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A General Method for the Preparation of Active Esters by Palladium Catalyzed Alkoxycarbonylation of Aryl Bromides.

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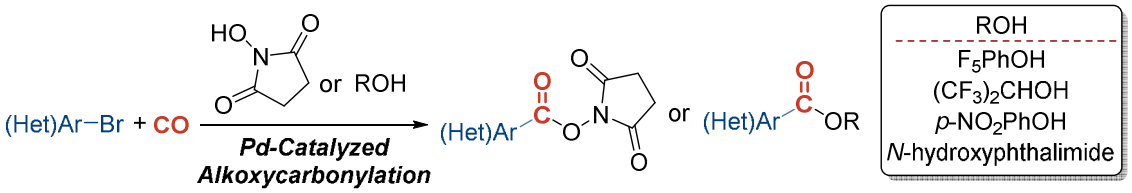


34 examples (50–98%), 5 different active esters
Low CO-pressure, Broad substrate scope
Amenable to ^{13}C-labeling

ABSTRACT: A useful method was developed for the synthesis of active esters by palladium-catalyzed alkoxycarbonylation of (hetero)aromatic bromides. The protocol was general for a range of oxygen nucleophiles including *N*-hydroxysuccinimide (NHS), pentafluorophenol (PFP), hexafluoroisopropanol (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.

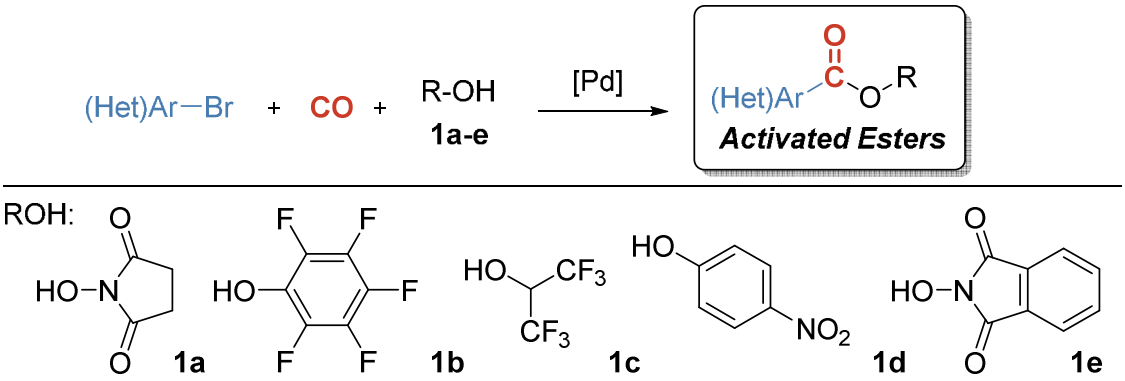
The use of active esters as coupling partners in acyl substitution reactions is a predominant strategy throughout the field of organic synthesis, and it is equally important in Nature, whereby e.g. acetyl-CoA serves as a widespread acetylating agent. By this method, a carboxylic acid can be converted 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] synthetic peptides,[5,6] and also to a large extent as crosslinking 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. $SOCl_2$ 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, and others.[10] However, all of these approaches require the presence or pre-installment of the carboxylic acid moiety, which, besides 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. To 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 towards activated esters is highly appealing due to the elaborate literature on the formation of sp^2 carbon-halogen bonds, such as electrophillic 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 alkoxycarbonylation of aromatic and heteroaromatic bromides. The scope of this methodology includes active esters formed from *N*-hydroxysuccinimide **1a** (NHS), pentafluorophenol **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 ^{13}C-isotope analog.

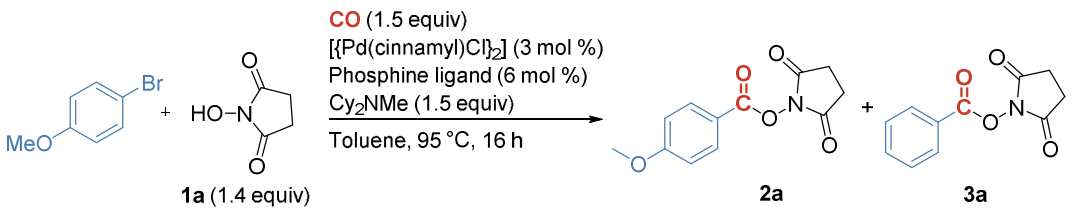
Scheme 1. Formation of Active Esters by Pd-Catalyzed Alkoxycarbonylation of Aryl Bromides



