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Radical-Induced Metal and Solvent-Free Cross-Coupling Using TBAI–TBHP: Oxidative Amidation of Aldehydes and Alcohols with *N*-Chloramines via C–H Activation

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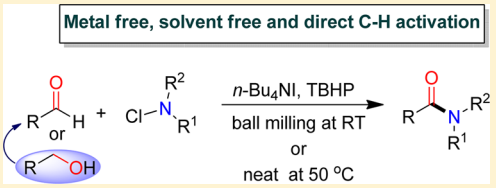
Supporting Information

ABSTRACT: A solvent-free cross-coupling method for oxidative amidation of aldehydes and alcohols via a metal-free radial pathway has been demonstrated. The proposed methodology uses the TBAI-TBHP combination which efficiently induces metal-free C–H activation of aldehydes under neat conditions at 50 °C or ball-milling conditions at room temperature.



Amide functionality is well-known in peptides and proteins. Due to its stability, high polarity, and conformational diversity, the amide bonds constitute the most abundant motif in various natural and non-natural products.[1] In medicinal chemistry, amides containing bioactive molecules are also well-explored. Development of convenient methodologies for amide functionalities under catalytic, metal-free, and chemoselective conditions is highly desirable and much in focus in recent years. Common methods for the synthesis of amides involve either coupling of carboxylic acids and amines in the presence of a coupling agent[2,3] or acylation of amines with activated carboxylic acid derivatives.[4,5] These strategies are efficient but unpopular due to involvement of hazardous conditions and use of expensive reagents and poor atom economy.[3] Therefore, a handful of alternatives have been reported, such as the Staudinger reaction,[6,7] Schmidt reaction,[8] Beckmann rearrangement,[9,10] aminocarbonylation of haloarenes,[11,12] direct synthesis from alcohols with amines,[13] oxidative amidation of aldehydes,[14−22] etc. Recently, transition-metal-catalyzed aldehyde amidation via oxidation of intermediate carbinolamines has become popular (Figure 1a).[17,19,23−25] One of the recently used catalyst is *N*-heterocyclic carbenes (NHCs).[26,27] In addition, *N*-hydroxyphthalimide[28] and *N*-hydroxysuccinimide[29] have also proved to be efficient as metal-free reagents for the amidation of aldehydes. In addition, coupling of acyl- and nitrogen-centered radicals to construct amides has recently been examined.[14,21] De Luca and co-workers have shown Cu(II)- and Fe(II)-catalyzed synthesis of amides from aldehyde and *N*-chloramines via a radical pathway (Figure 1b).[14,16]

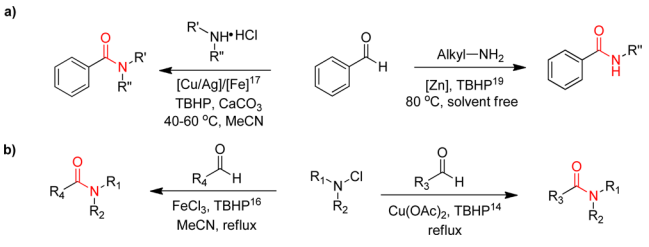


Figure 1. (a) Known synthesis of amides from aldehydes and amines. (b) Metal-catalyzed synthesis of amides using *N*-chloramine and aldehydes. References are shown as superscript.

Aiming to introduce environmentally benign reagents,[30,31] herein we report metal- and solvent-free cross-coupling oxidative amidation of alcohols and aldehydes with *N*-chloramines under neat or ball-milling conditions. The reagent used here is a TBAI (tetrabutylammonium iodide)–TBHP (*tert*-butyl hydroperoxide, *Caution!!* see Experimental Section)[21,32] combination. Under neat reaction condition, the substrates were mixed and the reactions were executed at an elevated temperature (50 °C). However, under ball-milling (frequency 21 Hz), the working temperature was 27 °C (room temperature). Thus, we have demonstrated an unprecedented example of TBAI–TBHP-mediated C–H activation[33] of aldehydes for oxidative amidation.

Reactions were performed for 4-chlorobenzaldehyde, *N*-benzyl-*N*-chloro-1-phenylmethanamine in the presence of TBAI (additive) and TBHP (oxidant) under solvent-free (neat) conditions at 50 °C, after which *N*,*N*-dibenzyl-4-chlorobenzamide was isolated in 68% yield (Table 1, entry 1). This reaction condition was optimized based on screening of various additives, and the results are presented in Table 1. TBHP is found to be a superior oxidant (Table 1, entries 1–6) to H_2O_2 (hydrogen peroxide), oxone, PIDA (phenyliodine diacetate), $AgNO_3$ (silver nitrate), or $(NH_4)_2S_2O_8$ (ammonium persulfate). In the absence of any of the catalysts or the oxidant, no expected products were identified (entries 7 and 11). The roles of countercations (n-Bu_4N^+) and anion (I^-) were established by comparing TBAI with different reagents. For

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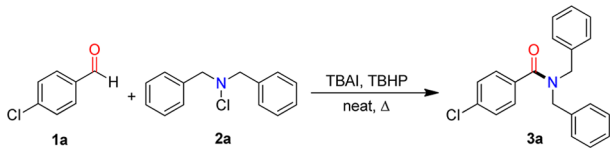
Table 1. Optimization of Reaction Condition[a]



entry	additive (mol %)	oxidant (equiv)	yield (%)[b]
1	TBAI (25)	TBHP (1.5)	68
2	TBAI (25)	H_2O_2 (1.5)	trace
3	TBAI (25)	oxone (1.5)	
4	TBAI (25)	PIDA (1.5)	trace
5	TBAI (25)	$AgNO_3$ (1.5)	
6	TBAI (25)	$(NH_4)_2S_2O_8$ (2)	
7	TBAI (25)		
8	TBAI (25)	TBHP (1)	59
9	TBAI (25)	TBHP (2)	77
10	TBAI (25)	TBHP (2.5)	75
11		TBHP (2)	
12	KI (25)	TBHP (2)	53
13	TBAB (25)	TBHP (2)	trace
14	I_2 (25)	TBHP (2)	23
15	NIS (25)	TBHP (2)	38
16	KI/I_2	TBHP (2)	45
17	TBAI (10)	TBHP (2)	64
18	TBAI (15)	TBHP (2)	73
19	TBAI (20)	TBHP (2)	78
20[c]	TBAI (20)	TBHP (2)	56
21[d]	TBAI (20)	TBHP (2)	62
22[e]	TBAI (20)	TBHP (2)	41

