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# Metal Free Thermal Activation of Molecular Oxygen Enabled Direct α-$CH_2$-Oxygenation of Free Amines

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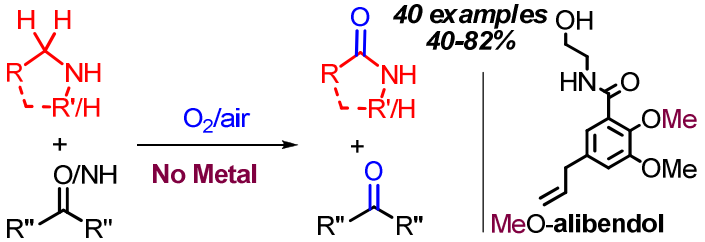


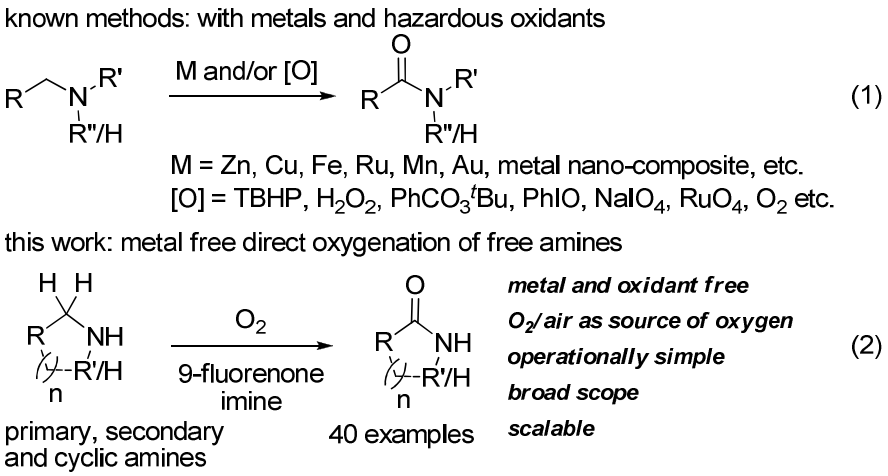

**Abstract:** Direct oxidation of α-$CH_2$ group of free amines is hard to achieve due to the higher reactivity of amine moiety. Therefore, oxidation of amines involves the use of sophisticated metallic reagents/catalyst in the presence or absence of hazardous oxidants under sensitive reaction conditions. A novel method for direct C-H oxygenation of aliphatic amines through a metal free activation of molecular oxygen has been developed. Both activated and unactivated free amines were oxygenated efficiently to provide a wide variety of amides (primary, secondary) and lactams under operationally simple conditions without the aid of metallic reagents and toxic oxidants. The method has been applied to the synthesis of highly functionalized amide containing medicinal drugs, such as O-Me-alibendol and –buclosamide.

## Introduction:

Amides and lactams are ubiquitously found as the core structural unit of both natural and synthetic molecules which are relevant to advanced materials and medicines.[1] Conventional methods for the amide synthesis utilize coupling reaction of carboxylic acids or its activated deriva-

tives with amines in the presence of ~~expensive~~ coupling reagents which produce a stoichiometric amount of byproducts.[2] To avoid this drawback, amidation reactions using catalytic amounts of coupling reagents have been developed.[3] Additionally, conversions of alcohol and aldehyde,[4,5] oximes and nitrile,[6] $\alpha$-keto acids, and $\alpha$-bromo nitroalkanes[7] to amides were developed as alternative direct methods. However, relatively less number of examples were known for the direct oxidation of $\alpha$-methylene group of free amines to corresponding amides because of the higher reactivity of the amine moiety. The known examples primarily involve metal-based reagents/catalysts or hazardous inorganic and organic oxidants (Scheme 1, eq 1).[8,9]

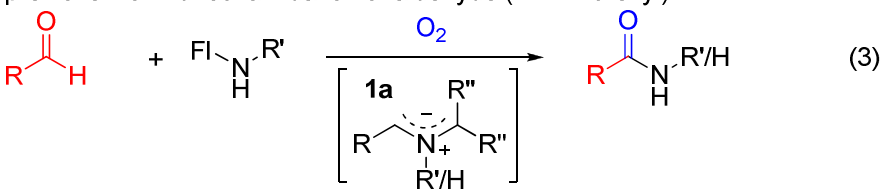
**Scheme 1. Synthesis of amides and lactams via direct oxygenation of amines.**




