DOI 10.1007/s10593-021-02888-5
Chemistry of Heterocyclic Compounds **2021**, *57*(2), 159–165

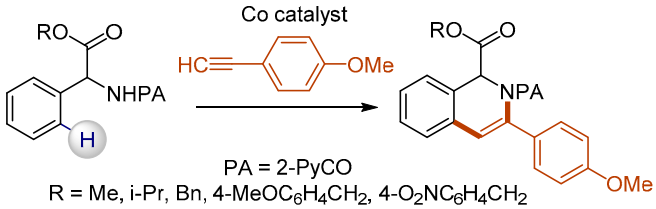
Synthesis of 1,2-dihydroisoquinoline-1-carboxylates under cobalt catalysis

Paula Amanda Zagorska[1], Liene Grigorjeva[1]*, Jekaterina Bolsakova[1]*

[1] *Latvian Institute of Organic Synthesis,*
21 Aizkraukles St., Riga LV-1006, Latvia; e-mail: jekaterina_bolsakova@osi.lv

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2021, *57*(2), 159–165

Submitted March 27, 2020
Accepted after revision January 28, 2021



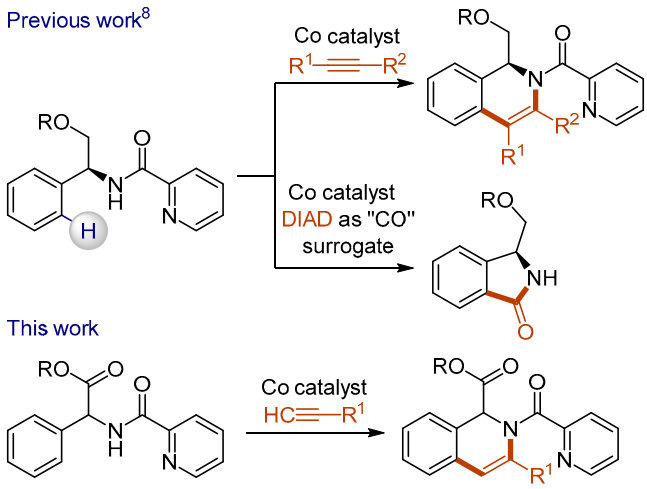
A study of cobalt-catalyzed C–H functionalization of phenylglycine derivatives with alkynes is described. During the optimization studies, a range of cobalt catalysts, oxidants, base additives, and reaction solvents were evaluated. Product yield dependence on phenylglycine ester substituent was evaluated. Conditions for 1,2-dihydroisoquinoline synthesis with acceptable yield were found.

Keywords: alkaloids, 1,2-dihydroisoquinoline, heterocycles, isoquinoline, phenylglycine.

1-Substituted tetrahydroisoquinoline is a key fragment of various naturally occurring alkaloids, e.g., saframycins,[1] renieramycins,[2] lemonomycin,[3] and possesses a broad range of biological activities, including antitumor and antimicrobial.[4] 1-Substituted 1,2-dihydroisoquinoline derivatives could also possess similar biological activity or serve as precursors for the synthesis of 1-substituted tetrahydroisoquinoline derivatives.[5] Cobalt-catalyzed C–H functionalization methodology has experienced immense interest in the past few years, and a large number of diverse C–H functionalization reactions based on this approach had been reported showing its potential.[6] Significant progress has been made for C(sp^2)–H bond functionalization using benzamides and benzylamines as substrates.[7] More complicated substrates such as amino alcohol or amino acid derivatives have been rarely explored. That might be related either to instability of the substrate in the presence of cobalt catalyst or the ability of substrate functional groups to coordinate transition metal, thereby deactivating the cobalt catalyst. Recently, we have shown, that phenylglycinol derivatives can be successfully used as substrates for cobalt-catalyzed C–H functionalization (Scheme 1).[8]

We were interested to study whether phenylglycine derivatives could be as effective substrates as phenylglycinols for cobalt-catalyzed C–H functionalization using alkynes exploiting picolinamide (PA) as a directing group. As far as we know, to date no literature precedents on cobalt-catalyzed C–H functionalization of phenylglycine derivatives have been reported. Herein we describe a study

Scheme 1. Cobalt-catalyzed C–H functionalization

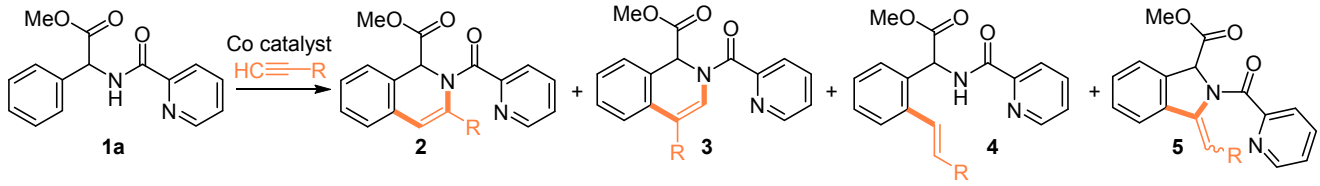


of the synthesis of 1,2-dihydroisoquinoline-1-carboxylates under cobalt-catalyzed, picolinamide-directed C–H functionalization of phenylglycine derivatives with 4-methoxyphenylacetylene.

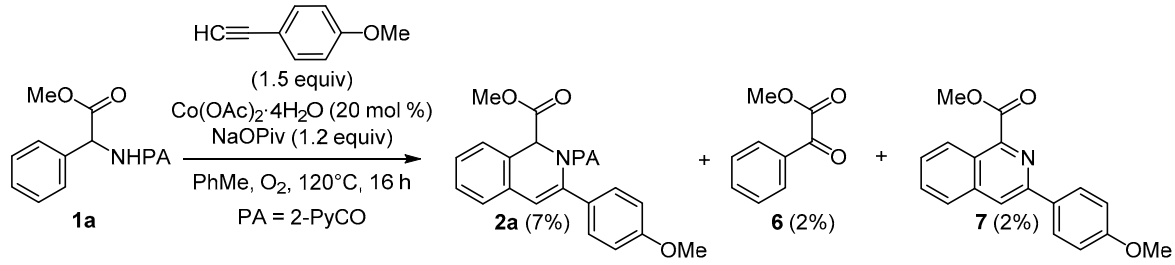
In C–H functionalization reaction of phenylglycine ester **1a** with alkyne, depending on reaction mechanistic pathway, several regioisomers could be formed, e.g., 1,2-dihydroisoquinoline derivatives **2** or **3**, alkenylated phenylglycine derivative **4**, or cyclic product **5** (Scheme 2).

