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Visible-Light-Enabled Aminocarbonylation of Unactivated Alkyl Iodides with Stoichiometric Carbon Monoxide for Application on Late-Stage Carbon Isotope Labeling

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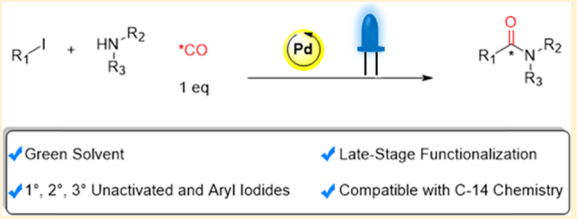
Supporting Information

ABSTRACT: A visible-light-mediated late-stage aminocarbonylation of unactivated alkyl iodides with stoichiometric amounts of carbon monoxide is presented. The method provides a mild, one-step route to [*carbonyl*-$^{13/14}$C] alkyl amides, thereby reducing radioactive waste, and handling of radioactive materials. Easily accessible and low-cost equipment and a palladium catalyst were successfully used for the synthesis of a wide range of alkyl amides.



INTRODUCTION

Carbon isotope labeling is a critical tool for the drug discovery and development program. Nearly all drug molecules contain carbon atoms; thus, no structural modification is required to incorporate a carbon isotope; moreover, the isotope effect is low for both C-13 and C-14.[1] The stable isotope, specifically C-13, is commonly used in conjunction with mass spectrometry (MS) for the quantification of the parent drug in biological samples.[2] Typically, a stable isotope-labeled internal standard is prepared as soon as a single compound is selected and is continuously supplied to the project over the course of the development and post-marketing surveillance. On the other hand, the long-lived carbon radioisotope, C-14 ($t_{1/2}$ = 5730 years), has virtually no background noise, which affords an exquisite signal-to-noise ratio that is utilized by drug discovery scientists to visualize, trace, and quantify drugs in vivo. Radiolabeled compounds are easily traced and quantified even after biochemical transformations since the detector response is independent of the structure of the compound; therefore, scintillation counting allows an accurate mass balance during (pre)clinical studies.[3] These qualities make C-14 the isotope of choice for absorption, distribution, metabolism, and excretion studies (ADME), quantitative whole body autoradiography (QWBA), and environmental fate studies.[3,4]

The labeled reagents used to prepare C-14-labeled compounds are highly expensive, for example, the most readily available starting material Ba^{14}CO$_3$ is around $1850 per mmol. In addition, the synthetic chemistry required to incorporate the radiolabel leads to significant radioactive waste. This waste can be difficult and expensive to dispose of. Therefore, strategies that reduce radiochemical waste are of high importance. Hence, approaches including the late-stage incorporation of the radiolabel that serve to minimize radiochemical waste typically require less radiochemical handling, thereby increasing the safety for the scientist.[5] Late-stage incorporation of the radiolabel also increases the overall efficiency of the carbon isotope incorporation.[6]

Carbonylation with carbon monoxide (CO) is a valuable technique for late-stage incorporation of carbon isotopes as it typically displays excellent functional group tolerance and can be applied to join two advanced intermediates.[6,7] Classical carbonylation methods utilize transition metal catalysis (i.e., Pd) to incorporate CO into complex drug-like molecules to afford ketones, carboxylic acids, esters, and amides.[8] However, most methods are only applicable with aryl or vinyl halides and triflate substrates for carbon labeling.[9,10] Most procedures describing the use of alkyl halides typically use an excess of CO.[11] While unlabeled CO is an inexpensive gas, ^{14}CO is expensive and thus preferably used as a limiting reagent. Substoichiometric ^{11}CO carbonylation was achieved by Chow et al.[12] using catalytic amounts of thermal radical initiator azobisisobutyronitrile (AIBN) (Scheme 1A). Despite the

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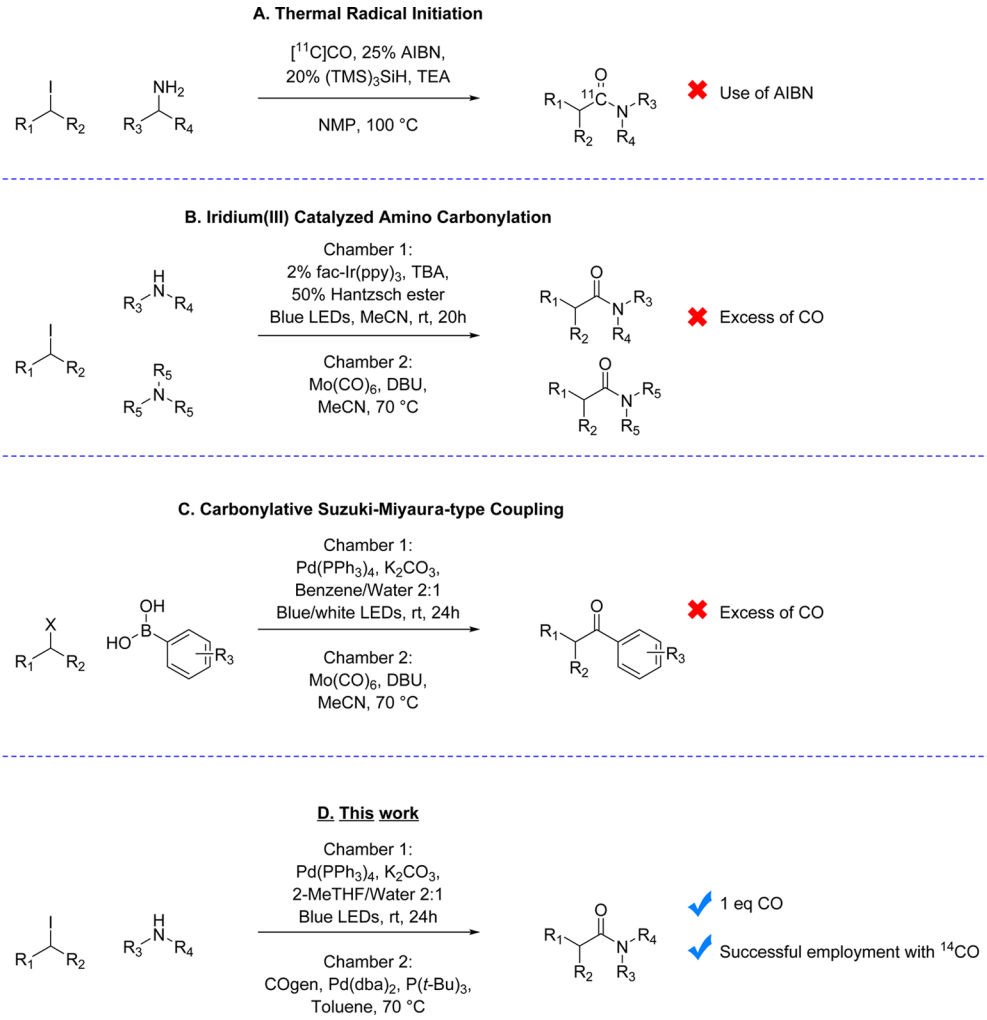
Scheme 1. Methodologies for Carbonylation of Unactivated Alkyl Halides



applicability of the AIBN-catalyzed method on a wide range of functional groups and compatibility with ^{11}CO (short-lived isotope of carbon), AIBN presents major drawbacks due to its safety profile and toxic nature. A milder approach using photochemistry with visible-light and 2−3 atm of CO has been applied for the functionalization of unactivated alkyl halides using aminocarbonylation[13] (Scheme 1B) and Pd-mediated cross-coupling with boronic acids[14] (Scheme 1C). Despite the synthetic utility of these methods and the advances they made in employing only moderate pressures of CO, in the context of isotope labeling, further lowering the amount would be highly desirable. Inspired by the photochemistry works of Chow[12] and Roslin[14], we explored the synthesis of amides via carbonylation of alkyl iodides with amines using only stoichiometric amounts of CO. The method could be successfully applied using palladium catalysis mediated by visible-light for late-stage aminocarbonylation.

