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Palladium-Catalyzed *N*-Acylation of Monosubstituted Ureas Using Near-Stoichiometric Carbon Monoxide

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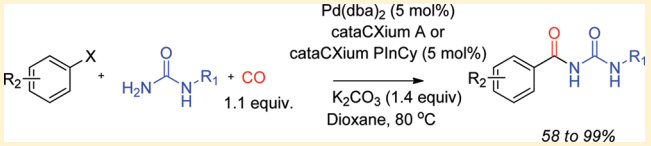
Supporting Information

ABSTRACT: The palladium-catalyzed carbonylation of urea derivatives with aryl iodides and bromides afforded *N*-benzoyl ureas (20 examples) in yields attaining quantitative via the application of near-stoichiometric amounts of carbon monoxide generated from the decarbonylation of the CO precursor, 9-methylfluorene-9-carbonyl chloride. The synthetic protocol displayed good functional group tolerance. The methodology is also highly suitable for ^{13}C isotope labeling, which was demonstrated through the synthesis of three benzoyl ureas, including the insecticide triflumuron, whereby ^{13}CO was incorporated into the core structure.



INTRODUCTION

N-Acyl ureas are common structural motifs in a variety of bioactive compounds exhibiting beneficial properties. Effects such as antiinflammatory, hypnotics, analgesic, antitumor, anthelmintic, antifungal, and insecticidal have all been reported in the literature (Scheme 1).[1,2] Such urea derivatives, more specifically benzoyl ureas, have found widespread use within the field of agrochemicals, such as insect growth regulators (IGRs).[2] Examples of IGRs in use are diflubenzuron, flufenoxuron, lufenuron, and novaluron, all interfering in the synthesis of the insect's exoskeleton formed from chitin (Figure 1).

Classical methods for the synthesis of *N*-acyl ureas includes the activation of the corresponding acid and coupling it to a urea, or the reaction between an amide and an isocyanate. Alternatively, the *N*-acyl urea motif could be obtained applying transition-metal-catalyzed carbonylation chemistry (Scheme 1).

To date, only two reports have been published using a palladium-catalyzed reaction between an aryl or vinyl halide and a substituted urea in the presence of carbon monoxide (CO).[3,4] Fuchikami and Ojima reported a method on the Pd-catalyzed synthesis of 5-trifluoromethyluracils starting from 2-bromo-3,3,3-trifluoropropene, CO, and substituted ureas.[3] Later, Roberts and co-workers reported a general palladium-catalyzed procedure for the formation of benzoyl ureas using either CO in combination with conventional heating or the application of in situ generation of CO from $Mo(CO)_6$ under microwave irradiation.[4] Although, both reports illustrate the advantages of a carbonylative approach in combination with catalysis for the construction of the *N*-acyl urea motif, the use of CO at elevated pressures (4.4−40 atm) or the application of $Mo(CO)_6$ as the in situ source of CO possess different problems. Running reactions with CO at pressures higher than 1 atm (balloon) requires specialized equipment (autoclaves) and furthermore a pressurized CO flask, which neccessitates handling of a flammable and toxic gas. These issues were resolved by Roberts et al. upon using a metal carbonyl complex as the in situ CO precursor, a method that has been applied successfully by Larhed and others.[5,6] In particular, $Mo(CO)_6$ has earned its reputation as a viable CO- source and has been applied in several carbonylation protocols.[6] However, the use of a toxic metal carbonyl complex in turn requires the addition of an additional transition-metal complex into the reaction mixture, often in stoichiometric quantities, hampering purification of the desired product. Furthermore, the presence of the metal carbonyl can lead to a decrease in overall functional group tolerance of the reaction.[6e]

With a new method for the ex situ production of CO in a two-chamber system at hand, recently developed in our group, in conjunction with the earlier work disclosed by Roberts and co-workers, we wish to report on our findings on the development of a simple and easy to perform synthesis of benzoyl ureas without the necessity of handling carbon monoxide flasks or transition-metal carbonyl complexes. On application of aryl iodides and bromides, substituted ureas, and carbon monoxide generated from a new CO precursor in a near-stoichiometric quantity in a Pd-catalyzed carbonylation reaction, excellent yields of the N-acyl ureas are obtained. Due to the equimolar amount of CO, the efficient ^{13}C labeling of the benzoylic carbonyl in the *N*-acyl urea is presented. This new approach provides straightforward access to benzoyl ureas from simple starting materials with the inherent good functional group tolerance from palladium catalysis.

RESULTS AND DISCUSSION

To optimize the carbonylation conditions for *N*-acyl urea synthesis, *m*-iodotoluene was chosen as the electrophile and phenylurea as its coupling partner (Table 1). For the ligands, we were inspired by several reports, including those of (a) Beletskaya et al. reporting on the *N*-arylation of urea using Xantphos or DPEphos as the ligands, (b) Buchwald on aminocarbonylations exploiting Xantphos, and (c)

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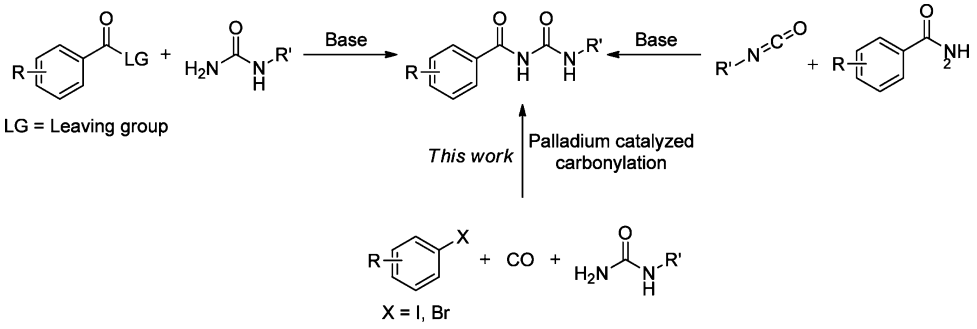
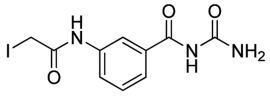
Scheme 1. Synthesis of *N*-Acyl Ureas





