

General Method for the Preparation of Active Esters by Palladium-Catalyzed Alkoxy carbonylation of Aryl Bromides

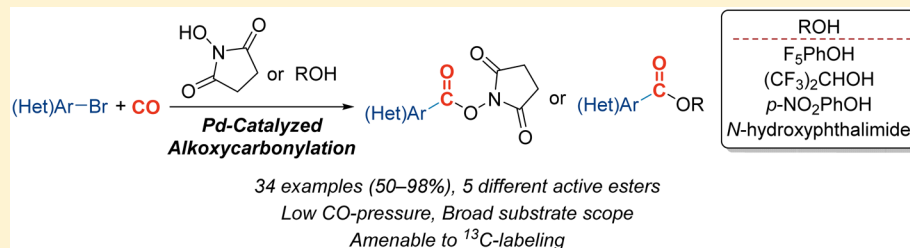
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Supporting Information



ABSTRACT: A useful method was developed for the synthesis of active esters by palladium-catalyzed alkoxy carbonylation of (hetero)aromatic bromides. The protocol was general for a range of oxygen nucleophiles including *N*-hydroxysuccinimide (NHS), pentafluorophenol (PFP), hexafluoroisopropyl alcohol (HFP), 4-nitrophenol, and *N*-hydroxyphthalimide. A high functional group tolerance was displayed, and several active esters were prepared with good to excellent isolated yields. The protocol was extended to access an important synthetic precursor to the HIV-protease inhibitor, saquinavir, by formation of an NHS ester followed by acyl substitution.

The use of active esters as coupling partners in acyl substitution reactions is a predominant strategy throughout the field of organic synthesis, and it is equally important in Nature, whereby, e.g., acetyl-CoA serves as a widespread acetylating agent. By this method, a carboxylic acid can be converted into an acylating agent, and the formation of C–O, C–N, and C–S bonds is easily achieved by subsequent acyl substitution. Active esters have found widespread use in the synthesis of natural products,^{1–3} pharmaceuticals,⁴ and synthetic peptides^{5,6} and also to a large extent as cross-linking reagents in bioconjugation.⁷ Many methods for the activation of carboxylic acids have been developed, including direct activation with strong acids (Fischer esterification), conversion into acid halides with, e.g., SOCl₂ or cyanuric acid, conversion into either mixed or symmetric anhydrides, Steglich-type carbodiimide activation (EDC, DCC) often in combination with coupling additives (HOBt, HOAt),^{8,9} and treatment with phosphonium salts, among others.¹⁰ However, all of these approaches require the presence or preinstallment of the carboxylic acid moiety, which, besides from additional synthetic manipulation, may be inconvenient or even absent. Therefore, the transformation of alternative functionalities other than carboxylic acids directly into an active ester is a desirable and equally efficient method. Toward this end, recent developments have been focused on the direct oxidative transformation of aldehydes into amides and esters,^{11,12} and in a one example, the

transformation of aldehydes directly into isolable active esters has been reported.¹³

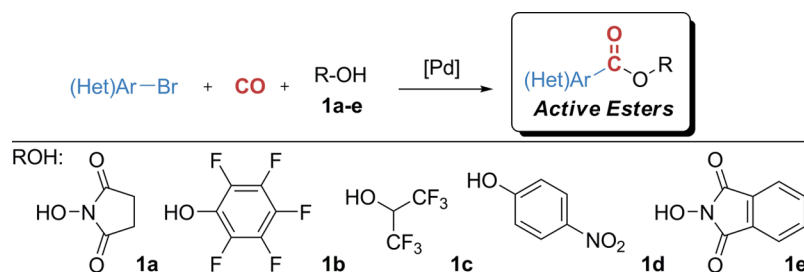
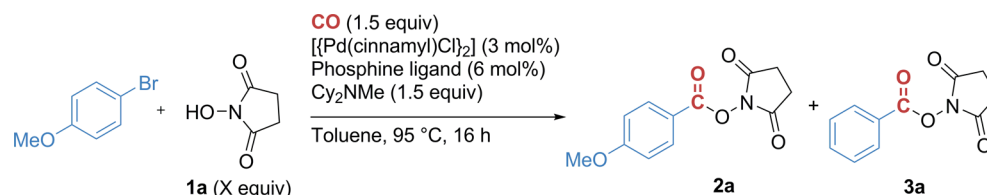
In 2003, a Pd-catalyzed carbonylation strategy for the preparation of *N*-hydroxysuccinimido esters was presented by Lou et al.¹⁴ In this work, a selection of aryl iodides and aryl triflates were coupled to *N*-hydroxysuccinimide (NHS) in the presence of carbon monoxide (CO). Bromobenzene was also employed as the electrophile but resulted in a mere 26% isolated yield of the desired NHS ester. A carbonylative strategy toward activated esters is highly appealing due to the elaborate literature on the formation of sp² carbon–halogen bonds, such as electrophilic aromatic substitution or Sandmeyer-type transformations, rendering highly functionalized aromatic halides readily available. Furthermore, the combination of these starting materials with a mild and selective Pd-catalyzed carbonylative protocol provides facile access to activated esters.¹⁵

In this context, we herein present an efficient and general method for the preparation of active esters by a Pd-catalyzed alkoxy carbonylation of aromatic and heteroaromatic bromides. The scope of this methodology includes active esters formed from *N*-hydroxysuccinimide (**1a**) (NHS), pentafluorophenol

Received: November 7, 2014

Published: January 7, 2015

Scheme 1. Formation of Active Esters by Pd-Catalyzed Alkoxycarbonylation of Aryl Bromides

Table 1. Key Entries in the Optimization of the Pd-Catalyzed Alkoxycarbonylation of Aryl Bromides with *N*-Hydroxysuccinimide^a

entry	1a (equiv)	ligand	conv ^b (%) (yield, %) ^c	2a:3a ^b
1	1.4	D'PrPF	42	100:0
2	1.4	dppf	82	100:0
3	1.4	rac-BINAP	48	100:0
4	1.4	PPF- ^t Bu	48	100:0
5	1.4	PPh ₃ ^d	100	100:0
6	1.4	Xantphos	100 (73)	80:20
7	1.4	HBF ₄ P ^t Bu ₃	100 (88)	100:0
8	1.05	HBF ₄ P ^t Bu ₃	100	100:0
9 ^e	1.05	HBF ₄ P ^t Bu ₃	100 (88)	100:0
10 ^f	1.05	HBF ₄ P ^t Bu ₃	50	100:0