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 including dppf, D*i*PrPF, BINAP, PPF-*t*Bu and PPh$_3$, all but one providing low rates of conversion (Tabe 1, entries 1-5). Although, PPh$_3$ 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, HBF_4PtBu_3 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 ^{1}H-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.[19,20,21] Applying HBF_4PtBu_3 as the ligand, lacking phenyl substituents, did clearly not lead to the formation of **3a** as a byproduct and was therefore chosen (entry 7). The same selectivity and high catalytic activity was 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 $[Pd(cinnamyl)Cl]_2/HBF_4PtBu_3$ 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 an increased CO-pressure impedes the catalytic efficiency of this alkoxycarbonylation.

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



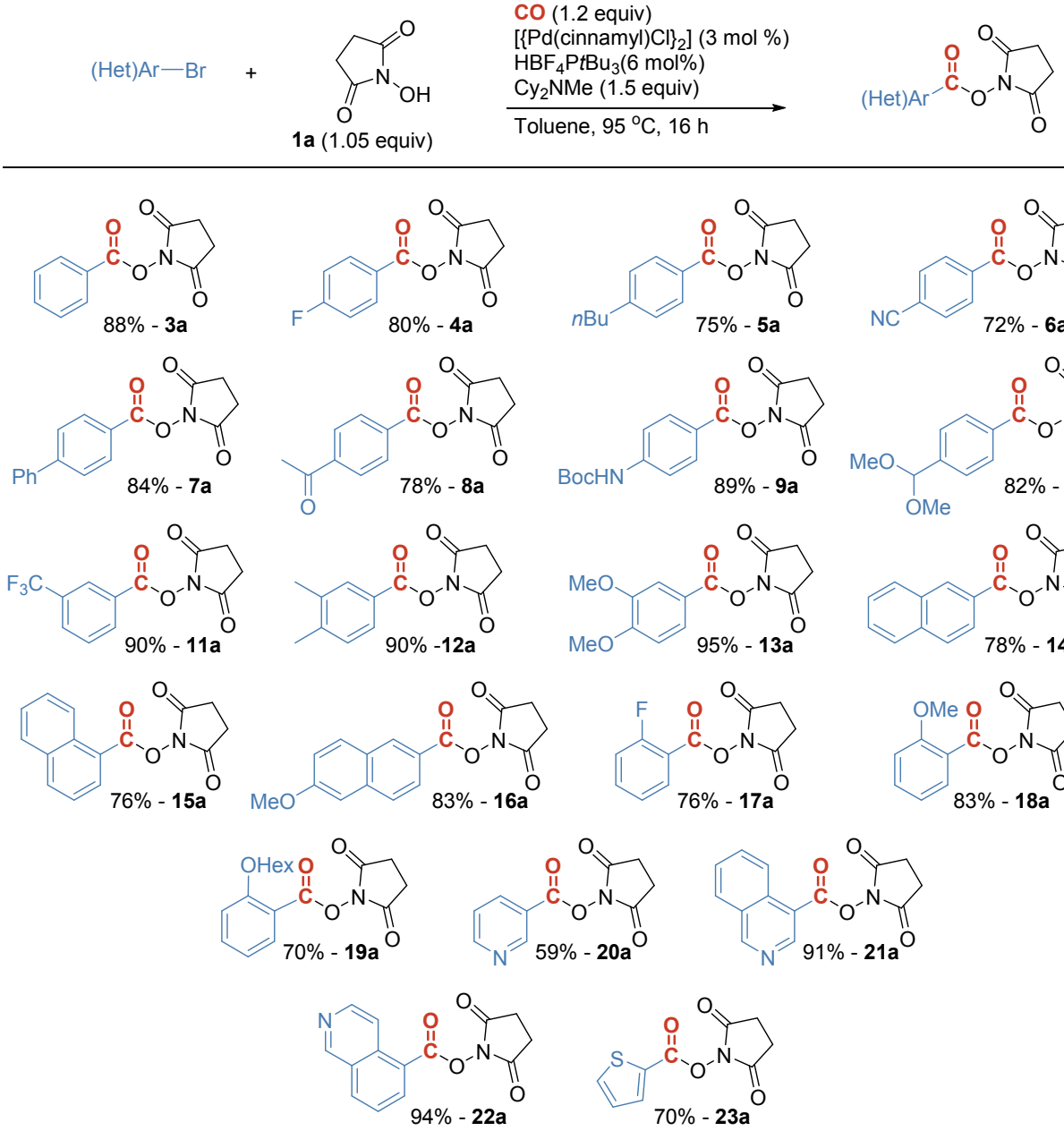
Entry	NHS (equiv)	Ligand	Conversion[b] (Yield%)[c]	2a : 3a[b]
1	1.4	D*i*PrPF	42 %	100 : 0
2	1.4	DPPF	82 %	100 : 0
3	1.4	rac-BINAP	48 %	100 : 0
4	1.4	PPF-*t*Bu	48 %	100 : 0

