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Palladium-Catalyzed Carbonylation of (Hetero)Aryl, Alkenyl and Allyl Halides by Means of *N*-Hydroxysuccinimidyl Formate as CO Surrogate

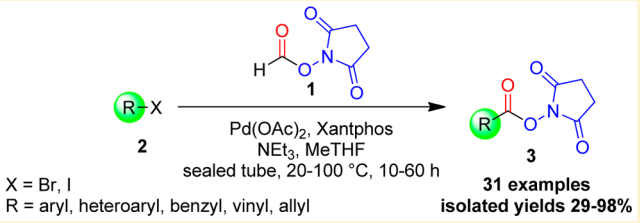
Anaïs Barré,[†,‡] Mihaela-Liliana Ţînţaş,[†] Florent Alix,[‡] Vincent Gembus,*[,‡] Cyril Papamicaël,[†] and Vincent Levacher*[,†]

[†]Normandie Univ, COBRA, UMR 6014 et FR 3038; Univ Rouen; INSA Rouen; CNRS, IRCOF, 1 rue Tesniére, 76821 Mont Saint Aignan Cedex, France

[‡]VFP Therapies, 15 rue François Couperin, 76000 Rouen, France

Supporting Information

ABSTRACT: An efficient Pd-catalyzed carbonylation protocol is described for the coupling of a large panel of aryl, heteroaryl, benzyl, vinyl and allyl halides **2** with the unusual *N*-hydroxysuccinimidyl (NHS) formate **1** as a CO surrogate to afford the corresponding valuable NHS esters **3**. High conversion to the coupling products was achieved with up to 98% yield by means of $Pd(OAc)_2$/Xantphos catalyst system.

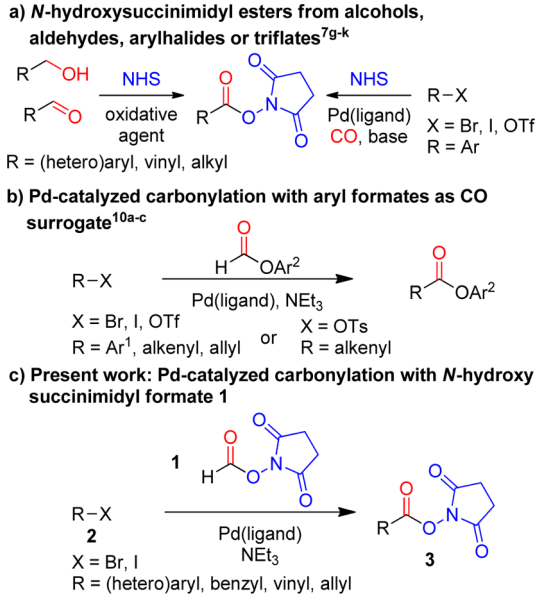


INTRODUCTION

N-Hydroxysuccinimidyl esters (NHS esters) are widely used as activated carboxylic acid derivatives to promote the reaction with most common heteronucleophiles such as amines, alcohols and thiols. They have the major advantages of being stable and easy to handle, while remaining highly reactive under very mild reaction conditions.[1] Their unique properties make them particularly attractive in bioconjugate chemistry,[2] peptide synthesis,[3] as well as in the preparation of natural products,[4] lactams,[5] and numerous bioactive compounds.[6]

Among the various methods described in the literature,[7] conversion of carboxylic acids via *N*,*N*′-dicyclohexylcarbodiimide (DCC) activation[7a] appears as the prevailing route for the preparation of NHS esters. However, this method suffers from several drawbacks such as the allergenic potential of the coupling agent and the formation of urea as byproduct, making difficult the isolation of pure NHS esters. Over the past decade, their preparation has witnessed a new wave of interest from several research groups. Among the different methods newly investigated, one can mention oxidative amidation of aromatic aldehydes or alcohols with NHS under oxidizing conditions (Scheme 1, a).[7g−i] In 2003, Wentland et al. reported an efficient preparation of NHS esters using a palladium-catalyzed carbonylation of aryl halides or triflates under carbon monoxide (CO) atmosphere in the presence of NHS.[7j] Most recently, an additional synthesis of NHS esters via palladium-catalyzed carbonylation of (hetero)aromatic bromides was elegantly reported by Skrydstrup et al.[7k] using an ex situ generation of CO gas by means of two-chamber equipment (Scheme 1, a).[8] Despite the great interest expressed by organic chemists in this palladium-catalyzed carbonylation approach, the use of highly toxic gaseous CO seriously impedes a safe and straightforward implementation of this attractive method in both academic and industrial laboratories.

Scheme 1. Selected Previous Works Related to the Method Presently Developed



As part of an ongoing research program aimed at developing potent central cholinesterase inhibitors,[9] highly functionalized NHS esters were needed to implement postfunctionalization strategies under mild conditions. We thus considered preparing

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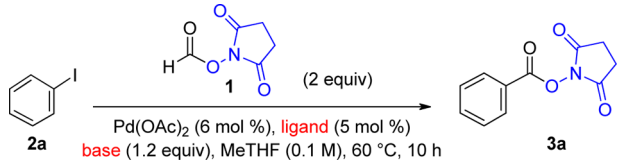
the desired NHS esters by a palladium carbonylative cross-coupling by means of a CO surrogate. Over the last few decades, many efforts have been devoted to develop CO surrogates to thwart the tricky use of CO gas in numerous carbonylation processes.[8,10] In particular, the Manabe[10a,b] and Tsuji[10c] groups have successfully reported the use of aryl formates as CO surrogates in palladium carbonylative transformations to generate phenolic esters (Scheme 1, b). Inspired by these pioneering results, we hypothesized that NHS esters **3** could be straightforwardly formed from halide derivatives **2** and *N*-hydroxysuccinimidyl formate **1** by a palladium-catalyzed carbonylative process (Scheme 1, c). Herein, we report an efficient procedure for the preparation of NHS esters **3** from the unusual but readily available *N*-hydroxysuccinimidyl formate **1**.

RESULTS AND DISCUSSION

NHS formate **1** was prepared in 99% yield from hydroxysuccinimide and formic acid according to a modified procedure.[11] It is worth mentioning that NHS formate **1** was isolated pure by simple evaporation as a highly crystalline compound and could be stored for several weeks under an inert atmosphere. With this putative CO surrogate **1** in hand, we first examined its aptitude to act as a CO source under various basic conditions. Overall, decarbonylation of NHS formate **1** is completed within a few minutes at 60 °C in the presence of triethylamine (NEt_3), *N*,*N*-diisopropylethylamine (DIPEA) or 4-dimethylaminopyridine (DMAP), whereas a few hours are required with less nucleophilic nitrogen bases such as pyridine (see Supporting Information).

In a first set of experiments, the performance of CO surrogate **1** was assessed via the carbonylation of iodobenzene **2a** by varying the main reaction parameters (Table 1). The reaction was performed in a sealed tube in the presence of $Pd(OAc)_2$, 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) and NEt_3 at 60 °C in various solvents (tetrahydrofuran (THF), dimethylformamide (DMF), acetonitrile (ACN), cyclopentyl methyl ether (CPME), dimethyl carbonate (DMC), diethyl carbonate (DEC), toluene, 2-methyltetrahydrofuran (MeTHF) (see Supporting Information). To our delight, iodobenzene **2a** was fully converted into NHS ester **3a** within 10 h regardless of the solvent used. Finally, since the solvent has no impact on the conversion, the more environmentally friendly MeTHF[12] was preferred to pursue this optimization study (Table 1, entry 1). The reaction could be advantageously achieved at room temperature without detrimental effect on the conversion, however, at the expense of the reaction time (Table 1, entry 2). Gratifyingly, attempts to decrease either the amount of the CO surrogate **1** (1.2 equiv) or the catalyst loading [3 mol % $Pd(OAc)_2$/2.5 mol % Xantphos] did not affect the conversion of the reaction (Table 1, entries 3−4). We next investigated the influence of the ligand and the base on the outcome of the reaction. As expected, when the reaction was conducted by failing to use either the ligand or the base, only traces of **3a** were observed (Table 1, entries 5−6). A screening of the base revealed that DIPEA and DMAP are as effective as NEt_3, while the less nucleophilic pyridine afforded NHS ester **3a** in only 20% yield (Table 1, entries 7−9). Lastly, inorganic bases such as Cs_2CO_3 were unable to promote the reaction (Table 1, entry 10). A survey of the literature indicated that Xantphos usually prevails in palladium-catalyzed carbonylation of aryl halide with aryl formate.[10c,d] In our case, the use of PPh_3 or $P(^tBu)_3$ as ligand led to a partial conversion in spite of a longer reaction time (entries 11−12), while 1,3-Bis(diphenylphosphino)propane (dppp) and 1,1′-Bis(diphenylphosphino)ferrocene (dppf) gave poor conversion to the desired NHS ester **3a** (entries 13−14).