RESULTS AND DISCUSSION

At the onset of our investigations, we aimed to evaluate the reactivity of cyclohexyl iodide **1** and morpholine **2** under visible-light conditions and Pd catalysis.[13,14] Unlabeled CO was used as the limiting reagent and was generated from 9-methylfluorene-9-carbonyl chloride (COgen), which provides a readily transferable, solid form of CO and has been used with labeled CO ($^{13/14}CO$).[6] In order to limit costs and generation of waste, the optimization of the procedure and part of the scope were performed using unlabeled COgen. We paid particular attention to the setup of the reaction in order to ensure direct implementation of the protocol onto C-14 radiolabeling. The dual chamber system (COware[9] (Figure 1A)) was used as previously described. As COgen is moisture-sensitive and undergoes hydrolysis, a fresh batch of COgen was made before using.[15]

To facilitate the visible-light chemistry in a parallel fashion, a photoreactor was constructed (Figure 1B,C). Blue light-emitting diodes (LEDs) surround a central compartment, which contains a heating block to enable the liberation of CO from COgen at 70 °C. The carbonylation chamber was kept at room temperature; a fan was used to circulate the air in the reactor to regulate the heat emitted from the LEDs. The setup could facilitate six parallel reactions; however, this setup could potentially be used for larger libraries too.

The work began with an aminocarbonylation for the synthesis of alkyl amides. The COware was loaded with cyclohexyl iodide **1**, 1.5 equiv morpholine **2**, 5% $Pd(PPh_3)_4$, 1 equiv K_2CO_3, and benzene/water (2:1, 3 mL) in the CO-consuming chamber (chamber A), and the CO-releasing chamber was loaded with 1 equiv COgen and the requisite reagents to release the CO (chamber B). Chamber B was heated to 70 °C for 24 h, while chamber A was kept at room

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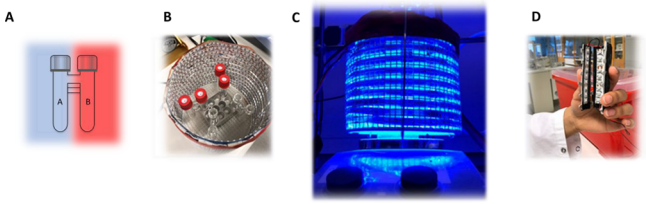
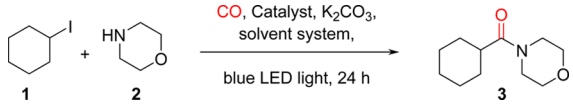


Figure 1. (A) Schematic view of the COware; red represents the heating of the chamber, and blue represents the blue visible-light irradiation. (B) Top view of the elevated photoreactor. (C) Elevated photoreactor, enabling six reactions in parallel, with a heating block in the middle to allow heating of chamber B while chamber A is kept at room temperature. (D) Single chamber photoreactor system. The pictures were taken by J. Bergman, and the schematic drawing of the two-chamber system was made by M. Sardana using Microsoft Office.

temperature and illuminated by blue LEDs to give a conversion of 44% to cyclohexyl(morpholino)methanone **3** (Table 1, entry 1). Motivated by this initial success, we optimized the reaction with respect to amine (equiv), solvent, catalyst, and base.

Table 1. Optimization of Reaction Conditions in the Carbonylation Chamber A[a]



1 2 3

entry	solvent (volume [mL][b])	catalyst	yield of 3[c] (%)
1	benzene/water 2:1 [3]	$Pd(PPh_3)_4$	44
2	benzene/water 2:1 [3]	$Pd(PPh_3)_4$	64
3[d]	benzene/water 2:1 [5]	$Pd(PPh_3)_4$	70 (55)
4[d]	benzene/water 2:1 [5]		
5[d]	benzene/water 2:1 [5]	PPh_3	
6[d,e]	benzene/water 2:1 [5]	$Pd(PPh_3)_4$	
7[d]	toluene/water 2:1 [5]	$Pd(PPh_3)_4$	37
8[d]	2-MeTHF/water 2:1 [5]	$Pd(PPh_3)_4$	81 (61)
9[d]	2-MeTHF [5]	$Pd(PPh_3)_4$	54
10[d]	CPME/water 2:1 [5]	$Pd(PPh_3)_4$	58
11[d,f]	2-MeTHF/water 2:1 [5]	$Pd(PPh_3)_4$	39
12[d,g]	2-MeTHF/water 2:1[5]	$Pd(PPh_3)_4$	62

[a]Standard conditions: Chamber A catalyst (5 mol %), K_2CO_3 (1 equiv), solvent, iodocyclohexane (0.3 mmol, 1 equiv), morpholine (1.5 equiv). CO is produced in chamber B: $Pd(dba)_2$ (5 mol %), COgen (1 equiv), toluene, $P(t\text{-}Bu)_3$ (0.05 equiv), and DIPEA (1.5 equiv). [b]The volume in both chambers. [c]Determined by ^1H NMR using anisole (1 equiv) as an internal standard. Number in parentheses represents the isolated yield. [d]0.6 mmol of iodocyclohexane and 3 equiv morpholine. [e]No light. [f]Reaction time = 5 h. [g]Reaction time = 18 h.

The systematic variation of reaction conditions enabled a better understanding of the factors governing the carbonylation process. Increasing the equivalents of morpholine to 3 equiv gave a yield of 64% (Table 1, entry 2). However, increasing morpholine beyond 3 equiv gave no further improvement (see Supporting Information, Table S1). To alleviate the poor solubility of CO in most organic solvents,[16] the reaction volume was maximized, in conjunction with increased reagent concentrations. This led to a decrease in headspace, thus improving the CO partitioning into the solvent (Table 1, entry 3) to give a yield of 70%. A drop to 38% in (isolated) yield was observed when the reaction was performed on a 1.2 mmol scale to give cyclohexyl(morpholino)methanone **3**. A similar result was observed by Roslin and Odell.[14] When the transformation was performed with ^{13}COgen on the same scale, no difference in the isolated yield was observed (36%). The reaction was demonstrated to require light and $Pd(PPh_3)_4$ (Table 1, entries 4–6). A catalyst screening was performed, and $Pd(PPh_3)_4$ was identified as the best catalyst. Due to the carcinogenic nature of benzene, finding an alternate solvent was imperative. Replacing benzene in the solvent system with toluene (Table 1, entry 7) showed a lower yield. Solvents with a higher density than water were the most detrimental for the yield. Green solvents such as 2-MeTHF and CPME (Table 1, entries 8–10) showed a comparable yield to benzene. 2-MeTHF showed good conversion with (61%) and without water (54%). A variety of bases, both organic and inorganic bases, were shown to be effective. The time of the reaction was also monitored, and the maximum yield of the reaction was observed after 18 h (Table 1, entries 11 and 12). Selected results from our optimization experiments are summarized in the Supporting Information, Table S1.