[a]Unless specified, the reactions were carried out at 50 °C. [b]Isolated yield. [c]Solvent was THF. [d]Solvent was acetonitrile. [e]Neat at 30 °C.

example, the reactions in the presence of KI (potassium iodide), NIS (*N*-iodosuccinimide, Table 1, entries 12 and 15), and tetrabutylammonium bromide (*n*-Bu_4NBr, Table 1, entry 13) resulted in poor yields. Similarly, changing solvents (entries 20 and 21), varying temperature (entry 22), and introducing other reagents such as iodine (I_2, entry 14), $KI–I_2$ (1:1, entry 16), etc., also did not lead to significant improvements.

The optimized conditions for the oxidative amidation reaction of the aldehyde are shown in Table 1. Aldehydes (1.0 equiv), *N*-chloramine (2.0 equiv), TBAI (20 mol %), and TBHP (2.0 equiv) led to best results. Using this methodology, the amide derivatives were obtained in good yields with heteroaromatic aldehyde (**3f**), aliphatic aldehydes (**3q**, **3r**, and **3s**), and aldehydes having electron-donating (**3b**, **3e**) substituents (Figure 2). Furthermore, aldehydes with electron-withdrawing groups such as chloro **3a**, trifluoromethyl **3d**, bromo **3g** and **3i**, nitro **3m** and **3p**, and fluoro **3o** were also found to be efficient for the amidation reaction. Similarly, various *N*-chloramines such as primary (*N*-chloro-1-phenylmethanamine) and secondary (*N*-chloro-*N*-methyl-1-phenylmethanamine, *N*-benzyl-*N*-chloro-1-phenylmethanamine) derivatives have also facilitated good yields.

X-ray crystal structure investigations were done for the synthesized compounds. Good qualities of crystals were obtained after slow evaporation of the solvent from ethyl acetate–hexane solution. The structures of compounds **3c** and **3l** are shown in Supporting Information (SI).

The efficiency and convenience of this methodology encouraged us to further explore the scope of multistep organic synthesis.[34] The oxidative amidation of primary

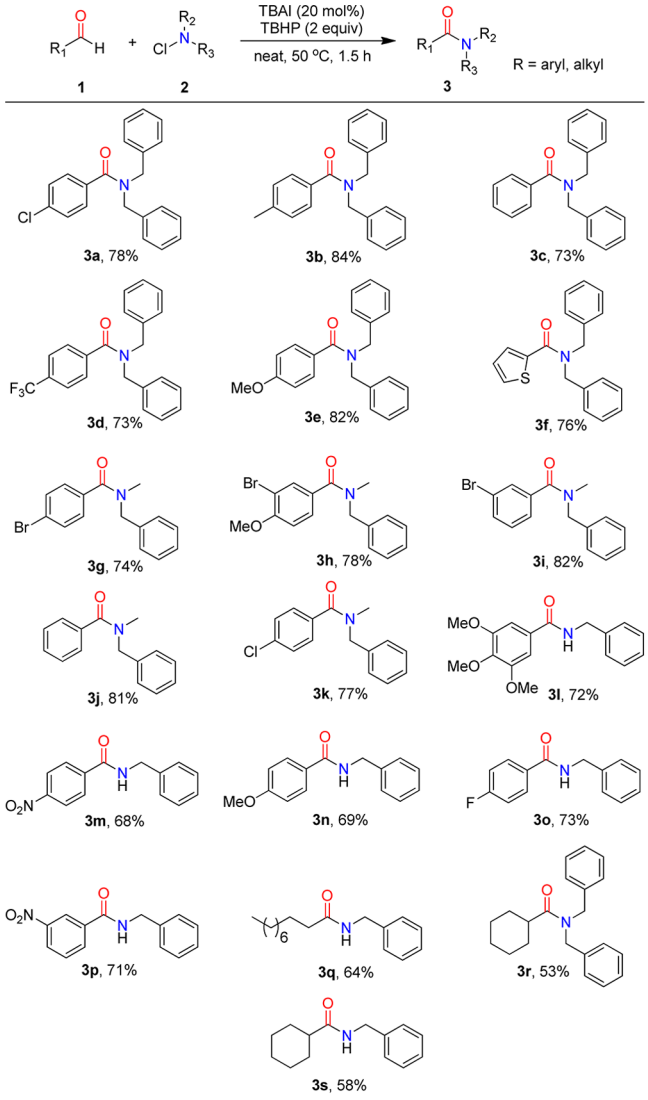


Figure 2. Results of amidation of aldehydes with *N*-chloramines under neat conditions.

alcohols with *N*-chloramines in the presence of TBHP (3 equiv) and TBAI (20 mol %) under neat conditions was performed (Figure 3). We presumed that an additional 1 equiv of TBHP was consumed for oxidation of alcohol to the aldehyde. The products were also isolated in good yields in a two-step process (Figure 3).

Furthermore, we have also explored this methodology under ball-milling (mechanochemical) conditions. The ball-milling synthesis[35–38] has drawn a significant interest due to its advantages over traditional solution-based methods.[39,40] A major benefit of this process is that it is solvent-free and thus minimizes any traditional workup.[40,41] Such processes are envisaged to have a positive impact on ecology besides being procedurally as well as time-wise economical. Higher conversion of reaction, less byproducts, and minimum/no purification requirements are extra benefits of these procedures.[42–44] Under ball-milling, the reactions were done in the absence of any solvents and at room temperature. Progress of the reactions was monitored by thin layer chromatography (TLC) or ^1H NMR. Products were isolated by dissolving the reaction mixture in ethyl acetate or dichloromethane and purified by chromatographic methods. The isolated yields for