5	1.4	PPh_3[d]	100 %	100 : 0
6	1.4	Xantphos	100 % (73 %)	80:20
7	1.4	HBF_4PtBu_3	100 % (88 %)	100 : 0
8	1.05	HBF_4PtBu_3	100 %	100 : 0
9[e]	1.05	HBF_4PtBu_3	100 % (88%)	100 : 0
10[f]	1.05	HBF_4PtBu_3	50 %	100 : 0

[a]Full experimental details are described in the Supporting Information. [b]As determined from the ^1H NMR spectrum of the crude reaction mixture. [c]Isolated yield of **2a**. [d] 12 mol % of PPh_3. [e]COgen (1.2 equiv). [f] 3.7 bars of CO-pressure applied. D*i*PrPF: 1,1′-bis(diisopropylphosphino)ferrocene DPPF: 1,1′-bis(diphenylphosphino)ferrocene, rac-BINAP: 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene PPF-*t*Bu: (*R*)-1-[(S_P)-2-(Diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine, Xantphos: 4,5-(diphenylphosphino)-9,9-dimethylxanthene, HBF_4PtBu_3: tri-*tert*-butylphophonium tetrafluoroborate.

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 **5a**, **12a**, **13a**, **18a**, and **19a** in yields ranging from 64–95% (Scheme 2).

Scheme 2. Pd-Catalyzed Alkoxycarbonylation of Aryl Bromides to Produce NHS-Esters[a]



[a]Full experimental details are described in the Supporting Information.

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 dimethylacetal protected aldehyde were also found to be compatible with the developed conditions, affording **9a** and **10a** in yields of 89% and 82%, resp. 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%, resp. Finally, 2-bromothiphene was transformed into **23a** in a 70% yield.