With the optimized conditions in hand (Table 1, entry 8), the scope of the amine coupling partner was investigated, including primary, secondary, and aryl amines, to establish the versatility of this protocol and probe the limitations. The results are summarized in Scheme 2. Good yields were obtained for primary and cyclic secondary amines providing the amide products **3**–**6** in 37% to 61% yield. Yields of substituted piperazine (**4** and **5**) were lower than the model substrates. Cyclohexylamine, to our surprise, did not show any product formation with water in the solvent system; interestingly, when employing anhydrous conditions, the product **6** was afforded in 57% isolated yield. 2-Aminopyridine afforded an 18% yield for product **7**, whereas aniline only showed a trace of product **19** on gas chromatography–mass spectrometry (GC–MS). 2-Aminopyridine is more basic and therefore likely demonstrates the lower limit of nucleophilicity the reaction will tolerate. Substituted benzyl amine performed well as a substrate, giving a moderate yield of the desired product **8**.

Cyclohexyl iodide performed well with a range of amines. Therefore, the substrate scope was extended to a range of primary and tertiary iodides. Under the optimized conditions, the iodides were reacted with morpholine as the nucleophile. Tertiary iodides underwent a satisfactory reaction to afford the amide products (**9** and **10**) in moderate yields, whereas 1-iodoadamantane returned the desired product **9** in a higher yield compared to *tert*-butyl iodide. The less reactive 1-bromoadamantane afforded the expected product **9** in a 13% yield. Primary alkyl iodide, iodomethylcyclopentane, gave the product (**11**) with a yield of 41%. However, the lack of or low product (**12** and **23**) formation for iodopropane and (2-iodoethyl)benzene is indicative of the competing direct alkylation reaction, which is favored over the pathway toward carbonylation.

The generality of this method was further evaluated by performing the aminocarbonylation method with iodobenzene, and to our delight, morpholino(phenyl)methanone **13** was isolated with a good yield. Para-substituted aryl iodides, *tert*-butyl (4-iodobenzyl)carbamate and 1-iodo-4-methoxybenzene, were used to give good yields, 70% (**14**) and 69% (**15**), respectively.

Lastly, pharmaceutically relevant compounds were carbonylated with the optimized conditions. Praziquantel **18** and

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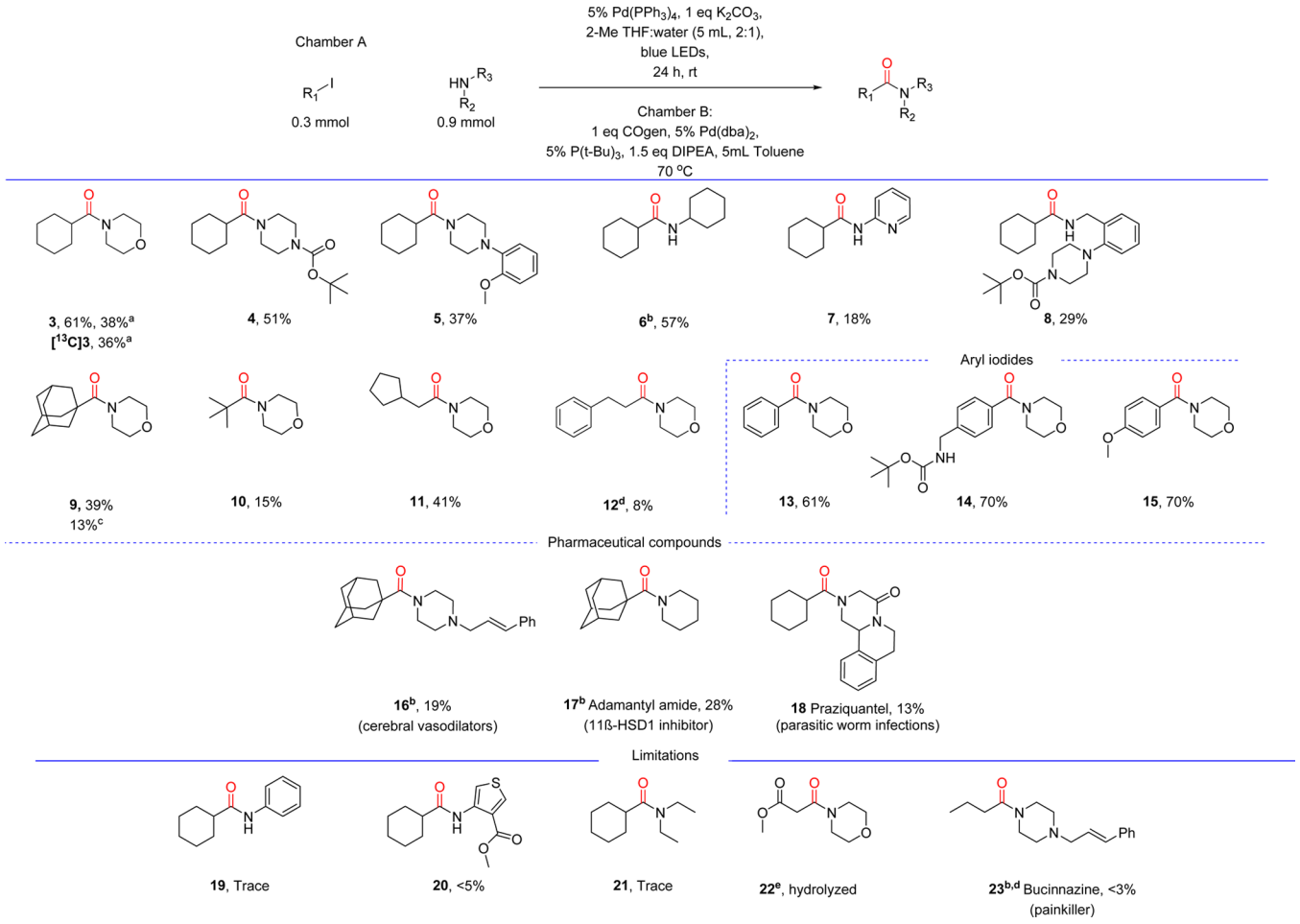
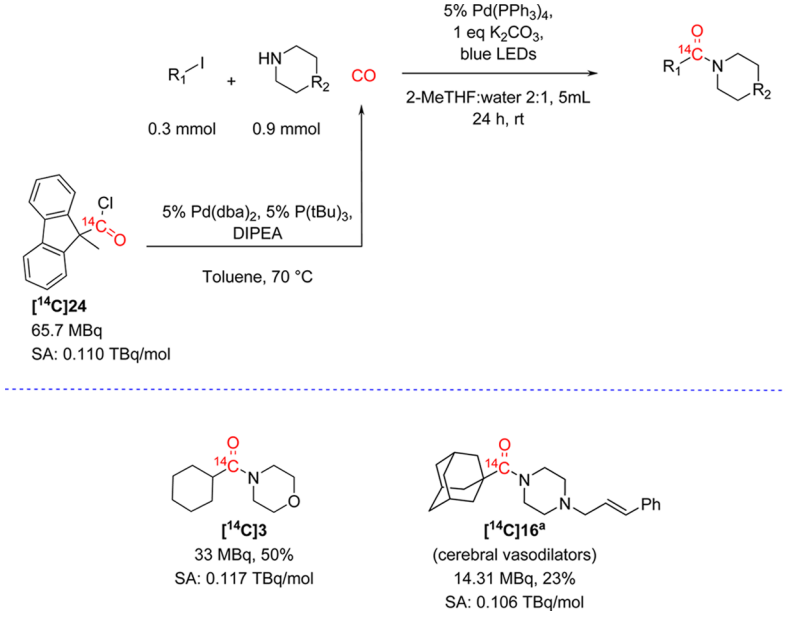
Scheme 2. Synthesis of Alkyl Amides by Carbonylative Coupling of Alkyl Iodides and Amines