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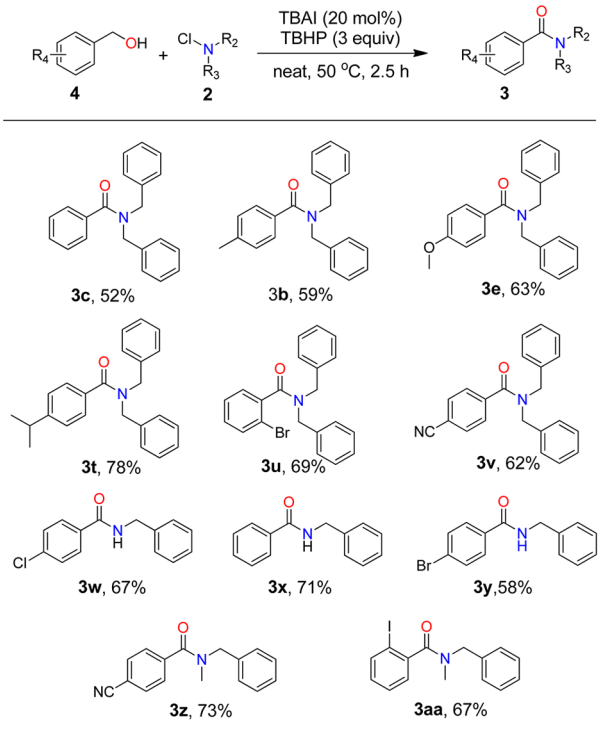


Figure 3. Metal-free oxidative amidation of alcohols and *N*-chloramines.

selected compounds are shown in Table 2, which are comparable to the results of neat conditions (Figure 2).

Table 2. Results for Amidation Aldehyde and *N*-Chloramines under Ball-Milling Conditions

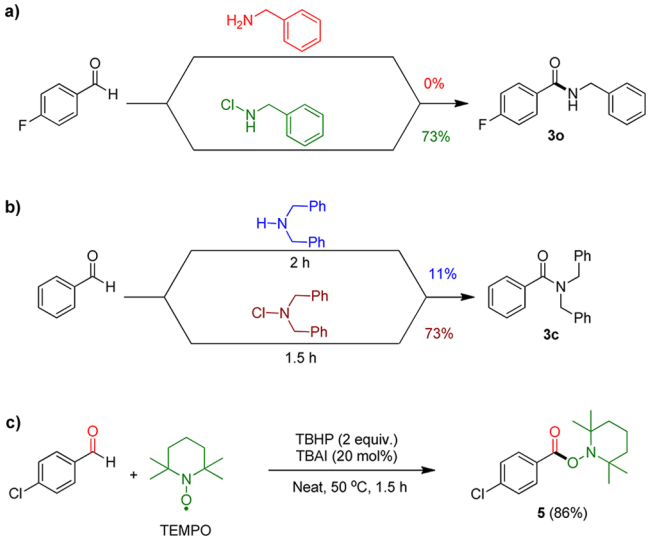
entry	compound	yield (%)	entry	compound	yield (%)
1	**3c**	72	6	**3i**	75
2	**3e**	75	7	**3k**	69
3	**3f**	63	8	**3o**	62
4	**3u**	66	9	**3z**	71
5	**3v**	64	10	**3aa**	68

Control experiments (Scheme 1) under neat conditions were performed to shed some light on the mechanism of the reaction. Upon replacement of *N*-chloramine with benzylamine, no amide was obtained (Scheme 1a) due to the formation of imine. Secondary amine led to only 11% of amide (Scheme 1b). The combination of TBAI, TBHP, benzaldehyde, and TEMPO (2,2,6,6-tetramethylpiperidin-1-yl-oxy radical) led to the formation of a TEMPO adduct (**5**, Scheme 1c).

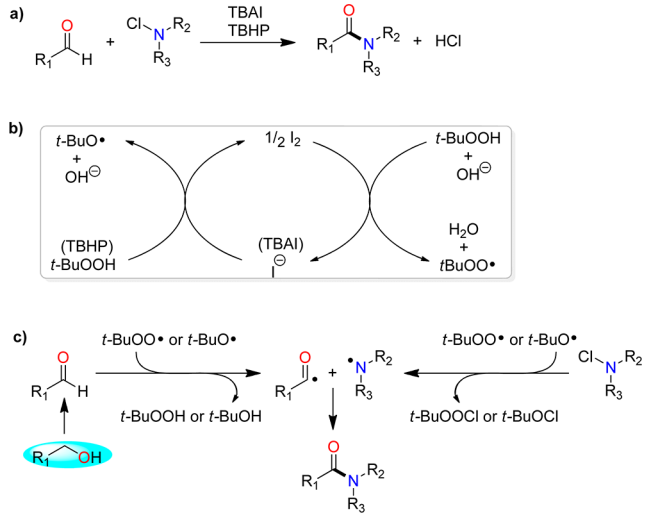
In Scheme 2, a plausible mechanism for the oxidative amidation reaction has been proposed. The formation of a TEMPO adduct (**5**, Scheme 1c) clearly establishes that the reaction proceeds via a radical pathway. The *tert*-butoxyl and/or *tert*-butylhydroperoxide radicals were generated from TBHP in the presence of TBAI (Scheme 2b). Further, acyl radical[16,21] and amino radicals[45] were produced from the aldehyde and *N*-chloramine, respectively. Finally, these acyl and amino radicals combine to result in the amide (Scheme 2c).