Table 1. Optimization of Reaction Conditions for Carbonylation of Iodobenzene 2a[a]



entry	ligand	base	yield[b] (%)
1	Xantphos	NEt_3	>95
2[c]	Xantphos	NEt_3	>95
3[d]	Xantphos	NEt_3	>95
4[e]	Xantphos	NEt_3	>95
5	none	NEt_3	<2
6	Xantphos	none	<2
7	Xantphos	DIPEA	>95
8	Xantphos	DMAP	>95
9	Xantphos	pyridine	20
10	Xantphos	Cs_2CO_3	4
11[f]	PPh_3	NEt_3	42
12[f]	$P(^tBu)_3{\cdot}HBF_4$	NEt_3	50
13	dppp	NEt_3	7
14	dppf	NEt_3	4

[a]Reactions were performed on 0.5 mmol in sealed tube under an argon atmosphere. [b]Estimated by ^1H NMR using Bn_2O as an internal standard. [c]Reaction performed at 20 °C, 48 h. [d]Reaction with 1.2 equiv of **1**. [e]Reaction with 3 and 2.5 mol % of $Pd(OAc)_2$ and Xantphos, respectively, at 0.2 M. [f]Reaction for 24 h.

Encouraged by these promising results, we next examined the substrate scope of this catalytic system by using a broad set of (hetero)aryl, vinyl, benzyl and allyl halides **2**. Initially, aryl iodide derivatives were studied under the optimized reaction conditions reported in Table 2. We were pleased to observe that a large range of aryl iodides **2b−n** bearing various electron-donating or -withdrawing groups afforded NHS esters **3b−n** in good to excellent yields (Table 2, entries 2−14). It is worth noting that starting from 1-bromo-4-iodobenzene **2m**, the coupling reaction proceeded regioselectively at room temperature to afford the NHS ester **3m** in 90% yield (Table 2, entry 13). However, when the reaction was conducted at 60 °C a mixture of mono- and dicarbonylated product was obtained, paving the way to the development of sequential carbonylation processes from aryl bromide/iodide derivatives. Reaction of 9-iodophenanthrene **2o** and 1-iodonaphthalene **2p** proceeded to afford the corresponding polycyclic aromatics NHS esters **3o** and **3p** in good yields (Table 2, entries 15−16). Remarkably, various aryl iodides possessing sensitive functional groups gave satisfactory results. Notably, 4-iodoaniline **2q** was completely converted into the desired NHS esters **3q** and isolated in 61% yield (Table 2, entry 17). Changing the substrate to 2-iodoaniline **2r** led to NHS ester **3r** in 82% yield, while 4-iodophenol **2s** gave rise to the expected product **3s** in 57% yield (Table 2, entries 18−19). Lastly, 3-bromobenzaldehyde **2t** furnished NHS ester **3t** in 60% ^1H NMR yield and was isolated in a modest 34% yield (Table 2, entry 20). At this stage, one should note that this protocol was also assessed with aryl bromides giving in numerous cases high yields (for example,

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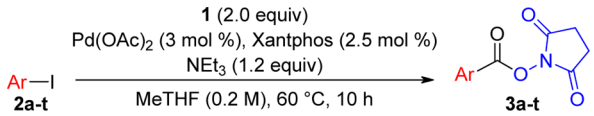
Table 2. Scope of Aryl Iodides 2a−t with NHS Formate 1[a]



entry	Ar-	3	yield (%)
1[b]	Ph-	**3a**	86
2	4-MeCO-C_6H_4-	**3b**	73[c]
3	4-Me-C_6H_4-	**3c**	84
4	3-Me-C_6H_4-	**3d**	78
5	4-NC-C_6H_4-	**3e**	72
6	4-MeO-C_6H_4-	**3f**	75
7	3,5-$(CF_3)_2$-C_6H_3-	**3g**	65
8	4-O_2N-C_6H_4-	**3h**	71
9	3-O_2N-C_6H_4-	**3i**	78
10	3-EtOCO-C_6H_4-	**3j**	94
11	2-MeOCO-C_6H_4-	**3k**	96
12	4-Cl-C_6H_4-	**3l**	86
13[d]	4-Br-C_6H_4-	**3m**	90
14	4-F-C_6H_4-	**3n**	78
15	9-phenanthryl-	**3o**	89
16	1-naphthyl-	**3p**	76
17	4-H_2N-C_6H_4-	**3q**	61
18	2-H_2N-C_6H_4-	**3r**	82
19	4-HO-C_6H_4-	**3s**	57
20	3-OHC-C_6H_4-[e]	**3t**	34 (60)[f]

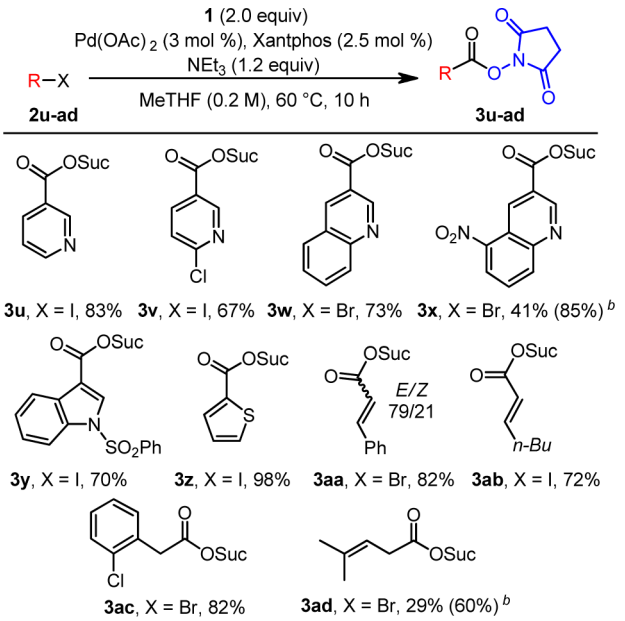
[a]Reactions were performed with 1.0 mmol of **2** in sealed tube under an argon atmosphere. Yields are for isolated products. [b]Reaction was performed with 0.5 mmol of **2a** at 0.1 M. [c]Reaction with 4′-bromoacetophenone gave **3b** in 89% yield; 4′-chloroacetophenone gave no reaction. [d]Reaction was performed at 25 °C for 60 h. [e]Reaction was performed with 3-bromobenzaldehyde **2t** at 100 °C for 12 h. [f]Estimated by ^{1}H NMR using Bn_2O as an internal standard.

see: Table 2, entry 2). Unfortunately, the protocol turned out not to be reproducible with a number of aryl bromides.