For initial studies, we used phenylglycine methyl ester **1a** and 4-methoxyphenylacetylene as alkyne component

Scheme 2. Potential products of cobalt-catalyzed C–H functionalization of phenylglycine ester **1a** with alkynes



Scheme 3. Reaction of phenylglycine methyl ester **1a** with 4-methoxyphenylacetylene



(Scheme 3). We were pleased to find that using $Co(OAc)_2·4H_2O$ as a catalyst, NaOPiv as a base, and molecular oxygen as an oxidant, product **2a** was formed as the only regioisomer (Scheme 3). The structure of product **2a** was confirmed by X-ray crystallographic analysis (Fig. 1).

We discovered that besides compound **2a**, in the reaction mixture, also α-keto ester **6** and isoquinoline **7** in trace amounts were formed in this reaction (Scheme 3). The formation of both byproducts indicate the instability of substrate **1a** and product **2a** under the reaction conditions. The formation of α-keto ester **6** could be explained by the oxidation of substrate amino group, followed by hydrolysis, while isoquinoline **7** is formed by directing group cleavage in product **2a**.

During the optimization studies, a range of cobalt catalysts, oxidants, and additives were screened. Oxidant screening showed that various oxidants are competent for this transformation, selected examples are shown in Table 1. The molecular oxygen, $K_2S_2O_8$, and AgOAc gave the target product in 5–13% yield and up to 10% of α-keto ester **6** (Table 1, entries 1–3). Using the iodobenzoic acid (IBX) as an oxidant (entry 4), we observed increase in product **2a** yield – 27%, but also notable increase in substrate decomposition. Using $Mn(OAc)_2$, $Mn(OAc)_2$/air, or Oxone did not improve the product yield (entries 5–7). The use of $NaIO_4$ as an oxidant increased the product **2a** yield to 33% (entry 8), but the formation of byproduct **6** was still observed in 13% yield. $Mn(OAc)_3·2H_2O$ (entry 9) showed the best results from all the oxidants screened – 34% of product **2a** and smaller amount of substrate **1a** decomposition product **6**. Saturation of the reaction mixture with oxygen gave product **2a** in 33% yield (entry 10) and increased α-keto ester formation to 22%.

Next, we performed screening of the reaction catalyst, selected examples are shown in Table 2. Unlike $Co(OAc)_2·4H_2O$ other cobalt salts, bis(2,2,6,6-tetramethyl-3,5-heptanedionate)cobalt(II) ($Co(dpm)_2$) and CoF_3, did not improve the reaction yield (Table 2, entries 2, 3). Cp*$Co(CO)I_2$ was not successful either (entry 4). Control experiment excluding the catalyst (entry 5) showed no reaction.

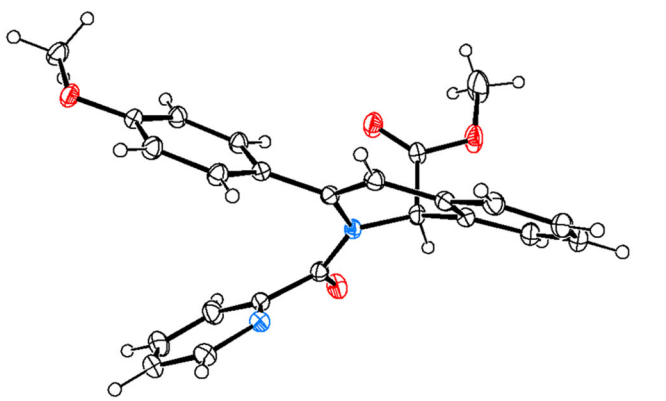
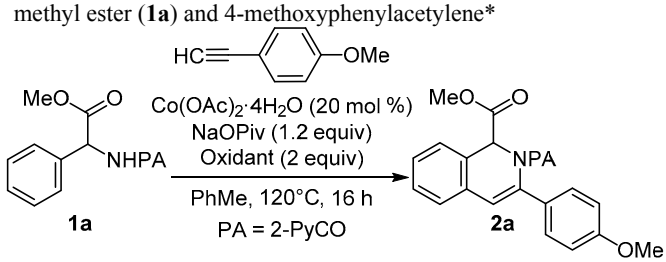


Figure 1. The molecular structure of product **2a** with atoms represented by thermal vibration ellipsoids of 50% probability.

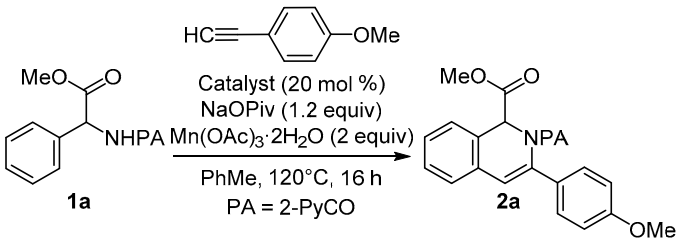
Table 1. Screening of oxidants in the reaction of phenylglycine methyl ester (**1a**) and 4-methoxyphenylacetylene*



Entry	Oxidant	Conversion, %	NMR yield of compound,** %		
			2a	**6**	**7**
1	O_2	27	7	2	2
2	$K_2S_2O_8$	35	13	3	–
3	AgOAc	30	5	10	–
4	IBX	83	27	42	5
5	$Mn(OAc)_2$	20	6	10	–
6	$Mn(OAc)_2$/air	56	20	20	3
7	Oxone	48	15	9	2
8	$NaIO_4$	82	33	13	–
9	**$Mn(OAc)_3·2H_2O$**	**74**	**34**	**9**	**4**
10	$Mn(OAc)_3·2H_2O/O_2$	86	33	22	2

* Reaction conditions: ester **1a** (0.1 mmol), 4-methoxyphenylacetylene (0.15 mmol, 1.5 equiv), $Co(OAc)_2·4H_2O$ (0.02 mmol, 20 mol %), NaOPiv (0.12 mmol, 1.2 equiv), oxidant (0.2 mmol, 2 equiv), PhMe (1 ml), 120°C.
** NMR yield using triphenylmethane as an internal standard.