In summary, we have developed a mild, efficient, and metal-free method for the synthesis of amides from alcohols and aldehydes using a TBHP–TBAI combination under solvent-free conditions. The cross-coupling reaction of the aldehydes

Scheme 1. (a,b) *N*-Chloramine Established To Be Essential for This Reaction and (c) Formation of a TEMPO Adduct with an Aldehyde Radical



Scheme 2. (a) Amidation Reaction, (b) Generation of *tert*-Butoxyl and *tert*-Butylhydroperoxide Radicals, and (c) Formation of Acyl Radical and Amino Radical Followed by Recombination to the Final Product



and *N*-chloramine is demonstrated as an example of metal-free C–H activation of the aldehydes. This methodology was found to be a compatible with various functional groups and requires easily accessible starting materials. Performing the reactions under ball-milling conditions may constitute an important addition in mechanochemical synthesis. Hence, we anticipate that our study may draw significant attention of chemists working on the development of synthetic methodologies as well as the researchers searching for better methods in organic mechanochemistry.[46]

EXPERIMENTAL SECTION

General Methods. The ball-milling (21 Hz) experiments were executed under open atmosphere. Column chromatographic purification of compounds was performed using silica gel (mesh 100–200) and a hexane–ethyl acetate mixture as eluent, unless otherwise specified. NMR spectra were recorded on a 400 MHz instrument at 25

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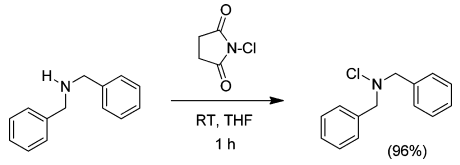
°C. The chemical shift values are reported in parts per million (ppm) with respect to residual chloroform (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). High-resolution mass spectra (HRMS) were recorded on ESI-TOF (time-of-flight) mass spectrometer. Infrared spectral data are reported in wavenumber (cm^{-1}). Melting points of the compounds were determined using a digital melting point apparatus and are uncorrected.

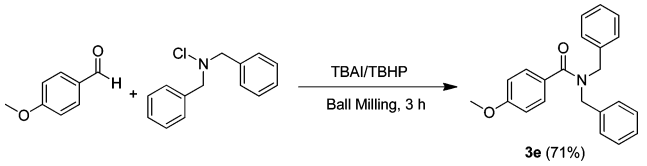
Preparation of *N*-Chloramine (*Caution!!*) Derivatives.[14]



In a representative procedure, dibenzylamine (10.4 mmol) was added to 10 mL of tetrahydrofuran followed by addition of *N*-chlorosuccinimide (11.4 mmol). The reaction mixture was allowed to stir at room temperature for 1 h. After that, tetrahydrofuran was evaporated under reduced pressure, and the compound was extracted with 50 mL of dichloromethane after being successively washed with water. The organic phase was dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure to isolate the desired product *N*-benzyl-*N*-chloro-1-phenylmethanamine (2.3 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.34 (m, 10H), 4.19 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 129.2, 128.5, 127.9, 67.2.

Safety Issues of N-Chloramine (Caution!!). A number of *N*-chloramines have been reported to be explosive.[47] However, none of the *N*-chloramine used here showed any sign explosiveness, but they are highly toxic in nature. Still, general safety concern at an organic chemistry laboratory should be carefully exercised. PPE (personal protective equipment) should be used during preparation and use of *N*-chloramines. *N*-Chloramines were stable up to few weeks when stored at −20 °C without sign of decomposition.

Procedure for Large-Scale Use of TBHP (*Caution!!*) under Ball-Milling.



Safety Issues of TBHP (Caution!!). TBHP is a potential shock-sensitive chemical. However, precautions like PPEs should be used during handling under ball-milling. Also, very high level of safety precautions should be exercised during the reaction with TBHP. The ball-milling instrument should be kept under an isolated fume hood, and fume hood sashes must be lowered to the fullest extent. The use of blast shields is mandatory at all times during reactions. For large-scale reactions, a recommended maximum loading should be 1/3 volume of the jar capacity.

Herein, the TBHP was used as 70% in water, and the reaction was continued for 3 h (additional 1.5 h after completion) for the synthesis of 0.96 g of **3e** using a 25 mL ZrO_2 milling jar. Notably, we did not observe any explosion or decomposition of the materials during the reaction.

In a typical procedure, 4-methoxybenzaldehyde (0.5 mL, 4.1 mmol), *N*-benzyl-*N*-chloro-1-phenylmethanamine (1.9 g, 8.2 mmol), TBAI (0.3 g, 20 mol %), TBHP (70% in water, 1.1 mL, 8.2 mmol), and one grinding ball (15 mm diameter, ZrO_2) were placed in a 25 mL ZrO_2 milling jar. After continuous milling for 3 h, the mass was dissolved in dichloromethane and *N*,*N*-dibenzyl-4-methoxybenzamide (71% yield) was purified by chromatography. Spectral data match the characterization data provided for **3e**.

Procedure for the Preparation of Amides under Neat Conditions. In a typical run, *N*-benzyl-*N*-chloro-1-phenylmethanamine (0.7 mmol) was added to a 25 mL round-bottom flask charged with a magnetic stirring bar and 4-chlorobenzaldehyde (0.35 mmol). TBAI (*n*-Bu_4NI, 20 mol %) and TBHP (70% in water, 0.7 mmol) were added to the mixture, and the round-bottom flask was kept at 50 °C (preheated oil bath). The reaction was monitored by TLC. After completion of the reaction, the mass was dissolved in dichloromethane and purified by column chromatography to obtain *N*,*N*-dibenzyl-4-chlorobenzamide[48] (93 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.29 (m, 12H), 7.14 (br s, 2H), 4.71 (br s, 2H), 4.40 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 135.9, 134.6, 129.7, 128.9, 128.6, 128.3, 127.8, 126.8, 51.6, 47.2.

Procedure for the Preparation of Amides under Ball-Milling. Benzaldehyde (0.29 mmol), *N*-benzyl-*N*-chloro-1-phenylmethanamine (0.59 mmol), TBAI (20 mol %), TBHP (70% in water, 0.59 mmol), and one grinding ball (15 mm diameter, ZrO_2) were placed in a 10 mL ZrO_2 milling jar. Progress of the reaction under milling conditions was checked by TLC or ^{1}H NMR, after which the reaction was started; this operation time was excluded from the reported reaction time. Once the reaction was completed, the mixture was dissolved in ethyl acetate or dichloromethane and *N*,*N*-dibenzylbenzamide (72% yield) was purified by column chromatography.

Monitoring the Reaction by TLC or ^{1}H NMR. To perform this operation, the ball-milling instrument was stopped and a small amount of the sample was collected from the jar to check either TLC or ^{1}H NMR. After that, the reaction was started and this operation time was excluded for reporting the reaction timing.

