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Aryl Triflates and [^{11}C]/(^{13}C)Carbon Monoxide in the Synthesis of ^{11}C-/^{13}C-Amides

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Palladium(0)-mediated carbonylation reactions using aryl triflates, amines, and a low concentration of [^{11}C]carbon monoxide were used in the syntheses of 13 ^{11}C-labeled amides. Lithium bromide was used as an additive to facilitate the reaction. The ^{11}C-labeled products were obtained with decay-corrected radiochemical yields in the range of 2−63%. The radiochemical purity of the final products exceeded 98%. As an example, a reaction starting with 1.79 GBq [^{11}C]carbon monoxide gave 0.38 GBq of LC-purified *N*-isopropyl-4-nitro-[^{11}C]benzamide within 27 min from the start of the carbonylation reaction (54% decay-corrected radiochemical yield). The specific radioactivity of this compound was 191 GBq/μmol, 35 min after the end of a 10 μAh bombardment. *N*-Benzylisoquinoline-1-(^{13}C)carboxamide was prepared and analyzed by NMR for confirmation of the labeling position. The triflates **16**, **20**, **21**, and **22** were synthesized from the corresponding alcohols and trifluoromethanesulfonic anhydride. The reference compounds **30a** and **30b** were prepared from the corresponding carboxylic acids and benzylamine. The other nine reference compounds **32a** to **32i** were synthesized from the respective acid chlorides and amines. The presented report shows that the sometimes more easily obtainable aryl triflates can be a useful alternative to the commonly used aryl halides in palladium(0)-mediated synthesis of ^{11}C/^{13}C-amides.

Introduction

Appropriate compounds labeled with positron emitting radionuclides are essential for investigations using PET (positron emission tomography). The demand for new radiolabeling methods is expanding with the increasing use of PET in medical and biomedical research. In such research, compounds labeled with ^{11}C are particularly attractive since their preparation is possible by substitution of the stable carbon isotopes with ^{11}C, and these compounds can be labeled with high specific radioactivity. Recently, the use of [^{11}C]carbon monoxide in labeling chemistry has broadened the possibility to label many biologically active compounds.[1] However, a substantial proportion of biologically interesting molecules still cannot be labeled by established methods. The methods most frequently used for introduction of ^{11}C in an organic molecule are O-, S-, or N-methylation or C−C coupling using [^{11}C]methyl iodide or triflate,[2] a Grignard reaction using [^{11}C]carbon dioxide,[3] and recently, palladium-mediated carbonylation using [^{11}C]carbon monoxide. Among these, palladium-mediated carbonylation is an increasingly employed ^{11}C-labeling strategy and has at present been used in the synthesis of a wide range of ^{11}C-labeled carbonyl compounds.[4] In all of these syntheses, aryl halides and [^{11}C]carbon monoxide were used as the precursors. Selenium-mediated carbonylation using [^{11}C]-carbon monoxide and amines, amino alcohols, or alcohols was also developed recently for the synthesis of ^{11}C-labeled carbamoyl compounds.[1] The use of organic triflates in palladium-catalyzed coupling reactions is well established.[5]Carbonylative cross-coupling using vinyl or aryl triflates and carbon monoxide has been used to synthesize a series of carbonyl compounds, e.g., ketones,[6] amides,[7] and carboxylic acids,[8] esters.[9] Although the use of organic triflates as electrophiles are common in synthetic organic chemistry, so far, aryl triflates have rarely been used as precursors in [^{11}C]carbonylation reactions. One advantage of organotriflates is that in some cases they are more easily available than the