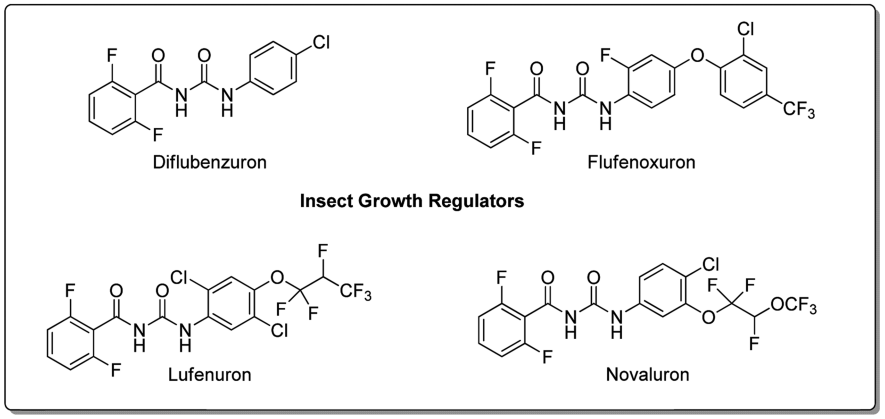
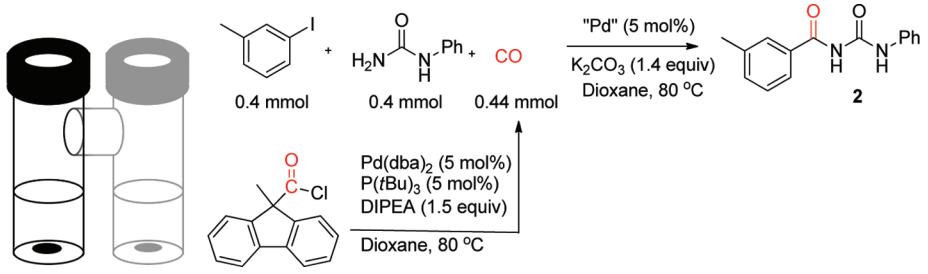


Figure 1. Biologically active *N*-acylated urea.

Table 1. Initial Optimization of the Reaction Conditions[a]



entry	Pd source (amt (mol %))	ligand (amt (mol %))	conversn (%)[b] (yield (%))[c]
1[d]	$Pd(OAc)_2$ (5)	Xantphos (7.5)	67
2[d]	$Pd(OAc)_2$ (5)	DPEphos (7.5)	90 (82)
3[d]	$Pd(OAc)_2$ (5)	CataCXium A (15)	99 (93)
4	$Pd(OAc)_2$ (5)	CataCXium A (15)	100 (98)
5	$Pd(dba)_2$ (5)	CataCXium A (10)	100
6	$Pd(dba)_2$ (5)	CataCXium A (5)	100 (92)

[a]Chamber A: COgen (0.44 mmol), $Pd(dba)_2$ (5 mol %), $P(tBu)_3$ (5 mol %), DIPEA (1.5 equiv) in dioxane (3 mL). Chamber B: *m*-iodotoluene (0.4 mmol), Pd-source (5 mol %), ligand (X mol %) phenylurea (0.4 mmol) in dioxane (3 mL). [b]Determined by ^1H NMR. [c]Isolated yields after flash chromatography. [d]Yield based on 0.33 mmol of COgen, with 0.5 mmol of halide.

Beller on the repeated success of cataCXium A in various Pd-catalyzed carbonylation reactions.[7−10]

Carbon monoxide was delivered to the coupling reaction by the two-chamber method we recently developed in our laboratories.[11] The method is based on a safe and controlled ex situ CO generation from the CO precursor, COgen (9-methylfluorene-9-carbonyl chloride).[12] The two-chamber technique allows a simple means for dosing the precise amount of CO necessary for the reaction, and it has found use in several other carbonylation protocols, including amino- and alkoxycarbonylations,

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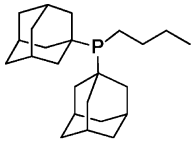
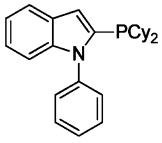
double carbonylations, carbonylative Heck reactions, and 1,3-diketone synthesis.[13,14]

As shown in Table 1, entries 1−3, the monodentate ligand cataCXium A proved to be the most efficient for the *N*-acylation of *N*-phenylurea, with $Pd(OAc)_2$ as the palladium source and with potassium carbonate as the stoichiometric base in dioxane. In these three examples, limiting CO was employed to examine the applicability of the system for carbon isotope labeling studies, hence demonstrating the efficiency of the system, as 93% of the CO released from COgen could be isolated in the *N*-acyl urea product (entry 3). Other solvents such as diglyme, THF, acetonitrile, and toluene resulted in lower conversions. This could be a result of the high solubility of CO in dioxane.[15] The bases Na_2CO_3 and Cs_2CO_3 also resulted in lower yields, while K_3PO_4 gave yields comparable to those for K_2CO_3 (results not shown). Although full consumption of the CO precursor was achieved within 15 min, the prolonged reaction times are required possibly due to the poor nucleophilic properties of the *N*-acyl ureas.