[a]1.2 mmol scale. [b]Anhydrous conditions were used with *only* 5 mL of 2-MeTHF in chamber A. [c]1-Bromoadamantane was used. [d]S_N2 product was observed. [e]Product was hydrolyzed.

Scheme 3. ^{14}CO Reaction with Model Substrates and Drug-like Compound 16



[a]Anhydrous conditions were used with *only* 5 mL of 2-MeTHF.

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bucinnazine analogue **16** gave yields of 13 and 19%, respectively. However, attempting the synthesis of bucinnazine **23** by carbonylation of isopropyl iodide and the corresponding piperazine gave predominantly the propylated piperazine. Adamantyl amide **17** was isolated with a moderate yield; surprisingly, in aqueous conditions, no product formation was observed.

The utility of this method toward C-14 labeling was demonstrated using cyclohexyl iodide and morpholine. To reduce the radioactive waste, ^{14}COgen was diluted with an unlabeled material; thus, 5% ^{14}COgen was used with a specific activity of 0.110 TBq/mol. The result was in good agreement with the unlabeled carbonylation of cyclohexyl(morpholino)-methanone **3** (Scheme 3), and the protocol was easily translated to a single photoreactor system (Figure 1D). [^{14}C]Cyclohexyl(morpholino)methanone [^{14}C]**3** was isolated with 50% yield with the expected specific activity within the error margin (Scheme 3).[17] Bucinnazine analogue [^{14}C]**16** was labeled to give 23% yield with the expected specific activity. To the best of our knowledge, no C-14 labeling procedures have been reported for either compound.

CONCLUSIONS

In summary, a mild and versatile radical aminocarbonylation protocol was developed for the late-stage isotopic labeling by carbonylation with good substrate compatibility. By using visible-light irradiation and palladium catalysis, alkyl halides were coupled with amines at ambient temperature with stoichiometric amounts of CO. Moderate to low yields were obtained for late-stage labeling with labeled CO. It is noteworthy that the reaction was enabled by $Pd(PPh_3)_4$, which is cheap and readily available. Additionally, the use of COgen allowed easy translation between the unlabeled reaction and labeled reaction. As for the substrate scope, a wide range of alkyl substrates can be carbonylated, such as the unactivated secondary and tertiary amines. Primary iodides, on the contrary, are difficult to achieve due to the competition with direct alkylation. To generalize the method, aryl iodides also reacted smoothly and were isolated with good yields; however, more investigations should be done to understand the mechanism and scope of this reaction. All in all, promising results have been achieved. These advances provide a powerful and broadly accessible tool for the labeling of functionalized alkyl amides.

EXPERIMENTAL SECTION

General Information. *General Reactions.* All reagents were purchased from commercial suppliers and used without further purification, unless mentioned otherwise. Anhydrous solvents were purchased from Sigma-Aldrich and stored under a nitrogen atmosphere. 9-Methyl-9*H*-fluorene-9-carbonyl chloride and 9-methylfluoren-9-[^{14}C]-carbonyl chloride (COgen and ^{14}COgen, respectively) were prepared according to the procedure of Skrydstrup et al.,[6] and two commercially available chamber glassware apparatus (COware) were purchased from Sytracks and used for the carbonylation reactions. Yields are based on the COgen and refer to a purified, isolated, homogeneous product and spectroscopically pure material, unless stated otherwise.

Reaction Setup. All reactions were carried out under a nitrogen atmosphere and were magnetically stirred. Electric heating plates and DrySyn were used for elevated temperatures, and a stated temperature corresponds to the external DrySyn temperature. Blue S6 LED strips (15 V, 15 W/meter, 4.67 m, λ = 465.2 nm) were used and provided by LED Teknik Boras Sweden, and no filters were used (see the Supporting Information for the full LED report (Figure S1)). The distance between the COware (borosilicate glass) and the blue LED strips is between 2 and 4 cm, reactions were repeated on all positions, and comparable results were obtained. Concentration was performed on a rotary evaporator with a heating bath at 40 °C.

Reaction Mixture. A crude reaction mixture was assayed by GC−MS or liquid chromatography−MS (LC−MS) and quantified by NMR with anisole as an internal standard. LC−MS analysis was performed on a Waters Acquity UPLC using either of the following:

1. Method A: BEH C18 column (50 mm × 2.1 mm, 1.7 μm of particles) with a 10−90% gradient over 2 or 4 min with MeCN-NH_4/NH_4CO_3.
2. Method B: BEH C18 column (50 mm × 2.1 mm, 1.8 μm of particles) with a 10−90% gradient over 2 or 4 min with MeCN−formic acid and electrospray ionization (EI).

GC−MS (EI) analysis was performed on a 7890A GC system and 5975C inert MSD system equipped with an Agilent 19091S-433L (30 m × 250 μ × 0.25 μm) capillary column using a gradient: 40−150 °C with a rate of 15 °C/min followed by 150−300 °C with a rate of 60 °C/min and electron impact ionization at 70 eV.

Thin layer chromatography was carried out using E. Merck silica glass plates (60F-254) with UV light (254 nm) and/or iodine vapor/potassium permanganate as the visualization agent.

Purification. Crude reaction mixtures were purified by either flash chromatography prepacked Isolute SI columns or Biotage SNAP columns using a Biotage automated flash systems with UV detection or preparative reversed-phase high-performance liquid chromatography (HPLC) purifications using a Gilson 322 pump equipped with a Gilson UV/Vis-152 lamp with an Xbridge Prep C-18 10 μm OBD, 19 × 250 mm column.