The successful results obtained with substituted aryl iodides prompted us to examine this carbonylation process with various heteroaryl substrates as well as vinyl, benzyl and allyl halides (Scheme 2). Pyridine derivatives such as 3-iodopyridine **2u** and 2-chloro-5-iodopyridine **2v** gave the corresponding NHS esters **3u** and **3v** in 83 and 67% yield, respectively. From 3-bromoquinoline **2w**, 5-nitro-3-bromoquinoline **2x** and 3-iodo-1-phenylsulfonyl-indole **2y** derivatives, the corresponding NHS esters **3w**, **3x** and **3y** were obtained in fair to good yields (73, 41 and 70%, respectively). Moreover, this carbonylation procedure was not limited to nitrogen-containing heteroaromatic halides. For example, 2-thienyl NHS ester **3z** was also prepared with an excellent yield of 98%. Gratifyingly, this method can also be applied to the preparation of vinyl or benzyl NHS esters (Scheme 2). Indeed, from vinyl bromide **2aa** or iodide derivatives **2ab**, vinyl NHS esters **3aa** and **3ab** were isolated in 82 and 72% yield, respectively. Furthermore, in the benzyl series, 2-chlorobenzyl bromide **2ac** was totally converted into the corresponding NHS ester **3ac** and isolated in 82% yield. Lastly, we also investigated the reaction with 3,3-dimethylallyl bromide **2ad**. While the conversion is complete along with a satisfactory ^{1}H NMR yield (60%), the corresponding NHS ester **3ad** was isolated in a modest yield (29%).

To illustrate the usefulness of this method, we examined a new synthetic route to known acetylcholinesterase inhibitors[9]

Scheme 2. Scope of Heteroaryl, Allyl, Vinyl and Benzyl Halides 2u−ad with NHS Formate 1[a]



[a]Reactions were performed with 1.0 mmol of **2** in sealed tube under an argon atmosphere. Yields are for isolated products. [b]Estimated by ^{1}H NMR using Bn_2O as an internal standard.

8a−e by implementing a carbonylative coupling reaction as the key step (Scheme 3). From commercially available 5-nitroquinoline **4**, 3-iodo-quinoline derivative **5** was easily prepared in five steps with an overall yield of 70% and was subsequently subjected to a carbonylative coupling reaction with NHS formate **1** to furnish the expected NHS ester **6** in 82% yield. Alternatively, the carbonylation may also be performed from the 3-bromoquinoline intermediate in somewhat lower yield (69%). The resulting NHS ester **6** was reacted with various nucleophiles (MeOH, EtOH, $HNMe_2$, NH_2Me, morpholine) under mild conditions prior to quaternization to provide quinolinium salts **8a−e** that exhibit anticholinergic activity.

CONCLUSION

To conclude, we have developed an efficient access to well-known NHS esters **3** via a palladium-catalyzed carbonylation by means of the readily available NHS formate **1** as a source of carbon monoxide. A large range of aryl, vinyl, allyl, and benzyl halides (iodide/bromide) **2** can be transformed to the corresponding NHS esters **3** in good to excellent yields under mild conditions (60 °C/10 h/MeTHF). The procedure tolerated various functional groups and could be successfully applied to the synthesis of known AChE inhibitors. Further developments of this methodology are ongoing in our laboratory to exploit both the straightforward access to NHS esters and their smooth reactivity toward a large variety of nucleophiles to construct bioactive compound libraries.

EXPERIMENTAL SECTION

General Information. All commercial reagents were used without further purification. The solvents were dried with appropriate desiccants and distilled prior to use or were obtained anhydrous from commercial suppliers. Silica gel (60, 230−400 mesh or 70−230 mesh) was used for column chromatography. Reactions were monitored by thin layer chromatography on silica gel precoated

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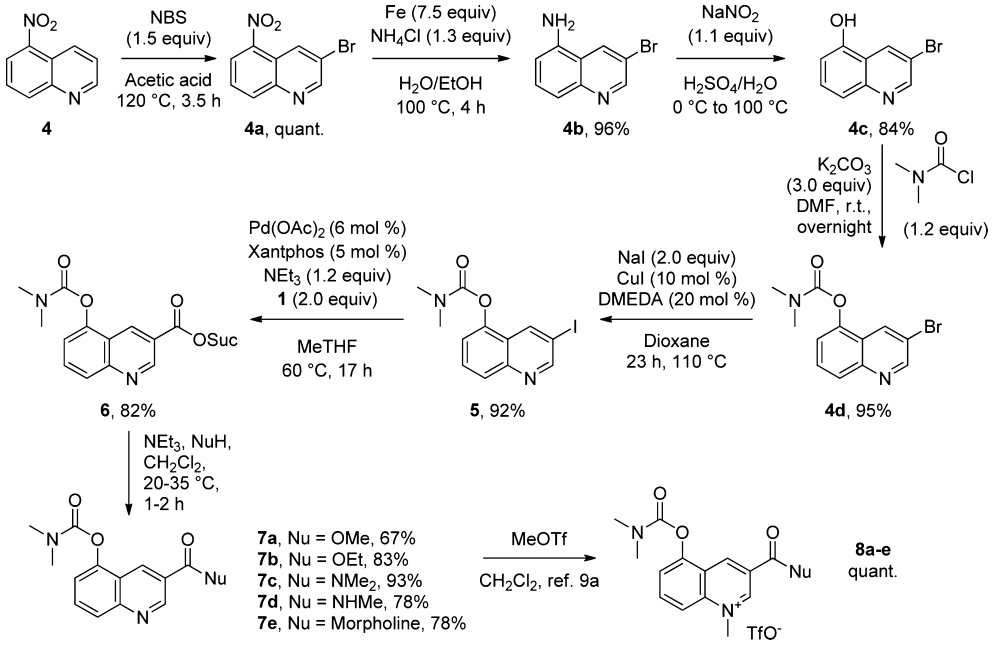
Scheme 3. Application to the Synthesis of Acetylcholinesterase (AChE) Inhibitors 8a−e



aluminum plates. UV light at 254 nm or $KMnO_4$ stains were used to visualize TLC plates. ^1H, $^{13}C\{^1H\}$ NMR spectra were recorded using a spectrometer operating at 300 and 75 MHz, respectively. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet, dd: doublet of doublet, br: broad and m: multiplet. Coupling constants J are in Hz and chemical shifts are given in ppm and calibrated with DMSO-d_6 or $CDCl_3$ (residual solvent signals). ^1H NMR spectra obtained in $CDCl_3$ were referenced to 7.26 ppm and in DMSO-d_6 were referenced to 2.50 ppm. $^{13}C\{^1H\}$ NMR spectra obtained in $CDCl_3$ were referenced to 77.16 ppm and in DMSO-d_6 were referenced to 39.52 ppm. NMR yields were determined by ^1H NMR with Bn_2O as internal standard. High resolution mass spectra were measured by ESI, APCI, EI, FI and FD. Molecular weights are given in g mol^{-1}. Melting points of solid compounds were measured on a melting point apparatus with a precision of ±1.5 °C. IR spectra were recorded on a FT-IR spectrometer. Absorption bands are given in cm^{-1}. Compounds **8a**, **8b**, **8c**, **8d**, **8e** were synthesized according to literature procedure as previously reported by our group.[9a] ***Caution!*** *Reaction vessels contain gas under pressure. Proper precautions should be taken for safe handling.*

Synthesis of 2,5-Dioxopyrrolidin-1-yl Formate 1.[11b] In a 250 mL flask, acetic anhydride (77 mL, 0.8 mol, 8.0 equiv) was cooled to 0 °C. Formic acid (38 mL, 1.0 mol, 10.0 equiv) was added slowly, and the solution was stirred at room temperature for 2 h. Then, 1-hydroxypyrrolidine-2,5-dione (11.7 g, 0.1 mol, 1.0 equiv) was added. The reaction mixture was stirred overnight and then evaporated to dryness and dried several hours in vacuo to afford the expected product **1** (14.4 g, 99% yield) as an odorless white solid. NHS formate **1** was stable enough to be stored for several weeks under inert atmosphere. However, it was observed that traces of formic acid can be formed over time. In that case, **1** was dried in vacuo prior to use. ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 2.86 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.6, 155.1, 25.7; IR ν_{max}/cm^{-1} 3000, 2952, 1694, 1208, 644; mp 114−115 °C.