Molecular oxygen would be a viable substitute of hazardous inorganic or organic oxidants. However, photochemical or metal mediated activation is generally required to activate kinetically inert oxygen before its reaction with other organic molecules.[10] Therefore, in some cases, molecular oxygen acts as the viable oxidant only in the presence of sophisticated metallic reagents/ catalysts.[9] Importantly, $\alpha$-oxygenation of free amines to amides is generally hard to achieve due to the associated side reactions producing corresponding imines and nitriles, and thus protection of amine moiety is required before oxidation reaction.[11] Therefore, the development of novel

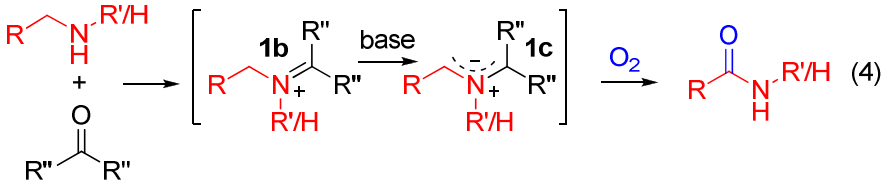
methodology for direct oxygenation of amines that work under the conditions free of metallic reagents/catalysts and hazardous oxidants avoiding undesired side reaction would be of particular importance. Here in, we report the first example of one-step, metal free and operationally simple direct oxygenation of free aliphatic amines to amides and lactams using molecular oxygen as the source of amide oxygen (eq 2).

previous work: direct amidation of aldehyde (Fl = fluorenyl)




(3)

*hypothesis for direct oxygenation of free amines*




(4)

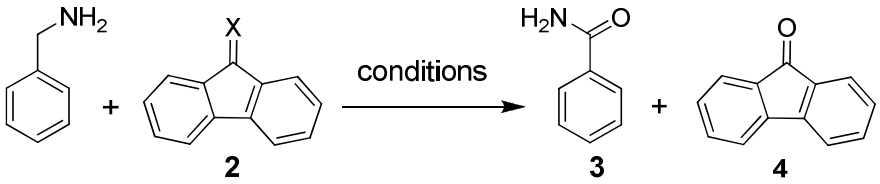
A biomimetic domino amination-oxygenation strategy for direct conversion of aldehydes to amides has been developed recently by our group (eq 3).[5] An azomethine ylide related to **1a**,[5, 12] which was formed from aldehyde and fluorenyl amine, reacted with molecular oxygen/air to provide the corresponding amide. We anticipated the formation of an iminium ion **1b**/zwitterion **1c** from the reaction of an aliphatic amine with the suitable ketone or its derivatives (eq 4).[12] Subsequent reaction of intermediate zwitterion **1c** with molecular oxygen could furnish desired amides. In this way, direct $\alpha$-oxygenation of free amines to amides can be achieved under metal and oxidant free conditions without forming undesired side products, such as imines and nitriles.

Results and Discussion:

We began our investigation with a reaction of benzylamine and 9-fluorenone (**2a**) in the presence of molecular oxygen (Table 1). However, the expected benzamide (**3**) was not formed (entry

1). Similarly, the reactions in the presence of various other carbonyl compounds were also found to be unsuccessful in providing the desired benzamide (SI, Table s1). Interestingly, benzylamine reacted with 9-fluorenone in the presence of Bronsted acid and molecular oxygen to provide the desired amide with maximum 40% isolated yield (entry 2). This indicated that the initial imine formation from the amine and carbonyl compound is crucial in achieving the $\alpha$-oxygenation of amines. We then decided to use 9H-fluoren-9-imine (**2b**) instead of 9-fluorenone to facilitate the imine formation via transimination reaction with benzylamine. Expectedly, the desired benzamide was isolated with 62% yield from the reaction of benzylamine with 9H-fluoren-9-imine in refluxing toluene for 4 h under oxygen environment (entry 3). An increase in the yield to 70% was observed upon an increase in the reaction time to 12 h (entries 4, 5, 7). Further improvement of the yield was not observed employing other reaction conditions using different solvents, temperature, etc. Slightly lower yield was obtained from the reaction in the presence of air as compared to the reaction carried out in the presence of oxygen (entry 13).