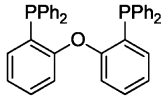
Surprisingly, using only 1.1 equiv of COgen, and hence only 1.1 equiv of CO, in comparison to the urea and *m*-iodotoluene resulted in full conversion and an excellent 98% isolated yield of the product (entry 4). Switching to a Pd(0) source allowed us to lower the ligand loading, and a high 92% isolated yield of the *N*-acyl urea could be obtained with only 5 mol % of cataCXium A (entry 6). Although the catalyst loading could be reduced down to 3 mol % with no deterioration of the coupling yield, we found that the use of a 5 mol % loading gave more consistent results.[16]



CataCXium A



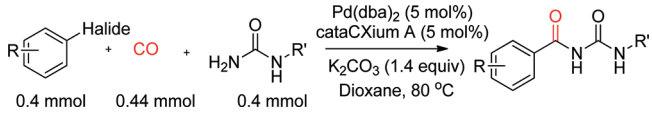
CataCXium PInCy

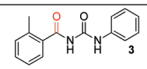
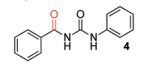
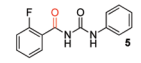
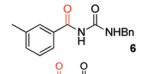
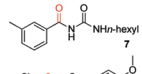
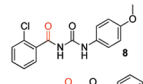
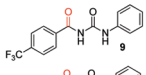
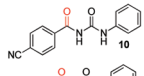
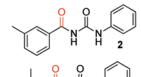
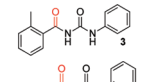
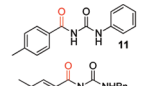
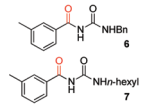
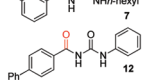
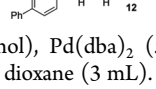


DPEPhos

Next, we examined the use of this protocol with other aryl iodides and ureas (Table 2). *o*-Iodotoluene and phenyl iodide also performed admirably under these coupling conditions (entries 1 and 2). Although 2-fluoroiodobenzene proved to be a good substrate (entry 3), the corresponding di-ortho-substituted substrate 2,6-fluoroiodobenzene only provided a 17% conversion with *N*-phenylurea (results not shown). Other *N*-substituted ureas furnished the corresponding *N*-acyl ureas in gratifying yields, as illustrated by entries 4−6. In the case of the *N*-alkyl ureas (entries 4 and 5), the coupling conditions required a stronger base (K_3PO_4) and higher reaction temperatures, which corresponds well with previous results reported by Lukin et al., demonstrating this base dependency in the synthesis of unsymmetrically substituted ureas by Pd-catalyzed amidation.[17] In addition, electron-deficient aryl halides such as *p*-trifluoromethyliodobenzene and *p*-cyanoiodobenzene proved viable as coupling partners with satisfying yields (entries 7 and 8). Finally, we demonstrated that certain aryl bromides can be excellent substrates for these reactions as well, as shown in entries 9−14 with *o*-, *m*-, and *p*-bromotoluene and *p*-bromobiphenyl. The almost quantitative yields obtained in several entries of Table 2 is a testimony to not only the effectiveness of the catalytic protocol but also the very high efficiency obtained by conducting carbonylation reactions in the two-chamber system. Only a 0.04 mmol excess of CO is generated, corresponding to a volume of roughly 1 mL at room temperature. This in combination with the 1:1 ratio between the aryl halide and the substituted urea affords a highly efficient carbonylation protocol with respect to the amount of CO applied. The coupling with *p*-bromobiphenyl (entry 14) provided full conversion at 100 °C but required recrystallization in acetonitrile

Table 2. Synthesis of *N*-Acylated Ureas[a]



Entry	R'	Ar-X	Product	Yield (%)[b]
1[c]	Ph			99
2	Ph			95
3	Ph			73
4[c]	Bn			93
5[c]	*n*-hexyl			99
6	*p*-anisole			88
7	Ph			65
8	Ph			69
9	Ph			99
10	Ph			95
11	Ph			79
12[c]	Bn			84
13[c]	*n*-hexyl			99
14[d]	Ph			67

[a]Chamber A: COgen (0.44 mmol), $Pd(dba)_2$ (5 mol %), $P(tBu)_3$ (5 mol %), DIPEA (1.5 equiv) in dioxane (3 mL). [b]Isolated yield after flash chromatography. [c]90 °C, K_3PO_4 instead of K_2CO_3. [d]100 °C.

after flash chromatography to achieve sufficient purity. Applying *p*-bromobenzonitrile as the coupling partner afforded a complex crude NMR and only modest conversion into product. Adding 1 equiv of potassium iodide to the reaction mixture, in order to promote the CO insertion, apparently resulted in a cleaner reaction with an excellent 94% conversion by ^1H NMR analysis of the crude reaction mixture; however, only 34% of the desired product could be secured upon column chromatography (results not shown).[18]

Not all aryl halides proved to be effective for these acylation reactions. For example, the reaction of *p*-iodoanisole with *N*-phenylurea and CO only afforded low conversion when applying the optimized conditions. However, an additional ligand screening quickly revealed that cataCXium PInCy was highly effective for promoting the acylation reaction with these substrates employing the two chamber system, providing an isolated yield of 99% of the desired *N*-acyl urea (Table 3, entry 1).[19] Even 2,4-dimethoxyiodobenzene, ethyl 4-iodobenzoate, and 4-iodo-*N*-methylaniline were good substrates in their coupling to *N*-phenylurea (entries 2−4) in the presence of cataCXium PInCy. Successful coupling was also achieved with 4-bromoacetophenone under identical conditions (entry 5). Although cataCXium A failed completely as a ligand for promoting the coupling of this *N*-arylurea with *p*-bromoanisole, a switch to cataCXium PInCy nonetheless resulted in the formation of the desired derivatized urea in an observed conversion of 49% (results not shown).[20]

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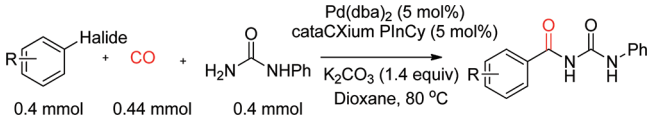
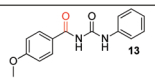
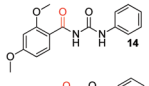
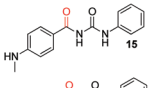
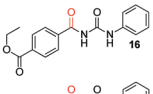
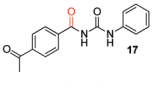
Table 3. Synthesis of *N*-Acylated of Ureas Using CataCXium PInCy as Ligand[a]



Entry	Ar-X	Product	Yield(%)[b]
1			99
2			92
3[c]			85
4			83
5			84

[a]Chamber A: **1** (0.44 mmol), $Pd(dba)_2$ (5 mol %), $P(tBu)_3$ (5 mol %), DIPEA (1.5 equiv) in dioxane (3 mL). [b]Isolated yield after flash chromatography. [c]1.4 equiv. of *N*-methyl-4-iodoaniline used.