General Procedure for Synthesis of NHS Esters 3a−3ad. Into an oven-dried 20 mL vial, equipped with a Teflon coated stir bar, were placed the halogenated compound (1.00 mmol, 1.0 equiv), 2,5-dioxopyrrolidin-1-yl formate **1** (288 mg, 2.00 mmol, 2.0 equiv), Xantphos (14.5 mg, 0.025 mmol, 2.5 mol %) and $Pd(OAc)_2$ (6.8 mg, 0.030 mmol, 3.0 mol %). The vial was sealed with a septum cap, evacuated and then purged three times with argon. Then 5 mL of dry MeTHF were added with a syringe. The mixture was stirred on an oil bath preheated at 60 °C, the argon balloon was removed, and NEt_3 (0.17 mL, 0.603 mmol, 1.2 equiv) was quickly added via syringe. Fast gas evolution was observed and the reaction was left to stir for 10 h at 60 °C. Then the reaction mixture was diluted with ethyl acetate (EtOAc) or dichloromethane, filtered through Celite and evaporated to dryness. The residue was taken up in dichloromethane, washed with water, with a saturated aqueous solution of sodium thiosulfate for iodinated substrates and with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, petroleum ether (PE)/ethyl acetate or dichloromethane, liquid deposit in dichloromethane) to afford the desired product.

*2,5-Dioxopyrrolidin-1-yl benzoate (**3a**).* From iodobenzene (102 mg, 56 μM, 0.50 mmol, 0.1 M). Purification by column chromatography (SiO_2, PE/EtOAc = 2/1, R_f = 0.28 [PE/EtOAc = 2/1]) afforded **3a** (94 mg, 86%) as an off-white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 7.4 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 2.87 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.4, 161.9, 135.0, 130.6, 128.9, 125.1, 25.7; HRMS (TOF-EI+) Calc. for $[M]^{+\bullet}$ $C_{11}H_9NO_4$ m/z 219.0526, found 219.0531; IR ν_{max}/cm^{-1} 3080, 2993, 1766, 1732, 1454, 1205, 1070, 996, 704; mp 135 °C.

*2,5-Dioxopyrrolidin-1-yl 4-acetylbenzoate (**3b**).* From 4′-iodoacetophenone (246 mg). Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.38 [EtOAc/PE = 1/1]) afforded **3b** (191 mg, 73%) as pale yellow crystals. From 4′-bromoacetophenone (100 mg, 0.500 mmol, 0.1 M). Purification by column chromatography (SiO_2, EtOAc/PE = 1/1, R_f = 0.38 [EtOAc/PE = 1/1]) afforded **3b** (117 mg, 89%) as pale yellow crystals. ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H), 2.87 (s, 4H), 2.61 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 197.1, 169.2, 161.2, 141.5, 130.8, 128.7, 128.5, 26.9, 25.6; HRMS (TOF-EI+) Calc. for $[M]^{+\bullet}$ $C_{13}H_{11}NO_5$ m/z 261.0632, found 261.0637; IR ν_{max}/cm^{-1} 3007, 2953, 1769, 1728, 1686, 1405, 1204, 996, 756; mp 110 °C.

*2,5-Dioxopyrrolidin-1-yl 4-methylbenzoate (**3c**).* From 1-iodo-4-methyl-benzene (218 mg). Purification by column chromatography (SiO_2, PE/EtOAc = 2/1, R_f = 0.25 [PE/EtOAc = 2/1]) afforded **3c** (196 mg, 84%) as a beige solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 2.87 (s, 4H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.5, 161.9, 146.2, 130.6, 129.6, 122.2, 25.7, 21.9; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{12}H_{11}NO_4$ m/z 233.0688, found 233.0685; IR ν_{max}/cm^{-1} 3000, 2953, 1760, 1728, 1608, 1181, 994, 741; mp 175 °C.

*2,5-Dioxopyrrolidin-1-yl 3-methylbenzoate (**3d**).* From 3-iodotoluene (128 μL). Purification by column chromatography (SiO_2,

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CH_2Cl_2, R_f = 0.26 [CH_2Cl_2]) afforded **3d** (182 mg, 78%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94−7.91 (m, 2H), 7.47 (d, J = 7.0 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 2.89 (s, 4H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.4, 162.1, 138.9, 135.8, 131.0, 128.8, 127.8, 125.0, 25.7, 21.2; HRMS (TOF-FI+) Calc. for $[M]^{+\bullet}$ $C_{12}H_{11}NO_4$ m/z 233.0688, found 233.0694; IR ν_{max}/cm^{-1} 3001, 2952, 2919, 1765, 1732, 1588, 1202, 1068, 736; mp 114−115 °C.

*2,5-Dioxopyrrolidin-1-yl 4-cyanobenzoate (**3e**).* From 4-iodobenzonitrile (229 mg). Purification by column chromatography (SiO_2, PE/EtOAc = 2:1 to EtOAc 100%, R_f = 0.21 [PE/EtOAc = 2/1]) afforded **3e** (175 mg, 72%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H), 2.93 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.9, 160.6, 132.7, 131.1, 129.1, 118.4, 117.5, 25.7; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{12}H_8N_2O_4$ m/z 244.0484, found 244.0485; IR ν_{max}/cm^{-1} 3102, 2947, 2229, 1770, 1728, 1205, 1072, 683; mp 230 °C (decomp.).

*2,5-Dioxopyrrolidin-1-yl 4-methoxybenzoate (**3f**).* From 4-iodoanisole (234 mg). Purification by column chromatography on SiO_2 (EtOAc/PE = 1/1, R_f = 0.42 [EtOAc/PE = 1/1]) afforded **3f** (187 mg, 75%) as off-white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17−7.98 (m, 2H), 7.02−6.87 (m, 2H), 3.87 (s, 3H), 2.87 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.6, 165.0, 161.5, 132.9, 117.1, 114.3, 55.7, 25.7; HRMS (TOF-FI+) Calc. for $[M]^{+\bullet}$ $C_{12}H_{11}NO_5$ m/z 249.0637, found 249.0646; IR ν_{max}/cm^{-1} 3113, 2941, 2849, 1764, 1730, 1602, 1212, 1183; mp 139−142 °C.

*2,5-Dioxopyrrolidin-1-yl 3,5-bis(trifluoromethyl)benzoate (**3g**).* From 1-iodo-3,5-bis(trifluoromethyl)benzene (340 mg). Purification by column chromatography on SiO_2 (EtOAc/PE = 1/1, R_f = 0.62 [EtOAc/PE = 1/1]) afforded **3g** (229 mg, 65%) as an off-white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 2H), 8.20 (s, 1H), 2.96 (s, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.7, 159.8, 132.9 (q, J = 34.6 Hz), 130.6 (m), 128.3 (m), 127.6, 122.5 (q, J = 274.3 Hz), 26.7; HRMS (TOF-FI+) $C_{13}H_7F_6NO_4$ Calc. for $[M]^{+\bullet}$ m/z 355.0279, found 355.0285; IR ν_{max}/cm^{-1} 3049, 2969, 1738, 1285, 1210, 1178, 1131; mp 126−127 °C.

*2,5-Dioxopyrrolidin-1-yl 4-nitrobenzoate (**3h**).* From 1-iodo-4-nitro-benzene (249 mg). Purification by column chromatography (SiO2, CH_2Cl_2/EtOAc = 9/1, R_f = 0.68 [CH_2Cl_2/EtOAc = 9/1]) afforded **3h** (187 mg, 71%) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (q, J = 9.0 Hz, 4H), 2.94 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.8, 160.4, 151.6, 131.9, 130.6, 124.1, 25.8; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{11}H_8N_2O_6$ m/z 264.0377, found 264.0386; IR ν_{max}/cm^{-1} 3114, 2999, 1770, 1733, 1528, 1193, 709; mp 207 °C.

*2,5-Dioxopyrrolidin-1-yl 3-nitrobenzoate (**3i**).* From 1-iodo-3-nitro-benzene (249 mg). Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.52 [CH_2Cl_2/EtOAc = 96/4]) afforded **3i** (205 mg, 78%) as a pale brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.52 (dd, J = 8.0, 1.1 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 2.92 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.9, 160.1, 148.3, 136.0, 130.4, 129.3, 126.9, 125.5, 25.7; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{11}H_8N_2O_6$ m/z 264.0377, found 264.0382; IR ν_{max}/cm^{-1} 3107, 3007, 1787, 1732, 1532, 1349, 709; mp 128 °C.