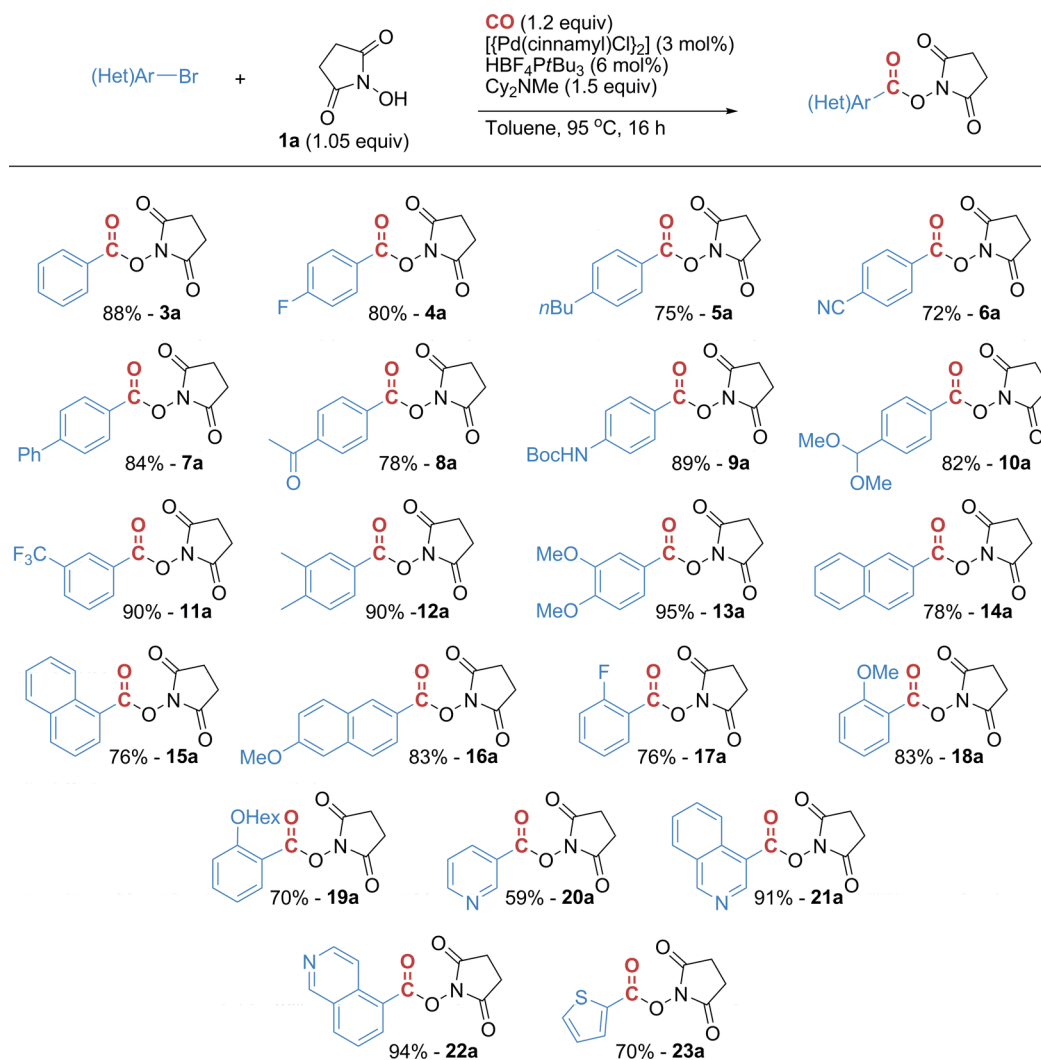
^aFull experimental details are described in the Supporting Information. ^bAs determined from the ¹H NMR spectrum of the crude reaction mixture. ^cIsolated yield of 2a. ^d12 mol % of PPh₃. ^eCOgen (1.2 equiv). ^f3.7 bar of CO pressure applied. D'PrPF: 1,1'-bis(diisopropylphosphino)ferrocene. dppf: 1,1'-bis(diphenylphosphino)ferrocene. rac-BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene. PPF-^tBu: (R)-1-[(S_p)-2-(diphenylphosphino)ferrocenyl]ethyl-di-*tert*-butylphosphine. Xantphos: 4,5-(diphenylphosphino)-9,9-dimethylxanthene. HBF₄P^tBu₃: tri-*tert*-butyl phosphonium tetrafluoroborate.

(1b), hexafluoroisopropyl alcohol (1c), *p*-nitrophenol (1d), and *N*-hydroxyphthalimide (1e), which were all found to be excellent coupling partners (Scheme 1) under the developed conditions. This extension of the Pd-catalyzed alkoxycarbonylation is not obvious, owing to the lowered nucleophilicity of the employed coupling partners when compared to more classic alcohols. Finally, the method was employed to generate an established precursor to the antiretroviral drug, saquinavir, and its ¹³C-isotope analogue.

As a starting point, the test reaction of 4-bromoanisole with NHS as the nucleophile was chosen. Based on preliminary work performed by the group of Beller, [Pd(cinnamyl)Cl]₂ was chosen as the catalyst precursor in combination with toluene as the solvent.¹⁶ All experiments were carried out using the previously reported COware/COgen two-chamber technique.^{17,18} Initial testing of various mono- and bidentate ligands included dppf, D'PrPF, BINAP, PPF-^tBu, and PPh₃, with all but one providing low rates of conversion (Table 1, entries 1–5). Although PPh₃ did provide full conversion, it was decided to seek out ligands of higher oxidative addition potential to avoid downstream problems with more complicated electrophiles. The ligands HBF₄P^tBu₃ and Xantphos led to more optimal turnovers and product distributions as both ligands provided full conversion of the starting bromide, and 73% and 88% isolated yields were obtained of the NHS-ester 2a, respectively

(Table 1, entries 6 and 7). A closer inspection of the ¹H NMR spectra of the crude reaction mixture from the reaction applying Xantphos revealed the formation of 3a (entry 6). We propose the origin of 3a to be an aryl-exchange reaction between a phenyl group of the phosphine ligand and the aryl–Pd(II)–Br complex formed after oxidative addition.^{19–21} Applying HBF₄P^tBu₃ as the ligand, lacking phenyl substituents, clearly did not lead to the formation of 3a as a byproduct and was therefore chosen (entry 7). The same selectivity and high catalytic activity were maintained even when the nucleophile and CO loading were lowered to 1.05 equiv and 1.2 equiv, respectively (entries 8 and 9). Attempts to lower the loading of the [Pd(cinnamyl)Cl]₂/HBF₄P^tBu₃ catalytic system led to incomplete conversion, and no further iterations of the conditions were attempted. Finally, an experiment was conducted in which the peak partial pressure of CO was increased to 3.7 bar (total peak pressure of 4.7 bar in the COware system), but only a 50% conversion was obtained (entry 10). The result in entry 10 indicates that increased CO pressure impedes the catalytic efficiency of this alkoxycarbonylation.

Having established an efficient catalytic system for the formation of NHS esters, we proceeded to test the generality of this system with a range of different aryl bromides. Initially, electron-rich aryl bromides were examined, providing substrates

Scheme 2. Pd-Catalyzed Alkoxy carbonylation of Aryl Bromides to Produce NHS-esters^a

^aFull experimental details are described in the Supporting Information.

5a, 12a, 13a, 18a, and 19a in yields ranging from 70 to 95% (Scheme 2).

