or spraying with $Ce(SO_4)_2$ solution in 5% H_2SO_4. Chromatography was carried out using Merck silica gel (Kieselgel 60, 0.063–0.200 mm) and petroleum ether/ethyl acetate as an eluent. The NMR spectra were obtained with Bruker AV-400 and AV-500 spectrometers operating at 400, and 500 MHz, respectively, for ^1H (TMS reference), at 126 for ^{13}C, and at 376 MHz for ^{19}F (CCl_3F reference) and 161 MHz for ^{31}P (H_3PO_4 reference). IR spectra were recorded on a Shimadzu IR Prestige 21 Spectrometer. Spectra were measured on the ZnSe single reflection ATR plate (ATR-attenuated total reflectance). High resolution mass spectra (HRMS) were measured on a Bruker maXis q-TOF instrument equipped with electrospray ionization (ESI) source.

General procedure for C–H activation/annulation of aryl hydroxamates. A dried 10 mL Schlenk tube equipped with a magnetic stirrer was charged with a corresponding acetylene (0.1 g, 0.3 mmol), TFE (3 mL), the corresponding aryl hydroxamate (0.06 g, 0.3 mmol), $[Cp^*RhCl_2]_2$ (5.6 mg, 9.1 μmol) and CsOAc (0.12 g, 0.6 mmol) under Ar. The reaction mixture was stirred at room temperature for 2.5–3 h until the completion of the reaction monitored by TLC. Then water (7 mL) was added to a residue and the aqueous mixture was extracted with ethyl acetate (3 x 7 mL). The organic layer was dried over $MgSO_4$, filtered from the drying agent, and evaporated to dryness. The residue was purified by

recrystallization (eluent petroleum ether/ethyl acetate) to give the desired product.

Methyl 2-(*tert*-butoxycarbonylamino)-3,3,3-trifluoro-2-((1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3a). Yield 70% as a white solid (eluent petroleum ether/ethyl acetate = 3/1); m.p. 182–184 °C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ = 11.07 (s, 1 H, NH), 8.15 (d, J = 7.8 Hz, 1 H, Ar, 1 H, NH), 7.69 (t, J = 7.5 Hz, 1 H, Ar), 7.59 (d, J = 8.0 Hz, 1 H, Ar), 7.48 (t, J = 7.6 Hz, 1 H, Ar), 6.39 (s, 1 H, Ar), 3.57 (s, 3 H, OCH_3), 3.26 (d, J = 14.3 Hz, 1 H, CH_2), 3.14 (d, J = 15.0 Hz, 1 H, CH_2), 1.38 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 165.8, 162.6, 154.4, 137.9, 134.8, 133.0, 126.9, 126.8, 126.6, 125.2, 124.6 (q, J = 287.5 Hz, CF_3), 106.8, 80.3, 65.0 (q, J = 26.5 Hz, $>C<$), 52.8, 34.7, 28.3 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.26 (s, 3 F, CF_3) ppm. IR (ATR): $\nu = cm^{-1}$ 3242 (M), 2926 (M), 1757 (M), 1727 (M), 1666 (M), 1634 (M), 1555 (M), 1534 (M), 1494 (M), 1482 (M), 1450 (M), 1434 (M), 1400 (W), 1366 (M), 1317 (M), 1275 (M), 1205 (M), 1159 (M), 1078 (M), 1023 (M), 997 (M), 881 (M), 758 (M). HRMS (ESI) *m/z* calcd. for $C_{19}H_{22}F_3N_2O_5$ $(M+H)^+$ 415.1481, found 415.1475.

Methyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-((1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3b). Yield 75% as a white solid (eluent petroleum ether/ethyl acetate = 3/1); m.p. 168–169 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 10.11 (s, 1 H, NH), 8.26 (d, J = 8.0 Hz, 1 H, Ar), 7.71–7.67 (m, 1 H, Ar), 7.54–7.48 (m, 2 H, Ar, 1 H, NH), 7.35 (s, 5 H, Ar), 6.45 (s, 1 H, Ar), 5.12 (d, J = 12.4 Hz, 1 H, CH_2), 5.05 (d, J = 12.3 Hz, 1 H, CH_2), 3.79 (s, 3 H, OCH_3), 3.71 (d, J = 14.9 Hz, 1 H, CH_2), 3.56 (d, J = 14.8 Hz, 1 H, CH_2) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ = 165.3, 163.4, 154.8, 138.0, 136.3, 134.1, 132.7, 128.3, 127.9, 127.8, 126.8, 126.6, 126.3, 124.8, 124.2 (q, J = 285.5 Hz, CF_3), 107.7, 66.6, 65.4 (q, J = 27.4 Hz, $>C<$), 52.6, 34.2 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.18 (s, 3 F, CF_3) ppm. IR (ATR): $\nu = cm^{-1}$ 3244 (M), 2923 (M), 1750 (M), 1732 (M), 1637 (S), 1606 (S), 1500 (M), 1433 (M), 1393 (M), 1368 (M), 1322 (M), 1272 (M), 1253 (M), 1230 (M), 1158 (M), 1077 (M), 1022 (M), 1002 (M), 862 (M), 780 (M). Elemental analysis calcd (%) for $C_{22}H_{19}F_3N_2O_5$: C, 58.93; H, 4.27; N, 6.25; found: C, 58.95; H, 4.48; N, 6.14.

Methyl 2-(*tert*-butoxycarbonylamino)-3,3,3-trifluoro-2-((6-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3c). Yield 61% as a white solid (eluent petroleum ether/ethyl acetate = 3/1); m.p. 201–202 °C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ = 10.96 (s, 1 H, NH), 8.13 (s, 1 H, NH), 8.03 (d, J = 8.1 Hz, 1 H, Ar), 7.37 (s, 1 H, Ar), 7.29 (d, J = 8.2 Hz, 1 H, Ar), 6.31 (s, 1 H, Ar), 3.56 (s, 3 H, OCH_3), 3.23 (d, J = 14.6 Hz, 1 H, CH_2), 3.12 (d, J = 14.8 Hz, 1 H, CH_2), 2.42 (s, 3 H, CH_3), 1.39 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 165.8, 162.5, 154.4, 143.1, 138.1, 134.8, 128.3, 127.0, 126.1, 124.6 (q, J = 287.4 Hz, CF_3), 123.1, 106.6, 80.3, 65.0 (q, J = 26.7 Hz, $>C<$), 52.8, 34.8, 28.3, 21.7 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.26 (s, 3 F, CF_3) ppm. HRMS (ESI) *m/z* calcd. for $C_{20}H_{24}F_3N_2O_5$ $(M+H)^+$ 429.1637, found 429.1632.

Methyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-((6-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3d). Yield 64% as a white solid (eluent petroleum ether/ethyl acetate = 3/1); m.p. 179–180 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 10.19 (s, 1 H, NH), 8.14 (d, J = 8.1 Hz, 1 H, Ar), 7.51 (s, 1 H, NH), 7.34–7.33 (m, 5 H, Ar), 7.31–7.30 (m, 2 H, Ar), 6.37 (s, 1 H, Ar), 5.12 (d, J = 12.4 Hz, 1 H, CH_2), 5.04 (d, J = 12.3 Hz, 1 H, CH_2), 3.77 (s, 3 H, OCH_3), 3.70 (d, J = 15.3 Hz, 1 H, CH_2), 3.54 (d, J = 14.9 Hz, 1 H, CH_2), 2.46 (s, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 165.5, 162.5, 155.0, 143.1, 138.0, 136.6, 134.6, 128.9, 128.6, 128.5, 128.4, 126.9, 126.2, 124.5 (q, J = 283.7 Hz, CF_3), 123.1, 106.7, 66.7, 65.1 (q, J = 27.4 Hz, $>C<$), 53.0, 34.7, 21.7 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.17 (s, 3 F, CF_3) ppm. Elemental analysis calcd (%) for $C_{23}H_{21}F_3N_2O_5$: C, 59.74; H, 4.58; N, 6.06; found: C, 59.53; H, 4.77; N, 6.15.

Methyl 2-(*tert*-butoxycarbonylamino)-3,3,3-trifluoro-2-((6-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3e). Yield 73% as a yellow solid (eluent petroleum ether/ethyl acetate = 3/1); m.p. 201–202 °C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ = 11.50 (s, 1 H, NH), 8.54 (d, J = 2.3 Hz, 1 H, Ar), 8.35 (d, J = 8.8 Hz, 1 H, Ar), 8.18 (dd, J = 8.9, 2.4 Hz, 1 H, Ar, 1 H, NH), 6.64 (s, 1 H, Ar), 3.61 (s, 3 H, OCH_3), 3.28 (d, J = 14.8 Hz, 1 H, CH_2), 3.17 (d, J = 14.8 Hz, 1 H, CH_2), 1.38 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 165.6, 161.5, 154.4, 150.4, 138.5, 137.5, 129.3, 128.7, 126.6 (q, J = 288.2 Hz, CF_3), 122.1, 120.3, 106.7, 80.4, 64.9 (q, J = 24.2 Hz, $>C<$), 53.0, 34.8, 28.3 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.38 (s, 3 F, CF_3) ppm. HRMS (ESI) *m/z* calcd. for $C_{19}H_{21}F_3N_3O_7$ $(M+H)^+$ 460.1332, found 460.1326.

Methyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-((6-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3f). Yield 80% as a yellow solid (eluent petroleum ether/ethyl acetate = 3/1); m.p. 185–187 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 10.31 (s, 1 H, NH), 8.46 (d, J = 8.8 Hz, 1 H, Ar), 8.41 (d, J = 1.8 Hz, 1 H, Ar), 8.22 (dd, J = 8.8, 2.0 Hz, 1 H, Ar), 7.59 (s, 1 H, NH), 7.34–7.32 (m, 5 H, Ar), 6.65 (s, 1 H, Ar), 5.13 (d, J = 12.3 Hz, 1 H, CH_2), 5.07 (d, J = 12.3 Hz, 1 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.78 (d, J = 15.0 Hz, 1 H, CH_2), 3.63 (d, J = 14.9 Hz, 1 H, CH_2) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 165.3, 161.6, 155.0, 150.4, 138.4, 137.4, 136.6, 129.3, 128.9, 128.8, 128.6, 128.5, 124.5 (q, J = 285.0 Hz, CF_3), 122.1, 120.4, 106.7, 66.8, 65.0 (q, J = 24.8 Hz, $>C<$), 53.2, 34.6 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.26 (s, 3 F, CF_3) ppm.

Elemental analysis calcd (%) for $C_{22}H_{18}F_3N_3O_7$: C, 53.56; H, 3.68; N, 8.52; found: C, 53.35; H, 3.92; N, 8.30.

Methyl 2-(*tert*-butoxycarbonylamino)-3,3,3-trifluoro-2-((1-oxo-6-(trifluoromethyl)-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3g). Yield 65% as a white solid (eluent petroleum ether/ethyl acetate = 3/1); m.p. 207–208 °C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ = 11.39 (s, 1 H, NH), 8.33 (d, J = 8.4 Hz, 1 H, Ar), 8.17 (s, 1 H, NH), 8.07 (s, 1 H, Ar), 7.75 (d, J = 8.5 Hz, 1 H, Ar), 6.55 (s, 1 H, Ar), 3.60 (s, 3 H, OCH_3), 3.27 (d, J = 13.7 Hz, 1 H, CH_2), 3.17 (d, J = 15.0 Hz, 1 H, CH_2), 1.37 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 165.7, 161.8, 154.4, 138.1, 136.8, 132.9 (J = 31.6 Hz, C_{Ar}-CF_3), 128.5, 127.6, 124.6 (q, J = 287.6 Hz, CF_3), 124.3 (q, J = 273.2 Hz, C_{Ar}-CF_3), 124.0, 122.5, 106.5, 80.4, 64.9 (q, J = 23.1 Hz, $>C<$), 53.0, 34.8, 28.3 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −63.54 (s, 3 F, C_{Ar}-CF_3), −74.36 (s, 3 F, C_{Ar}-CF_3) ppm. Elemental analysis calcd (%) for $C_{20}H_{20}F_6N_2O_5$: C, 49.80; H, 4.18; N, 5.81; found: C, 49.61; H, 4.48; N, 5.64.

Methyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-((1-oxo-6-(trifluoromethyl)-1,2-dihydroisoquinolin-3-yl)methyl) propanoate (3h). Yield 65% as a white solid (eluent petroleum ether/ethyl acetate = 3/1); m.p. 199–200 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 11.46 (s, 1 H, NH), 8.67 (s, 1 H, NH), 8.33 (d, J = 8.3 Hz, 1 H, Ar), 8.02 (s, 1 H, Ar), 7.76 (d, J = 8.2 Hz, 1 H, Ar), 7.37 (s, 5 H, Ar), 6.54 (s, 1 H, Ar), 5.09 (d, J = 13 Hz, 1 H, CH_2), 5.05 (d, J = 12.4 Hz, 1 H, CH_2), 3.61 (s, 3 H, OCH_3), 3.32 (d, J = 15.3 Hz, 1 H, CH_2), 3.23 (d, J = 14.5 Hz, 1 H, CH_2) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 165.4, 161.8, 155.1, 138.0, 136.7, 136.6, 132.8 (q, J = 31.7 Hz, C_{Ar}-CF_3), 128.8, 128.7, 128.6, 128.5, 127.6, 124.5 (q, J = 286.5 Hz, CF_3), 124.3 (q, J = 271.0 Hz, C_{Ar}-CF_3), 124.0, 122.5, 106.5, 66.8, 65.0 (q, J = 24.3 Hz, $>C<$), 53.2, 34.6 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2SO$): δ = −61.44 (s, 3 F, CF_3), −72.31 (s, 3 F, CF_3) ppm. Elemental analysis calcd (%) for $C_{23}H_{18}F_6N_2O_5$: C, 53.50; H, 3.51; N, 5.42; found: C, 53.36; H, 3.57; N, 5.49.

Methyl 2-(*tert*-butoxycarbonylamino)-3,3,3-trifluoro-2-((5-methoxy-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3ia) and methyl 2-(*tert*-butoxycarbonylamino)-3,3,3-trifluoro-2-((7-methoxy-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3ib). Yield 83% as a off-white solid containing an inseparable 3:2 regioisom-

ers mixture 3ia and 3ib (eluent petroleum ether/ethyl acetate = 3/1); m.p. (mixture of regioisomers) 183–192 °C. Major regioisomer (3ia): ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 10.37 (s, 1 H, NH), 7.82 (d, J = 8.0 Hz, 1 H, Ar), 7.41 (t, J = 8.0 Hz, 1 H, Ar), 7.22 (d, J = 8.0 Hz, 1 H, Ar), 7.09 (s, 1 H, NH), 6.72 (s, 1 H, Ar), 3.96 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.72–3.63 (m, 1 H, CH_2), 3.56–3.47 (m, 1 H, CH_2), 1.34 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ = 165.9, 162.9, 154.5, 154.3, 133.5, 128.9, 127.9, 126.1, 124.2 (q, J = 287.8 Hz, CF_3), 122.7, 112.0, 107.2, 80.1, 65.6 (q, J = 26.9 Hz, >C<), 55.4, 52.6, 34.0, 27.3 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.17 (s, 3 F, CF_3) ppm. Elemental analysis calcd (%) for a $C_{20}H_{23}F_3N_2O_6$: C, 54.05; H, 5.22; N, 6.30; found: C, 54.42; H, 5.34; N, 6.24. Minor regioisomer (3ib): ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 10.32 (s, 1 H, NH), 7.68 (d, J = 2.7 Hz, 1 H, Ar), 7.55 (d, J = 8.7 Hz, 1 H, Ar), 7.30 (dd, J = 8.0, 2.7 Hz, 1 H, Ar), 7.09 (s, 1 H, NH), 6.44 (s, 1 H, Ar), 3.90 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.72–3.63 (m, 1 H, CH_2), 3.56–3.47 (m, 1 H, CH_2) 1.32 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ = 165.8, 162.8, 158.7, 154.3, 132.2, 131.7, 128.9, 126.3, 124.3 (q, J = 287.3 Hz, CF_3), 118.5 107.3, 101.5, 80.1, 65.5 (q, J = 27.1 Hz, >C<), 54.9, 52.7, 34.0, 27.3 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.28 (s, 3 F, CF_3) ppm. Elemental analysis calcd (%) for a $C_{20}H_{23}F_3N_2O_6$: C, 54.05; H, 5.22; N, 6.30; found: C, 54.42; H, 5.34; N, 6.24.

Methyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-((5-methoxy-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3ja) and methyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-((7-methoxy-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (3jb). Yield 70% as amorphous solid containing an inseparable 3:1 regioisomers mixture 3ja and 3jb (eluent petroleum ether/ethyl acetate = 3/1). Major regioisomer (3ja): ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ = 10.83 (s, 1 H, NH), 7.84 (d, J = 8.0 Hz, 1 H, Ar), 7.60 (s, 1 H, NH), 7.41 (t, J = 8.0 Hz, 1 H, Ar), 7.30–7.24 (m, 5 H, Ar), 7.22 (d, J = 7.9 Hz, 1 H, Ar), 6.77 (s, 1 H, Ar), 5.05 (d, J = 12.3 Hz, 1 H, CH_2), 4.96 (d, J = 12.4 Hz, 1 H, CH_2), 3.94 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.71–3.61 (m, 1 H, CH_2), 3.57–3.49 (m, 1 H, CH_2) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ = 165.4, 163.1, 154.9, 154.5, 136.2, 133.2, 128.4, 128.3, 127.9, 127.7, 127.0, 125.9, 124.3 (q, J = 285.4 Hz, CF_3), 122.7, 112.1, 107.1, 66.7, 65.8 (q, J = 27.3 Hz, >C<), 55.4, 52.5, 34.5 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.21 (s, 3 F, CF_3) ppm. Elemental analysis calcd (%) for a $C_{23}H_{21}F_3N_2O_6$: C, 57.74; H, 4.42; N, 5.86; found: C, 57.62; H, 4.34; N, 5.84. Minor regioisomer (3ja): ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ = 10.73 (s, 1 H, NH), 7.69 (d, J = 2.6 Hz, 1 H, Ar), 7.56 (s, 1 H, NH), 7.49 (t, J = 8.7 Hz, 1 H, Ar), 7.30–7.24 (m, 5 H, Ar, 1 H, Ar), 6.45 (s, 1 H, Ar), 5.05 (d, J = 12.4 Hz, 1 H, CH_2), 4.97 (d, J = 12.4 Hz, 1 H, CH_2), 3.88 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.67–3.61 (m, 1 H, CH_2), 3.57–3.49 (m, 1 H, CH_2) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ = 165.5, 163.0, 158.7, 154.5, 136.3, 132.0, 131.4, 128.8, 128.0, 127.9, 127.8, 126.1, 125.9, 124.3 (q, J = 285.4 Hz, CF_3), 118.4, 107.5, 101.8, 66.2, 65.8 (q, J = 27.3 Hz, >C<), 55.9, 52.6, 34.1 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −74.17 (s, 3 F, CF_3) ppm. Elemental analysis calcd (%) for a $C_{23}H_{21}F_3N_2O_6$: C, 57.74; H, 4.42; N, 5.86; found: C, 57.62; H, 4.34; N, 5.84.

Benzyl (2-(diethoxyphosphoryl)-1,1,1-trifluoro-3-(1-oxo-1,2-dihydroisoquinolin-3-yl)propan-2-yl)carbamate (4a). Yield 59% as a white solid (eluent petroleum ether/ethyl acetate = 1/1); m.p. 174–176 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 10.06 (s, 1 H, NH), 8.25 (d, J = 7.8 Hz, 1 H, Ar), 7.68 (t, J = 7.6 Hz, 1 H, Ar), 7.51–7.46 (m, 2 H, Ar), 7.46–7.36 (m, 5 H, Ar), 7.03 (d, J = 7.8 Hz, 1 H, NH), 6.52 (s, 1 H, Ar), 5.23 (d, J = 12.4 Hz, 1 H, CH_2), 5.17 (d, J = 12.4 Hz, 1 H, CH_2), 4.32–4.13 (m, 4 H, 2 OCH_2), 3.88 (dd, J = 20.5, 15.0 Hz, 1 H, CH_2), 3.66 (dd, J = 15.0, 8.7 Hz, 1 H, CH_2), 1.30 (t, J = 7.0 Hz, 3 H, CH_3), 1.20 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 162.4, 155.0, 138.0, 137.0, 135.0 (d, J = 9.0 Hz), 132.9, 128.9, 128.5, 128.4, 126.9, 126.7, 126.6, 125.2, 124.8 (q, J = 282.4 Hz, CF_3), 107.1, 66.5, 64.2 (d, J = 7.0 Hz), 63.5 (d, J = 7.0 Hz), 62.7 (dq, J = 152.5, 27.4 Hz, >C<), 33.2, 16.4–16.5 (m) ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −69.62 (s, 3 F, CF_3) ppm. ^{31}P NMR (161 MHz, $(CD_3)_2CO$): δ = 15.27 (s) ppm. IR (ATR): ν = cm^{-1} 3255 (M), 3202 (M), 2986 (M), 2926 (M), 1747 (M), 1732 (S), 1664 (S), 1644 (M), 1609 (M), 1546 (M), 1497 (M), 1475 (M), 1439 (M), 1297 (M), 1232 (S), 1192 (S), 1177 (S), 1040 (S), 1026 (S), 978 (M), 941 (M), 831 (S), 755 (S). Elemental analysis calcd (%) for $C_{24}H_{26}F_3N_2O_6P$: C, 54.76; H, 4.98; N, 5.32; found: C, 54.35; H, 4.92; N, 5.10.

Benzyl (2-(diethoxyphosphoryl)-1,1,1-trifluoro-3-(6-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)propan-2-yl)carbamate (4b). Yield 75% as a white solid (eluent petroleum ether/ethyl acetate = 1/1); m.p. 180–181 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 9.96 (s, 1 H, NH), 8.13 (d, J = 8.0 Hz, 1 H, Ar), 7.42–7.39 (m, 5 H, Ar), 7.31–7.24 (m, 2 H, Ar), 7.0 (s, 1 H, NH), 6.41 (s, 1 H, Ar), 5.24 (d, J = 11.8 Hz, 1 H, CH_2), 5.15 (d, J = 12.0 Hz, 1 H, CH_2), 4.29–4.14 (m, 4 H, 2 OCH_2), 3.91–3.81 (m, 1 H, CH_2), 3.66–3.61 (m, 1 H, CH_2), 2.46 (s, 3 H, CH_3), 1.30 (t, J = 6.8 Hz, 3 H, CH_3), 1.20 (t, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 162.4, 155.0, 142.9, 138.1, 137.0, 135.0 (d, J = 8.9 Hz), 128.9, 128.6, 128.5, 128.2, 126.9, 126.1, 124.8 (dq, J = 287.0, 4.8 Hz, CF_3), 123.0, 106.8, 66.4, 64.2 (d, J = 7.1 Hz), 63.6 (d, J = 7.1 Hz), 62.7 (dq, J = 152.5, 27.2 Hz, >C<), 33.1, 21.7, 16.4–16.5 (m) ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −69.55 (s, 3 F, CF_3) ppm. ^{31}P NMR (161 MHz, $(CD_3)_2CO$): δ = 15.28 (s) ppm. Elemental analysis calcd (%) for $C_{25}H_{28}F_3N_2O_6P$: C, 55.56; H, 5.22; N, 5.18; found: C, 55.21; H, 5.49; N, 5.09.