Trapping of Acyl Radical by TEMPO. TEMPO (0.54 mmol) was added to a 25 mL round-bottom flask charged with a magnetic stirring bar and 4-chlorobenzaldehyde (0.36 mmol). TBAI (*n*-Bu_4NI, 20 mol %) and TBHP (70% in water, 0.72 mmol) were added to the mixture, and the round-bottom flask was kept at 50 °C. The reaction was monitored by TLC. After completion of the reaction, the mass was dissolved in dichloromethane and purified by column chromatography to obtain 2,2,6,6-tetramethylpiperidin-1-yl-4-chlorobenzoate (**5**): yield 86% (91 mg); R_f = 0.40 (diethyl ether/hexane = 0.25:4.75); reddish white solid; mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 1.85−1.45 (m, 6H), 1.30 (s, 6H), 1.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 138.6, 130.2, 128.1, 127.4, 59.7, 38.3, 31.2, 20.1, 16.2; IR (KBr) $\tilde{\nu}$ 3457 (w), 2973 (s), 2935 (s), 1746 (m), 1633 (m), 1252 (m), 1071 (m), 754 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{23}ClNO_2$ ($M + H^+$) 296.1412, found 296.1432.

*N,N-Dibenzyl-4-chlorobenzamide (**3a**):* R_f = 0.17 (ethyl acetate/hexane = 0.25:4.75); white solid; yield 78% (93 mg); mp 102−104 °C (lit.[48] 103−104 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.29 (m, 12H), 7.14 (br s, 2H), 4.71 (br s, 2H), 4.40 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 135.9, 134.6, 129.7, 128.9, 128.6, 128.3, 127.8, 126.8, 51.6, 47.2; IR (KBr) $\tilde{\nu}$ 3459 (w), 3030 (w), 2925 (w), 1637(s), 1450 (m), 1420 (m), 1258 (m), 1089 (m), 750 (m), 700 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{19}ClNO$ ($M + H^+$) 336.1150, found 336.1182.

*N,N-Dibenzyl-4-methylbenzamide (**3b**):*[49] R_f = 0.20 (ethyl acetate/hexane = 0.25:4.75); white solid; yield 84% (112 mg); mp 87−90 °C (no literature report on melting points); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.28 (m, 10H), 7.19 (d, J = 8 Hz, 4H), 4.71 (br s, 2H), 4.44 (br s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 144.3, 139.9, 133.2, 130.2, 129.2, 128.8, 127.6, 126.9, 51.7, 47.0, 21.4; IR (KBr) $\tilde{\nu}$ 3440 (w), 3028 (w), 2923 (w), 1633 (s), 1449 (m), 1419 (m), 1259 (m), 751 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{22}NO$ ($M + H^+$) 316.1696, found 316.1716.

*N,N-Dibenzylbenzamide (**3c**):* R_f = 0.20 (ethyl acetate/hexane = 0.25:4.75); white solid; yield 73% (108 mg); mp 113−115 °C (lit.[50] 114−115 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.31 (m, 13H), 7.16 (br s, 2H), 4.72 (br s, 2H), 4.42 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 136.2, 129.7, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 127.7, 127.6, 127.1, 126.8, 51.6, 46.9; IR (KBr) $\tilde{\nu}$ 3442 (w), 1633 (s), 1494 (m), 1451(m), 1261 (m), 697 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{20}NO$ ($M + H^+$) 302.1539, found 302.1532.

*N,N-Dibenzyl-4-(trifluoromethyl)benzamide (**3d**):*[49] R_f = 0.35 (ethyl acetate/hexane = 0.5:4.5); white solid; yield 73% (99 mg); mp 88−91 °C (no literature report on melting points); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.53 (m, 4H), 7.33−7.20 (m, 8H), 7.08 (br s, 2H), 4.67 (br s, 2H), 4.30 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 139.8, 136.7, 136.0, 131.8 (q, $^2J_{FC}$ = 65.1 Hz), 129.1, 128.9,

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128.6, 128.0, 127.9, 127.2, 127.0, 125.8 (q, $^3J_{FC}$ = 7.4 Hz), 123.8 (d, $^1J_{FC}$ = 271 Hz), 51.5, 47.2; IR (KBr) $\tilde{\nu}$ 3473 (w), 3063 (m), 3031 (m), 2927 (m), 1640 (s), 1451 (m), 1425 (m), 1326 (s), 1261 (m), 1167 (s), 1128 (m), 1065 (s), 850 (s), 747 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{19}F_3NO$ (M + H$^+$) 370.1413, found 370.1440.

N,N-Dibenzyl-4-methoxybenzamide (**3e**): R_f = 0.30 (ethyl acetate/hexane = 1:4); colorless solid; yield 82% (112 mg); mp 118−120 °C (lit.[14] 120−122 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8 Hz, 2H), 7.38−7.23 (m, 10H), 6.88 (d, J = 8 Hz, 2H), 4.66 (br s, 2H), 4.49 (br s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 160.8, 137.0, 128.8, 128.7, 128.3, 127.6, 113.9, 55.4, 51.8, 47.2; IR (KBr) $\tilde{\nu}$ 3440 (w), 2054 (w), 1632 (s), 1451 (m), 1420 (m), 1249 (s), 1029 (m), 992 (m), 839 (m), 699 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{22}NO_2$ (M + H$^+$) 332.1645, found 332.1665.

N,N-Dibenzylthiophene-2-carboxamide (**3f**): R_f = 0.24 (ethyl acetate/hexane = 0.5:4.5); white solid; yield 76% (125 mg); mp 46−47 °C (lit.[50] 48−50 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8 Hz, 1H), 7.39−7.27 (m, 11H), 6.96 (dd, J_1 = J_2 = 4 Hz, 1H), 4.73 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 137.8, 136.7, 129.5, 128.9, 128.7, 127.7, 127.0, 126.8, 51.7, 49.2; IR (KBr) $\tilde{\nu}$ 3444 (w), 2880 (m), 1620 (s), 1615 (s), 1452 (m), 1427 (m), 1252 (m), 975 (s), 735 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{18}NOS$ (M + H$^+$) 308.1109, found 308.1093.