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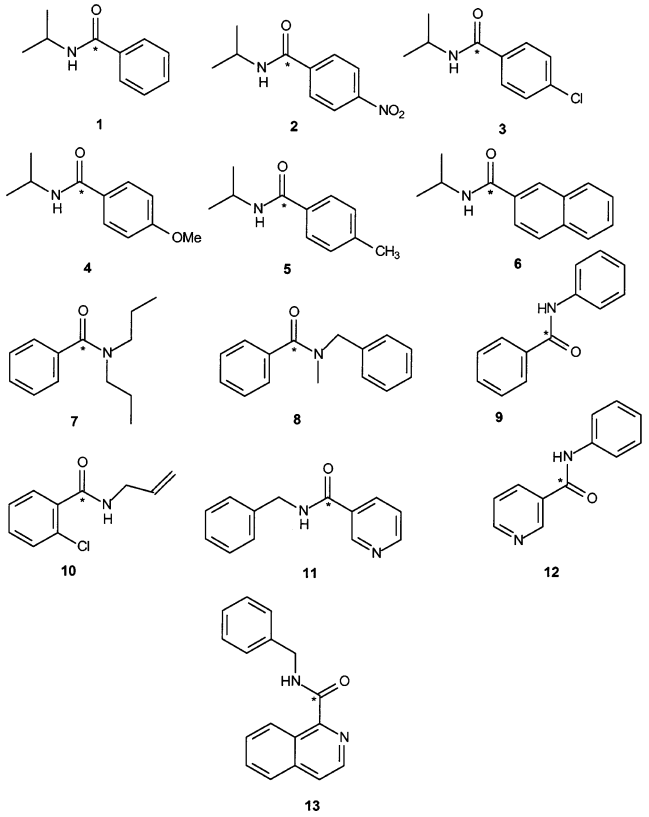


FIGURE 1. Target molecules. * = ^{11}C.

corresponding halides. Such an example was reported in a previous paper that described an alternative labeling method for a benzodiazepine receptor ligand, PK11195.[10] In that case, the aryl triflate 1-(2-chlorophenyl)isoquinolin-3-yl triflate was used. In cross-coupling reactions with organotriflates, the order of reactivity compared to organohalides is Ar−I > Ar−Br ∼ Ar−OTf ≫ Ar−Cl .[11] This information and our previous observation[10] encouraged us to investigate the scope and limitations of [^{11}C]-carbonylation reactions utilizing aryl triflates more generally. Thirteen different amides (**1**−**13**, Figure 1) were labeled with ^{11}C by palladium-mediated carbonylation using aryl triflates, amines, and a low concentration of [^{11}C]carbon monoxide. Nine different triflates (**14**−**22**, Figure 2) and six different amines (**23**−**28**, Figure 3) were employed in these syntheses.

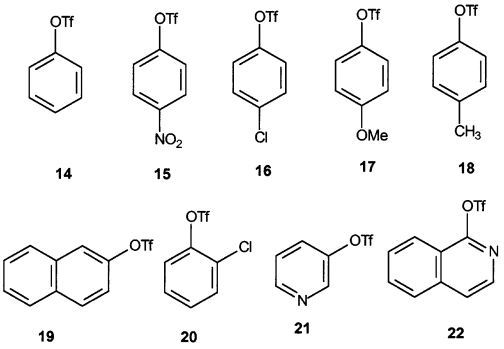


FIGURE 2. Aryl triflates used in the syntheses.

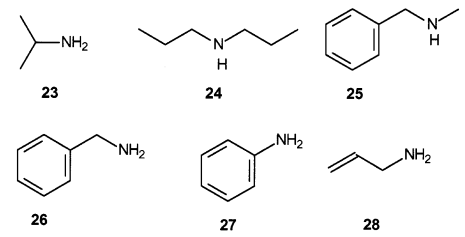
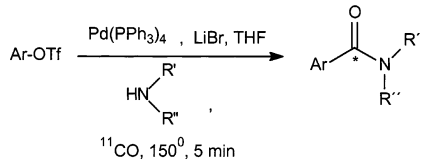


FIGURE 3. Amines used in the syntheses.

SCHEME 1[a]



[a] * = ^{11}C.