Upon recrystallization of **13** fine crystals precipitated suitable for X-ray structural analysis. The obtained crystal structure of **13** (Figure 2) confirmed the presence of an

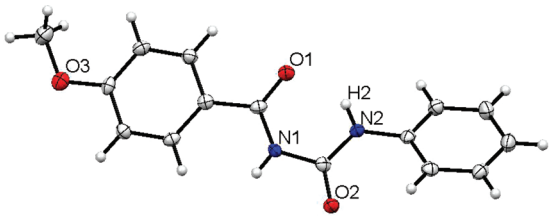
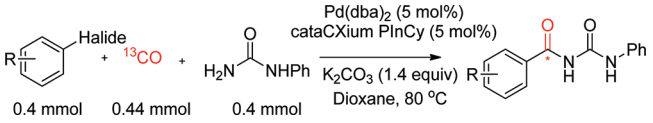


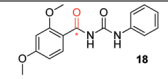
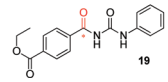
Figure 2. Crystal structure analysis of **13** with ellipsoids at the 50% probability level.

intramolecular hydrogen bond, explaining the high shift of the amide proton signals obtained in all ^1H NMR spectra of the benzoyl ureas (typically found between 10 to 11 ppm in $CDCl_3$).

Finally, the developed carbonylation protocol was tested for its utility in ^{13}C isotope labeling using ^{13}CO generated from ^{13}COgen. During the optimization studies, it was observed that a high 93% isolated yield of **2**, based on limiting CO, was obtained (Table 1, entry 3). This result indicates that the incorporation of CO is very facile under the optimized catalytic conditions and opens the possibility to introduce a isotopically labeled carbonyl group at the benzoylic position of the *N*-acylated urea. For this purpose, 2,4-dimethoxyiodobenzene and ethyl 4-iodobenzoate were successfully labeled in excellent 92% and 97% isolated yields (Table 4, entries 1 and 2).

Table 4. Labeling Reactions with 2,4-Dimethoxyiodobenzene and Ethyl 4-Iodobenzoate



Entry	Ar-X	Product	Yield(%)[b]
1			92
2			97

[a]Chamber A: **1** (0.44 mmol), $Pd(dba)_2$ (5 mol %), $P(tBu)_3$ (5 mol %), DIPEA (1.5 equiv) in dioxane (3 mL). [b]isolated yield after flash chromatography.

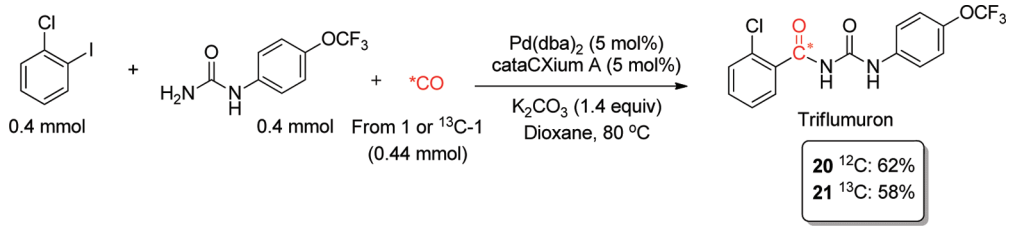
To demonstrate the applicability of the method in the synthesis of bioactive compounds, the insecticide triflumuron was chosen due to the presence of a core *N*-acylurea motif.[21] Coupling of 2-chlorophenyl iodide with *N*-*p*-trifluoromethoxyphenylurea in the presence of a slight excess of CO provided triflumuron in a satisfactory yield of 62% (Scheme 2). As expected, substituting COgen with its ^{13}C-labeled counterpart, ^{13}COgen, led to the synthesis of the ^{13}C-isotope labeled triflumuron, which could be isolated in 58% yield.

CONCLUSIONS

A new catalytic system for the preparation of *N*-acyl ureas, applying near-stoichiometric loadings of CO, was successfully developed. Several benzoyl urea derivatives were synthesized, proving the broad chemical scope of this palladium-catalyzed protocol. Due to the near 1:1:1 relationship among the aryl halide, the substituted urea, and carbon monoxide, this protocol proved also to be adaptable to ^{13}C isotope labeling. When ^{13}COgen was applied instead of COgen, three *N*-acyl ureas including the insecticide triflumuron were labeled, incorporating ^{13}CO into the core motif.

Although the molecular weight of COgen would not make this CO precursor competitive with CO gas from a cylinder for large-scale production of the *N*-acyl ureas, the use of this precursor allows easy-to-perform small-scale reactions without the use of a CO cylinder and the precautions associated with its employment. Furthermore, this methodology allows for the identification of catalytic carbonylative conditions employing only stoichiometric CO, which could be very useful conditions for large-scale production employing carbon monoxide gas.