**Table 1: Screening of reaction conditions.**[a]




| entry | conditions | Isolated yield (%) |
|---|---|---|
| 1 | **2a**, oxygen, toluene, RT, 24 h | 0 |
| 2[b] | **2a**, oxygen, amberlyst-15, toluene, reflux, 24 h | 40 |
| 3 | **2b**, oxygen, toluene, reflux, 4 h | 62 |

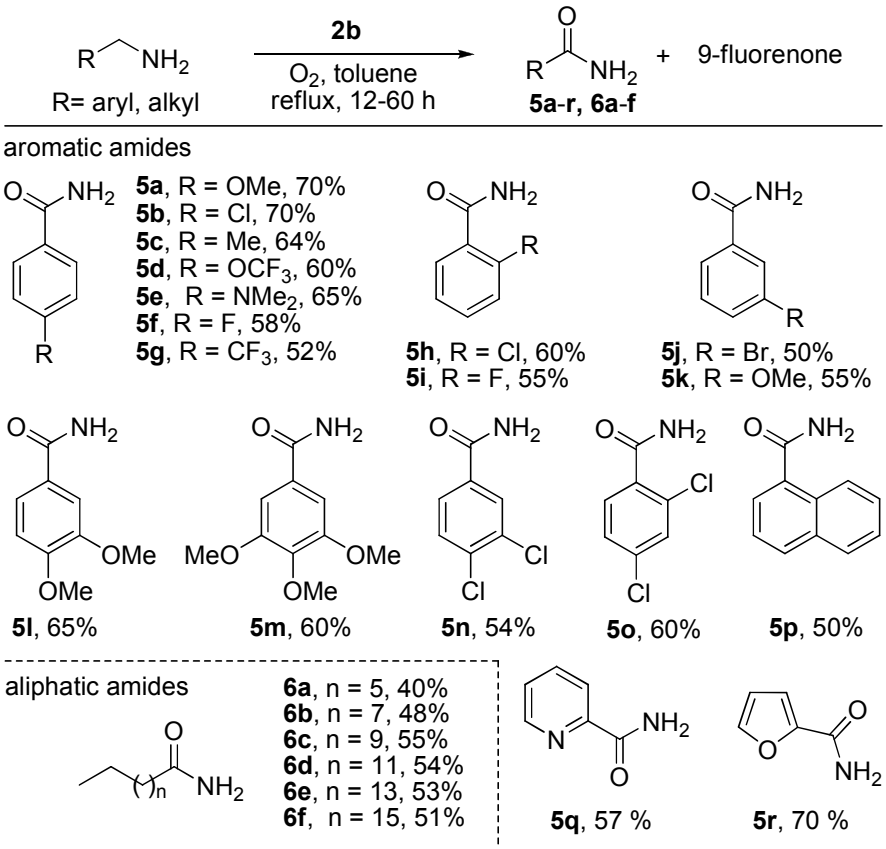
| | | |
|---|---|---|
| 4 | **2b**, oxygen, toluene, reflux, 8 h | 67 |
| 5 | **2b**, oxygen, toluene, reflux, 12 h | 70 |
| 6 | **2b**, oxygen, toluene, 80 $^{o}$C, 24 h | 65 |
| 7 | **2b**, oxygen, toluene, reflux, 24 h | 70 |
| 8[c] | **2b**, oxygen, toluene, reflux, 24 h | 25 |
| 9 | **2b**, oxygen, benzene, reflux, 24 h | 65 |
| 10[d] | **2b**, oxygen, $Et_3N$, toluene, reflux, 12 h | 70 |
| 11 | **2b**, oxygen, xylene, reflux, 12 h | 70 |
| 12 | **2b**, oxygen, xylene, 110 $^{o}$C, 12 h | 69 |
| 13[e] | **2b**, toluene 110 $^{o}$C, 12 h | 57 |
| 14[d, e] | **2b**, toluene 110 $^{o}$C, $Et_3N$, 12 h | 48 |
| 15 | **2b**, oxygen, $^{t}$BuOK, toluene, reflux, 12 h | 72 |
| 16 | **2b**, oxygen, DCM, reflux, 24 h | 15 |
| 17 | **2b**, oxygen, toluene, RT, 24 h | 5 |

[a]Amine (0.56 mmol) was reacted with **2** (0.56 mmol) in air or oxygen atmosphere. [b]Use of 50 mol% of the **2a** provided only 35% yield. [c]Catalytic (20 mol%) amount of **2b** was used. [d]Reactions were carried out in the presence of 20 mol% of triethylamine. [e]Reactions were performed in the presence of an air balloon.