Results and Discussion

The ^{11}C-labeled amides (**1**−**13**, Figure 1) were synthesized in a micro-autoclave of 200 μL volume using tetrakis(triphenylphosphine)palladium(0), aryl triflates (**14**−**22**, Figure 2), amines (**23** to **28**, Figure 3), lithium bromide, and a low concentration of [^{11}C]carbon monoxide (Scheme 1).

The concentrations of aryl triflates, amines, tetrakis-(triphenylphosphine)palladium(0), and lithium bromide were 88.4, 469.6, 17.2, and 9.2 mM, respectively, whereas the concentration of [^{11}C]carbon monoxide was ca. 10^{-5} M. The conversion of [^{11}C]carbon monoxide to products (trapping efficiency[4c]) was above 90% for most of the compounds, and the decay-corrected radiochemical yields of LC-purified amides, calculated from [^{11}C]carbon monoxide, were in the range 2−63% (Table 1).

The radiochemical purity exceeded 98%. As an example, a reaction starting with 1.79 GBq [^{11}C]carbon monoxide gave 0.38 GBq of LC-purified *N*-isopropyl-4-nitro-[^{11}C]benzamide within 27 min from the start of the carbonylation reaction (54% decay-corrected radiochemical yield). The specific radioactivity was determined for this compound (**2**) and was 191 GBq/μmol, 35 min after the end of a 10 μAh bombardment. The identities of the amides were assessed using LC−MS. Preliminary identification was performed using analytical LC with co-injection of non-radioactive reference compounds. The labeling position of compound **13** was confirmed by comparison of the ^{13}C NMR spectra of the ^{13}C-substituted

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TABLE 1. Trapping Efficiencies and Radiochemical Yields for the ^{11}C-Labeled Amides Shown in Figure 1

entry	aryl triflate	amine	product	catalyst	trapping efficiency (%)[a]	isolated rcy[b] (%), (*n*)[c]
1	14	23	1	$Pd(PPh_3)_4$	93 ± 1	42 ± 3 (3)
2	15	23	2	$Pd_2(dba)_3/Ph_3As$ (1:4)	96 ± 2	54 ± 3 (3)
3	16	23	3	$Pd(PPh_3)_4$	94 ± 1	12 (3)
4	17	23	4	$Pd(PPh_3)_4$	96 ± 1	28±1 (3)
5	18	23	5	$Pd(PPh_3)_4$	93 ± 5	33 ± 4 (3)
6	19	23	6	$Pd(PPh_3)_4$	96	32 (1)
7	14	24	7	$Pd(PPh_3)_4$	98 ± 1	13 ± 2 (3)
8	14	25	8	$Pd(PPh_3)_4$	96	19 (1)
9	14	27	9	$Pd(PPh_3)_4$	60	6 (1)
10	20	28	10	Pd(PPh3)4	64	5 (1)
11	21	26	11	$Pd(PPh_3)_4$	90 ± 5	23 ± 3 (3)
12	21	27	12	$Pd(PPh_3)_4$	50 ± 1	2 (3)
13	22	26	13	$Pd(PPh_3)_4$	93 ± 3	63 ± 2 (3)

[a] Decay-corrected, the fraction of radioactivity left in the crude product after purging with nitrogen. [b] RCY= radiochemical yield; decay-corrected, calculated from the amount of radioactivity in the crude product before nitrogen purging, and the radioactivity of the LC purified product. [c] Values in parentheses show the number of runs.

product with that of the non-radioactive reference compound **30b**. The ^{13}C-substituted **13** was prepared using (^{13}C)carbon monoxide, 1-isoquinolyl trifluoromethanesulfonate and benzylamine under similar conditions used for the synthesis of the corresponding ^{11}C-labeled compound. The ^{13}C NMR analysis showed a peak at166.1 ppm matching the carbonyl peak of reference compound **30b**.