Benzyl (2-(diethoxyphosphoryl)-1,1,1-trifluoro-3-(6-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)propan-2-yl)carbamate (4c). Yield 76% as a yellow solid (eluent petroleum ether/ethyl acetate = 1/1); m.p. 202–204 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 11.32 (s, 1 H, NH), 8.37-8.36 (m, 1 H, Ar), 8.34 (s, 1 H, NH), 8.29 (d, J = 8.9 Hz, 1 H, Ar), 8.16 (dd, J = 8.8, 2.3 Hz, 1 H, Ar), 7.45–7.34 (m, 5 H, Ar), 6.68 (s, 1 H, Ar), 5.20 (d, J = 12.5 Hz, 1 H, CH_2), 5.14 (d, J = 12.5 Hz, 1 H, CH_2), 4.19–4.05 (m, 4 H, 2 OCH_2), 3.55 (dd, J = 15.1, 5.3 Hz, 1 H, CH_2), 3.38–3.32 (m, 1 H, CH_2 + $(CD_3)_2SO$), 1.20 (q, J = 7.0 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 161.4, 155.0, 150.4, 138.5, 137.4 (d, J = 8.7 Hz), 137.0, 129.3, 128.9, 128.6, 128.5, 128.4, 124.7 (dq, J = 286.8, 4.8 Hz, CF_3), 121.9, 120.2, 106.8, 66.5, 64.4 (d, J = 7.2 Hz), 63.7 (d, J = 7.1 Hz), 62.6 (dq, J = 152.5, 27.1 Hz, >C<), 33.1, 16.4–16.5 (m) ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ = −64.68 (s, 3 F, CF_3) ppm. ^{31}P NMR (161 MHz, $(CD_3)_2CO$): δ = 15.16 (s) ppm. Elemental analysis calcd (%) for $C_{24}H_{25}F_3N_3O_8P$: C, 50.44; H, 4.41; N, 7.35; found: C, 50.18; H, 4.62; N, 7.37.

Benzyl (2-(diethoxyphosphoryl)-1,1,1-trifluoro-3-(1-oxo-6-(trifluoromethyl)-1,2-dihydroisoquinolin-3-yl)propan-2-yl) carbamate (4d). Yield 65% as a white solid (eluent petroleum ether/ethyl acetate = 1/1); m.p. 177–178 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 11.24 (s, 1 H, NH), 8.31 (t, J = 10.0 Hz, 2 H, Ar), 7.85 (s, 1 H, NH), 7.75 (d, J = 8.5 Hz, 1 H, Ar), 7.33–7.45 (m, 5 H, Ar), 6.58 (s, 1 H, Ar), 5.20 (d, J = 12.5 Hz, 1 H, CH_2), 5.13 (d, J = 12.4 Hz, 1 H, CH_2), 4.21–4.02 (m, 4 H, 2 OCH_2), 3.55 (dd, J = 14.7, 4.8 Hz, 1 H, CH_2), 3.31 (d, J = 16.0 Hz, 1 H, CH_2), 1.20 (q, J = 6.8 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 161.7, 155.0, 138.1, 137.3, 137.2, 137.0, 132.8 (q, J = 32.0 Hz, C_{Ar}-CF_3), 128.8, 128.6, 128.5, 127.5, 124.8 (q, J = 285.0 Hz, CF_3), 124.3 (q, J = 271.0 Hz, C_{Ar}-CF_3), 123.9, 122.3, 106.6, 66.5, 64.3 (d, J = 7.0 Hz), 63.7 (d, J = 7.0 Hz), 62.7 (dq, J = 153.7, 27.0 Hz, >C<), 33.0, 16.4–16.5 (m) ppm. ^{19}F NMR (376 MHz, $(CD_3)_2SO$): δ = −61.42 (s, 3 F, CF_3), −67.75 (s, 3 F, CF_3) ppm. ^{31}P NMR (161 MHz, $(CD_3)_2SO$): δ = 14.59 (s) ppm. Elemental analysis calcd (%) for $C_{25}H_{25}F_6N_2O_6P$: C, 50.51; H, 4.24; N, 4.71; found: C, 50.21; H, 4.41; N, 4.41.

Typical procedure of hydrogenation. To a solution of corresponding unsaturated amine (0.13 g, 0.30 mmol) in methanol (20 mL) 10% Pd/C (1.61 mg, 0.15 µmol) was added and a slow stream of hydrogen was bubbled through the mixture at room temperature. When TLC indicated no starting material (about 3–10 h), the

mixture was filtered and the solvent was evaporated to dryness lead to the product without any purification.

Methyl 2-amino-3,3,3-trifluoro-2-((1-oxo-1,2-dihydro isoquinolin-3-yl)methyl)-propanoate (5a). Yield 87% as a white solid; m.p. 205–207 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): $\delta = 11.06$ (s, 1 H, NH), 8.14 (d, $J = 8.0$ Hz, 1 H, Ar), 7.68 (t, $J = 7.5$ Hz, 1 H, Ar), 7.60 (d, $J = 8.0$ Hz, 1 H, Ar), 7.46 (t, $J = 7.4$ Hz, 1 H, Ar), 6.37 (s, 1 H, Ar), 3.75 (s, 3 H, OCH_3), 3.24 (d, $J = 14.1$ Hz, 1 H, CH_2), 2.95 (d, $J = 14.1$ Hz, 1 H, CH_2), 2.70 (s, 2 H, NH_2) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): $\delta = 168.2$, 162.4, 138.1, 136.1, 132.9, 126.9, 126.7, 126.6, 125.3 (q, $J = 286.5$ Hz, CF_3), 125.2, 105.5, 65.7 (q, $J = 26.2$ Hz, $>C<$), 53.7, 35.8 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2SO$): $\delta = -76.38$ (s, 3 F, CF_3) ppm. IR (ATR): $\nu =$ cm^{-1} 3425 (M), 3335 (M), 2835 (M), 1738 (M), 1663 (S), 1638 (S), 1553 (M), 1502 (M), 1476 (M), 1440 (M), 1354 (M), 1250 (M), 1216 (M), 1175 (S), 1134 (M), 1006 (M), 972 (M), 902 (M), 846 (M), 759 (S). HRMS (ESI) *m/z* calcd. for $C_{14}H_{14}F_3N_2O_3$ $(M+H)^+$ 315.0957, found 315.0951.