*2,5-Dioxopyrrolidin-1-yl ethyl isophthalate (**3j**).* From ethyl 3-iodobenzoate (168 μL). Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.36 [EtOAc/PE = 1/1]) afforded **3j** (274 mg, 94%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.83 (s, 4H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.2, 164.8, 161.0, 135.4, 134.2, 131.2, 131.2, 129.1, 125.3, 61.4, 25.5, 14.0; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{14}H_{13}NO_6$ m/z 291.0737, found 291.0747; IR ν_{max}/cm^{-1} 2985, 1773, 1735, 1717, 1198, 1066, 718.

*2,5-Dioxopyrrolidin-1-yl methyl phthalate (**3k**).* From methyl 2-iodobenzoate (147 μL). Purification by column chromatography (SiO_2, PE/EtOAc = 2/1 to 1/1, R_f = 0.49 [PE/EtOAc = 1/1]) afforded **3k** (266 mg, 96%) as pale yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (td, J = 7.4, 2.5 Hz, 2H), 7.66−7.47 (m, 2H), 3.83 (s, 3H), 2.80 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.0, 166.3, 163.0, 132.5, 131.6, 131.4, 129.7, 129.4, 127.2, 52.8, 25.5; HRMS (TOF-FD+) Calc. for $[M + H]^+$ $C_{13}H_{11}NO_6$ m/z 278.0659, found 278.0653; IR ν_{max}/cm^{-1} 2965, 1739, 1721, 1195, 991; mp 78 °C.

*2,5-Dioxopyrrolidin-1-yl 4-chlorobenzoate (**3l**).* From 1-chloro-4-iodo-benzene (238 mg). Purification by column chromatography (SiO_2, PE/EtOAc = 3/1, R_f = 0.35 [PE/EtOAc = 3/1]) afforded **3l** (218 mg, 86%) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 2.90 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.2, 161.2, 141.7, 131.9, 129.4, 123.6, 25.7; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{11}H_8ClNO_4$ m/z 253.0142, found 253.0130; IR ν_{max}/cm^{-1} 3087, 2993, 1771, 1726, 1211, 996, 743; mp 206 °C.

*2,5-Dioxopyrrolidin-1-yl 4-bromobenzoate (**3m**).* From 1-bromo-4-iodo-benzene (283 mg). The reaction was carried out at 25 °C for 60 h. Purification by column chromatography (SiO_2, PE/EtOAc = 2:1 to EtOAc 100%, R_f = 0.32 [PE/EtOAc =2/1]) afforded **3m** (268 mg, 90%) as a pale brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 2.91 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.2, 161.4, 132.4, 132.0, 130.6, 124.1, 25.7; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{11}H_8BrNO_4$ m/z 296.9637, found 296.9640; IR ν_{max}/cm^{-1} 3093, 2985, 1770, 1723, 1588, 1207, 990, 739; mp 223 °C.

*2,5-Dioxopyrrolidin-1-yl 4-fluorobenzoate (**3n**).* From 1-fluoro-4-iodo-benzene (124 μL). Purification by column chromatography (SiO_2, PE/EtOAc = 2/1, R_f = 0.33 [PE/EtOAc = 2/1]) afforded **3n** (199 mg, 78%) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17−8.13 (m, 2H), 7.18 (t, J = 8.6 Hz, 2H), 2.89 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.3, 168.6, 165.2, 161.0, 133.4 (d, J = 9.8 Hz), 121.4 (d, J = 3.1 Hz), 116.4 (d, J = 22.3 Hz), 25.7; HRMS (TOF-FI+) Calc. for $[M]^{+\bullet}$ $C_{11}H_8FNO_4$ m/z 237.0432, found 237.0437; IR ν_{max}/cm^{-1}; 3087, 2989, 1771, 1724, 1602, 1209, 1075, 752; mp 111 °C.

*2,5-Dioxopyrrolidin-1-yl phenanthrene-9-carboxylate (**3o**).* From 9-iodophenanthrene (304 mg). Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.44 [EtOAc/PE = 1/1]) afforded **3o** (284 mg, 89%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82−8.77 (m, 1H), 8.75 (s, 1H), 8.72−8.67 (m, 1H), 8.64 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 7.3 Hz, 1H), 7.82−7.74 (m, 1H), 7.74−7.61 (m, 3H), 2.96 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.6, 162.3, 134.9, 132.9, 130.6, 130.5, 130.2, 129.4, 128.4, 128.0, 127.5, 127.4, 126.1, 123.0, 122.8, 120.7, 25.8; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{19}H_{13}NO_4$ m/z 319.0839, found 319.0854; IR ν_{max}/cm^{-1} 3019, 2987, 2933, 1763, 1738, 1201, 910, 757; mp 187 °C.

*2,5-Dioxopyrrolidin-1-yl 1-naphthoate (**3p**).* From 1-iodonaphthalene (146 μL). Purification by column chromatography (SiO_2, EtOAc/PE = 1/1 to 2/1, R_f = 0.51 [EtOAc/PE = 1/1]) afforded **3p** (205 mg, 76% yield) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J = 8.6 Hz, 1H), 8.44 (d, J = 7.3 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.61−7.50 (m, 2H), 2.92 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.6, 162.2, 135.6, 133.7, 131.9, 131.4, 128.8, 128.8, 126.9, 125.2, 124.5, 121.5, 25.8; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{15}H_{11}NO_4$ m/z 269.0683, found 269.0691; IR ν_{max}/cm^{-1} 2987, 1772, 1720, 1207, 1073, 776; mp 140 °C.

*2,5-Dioxopyrrolidin-1-yl 4-aminobenzoate (**3q**).* From 4-iodoaniline (219 mg). Purification by column chromatography (SiO_2, CH_2Cl_2/EtOAc = 96/4 to 90/10, R_f = 0.34 [CH_2Cl_2/EtOAc = 90/10]) afforded **3q** (142 mg, 61%) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 4.27 (s, 2H, NH_2), 2.89 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.8, 161.7, 152.6, 133.1, 114.0, 113.7, 25.8; HRMS (TOF-EI+) Calc. for $[M]^{+\bullet}$ $C_{11}H_{10}N_2O_4$ m/z 234.0635, found 234.0641; IR ν_{max}/cm^{-1} 3470, 3376, 1748, 1717, 1598, 1217, 974; mp 199 °C.

*2,5-Dioxopyrrolidin-1-yl 2-aminobenzoate (**3r**).* From 2-iodoaniline (219 mg). Purification by column chromatography (SiO_2, PE/EtOAc = 2/1, R_f = 0.16 [PE/EtOAc = 2/1]) afforded **3r** (193 mg, 82%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 6.77−6.60 (m, 2H), 5.65 (br s, 2H, NH_2), 2.89 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.8,

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162.8, 151.8, 136.3, 131.2, 116.8, 116.7, 105.0, 25.7; HRMS (TOF-AP+) Calc. for $[M + H]^+$ $C_{11}H_{11}N_2O_4$ m/z 235.0713, found 235.0718; IR ν_{max}/cm^{-1} 3500, 3390, 1727, 1618, 1205, 978, 752; mp 154 °C.

*2,5-Dioxopyrrolidin-1-yl 4-hydroxybenzoate (**3s**).* From 4-iodophenol (220 mg). Purification by column chromatography on SiO_2 (EtOAc/PE = 1/1, R_f= 0.31 [EtOAc/PE = 1/1]) afforded **3s** (134 mg, 57%) as an off-white powder. ^1H NMR (300 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.95 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 2.87 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 170.6, 164.0, 161.4, 132.7, 116.2, 114.6, 25.5; HRMS (TOF-FI+) Calc. for $[M]^{+\bullet}$ $C_{11}H_9NO_5$ m/z 235.0481, found 235.0488; IR ν_{max}/cm^{-1} 3263, 2922, 1705, 1202, 1161, 1067; mp 180−183 °C.