Next, the best conditions were used to investigate the substrate scope of this novel amidation reaction (Scheme 2). Arylmethylamines having electron donating as well as electron withdrawing groups at different positions of aryl moiety provided the desired benzamides **5a-p** with good

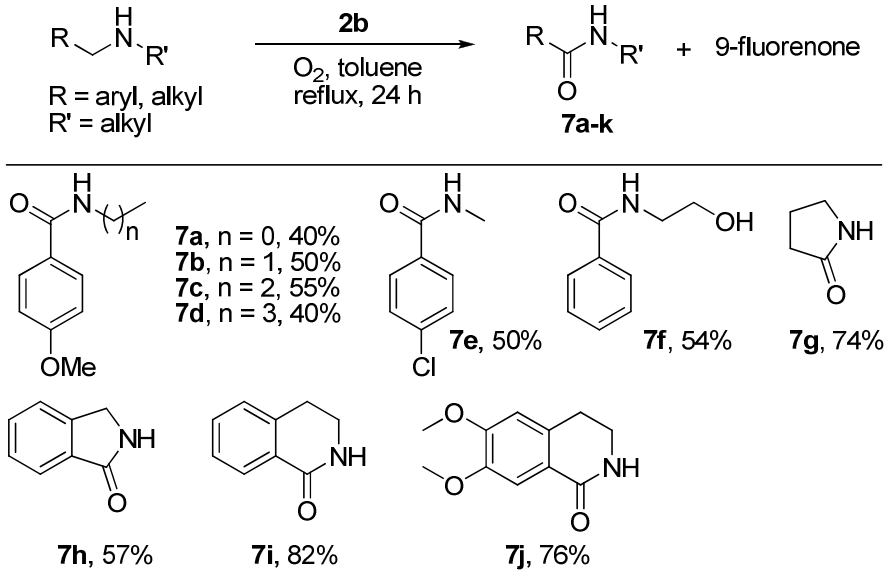
to moderate yields. Amines containing heteroaryl group like picolylamine or 2-amino furan also reacted smoothly to afford corresponding amides **5q** and **5r**, respectively. Importantly, selective $\alpha$-oxygenation of amines occurred to provide the corresponding amides while other reactive hetero-functional groups (e.g, –OR, -Br, -F, -Cl, -$NMe_2$) remained unreacted.

**Scheme 2. Scope of oxygenation of primary aromatic and aliphatic amines.**




The scope of direct C-H oxygenation of unactivated aliphatic primary amines was tested next. Accordingly, the long chain aliphatic primary amines with varying chain lengths were reacted to obtain corresponding amides **6a-f**. Higher reaction time (60 h) was required to obtain the amides with moderate to good yields.