Scheme 2. Synthesis of Triflumuron



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EXPERIMENTAL PROCEDURES

General Methods. Solvents were dried according to standard procedures. Flash chromatography was performed on silica gel 60 (230−400 mesh). The ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at 400, 100, and 367 MHz, respectively. The chemical shifts of the NMR spectra are reported in parts per million (ppm) relative to the solvent residual peak.[22] NMR spectra are reported as follows (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, b = broad). MS and HRMS spectra were recorded on a LC TOF (ES) apparatus. All purchased chemicals were used as received without further purification. The reactions were performed in a previously reported two-chamber system.[11]

3-Methyl-*N*-(phenylcarbamoyl)benzamide (2). General Procedure.[23] *Chamber A.* In a glovebox under argon, in chamber A of the two-chamber system were added COgen (9-methylfluorene-9-carbonyl chloride) (106.8 mg, 0.440 mmol), P(*t*Bu)$_3$ (4.5 mg, 0.022 mmol), Pd(dba)$_2$ (12.7 mg, 0.022 mmol), dioxane (3 mL), and *N*,*N*-diisopropylethylamine (115 μL, 0.660 mmol), in that order. The chamber was sealed with a screw cap fitted with a Teflon seal.

Chamber B. In a glovebox under argon, in chamber B of the two-chamber system were added 3-iodotoluene (87.2 mg, 0.400 mmol), phenylurea (54.6 mg, 0.400 mmol), Pd(dba)$_2$ (11.5 mg, 0.020 mmol), cataCXium A (7.2 mg, 0.020 mmol), K_2CO_3 (77.4 mg, 0.56 mmol), and dioxane (3 mL), in that order. The chamber was sealed with a screw cap fitted with a Teflon seal.

The loaded two-chamber system was heated to 80 °C for 18 h. The title compound was obtained after flash chromatography (1−6% gradient of diethyl ether in $CHCl_3$) as a colorless solid (93.5 mg, 0.370 mmol, 92%). Mp: 160−163 °C (lit.[23] mp 157.5−158.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.89 (bs, 1H), 9.19 (bs, 1H), 7.77−7.80 (m, 2H), 7.57−7.60 (m, 2H), 7.33−7.43 (m, 4H), 7.12−7.16 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 168.7, 151.6, 139.2, 137.3, 134.3, 132.3, 129.2 (2C), 129.0, 128.5, 124.9, 124.6, 120.6 (2C), 21.5. HRMS for $C_{15}H_{14}N_2NaO_2$ [M + Na]$^+$: calculated, 277.0953, found, 277.0954. The same stoichiometry of reagents and purification were used when 3-bromotoluene was applied to synthesize the title compound in 99% isolated yield.

2-Methyl-*N*-(phenylcarbamoyl)benzamide (3). The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using 2-iodotoluene (87.2 mg, 0.400 mmol). The title compound was obtained after flash chromatography (1−6% gradient of diethyl ether in $CHCl_3$) as a colorless solid (102.0 mg, 0.400 mmol, 99%). Mp: 184−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.69 (bs, 1H), 8.77 (bs, 1H) 7.52−7.58 (m, 3H), 7.43−7.47 (m, 1H), 7.28−7.34 (m, 4H), 7.11−7.15 (m, 1H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 170.7, 151.1, 137.5, 137.1, 133.3, 129.0 (2C), 126.1, 124.3, 120.3 (2C), 20.1. HRMS for $C_{15}H_{14}N_2NaO_2$ [M + Na]$^+$: calculated, 277.0953; found, 277.0956. The same stoichiometry of reagents and purification were used when 2-bromotoluene was applied to synthesize the title compound in 95% isolated yield.

***N*-(Phenylcarbamoyl)benzamide (4).**[4] The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using iodobenzene (81.6 mg, 0.400 mmol). The title compound was obtained after flash chromatography (0−5% gradient of MeOH in $CHCl_3$) as a colorless solid (90.9 mg, 0.378 mmol, 95%). Mp: 188−192 °C (lit.[4] mp: 191−193 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.86 (bs, 1H), 9.12 (bs, 1H), 7.98−8.00 (m, 2H), 7.63−7.67 (m, 1H), 7.58−7.61 (m, 2H), 7.51−7.56 (m, 2H), 7.35−7.39 (m, 2H), 7.13−7.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 168.6, 151.9, 137.3, 133.5, 132.3, 129.2, 129.1, 128.0, 124.6, 120.6. HRMS for $C_{14}H_{12}N_2NaO_2$ [M + Na]$^+$: calculated, 263.0796; found, 263.0789.

2-Fluoro-*N*-(phenylcarbamoyl)benzamide (5). The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using 2-fluoroiodobenzene (88.8 mg, 0.400 mmol). The title compound was obtained after flash chromatography (1−5% gradient of diethyl ether in $CHCl_3$) as a colorless solid (75.5 mg, 0.292 mmol, 73%). Mp: 145−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.67 (bs, 1H), 8.68 (d, J = 13.2 Hz, 1H), 8.12 (dt, J = 1.6 Hz, J = 7.6 Hz, 1H), 7.56−7.65 (m, 3H), 7.33−7.38 (m, 3H), 7.20−7.24 (m, 1H), 7.12−7.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 164.4, 160.9 (d, J = 249 Hz), 150.4, 137.3, 135.7 (d, J = 9.6 Hz), 132.2, 129.2 (2C), 125.5 (d, J = 3.4 Hz) 124.6, 120.5 (2C), 119.3 (d, J = 10.0 Hz) 116.8 (d, J = 24.2 Hz). ^{19}F NMR (367 MHz, $CDCl_3$): δ_F (ppm) −111.6. HRMS for $C_{14}H_{11}FN_2NaO_2$ [M + Na]$^+$: calculated, 281.0702; found, 281.0704.