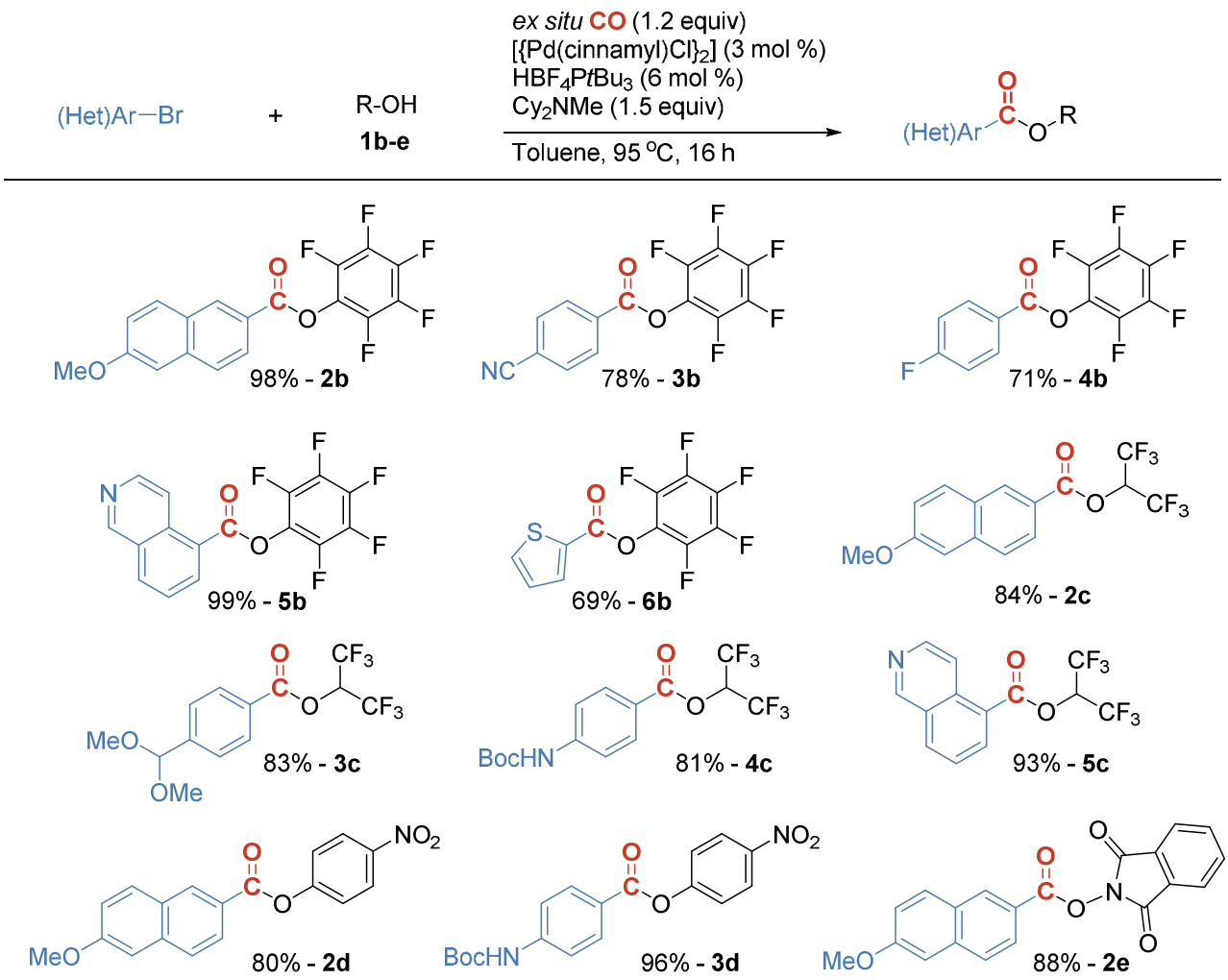
Next, our attention was turned towards other active ester derivatives obtained using similar alkoxycarbonylation reaction conditions. The results of this work are depicted in Scheme 3. The use of active esters derived from pentafluorophenol is broadly established and has been especially expedient as 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 hexafluoroisopropanol 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 equivalents 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%, resp., after column chromatography.[27-29] Finally, *N*-hydroxyphthalimide was applied in the carbonylative coupling to 2-bromo-6-methoxynaphthalene. Although, not commonly used as acyl transfer agents, the product constitutes a phthalimide-protected *O*-acylhydroxylamine, which may be released by hydrazinolysis.[30] Various *O*-substituted hydroxylamine motifs have found widespread use in the bioconjungation of diverse groups such as carbohydrates,[31] peptides[32] and proteins[33] among others, and thus, this carbonylative approach towards *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 aminooxy derivative **2e** could be obtained in an 88% isolated yield.

Scheme 3. Active Ester Formation by Pd-Catalyzed Alkoxycarbonylation of Aryl Bromides[a]



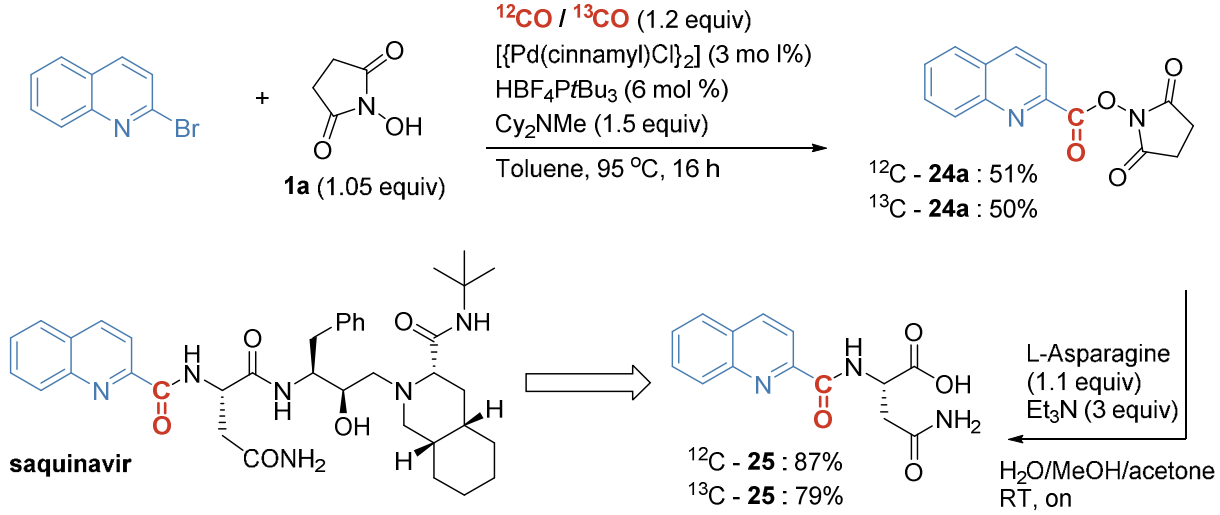
[a]Full experimental details are described in the Supporting Information.