The synthesis of ^{11}C-labeled amides by carbonylation reactions using aryl halides, amines, Pd^0, and [^{11}C]carbon monoxide has been previously published.[4c] When aryl triflates were employed under similar conditions no amide was formed. It was reported that the palladium-catalyzed cross-coupling reactions between vinyl triflates and organostannanes required the addition of lithium halide,[12]and therefore, we investigated if the addition of lithium chloride would be beneficial. The addition of lithium chloride resulted in the formation of labeled amides, but the radiochemical yields were low. Furthermore, the low solubility of lithium chloride in THF caused technical problems due to precipitation of lithium chloride in the synthesis system. By switching to the more soluble lithium bromide the problem with precipitation was overcome but the radiochemical yields were still low (e.g., 16%). Two labeled side products were formed, and one of them was identified as the corresponding carboxylic acid. We tried to suppress the formation of these side products by changing reaction temperature and the concentrations of the reagents. At very high temperature (220 °C), the radiochemical yield was increased (e.g., 30%) and the formation of carboxylic acid decreased. However, for the completion of the reaction, a longer reaction time was needed which could not be applied in our synthesis due to the short half-life ($t_{1/2}$ = 20.3 min) of ^{11}C. Due to technical limitations, even high temperatures could not be used. The reaction was then optimized with respect to the concentration of the reagents. We found that the formation of the carboxylic acid was related to the concentration of LiBr used in the synthesis. In a previous paper, 1−3 equiv of lithium halides was used in the cross-coupling reactions.[12a] In our labeling reactions, however, the concept of molar equivalent was not applicable, as the amount of [^{11}C]carbon monoxide used was very low and the other reagents were used in large excess. Therefore, the concentration of lithium bromide was more important than the molar relationship. With a higher concentration of LiBr (75 mM), the main product was the carboxylic acid and the radiochemical yield (determined by analytical HPLC) for target compound was only 16%. The optimal concentration of LiBr (9.2 mM) gave 52% radiochemical yield (determined by analytical HPLC) within 5 min at 150 °C. The optimization was performed for phenyl triflate and isopropylamine and was then used with the other syntheses.

The effect of changing the ligands was also investigated. Besides triphenylphosphine, triphenylarsine was used. The catalyst $Pd(AsPh_3)_4$ was prepared in situ by the reaction between triphenylarsine and $Pd_2(dba)_3$. In Stille coupling reactions, the change from triphenylphosphine to triphenylarsine has been reported to give a large rate enhancement in some cases[13] but this was not observed in our amide labeling reactions. Although the trapping efficiency was as good as with triphenylphosphine for almost all of the substrates we investigated, the radiochemical yield was much lower. Only one substrate, *p*-nitrophenyl triflate, gave a higher radiochemical yield with the triphenylarsine ligand.

Experimental Section

General Methods. [^{11}C]Carbon dioxide was prepared by the ^{14}N(p,α)^{11}C reaction using a cyclotron at the Uppsala University PET Centre. The nuclear reaction was performed in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA. Oxygen 4.8) by bombardment with 17 MeV protons. [^{11}C]Carbon monoxide was produced by the reduction of [^{11}C]carbon dioxide in a zinc furnace at 400 °C by utilizing the procedures and apparatus described elsewhere.[14]

Liquid chromatographic analyses (LC) were performed with a gradient pump and a variable-wavelength UV detector in series with a β^+-flow detector. The following mobile phases were used: 0.05 M ammonium formate, pH 3.5 (A), acetonitrile (B), acetonitrile/H_2O 50/7 (C) and 0.01 M formic acid in H_2O (D). For analytical LC, a C_{18}, 4 μm, 250 × 4.6 mm (i.d.) column was used with a flow of 1.5 mL/min. For semipreparative LC, a C_{18}, 4 μm, 250 × 10 mm (i.d.), column was used with a flow

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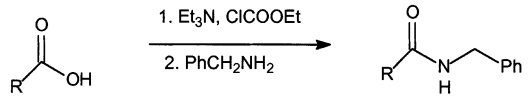
SCHEME 2[a]



29 30

[a] R = 3-pyridyl (**30a**), R = 1-isoquinolyl (**30b**).