***N*-(Benzylcarbamoyl)-3-methylbenzamide (6).** The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using benzylurea (60.1 mg, 0.400 mmol), K_3PO_4 (118.9 mg, 0.56 mmol), and heating to 90 °C. The title compound was obtained after flash chromatography (1−6% gradient of diethyl ether in $CHCl_3$) as a colorless solid (100.1 mg, 0.373 mmol, 93%). Mp: 152−154 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 10.14 (bs, 1H), 9.57 (bs, 1H), 8.34 (s, 1H) 8.30 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.84−7.87 (m, 3H), 7.78−7.82 (m, 2H), 7.70−7.74 (m, 1H), 5.01 (d, J = 6 Hz, 2H), 2.85 (s, 3H). ^{13}C NMR (100 MHz, $CHCl_3$): δ_C (ppm) 168.4, 154.3, 139.0, 138.2, 134.1, 132.5, 128.9, 128.8 (2C), 128.4, 127.7 (2C), 127.6, 124.9, 44.0, 21.5. HRMS for $C_{16}H_{16}N_2NaO_2$ [M + Na]$^+$: calculated, 291.1109; found, 291.1109. The same stoichiometry of reagents and purification were used when 3-bromotoluene was applied to synthesize the title compound in 84% isolated yield.

***N*-(Hexylcarbamoyl)-3-methylbenzamide (7).** The same procedure as for *N*-(benzylcarbamoyl)-3-methylbenzamide was applied, using hexylurea (57.7 mg, 0.400 mmol). The title compound was obtained after flash chromatography (1−7% gradient of diethyl ether in $CHCl_3$) as a slightly yellow oil (104.7 mg, 0.399 mmol, 99%). ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 9.48 (bs, 1H), 8.76 (bs, 1H), 7.80 (s, 1H), 7.75−7.77 (m, 1H), 7.34−7.40 (m, 2H), 3.37 (q, J = 7.2 Hz, 2H), 2.43 (s, 3H), 1.60 (quin, J = 7.6 Hz, 2H), 1.29−1.40 (m, 6H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CHCl_3$): δ_C (ppm) 167.5, 153.5, 137.7, 132.9, 131.6, 127.5, 124.1, 39.1, 30.6, 28.7, 25.8, 21.7, 20.5, 13.2. HRMS for $C_{15}H_{22}N_2NaO_2$ [M + Na]$^+$: calculated, 285.1579; found, 285.1581. The same stoichiometry of reagents and purification were used when 3-bromotoluene was applied to synthesize the title compound in 99% isolated yield.

2-Chloro-*N*-((4-methoxyphenyl)carbamoyl)benzamide (8).[24] The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using 2-chloroiodide (95.4 mg, 0.400 mmol) and *p*-anisole urea (66.5 mg, 0.400 mmol). The title compound was obtained after flash chromatography (3−7% gradient of diethyl ether in $CHCl_3$) as a colorless solid (107.0 mg, 0.351 mmol, 88%). Mp: 190−192 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 11.14 (bs, 1H), 10.27 (bs, 1H), 7.58−7.62 (m, 1H), 7.53−7.58 (m, 2H), 7.43−7.52 (m, 3H), 6.93 (d, J = 8.8 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 168.5, 155.8, 150.4, 134.7, 131.9, 130.4, 129.8, 129.7, 129.0, 127.2, 121.6 (2C), 114.1 (2C), 55.2. HRMS for $C_{15}H_{13}ClN_2NaO_3$ [M + Na]$^+$: calculated, 327.0512; found, 327.0512.

***N*-(Phenylcarbamoyl)-4-(trifluoromethyl)benzamide (9).** The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using 1-iodo-4-(trifluoromethyl)benzene (108.8 mg, 0.400 mmol). The title compound was obtained after flash column chromatography (1−5% gradient of MeOH in $CHCl_3$) as a colorless solid (79.9 mg, 0.259 mmol, 65%). Mp: 223−226 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm0 11.25 (bs, 1H), 10.51 (bs, 1H), 8.77 (d, J = 8.0 Hz, 2H), 8.39 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 7.6 Hz, 2H), 7.82 (t, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 167.7, 150.8, 137.5, 136.3, 132.4 (q, J = 32 Hz), 129.2 (2C), 129.0 (2C), 125.5 (q, J = 3 Hz), 123.9, 119.9 (2C), 109.5. ^{19}F NMR (367 MHz, d_6-DMSO): δ_F (ppm) −61.6. HRMS for $C_{15}H_{10}F_3N_2O_2$ [M − H]$^-$: calculated, 307.0700; found, 307.0695.

4-Cyano-*N*-(phenylcarbamoyl)benzamide (10). The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using *p*-iodobenzonitrile (91.6 mg, 0.44 mmol). The title compound was obtained after flash column chromatography (0−6% gradient of MeOH in $CHCl_3$) as a colorless solid (73.5 mg, 0.277 mmol, 69%). Mp: 230−233 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 11.24 (bs, 1H), 10.62 (bs, 1H), 8.11 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 7.35 (t, J = 7.2 Hz, 2H), 7.10 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm)

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167.9, 151.2, 137.9, 137.0, 132.9 (2C), 129.5 (2C), 129.4 (2C), 124.3, 120.3 (2C), 118.5, 115.5. HRMS for $C_{15}H_{10}N_3O_2$ $[M - H]^-$: calculated, 264.0779; found, 264.0772.

4-Methyl-*N*-(phenylcarbamoyl)benzamide (11). The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using 4-bromotoluene (48.1 mg, 0.400 mmol). The title compound was obtained after flash column chromatography (1−6% gradient of diethyl ether in $CHCl_3$) as a colorless solid (80.7 mg, 0.317 mmol, 79%). Mp: 195−196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.90 (bs, 1H), 9.13 (bs, 1H), 7.88−7.91 (m, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.31−7.38 (m, 4H), 7.15 (t, J = 7.2 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 168.4, 151.8, 144.5, 137.4, 129.8 (2C), 129.4, 129.2 (2C), 128.0, 124.5 (2C), 120.6 (2C), 21.8. HRMS for $C_{15}H_{14}N_2NaO_2$ $[M + Na]^+$: calculated, 277.0953; found, 277.0954. The same stoichiometry of reagents and purification were used when 4-bromotoluene was applied to synthesize the title compound in 79% isolated yield.