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 ^{13}C-labeling experiments by substituting the CO-precursor for its ^{13}C-isotopically labeled version.[10] By the application of this technique, both the NHS-ester of quinoline-2-carboxylic acid and its ^{13}C-labeled counterpart (^{12}C and ^{13}C-**24a**) were synthesized starting from 2-bromoquinoline (Scheme 4). Although the carbonylative coupling of 2-bromoquinoline proved more problematic than for the isoquinoline

analogs (Scheme 2, compounds **21a** and **22a**), ^{12}C- and ^{13}C-**24a** could be isolated in 51% and 50% isolated yields, resp., after column chromatography. Subsequent acyl transfer of these building blocks to non-protected 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]

Scheme 4. Formal Synthesis of Saquinavir and its ^{13}C-Labeled Analog[a]



[a] Full experimental details are described in the supporting information.

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 ^{1}H 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 (∂ = 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), HBF_4P*t*Bu_3 (4.3 mg, 0.015 mmol), 9-methyl-9*H*-fluorene-9-carbonyl chloride (145.6 mg, 0.60 mmol), dioxane (3 mL) and and Cy_2NMe (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), $HBF_4P^tBu_3$ (8.7 mg, 0.03 mmol), toluene (3 mL) and Cy_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 ^{o}C. The crude reaction mixture was then removed from the heat and a small aliquot (40 µL) was removed for ^{1}H 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.

2,5-Dioxopyrrolidin-1-yl 4-methoxybenzoate (2a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (109.5 mg, 88%); mp 140-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{12}H_{11}NO_5Na$ 272.0529; Found 272.0531.

2,5-Dioxopyrrolidin-1-yl benzoate (3a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (96.6 mg, 88%); mp 137-138 °C. ^1H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{11}H_9NO_4Na$ 242.0424; Found 242.0427.

2,5-Dioxopyrrolidin-1-yl 4-fluorobenzoate (4a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (94.8 mg, 80%); mp 112-113 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.19-8.15 (m, 2H), 7.20 (m, 2H), 2.91 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.1, 166.9 (d, J_{C-F} = 256.0 Hz), 160.9, 133.4 (d, J_{C-F} = 10.0 Hz), 121.4 (d, J_{C-F} = 3.0 Hz), 116.3 (d, J_{C-F} = 22.0 Hz), 25.7. ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) -101.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_8FNO_4Na$ 260.0330; Found 260,0313.

2,5-Dioxopyrrolidin-1-yl 4-butylbenzoate (5a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (103.3 mg, 75%); mp 65-66 °C. ^1H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{15}H_{17}NO_4Na$ 298.1050; Found 298,1052.

2,5-Dioxopyrrolidin-1-yl 4-cyanobenzoate (6a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (87.9 mg, 72%); mp 239-240 °C. ^1H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{12}H_8N_2O_4Na$ 267.0376; Found 267.0371.

2,5-Dioxopyrrolidin-1-yl biphenyl-4-carboxylate (7a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (123.7 mg, 84%); mp 208-209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{17}H_{13}NO_4Na$ 318.0737; Found 318.0739.

2,5-Dioxopyrrolidin-1-yl 4-acetylbenzoate (8a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (101.3 mg, 78%); mp 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{13}H_{11}NO_5Na$ 284.0529; Found 284.0539.

2,5-Dioxopyrrolidin-1-yl 4-(*tert*-butoxycarbonylamino)benzoate (9a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (148.7 mg, 89%); mp 177-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{16}H_{18}N_2O_6Na$ 357.1057; Found 357.1064.

2,5-Dioxopyrrolidin-1-yl 4-(dimethoxymethyl)benzoate (10a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (120.5 mg, 82%); mp 108-109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{14}H_{15}NO_6K$ 332.0531; Found 332.0552.