**Scheme 3. Scope in oxidation of secondary acyclic and cyclic amines.**



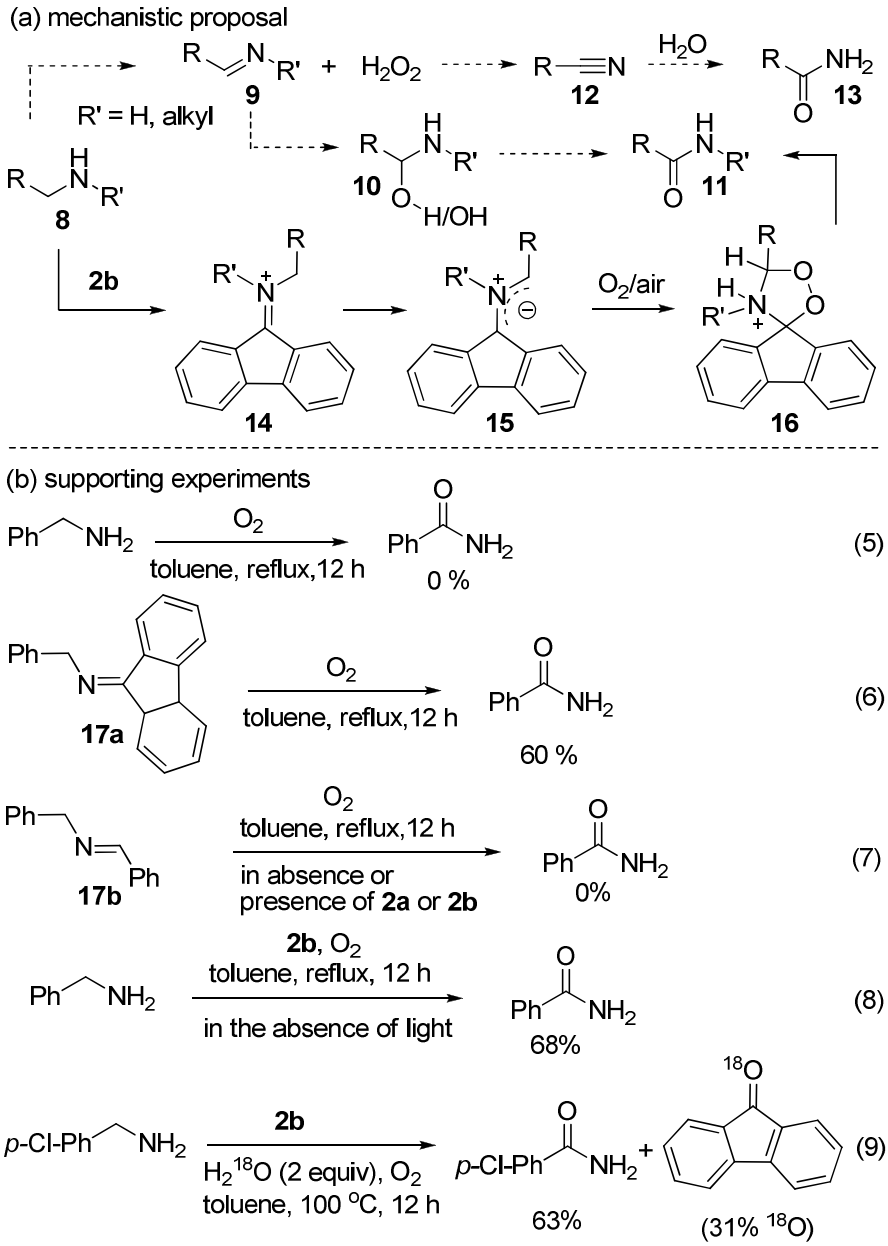

With the success in oxygenation of primary amines, reactions using secondary amines were carried out to examine the generality of this method (Scheme 3). Oxidation of cyclic and acyclic aliphatic secondary amines occurred smoothly to yield corresponding secondary benzamides **7a-f** and lactams **7g-j**, respectively. A longer reaction time (24 h) of secondary amines as compared to that of primary benzylamines was necessary for good conversion due to the reduced reactivity of sterically demanding secondary amines. However, N-substituted benzamides **7a-f** were isolated with slightly lower yields as compared to lactams. Interestingly, $\alpha$-C-H oxygenation of pyrrolidine was achieved using 9-fluorenone to obtain γ-lactam with 60% isolated yield (SI, Table s2). However, better yields of the lactams were obtained using 9H-fluoren-9-imine (**2b**). Tetrahydroisoquinoline gave the highest yield (82%) of the desired lactam.

To demonstrate the synthetic utility of this method, a reaction of benzylamine was carried out in gram scale (1.8 g) under optimized conditions to afford the desired benzamides in grams quan-

tity (1.1 g). 9-fluorenone, which was produced (with 88%) as the only by product, can be easily separated via simple washing and recycled after its conversion to 9H-fluoren-9-imine.

Different mechanistic possibilities, which are shown in scheme 4a, may be operative for the direct conversion of amines to corresponding amides and lactams. Direct oxidation of amines **8** by molecular oxygen followed by reaction of resulting imines **9** (via **10**) under oxidizing conditions may lead to corresponding amides **11**.[13] Conversion of imines **9** to corresponding nitriles **12** and its subsequent hydrolysis could also be another pathway for formation of amide **13**. These mechanistic possibilities can be eliminated as the reaction of only benzylamine under optimized conditions did not produce the desired amide (Scheme 4b, eq 5). On the other hand, the reaction of preformed imine **17a** under the same reaction conditions provided the desired benzamide with 60% yield (eq 6). However, the yield of benzamide increased to 72% when the reaction was carried out in the presence of catalytic amount of triethylamine. Therefore, the reaction proceeded through the imine/iminum ion **14** which could be formed from the condensation of amine **8** and 9H-fluoren-9-imine (**2b**). Amine assisted deprotonation of **14** to form the azomethine anion/ylide **15** which subsequently reacted with molecular oxygen to provide the peroxide intermediate **16**.[12g] Related 1,2,4-dioxazolidine were known to be prepared from the reaction of $\alpha$-hydroperoxy-amine with carbonyl compounds and from the reaction of carbonyl oxide with imine.[14] Thermal disintegration of peroxide **16** provided the desired amide/lactam and 9-fluorenone.[5, 14] Interestingly, imine **17b** derived from benzaldehyde and benzylamine did not provide the desired amides under the standard conditions (eq 7). Therefore, easy formation of azomethine anion/ylide **15** and its enhanced stability due to the aromatic nature of fluorenyl anion turned out to be crucial for this transformation.