***N*-(Phenylcarbamoyl)-[1,1′-biphenyl]-4-carboxamide (12).** The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using 4-bromobiphenyl (93.2 mg, 0.400 mmol) and 100 °C. The title compound was obtained after flash chromatography (10% MeOH, 20% acetone, 70% toluene) and a hot/cold recrystallization in acetonitrile as a colorless solid (84.7 mg, 0.268 mmol, 67%). Mp: 225−228 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 11.07 (bs, 1H), 10.79 (bs, 1H), 8.14 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.76−7.79 (m, 2H), 7.68 (dd, J = 1.2 Hz, J = 8.8 Hz, 2H), 7.50−7.54 (m, 2H), 7.42−7.46 (m, 1H), 7.35−7.39 (m, 2H), 7.10−7.14 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 168.8, 151.7, 144.9, 139.2, 138.1, 131.6, 129.6 (2C), 129.5 (2C), 129.4 (2C), 128.9, 127.4 (2C), 127.71 (2C), 124.2, 120.3 (2C). HRMS for $C_{20}H_{15}N_2O_2$ $[M - H]^-$: calculated, 315.1139; found, 315.1134.

4-Methoxy-*N*-(phenylcarbamoyl)benzamide (13). The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using 4-iodoanisole (93.6 mg, 0.400 mmol) and cataCXium PInCy (7.8 mg, 0.020 mmol). The title compound was obtained after flash chromatography (0.5−4% MeOH in $CHCl_3$) as a colorless solid (109.1 mg, 0.400 mmol, 99%). Mp: 219−221 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 10.93 (bs, 1H), 10.86 (bs, 1H), 8.06 (d, J = 8.8 Hz, 2H), 7.57−7.60 (m, 2H), 7.34−7.38 (m, 2H), 7.06−7.12 (m, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 168.0, 163.1, 151.3, 137.7, 130.5 (2C), 129.0 (2C), 124.1, 123.7, 119.8 (2C), 113.9 (2C), 55.61. HRMS for $C_{15}H_{14}N_2NaO_3$ $[M + Na]^+$: calculated, 293.0902; found, 293.0903.

2,4-Dimethoxy-*N*-(phenylcarbamoyl)benzamide (14). The same procedure as for 4-methoxy-*N*-(phenylcarbamoyl)benzamide was applied, using 2,4-dimethoxyiodobenzene (105.6 mg, 0.400 mmol). The title compound was obtained after flash chromatography (0.5−3% gradient MeOH in $CHCl_3$) as a colorless solid (111.0 mg, 0.370 mmol, 92%). Mp: 221−222 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 10.80 (bs, 1H), 10.09 (bs, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 6.73 (m, 2H), 3.99 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 166.2, 164.6, 159.3, 150.5, 137.6, 132.8, 129.0 (2C), 123.7, 119.7 (2C), 112.6, 106.7, 98.8, 56.6, 55.8. HRMS for $C_{16}H_{16}N_2NaO_4$ $[M + Na]^+$: calculated, 323.1008; found, 323.1003.

4-(Methylamino)-*N*-(phenylcarbamoyl)benzamide (15). The same procedure as for 4-methoxy-*N*-(phenylcarbamoyl)benzamide was applied, using 4-iodo-*N*-methylaniline (133.3 mg, 0.560 mmol). The title compound was obtained after flash chromatography (8−16% gradient of diethyl ether in $CHCl_3$) as a colorless solid (91.2 mg, 0.339 mmol, 85%). Mp: 220−223 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 11.15 (bs, 1H), 10.50 (bs, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 6.64 (d, J = 4.4 Hz, 1H), 6.57 (d, J = 8.0 Hz, 2H), 2.75 (d, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 168.5, 154.3, 152.1, 138.3, 130.8 (2C), 129.4 (2C), 123.9, 120.1 (2C), 117.9, 111.0, 29.6. HRMS for $C_{15}H_{15}N_3O_2Na$ $[M + Na]^+$: calculated, 292.1062; found, 292.1062.

Ethyl 4-((Phenylcarbamoyl)carbamoyl)benzoate (16). The same procedure as for 4-methoxy-*N*-(phenylcarbamoyl)benzamide was applied, using ethyl 4-iodobenzoate (110.4 mg, 0.400 mmol). The title compound was obtained after flash chromatography (4−7% diethyl ether + 1% MeOH in $CHCl_3$) as a colorless solid (103.4 mg, 0.330 mmol, 83%). Mp: 163−165 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 11.21 (bs, 1H), 10.70 (bs, 1H), 8.12 (d, J = 8.4 Hz, AB-system, 2H), 8.08 (d, J = 8.4 Hz, AB system, 2H), 7.59 (m, 2H), 7.37 (m, 2H), 7.12 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 168.0, 165.0, 150.8, 137.5, 136.4, 133.4, 129.1 (2C), 129.0 (2C), 128.7 (2C), 123.8, 119.9 (2C), 61.2, 14.1. HRMS for $C_{17}H_{15}N_2O_4$ $[M - H]^-$: calculated, 311.1037; found, 311.1032.

4-Acetyl-*N*-(phenylcarbamoyl)benzamide (17). The same procedure as for 4-methoxy-*N*-(phenylcarbamoyl)benzamide was applied, using 1-(4-bromophenyl)ethanone (199.0 mg, 0.400 mmol). The title compound was obtained after flash chromatography (1−6% gradient of MeOH in $CHCl_3$) as a colorless solid (94.4 mg, 0.334 mmol, 84%). Mp: 230−233 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 11.20 (bs, 1H), 10.73 (bs, 1H), 8.13 (d, J = 8.4 Hz, AB-system, 2H), 8.07 (d, J = 8.8 Hz, AB-system, 2 Hz), 7.59 (d, J = 8.8 Hz, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.12 (t, J = 7.2 Hz, 1H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 197.7, 168.0, 150.9, 139.8, 137.5, 136.1, 129.4, 128.6 (2C), 128.6 (2C), 128.2 (2C), 123.8, 119.9 (2C), 27.1. HRMS for $C_{16}H_{13}N_2O_3$ $[M - H]^-$: calculated, 281.0932; found, 281.0925.