Analysis. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III system running at a proton frequency of 500.1 MHz with a cryogenic probe or on a Bruker Avance Nanobay system at 400.13 MHz and processed with the NMR software MestreNova (Mestrelab Research SL). NMR experiments were run in $CDCl_3$ at 25 °C, unless stated otherwise. ^{1}H chemical shifts are referenced relative to the residual solvent peak at 7.26 ppm, and ^{13}C chemical shifts are referenced to 77.67 ppm for $CDCl_3$. Signals are listed in ppm, and multiplicity was identified as s = singlet, br = broad, d = doublet, dt = doublet of a triplet, t = triplet, tt = triplet of a triplet, q = quartet, quin = quintet, h = hextet, and m = multiplet; coupling constants in Hz; integration. ^{13}C NMR data is reported as with chemical shifts. For purity, quantitative NMR spectroscopy (qNMR) was performed with 2,3,5,6-tetrachloronitrobenzene (Tokyo Chemical Industry Co. Ltd. Japan, lot 242) (unless mentioned otherwise) as an internal calibrant in 0.6 mL of $CDCl_3$ (glass ampules, Sigma-Aldrich).[18] Purity was calculated with the NMR processing software, MestreNova. Accurate mass values were determined on a Waters Xevo Q-TOF mass spectrometer with an electrospray ion source in positive mode. Purity assays were also performed on the aforementioned LC−MS and GC−MS systems. Radiochemical purity was determined by HPLC using either of the following:

1. Setup 1: Waters 2695 Separations module equipped with Waters x Select CSH C18 2.5 μm, 3 × 100 mm column and with a radioactivity flow monitor using a Perkin-Elmer Radiomatic 500 TR with Ultima Gold cocktail. A gradient method was used for radiochemical purity determination with mobile phase A (water with 0.2% formic acid adjusted to pH 3) and mobile phase B (95% MeCN/water 0.2% formic acid, pH 3) with gradient elution (50% B for 0−3 min, then ramp to 100% B over 17 min and hold at 100% B for 5 min).
2. Setup 2: Waters Acquity UPLC with Waters Xbridge C18 3.5 μm, 4.6 × 100 mm column was used along with a Perkin-Elmer TRI-CARB 2500 liquid scintillation analyzer with Ultima Gold cocktail. A gradient method was used for radiochemical purity determination with mobile phase A (10 mM NH_4HCO_3 buffered with NH_4OH) and mobile phase B (MeCN) with gradient elution (5% for 0−3 min, then ramp to 95% over 22 min and hold at 95% for 5 min).

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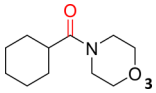
General Procedures. *General Procedure for Chamber B, CO-Producing Chamber.* Chamber B was loaded in the following order: $Pd(dba)_2$ (5%, 0.03 mmol), toluene (3 mL), tri-*tert*-butylphosphine (5%, 0.03 mmol), and *N*,*N*-diisopropylethylamine (1.5 equiv, 0.90 mmol). The chamber was sealed with Teflon-lined PTFE septa and a stabilizing disc. The chamber is purged with N_2, after which COgen (1 equiv, 0.60 mmol in toluene, 2 mL) is added and the chamber is stirred and heated to 70 °C.

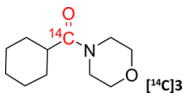
General Procedure for Amino Carbonylation Chamber A, CO-Consuming Chamber. To chamber A were added $Pd(PPh_3)_4$ (5%, 0.03 mmol), K_2CO_3, (1 equiv, 0.60 mmol), 2-MeTHF (3.5 mL), alkyl iodide (1 equiv, 0.60 mmol), amine (3 equiv, 1.80 mmol), and water (1.5 mL). The chamber was sealed with Teflon-lined PTFE septa and a stabilizing disc. The chamber was purged for 5 min. The chamber was irradiated with visible blue light and stirred for 24 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) over a phase separator and concentrated in vacuo, unless mentioned otherwise. Purification was performed using either a manual system, Biotage automated normal purification system, or reversed-phase HPLC purification.



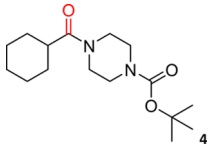
Preparation of Cyclohexyl(morpholino)methanone ***3*** *(CAS 29338-96-3).*[13] Chamber A was loaded according to the general procedure with iodocyclohexane (78 μL, 0.60 mmol) and morpholine (155 μL, 1.80 mmol) in 2-MeTHF (3.5 mL) and water (1.5 mL) as the solvent system. Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 25 g SNAP column with 25% EtOAc in heptane over 20 min. Fractions containing the product were pooled and concentrated to give the desired product (72.2 mg, 61%). Data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17−1.32 (m, 3H), 1.52 (m, 2H), 1.70 (d, J = 12.94 Hz, 5H), 2.42 (tt, J = 3.41, 3.41, 11.58, 11.58 Hz, 1H), 3.44−3.71 (m, 8H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ 174.6, 67.0, 66.8, 45.8, 41.9, 40.2, 29.3, 25.75, 25.74. NMR purity assay: 95%.

Preparation of [^{13}C]Cyclohexyl(morpholino)methanone [^{13}C]3 (scale: 1.2 mmol). Chamber A was loaded according to the general procedure with iodocyclohexane (155 μL, 1.20 mmol), morpholine (311 μL, 3.60 mmol), K_2CO_3 (166 mg, 1.20 mmol), and $Pd(PPh_3)_4$ (69.3 mg, 0.06 mmol) in 2-MeTHF (3.5 mL) and water (1.5 mL) as the solvent system. Chamber B was loaded according to the general procedure for the CO-releasing chamber with $Pd(dba)_2$ (34.5 mg, 0.06 mmol), P(*t*-Bu)$_3$ (60 μL, 0.06 mmol), and *N*,*N*-diisopropylamine (315 μL, 1.81 mmol) in toluene (5 mL), and lastly [^{13}C]COgen (292 mg, 1.20 mmol). Purification was performed on a 25 g SNAP column with 0−60% EtOAc in heptane. Fractions containing the product were pooled and concentrated to give the desired product (86.3 mg, 38%). NMR purity assay: 96.1%.

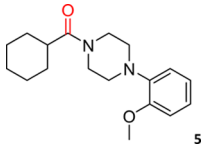
Preparation of Cyclohexyl(morpholino)methanone ***3*** *(scale: 1.2 mmol).* Chamber A was loaded according to the general procedure with iodocyclohexane (155 μL, 1.20 mmol), morpholine (311 μL, 3.60 mmol), K_2CO_3 (166 mg, 1.20 mmol), and $Pd(PPh_3)_4$ (69.3 mg, 0.06 mmol) in 2-MeTHF (3.5 mL) and water (1.5 mL) as the solvent system. Chamber B was loaded according to the general procedure for the CO-releasing chamber with $Pd(dba)_2$ (34.5 mg, 0.06 mmol), P(*t*-Bu)$_3$ (60 μL, 0.06 mmol), and *N*,*N*-diisopropylamine (315 μL, 1.81 mmol) in toluene (1 mL), and lastly COgen (291 mg, 1.20 mmol, 0.3 M, 4 mL). Purification was performed on a 25 g SNAP column with 0−60% EtOAc in heptane. Fractions containing the product were pooled and concentrated to give the desired product (85 mg, 36%). NMR purity assay: 96.6%.



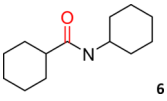
Preparation of [^{14}C]Cyclohexyl(morpholino)methanone ***3***. Chamber A was loaded according to the general procedure and reaction procedure for **3**. Chamber B was loaded according to the general procedure for the CO-releasing chamber COgen (129 mg, 0.57 mmol), and [^{14}C]COgen (65.7 MBq, 0.03 mmol) was used. Purification was performed on a 20 g Flash Si column with 25% EtOAc in heptane. Fractions containing the product were pooled and concentrated in vacuo to give the desired product (32.96 MBq, 0.117 TBq/mol, 50%). Radio-HPLC (setup 1): 98.87%.