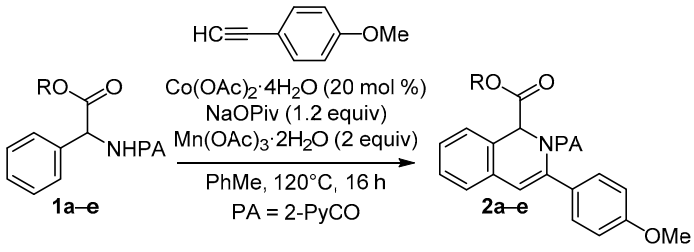
Table 2. Optimization of the catalyst in the reaction of phenylglycine methyl ester **1a** and 4-methoxyphenylacetylene*



Entry	Catalyst	Conversion, %	NMR yield of compound,** %		
			2a	**6**	**7**
1	$Co(OAc)_2·4H_2O$	74	34	9	4
2	$Co(dpm)_2$	53	25	11	–
3	CoF_3	72	32	34	–
4	$Cp^*Co(CO)I_2$	20	<1	–	–
5	Without catalyst	0	–	–	–

* Reaction conditions: ester **1a** (0.1 mmol), 4-methoxyphenylacetylene (0.15 mmol, 1.5 equiv), catalyst (0.02 mmol, 20 mol %), NaOPiv (0.12 mmol, 1.2 equiv), $Mn(OAc)_3·2H_2O$ (0.2 mmol, 2 equiv), PhMe (1 ml), 120°C.
** NMR yield using triphenylmethane as an internal standard.

Table 3. C–H functionalization of phenylglycine esters **1a–e***



Entry	Compound	R	Conversion, %	Product	NMR yield,** %
1	**1a**	Me	74	**2a**	34
2	**1b**	*i*-Pr	59	**2b**	29
3	**1c**	Bn	65	**2c**	29
4	**1d**	$4\text{-}MeOC_6H_4CH_2$	60	**2d**	27
5	**1e**	$4\text{-}O_2NC_6H_4CH_2$	77	**2e**	19

* Reaction conditions: ester **1a–e** (0.1 mmol), 4-methoxyphenylacetylene (0.15 mmol, 1.5 equiv), $Co(OAc)_2·4H_2O$ (0.02 mmol, 20 mol %), NaOPiv (0.12 mmol, 1.2 equiv), $Mn(OAc)_3·2H_2O$ (0.2 mmol, 2 equiv), PhMe (1 ml), 120°C.
** NMR yield using triphenylmethane as an internal standard.

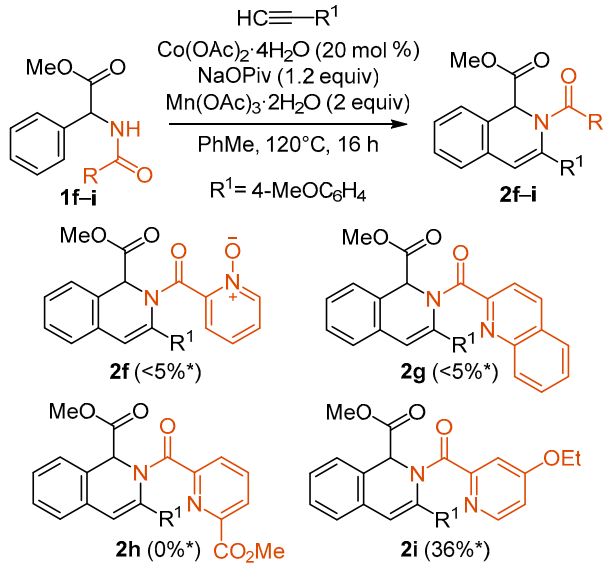
The reaction solvent screening revealed that PhMe is the solvent of choice. No product formation was observed under standard conditions, using 1,4-dioxane, diethoxymethane, THF, DMF, $MeNO_2$, MeOH, TFE, and MeCN. Reaction in such solvents as PhCl, mesitylene, and *t*-BuOAc afforded product **2a** in lower yields and promoted faster substrate decomposition. Various ligands were also screened (PPh_3, dipivaloylmethane, cyclooctadiene, pyridine, etc.). We found, that addition of the complementary ligand to the reaction did not improve the product yield or stability under the reaction conditions.

C–H functionalization of phenylglycine esters **1a–e** with 4-methoxyphenylacetylene (Table 3) showed, that substrate decomposition takes place using both aliphatic esters **1a** and **1b** (entries 1, 2) and benzylic esters **1c–e** (entries 3–5).

In order to improve the substrate stability and to minimize byproduct formation, we prepared additional substrates **1f–i** with modified directing group. Unfortunately, substrates containing picolinamide *N*-oxide **1f** or quinolinamide **1g** were not suitable for the C–H functionalization reaction and gave the corresponding products only in trace amounts under the same reaction conditions according to NMR data (Scheme 4). Substrate **1h**, which contains ester group in pyridine ring did not gave product at all. Promising result was achieved using substrate **1i** that contained ethoxy substituent at pyridine ring – product was formed in 36% yield. With this promising result in hand, our future investigation will involve in-depth study of the electronic effects of the substrate directing group in order to improve the product yield and substrate stability toward cobalt-catalyzed C–H functionalization of phenylglycine esters with alkynes.

In conclusion, we have studied cobalt-catalyzed C–H functionalization of phenylglycine derivatives with alkynes. During the optimization studies, a range of cobalt catalysts, oxidants, base additives, and reaction solvents were evaluated. Product yield dependence on phenylglycine ester group was evaluated. Conditions for 1,2-dihydroisoquinoline synthesis with acceptable yield were found. Future directions of the work involve substrate directing group modification in order to increase substrate stability under the reaction conditions.