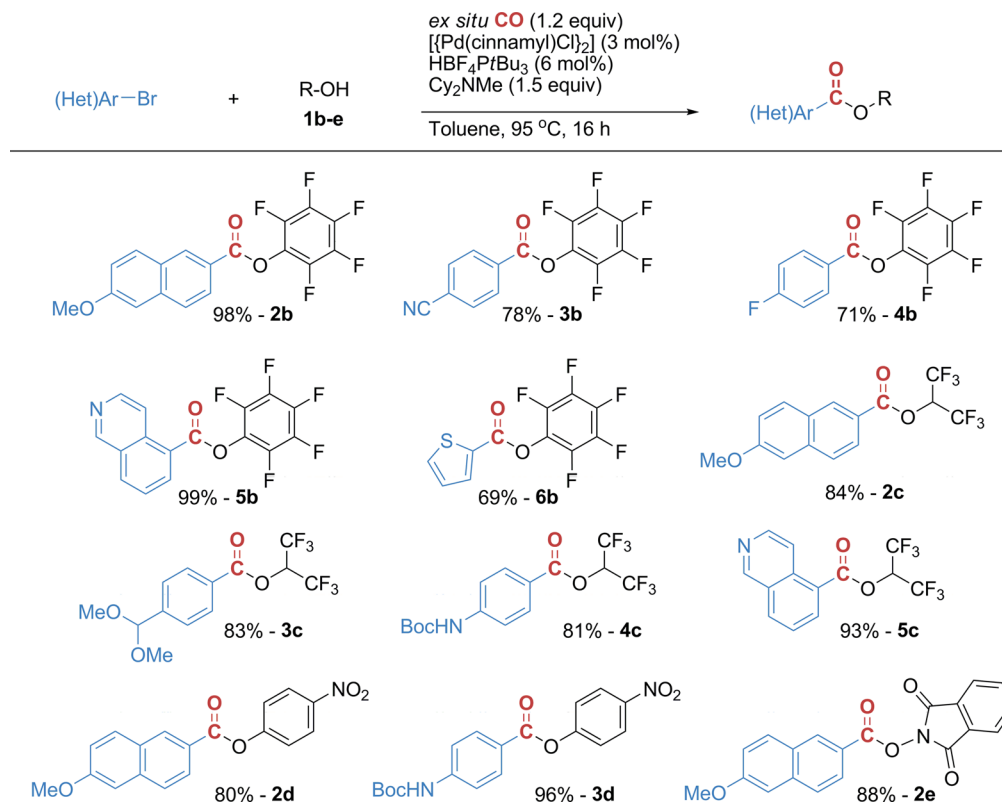
Electron-deficient aryl bromides also worked well, providing 4a, 6a, 7a, 8a, 11a, and 17a in 72–90% yields. In the case of the active esters 17a, 18a, and 19a, high yields were obtained despite the presence of an *ortho*-substituent in the starting material. A Boc-protected amine and a dimethyl acetal protected aldehyde were also found to be compatible with the developed conditions, affording 9a and 10a in yields of 89% and 82%, respectively. Heteroaromatic bromides proved reactive under the developed conditions, and 3-bromopyridine was converted into its corresponding NHS ester 20a in a good 59% isolated yield. 4-Bromoisoquinoline and 6-bromoisoquinoline both reacted cleanly, affording the desired NHS esters 21a and 22a in excellent isolated yields of 91% and 94%, respectively. Finally, 2-bromothiophene was transformed into 23a in a 70% yield.

Next, our attention was turned toward other active ester derivatives obtained using similar alkoxy carbonylation reaction conditions. The results of this work are depicted in Scheme 3. The use of active esters derived from pentafluorophenol is broadly established and has been especially expedient as an intermediate in the conversion of carboxylic acids into primary

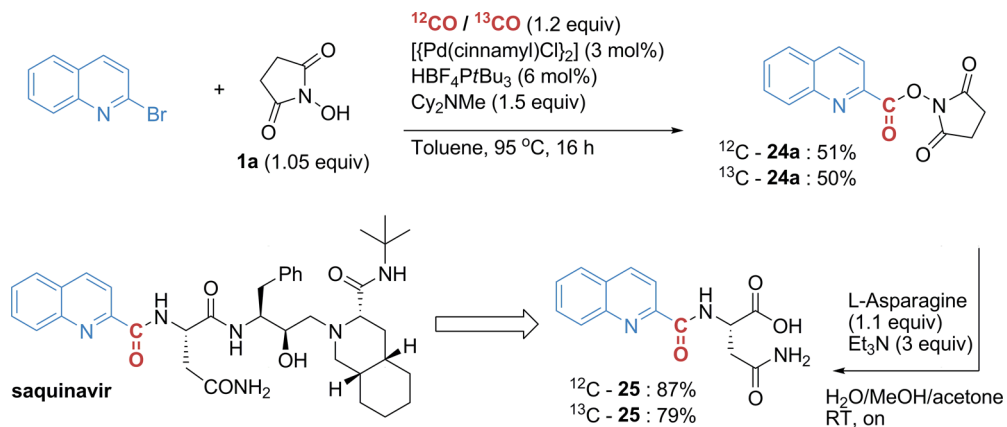
amides. This facile conversion occurs by aminolysis of the active ester with ammonia at room temperature in the course of minutes.^{22–24} When subjected to the developed conditions, the corresponding pentafluorophenyl benzoates 2b–6b were obtained in isolated yields ranging from 69–99%.

Hexafluoroisopropyl alcohol was then tested. Active esters obtained using this fluorinated alcohol serve as practical acylating reagents since the released hexafluoroisopropyl alcohol produced upon conjugation is readily removed by evaporation, thereby simplifying purification. Furthermore, acyl transfer reactions based on this ester have been shown to occur at low temperatures.^{25,26} A small increase in the CO loading from 1.2 to 1.5 equiv was required in order to obtain satisfactory conversion using this fluorinated alcohol as the nucleophile, and by doing so, compounds 2c–5c were obtained in isolated yields as high as 93%.

4-Nitrophenol also proved reactive under these slightly modified conditions, and two examples, 2d and 3d, were isolated in excellent 80% and 96%, respectively, after column chromatography.^{27–29} Finally, *N*-hydroxyphthalimide was applied in the carbonylative coupling to 2-bromo-6-methoxy-naphthalene. Although not commonly used as acyl-transfer agents, the product constitutes a phthalimide-protected *O*-

Scheme 3. Active Ester Formation by Pd-Catalyzed Alkoxy carbonylation of Aryl Bromides^a

^aFull experimental details are described in the Supporting Information.

Scheme 4. Formal Synthesis of Saquinavir and Its ¹³C-Labeled Analogue^a

^aFull experimental details are described in the Supporting Information.

acylhydroxylamine, which may be released by hydrazinolysis.³⁰ Various *O*-substituted hydroxylamine motifs have found widespread use in the bioconjugation of diverse groups such as carbohydrates,³¹ peptides,³² and proteins,³³ among others, and thus, this carbonylative approach toward *O*-acylhydroxylamines from aryl halides remains interesting. By applying *N*-hydroxyphthalimide as the limiting reagent and at a reaction temperature of 105 °C, the corresponding phthalimide-protected aminoxy derivative **2e** could be obtained in an 88% isolated yield.

The alcohols employed in Scheme 3 display marked variation in structural and electronic properties, and when *N*-

hydroxyphthalimide is disregarded, they are in general considered poor nucleophiles.