N-Benzyl-4-bromo-N-methylbenzamide (**3g**):[51] R_f = 0.22 (ethyl acetate/hexane = 0.5:4.5); colorless oil; yield 74% (61 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.44 (m, 4H), 7.39−7.30 (m, 12H), 7.16 (br s, 2H), 4.74, 4.50 (two singlets for two rotamers, 4H), 3.03, 2.86 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 133.5, 131.8, 130.2, 128.9, 128.5, 128.3, 127.8, 124.1, 55.3, 51.0, 37.1, 33.5; IR (KBr) $\tilde{\nu}$ 3466 (w), 3062 (m), 3030 (m), 2924 (s), 2854 (s), 1714 (s), 1633 (m), 1453 (m), 1402 (s), 1264 (s), 1073 (s), 1012 (s), 836 (s), 734 (m), 699 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrNO$ (M + H$^+$) 304.0332, found 304.0358.

N-Benzyl-3-bromo-4-methoxy-N-methylbenzamide (**3h**): R_f = 0.20 (ethyl acetate/hexane = 1:4); colorless oil; yield 78% (60 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.42−7.18 (m, 6H), 6.89 (br s, 1H), 4.69, 4.58 (two singlets for two rotamers, 2H), 3.90 (s, 3H), 2.94 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 157.0, 136.8, 132.6, 129.6, 128.9, 128.2, 128.0, 128.0, 127.7, 111.6, 111.4, 56.4, 55.4, 51.1, 37.2, 33.6; IR (KBr) $\tilde{\nu}$ 3459 (w), 2924 (s), 2853 (s), 1632 (m), 1600 (s), 1454 (m), 1402 (m), 1293 (s), 1262 (m), 1052 (m), 816 (m), 730 (m), 698 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{17}BrNO_2$ (M + H$^+$) 334.0437, found 334.0453.

N-Benzyl-3-bromo-N-methylbenzamide (**3i**):[52] R_f = 0.40 (ethyl acetate/hexane = 1:4); colorless oil; yield 82% (107 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.52 (m, 4H), 7.45−7.28 (m, 12H), 7.23−7.15 (m, 2H), 4.74, 4.49 (two singlets for two rotamers, 4H), 3.02, 2.85 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 138.1, 136.6, 136.1, 133.2, 132.7, 130.1, 130.0, 128.9, 128.8, 128.3, 128.2, 127.7, 126.7, 125.6, 125.2, 122.6, 55.2, 50.9, 37.0, 33.3; IR (KBr) $\tilde{\nu}$ 3459 (w), 3063 (m), 3030 (m), 2925 (m), 1713 (m), 1633 (s), 1562 (m), 1495 (m), 1452 (m), 1400 (m), 1255 (m), 1077 (m), 735 (m), 699 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrNO$ (M + H$^+$) 304.0332, found 304.0363.

N-Benzyl-N-methylbenzamide (**3j**):[53] R_f = 0.27 (ethyl acetate/hexane = 1:4); colorless oil; yield 81% (180 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.27 (m, 18H), 7.17 (br s, 2H), 4.77, 4.51 (two singlets for two rotamers, 4H), 3.04, 2.86 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 171.7, 137.0, 136.5, 136.1, 133.0, 130.2, 130.0, 129.7, 128.8, 128.4, 128.3, 128.2, 127.6, 127.0, 126.8, 55.2, 50.8, 37.0, 33.2; IR (KBr) $\tilde{\nu}$ 3468 (w), 3060 (m), 3029 (m), 2923 (m), 1631 (s), 1450 (m), 1401 (s), 1264 (m), 1070 (s), 717 (m), 698 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}NO$ (M + H$^+$) 226.1226, found 226.1223.

N-Benzyl-4-chloro-N-methylbenzamide (**3k**):[53] R_f = 0.38 (ethyl acetate/hexane = 1:4); colorless oil; yield 77% (70 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.29 (m, 16H), 7.16 (br s, 2H), 4.74, 4.51 (two singlets for two rotamers, 4H), 3.03, 2.86 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.6, 135.8, 133.2, 131.4, 130.1, 129.7, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 127.7, 127.0, 126.8, 126.6, 55.2, 51.0, 37.0, 33.5; IR (KBr) $\tilde{\nu}$ 3449 (w), 3062 (m), 3029 (m), 2925 (s), 2855 (m), 1717 (m), 1632 (s), 1478 (m), 1451 (m), 1401 (s), 1263 (m), 1090 (s), 1069 (s), 734 (m), 700 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{14}ClNNaO$ (M + Na$^+$) 282.0656, found 282.0687.

N-Benzyl-3,4,5-trimethoxybenzamide (**3l**): R_f = 0.20 (ethyl acetate/hexane = 1:4); white solid; yield 72% (55 mg); mp 139−140 °C (lit.[54] 141 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 7.02 (s, 2H), 6.38 (br s, 1H), 4.645 (d, J = 4 Hz, 2H), 3.89 (s, 6H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 153.3, 141.1, 138.3, 129.9, 128.9, 128.1, 127.8, 104.5, 61.0, 56.5, 44.4; IR (KBr) $\tilde{\nu}$ 3321 (w), 2941 (m), 2838 (m), 1697 (m), 1644 (s), 1585 (s), 1500 (s), 1463 (m), 1415 (s), 1334 (s), 1232 (s), 1127 (s), 1002 (s), 764 (m), 699 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{20}NO_4$ (M + H$^+$) 302.1392, found 302.1407.

N-Benzyl-4-nitrobenzamide (**3m**): R_f = 0.25 (ethyl acetate/hexane = 1:4); white solid; yield 68% (58 mg); mp 134−137 °C (lit.[55] 136−137 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8 Hz, 2H), 7.95 (d, J = 8 Hz, 2H), 7.39−7.37 (m, 5H), 6.46 (br s, 1H), 4.67 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 149.8, 140.0, 137.5, 129.1, 128.3, 128.2, 128.1, 124.0, 44.6; IR (KBr) $\tilde{\nu}$ 3449 (w), 2923 (s), 2848 (s), 1638 (m), 1344 (s), 1018 (s), 703 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}N_2O_3$ (M + H$^+$) 257.0926, found 257.0912.