Scheme 4. Reaction of phenylglycine methyl esters **1f–i** with 4-methoxyphenylacetylene



* NMR yield using triphenylmethane as an internal standard.

Experimental

^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker spectrometer (400 and 101 MHz, respectively) in $CDCl_3$, using residual solvent peak as internal standard (7.26 ppm for ^1H nuclei and 77.2 ppm for ^{13}C nuclei). HRMS analyses were performed by positive mode electrospray ionization using a Waters Synapt G2-Si mass-

spectrometer. Thin-layer chromatography was performed on silica gel using Merck TLC Silica gel 60 F_{254} aluminum sheets, visualization under UV light and by staining with $KMnO_4$. Column chromatography was performed using Kieselgel silica gel (35–70 and 60–200 μm).

Reactions were performed using standard glassware or were run in 4-ml vials using w/polyseal screw caps. Reactions were heated using Chemglass aluminum reaction blocks.

All procedures were performed under air unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used without further purification unless otherwise noted.

Methyl phenyl[(pyridin-2-ylcarbonyl)amino]acetate (1a) was prepared according to a published procedure.[8]

Propan-2-yl phenyl[(pyridin-2-ylcarbonyl)amino]-acetate (1b). Step 1. 2-Amino-2-phenylacetic acid (0.50 g, 3.30 mmol, 1.00 equiv) was suspended in *i*-PrOH (5 ml) under an argon atmosphere. The solution was cooled to 0°C, and oxalyl chloride (0.72 ml, 8.25 mmol, 2.50 equiv) was slowly added dropwise. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure to obtain crude isopropyl 2-amino-2-phenylacetate hydrogen chloride as a pale solid. The crude product was used in the next step without further purification.

Step 2. Under an argon atmosphere, isopropyl 2-amino-2-phenylacetate hydrogen chloride (3.30 mmol, 1.00 equiv), picolinic acid (0.45 g, 3.63 mmol, 1.10 equiv), and *N*,*N*,*N*',*N*'-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (2.50 g, 6.60 mmol, 2.00 equiv) were dissolved in DMF (7 ml). Pyridine (0.80 ml, 9.90 mmol, 3.00 equiv) was added to the solution directly. The reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was diluted with EtOAc and H_2O and filtered. The organic phase was separated, and the aqueous phase was extracted with EtOAc; the combined organic phase was washed with distilled H_2O and brine, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether – EtOAc, 3:1, as an eluent. Yield 0.74 g (75%), colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (3H, d, *J* = 6.3, CH_3); 1.31 (3H, d, *J* = 6.3, CH_3); 5.11 (1H, septet, *J* = 6.3, C<u>H</u>$(CH_3)_2$); 5.76 (1H, d, *J* = 7.7, CH); 7.30–7.54 (6H, m, H Ar, H Py); 7.85 (1H, td, *J* = 7.8, *J* = 1.7, H Py); 8.18 (1H, d, *J* = 7.8, H Py); 8.61 (1H, d, *J* = 5.1, H Py); 8.99 (1H, d, *J* = 7.2, NH). ^{13}C NMR spectrum, δ, ppm: 21.5; 21.9; 56.8; 69.8; 122.5; 126.5; 127.4; 128.5; 129.0; 137.0; 137.4; 148.4; 149.6; 163.9; 170.3. Found, *m*/*z*: 299.1398 $[M+H]^+$. $C_{17}H_{19}N_2O_3$. Calculated, *m*/*z*: 299.1391.

Benzyl phenyl[(pyridin-2-ylcarbonyl)amino]acetate (1c). Step 1. Methyl phenyl[(pyridin-2-ylcarbonyl)amino]-acetate (**1a**) (500 mg, 1.85 mmol, 1.00 equiv) was dissolved in THF (10 ml). The solution was cooled to 0°C, and 1 M NaOH (10 ml) was added dropwise. The reaction mixture was stirred at room temperature for 3 h (TLC showed conversion of starting material). The THF solvent was evaporated under reduced pressure. The aqueous phase was extracted with Et_2O. Using 2 M HCl, the pH of the aqueous phase was adjusted to ~5. The aqueous phase was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to afford crude phenyl[(pyridin-2-ylcarbonyl)amino]acetic acid as yellowish oil. The crude product was used in the next step without further purification.

Step 2. Phenyl[(pyridin-2-ylcarbonyl)amino]acetic acid (474 mg, 1.85 mmol, 1.00 equiv) and DBU (0.33 ml, 2.22 mmol, 1.20 equiv) were combined in MeCN (18 ml). Benzyl bromide (0.24 ml, 2.03 mmol, 1.10 equiv) was added at room temperature, and the reaction mixture was stirred. Upon completion as determined by TLC, aqueous $NaHCO_3$ was added to the reaction mixture and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether – EtOAc, 3:1, as an eluent. Yield 290 mg (45%), colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.12 (2H, q, *J* = 12.4, OCH_2); 5.75 (1H, d, *J* = 7.6, CH); 7.17–7.25 (2H, m, H Ar); 7.24–7.41 (7H, m, H Ar); 7.41– 7.47 (2H, m, H Ar, H Py); 7.72 (1H, td, *J* = 7.7, *J* = 1.6, H Py); 8.06 (1H, dt, *J* = 7.8, *J* = 0.9, H Py); 8.55 (1H, d, *J* = 4.8, H Py); 8.89 (1H, d, *J* = 7.2, NH). ^{13}C NMR spectrum, δ, ppm: 56.8; 67.5; 122.5; 126.6; 127.6; 128.1; 128.4; 128.6; 128.7; 129.1; 135.4; 136.6; 137.4; 148.4; 149.4; 163.9; 170.6. Found, *m*/*z*: 347.1403 $[M+H]^+$. $C_{21}H_{19}N_2O_3$. Calculated, *m*/*z*: 347.1391.