An additional advantage of using *ex situ* generated CO is the ease of performing ¹³C-labeling experiments by substituting the CO precursor for its ¹³C-isotopically labeled version.¹⁰ By the application of this technique, both the NHS ester of quinoline-2-carboxylic acid and its ¹³C-labeled counterpart (¹²C and ¹³C-**24a**) were synthesized starting from 2-bromoquinoline (Scheme 4). Although the carbonylative coupling of 2-bromoquinoline proved more problematic than for the isoquinoline analogues (Scheme 2, compounds **21a** and **22a**), ¹²C- and ¹³C-**24a** could be isolated in 51% and 50% isolated yields, respectively, after column chromatography. Subsequent

acyl transfer of these building blocks to nonprotected asparagine, led to unlabeled and ^{13}C -labeled **25** in good yields, the former of which is a known synthetic intermediate for the preparation of saquinavir,³⁴ an HIV-protease inhibitor approved for the treatment of patients suffering HIV infection.¹⁶

In conclusion, general conditions have been reported for the Pd-catalyzed alkoxycarbonylation of aromatic and heteroaromatic bromides with sterically and electronically demanding alcohols, affording active esters such as the classical NHS esters. These transformations can be carried out with near stoichiometric amounts of both the alcohol and CO under mild conditions employing palladium catalysis allowing a broad substrate scope. Even changes in the alcohol nucleophile afforded the corresponding activated carboxylic acid derivatives in high yields, proving the generality of the protocol. We believe that the developed approach will serve as a practical addition or alternative to already existing methods when designing the synthesis of acylating reagents. Finally, because of the simple setup and the use of stoichiometric CO, the methodology is adaptable to ^{13}C -labeling, which was applied for preparing a ^{13}C -isotope-labeled synthetic intermediate of the HIV protease inhibitor, saquinavir.

EXPERIMENTAL SECTION

General Methods. All purchased chemicals were used as received without further purification. Solvents were dried according to standard procedures. Flash chromatography was carried out on silica gel 60 (230–400 mesh). The chemical shifts are reported in ppm relative to solvent residual peak. The ^1H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz, and ^{19}F NMR spectra were recorded at 376 MHz. Chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) using the following peak pattern abbreviations: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; pent, pentet; sext, sextet; sept, septet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets, and td, triplet of doublets. HRMS was recorded on an LC TOF (ES).

General Method: Carbonylative Coupling of Aryl Halides with *N*-Hydroxysuccinimide (NHS). Chamber A: Pd(dba)₂ (8.6 mg, 0.015 mmol), HBF₄P⁺Bu₃⁻ (4.3 mg, 0.015 mmol), 9-methyl-9H-fluorene-9-carbonyl chloride (145.6 mg, 0.60 mmol), dioxane (3 mL), and Cy₂NMe (257 μL , 1.2 mmol) were added in that order to chamber A of the two-chamber system in a glovebox under argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. Chamber B: Aryl halide (0.50 mmol), *N*-hydroxysuccinimide (NHS) (0.53 mmol), [Pd(cinnamyl)Cl]₂ (7.8 mg, 0.015 mmol), HBF₄P⁺Bu₃⁻ (8.7 mg, 0.03 mmol), toluene (3 mL), and Cy₂NMe (160 μL , 0.75 mmol) were added in that order to chamber B of the two-chamber system (20 mL total volume) in a glovebox under argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. The two-chamber system was removed from the glovebox and placed in a preheated heatblock and was left for 16 h with vigorous stirring at 95 °C. The crude reaction mixture was then removed from the heat, and a small aliquot (40 μL) was removed for ^1H NMR analysis using CDCl₃ as solvent. The remaining crude reaction mixture was concentrated in vacuo and purified by flash column chromatography to afford the desired products.

2,5-Dioxopyrrolidin-1-yl 4-Methoxybenzoate (2a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (109.5 mg, 88%). Mp: 140–141 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.08 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 8.0$ Hz, 2H), 3.88 (s, 3H), 2.89 (s, 4H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 169.8, 165.3, 161.8, 133.2, 117.4, 114.5, 55.9, 26.0. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₂H₁₁NO₃Na 272.0529, found 272.0531.

2,5-Dioxopyrrolidin-1-yl Benzoate (3a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (96.6 mg, 88%). Mp: 137–138 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.14 (d, $J = 8.0$ Hz, 2H), 7.68 (t, $J = 8.0$ Hz, 1H), 7.53 (t, $J = 8.0$ Hz, 2H), 2.91 (s, 4H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 169.6, 162.2, 135.3, 130.9, 129.2, 125.5, 26.0. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₁H₉NO₄Na 242.0424, found 242.0427.

2,5-Dioxopyrrolidin-1-yl 4-Fluorobenzoate (4a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (94.8 mg, 80%). Mp: 112–113 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.19–8.15 (m, 2H), 7.20 (m, 2H), 2.91 (s, 4H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 169.1, 166.9 (d, $J_{\text{C-F}} = 256.0$ Hz), 160.9, 133.4 (d, $J_{\text{C-F}} = 10.0$ Hz), 121.4 (d, $J_{\text{C-F}} = 3.0$ Hz), 116.3 (d, $J_{\text{C-F}} = 22.0$ Hz), 25.7. ^{19}F NMR (400 MHz, CDCl₃): δ (ppm) –101.3. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₁H₈FNO₄Na 260.0330, found 260.0313.

2,5-Dioxopyrrolidin-1-yl 4-Butylbenzoate (5a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (103.3 mg, 75%). Mp: 65–66 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.03 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 2.68 (s, 4H), 2.89 (t, $J = 8.0$ Hz, 2H), 1.63–1.59 (m, 2H), 1.35 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 169.7, 162.2, 151.3, 130.9, 129.3, 122.7, 36.2, 33.4, 25.9, 22.5, 14.1. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₅H₁₇NO₄Na 298.1050, found 298.1052.

2,5-Dioxopyrrolidin-1-yl 4-Cyanobenzoate (6a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (87.9 mg, 72%). mp 239–240 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.24 (d, $J = 8.0$ Hz, 2H), 7.84 (d, $J = 8.0$ Hz, 2H), 2.93 (s, 4H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 169.1, 160.9, 132.9, 131.3, 129.4, 118.7, 117.7, 26.0. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₂H₈N₂O₄Na 267.0376, found 267.0371.

2,5-Dioxopyrrolidin-1-yl Biphenyl-4-carboxylate (7a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (123.7 mg, 84%). Mp: 208–209 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.23 (d, $J = 8.8$ Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 7.2$ Hz, 2H), 7.51–7.41 (m, 3H), 2.94 (s, 4H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 169.6, 162.1, 148.0, 139.8, 131.5, 129.4, 128.9, 127.8, 127.7, 124.1, 26.1. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₇H₁₃NO₄Na 318.0737, found 318.0739.

2,5-Dioxopyrrolidin-1-yl 4-Acetylbenzoate (8a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (101.3 mg, 78%). Mp: 114–115 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.22 (d, $J = 8.4$ Hz, 2H), 8.06 (d, $J = 8.4$ Hz, 2H), 2.92 (s, 4H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 197.4, 169.3, 161.5, 141.9, 131.2, 129.1, 128.8, 27.2, 26.0. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₃H₁₁NO₃Na 284.0529, found 284.0539.

2,5-Dioxopyrrolidin-1-yl 4-(tert-Butoxycarbonylamino)benzoate (9a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (148.7 mg, 89%). Mp: 177–178 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.05 (d, $J = 8.8$ Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 2H), 6.76 (br s, 1H), 2.90 (s, 4H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 169.7, 161.7, 152.2, 144.9, 132.5, 119.1, 117.8, 81.9, 28.6, 26.0. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₁₆H₁₈N₂O₆Na 357.1057, found 357.1064.