2,5-Dioxopyrrolidin-1-yl 3-(trifluoromethyl)benzoate (11a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (130.5 mg, 90%); mp 96-97 °C. ^{1}H NMR (400

MHz, $CDCl_3$): δ (ppm) 8.40 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.69 (dd, *J* = 8.0, 8.0 Hz, 1H), 2.93 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 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. ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) -62.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_8F_3NO_4Na$ 310.0298; Found 310.0298.

2,5-Dioxopyrrolidin-1-yl 3,4-dimethylbenzoate (12a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (111.1 mg, 90%); mp 157-158 °C. ^1H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{13}H_{13}NO_4Na$ 270.0737; Found 270.0735.

2,5-Dioxopyrrolidin-1-yl 3,4-dimethoxybenzoate (13a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (133.2 mg, 95%); mp 178-179 °C. ^1H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{13}H_{13}NO_6Na$ 302.0635; Found 302.0637.

2,5-Dioxopyrrolidin-1-yl 2-naphthoate (14a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (104.7 mg, 78%); mp 164-165 °C. ^1H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{15}H_{11}NO_4Na$ 292.0580; Found 292.0579.

2,5-Dioxopyrrolidin-1-yl 1-naphthoate (15a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (101.8 mg, 76%); mp 140-141 °C. ^1H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{15}H_{11}NO_4Na$ 292.0580; Found 292.0579.

2,5-Dioxopyrrolidin-1-yl 6-methoxy-2-naphthoate (16a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (124.0 mg, 83%); mp 199-200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{16}H_{13}NO_5Na$ 322.0686; Found 322.0687.

2,5-Dioxopyrrolidin-1-yl 2-fluorobenzoate (17a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (90.5 mg, 76%); mp 109-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10-8.06 (m, 1H), 7.69-7.64 (m, 1H), 7.31-7.20 (m, 2H), 2.91 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.3, 161.9 (d, $J_{C\text{-}F}$ = 262.8 Hz), 159.6 (d, $J_{C\text{-}F}$ = 4.2 Hz), 137.1 (d, $J_{C\text{-}F}$ = 9.2 Hz), 133.0, 124.8 (d, $J_{C\text{-}F}$ = 4.8 Hz), 117.7 (d, $J_{C\text{-}F}$ = 21.5 Hz), 114.2 (d, $J_{C\text{-}F}$ = 9.9 Hz), 26.0. ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) -105.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_8FNO_4Na$ 260.0330; Found 260.0326.

2,5-Dioxopyrrolidin-1-yl 2-methoxybenzoate (18a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (79.8 mg, 64%); mp 179-180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (dd, J = 8.0 Hz, 1.6, 1H), 7.62-7.57 (m, 1H), 7.05-7.01 (m, 2H), 3.92 (s, 3H), 2.88 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{11}NO_5Na$ 272.0529; Found 272.0533.

2,5-Dioxopyrrolidin-1-yl 2-(hexyloxy)benzoate (19a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (112.2 mg, 70%); mp 66-67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{21}NO_5Na$ 342.1312; Found 342.1314.

2,5-Dioxopyrrolidin-1-yl nicotinate (20a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (64.4 mg, 59%); mp 137-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 161.1, 155.5, 151.8, 138.1, 123.9, 121.9, 26.0. Spectral data was in according with those reported in the literature.[35]

2,5-Dioxopyrrolidin-1-yl isoquinoline-4-carboxylate (21a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (122.3 mg, 91%); mp 172-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{14}H_{10}N_2O_4Na$ 293.0533; Found 293.0513.

2,5-Dioxopyrrolidin-1-yl isoquinoline-5-carboxylate (22a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (126.9 mg, 94%); mp 202-203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{14}H_{11}N_2O_4$ 271.0713; Found 271.0713.

2,5-Dioxopyrrolidin-1-yl thiophene-2-carboxylate (23a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (78.6 mg, 70%); mp 157-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_9H_7NO_4SK$ 263.9727; Found 263.9748.

2,5-Dioxopyrrolidin-1-yl quinoline-2-carboxylate (24a). The product was obtained according to general procedure, as a white solid. Eluent 20% acetone in pentane (69.0 mg, 51%); mp 172-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{14}H_{11}N_2O_4$ 271.0713; Found 271.0738.

[^{13}C]-2,5-Dioxopyrrolidin-1-yl quinoline-2-carboxylate (24a). The product was obtained according to general procedure, as a white solid. Eluent 30% acetone in pentane (67.5 mg, 50%); mp 172-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.1 (^{13}C enriched -**C**OO-). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}N_2O_4$ 271.0713; Found 271.0734.