**Scheme 4. (a) Proposed mechanism. (b) Controlled and labelling experiments.**

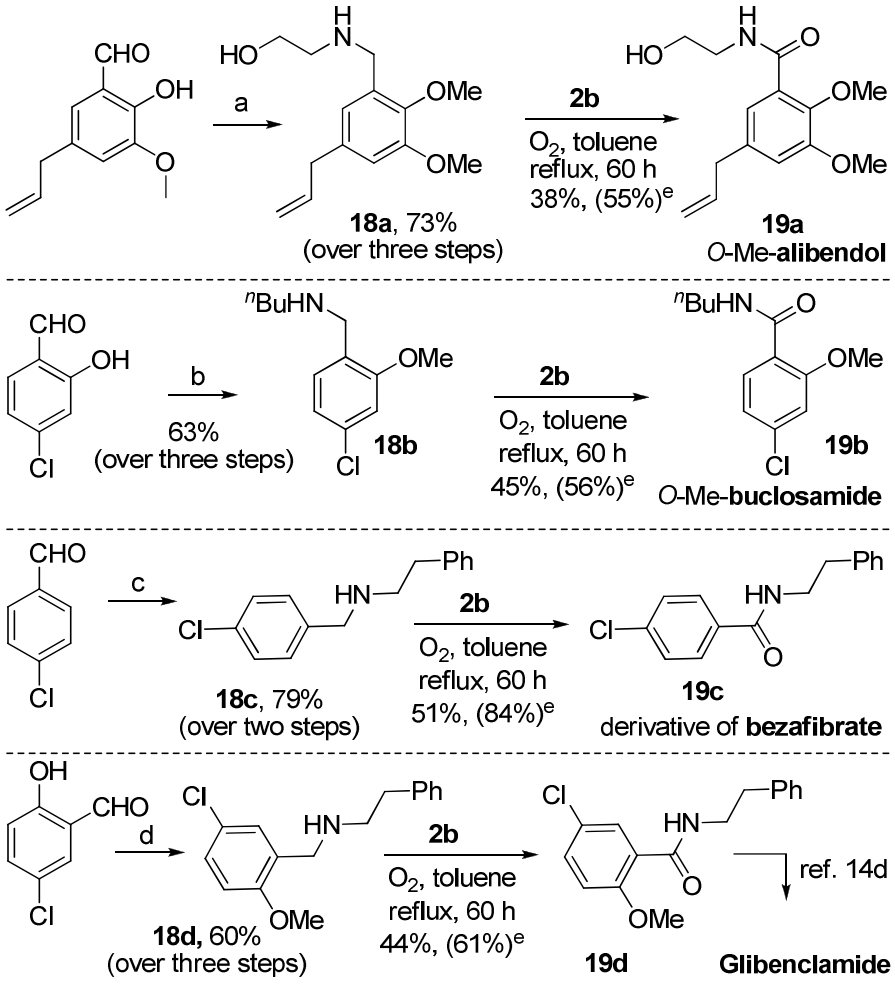



Alternatively, imine/iminum ion **14** or its regioisomer could participate in an Alder-ene reaction with singlet oxygen to produce corresponding hydroperoxides which could subsequently react directly or through the formation of **16** to provide the desired amide.[15] However, the reaction of imine **17b** in the presence of either **2a** or **2b** did not produce the desired amide under

standard reaction condition (eq 7). Moreover, the desired amide was formed with 68% from a reaction which was carried out without exposing the reaction mixture to the light (eq 8). Therefore, these observations are unsupportive to the singlet-oxygen-ene reaction pathway.