2,5-Dioxopyrrolidin-1-yl 4-(Dimethoxymethyl)benzoate (10a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (120.5 mg, 82%). Mp: 108–109 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.14 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H), 5.48 (s, 1H), 3.32 (s, 6H), 2.91 (s, 4H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 169.5, 161.9, 145.5, 130.9, 127.7, 125.4, 102.2, 52.9, 26.0. HRMS (ESI-TOF) m/z : [M + K]⁺ calcd for C₁₄H₁₅NO₆K 332.0531, found 332.0552.

2,5-Dioxopyrrolidin-1-yl 3-(Trifluoromethyl)benzoate (11a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (130.5 mg, 90%). Mp: 96–97 °C. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 8.40 (s, 1H), 8.33 (d, $J = 8.0$

H_z, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.69 (dd, *J* = 8.0, 8.0 Hz, 1H), 2.93 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.2, 161.1, 134.0, 132.2 (q, *J*_{C-F} = 33.0 Hz), 131.7 (q, *J*_{C-F} = 3.0 Hz), 130.0, 127.8 (q, *J*_{C-F} = 4.0 Hz), 126.5, 123.6 (q, *J*_{C-F} = 271.0 Hz), 26.0. ¹⁹F NMR (400 MHz, CDCl₃): δ (ppm) -62.9. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₂H₈F₃NO₄Na 310.0298, found 310.0298.

2,5-Dioxopyrrolidin-1-yl 3,4-Dimethylbenzoate (12a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (111.1 mg, 90%). Mp: 157–158 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.90 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 2.90 (s, 4H), 2.35 (s, 3H), 2.32 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.8, 161.9, 155.0, 149.3.2, 125.7, 117.4, 112.8, 110.9, 56.5, 56.4, 25.9. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₃H₁₃NO₄Na 270.0737, found 270.0735.

2,5-Dioxopyrrolidin-1-yl 3,4-Dimethoxybenzoate (13a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (133.2 mg, 95%). Mp: 178–179 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.82 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 6.93 (d, 8.4 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 2.90 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.8, 161.9, 155.0, 149.3.2, 125.7, 117.4, 112.8, 110.9, 56.5, 56.4, 25.9. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₃H₁₃NO₆Na 302.0635, found 302.0637.

2,5-Dioxopyrrolidin-1-yl 2-Naphthoate (14a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (104.7 mg, 78%). Mp: 164–165 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.77 (s, 1H), 8.08 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.99–7.90 (m, 3H), 7.69–7.58 (m, 2H), 2.93 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.7, 162.4, 136.6, 133.3, 132.6, 129.9, 129.7, 129.2, 128.2, 127.5, 125.4, 122.5, 26.0. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₅H₁₁NO₄Na 292.0580, found 292.0579.

2,5-Dioxopyrrolidin-1-yl 1-Naphthoate (15a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (101.8 mg, 76%). Mp: 140–141 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.80 (d, *J* = 8.4 Hz, 1H), 8.45 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.68–7.65 (m, 1H), 7.61–7.55 (m, 2H), 2.95 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.7, 162.4, 135.8, 133.9, 132.1, 131.7, 129.0, 128.9, 127.1, 125.5, 124.7, 121.8, 26.0. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₅H₁₁NO₄Na 292.0580, found 292.0579.

2,5-Dioxopyrrolidin-1-yl 6-Methoxy-2-naphthoate (16a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (124.0 mg, 83%). Mp: 199–200 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.66 (s, 1H), 8.04 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.23 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 2.93 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.8, 162.5, 160.8, 138.5, 133.0, 131.6, 128.0, 127.7, 126.3, 120.6, 120.1, 106.2, 55.8, 26.1. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₆H₁₃NO₅Na 322.0686, found 322.0687.

2,5-Dioxopyrrolidin-1-yl 2-Fluorobenzoate (17a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (90.5 mg, 76%). Mp: 109–110 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.10–8.06 (m, 1H), 7.69–7.64 (m, 1H), 7.31–7.20 (m, 2H), 2.91 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.3, 161.9 (d, *J*_{C-F} = 262.8 Hz), 159.6 (d, *J*_{C-F} = 4.2 Hz), 137.1 (d, *J*_{C-F} = 9.2 Hz), 133.0, 124.8 (d, *J*_{C-F} = 4.8 Hz), 117.7 (d, *J*_{C-F} = 21.5 Hz), 114.2 (d, *J*_{C-F} = 9.9 Hz), 26.0. ¹⁹F NMR (400 MHz, CDCl₃): δ (ppm) -105.2. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₁H₈FNO₄Na 260.0330, found 260.0326.

2,5-Dioxopyrrolidin-1-yl 2-Methoxybenzoate (18a). The product was obtained according to the general procedure as a white solid. Eluent 20% acetone in pentane (79.8 mg, 64%). Mp: 179–180 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.05 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.62–7.57 (m, 1H), 7.05–7.01 (m, 2H), 3.92 (s, 3H), 2.88 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.8, 161.0, 160.7, 136.3, 133.1, 120.6, 114.3, 112.5, 56.4, 26.0. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₂H₁₁NO₅Na 272.0529, found 272.0533.

2,5-Dioxopyrrolidin-1-yl 2-(Hexyloxy)benzoate (19a). The product was obtained according to the general procedure as a white solid,

eluent 20% acetone in pentane (112.2 mg, 70%). Mp: 66–67 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.02 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.58–7.53 (m, 1H), 7.02–6.98 (m, 2H), 4.05 (t, *J* = 8.0 Hz, 2H), 2.88 (s, 4H), 1.83 (m, 2H), 1.33–1.29 (m, 2H), 0.89 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.8, 160.7, 160.6, 136.1, 133.0, 120.4, 114.6, 113.5, 69.4, 31.8, 29.3, 26.0, 25.8, 22.9, 14.3. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₇H₂₁NO₅Na 342.1312, found 342.1314.

2,5-Dioxopyrrolidin-1-yl Nicotinate (20a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (64.4 mg, 59%). Mp: 137–138 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.33 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.90 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.39 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.49–7.46 (m, 1H), 2.92 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.2, 161.1, 155.5, 151.8, 138.1, 123.9, 121.9, 26.0. Spectral data were in accordance with those reported in the literature.³⁵

2,5-Dioxopyrrolidin-1-ylisoquinoline-4-carboxylate (21a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (122.3 mg, 91%). Mp: 172–173 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.45 (s, 1H), 9.37 (s, 1H), 8.75 (d, *J* = 8.8 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.88–7.84 (m, 1H), 7.73–7.69 (m, 1H), 2.95 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.5, 161.8, 159.0, 148.1, 133.9, 133.5, 128.9, 128.7, 128.6, 124.8, 116.4, 26.0. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₄H₁₀N₂O₄Na 293.0533, found 293.0513.

2,5-Dioxopyrrolidin-1-ylisoquinoline-5-carboxylate (22a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (126.9 mg, 94%). Mp: 202–203 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.34 (s, 1H), 8.69–8.60 (m, 3H), 8.28 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 2.95 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.6, 161.4, 153.5, 146.1, 136.2, 135.6, 134.7, 129.1, 126.4, 120.9, 118.2, 26.0. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₁₁N₂O₄ 271.0713, found 271.0713.