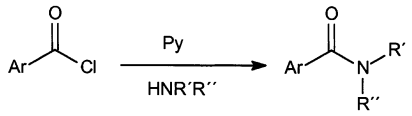
of 4 mL/min. An automated synthesis system[15] was used for LC injection and fraction collection.

Radioactivity was measured in an ion chamber. For coarse estimations of radioactivity during production and for safety, a portable dose−rate meter was used.

For the determination of yields and purity of the products, unlabeled reference substances were used for comparison when LC runs were performed. Identities of precursors and reference compounds were determined using ^{1}H and ^{13}C NMR and GC−MS. NMR spectra were recorded on a 400 MHz NMR instrument. Tetramethylsilane or chloroform-d_1 was used as the internal standard. LC−MS was performed using an instrument with electrospray ionization (ESI+). An autosampler and an ODS C_{18} (5 μm, 100 × 4.6 mm i.d.) column were used. Mobile phases were D and B. GC−MS was performed with a mass spectrometer coupled to a GC.

All of the triflates, except 3-pyridyl, 2- and 4-chlorophenyl ,and 1-isoquinolyl triflates, and all of the amines used in this work were commercially available. The triflate, 3-pyridyl trifluoromethanesulfonate (**21**), was prepared by the reaction of 3-hydroxypyridine with trifluoromethanesulfonic anhydride.[16] This compound was prepared previously by different methods.[17] The preparation of 2- and 4-chlorophenyl trifluoromethanesulfonates[16] (**16** and **20**) and isoquinolin-1-yl trifluoromethanesulfonate[18] (**22**) has been described previously, and the same procedure was followed. Two of the reference compounds, *N*-phenylbenzamide and *N*-phenylnicotinamide, were commercially available. Reference compounds **30a** and **30b** were synthesized from the corresponding carboxylic acids and benzylamine using method A (Scheme 2),[19] and compounds **32a**−**i** were synthesized from the corresponding acid chlorides and different amines using method B (Scheme 3).[20] The yields were 65−95% (Table 2). Analytical data to identify the reference compounds **30a**,[21] **30b**,[22] **32a**,[23] **32b**,[24] **32c**,[25] **32d**,[25] **32e**,[25] **32h**,[26] and **32i**[27] were compared with the literature values. No such data for compounds **32f** and **32g** are available in the literature and presented here. The reagents lithium

SCHEME 3[a]



31 32

[a] Ar = phenyl, R′ = isopropyl and R″ = H (**32a**), Ar = 4-nitrophenyl, R′ = isopropyl and R″ = H (**32b**), Ar = 4-chlorophenyl, R′ = isopropyl and R″ = H (**32c**), Ar = 4-methoxyphenyl, R′ = isopropyl and R″ = H (**32d**), Ar = 4-methylphenyl, R′ = isopropyl and R‴ = H (**32e**), Ar = 2-naphthyl, R′= isopropyl and R″ = H (**32f**), Ar = phenyl and R′ = R″ = *n*-propyl (**32g**), Ar = phenyl, R′= benzyl and R′ = methyl (**32h**), Ar = 2-chlorophenyl, R′= allyl and R″ = H (**32i**).