*2,5-Dioxopyrrolidin-1-yl 3-formylbenzoate (**3t**).* From 3-bromobenzaldehyde (122 μL). Reaction was carried out at 100 °C for 12 h. Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.56 [CH_2Cl_2/EtOAc = 95/5]) afforded **3t** (83 mg, 34%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.58 (s, 1H), 8.33 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 2.90 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 190.7, 169.1, 161.0, 136.8, 135.8, 134.9, 132.0, 129.9, 126.3, 25.7; HRMS (TOF-FI+) Calc. for $[M]^{+\bullet}$ $C_{12}H_9NO_5$ m/z 247.0475, found 247.0473; IR ν_{max}/cm^{-1} 3061, 2952, 1732, 1696, 1202, 645; mp 135−137 °C.

*2,5-Dioxopyrrolidin-1-yl nicotinate (**3u**).* From 3-iodopyridine (205 mg). Purification by column chromatography (SiO_2, EtOAc/PE, R_f = 0.27 [EtOAc/PE = 2/1]) afforded **3u** (183 mg, 83%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J = 1.6 Hz, 1H), 8.81 (dd, J = 4.9, 1.6 Hz, 1H), 8.31 (dt, J = 8.0, 1.6 Hz, 1H), 7.41 (dd, J = 8.0, 4.9 Hz, 1H), 2.85 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.0, 160.7, 155.1, 151.2, 137.7, 123.6, 121.5, 25.6; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{10}H_8N_2O_4$ m/z 220.0484, found 220.0495; IR ν_{max}/cm^{-1} 3080, 2940, 1773, 1722, 1202, 1012, 989, 722; mp 132 °C.

*2,5-Dioxopyrrolidin-1-yl 6-chloronicotinate (**3v**).* From 2-chloro-5-iodo-pyridine (239 mg). Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.31 [CH_2Cl_2/EtOAc = 96/4]) afforded **3v** (170 mg, 67%) as a pale brow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.10 (d, J = 2.3 Hz, 1H), 8.32 (dd, J = 8.4, 2.3 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 2.93 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.9, 160.2, 157.8, 151.8, 140.2, 124.8, 120.6, 25.7; HRMS (TOF-EI+) Calc. for $[M]^{+\bullet}$ $C_{10}H_7ClN_2O_4$ m/z 254.0089, found 254.0091; IR ν_{max}/cm^{-1} 3091, 2993, 1770, 1727, 1586, 1201,1074, 753; mp 206 °C.

*2,5-Dioxopyrrolidin-1-yl quinoline-3-carboxylate (**3w**).* From 3-bromoquinoline (136 μL). Reaction was carried out for 27 h. Purification by column chromatography (SiO_2, EtOAc/PE = 1/2, R_f = 0.26 [PE/EtOAc = 1/1]) afforded **3w** (198 mg, 73%) as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, J = 2.0 Hz, 1H), 9.01 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.00−7.88 (m, 2H), 7.69 (t, J = 7.4 Hz, 1H), 2.97 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.2, 160.9, 150.4, 149.4, 140.5, 133.3, 129.6, 129.5, 128.2, 126.4, 118.3, 25.7; HRMS (TOF-ESI+) Calc. for $[M + H]^+$ $C_{14}H_{11}N_2O_4$ m/z 271.0713, found 271.0715; IR ν_{max}/cm^{-1} 3069, 2943, 1720, 1204, 1187, 1073, 938, 752, 637; mp 172−175 °C.

*2,5-Dioxopyrrolidin-1-yl 5-nitroquinoline-3-carboxylate (**3x**).* From 3-bromo-5-nitro-quinoline (105 mg, 0.451 mmol). Purification by column chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/EtOAc = 9/1, R_f = 0.26 [CH_2Cl_2/EtOAc = 9/1]) afforded **3x** (53 mg, 41%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 9.59 (d, J = 1.8 Hz, 1H), 8.52 (d, J = 7.7 Hz, 2H), 8.01 (t, J = 8.1 Hz, 1H), 2.97 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.8, 160.4, 150.8, 150.2, 146.1, 136.8, 136.5, 131.0, 126.1, 121.2, 119.8, 25.8; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{14}H_9N_3O_6$ m/z 315.0491, found 315.0488; IR ν_{max}/cm^{-1} 3120, 2952, 1772, 1733, 1527, 1202, 751; mp 221 °C.

*2,5-Dioxopyrrolidin-1-yl 1-(phenylsulfonyl)-1H-indole-3-carboxylate (**3y**).* From 1-(benzenesulfonyl)-3-iodo-indole (383 mg). Purification by column chromatography (SiO_2, EtOAc/PE = 1/1, R_f = 0.41 [EtOAc/PE = 1/1]) afforded **3y** (305 mg, 77%) as a beige solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.06 (dd, J = 7.6, 1.5 Hz, 1H), 8.02−7.96 (m, 3H), 7.63 (d, J = 7.4 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.47−7.33 (m, 2H), 2.93 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.5, 158.4, 137.2, 135.0, 134.7, 134.0, 129.9, 127.4, 127.3, 126.2, 125.1, 122.1, 113.5, 107.8, 25.8; HRMS (TOF-FD+) Calc. for $[M]^{+\bullet}$ $C_{19}H_{14}N_2O_6S$ m/z 398.0573, found 398.0555; IR ν_{max}/cm^{-1} 3173, 1765, 1732, 991, 592, 571; mp 207 °C.

*2,5-Dioxopyrrolidin-1-yl thiophene-2-carboxylate (**3z**).* From 2-iodothiophene (111 μL). Purification by column chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/EtOAc = 9/1, R_f = 0.54 [EtOAc/PE = 1/1]) afforded **3z** (220 mg, 98%) as a pale brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, J = 3.8, 1.1 Hz, 1H), 7.77 (dd, J = 5.0, 1.1 Hz, 1H), 7.24−7.14 (m, 1H), 2.89 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.3, 157.4, 136.8, 135.8, 128.5, 126.9, 25.7; HRMS (TOF-FI+) Calc. for $[H]^+$ $C_9H_7NO_4S$ m/z 225.009, found 225.0101; IR ν_{max}/cm^{-1} 3104, 2953, 1748, 1732, 1206, 742; mp 156 °C.

*2,5-Dioxopyrrolidin-1-yl 3-phenyl acrylate (**3aa**).* From [(*E*/*Z*)-2-bromovinyl]benzene (128 μL). Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.51 [EtOAc/PE = 1/1]) afforded **3aa** (201 mg, 82%, mixture of *E*/*Z* 79/21) as a white solid. ***Z isomer***: ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 16.1 Hz, 1H), 7.64−7.24 (m, 5H), 6.50 (d, J = 16.1 Hz, 1H), 2.78 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.5, 162.1, 150.1, 133.4, 131.6, 129.1, 128.7, 111.5, 25.6. ***E isomer***: ^1H NMR (300 MHz, $CDCl_3$) δ ^1H NMR (300 MHz, $CDCl_3$) δ 7.63−7.24 (m, 5H), 7.21 (d, J = 11.6 Hz, 1H), 6.06 (d, J = 12.6 Hz, 1H), 2.74 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.5, 160.7, 150.4, 133.5, 130.4, 130.3, 128.3, 112.3, 25.6. HRMS (TOF-FI+) Calc. for $[M]^{+\bullet}$ $C_{13}H_{11}NO_4$ m/z 245.0688, found 245.0700; IR ν_{max}/cm^{-1} 2953, 1757, 1737,1071, 765; mp 170−172 °C.

*(E)-2,5-Dioxopyrrolidin-1-yl hept-2-enoate (**3ab**).* From (*E*)-1-iodohex-1-ene (249 mg). Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.28 [CH_2Cl_2]) afforded **3ab** (192 mg, 72%) as a brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (dt, J = 15.7, 7.1 Hz, 1H), 5.94 (d, J = 15.7 Hz, 1H), 2.75 (s, 4H), 2.23 (q, J = 6.8 Hz, 2H), 1.48−1.21 (m, 4H), 0.84 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.5, 161.3, 156.2, 115.1, 32.4, 29.5, 25.5, 22.1, 13.6; HRMS (TOF-FI+) Calc. for $[M]^{+\bullet}$ $C_{11}H_{15}NO_4$ m/z 225.0996, found 225.1007; IR ν_{max}/cm^{-1} 2960, 2933, 2880, 1770, 1737, 1645,1201, 1067; mp 58−59 °C.