Methyl 2-amino-3,3,3-trifluoro-2-((1-oxo-6-(trifluoromethyl)-1,2-dihydroisoquinolin-3-yl)methyl)propanoate (5b). Yield 85% as a white solid; m.p. 218–220 °C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): $\delta = 11.36$ (s, 1H, NH), 8.32 (d, $J = 8.4$ Hz, 1 H, Ar), 8.10 (s, 1 H, Ar), 7.73 (dd, $J = 8.4$, 1.8 Hz, 1 H, Ar), 6.53 (s, 1 H, Ar), 3.78 (s, 3 H, OCH_3), 3.26 (d, $J = 14.0$ Hz, 1 H, CH_2), 2.98 (d, $J = 14.1$ Hz, 1 H, CH_2), 2.69 (s, 2 H, NH_2) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): $\delta = 168.1$, 161.6, 138.2, 138.1, 132.7 (q, $J = 31.8$ Hz, C_{Ar}-CF_3), 128.5, 127.5, 125.3 (q, $J = 287.1$ Hz, CF_3), 124.3 (q, $J = 273.0$ Hz, C_{Ar}-CF_3), 124.1, 122.2, 105.2, 65.7 (q, $J = 26.4$ Hz, $>C<$), 53.9, 35.8 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2SO$): $\delta = -61.46$ (s, 3 F, CF_3), -76.42 (s, 3 F, CF_3) ppm. IR (ATR): $\nu =$ cm^{-1} 3412 (M), 3326 (M), 2916 (M), 2833 (M), 1750 (M), 1667 (S), 1643 (S), 1560 (M), 1471 (M), 1451 (M), 1359 (M), 1331 (M), 1303 (S), 1276 (M), 1221 (S), 1136 (S), 1071 (M), 923 (S), 899 (S), 848 (M), 790 (M), 735 (S). HRMS (ESI) *m/z* calcd. for $C_{15}H_{13}F_6N_2O_3$ $(M+H)^+$ 383.0830, found 383.0825.

Methyl 2-((6-amino-1-oxo-1,2-dihydroisoquinolin-3-yl)methyl)-2-(*tert*-butoxycarbonyl-amino)-3,3,3-trifluoro propanoate (6). Yield 92% as a white solid; m.p. 145–146 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): $\delta = 10.44$ (s, 1 H, NH), 8.09 (s, 1 H, NH), 7.79 (d, $J = 8.7$ Hz, 1 H, Ar), 6.68 (dd, $J = 8.7$, 2.1 Hz, 1 H, Ar), 6.46 (d, $J = 2.1$ Hz, 1 H, Ar), 6.04 (s, 1 H, Ar), 5.88 (s, 2 H, NH_2), 3.55 (s, 3 H, OCH_3), 3.14 (d, $J = 14.7$ Hz, 1 H, CH_2), 3.04 (d, $J = 14.7$ Hz, 1 H, CH_2), 1.39 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): $\delta = 165.9$, 162.4, 154.3, 153.0, 139.9, 134.3, 128.5, 124.6 (q, $J = 287.6$ Hz, CF_3), 115.3, 114.9, 106.3, 80.3, 65.0 (q, $J = 23.8$ Hz, $>C<$), 52.7, 34.7, 28.3, 21.5 ppm. ^{19}F NMR (376 MHz, $(CD_3)_2CO$): $\delta = -72.12$ (s, 3 F, CF_3) ppm. IR (ATR): $\nu =$ cm^{-1} 3372 (M), 3224 (M), 2974 (M), 1752 (M), 1714 (M), 1603 (S), 1498 (M), 1457 (M), 1436 (M), 1393 (M), 1368 (M), 1322 (M), 1253 (M), 1155 (M), 1078 (M), 1004 (M), 865 (M), 830 (M), 782 (M). HRMS (ESI) *m/z* calcd. for $C_{19}H_{23}F_3N_3O_5$ $(M+H)^+$ 430.1590, found 430.1584.

Deposition Number 2039218 (for **3f**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

This work was financially supported by the RFBR (N20-03-00481). NMR studies, spectral characterization and elemental analysis were performed with the support from the Ministry of Science and Higher Education of the Russian Federation using the equipment of the Center for Molecular Composition Studies of INEOS RAS. High resolution spectra were recorded in the Department of Structural Studies of Zelinsky Institute of Organic Chemistry, Moscow. The publication was also prepared with the support of the RUDN University Program 5-100.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amino phosphonates · Catalysis · C–H activation · Fluorinated amino acids · Isoquinolones

[1] a) T. Nagatsu, *Neurosci. Res.* **1997**, *29*, 99–111; b) K. Bhadra, G. S. Kumar, *Mini-Rev. Med. Chem.* **2010**, *10*, 1235–1247; c) A. Capasso, S. Piacente, N. De Tommasi, L. Rastrelli, C. Pizza, *Curr. Med. Chem.* **2006**, *13*, 807–812; d) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444–463; e) K. W. Bentley, *Nat. Prod. Rep.* **2005**, *22*, 249–268; f) L.-J. He, D.-L. Yang, S.-Q. Li, Y.-J. Zhang, Y. Tang, J. Lei, B. Frett, H.-K. Lin, H.-Y. Li, Z.-Z. Chen, Z.-G. Xu, *Bioorg. Med. Chem.* **2018**, *26*, 3899–3908; g) Z. Zhang, Z. You, R. T. Dobrowsky, T. Rick, B. S. J. Blagg, *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2701–2704.