4-Methoxybenzyl phenyl[(pyridin-2-ylcarbonyl)amino]-acetate (1d). Step 1. Methyl phenyl[(pyridin-2-ylcarbonyl)-amino]acetate (**1a**) (500 mg, 1.85 mmol, 1.00 equiv) was dissolved in THF (10 ml). The solution was cooled to 0°C, and 1 M NaOH (10 ml) was added dropwise. The reaction mixture was stirred at room temperature for 3 h (TLC showed conversion of starting material). The THF solvent was evaporated under reduced pressure. The aqueous phase was extracted with Et_2O. Using 2 M HCl, the pH of the aqueous phase was adjusted to ~5. The aqueous phase was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to afford crude phenyl[(pyridin-2-ylcarbonyl)amino]acetic acid as yellowish oil. The crude product was used in the next step without further purification.

Step 2. Phenyl[(pyridin-2-ylcarbonyl)amino]acetic acid (474 mg, 1.85 mmol, 1.00 equiv) and Cs_2CO_3 (723 mg, 2.22 mmol, 1.20 equiv) were combined in DMF (18 ml). 1-(Bromomethyl)-4-methoxybenzene (0.30 ml, 2.04 mmol, 1.10 equiv) was added at room temperature, and the reaction mixture was stirred. Upon completion as determined by TLC, aqueous $NaHCO_3$ was added to the reaction mixture and extracted with EtOAc. The combined organic layers were washed with brine (200 ml), dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using

petroleum ether – EtOAc, 2:1, as an eluent. Yield 294 mg (42%), colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.79 (3H, s, OCH_3); 5.10 (1H, d, *J* = 12.0, OCH_2); 5.19 (1H, d, *J* = 12.0, OCH_2); 5.80 (1H, d, *J* = 7.5, CH); 6.83 (2H, d, *J* = 8.7, H-3,5 C_6H_4OMe); 7.18 (2H, d, *J* = 8.7, H-2,6 C_6H_4OMe); 7.28–7.37 (3H, m, H Ar); 7.40–7.47 (3H, m, H Ar, H Py); 7.83 (1H, td, *J* = 7.7, *J* = 1.7, H Py); 8.15 (1H, dt, *J* = 7.7, *J* = 1.0, H Py); 8.58 (1H, ddd, *J* = 4.8, *J* = 1.7, *J* = 0.9, H Py); 8.97 (1H, d, *J* = 7.5, NH). ^{13}C NMR spectrum, δ, ppm: 55.4; 56.8; 67.5; 114.0; 122.5; 126.6; 127.6; 128.6; 128.8; 129.1; 130.0; 136.7; 137.4; 148.4; 149.5; 159.8; 163.9; 170.7. Found, *m*/*z*: 399.1316 $[M+Na]^+$. $C_{22}H_{20}N_2NaO_4$. Calculated, *m*/*z*: 399.1316.

4-Nitrobenzyl phenyl[(pyridin-2-ylcarbonyl)amino]-acetate (1e) was synthesized by the method analogous to the synthesis of compound **1d** from phenyl[(pyridin-2-yl-carbonyl)amino]acetic acid (474 mg, 1.85 mmol, 1.00 equiv), Cs_2CO_3 (723 mg, 2.22 mmol, 1.20 equiv), 1-(bromomethyl)-4-nitrobenzene (440 mg, 2.03 mmol, 1.10 equiv), and DMF (19 ml). Yield 190 mg (26%), colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.27 (1H, d, *J* = 13.5, OCH_2); 5.32 (1H, d, *J* = 13.5, OCH_2); 5.82 (1H, d, *J* = 7.2, CH); 7.33 (2H, d, *J* = 8.8, H-2,6 $C_6H_4NO_2$); 7.36–7.51 (6H, m, H Ar, H Py); 7.85 (1H, td, *J* = 7.7, *J* = 1.7, H Py); 8.10–8.19 (3H, m, H Py, H-3,5 $C_6H_4NO_2$); 8.58 (1H, d, *J* = 4.7, H Py); 8.90 (1H, d, *J* = 7.2, NH). ^{13}C NMR spectrum, δ, ppm: 56.9; 65.8; 122.5; 123.9; 126.7; 127.6; 128.1; 129.1; 129.3; 135.9; 137.5; 142.7; 147.8; 148.5; 149.2; 164.1; 170.4. Found, *m*/*z*: 392.1252 $[M+H]^+$. $C_{21}H_{18}N_3O_5$. Calculated, *m*/*z*: 392.1242.

Methyl {[(1-oxidopyridin-2-yl)carbonyl]amino}(phenyl)-acetate (1f). Methyl phenyl[(pyridin-2-ylcarbonyl)amino]-acetate (**1a**) (200 mg, 0.74 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (7 ml) under an argon atmosphere. The solution was cooled to 0°C, and 3-chloroperoxybenzoic acid (230 mg, 1.33 mmol, 1.80 equiv) was slowly added. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using EtOAc – petroleum ether, 2:1, as an eluent. Yield 191 mg (90%), white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.76 (3H, s, OCH_3); 5.75 (1H, d, *J* = 6.8, CH); 7.30–7.52 (7H, m, H Ph, H Py); 8.23–8.34 (1H, m, H Py); 8.39 (1H, dd, *J* = 7.9, *J* = 2.3, H Py); 12.28 (1H, d, *J* = 6.3, NH). ^{13}C NMR spectrum, δ, ppm: 53.0; 57.6; 127.2; 127.6; 127.7; 128.8; 129.1; 129.2; 136.1; 140.4; 140.7; 159.3; 170.7. Found, *m*/*z*: 287.1032 $[M+H]^+$. $C_{15}H_{15}N_2O_4$. Calculated, *m*/*z*: 287.1027.