^{13}C-Labeled 2,4-Dimethoxy-*N*-(phenylcarbamoyl)-benzamide (18). When the ^{13}C-labeled version was synthesized, the same general method and purification were employed as for **14**, using the ^{13}C-labeled counterpart of **1** (107.2 mg, 0.440 mmol). The title compound was obtained as a colorless solid (121,2 mg, 0.388 mmol, 97%). Mp: 220−222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.96 (bs, 1H), 9.85 (bs, 1H), 8.18 (ddd, J = 1.2 Hz, J = 4.8 Hz, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.11 (dt, J = 1.2 Hz, J = 8.2 Hz, 1H), 6.67 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 6.53 (d, J = 1.2 Hz, 1H), 4.03 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 166.0, 165.4, 159.6, 151.4, 137.8, 134.6, 129.1 (2C), 124.1, 120.4 (2C), 112.7, 112.0, 106.4 (d, J = 4.3 Hz), 98.9, (d, J = 3.2 Hz), 56.5, 55.9. HRMS for $C_{15}{}^{13}CH_{16}N_2NaO_4$ $[M + Na]^+$: calculated, 324.1041; found, 324.1042.

^{13}C-Labeled Ethyl 4-((Phenylcarbamoyl)carbamoyl)-benzoate (19). When the ^{13}C-labeled version was synthesized, the same general method and purification were employed as for **16**, using the ^{13}C-labeled counterpart of **1** (107.2 mg, 0.440 mmol). Mp: 166−168 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ_H (ppm) 11.21 (bs, 1H), 10.70 (bs, 1H), 8.13 (dd, J = 3.6 Hz, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.12 (t, J = 7.6 Hz, 1H), 4.36 (q, J = 6.8 Hz, 2H), 1.35 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C (ppm) 168.0, 164.9, 150.8, 137.5, 136.3 (d, J = 65.1 Hz), 133.4, 129.1 (d, J = 4.4 Hz), 129.0, 128.7 (d, J = 2.8 Hz), 123.8, 119.8 (2C), 61.2, 14.1. HRMS for $C_{16}{}^{13}CH_{15}N_2O_4$ $[M - H]^-$: calculated, 312.1071; found, 312.1065.

Triflumuron, 2-Chloro-*N*-((4-(trifluoromethoxy)phenyl)-carbamoyl)benzamide (20).[25] The same procedure as for 3-methyl-*N*-(phenylcarbamoyl)benzamide was applied, using 2-chloroiodobenzene (95.4 mg, 0.400 mmol) and 1-(4-(trifluoromethoxy)-phenyl)urea (88.1 mg, 0.400 mmol). The title compound was obtained after flash chromatography (1−3% gradient of diethyl ether in $CHCl_3$) as a colorless solid (89.4 mg, 0.249 mmol, 62%). Mp: 189−193 °C (lit.[25] mp 188−190 °C). ^{1}H NMR (400 MHz, 1:1 d_4-MeOH, $CDCl_3$): δ_H (ppm0 10.50 (bs, 1H), 7.36−7.41 (m, 3H), 7.28−7.29 (m, 2H), 7.18−7.22 (m, 1H), 7.01 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, 1:1 d_4-MeOH, $CDCl_3$): δ_C (ppm) 168.9 (d, J = 4.2 Hz), 151.0 (d, J = 10.5 Hz), 145.3 (t, J = 1.5 Hz), 135.7, 135.6, 133.5, 132.1, 130.2, 128.9, 126.8, 121.5 (2C), 121.4, 120.4 (q, J = 254 Hz). ^{19}F NMR (367 MHz, $CDCl_3$): δ_F (ppm) −58.66. HRMS for $C_{15}H_{10}ClF_3N_2O_3$ $[M + Na]^+$: calculated, 381.0230; found, 381.0233.

^{13}C-Labeled Triflumuron, 2-Chloro-*N*-((4-(trifluoromethoxy)-phenyl)carbamoyl)benzamide (21). The same procedure as for unlabeled triflumuron (**20**) was applied, using the ^{13}C-labeled CO precursor (107.2 mg, 0.440 mmol). The title compound was obtained after flash chromatography (1−3% gradient of diethyl ether in $CHCl_3$) as a colorless solid (84.0 mg, 0.233 mmol, 58%). Mp: 190−193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.60 (bs, 1H), 8.54 (bs, 1H),

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7.72−7.76 (m, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.50−7.52 (m, 2H), 7.41−7.45 (m, 1H), 7.21 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 167.9 (^{13}C labeled carbon), 150.8, 145.6 (d, J = 1.8 Hz), 135.8, 133.1, 132.5, 131.4, 131.0 (d, J = 3 Hz), 130.2 (d, J = 1.6 Hz), 127.5 (d, J = 4.1 Hz), 121.9 (2C), 121.6 (2C), 120.6 (q, J = 255 Hz).. ^{19}F NMR (367 MHz, $CDCl_3$): δ_F (ppm) −58.14. HRMS for $C_{14}{}^{13}CH_{10}ClF_3N_2O_3$ $[M + Na]^+$: calculated, 382.0263; found, 382.0261.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and a CIF file giving ^{1}H, ^{13}C, and ^{19}F NMR spectra for all the coupling products and crystal data for **13**. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 869569 also contains supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K. (fax +44 1223 336033).

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Notes

The authors declare no competing financial interest.

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