[2] a) S. Guo, F. Wang, L. Sun, X. Zhang, X. Fan, *Adv. Synth. Catal.* **2018**, *360*, 2537–2541; b) B. Thirupataiah, G. S. Reddy, S. S. Ghule, J. S. Kumar, G. Mounika, K. A. Hossain, J. Mudgal, J. E. Mathew, G. G. Shenoy, K. V. L. Parsa, M. Pal, *Bioorg. Chem.* **2020**, *97*, 103691; c) S. Guo, L. Sun, F. Wang, X. Zhang, X. Fan, *J. Org. Chem.* **2018**, *83*, 12034–12043; d) B. L. Coles-Taylor, M. S. McCallum, J. Scott Lee, B. W. Michel, *Org. Biomol. Chem.* **2018**, *16*, 8639–8646; e) J.-Q. Wu, S.-S. Zhang, H. Gao, Z. Qi, C.-J. Zhou, W.-W. Ji, Y. Liu, Y. Chen, Q. Li, X. Li, H. Wang, *J. Am. Chem. Soc.* **2017**, *139*, 3537–3545; f) E. Salvati, L. Botta, J. Amato, F. Saverio Di Leva, P. Zizza, A. Gioiello, B. Pagano, G. Graziani, M. Tarsounas, A. Randazzo, E. Novellino, A. Biroccio, S. Cosconati, *J. Med. Chem.* **2017**, *60*, 3626–3635; g) Y. Wu, P. Sun, K. Zhang, T. Yang, H. Yao, A. Lin, *J. Org. Chem.* **2016**, *81*, 2166–2173.

[3] a) R. P. Korivi, Y.-C. Wu, C.-H. Cheng, *Chem. Eur. J.* **2009**, *15*, 10727–10737; b) C.-C. Liu, K. Parthasarath, C.-H. Cheng, *Org. Lett.* **2010**, *12*, 3518–3521; c) S. Pimparkar, M. Jeganmohan, *Chem. Commun.* **2014**, *50*, 12116–12119; d) X. Peng, W. Wang, C. Jiang, D. Sun, Z. Xu, C.-H. Tung, *Org. Lett.* **2014**, *16*, 5354–5357; e) W. Wang, X. Peng, X. Qin, X. Zhao, C. Ma, C.-H. Tung, *J. Org. Chem.* **2015**, *80*, 2835–2841.

[4] a) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744–746; b) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569; c) F. Wang, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5430–5433; d) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379–6382; *Angew. Chem.* **2011**, *123*, 6503–6506; e) L. Ackermann, A. V. Lygin, N. Hofmann, *Org. Lett.* **2011**, *13*, 3278–3281; f) B. Li, H. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2012**, *18*, 12873–12879; g) K. Parthasarathy, N. Senthilkumar, J. Jayakumar, C.-H. Cheng, *Org. Lett.* **2012**, *14*, 3478–3481; h) M. C. Reddy, R. Manikandan, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 6060–6062; i) V. Kanchupalli, R. K. Shukla, A. Singh, C. M. R. Volla, *Eur. J. Org. Chem.* **2020**, *2020*, 4494–4498.

[5] a) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457; b) B. Li, H. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2011**, *17*, 12573–12577; c) L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548–6551; d) B. Li, J. Ma, N. Wang, H. Feng, S. Xu, B. Wang, *Org. Lett.* **2012**, *14*, 736–739; e) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353; f) G. Song, X. Gong, X. Li, *J. Org. Chem.* **2011**, *76*, 7583–7589; g) M. Bian, L. Ma, M. Wu, L. Wu, H. Gao, W. Yi, C. Zhang, Z. Zhou, *ChemPlusChem* **2020**, *85*, 405–410.

[6] For Rh-catalyzed isoquinolone syntheses see selected examples: a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908–6909; b) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569; c) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744–746; d) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457; e) X. Xu, Y. Liu, C.-M. Park, *Angew. Chem. Int. Ed.* **2012**, *51*, 9372–9376; f) H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 19592–19595; g) J. R. Huckins, E. A. Bercot, O. R. Thiel, T.-L. Hwang, M. M. Bio, *J. Am. Chem. Soc.* **2013**, *135*, 14492–14495; h) D.-G. Yu, F. de Azambuja, F. Glorius, *Angew. Chem. Int. Ed.*

2014, *53*, 2754–2758; i) F. Wang, Z. Qi, Y. Zhao, S. Zhai, G. Zheng, R. Mi, Z. Huang, X. Zhu, X. He, X. Li, *Angew. Chem. Int. Ed.* **2020**, *59*, 13288–13294; j) J. Chen, L. Zhang, X. Zheng, J. Zhou, T. Zhong, C. Yu, *Synth. Commun.* **2020**, *50*, 1799–1805.

[7] For other metal-catalyzed isoquinolone syntheses, see selected examples: a) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379–6382; b) B. Li, H. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2011**, *17*, 12573–12577; c) B. Li, H. Feng, N. Wang, J. Ma, H. Song, S. Xu, B. Wang, *Chem. Eur. J.* **2012**, *18*, 12873–12879; d) M. Deponti, S. I. Kozhushkov, D. S. Yufit, L. Ackermann, *Org. Biomol. Chem.* **2013**, *11*, 142–148; e) C. Kornhaa, C. Kuper, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1619–1624; f) B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 7896–7899; g) H. Zhong, D. Yang, S. Wang, J. Huang, *Chem. Commun.* **2012**, *48*, 3236–3238; h) Y. Kajita, S. Matsubara, T. Kurahashi, *J. Am. Chem. Soc.* **2008**, *130*, 6058–6059; i) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955; j) T. Miura, M. Yamauchi, M. Murakami, *Org. Lett.* **2008**, *10*, 3085–3088; k) J. Yang, L. Wu, H. Xu, H. Gao, Z. Zhou, W. Yi, *Org. Lett.* **2019**, *21*, 9904–9908; l) M. Liu, J.-L. Niu, D. Yang, M.-P. Song, *J. Org. Chem.* **2020**, *85*, 4067–4078.