Methyl phenyl[(quinolin-2-ylcarbonyl)amino]acetate (1g). Under an argon atmosphere, methyl 2-amino-2-phenyl-acetate hydrogen chloride (200 mg, 1.00 mmol, 1.00 equiv), quinaldic acid (190 mg, 1.10 mmol, 1.10 equiv), and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexa-fluorophosphate (0.76 g, 2.00 mmol, 2.00 equiv) were dissolved in DMF (2 ml). Pyridine (0.24 ml, 3.00 mmol, 3.00 equiv) was added to the solution directly. The reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was diluted with EtOAc and H_2O. The organic phase was separated, and the aqueous phase was extracted with EtOAc; the combined organic phase was washed with distilled H_2O and brine, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether – EtOAc, 2:1, as an eluent. Yield 304 mg (95%), white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.80 (3H, s, OCH_3); 5.85 (1H, d, *J* = 7.4, CH); 7.33–7.45 (3H, m, H Ph); 7.51–7.57 (2H, m, H Ph); 7.58–7.66 (1H, t, *J* = 7.1, H quinoline); 7.73–7.82 (1H, m, H quinoline); 7.87 (1H, d, *J* = 8.2, H quinoline); 8.17 (1H, d, *J* = 8.5, H quinoline); 8.26 (1H, d, *J* = 8.5, H quinoline); 8.30 (1H, d, *J* = 8.5, H quinoline); 9.16 (1H, d, *J* = 7.4, NH). ^{13}C NMR spectrum, δ, ppm: 53.0; 56.9; 118.9; 127.6; 127.8; 128.2; 128.7; 129.2; 129.6; 130.1; 130.2; 136.7; 137.6; 146.7; 149.2; 164.2; 171.4. Found, *m*/*z*: 321.1239 $[M+H]^+$. $C_{19}H_{17}N_2O_3$. Calculated, *m*/*z*: 321.1234.

Methyl 6-[(2-methoxy-2-oxo-1-phenylethyl)carbamoyl]-pyridine-2-carboxylate (1h). Under an argon atmosphere, methyl 2-amino-2-phenylacetate hydrogen chloride (300 mg, 1.49 mmol, 1.00 equiv), 6-(methoxycarbonyl)-2-pyridine-carboxylic acid (320 mg, 1.79 mmol, 1.10 equiv), and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexa-fluorophosphate (1.13 g, 2.98 mmol, 2.00 equiv) were dissolved in DMF (3 ml). Pyridine (0.36 ml, 4.46 mmol, 3.00 equiv) was added to the solution directly. The reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was diluted with EtOAc and H_2O. The organic phase was separated, and the aqueous phase was extracted with EtOAc; the combined organic phase was washed with distilled H_2O and brine, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether – EtOAc, 2:1, as an eluent. Yield 420 mg (86%), white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, OCH_3); 4.02 (3H, s, OCH_3); 5.78 (1H, d, *J* = 7.3, CH); 7.33–7.42 (3H, m, H Ph); 7.45–7.53 (2H, m, H Ph); 8.00 (1H, t, *J* = 7.8, H Py); 8.24 (1H, dd, *J* = 7.8, *J* = 1.1, H Py); 8.34 (1H, dd, *J* = 7.8, *J* = 1.1, H Py); 8.93 (1H, d, *J* = 7.3, NH). ^{13}C NMR spectrum, δ, ppm: 53.0; 53.1; 56.9; 125.6; 127.6; 127.7; 128.8; 129.2; 136.3; 138.6; 147.0; 149.6; 163.2; 165.1; 171.1. Found, *m*/*z*: 351.0957 $[M+Na]^+$. $C_{17}H_{16}N_2NaO_5$. Calculated, *m*/*z*: 351.0952.

Methyl {[(4-ethoxypyridin-2-yl)carbonyl]amino}-(phenyl)acetate (1i). Step 1. 4-Chloropicolinic acid (300 mg, 1.90 mmol, 1.00 equiv) was dissolved in DMF (10 ml) under an argon atmosphere. The solution was cooled to 0°C, and NaOEt (21%, 2.10 ml, 5.71 mmol, 3.00 equiv) was slowly added dropwise. The reaction mixture was stirred overnight at 90°C. The solvent was evaporated under reduced pressure to obtain crude sodium 4-ethoxypicolinate as a pale solid. The crude product was used in the next step without further purification.

Step 2. Under an argon atmosphere, sodium 4-ethoxy-picolinate (1.90 mmol, 1.20 equiv), methyl 2-amino-2-phenyl-acetate hydrogen chloride (318 mg, 1.58 mmol, 1.00 equiv), and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (1200 mg, 3.16 mmol, 2.00 equiv)

were dissolved in DMF (10 ml). Pyridine (0.26 ml, 3.16 mmol, 2.00 equiv) was added to the solution directly. The reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was diluted with EtOAc and H_2O. The organic phase was separated, and the aqueous phase was extracted with EtOAc; the combined organic phase was washed with distilled H_2O and brine, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether – EtOAc, 2:1, as an eluent. Yield 295 mg (59%), yellowish solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.43 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 3.77 (3H, s, OCH_3); 4.14 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.75 (1H, d, *J* = 7.5, CH); 6.90 (1H, dd, *J* = 5.6, *J* = 2.5, H Py); 7.32–7.41 (3H, m, H Ph); 7.44–7.50 (2H, m, H Ph); 7.67 (1H, d, *J* = 2.5, H Py); 8.36 (1H, d, *J* = 5.6, H Py); 8.94 (1H, d, *J* = 7.3, NH). ^{13}C NMR spectrum, δ, ppm: 14.6; 53.0; 56.8; 64.1; 108.1; 113.7; 127.6; 128.7; 129.2; 136.6; 149.6; 151.4; 164.0; 166.4; 171.2. Found, *m*/*z*: 315.1345 $[M+H]^+$. $C_{17}H_{19}N_2O_4$. Calculated, *m*/*z*: 315.1340.