Preparation of tert-Butyl 4-(cyclohexanecarbonyl)piperazine-1-carboxylate ***4*** *(CAS 1328099-31-5).* Chamber A was loaded according to the general procedure with iodocyclohexane (78 μL, 0.6 mmol) and *tert*-butyl piperazine-1-carboxylate (343.2 mg, 1.84 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 10 g Flash Si column with 25% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the desired product (88.7 mg, 50%). Data for **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.28 (m, 2H), 1.44−1.59 (m, 11H), 1.65−1.84 (m, 5H), 2.44 (tt, J = 11.6, 3.3 Hz, 1H), 3.31−3.65 (m, 8H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.9, 154.7, 80.4, 77.5, 77.4, 77.2, 76.8, 45.3, 43.9, 41.5 (broad peaks due to conformation change), 40.6, 29.5, 28.5, 25.96, 25.94. NMR purity assay: 90%. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{28}N_2O_3$ 297.2178; Found 297.2195.



Preparation of Cyclohexyl(4-(2-methoxyphenyl)piperazin-1-yl)-methanone ***5***. Chamber A was loaded according to the general procedure with iodocyclohexane (1 equiv, 78 μL, 0.60 mmol) and 1-(2-methoxyphenyl)piperazine hydrochloride (2.52 equiv, 346 mg, 1.51 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed via HPLC (5−70% MeCN/0.1% TFA in water over 20 min, wavelength of 220 nm, 15 mL/min). Fractions containing the product were pooled and lyophilized to give the product as TFA salt. The product was partitioned in 5 mL of CH_2Cl_2 and 5 mL of Na_2CO_3. The layers are separated over a phase separator. The aqueous layer was washed with CH_2Cl_2 (5 × 5 mL). The organic layers were combined and concentrated to give the free product (67.1 mg, 37%). Data for **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.37 (m, 3H), 1.5−1.63 (m, 2H), 1.66−1.86 (m, 6H), 2.52 (tt, J = 3.31, 3.31, 11.55, 11.55 Hz, 1H), 3.05 (dt, J = 4.78, 4.78, 17.63 Hz, 4H), 3.67−3.73 (m, 2H), 3.79−3.84 (m, 2H), 3.89 (s, 3H), 6.87−6.97 (m, 3H), 7−7.1 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.6, 152.2, 123.6, 121.0, 118.5, 111.3, 77.3, 77.2, 77.0, 76.7, 55.4, 51.3, 50.7, 45.6, 41.7, 40.4, 29.4, 25.89, 25.86. A peak at 140 ppm was missing; however, a strong correlation on HMBC suggests that it is a quaternary aromatic carbon. NMR purity assay: 96.7%. LCMS (method B, 4 min): 303.0 $[M + H]^+$, rt 2.07 min (100%). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{26}N_2O_2$ 303.2072; Found 303.2070.



Preparation of N-Cyclohexylcyclohexanecarboxamide ***6*** *(CAS 7474-36-4).*[12] Chamber A was loaded according to the general procedure with iodocyclohexane (78 μL, 0.60 mmol) and cyclohexanamine (206 μL, 1.80 mmol) and 5 mL of 2-methyl THF. Chamber B was loaded according to the general procedure for the

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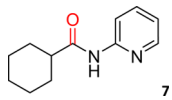
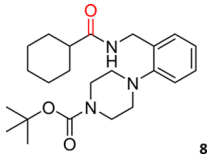
CO-releasing chamber. The reaction mixture concentrated in vacuo. Purification was performed on a 10 g Flash Si column with 25% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the the desired product (72.1 mg, 57%). Data for **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02−1.48 (m, 11H), 1.57−1.94 (m, 10H), 2.01 (tt, J = 3.40, 3.40, 11.83, 11.83 Hz, 1H), 3.68−3.82 (m, 1H), 5.24 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.1, 77.2, 77.0, 76.8, 47.7, 45.8, 33.3, 29.8, 25.8, 25.6, 24.9. NMR purity assay: 96.1%. GC−MS: 209.2 [M], rt 9.83 min (100%).



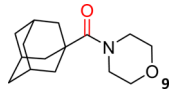
7

*Preparation of N-(Pyridin-2-yl)cyclohexanecarboxamide **7** (CAS 68134-77-0).*[19] Chamber A was loaded according to the general procedure with iodocyclohexane (78 μL, 0.60 mmol) and pyridine-2-amine (165.2 mg, 1.76 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 10 g SNAP column with 8−66% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo. The obtained product was further purified on a 10 g Isolute SI column. Fractions containing the product were pooled and concentrated in vacuo to give the product (22.4 mg, 18%). Data for **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25−1.38 (m, 3H), 1.49−1.62 (m, 2H), 1.71 (d, J = 10.9 Hz, 1H), 1.79−1.88 (m, 2H), 2.01 (d, J = 13.0 Hz, 2H), 2.38 (t, J = 12.1 Hz, 1H), 7.14 (t, J = 6.6 Hz, 1H), 7.87 (t, J = 7.6 Hz, 1H), 8.21 (d, J = 5.1 Hz, 1H), 8.43 (d, J = 8.5 Hz, 1H), 9.35 (s, 1H). ^{13}C{^{1}H} NMR (100.59 MHz, $CDCl_3$) δ 176.08, 150.8, 142.6, 142.1, 119.4, 115.8, 46.5, 29.4, 25.7, 25.3. NMR purity assay: 88%. LCMS (method B, 4 min): 205.07 [M + H]$^+$, rt 1.35 min (100%).



8

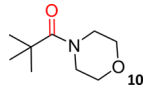
*Preparation of tert-Butyl 4-(2-(Cyclohexanecarboxamidomethyl)phenyl)piperazine-1-carboxylate **8**.* Chamber A was loaded according to the general procedure with iodocyclohexane (1 equiv, 78 μL, 0.60 mmol) and *tert*-butyl 4-(2-(aminomethyl)phenyl)piperazine-1-carboxylate (3 equiv, 522.5 mg, 1.79 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 10 g SNAP column with EtOAc in heptane (0−70%) over 20 min. Fractions containing the product were pooled and concentrated to give the desired product (70.2 mg, 29%). Data for **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 3H), 1.39−1.52 (m, 11H), 1.64−1.72 (m, 1H), 1.76−1.85 (m, 2H), 1.86−1.95 (m, 2H), 2.12 (tt, J = 3.48, 3.48, 11.73, 11.73 Hz, 1H), 2.82−2.92 (m, 4H), 3.58 (t, J = 4.90, 4.90 Hz, 4H), 4.55 (d, J = 5.57 Hz, 2H), 6.19 (t, J = 4.34, 4.34 Hz, 1H), 7.07−7.15 (m, 2H), 7.24−7.3 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, 26 °C) δ 175.73, 154.74, 151.03, 133.1, 129.2, 128.4, 124.6, 120.2, 79.9, 77.3, 77.0, 76.7, 52.5, 45.7, 39.6, 29.8, 28.4, 25.8. NMR purity assay: 98.9%. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{35}N_3O_3$ 402.2757; Found 402.2761.