(Quinoline-2-carbonyl)-L-asparagine (^{12}C-25). In a round bottom flask, 2,5-dioxopyrrolidin-1-yl quinoline-2-carboxylate (^{12}C-**24a**) (150 mg, 0.56 mmol) and L-Asparagine (80.9 mg, 0.62 mmol) was dissolved in H_2O (7.5 mL), MeOH (11 mL) and acetone (400 µL). To this mixture was added Et_3N (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 pH of the aqueous layer was adjusted to approx. 1 by addition of 2M HCl. The organic phase was separated, and the aqueous layer was extracted with further 3 portions of EtOAc (70 mL) and 2 portions of DCM (70 mL). The combined organic phases were then washed with brine, dried with $NaSO_4$, filtered and concentrated *in vacuo* to leave a solid residue. The solids were washed with cold CH_2Cl_2 (3x2 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. ^{1}H NMR (400 MHz, DMSO-*d6*): 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).

^{13}C NMR (100 MHz, DMSO-*d6*): 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 $C_{14}H_{14}N_3O_4$ 288.0979; Found 288.0979.

(Quinoline-2-carbonyl)-L-asparagine (^{13}C-25). In a round bottom flask, 2,5-dioxopyrrolidin-1-yl quinoline-2-carboxylate (^{13}C-**24a**) (44 mg, 0.16 mmol), L-Asparagine (23.7 mg, 0.18 mmol) was dissolved in H_2O (2.2 mL), MeOH (3.3 mL) and acetone (100 µL). To this mixture was added Et_3N (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 approx. 1 by addition of 2M HCl. The organic phase was separated, and the aqueous layer was extracted w. further 3 portions of EtOAc (20 mL) and 2 portions of DCM (20 mL). The combined organic phases were then washed with brine, dried with $NaSO_4$, filtered and concentrated *in vacuo* to leave a solid residue. The solids were washed with cold CH_2Cl_2 (3x1 mL) to leave a white solid which were collected and dried to leave the product compound as a colorless powder (34 mg, 74%); mp 198-199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.4 (s, ^{13}C-enriched). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_3O_4$ 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), HBF_4P*t*Bu_3 (4.3 mg, 0.015 mmol), 9-methyl-9*H*-fluorene-9-carbonyl chloride (145.6 mg, 0.60 mmol), dioxane (3 mL) and and Cy_2NMe (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), $HBF_4P^tBu_3$ (8.7 mg, 0.03 mmol), toluene (3 mL) and Cy_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 ^{o}C. The crude reaction mixture was then removed from the heat and a small aliquot (40 μL) was removed for ^{1}H 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.

Perfluorophenyl 6-methoxy-2-naphthoate (2b). The product was obtained according to general procedure, as a white solid. Eluent 20% dichloromethane in pentane (179.8 mg, 98%); mp 98-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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. ^{19}F NMR (400 MHz, $CDCl_3$): 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 $C_{18}H_{10}F_5O_3$ 369.0545; Found 369.0534.

Perfluorophenyl 4-cyanobenzoate (3b). The product was obtained according to general procedure, as a white solid. Eluent 30% dichloromethane in pentane (122.7 mg, 78%); mp 115-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.32 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.86 (dd, *J* = 8.4, 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.5, 133.0, 131.5, 131.1, 118.5, 117.8. ^{19}F NMR (400 MHz, $CDCl_3$): 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 $C_{14}H_5F_5NO_2$ 314.0235; Found 314.0249.

Perfluorophenyl 4-fluorobenzoate (4b). The product was obtained according to general procedure, as a white solid. Eluent 10% dichloromethane in pentane (108.7 mg, 71%); mp 61-62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.25-8.22 (m, 2H), 7.26-7.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.2 (d, $J_{C\text{-}F}$ = 255.8 Hz), 161.9, 133.9 (d, $J_{C\text{-}F}$ = 9.7 Hz, 2C), 123.5 (d, $J_{C\text{-}F}$ = 6.0 Hz), 116.6 (d, $J_{C\text{-}F}$ = 22.1 Hz, 2C), 25.7. ^{19}F NMR (400 MHz, $CDCl_3$): 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 $C_{13}H_4F_6O_2K$ 344.9753; Found 344.9743.