Synthesis of isoquinolines 2a–e,i (General method). A 4 ml-vial with a screw cap (PTFE/Liner) was charged with phenylglycine ester **1a**–**e**,**i** (0.10 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (53.6 mg, 0.20 mmol, 2.00 equiv), NaOPiv (14.9 mg, 0.12 mmol, 1.20 equiv), $Co(OAc)_2{\cdot}4H_2O$ (5.0 mg, 0.02 mmol, 20 mol %), 4-ethynylanisole (19 μl, 0.15 mmol, 1.50 equiv), and PhMe (1.0 ml). Resulting mixture was heated at 120°C for 16 h, cooled to room temperature, and analyzed by TLC (hexane–EtOAc, 4:1). To reaction mixture, Ph_3CH (24.4 mg, 0.10 mmol, 1.00 equiv) was added; the mixture was diluted with distilled H_2O (1.5 ml) and extracted with EtOAc (3×1.5 ml). The combined organic phase was separated, dried over anhydrous Na_2SO_4, filtered, evaporated. The residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy. Analytical sample was isolated by column chromatography on silica gel using petroleum ether – EtOAc as an eluent, gradient from 4:1 to 1:1.

Methyl 3-(4-methoxyphenyl)-2-(pyridin-2-ylcarbonyl)-1,2-dihydroisoquinoline-1-carboxylate (2a). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.69 (3H, s, OCH_3); 3.74 (3H, s, OCH_3); 6.19 (1H, s, CH); 6.54 (1H, s, H Ar); 6.59 (2H, d, *J* = 8.6, H-3,5 C_6H_4OMe); 6.94–7.02 (1H, m, H Ar); 7.23–7.44 (7H, m, H Ar, H Py); 7.49 (1H, d, *J* = 7.1, H Py); 8.28 (1H, d, *J* = 4.3, H Py). ^{13}C NMR spectrum, δ, ppm: 52.9; 55.4; 58.6; 113.1; 113.6; 124.6; 124.7; 125.6; 127.3; 128.2; 128.8 (2C); 129.4; 131.4; 131.7; 136.2; 139.4; 148.3; 154.1; 159.3; 169.0; 170.4. Found, *m*/*z*: 401.1491 $[M+H]^+$. $C_{24}H_{21}N_2O_4$. Calculated, *m*/*z*: 401.1418.

Isopropyl 3-(4-methoxyphenyl)-2-(pyridin-2-ylcarbonyl)-1,2-dihydroisoquinoline-1-carboxylate (2b). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 (3H, d, *J* = 6.2, CH_3); 1.25 (3H, d, *J* = 6.2, CH_3); 3.69 (3H, s, OCH_3); 5.02 (1H, hept, *J* = 6.2, $C\underline{H}(CH_3)_2$); 6.19 (1H, s, CH); 6.48 (1H, s, H Ar); 6.58 (2H, d, *J* = 8.6, H-3,5 C_6H_4OMe); 6.93–7.04 (1H, m, H Ar); 7.20–7.34 (4H, m, H Ar, H Py); 7.36–7.44 (3H, m, H-2,6 C_6H_4OMe, H Py); 7.48 (1H, d, *J* = 7.2, H Py); 8.28 (1H, d, *J* = 4.3, H Py). ^{13}C NMR spectrum, δ, ppm: 21.8; 21.9; 55.4; 58.8; 69.8; 113.0; 113.4; 124.4; 124.5; 125.5; 127.1; 128.2; 128.6; 128.8; 129.9; 131.4; 131.5; 136.1; 139.4; 148.4; 154.2; 159.3; 169.0; 169.4. Found, *m*/*z*: 429.1814 $[M+H]^+$. $C_{26}H_{25}N_2O_4$. Calculated, *m*/*z*: 429.1809.

Benzyl 3-(4-methoxyphenyl)-2-(pyridin-2-ylcarbonyl)-1,2-dihydroisoquinoline-1-carboxylate (2c). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.60 (3H, s, OCH_3); 5.01–5.17 (2H, m, OCH_2); 6.12 (1H, s, CH); 6.42 (2H, d, *J* = 8.5, H-3,5 C_6H_4OMe); 6.53 (1H, s, H Ar); 6.86–6.95 (1H, m, H Ar); 7.12–7.19 (3H, m, H Ar); 7.20–7.27 (8H, m, H Ar, H Py); 7.33 (1H, t, *J* = 7.4, H Py); 7.43 (1H, d, *J* = 7.2, H Py); 8.20 (1H, d, *J* = 4.2, H Py). ^{13}C NMR spectrum, δ, ppm: 55.4; 58.7; 67.5; 113.1; 113.4; 124.5; 124.6; 125.6; 127.3; 128.0; 128.3; 128.6; 128.8; 128.9; 129.5; 131.3; 131.7; 135.5; 136.1; 139.4; 148.3; 154.1; 159.2; 169.0; 169.8. Found, *m*/*z*: 477.1814 $[M+H]^+$. $C_{30}H_{25}N_2O_4$. Calculated, *m*/*z*: 477.1809.

4-Methoxybenzyl 3-(4-methoxyphenyl)-2-(pyridin-2-ylcarbonyl)-1,2-dihydroisoquinoline-1-carboxylate (2d). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 5.04 (1H, d, *J* = 12.1, OCH_2); 5.15 (1H, d, *J* = 12.1, OCH_2); 6.19 (1H, s, CH); 6.49 (2H, d, *J* = 8.5, H-3,5 C_6H_4OMe); 6.56 (1H, s, H Ar); 6.82 (2H, d, *J* = 8.6, H-3,5 C_6H_4OMe); 6.93–7.00 (1H, m, H Ar); 7.13–7.20 (3H, m, H Ar); 7.22–7.36 (5H, m, H Ar, H Py); 7.37–7.44 (1H, m, H Py); 7.45–7.51 (1H, m, H Py); 8.28 (1H, d, *J* = 4.2, H Py). ^{13}C NMR spectrum, δ, ppm: 55.3; 55.4; 58.7; 67.4; 113.1; 113.4; 114.0; 124.5; 124.5; 125.4; 125.5; 127.2; 128.4; 128.7; 129.2; 129.6; 130.0; 131.6; 136.1; 138.0; 139.4; 148.3; 154.1; 159.2; 159.7; 169.0; 169.9. Found, *m*/*z*: 507.1920 $[M+H]^+$. $C_{31}H_{27}N_2O_5$. Calculated, *m*/*z*: 507.1915.