N-Benzyl-4-methoxybenzamide (**3n**): R_f = 0.20 (ethyl acetate/hexane = 1:4); white solid; yield 69% (61 mg); mp 128−131 °C (lit.[56] 129−130 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8 Hz, 2H), 7.36−7.28 (m, 5H), 6.92 (d, J = 8 Hz, 2H), 6.33 (br s, 1H), 4.635 (d, J = 4 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.3, 138.5, 128.9, 128.9, 128.0, 127.7, 126.7, 113.9, 55.5, 44.2; IR (KBr) $\tilde{\nu}$ 3521 (w), 3294 (m), 1633 (s), 1538 (m), 1505 (s), 1255 (s), 1180 (m), 846 (m), 726 (m), 696 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}NO_2$ (M + H$^+$) 242.1176, found 242.1189.

N-Benzyl-4-fluorobenzamide (**3o**): R_f = 0.30 (ethyl acetate/hexane = 1:4); colorless solid; yield 73% (79 mg); mp 140−141 °C (lit.[57] 143−144 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8 Hz, 2H), 7.33 (br s, 5H), 7.08 (d, J = 8 Hz, 2H), 6.59 (br s, 1H), 4.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.8 (d, $^1J_{FC}$ = 250.4 Hz), 138.2, 130.6 (d, $^4J_{FC}$ = 3.1 Hz), 129.5 (d, $^3J_{FC}$ = 8.8 Hz), 128.9, 128.0, 127.7, 115.7 (d, $^2J_{FC}$ = 21.8 Hz), 44.3; IR (KBr) $\tilde{\nu}$ 3323 (m), 3068 (s), 2927 (s), 2848 (s), 1639 (m), 1544 (s), 1421 (s), 1360 (s), 1255 (s), 1057 (s), 854 (s), 723 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}FNO$ (M + H$^+$) 230.0981, found 230.0954.

N-Benzyl-3-nitrobenzamide (**3p**): R_f = 0.20 (ethyl acetate/hexane = 1:4); white solid; yield 71% (60 mg); mp 100−103 °C (lit.[58] 100−101 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.36−8.33 (m, 1H), 8.18−8.16 (m, 1H), 7.63 (t, J = 8 Hz, 1H), 7.38−7.28 (m, 5H), 6.73 (br s, 1H), 4.655 (d, J = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 148.3, 137.6, 136.0, 133.4, 130.0, 129.0, 128.1, 128.0, 126.2, 121.9, 44.6; IR (KBr) $\tilde{\nu}$ 3322 (w), 3087 (m), 1720 (m), 1644 (s), 1528 (s), 1350 (s), 1322 (m), 1080 (m), 911 (m), 815 (m), 719 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}N_2O_3$ (M + H$^+$) 257.0921, found 257.0948.

N-Benzyldecanamide (**3q**): R_f = 0.33 (ethyl acetate/hexane = 1:4); colorless solid; yield 64% (75 mg); mp 60−61 °C (lit.[59] 60−62 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 5.74 (br s, 1H), 4.445 (d, J = 4 Hz, 2H), 2.21 (t, J_1 = J_2 = 8 Hz, 2H), 1.67−1.64 (m, 2H), 1.29−1.26 (m, 12H), 0.88 (t, J_1 = J_2 = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 138.4, 128.8, 128.0, 127.6, 43.8, 37.0, 32.0, 29.5, 29.4, 29.4, 29.4, 25.9, 22.8, 14.2; IR (KBr) $\tilde{\nu}$ 3438 (w), 2919 (m), 2850 (m), 1633 (m), 695 (w) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{28}NO$ (M + H$^+$) 262.2165, found 262.2189.

N,N-Dibenzylcyclohexanecarboxamide (**3r**): R_f = 0.34 (ethyl acetate/hexane = 1:4); colorless solid; yield 53%; mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 6H), 7.25−7.15 (m, 4H), 4.58 (s, 2H), 4.46 (s, 2H), 2.58−2.52 (m, 1H), 1.81−1.63 (m, 7H), 1.30−1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 137.7, 137.0, 129.0, 128.6, 128.1, 127.7, 127.3, 126.5, 77.4, 77.1, 76.8,

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49.7, 47.8, 40.9, 29.8, 25.8; IR (KBr) $\tilde{\nu}$ 3059 (s), 3029 (s), 2927 (m), 2854 (m), 1643 (m), 1494 (s), 1450 (m), 1359 (s), 1244 (s), 1205 (m), 1176 (s), 1079 (s), 1028 (s), 948 (s), 731 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO$ (M + H^+) 308.2009, found 308.2026.

*N-Benzylcyclohexanecarboxamide (**3s**):* R_f = 0.30 (ethyl acetate/hexane = 1:4); colorless solid; yield 58%; mp 110−114 °C (lit.[60] 113 °C); 1:4 mixture of rotamers (data for major isomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 10H), 7.25 (s, 1H), 5.73 (br s, 1H), 4.43 (d, J = 4 Hz, 2H); 2.18−2.05 (m, 1H), 1.99−1.85 (m, 2H), 1.84−1.75 (m, 2H), 1.73−1.61 (m, 2H), 1.54−1.39 (m, 2H), 1.35−1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 138.6, 128.8, 127.8, 127.5, 45.7, 44.3, 43.5, 29.8, 25.8; IR (KBr) $\tilde{\nu}$ 3286 (m), 3085 (s), 3028 (s), 2927 (m), 2851 (s), 1639 (m), 1543 (m), 1492 (s), 1449 (s), 1311 (s), 1258 (s), 1219 (s), 1140 (s), 1079 (s), 991 (s) cm-1; HRMS (ESI-TOF) calcd for $C_{14}H_{20}NO$ (M + H^+) 218.1539, found 218.1545.

*N,N-Dibenzyl-4-isopropylbenzamide (**3t**):* R_f = 0.30 (ethyl acetate/hexane = 0.5:4.5); colorless solid; yield 78% (89 mg); mp 80−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8 Hz, 2H), 7.34−7.28 (m, 4H), 7.24−7.18 (m, 6H), 7.13 (br s, 2H), 4.66 (br s, 2H), 4.40 (br s, 2H), 2.95−2.78 (m, 1H), 1.19 (d, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 150.8, 137.1, 136.7, 133.6, 128.9, 128.8, 128.5, 127.7, 127.5, 127.1, 127.0, 126.7, 51.7, 46.9, 34.1, 23.9; IR (KBr) $\tilde{\nu}$ 3442 (w), 3031 (m), 2961 (m), 1633 (m), 1452 (m), 1417 (m), 1258 (m), 1148 (m), 993 (m), 842 (s), 733 (m), 699 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{26}NO$ (M + H^+) 344.2009, found 344.2042.