2,5-Dioxopyrrolidin-1-ylthiophene-2-carboxylate (23a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (78.6 mg, 70%). Mp: 157–158 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.03 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.78 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.21–7.19 (m, 1H), 2.90 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.4, 157.7, 136.9, 136.0, 128.7, 127.3, 26.0. HRMS (ESI-TOF) *m/z*: [M + K]⁺ calcd for C₉H₇NO₄SK 263.9727, found 263.9748.

2,5-Dioxopyrrolidin-1-ylquinoline-2-carboxylate (24a). The product was obtained according to the general procedure as a white solid, eluent 20% acetone in pentane (69.0 mg, 51%). Mp: 172–173 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.35 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.82–7.80 (m, 1H), 7.71–7.68 (m, 1H), 2.94 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 169.2, 161.0, 148.1, 137.9, 131.3, 131.1, 130.1, 129.9, 127.9, 121.9, 26.1. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₁₁N₂O₄ 271.0713, found 271.0738.

[¹³C]-2,5-Dioxopyrrolidin-1-ylquinoline-2-carboxylate (24a). The product was obtained according to the general procedure as a white solid, eluent 30% acetone in pentane (67.5 mg, 50%). Mp: 172–173 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.37 (d, *J* = 8.8 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.22 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.86–7.82 (m, 1H), 7.74–7.70 (m, 1H), 2.95 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 161.1 (¹³C enriched -COO-). HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₁₁N₂O₄ 271.0713, found 271.0734.

(Quinoline-2-carbonyl)-L-asparagine (¹²C-25). In a round-bottom flask, 2,5-dioxopyrrolidin-1-yl quinoline-2-carboxylate (¹²C-24a) (150 mg, 0.56 mmol) and L-asparagine (80.9 mg, 0.62 mmol) were dissolved in H₂O (7.5 mL), MeOH (11 mL), and acetone (400 μL). To this mixture was added Et₃N (188 μL, 1.35 mmol), and the reaction was stirred at rt for 12 h after which TLC analysis indicated full conversion of the starting material. EtOAc (50 mL) was added, and the pH of the aqueous layer was adjusted to approximately 1 by addition of 2 M HCl. The organic phase was separated, and the aqueous layer was extracted with three portions of EtOAc (70 mL)

and two portions of DCM (70 mL). The combined organic phases were then washed with brine, dried with NaSO₄, filtered, and concentrated in vacuo to leave a solid residue. The solids were washed with cold CH₂Cl₂ (3 × 2 mL) to leave a white solid which were collected and dried to leave the product compound as a colorless powder (140 mg, 87%). Mp: 198–199 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.85 (br s, 1H), 9.18 (d, *J* = 8.0 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.89 (ddd, *J* = 8.4 Hz, 6.8 Hz, 1.6 Hz, 1H), 7.74 (ddd, *J* = 8.0 Hz, 6.8 Hz, 0.08 Hz, 1H), 7.52 (br s, 1H), 7.01 (br s, 1H), 4.83 (dt, *J* = 8.6, 5.3 Hz, 1H), 2.87 (dd, *J* = 16 Hz, 6 Hz, 1H), 2.74 (dd, *J* = 16 Hz, 4.8 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 173.0, 172.3, 163.9, 149.9, 146.4, 138.6, 131.1, 129.7, 129.4, 128.7, 128.6, 119.0, 49.3, 36.8. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₁₄N₃O₄ 288.0979, found 288.0979.

(Quinoline-2-carbonyl)-L-asparagine (¹³C-25). In a round-bottom flask, 2,5-dioxopyrrolidin-1-yl quinoline-2-carboxylate (¹³C-24a) (44 mg, 0.16 mmol) and L-asparagine (23.7 mg, 0.18 mmol) were dissolved in H₂O (2.2 mL), MeOH (3.3 mL), and acetone (100 μL). To this mixture was added Et₃N (55 μL, 0.39 mmol), and the reaction was stirred at rt. for 12 h after which TLC analysis indicated full conversion of the starting material. EtOAc (20 mL) was added, and pH of the aqueous layer was adjusted to approximately 1 by addition of 2 M HCl. The organic phase was separated, and the aqueous layer was extracted with three portions of EtOAc (20 mL) and two portions of DCM (20 mL). The combined organic phases were then washed with brine, dried with NaSO₄, filtered, and concentrated in vacuo to leave a solid residue. The solids were washed with cold CH₂Cl₂ (3 × 1 mL) to leave a white solid which was collected and dried to leave the product compound as a colorless powder (34 mg, 74%). Mp: 198–199 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 12.85 (br s, 1H), 9.18 (d, *J* = 8.0 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.89 (ddd, *J* = 8.4 Hz, 6.8 Hz, 1.6 Hz, 1H), 7.74 (ddd, *J* = 8.0 Hz, 6.8 Hz, 0.08 Hz, 1H), 7.52 (br s, 1H), 7.01 (br s, 1H), 4.83 (m, 1H), 2.87 (dd, *J* = 16 Hz, 6 Hz, 1H), 2.74 (dd, *J* = 16 Hz, 4.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 163.4 (s, ¹³C-enriched). HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₁₄N₃O₄ 289.1012, found 289.1015.

General Method for Carbonylative Coupling of Aryl Halides with Pentafluorophenol. Chamber A: Pd(dba)₂ (8.6 mg, 0.015 mmol), HBF₄P^tBu₃ (4.3 mg, 0.015 mmol), 9-methyl-9H-fluorene-9-carbonyl chloride (145.6 mg, 0.60 mmol), dioxane (3 mL), and Cy₂NMe (257 μL, 1.2 mmol) were added in that order to chamber A of the two-chamber system in a glovebox under argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. Chamber B: Aryl halide (0.50 mmol), pentafluorophenol (0.53 mmol), [Pd(cinnamyl)Cl]₂ (7.8 mg, 0.015 mmol), HBF₄P^tBu₃ (8.7 mg, 0.03 mmol), toluene (3 mL), and Cy₂NMe (160 μL, 0.75 mmol) were added in that order to chamber B of the two-chamber system (20 mL total volume) in a glovebox under argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. The two-chamber system was removed from the glovebox and placed in a preheated heatblock and was left for 16 h with vigorous stirring at 95 °C. The crude reaction mixture was then removed from the heat, and a small aliquot (40 μL) was removed for ¹H NMR analysis using CDCl₃ as solvent. The remaining crude reaction mixture was concentrated in vacuo and purified by flash column chromatography to afford the desired products.

Perfluorophenyl 6-Methoxy-2-naphthoate (2b). The product was obtained according to the general procedure as a white solid, eluent 20% dichloromethane in pentane (179.8 mg, 98%). Mp: 98–99 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.72 (s, 1H), 8.12 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.25 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 3.98 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 163.2, 160.8, 138.5, 133.1, 131.6, 128.2, 127.8, 126.5, 122.0, 120.6, 106.2, 55.8. ¹⁹F NMR (400 MHz, CDCl₃): δ (ppm) –152.39 to –152.49 (m, 2F), –158.21 (t, *J* = 23.2 Hz, 1F), –162.38 to –162.53 (m, 2F). HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₈H₁₀F₅O₃ 369.0545, found 369.0534.