TABLE 2. Chemical Yields and Melting Points of the Reference Compounds

entry	products	yields (%)	mp (°C)
1	**30a**	92	83 (lit.[21] 85−85.5)
2	**30b**	87	88 (lit.[22] 85)
3	**32a**	90	95 (lit.[23] 99−103)
4	**32b**	66	153 (lit.[24] 151−153)
5	**32c**	91	142 (lit.[25] 144)
6	**32d**	89	123 (lit.[25] 120−122)
7	**32e**	91	133 (lit.[25] 131−132)
8	**32f**	84	170 (lit.[26] 168.5−169.5)
9	**32g**	95	colorless oil
10	**32h**	93	colorless oil
11	**32i**	94	66[27]

chloride, lithium bromide, tetrakis(triphenylphosphine)palladium(0), Ph_3As, and $Pd_2(dba)_3$ were commercially available and used without further purification. THF was distilled under nitrogen from sodium/benzophenone. Pyridine was distilled under nitrogen from CaH_2.

Synthesis of [Carbonyl-^{11}C]Amides. General Procedure. Tetrakis(triphenylphosphine)palladium(0) (5.0 mg, 4.3 μmol) was placed in a vial (1 mL) which was flushed with nitrogen and dissolved in THF (250 μL). Aryl triflate (22.1 μmol) and LiBr (5 μL of 0.46 M solution in THF, 2.3 μmol) were added. The mixture was shaken until the solution was homogeneous. Amine (117.4 μmol) was added, and the resulting mixture was injected into the injection loop of the synthesis apparatus. The appropriate volume (200 μL) was then transferred under pressure (35 Mpa) to the micro-autoclave precharged with [^{11}C]carbon monoxide in helium. The micro-autoclave was heated (150 °C) for 5 min. The crude product was transferred to a preevacuated, septum-fitted vial (5 mL). The micro-autoclave was filled with THF (200 μL) and emptied into the collection vial. The radioactivity was measured before and after the vial was purged with nitrogen. The solvent volume was reduced to less than 0.2 mL by heating at 75 °C and purging with nitrogen. Acetonitrile/water: 1/1 (2 mL) was added, and the resulting solution was injected onto the semipreparative LC. Solvent A−B (70:30) linear gradient to 20:80 in 10 min, flow 4 mL/min, t_R = 9.1, 10.3, 11.5, 9.3, 10.6, 12.4, 12.2, 12.8, 12.7, 9.6, 8.6, 8.4 and 14.6 min for products **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, and **13**, respectively. The identity and radiochemical purity of the collected fraction were assessed by analytical LC: solvent A−C (70:30) linear gradient to 0:100 in 10 min, flow 1.5 mL/min, wavelength 254 nm, t_R = 4.7, 5.8, 6.2, 5.2, 5.8, 7.3, 8.0, 7.8, 7.2, 5.1, 4.5, 4.0, and 9.1 min for products **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, and **13**, respectively.

MS(ESI+) *m*/*z* = 164, 209, 198, 194, 178, 214, 206, 226, 198, 196, 213, 199, and 263 (M + 1) for products **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, and **13**, respectively.

Synthesis of *N*-Benzylisoquinoline-1-(^{13}C)carboxamide. Tetrakis(triphenylphosphine)palladium(0) (15.0 mg, 13.8 μmol) was placed in a vial (1 mL), flushed with nitrogen, and

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dissolved in THF (250 μL). Isoquinolin-1-yl trifluoromethanesulfonate **22** (24.0 mg, 88 μmol) and LiBr (25 μL of 0.46 M solution in THF, 11.5 μmol) were added. The mixture was shaken until an homogeneous solution was obtained. Benzylamine (38 μL, 37.2 mg, 348 μmol) was added. The resulting mixture and (^{13}C)carbon monoxide were transferred with pressure (35 Mpa) to the micro-autoclave (200 μL). The micro-autoclave was heated (150 °C) for 10 min. The crude product was collected into a preevacuated, septum-fitted vial (5 mL), and the solvent was evaporated by purging with nitrogen at 75 °C. A sufficient amount of the previously synthesized corresponding ^{11}C-labeled compound was added, and the product was purified by semipreparative LC. The chromatographic method used was the same as described for the ^{11}C-labeled compound. The radioactive fraction was collected and evaporated under reduced pressure to yield the title compound (15.2 mg, 66 % calculated from the triflate).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.6 (m, 1H), 8.6 (bs, 1H), 8.4 (d, 1H), 7.8 (m, 1H), 7.7 (d, 1H), 7.6 (m, 2H), 7.4 (d, 2H), 7.3 (m, 2H), 7.2 (m, 1H), 4.7 (d, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (main peak, carbonyl carbon), 130.6, 128.8, 128.0, 127.5, 126.9, 124.5, 43.1.