[8] a) G. Haufe, F. Leroux, *Fluorine in Life Sciences: Pharmaceuticals*, Medicinal Diagnostics, and Agrochemicals: Progress in Fluorine Science Series, (Eds. : G. Haufe, F. Leroux), 1st ed., Academic Press, **2018**, pp. 1–686; b) H. Groult, F. Leroux, A. Tressaud, *Modern Synthesis Processes and Reactivity of Fluorinated Compounds*: Progress in Fluorine Science, (Eds.: H. Groult, F. Leroux, A. Tressaud), Elsevier, Amsterdam, 1st ed., **2016** pp. 1–760; c) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797–11819.

[9] a) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880; b) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832–2842; c) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, F. D. Toste, *Chem. Rev.* **2018**, *118*, 3887–3964.

[10] a) H. Chen, S. Viel, F. Ziarelli, L. Peng, *Chem. Soc. Rev.* **2013**, *42*, 7971–7979; b) E. N. G. Marsh, Y. Suzuki, *ACS Chem. Biol.* **2014**, *9*, 1242–1250; c) N. C. Yoder, K. Kumar, *Chem. Soc. Rev.* **2002**, *31*, 335–341; d) M. Salwiczek, E. K. Nyakatura, U. I. M. Gerling, S. Ye, B. Koksch, *Chem. Soc. Rev.* **2012**, *41*, 2135–2171; e) E. N. G. Marsh, *Acc. Chem. Res.* **2014**, *47*, 2878–2886; f) I. Tirotta, V. Dichiarante, C. Pigliacelli, G. Cavallo, G. Terraneo, F. B. Bombelli, P. Metrangolo, G. Resnati, *Chem. Rev.* **2015**, *115*, 1106–1129; g) L. Cai, S. Lu, V. W. Pike, *Eur. J. Org. Chem.* **2008**, *2008*, 2853–2873; h) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci.* **2014**, *5*, 4545–4553.

[11] a) P. Bey, F. Gerhart, V. Van Dorsselaer, C. Danzin, *J. Med. Chem.* **1983**, *26*, 1551–1556; b) X.-L. Qiu, W.-D. Meng, F.-L. Qing, *Tetrahedron* **2004**, *60*, 6711–6745; c) R. Smits, C. D. Cadicamo, K. Burger, B. Koksch, *Chem. Soc. Rev.* **2008**, *37*, 1727–1739; d) J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes, B. Koksch, *Chem. Rev.* **2019**, *119*, 10718–10801; e) H. Mei, J. Han, S. White, D. J. Graham, K. Izawa, T. Sato, S. Fustero, N. A. Meanwell, V. A. Soloshonok, *Chem. Eur. J.* **2020**, *26*, 11349–11390.

[12] a) S. N. Osipov, A. S. Golubev, N. Sewald, K. Burger, *Tetrahedron Lett.* **1997**, *38*, 5965–5966; b) M. Eckert, F. Monnier, G. T. Shchetnikov, I. D. Titanyuk, S. N. Osipov, S. Dérien, P. H. Dixneuf, *Org. Lett.* **2005**, *7*, 3741–3743; c) G. T. Shchetnikov, S. N. Osipov, C. Bruneau, P. H. Dixneuf, *Synlett* **2008**, *4*, 578–582; d) M. Eckert, S. Moulin, F. Monnier, I. D. Titanyuk, S. N. Osipov, T. Roisnel, S. Derien, P. H. Dixneuf, *Chem. Eur. J.* **2011**, *17*, 9456–9462; e) A. K. Mailyan, I. M. Krylov, C. Bruneau, P. H. Dixneuf, S. N. Osipov, *Eur. J. Org. Chem.* **2013**, 5353–5363; f) D. V. Vorobyeva, A. S. Peregudov, G.-V. Röschenthaler, S. N. Osipov, *J. Fluorine Chem.* **2015**, *175*, 60–67; g) A. N. Philippova, D. V. Vorobyeva, F. Monnier, S. N. Osipov, *Org. Biomol. Chem.* **2020**, *18*, 3274–3280.

[13] a) G. T. Shchetnikov, A. S. Peregudov, S. N. Osipov, *Synlett* **2007**, *1*, 136–140; b) D. V. Vorobyeva, N. M. Karimova, T. P. Vasilyeva, S. N. Osipov, G. T. Shchetnikov, I. L. Odinets, G.-V. Röschenthaler, *J. Fluorine Chem.* **2010**, *131*, 378–389.

[14] a) C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2012**, *14*, 656–659; b) T. K. Hyster, K. E. Ruhl, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 5364–5367; c) X. Wu, B. Wang, S. Zhou, Y. Zhou, H. Liu, *ACS Catal.* **2017**, *7*, 2494–2499; d) X. Wu, B. Wang, Y. Zhou, H. Liu, *Org. Lett.* **2017**, *19*, 1294–1297.

[15] S. Dana, P. Sureshbabu, C. Kumar Giri, M. Baidya, *Eur. J. Org. Chem.* **2021**, *2021*, 10.1002/ejoc.202001632.

[16] a) V. P. Kukhar, H. R. Hudson, *Aminophosphonic and Amino-phosphinic Acids – Chemistry and Biological Activity* (Eds.: V. P. Kukhar, H. R. Hudson), Wiley, Chichester, **2000**, pp. 1–660; b) V. D. Romanenko, V. P. Kukhar, *Chem. Rev.* **2006**, *106*, 3868–3935; c) M. Ordonez, F. J. Sayago, C. Cativiela, *Tetrahedron* **2012**, *68*, 6369–6412; d) E. D. Naydenova, P. T. Todorov, K. D. Troev, *Amino Acids* **2010**, *38*, 23–30; e) F. Orsini, G. Sello, M. Sisti, *Curr. Med. Chem.* **2010**, *17*, 264–289; f) D. Zhao, R. Wang, *Chem. Soc. Rev.* **2012**, *41*, 2095–2108; g) S. Bhagat, P. Shah, S. K. Garg, S. Mishra, P. K. Kaur, S. Singh, A. K. Chakraborti, *MedChemComm* **2014**, *5*, 665–670.

Manuscript received: January 13, 2021
Revised manuscript received: March 1, 2021
Accepted manuscript online: March 2, 2021