Perfluorophenyl 4-Cyanobenzoate (3b). The product was obtained according to the general procedure as a white solid, eluent 30% dichloromethane in pentane (122.7 mg, 78%). Mp: 115–116 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.32 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.86 (dd, *J* = 8.4, 2.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 161.5, 133.0, 131.5, 131.1, 118.5, 117.8. ¹⁹F NMR (400 MHz, CDCl₃): δ (ppm) –152.23 to –152.32 (m, 2F), –156.77 (t, *J* = 23.2 Hz, 1F), –161.53 to –161.69 (m, 2F). HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₅F₅NO₂ 314.0235, found 314.0249.

Perfluorophenyl 4-Fluorobenzoate (4b). The product was obtained according to the general procedure as a white solid, eluent 10% dichloromethane in pentane (108.7 mg, 71%). Mp: 61–62 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.25–8.22 (m, 2H), 7.26–7.20 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 167.2 (d, *J*_{C-F} = 255.8 Hz), 161.9, 133.9 (d, *J*_{C-F} = 9.7 Hz, 2C), 123.5 (d, *J*_{C-F} = 6.0 Hz), 116.6 (d, *J*_{C-F} = 22.1 Hz, 2C), 25.7. ¹⁹F NMR (400 MHz, CDCl₃): δ (ppm) –101.92 (s, 1F), –152.46 to –152.56 (m, 2F), –157.73 (t, *J* = 22.8 Hz, 1F), –162.13 to –162.28 (m, 2F). HRMS (ESI-TOF) *m/z*: [M + K]⁺ calcd for C₁₃H₄F₆O₂K 344.9753, found 344.9743.

Perfluorophenyl Isoquinoline-5-carboxylate (5b). The product was obtained according to the general procedure as a white solid, eluent 30% dichloromethane in pentane (168.1 mg, 99%). Mp: 142–143 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.38 (dd, *J* = 5.2, 1.2 Hz, 1H), 8.78–8.72 (m, 3H), 8.33 (d, *J* = 8.4 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 161.7, 153.3, 145.9, 136.4, 135.4, 134.7, 128.9, 126.2, 122.1, 117.9. ¹⁹F NMR (400 MHz, CDCl₃): δ (ppm) –152.30 to –152.39 (m, 2F), –157.34 (t, *J* = 22.8 Hz, 1F), –161.86 to –162.01 (m, 2F). HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₆H₇F₅NO₂ 340.0391, found 340.0387.

Perfluorophenyl Thiophene-2-carboxylate (6b). The product was obtained according to the general procedure as a white solid, eluent 30% dichloromethane in pentane (102.1 mg, 69%). Mp: 46–47 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.06 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.78 (dd, *J* = 6.0, 1.2 Hz, 1H), 7.24–7.22 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 158.2, 136.8, 135.7, 129.9, 128.8. ¹⁹F NMR (400 MHz, CDCl₃): δ (ppm) –152.20 to –152.39 (m, 2F), –157.67 (t, *J* = 22.8 Hz, 1F), –162.16 to –162.31 (m, 2F). HRMS could not be obtained for compound 6b, possibly due to rapid hydrolysis in solution. However, when 6b (2 mg) was stirred with KOH (5 mg) at rt in MeCN/H₂O (1:1) until full consumption of the starting ester was observed as indicated by TLC analysis, the presence of the corresponding 2-thiophenecarboxylic acid and perfluorophenol was confirmed by HRMS. **Thiophene-2-carboxylic acid.** HRMS (ESI-TOF) *m/z*: [M][–] calcd for C₅H₃O₂S 126.9859, found 126.9857. **Perfluorophenol.** HRMS (ESI-TOF) *m/z*: [M][–] calcd for C₆F₅O 182.9875, found 182.9880.

General Method for Carbonylative Coupling of Aryl Halides with Hexafluoroisopropyl Alcohol. Chamber A: Pd(dba)₂ (10.8 mg, 0.019 mmol), HBF₄P^tBu₃ (4.3 mg, 0.015 mmol), 9-methyl-9H-fluorene-9-carbonyl chloride (182.0 mg, 0.75 mmol), dioxane (3 mL), and Cy₂NMe (321 μL, 1.5 mmol) were added in that order to chamber A of the two-chamber system in a glovebox under argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. Chamber B: Aryl halide (0.50 mmol), hexafluoroisopropyl alcohol (1.25 mmol), [Pd(cinnamyl)Cl]₂ (7.8 mg, 0.015 mmol), HBF₄P^tBu₃ (8.7 mg, 0.03 mmol), toluene (3 mL), and Cy₂NMe (160 μL, 0.75 mmol) were added in that order to chamber B of the two-chamber system (20 mL total volume) in a glovebox under Argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. The two-chamber system was removed from the glovebox and placed in a preheated heatblock and was left for 16 h with vigorous stirring at 95 °C. The crude reaction mixture was then removed from the heat, and a small aliquot (40 μL) was removed for ¹H NMR analysis using CDCl₃ as solvent. The remaining crude reaction mixture was concentrated in vacuo and purified by flash column chromatography to afford the desired products.

1,1,1,3,3,3-Hexafluoropropan-2-yl 6-Methoxy-2-naphthoate (2c). The product was obtained according to the general procedure as a

white solid, eluent 30% dichloromethane in pentane (147.2 mg, 84%). Mp: 64–65 °C. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.61 (d, $J = 1.2$ Hz, 1H), 8.05 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.89 (d, $J = 8.8$ Hz, 1H), 7.81 (d, $J = 8.8$ Hz, 1H), 7.24 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.18 (d, $J = 8.8$ Hz, 1H), 6.10 (m, 1H), (3.98 (s, 3H)). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 163.9, 160.8, 138.5, 132.8, 131.6, 128.1, 127.7, 126.2, 121.9, 121.0 (q, $J = 283.3$ Hz, 2C), 120.6, 106.1, 67.2 (spt, $J = 34.4$ Hz, 1C), 55.8. ^{19}F NMR (400 MHz, CDCl_3): δ (ppm) –73.12 (d, $J = 6.4$ Hz). HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{11}\text{F}_6\text{O}_3$ 353.0607, found 353.0598.

1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(Dimethoxymethyl)benzoate (3c). The product was obtained according to the general procedure as a white solid. Eluent 30% dichloromethane in pentane (147.9 mg, 83%). Mp: 51–52 °C. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.12 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 6.02 (spt, $J = 6.0$ Hz, 1H), 3.34 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 163.4, 145.5, 130.8, 127.7, 127.2, 120.9 (q, $J = 283.2$ Hz, 2C), 102.3, 67.3 (spt, $J = 34.6$ Hz, 1C), 52.9. ^{19}F NMR (400 MHz, CDCl_3): δ (ppm) –73.24 (d, $J = 4.8$ Hz). HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{F}_6\text{O}_4$ 347.0713, found 347.0741.

1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(tert-Butoxycarbonylamino)benzoate (4c). The product was obtained according to the general procedure as a white solid. Eluent 30% dichloromethane in pentane (156.8 mg, 81%). Mp: 62–63 °C. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.04 (dd, $J = 6.8, 2.0$ Hz, 2H), 7.50 (dd, $J = 7.2, 2.0$ Hz, 2H), 6.77 (br s, 1H), 5.99 (spt, $J = 6.4$ Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 163.1, 152.3, 144.8, 132.3, 121.0, 120.9 (q, $J = 280.5$ Hz, 2C), 117.9, 82.0, 67.1 (spt, $J = 34.4$ Hz, 1C), 28.6. ^{19}F NMR (400 MHz, CDCl_3): δ (ppm) –73.21. HRMS (ESI-TOF) m/z : $[\text{M} + \text{K}]^+$ calcd for $\text{C}_{15}\text{H}_{15}\text{F}_6\text{NO}_4\text{K}$ 426.0537, found 426.0516.