Preparation of 3-Pyridyl Trifluoromethanesulfonate (21). 3-Hydroxypyridine (1.0 g, 10.5 mmol) was dissolved in freshly distilled pyridine (20 mL), and argon was flushed through the flask. The mixture was cooled on an ice bath, and trifluoromethanesulfonic anhydride (2.0 mL, 12.0 mmol) was added slowly. The reaction mixture was stirred overnight at ambient temperature under argon. The solvent was removed under reduced pressure, and the residue was partitioned between water (100 mL) and ether (100 mL). The ether extract was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography using pentane/ether (1:1) to give the title compound as a yellow oil (1.6 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.5−8.6 (m, 2H), 7.5 (m, 1H), 7.3 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 146.8, 142.8, 128.9, 124.6, 113.9−123.4 (q).

MS(EI): m/z = 227 ($M^{\bullet+}$, 78), 163 (97), 115 (18), 94 (18), 77 (28), 69 (100).

Preparation of Reference Compounds. Method A. A suspension of the appropriate carboxylic acid (5.78 mmol) in CH_2Cl_2 (40 mL) was treated with triethylamine (0.9 mL, 6.0 mmol). The mixture was cooled to 10 °C, treated with ethyl chloroformate (0.6 mL, 6 mmol), and stirred at ambient temperature for 30 min. Amine (6.5 mmol) was added, and the mixture was stirred at ambient temperature for 20 h. The mixture was concentrated under reduced pressure, and the residue was suspended in saturated aqueous Na_2CO_3 (50 mL). The product was extracted with ethyl acetate (2 × 50 mL), and the organic extract was washed with water (2 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography using pentane/EtOAc (1:1) as the eluent.

Method B. The appropriate amine (37.7 mmol) was dissolved in dry THF (50 mL) and cooled to 0 °C, and freshly distilled pyridine (3.1 mL, 37.7 mmol) was added. A solution of the appropriate acid chloride (38.0 mmol) in dry THF (35 mL) was slowly added. The mixture was stirred at ambient temperature for 45 min and concentrated under reduced pressure. The residue was partitioned between EtOAc (200 mL) and water (200 mL). The organic layer was separated, washed with 5% HCl (100 mL), 5% aq NaOH (100 mL) and water (2 × 100 mL) successively, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the product.

***N*-Isopropyl-2-naphthoesaeuremide (32f).** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (s, 1H), 7.8 (m, 4H), 7.5 (m, 2H), 6.3 (bs, 1H), 4.4 (m, 1H), 1.3 (d, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 134.5, 132.5, 132.1, 128.7, 128.2, 127.5, 127.3, 127.0, 126.5, 123.5, 41.9, 22.7.

MS(EI): m/z = 213 ($M^{\bullet+}$, 51), 198 (6), 171 (7), 155 (100), 127 (33), 126 (7), 77 (3).

***N,N*-Dipropyl-benzamide (32 g).** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2 (m, 5H), 3.3 (m, 2H), 3.0 (m, 2H), 1.6 (m, 2H), 1.4 (m, 2H), 0.8 (m, 3H), 0.6 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 137.1 128.8, 128.1, 126.2, 50.5, 46.1, 21.7, 20.5, 11.2, 10.8.

MS(EI): m/z = 205 ($M^{\bullet+}$, 13), 204 (49), 176 (9), 134 (5), 105 (100), 77 (42).

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