*N,N-Dibenzyl-2-bromobenzamide (**3u**):*[61] R_f = 0.30 (ethyl acetate/hexane = 0.5:4.5); colorless solid; yield 69% (70 mg); mp 130−134 °C (no literature report on melting points); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.40−7.30 (m, 10H), 7.17 (br s, 2H), 4.73 (s, 2H), 4.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 136.2, 129.7, 128.9, 128.7, 128.6, 128.4, 127.7, 127.6, 127.1, 126.7, 51.6, 46.9; IR (KBr) $\tilde{\nu}$ 3436 (w), 3081 (s), 3059 (s), 3028 (s), 2923 (s), 1637 (m), 1420 (m), 1248 (m), 1144 (s), 1027 (s), 990 (s),732 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{19}BrNO$ (M + H^+) 380.0650, found 380.0629.

*N,N-Dibenzyl-4-cyanobenzamide (**3v**):* R_f = 0.40 (ethyl acetate/hexane = 1:4); colorless solid; yield 62% (76 mg); mp 115−117 °C (lit.[50] 114−116 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.675 (d, J = 12 Hz, 2H), 7.57 (d, J = 8 Hz, 2H), 7.39−7.30 (m, 8H), 7.11 (br s, 2H), 4.72 (br s, 2H), 4.34 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 140.6, 136.5, 135.8, 132.5, 129.2, 128.9, 128.6, 128.1, 127.9, 127.5, 126.9, 118.1, 113.6, 51.5, 47.4; IR (KBr) $\tilde{\nu}$ 3442 (w), 2927 (s), 2229 (s), 1638 (m), 1425 (s), 1261 (s), 1077 (s), 991 (s), 847 (s), 750 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{19}N_2O$ (M + H^+) 327.1497, found 327.1482.

*N-Benzyl-4-chlorobenzamide (**3w**):* R_f = 0.27 (ethyl acetate/hexane = 1:4); colorless solid; yield 67% (58 mg); mp 158−160 °C (lit.[62] 162 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 7.36−7.30 (m, 5H), 6.46 (br s, 1H), 4.625 (d, J = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.0, 137.9, 132.8, 131.6, 128.9, 128.5, 128.0, 127.8, 44.3; IR (KBr) $\tilde{\nu}$ 3317 (w), 1634 (m), 1416 (m), 1093 (s), 849 (s), 711 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}ClNO$ (M + H^+) 246.0686, found 246.0672.

*N-Benzylbenzamide (**3x**):* R_f = 0.3 (ethyl acetate/hexane = 1:4); colorless solid; yield 71% (69 mg); mp 105−107 °C (lit.[53] 106 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8 Hz, 2H), 7.52−7.27 (m, 8H), 6.49 (br s, 1H), 4.645 (d, J = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 138.3, 134.5, 131.6, 128.9, 128.7, 128.0, 127.7, 127.0, 44.2; IR (KBr) $\tilde{\nu}$ 3329 (w), 1641 (s), 1577 (m), 1547 (m), 1418 (m), 1258 (m), 727 (m), 692 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{14}NO$ (M + H^+) 212.1070, found 212.1065.

*N-Benzyl-4-bromobenzamide (**3y**):* R_f = 0.40 (ethyl acetate/hexane = 1:4); colorless solid; yield 58% (45 mg); mp 157−160 °C (lit.[63] 160−162 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8 Hz, 2H), 7.56 (d, J = 8 Hz, 2H), 7.38−7.29 (m, 5H), 6.37 (br s, 1H), 4.635 (d, J = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.0, 133.3, 131.9, 129.0, 128.7, 128.1, 127.9, 126.4, 44.4; IR (KBr) $\tilde{\nu}$ 3437 (w), 2918 (s), 1634 (m), 1550 (m), 1257 (s), 846 (s), 731 (s), 701 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}BrNO$ (M + H^+) 290.0181, found 290.0164.

*N-Benzyl-4-cyano-N-methylbenzamide (**3z**):*[64] R_f = 0.20 (ethyl acetate/hexane = 1:4); colorless oil; yield 73% (67 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.64 (m, 4H), 7.54 (d, J = 8 Hz, 4H), 7.38−7.28 (m, 8H), 7.12 (d, J = 8 Hz, 2H), 4.74, 4.44 (two singlets for two rotamers, 4H), 3.05, 2.82 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 136.4, 132.4, 129.1, 128.9, 128.8, 128.2, 128.0, 127.8, 127.7, 127.5, 126.5, 118.1, 113.4, 55.0, 50.9, 36.8, 36.4; IR (KBr) $\tilde{\nu}$ 3454 (w), 3085 (s), 3063 (s), 3028 (s), 2925 (m), 2230 (m), 1633 (m), 1451 (m), 1402 (m), 1264 (m), 1070 (s), 850 (s), 702 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2O$ (M + H^+) 251.1184, found 251.1201.

*N-Benzyl-2-iodo-N-methylbenzamide (**3aa**):*[65] R_f = 0.40 (ethyl acetate/hexane = 1:4); colorless oil; yield 67% (60 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.29 (m, 16H), 7.18 (br s, 2H), 4.77, 4.52 (two singlets for two rotamers, 4H), 3.03, 2.86 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.7, 139.3, 137.1, 136.7, 136.2, 133.2, 130.1, 129.7, 128.9, 128.7, 128.5, 128.4, 128.3, 127.9, 127.6, 127.3, 127.1, 126.9, 55.3, 50.9, 37.1, 33.3; IR (KBr) $\tilde{\nu}$ 3459 (w), 3061 (m), 3029 (m), 2923 (m), 1631 (s), 1479 (m), 1450 (m), 1400 (m), 1264 (m), 1069 (s), 718 (m), 698 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}INO$ (M + H^+) 352.0193, found 352.0165.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds; crystal data (CIF) for **3c** and **3l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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