1,1,1,3,3,3-Hexafluoropropan-2-yl Isoquinoline-7-carboxylate (5c). The product was obtained according to the general procedure as a white solid, eluent 1% methanol in dichloromethane (150.6 mg, 93%). Mp: 118–119 °C. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 9.36 (s, 1H), 8.76–8.72 (m, 2H), 8.60 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.30 (d, $J = 8.0$ Hz, 1H), 7.73 (t, $J = 7.6$ Hz, 1H), 6.13 (spt, $J = 6.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 162.6, 153.7, 146.3, 136.4, 135.8, 134.9, 129.2, 126.5, 122.3, 120.9 (q, $J = 280.5$ Hz, 2C), 118.2, 67.2 (spt, $J = 34.6$ Hz, 1C). ^{19}F NMR (400 MHz, CDCl_3): δ (ppm) –72.99. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_8\text{F}_6\text{NO}_2$ 324.0454, found 324.0451.

General Method for Carbonylative Coupling of Aryl Halides with *p*-Nitrophenol. Chamber A: $\text{Pd}(\text{dba})_2$ (10.8 mg, 0.019 mmol), $\text{HBF}_4\text{P}^t\text{Bu}_3$ (5.4 mg, 0.015 mmol), 9-methyl-9H-fluorene-9-carbonyl chloride (182.0 mg, 0.75 mmol), dioxane (3 mL), and C_2NMe (321 μL , 1.5 mmol) were added in that order to chamber A of the two-chamber system in a glovebox under argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon-seal. Chamber B: Aryl halide (0.50 mmol), *p*-nitrophenol (0.75 mmol), $[\{\text{Pd}(\text{cinnamyl})\text{Cl}\}_2]$ (7.8 mg, 0.015 mmol), $\text{HBF}_4\text{P}^t\text{Bu}_3$ (8.7 mg, 0.03 mmol), toluene (3 mL), and C_2NMe (160 μL , 0.75 mmol) were added in that order to chamber B of the two-chamber system (20 mL total volume) in a glovebox under Argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. The two-chamber system was removed from the glovebox and placed in a preheated heatblock and was left for 16 h with vigorous stirring at 95 °C. The crude reaction mixture was then removed from the heat, and a small aliquot (40 μL) was removed for ^1H NMR analysis using CDCl_3 as solvent. The remaining crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to afford the desired products.

4-Nitrophenyl 6-Methoxy-2-naphthoate (2d). The product was obtained according to the general procedure as a white solid, eluent 30% dichloromethane in pentane (128.9 mg, 80%). Mp: 161–162 °C. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.70 (s, 1H), 8.34 (dd, $J = 7.2, 2.4$ Hz, 2H), 8.13 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.90 (d, $J = 8.8$ Hz, 1H), 7.84 (d, $J = 8.8, 1\text{H}$), 7.46 (dd, $J = 6.8, 2.0$ Hz, 2H), 7.25 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.20 (d, $J = 2.4$ Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 164.9, 160.6, 156.3, 145.7, 138.2, 132.5, 131.5,

128.2, 127.7, 126.4, 125.6, 123.7, 123.0, 120.5, 106.2, 55.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{14}\text{NO}_5$ 324.0866, found 324.0884.

4-Nitrophenyl 4-(tert-Butoxycarbonylamino)benzoate (3d). The product was obtained according to the general procedure as a white solid, eluent dichloromethane (132.0 mg, 96%). Mp: 185–186 °C. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.31 (dd, $J = 7.2, 2.4$ Hz, 2H), 8.12 (dd, $J = 6.8, 1.6$ Hz, 2H), 7.53 (d, $J = 8.8$ Hz, 2H), 7.41 (dd, $J = 6.8, 2.0$ Hz, 2H), 6.78 (b, 1H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 164.1, 156.2, 152.4, 145.6, 144.3, 132.1, 125.6, 123.0, 122.8, 117.9, 81.9, 28.6. HRMS (ESI-TOF) m/z : $[\text{M} + \text{K}]^+$ calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_6\text{K}$ 397.1057, found 397.1059.

General Method for Carbonylative Coupling of Aryl Halides with *N*-Hydroxyphthalimide. Chamber A: $\text{Pd}(\text{dba})_2$ (10.8 mg, 0.019 mmol), $\text{HBF}_4\text{P}^t\text{Bu}_3$ (5.4 mg, 0.015 mmol), 9-methyl-9H-fluorene-9-carbonyl chloride (182.0 mg, 0.75 mmol), dioxane (3 mL), and C_2NMe (321 μL , 1.5 mmol) were added in that order to chamber A of the two-chamber system in a glovebox under argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. Chamber B: Aryl halide (1.0 mmol), *N*-hydroxyphthalimide (0.5 mmol), $[\{\text{Pd}(\text{cinnamyl})\text{Cl}\}_2]$ (7.8 mg, 0.015 mmol), $\text{HBF}_4\text{P}^t\text{Bu}_3$ (8.7 mg, 0.03 mmol), toluene (3 mL), and C_2NMe (160 μL , 0.75 mmol) were added in that order to chamber B of the two-chamber system (20 mL total volume) in a glovebox under Argon atmosphere. The chamber was sealed tightly with a screwcap fitted with a Teflon seal. The two-chamber system was removed from the glovebox and placed in a preheated heatblock and was left for 16 h with vigorous stirring at 95 °C. The crude reaction mixture was then removed from the heat, and a small aliquot (40 μL) was removed for ^1H NMR analysis using CDCl_3 as solvent. The remaining crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to afford the desired products.

1,3-Dioxoisindolin-2-yl 6-Methoxy-2-naphthoate (2e). The product was obtained according to the general procedure as a white solid, eluent 20% ethyl acetate in pentane (152.0 mg, 88%). Mp: 178–179 °C. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.72 (s, 1H), 8.09 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.95–7.93 (m, 2H), 7.88 (d, $J = 9.2$ Hz, 1H), 7.84–7.81 (m, 3H), 7.24 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 163.4, 162.6, 160.8, 138.5, 135.1, 133.0, 131.6, 129.4, 128.0, 127.7, 126.3, 124.3, 120.6, 120.3, 106.2, 55.8. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{14}\text{NO}_5$ 348.0866, found 348.0849.

■ ASSOCIATED CONTENT

● Supporting Information

General methods; description of COware and the H-Cap system; copies of ^1H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are deeply appreciative of generous financial support from the Danish National Research Foundation (Grant No. DNRF59), the Villum Foundation, the Danish Council for Independent Research: Technology and Production Sciences, the Lundbeck Foundation, the Carlsberg Foundation, and Aarhus University for financial support of this work. Furthermore, we thank the Coordenação de Aperfeiçoamento

de Pessoal de Nível Superior (CAPES) for a grant to Angelina Maria de Almeida (No. BEX 6280/13-7) and FAPEMIG.

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