9

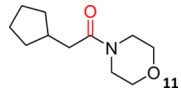
*Preparation of Adamantan-1-yl(morpholino)methanone **9** (CAS 22508-50-5).*[12] Chamber A was loaded according to the general procedure with 1-iodoadamantane (158.4 mg, 0.60 mmol) and morpholine (3 equiv, 155 μL, 1.80 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 10 g Flash Si column with 25% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the desired product (57.9 mg, 39%). Data for **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66−1.78 (m, 6H), 1.97−2.01 (m, 6H), 2.02−2.07 (m, 3H), 3.63−3.73 (m, 8H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.9, 77.2, 77.0, 76.8, 67.1, 46.0, 41.7, 39.0, 36.6, 28.5, 28.3. NMR purity assay: 92%. LCMS (method B, 4 min): 250.1 [M + H]$^+$, rt 1.77 min (100%).

*Preparation of Adamantan-1-yl(morpholino)methanone **9** (CAS 22508-50-5) from 1-Bromoadamantane.* Chamber A was loaded according to the general procedure with 1-bromoadamantane (137.5 mg, 0.64 mmol) and morpholine (3 equiv, 155 μL, 1.80 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 20 g Flash Si column with 0−25% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the desired product (19.3 mg, 13%). NMR purity assay: 88%.



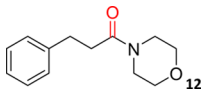
10

*Preparation of 2,2-Dimethyl-1-morpholinopropan-1-one **10** (CAS 70414-49-2).* Chamber A was loaded according to the general procedure with 2-iodo-2-methylpropane (72 μL, 0.60 mmol) and morpholine (155 μL, 1.80 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 20 g Flash Si column with 0−25% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the translucent crystals (15.8 mg, 15%). Data for **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 3.65 (d, J = 7.3 Hz, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.6, 77.5, 77.2, 76.9, 67.0, 45.9, 38.7, 28.4. NMR purity assay: 99%. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_9H_{17}NO_2$ 172.1337; Found 172.1326.



11

*Preparation of 2-Cyclopentyl-1-morpholinoethan-1-one **11**.* Chamber A was loaded according to the general procedure with (iodomethyl)cyclopentane (127.9 mg, 0.61 mmol) and morpholine (155 μL, 1.80 mmol). Chamber B was loaded according to the general procedure. Purification was performed on a 10 g SI column with 25% EtOAc in heptane. Fractions containing the product were pooled and concentrated to give the product (42.3 mg, 36%). Data for **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04−1.19 (m, 2H), 1.45−1.66 (m, 4H), 1.74−1.89 (m, 2H), 2.11−2.28 (m, 1H), 2.31 (d, J = 7.4 Hz, 2H), 3.38−3.51 (m, 2H), 3.53−3.68 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.7, 77.5, 77.2, 76.8, 67.2, 66.9, 46.3, 42.0, 39.2, 36.8, 32.9, 25.1. NMR purity assay: 85%. LCMS (method A, 4 min): 198 [M + H]$^+$, rt 1.16 min (100%). HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{11}H_{19}NO_2$ 198.1494; Found 198.1493.



12

*Preparation of 1-Morpholino-3-phenylpropan-1-one **12**.* Chamber A was loaded according to the general procedure with (2-iodoethyl)benzene (87 μL, 0.60 mmol) and morpholine (155 μL, 1.80 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 25 g SNAP column with EtOAc in heptane (2−100% EtOAc). Fractions were pooled, concentrated, and subjected to HPLC purification (5−75% MeCN/0.2% NH3 in H_2O/MeCN (95:5) over 15 min, wavelength of 220 nm, 15 mL/min). Fractions containing the product were pooled and lyophilized to give the desired product (10.9 mg, 8%). Data for **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58−2.66 (m, 2H), 2.94−3.03 (m, 2H), 3.31−3.41 (m, 2H), 3.47−3.56 (m, 2H), 3.62 (s, 4H), 7.18−7.24 (m, 3H), 7.27−7.32 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.0, 141.2, 128.7, 128.6, 126.4, 77.5, 77.2, 76.8, 67.0, 66.6, 46.1, 42.1, 35.0, 31.6.

DOI: 10.1021/acs.joc.9b02575
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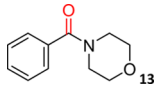
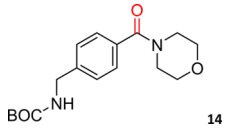
LCMS (method A, 4 min): 220 $[M + H]^+$, rt 1.13 min (100%). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}NO_2$ 220.1137; Found 220.1135.



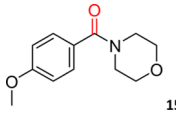
13

Preparation of Morpholino(phenyl)methanone ***13*** *(CAS 1468-28-6).*[20] Chamber A was loaded according to the general procedure with iodobenzene (1 equiv, 67 μL, 0.60 mmol) and morpholine (3 equiv, 155 μL, 1.80 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed via HPLC (5−70% MeCN/0.1% TFA in water over 20 min, wavelength of 220 nm, 15 mL/min). Fractions containing the product were pooled and lyophilized to give the desired product (69.7 mg, 61%). Data for **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25−3.87 (m, 8H), 7.3−7.41 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.3, 135.3, 129.8, 128.5, 127.0, 77.5, 77.2, 76.8, 66.8, 48.1, 42.5. NMR purity assay: 98.1%. LCMS (method B, 4 min): 192.01 $[M + H]^+$, rt 0.87 min (100%).



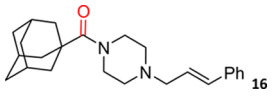
14

Preparation of tert-Butyl (4-(Morpholine-4-carbonyl)benzyl)-carbamate ***14*** *(CAS 1110964-59-4).* Chamber A was loaded according to the general procedure with *tert*-butyl (4-iodobenzyl)-carbamate (204.5 mg, 0.61 mmol) and morpholine (155 μL, 1.80 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 20 g Isolute SPE Si column with 25%−100% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the desired product (133.9 mg, 70%). Data for **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.2−3.99 (m, 8H), 4.33 (d, J = 5.7 Hz, 2H), 4.92 (s, 1H), 7.28−7.41 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.3, 156.0, 141.2, 134.4, 127.6, 127.5, 79.9, 77.5, 77.4, 77.2, 76.8, 67.0, 44.4, 28.5. NMR purity assay: 88%. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{24}N_2O_4$ 321.1814; Found 321.1818.



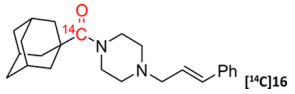
15

Preparation of (4-Methoxyphenyl)(morpholino)methanone ***15*** *(CAS 7504-58-7).* Chamber A was loaded according to the general procedure with 1-iodo-4-methoxybenzene (139 mg, 0.59 mmol) and morpholine (155 μL, 1.80 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 20 g Flash Si column with 40%−100% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the desired product (92.8 mg, 70%). Data for **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (d, J = 17.5 Hz, 8H), 3.82 (s, 3H), 6.82−6.98 (m, 2H), 7.29−7.44 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.5, 161.0, 129.3, 127.5, 113.9, 77.5, 77.2, 76.8, 67.0, 55.5. NMR purity assay: 83.6%. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}NO_3$ 222.1130; Found 222.1112.