*2,5-Dioxopyrrolidin-1-yl 2-(2-chlorophenyl)acetate (**3ac**).* From 1-(bromomethyl)-2-chlorobenzene (130 μL). Purification by column chromatography (SiO_2, EtOAc/PE = 1/1, R_f = 0.3 [EtOAc/PE = 1/1]) afforded **3ac** (220 mg, 82%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.33 (m, 2H), 7.32−7.22 (m, 2H), 4.09 (s, 2H), 2.84 (s, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.0, 166.0, 134.6, 131.4, 130.0, 129.7, 129.5, 127.2, 35.7, 25.6; HRMS (TOF-FD+) Calc. for $[H]^+$ $C_{12}H_{10}ClNO_4$ m/z 267.0293, found 267.0298; IR ν_{max}/cm^{-1} 2993, 2927, 1729, 1207, 1069, 757, 643; mp 109 °C.

*2,5-Dioxopyrrolidin-1-yl 4-methylpent-3-enoate (**3ad**).* From 1-bromo-3-methyl-but-2-ene (122 μL). Purification by column chromatography (SiO_2, CH_2Cl_2, R_f = 0.63 [EtOAc/PE = 1/1]) afforded **3ad** (62 mg, 29%) as colorless crystals. ^1H NMR (300 MHz, $CDCl_3$) δ 5.31−5.19 (m, 1H), 3.28 (d, J = 7.0 Hz, 2H), 2.77 (s, 4H), 1.72 (s, 3H), 1.63 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.3, 167.4, 137.9, 113.0, 30.3, 25.5, 25.5, 18.0; HRMS (TOF-EI+) Calc. for $[M]^{+\bullet}$ $C_{10}H_{13}NO_4$ m/z 211.0839, found 211.0849; IR ν_{max}/cm^{-1} 2967, 2915, 1818, 1780, 1727, 1202, 1063, 644; mp 75 °C.

Synthesis of 3-Iodoquinolin-5-yl Dimethylcarbamate (5). Step 1: 5-Nitroquinoline **4** (20 g, 0.115 mol, 1.0 equiv) and *N*-bromosuccinimide (NBS) (30.7 g, 0.172 mol, 1.5 equiv) were dissolved in acetic acid (115 mL) and refluxed. The reaction was monitored by thin layer chromatography until disappearance of 5-nitroquinoline (ca. 3.5 h). Half of the solvent was removed in vacuo, water was added, and the mixture was neutralized with 6 M NaOH. The product was then extracted twice with dichloromethane, washed with brine, dried over $MgSO_4$ and evaporated to dryness to afford 3-bromo-5-nitro-quinoline **4a** (29.0 g, 100%) as a yellow solid (R_f = 0.24 [CH_2Cl_2/PE = 1/1]). ^1H NMR (300 MHz, $CDCl_3$) δ 9.12−9.10 (m, 1H), 8.92 (d, J = 2.2 Hz, 1H), 8.40−8.28 (m, 2H), 7.77 (t, J = 8.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 152.8, 146.1, 144.1, 136.7, 133.4, 127.7, 125.8, 121.7, 121.2; HRMS (TOF-AP+) Calc. for $[M + H]^+$ $C_9H_6BrN_2O_2$ m/z 252.9608 and 254.9587, found 252.9620 and 254.9599; IR ν_{max}/cm^{-1} 3056, 1515, 1322, 882, 832, 737; mp 135 °C.

Step 2: 3-Bromo-5-nitro-quinoline **4a** (29 g, 0.114 mol, 1.0 equiv), iron powder (48 g, 0.890 mol, 7.5 equiv) and NH_4Cl (7.7 g, 1.3 equiv)

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were placed in a 1 L flask with a mechanic stirred and a condenser. The mixture was refluxed in water (80 mL) and ethanol (190 mL) for 4 h. The suspension was filtered through Celite and evaporated to dryness. The residue was taken up in dichloromethane and in NaOH 0.5 M. The product was extracted 3 times with dichloromethane, dried over $MgSO_4$ and concentrated in vacuo to afford the expected compound **4b** (24.7 g, 96%) as a dark yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, J = 2.1 Hz, 1H), 8.33 (d, J = 2.1 Hz, 1H), 7.57−7.48 (m, 2H), 6.85 (dd, J = 5.9, 2.6 Hz, 1H), 4.16 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 151.1, 147.1, 141.7, 131.5, 130.4, 120.1, 119.7, 115.6, 111.1; HRMS (TOF-ESI+) Calc. for $[M + H]^+$ $C_9H_8BrN_2$ m/z 222.9866 and 224.9845, found 222.9870 and 224.9855; IR ν_{max}/cm^{-1} 3426, 3315, 3192, 1574, 1461, 1366, 1087, 804; mp 136 °C; R_f = 0.39 [CH_2Cl_2/EtOAc = 9/1].

Step 3: At 0 °C a solution of $NaNO_2$ (1.52 g, 21.99 mol, 1.1 equiv) in 1 mL of water was slowly added to a red solution of **4b** (4.46 g, 19.99 mmol, 1.0 equiv) in 6 M sulfuric acid (135 mL). The reaction was stirred at 0 °C for 30 min, a pale brown solid was formed. The mixture was then slowly added to a solution of 150 mL of 6 M H_2SO_4, preheated at 100 °C. The mixture was stirred at 100 °C for 30 min, cooled to rt and neutralized with 100 mL of NH_4OH and 40 mL of 6 M NaOH. The resulting suspension was filtered off and rinsed with water to afford 3-bromoquinolin-5-ol **4c** (3.77 g, 84%) as a brown solid. R_f = 0.34 (EtOAc/PE = 1/3]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.90 (d, J = 2.4 Hz, 1H), 8.64 (d, J = 1.9 Hz, 1H), 7.72−7.55 (m, 1H), 7.48 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 152.5, 150.9, 146.9, 132.0, 130.6, 120.4, 119.2, 115.3, 109.6; HRMS (TOF-ESI+) Calc. for $[M + H]^+$ C_9H_7BrNO m/z 223.9706 and 225.9686, found 223.9717 and 225.9696; IR ν_{max}/cm^{-1} 2554, 1575, 1043, 808, 494; mp 235 °C.

Step 4: Under argon atmosphere, 3-bromoquinolin-5-ol **4c** (200 mg, 0.89 mmol) and K_2CO_3 (370 mg, 2.68 mmol, 3.0 equiv) were suspended in dry DMF (9 mL). The mixture was cooled to 0 °C and *N*,*N*-dimethylcarbamoyl chloride (94 μL, 1.03 mmol, 1.2 equiv) was added. The reaction was stirred for 1 night at room temperature, poured into water and extracted three times with EtOAc. The organic phases were washed with NH_4Cl sat., with brine, dried over $MgSO_4$ and evaporated to dryness to afford **4d** (250 mg, 95%) as a black solid. R_f = 0.33 [EtOAc/PE = 1/2]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.39 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 3.27 (s, 3H), 3.09 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.0, 151.4, 146.6, 145.7, 131.4, 129.0, 126.4, 123.4, 119.6, 117.4, 36.8, 36.5; HRMS (TOF-ESI+) Calc. for $[M + H]^+$ $C_{12}H_{12}BrN_2O_2$ m/z 295.0077 and 297.0070, found 295.0089 and 297.0083; IR ν_{max}/cm^{-1} 2940, 1711, 1390, 1162, 753; mp 124 °C.