Perfluorophenyl isoquinoline-5-carboxylate (5b). The product was obtained according to general procedure, as a white solid. Eluent 30% dichloromethane in pentane (168.1 mg, 99%); mp 142-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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) . ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.7, 153.3, 145.9, 136.4, 135.4, 134.7, 128.9, 126.2, 122.1, 117.9. ^{19}F NMR (400 MHz, $CDCl_3$): 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 $C_{16}H_7F_5NO_2$ 340.0391; Found 340.0387.

Perfluorophenyl thiophene-2-carboxylate (6b). The product was obtained according to general procedure, as a white solid. Eluent 30% dichloromethane in pentane (102.1 mg, 69%); mp 46-47 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158.2, 136.8, 135.7, 129.9, 128.8. ^{19}F NMR (400 MHz, $CDCl_3$): 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/H_2O (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 $C_5H_3O_2S$ 126.9859; Found 126.9857. *Perfluorophenol:* HRMS (ESI-TOF) m/z: $[M]^-$ Calcd for C_6F_5O 182.9875; Found 182.9880.

General Method for Carbonylative Coupling of Aryl Halides with Hexafluoroisopropanol. ***Chamber A:*** $Pd(dba)_2$ (10.8 mg, 0.019 mmol), HBF_4P*t*Bu_3 (4.3 mg, 0.015 mmol), 9-methyl-9*H*-fluorene-9-carbonyl chloride (182.0 mg, 0.75 mmol), dioxane (3 mL) and and Cy_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), Hexafluoroisopropanol (1.25 mmol), $[\{Pd(cinnamyl)Cl\}_2]$ (7.8 mg, 0.015 mmol), $HBF_4P^tBu_3$ (8.7 mg, 0.03 mmol), toluene (3 ml) and Cy_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 ^{o}C. The crude reaction mixture was then removed from the heat and a small aliquot (40 μL) was removed for ^{1}H 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.

1,1,1,3,3,3-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 . ^{1}H 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: $[M + H]^+$ Calcd for $C_{15}H_{11}F_6O_3$ 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. ^{1}H 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: $[M + H]^+$ Calcd for $C_{13}H_{13}F_6O_4$ 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. ^{1}H 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: $[M + K]^+$ Calcd for $C_{15}H_{15}F_6NO_4K$ 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. ^{1}H 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: $[M + H]^+$ Calcd for $C_{13}H_8F_6NO_2$ 324.0454; Found 324.0451.

General Method for Carbonylative Coupling of Aryl Halides with *p*-Nitrophenol. ***Chamber A:*** $Pd(dba)_2$ (10.8 mg, 0.019 mmol), HBF_4P*t*Bu_3 (5.4 mg, 0.015 mmol), 9-methyl-9*H*-fluorene-9-carbonyl chloride (182.0 mg, 0.75 mmol), dioxane (3 mL) and and Cy_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), $[\{Pd(cinnamyl)Cl\}_2]$ (7.8 mg, 0.015 mmol), $HBF_4P^tBu_3$ (8.7 mg, 0.03 mmol), toluene (3 mL) and Cy_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 ^{1}H 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 general procedure, as a white solid. Eluent 30% dichloromethane in pentane (128.9 mg, 80%); mp 161-162 °C. ^{1}H 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, 1H), 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: $[M + H]^+$ Calcd for $C_{18}H_{14}NO_5$ 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. ^{1}H 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: $[M + K]^+$ Calcd for $C_{18}H_{18}N_2O_6K$ 397.1057; Found 397.1059.

General Method for Carbonylative Coupling of Aryl Halides with *N*-Hydroxyphthalimide. ***Chamber A:*** $Pd(dba)_2$ (10.8 mg, 0.019 mmol), HBF_4P*t*Bu_3 (5.4 mg, 0.015 mmol), 9-methyl-9*H*-fluorene-9-carbonyl chloride (182.0 mg, 0.75 mmol), dioxane (3 mL) and and Cy_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), [{Pd(cinnamyl)Cl}$_2$] (7.8 mg, 0.015 mmol), $HBF_4P^tBu_3$ (8.7 mg, 0.03 mmol), toluene (3 mL) and Cy_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 ^{o}C. The crude reaction mixture was then removed from the heat and a small aliquot (40 μL) was removed for ^{1}H 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-Dioxoisoindolin-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. ^{1}H 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: $[M + H]^+$ Calcd for $C_{20}H_{14}NO_5$ 348.0866; Found 348.0849.

ASSOCIATED CONTENT

Supporting Information

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

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