4-Nitrobenzyl 3-(4-methoxyphenyl)-2-(pyridin-2-ylcarbonyl)-1,2-dihydroisoquinoline-1-carboxylate (2e). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.67 (3H, s, OCH_3); 5.24 (1H, d, *J* = 13.5, OCH_2); 5.29 (1H, d, *J* = 13.4, OCH_2); 6.20 (1H, s, CH); 6.52 (2H, d, *J* = 8.5, H-3,5 C_6H_4OMe); 6.64 (1H, s, H Ar); 6.93–7.06 (1H, m, H Ar); 7.24–7.50 (9H, m, H Ar, H Py); 7.81–7.91 (1H, m, H Py); 8.12 (2H, d, *J* = 8.7, H-3,5 $C_6H_4NO_2$); 8.28 (1H, d, *J* = 3.8, H Py).

Methyl 2-(4-ethoxypyridin-2-ylcarbonyl)-3-(4-methoxyphenyl)-1,2-dihydroisoquinoline-1-carboxylate (2i). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$); 3.71 (3H, s, OCH_3); 3.74 (3H, s, OCH_3); 3.84–4.04 (2H, m, $C\underline{H}_2CH_3$); 6.17 (1H, s, CH); 6.45–6.53 (2H, m, H Ar); 6.61 (2H, d, *J* = 8.4, H-3,5 C_6H_4OMe); 6.78 (1H, s, H Py); 7.19–7.25 (1H, m, H Ar); 7.27–7.35 (2H, m, H Ar); 7.39 (2H, d, *J* = 8.1, H Ar); 7.38–7.43 (1H, m, H Py); 8.08 (1H, d, *J* = 5.6, H Py). ^{13}C NMR spectrum, δ, ppm: 14.4; 52.9; 55.4; 58.5; 63.8; 110.6; 111.8; 113.2; 113.5; 125.6; 127.3; 128.2; 128.8; 128.9; 129.3; 131.4; 131.6; 139.2; 149.3; 155.4; 159.3; 165.1; 168.9; 170.4. Found, *m*/*z*: 445.1766 $[M+H]^+$. $C_{26}H_{25}N_2O_5$. Calculated, *m*/*z*: 445.1759.

X-ray structural analysis of compound 2a. Crystals were obtained by crystallization from Et_2O. Single crystal X-ray crystallographic data were collected at 190(2)K on a RIGAKU XtaLAB Synergy S, Dualflex, HyPix diffractometer with microfocus sealed CuKα X-ray tube using ω-scan method. Integration and reduction of data were accomplished using the CrysAlisPro program suite.[9] The structure was solved by direct method, and all non-hydrogen atoms were refined by full-matrix least-squares

technique on F^2 using SHELXL97 program.[10] H atoms were positioned geometrically and treated as rigid on their parent C atoms. Crystal data for compound **2a**: $C_{24}H_{20}N_2O_4$, M 400.42; orthorhombic space group $P2_12_12_1$; a 8.3029(1), b 12.1063(1), c 20.1870 (1) Å; V 2029.14(3) Å^3; T 190K; Z 4; d_{calc} 1.311 g/cm^3; μ 0.736 mm^{-1}; 25478 reflections measured ($4.258 < \theta < 77.139°$; 4310 unique (R_{int} 0.0264), which were used in all calculations. The final R_1 was 0.0263 ($I > 2\sigma(I)$), and wR_2 was 0.0727 (all data). The complete crystallographic dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2057726).

This research was financially supported by ERDF project No. 1.1.1.5/17/A/004.

Authors thank Dr. A. Mishnev (Latvian Institute of Organic Synthesis) for X-ray crystallographic analysis.

References

1. Kimura, S.; Saito, N. *Tetrahedron* **2018**, *74*, 4504.
2. Chamni, S.; Sirimangkalakitti, N.; Chanvorachote, P.; Saito, N.; Suwanborirux, K. *J. Nat. Prod.* **2017**, *80*, 1541.
3. Ashley, E. R.; Cruz E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000.
4. (a) Bentley, K. W. *Nat. Prod. Rep.* **1992**, *8*, 365. (b) Bentley, K. W. *Nat. Prod. Rep.* **2005**, *22*, 249.
5. Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2010**, 4017.
6. (a) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209. (b) Planas, O.; Whiteoak, C. J.; Company, A.; Ribas, X. *Adv. Synth. Catal.* **2015**, 4003. (c) Kalsi, D.; Sundararaju, B. *Org. Lett.* **2015**, *17*, 6118. (d) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. *ACS Catal.* **2016**, *6*, 551. (e) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4684. (f) Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822. (g) Gandeepan, P.; Rajamalli, P.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 4308. (h) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4688. (i) Ni, J.; Li, J.; Fan, Z.; Zhang, A. *Org. Lett.* **2016**, *18*, 5960. (j) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. *Chem. Commun.* **2017**, *53*, 5136. (k) Zeng, L.; Tang, S.; Wang, D.; Deng, Y.; Chen, J.-L.; Lee, J.-F.; Lei, A. *Org. Lett.* **2017**, *19*, 2170. (l) Martínez, Á. M.; Rodríguez, N.; Gómez-Arrayás, R.; Carretero, J. C. *Chem.–Eur. J.* **2017**, *23*, 11669.
7. (a) Hyster, T. K. *Catal. Lett.* **2015**, *145*, 458. (b) Kommagalla, Y.; Chatani, N. *Coord. Chem. Rev.* **2017**, *350*, 117. (c) Ujwaldev, S. M.; Harry, N. A.; Divakar, M. A.; Anilkumar, G. *Catal. Sci. Technol.* **2018**, *8*, 5983. (d) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192.
8. (a) Bolsakova, J.; Lukasevics, L.; Grigorjeva, L. *J. Org. Chem.* **2020**, *85*, 4482. (b) Lukasevics, L.; Cizikovs, A.; Grigorjeva, L. *Org. Lett.* **2020**, *22*, 2720.
9. *CrysAlis PRO 1.171.40.35a* (Rigaku OD, 2018); Agilent Technologies Ltd.: Yarnton.
10. Sheldrick, G. M. *Acta Crystallogr*., *Sect. C*: *Struct. Chem.* **2015**, *C71*, 3.