Step 5: **4d** (1.50 g, 5.08 mmol, 1.0 equiv), NaI (1.52 g, 10.16 mmol, 2.0 equiv), CuI (97 mg, 0.51 mmol, 0.1 equiv) were placed in a sealed tube under an argon atmosphere and dissolved in dry dioxane (20 mL). *N*,*N*′-Dimethylethylenediamine (109 μL, 1.02 mmol, 0.2 equiv) was added and the mixture was stirred at 110 °C for 23 h. The reaction was allowed to cool to room temperature and then filtered and rinsed with CH_2Cl_2. The filtrate was poured into 20 mL of 35% aqueous ammonia and 100 mL of water. The product was extracted three times with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated to dryness to afford the expected product **5** (1.60 g, 92%) as a pale gray powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 1.5 Hz, 1H), 8.56 (d, J = 1.5 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.66 (t, J = 8.2 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 3.20 (s, 3H), 3.03 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.8, 154.1, 146.8, 145.6, 137.9, 129.4, 126.6, 124.2, 119.5, 90.2, 36.9, 36.6; HRMS (TOF-ESI+) Calc. for $[M + H]^+$ $C_{12}H_{11}IN_2O_2$ m/z 342.9938, found 342.9952; IR ν_{max}/cm^{-1} 2927, 1705, 1389, 1160, 753; mp 116−117 °C.

*2,5-Dioxopyrrolidin-1-yl 5-((dimethylcarbamoyl)oxy)quinoline-3-carboxylate (**6**).* Following the general procedure described above for the synthesis of **3a**−**3ad**, from compound **5** (684 mg, 2.0 mmol, 1.0 equiv) and **1** (429 mg, 3.0 mmol, 1.5 equiv), NHS ester **6** (589 mg, 82%) was obtained as a pale yellow solid after purification by column chromatography (SiO_2, EtOAc, R_f = 0.45 [EtOAc]). Or from 3-bromoquinolin-5-yl dimethylcarbamate **4d** (295 mg, 1.0 mmol, 1.0 equiv), **1** (286 mg, 2.0 mmol, 2.0 equiv), Xantphos (5 mol %) and $Pd(OAc)_2$ (6.0 mol %), the reaction was carried out at 80 °C for 17 h. Purification by column chromatography afforded **6** (245 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, J = 2.0 Hz, 1H), 9.09 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.89 (t, J = 8.1 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 3.26 (s, 3H), 3.08 (s, 3H), 2.94 (s, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.1, 160.9, 154.0, 150.9, 149.7, 147.9, 134.9, 132.9, 126.7, 121.3, 120.2, 118.3, 37.1, 36.8, 25.8; HRMS (TOF-ESI+) Calc. for $[M + Na]^+$ $C_{17}H_{15}N_3O_6Na$ m/z 380.0853, found 380.0861; IR ν_{max}/cm^{-1} 2941, 1770, 1725,1196, 1148, 1169; mp 171−173 °C.

*Methyl 5-((dimethylcarbamoyl)oxy)quinoline-3-carboxylate (**7a**).* **6** (60 mg, 0.168 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (1 mL) and dry methanol (0.5 mL). NEt_3 (28 μL, 0.201 mmol, 1.2 equiv) was added and after 2 h the reaction mixture was evaporated to dryness, taken up in CH_2Cl_2, washed with water, extracted 3 times with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated to dryness to afford **7a** (31 mg, 67%) as a pale yellow solid. Spectroscopic data obtained for **7a** were in agreement with those previously reported by our laboratory.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 1.8 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.80 (t, J = 8.6 Hz, 1H), 7.50−7.35 (m, 1H), 4.01 (s, 3H), 3.28 (s, 3H), 3.09 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.8, 154.3, 150.3, 150.2, 147.9, 133.3, 131.6, 126.7, 123.1, 121.7, 119.7, 52.7, 37.1, 36.8.

*Ethyl 5-((dimethylcarbamoyl)oxy)quinoline-3-carboxylate (**7b**).* **6** (60 mg, 0.168 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (1 mL) and ethanol (0.5 mL). NEt_3 (122 μL, 0.873 mmol, 5.2 equiv) was added and the reaction mixture was heated to 35 °C. After 1 h the reaction mixture was evaporated to dryness, taken up in CH_2Cl_2, washed with water, extracted 3 times with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated to dryness to afford **7b** (48 mg, 83%) as a pale yellow solid. Spectroscopic data obtained for **7b** were in agreement with those previously reported by our laboratory.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (d, J = 2.1 Hz, 1H), 8.95 (d, J = 1.4 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.93−7.74 (m, 1H), 7.43 (d, J = 7.5 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 3.29 (s, 3H), 3.10 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.3, 154.3, 150.3 (2C), 147.8, 133.1, 131.4, 126.6, 123.3, 121.6, 119.5, 61.7, 37.0, 36.7, 14.4.

*3-(Dimethylcarbamoyl)quinolin-5-yl dimethylcarbamate (**7c**).* **6** (60 mg, 0.168 mmol, 1.0 equiv) and *N*-methylmethanamine hydrochloride (21 mg, 269 mmol, 1.6 equiv) were dissolved in dry CH_2Cl_2 (1.5 mL). NEt_3 (70 μL, 0.504 mmol, 3.0 equiv) was added, and after 1 h the reaction mixture was evaporated to dryness, taken up in CH_2Cl_2, washed with water, extracted 3 times with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated to dryness to afford **7c** (45 mg, 93%) as a pale yellow solid. Spectroscopic data obtained for **7c** were in agreement with those previously reported by our laboratory.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J = 1.8 Hz, 1H), 8.36 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.71 (t, J = 8.1 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 3.20 (s, 3H), 3.14 (s, 3H), 3.02 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.0, 154.3, 148.7, 148.5, 147.2, 130.2, 129.9, 129.2, 126.6, 121.9, 119.6, 39.7, 37.0, 36.7, 35.6.

*3-(Methylcarbamoyl)quinolin-5-yl dimethylcarbamate (**7d**).* **6** (60 mg, 0.168 mmol, 1.0 equiv) and methanamine hydrochloride (17 mg, 252 mmol, 1.5 equiv) were dissolved in dry CH_2Cl_2 (1.5 mL). NEt_3 (38 μL, 0.269 mmol, 1.6 equiv) was added, and after 1 h the reaction mixture was evaporated to dryness, taken up in CH_2Cl_2, washed with water, extracted 3 times with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated to dryness to afford **7d** (39 mg, 78%) as a white solid. Spectroscopic data obtained for **7d** were in agreement with those previously reported by our team.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.63 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.69 (t, J = 8.1 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 3.4 Hz, 1H, NH), 3.18 (s, 3H), 3.00 (s, 3H), 2.90 (d, J = 4.5 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166, 154.5, 149.0, 148.5, 147.3, 130.3, 130.0, 127.2, 126.2, 121.5, 119.0, 36.8, 36.0, 26.7.

*3-(Morpholine-4-carbonyl)quinolin-5-yl dimethylcarbamate (**7e**).* **6** (60 mg, 0.168 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (1.5 mL). Morpholine (22 μL, 252 mmol, 1.5 equiv) was added, and after 1 h the reaction mixture was evaporated to dryness, taken up in CH_2Cl_2, washed with water, extracted 5 times with CH_2Cl_2, washed with brine,

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dried over $MgSO_4$ and evaporated to dryness to afford **7e** (43 mg, 78%) as a pale yellow solid. Spectroscopic data obtained for **7e** were in agreement with those previously reported by our team.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.74 (t, J = 8.1 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 3.87−3.57 (m, 6H), 3.47 (d, J = 12.8 Hz, 2H), 3.22 (s, 3H), 3.04 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, MeOD) δ 169.1, 155.9, 149.9, 149.5, 148.7, 131.9, 131.3, 129.7, 127.0, 123.0, 121.2, 67.6 (2C), 37.1, 36.9.

■ ASSOCIATED CONTENT

Supporting Information

The screening of various solvents and the decarbonylation study of **1** are reported. Copies of ^{1}H and $^{13}C\{^1H\}$ NMR spectra for all synthesized compounds are provided. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01119.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: vgembus@vfp-therapies.com.

*E-mail: vincent.levacher@insa-rouen.fr.

Notes

The authors declare no competing financial interest.

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