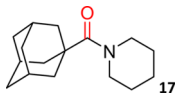
16

Preparation of 1-Adamantyl-[4-[(E)-cinnamyl]piperazin-1-yl]-methanone ***16*** *(CAS 60277-86-3).*[21] Chamber A was loaded according to the general procedure with 1-iodoadamantane (157 mg, 0.60 mmol) and *trans*-1-cinnamylpiperazine (364 mg, 1.80 mmol) and 5 mL of 2-MeTHF. Chamber B was loaded according to the general procedure. Purification was performed via HPLC (35−95% MeCN/0.2% NH_3 in H_2O/MeCN (95:5) over 25 min, wavelength of 250 nm, 20 mL/min). Fractions were pooled and lyophilized to give the product as a brown sticky oil (40.8 mg, 19%). Data for **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66−1.77 (m, 6H), 1.95−2.06 (m, 9H), 2.42−2.53 (m, 4H), 3.12−3.19 (m, 2H), 3.64−3.81 (m, 4H), 6.25 (dt, J = 15.8, 6.8 Hz, 1H), 6.52 (d, J = 15.9 Hz, 1H), 7.2−7.26 (m, 1H), 7.28−7.34 (m, 2H), 7.35−7.39 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.8, 136.9, 133.6, 128.7, 127.8, 126.5, 126.1, 77.5, 77.2, 76.8, 61.1, 53.6, 45.4, 41.8, 39.2, 36.8, 28.6. NMR purity assay: 87.7%. LCMS: 365 $[M + H]^+$, rt 2.63 min (base 4 min) (87%). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{32}N_2O$ 365.2593; Found 365.2589.



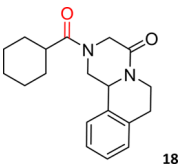
[^{14}C]16

Preparation of 1-Adamantyl-[4-[(E)-cinnamyl]piperazin-1-yl]-methanone [^{14}*C]16.* Chamber A was loaded according to the general procedure with 1-iodoadamantane (157 mg, 0.60 mmol) and *trans*-1-cinnamylpiperazine (384 mg, 1.90 mmol) and 5 mL of 2-MeTHF. Chamber B was loaded according to the general procedure for the CO-releasing chamber COgen (128.5 mg, 0.57 mmol), and [^{14}C]COgen (69.06 MBq, 0.03 mmol) was used. Purification was performed via HPLC (60−80% MeCN/0.2% NH_3 in H_2O/MeCN (95:5) over 15 min, wavelength of 250 nm, 20 mL/min). Fractions were pooled and lyophilized to give the product as a light yellow sticky oil (14.31 MBq, 0.106 TBq/mol, 23%). Radio-HPLC (setup 2): 97.48%.



17

Preparation of Adamantan-1-yl(piperidin-1-yl)methanone ***17*** *(CAS 22508-49-2).*[12] Chamber A was loaded according to the general procedure with 1-iodoadamantane (157 mg, 0.60 mmol) and piperidine (178 μL, 1.80 mmol). Chamber B was loaded according to the general procedure for the CO-releasing chamber. Purification was performed on a 25 g SNAP column with 0−25% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the translucent crystals (42 mg, 28.3). Data for **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49−1.59 (m, 4H), 1.61−1.67 (m, 2H), 1.69−1.77 (m, 6H), 1.97−2.07 (m, 9H), 3.52−3.67 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.7, 77.5, 77.2, 76.8, 46.6, 41.9, 39.2, 36.9, 28.7, 26.5, 25.0. NMR purity assay: 96%.



18

Preparation of 2-(Cyclohexanecarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one ***18*** *(Praziquantel, CAS 55268-74-1).*[22] Chamber A was loaded according to the general procedure with 1-iodocyclohexane (78 μL, 0.60 mmol) and 1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (350.9 mg, 1.73 mmol). Chamber B was loaded according to the general procedure. Purification was performed on a 25 g SNAP column with 12−100% EtOAc in *n*-heptane. Fractions containing the product were pooled and concentrated in vacuo to give the product (53.5 mg, 28.5%). This was subjected to recrystallization by dissolution in warm EtOH and then stored in the freezer. Filtration gave fluffy crystals (24.8 mg, 13%). Data for **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23−1.42 (m, 3.3H, major + minor), 1.48−1.65 (m, 2H, major + minor), 1.7−1.9 (m, 5.4H, major + minor), 2.43−2.62 (m, 1H, major + minor), 2.76−3.05 (m, 4H), 3.27 (t, J = 11.7 Hz, 0.21H, minor), 3.88

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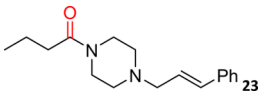
(d, J = 18.5 Hz, 0.21H, minor), 4.10 (d, J = 17.4 Hz, 0.76H, major), 4.39 (d, J = 12.8 Hz, 0.21H, minor), 4.49 (d, J = 17.4 Hz, 0.77H, major), 4.75−4.96 (m, 2.3H, major + minor), 5.18 (d, J = 13.1 Hz, 0.76H, major), 7.15−7.25 (m, 1.3H), 7.27−7.36 (m, 2.7H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 174.8 (major), 174.3 (minor), 165.6 (minor), 164.4 (major), 135.5 (minor), 134.7 (major), 132.8 (major), 132.1 (minor), 129.7 (minor), 129.3 (major), 127.7 (minor), 127.5 (major), 127.0, 125.5 (major), 125.2 (minor), 55.8 (minor), 55.0 (major), 49.6 (minor), 49.0 (major), 46.3 (minor), 45.2 (major), 40.8, 39.1 (major), 38.7 (minor), 29.5 (minor), 29.3 (major), 29.2 (minor), 29.0 (major), 28.9 (minor), 28.7 (major), 25.7. NMR purity assay: 96.6%. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{24}N_2O_2$ 313.1916; Found 313.1908.



Preparation of 1-(4-Cinnamylpiperazin-1-yl)butan-1-one ***23*** *(Bucinnazine, CAS 17719-89-0).*[23] Chamber A was loaded according to the general procedure with 1-iodopropane (59 μL, 0.60 mmol) and *trans*-1-cinnamylpiperazine (364 mg, 1.80 mmol) and 5 mL of 2-MeTHF. Chamber B was loaded according to the general procedure. Purification was performed via HPLC (30−90% MeCN/0.2% NH_3 in H_2O/MeCN (95:5) over 25 min, wavelength of 250 nm, 20 mL/min). Fractions were pooled and lyophilized to give the product (5.37 mg, 3%). Data for **23**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.67 (h, J = 7.4 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 2.97 (broad s, 4H), 3.39−4.15 (m, 6H), 6.27 (dt, J = 15.4, 7.3 Hz, 1H), 6.69 (d, J = 15.8 Hz, 1H), 7.28−7.43 (m, 5H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.4, 128.8, 126.9, 77.3, 77.0, 76.8, 59.8, 51.5, 43.2, 39.1, 34.9, 18.6, 13.9.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b02575.

LED report, general procedure for optimization of amino carbonylation reaction, ^1H and ^{13}C NMR spectra of the amide products, and LCMS chromatograms of the $[^{14}C]$-labeled amide products, and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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