*p*-Chlorobenzylamine and **2b** were reacted under standard reaction conditions in the presence of $H_2O^{18}$ to identify the source of amide oxygen (eq 9). Expectedly, the formation of $^{18}O$-amide was not observed which supported our proposed mechanism that the amide oxygen has been incorporated from molecular $O_2$ and not from $H_2O$. Incorporation of 31% $^{18}O$ into 9-fluorenone occurred through the partial hydrolysis of 9H-fluoren-9-imine in the presence of $H_2{}^{18}O$.

**Scheme 5. Application in syntheses of medicinal drugs and their derivatives.**



(a) (i) $Me_2SO_4$, $K_2CO_3$, acetone, reflux, 12 h, 90%, (ii) 2-aminoethanol, 4 Å MS, DCM, rt, 12 h, 85%, (iii) $NaCNBH_3$, MeOH, 40 $^oC$, 4 h, 95%; (b) (i) $Me_2SO_4$, $K_2CO_3$, acetone, reflux, 12 h, 80%, (ii) n-butylamine, 4 Å MS, DCM, rt, 12 h, 88%, (iii) $NaCNBH_3$, MeOH, 40 $^oC$, 4 h, 90%; (c) (i) 2-phenylethanamine, 4 Å MS, DCM, rt, 12 h, 88%; (ii) $NaCNBH_3$, MeOH, 40 $^oC$, 4 h, 90%; (d) (i) $Me_2SO_4$, $K_2CO_3$, acetone, reflux, 12 h, 78%; (ii) 2-phenylethanamine, 4 Å MS, DCM, rt, 12 h, 85%, (iii) $NaCNBH_3$, MeOH, 40 $^oC$, 4 h, 90%. $^e$Yields based on recovered starting materials.

Amide functionality in medicinal drugs is generally installed via condensation of the corresponding carboxylic acid derivatives with the amines. The overall synthetic sequence involve the use of toxic oxidants and coupling reagents.[16] We applied this novel strategy for the direct conversion of amines to amides under metal and toxic oxidant free conditions for the synthesis of the analogues of amide containing medicinal drugs (Scheme 5). O-Me-alibendol **19a** and –buclosamide **19b** were obtained readily from the reaction of respective secondary amines **18a** and **18b**, which were prepared from commercially available aldehydes. Similarly, a derivative of bezafibrate **19c** and synthetic precursor **19d** for glibenclamide were prepared from benzyl amines **18c** and **18d**, respectively.

Conclusion:

In summary, we have developed a conceptually novel method for direct $\alpha$-oxidation of free aliphatic amines to amides and lactams without the aid of metallic reagents and toxic oxidants. $\alpha$-C(sp3)-H oxygenation was achieved through a metal free thermal activation of molecular oxygen. The reaction is operationally simple, efficient and applicable to a broad class of primary amines (activated benzyl or unactivated alkyl amines), cyclic and acyclic secondary amines. The

elegant syntheses of highly functionalized *N*-alkyl benzamide moieties of medicinal drugs using this method showed its synthetic potential.

Experimental Section:

**General**: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Commercial grade dichloromethane ($CH_2Cl_2$), xylene, benzene and toluene were distilled over $CaH_2$ before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. $^1H$, $^{13}C$ NMR spectroscopy: *Varian Mercury plus 400 MHz, Bruker 600 MHz, Jeol 400 MHz* (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS δ ($^1H$) 0.0 ppm, δ ($^{13}C$) 0.0 ppm) which was used as the inner reference. Otherwise, the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ ($^1H$) 7.26 ppm, δ ($^{13}C$) 77.2 ppm; $CD_3OD$, ($^1H$) 3.31 ppm, δ ($^{13}C$) 49.0 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

**General procedure for the synthesis of aryl amides from primary benzylamines (I):**

Primary amine (0.56 mmol) was added to a solution of 9*H*-fluoren-9-imine (1 equiv) in toluene (2 mL) and the mixture was refluxed for 12 h. After the disappearance of the starting material indicated from TLC, solvent was evaporated in vacuum and crude product was subjected to silica gel chromatography (EtOAc: hexane, 1:1) to afford the analytically pure amides.

**Benzamide**[4d] **(3):** White solid (47 mg, 70%). **4-Methoxybenzamide** [5] **(5a):** White solid (60 mg, 70%). **4-Chlorobenzamide**[4d] **(5b):** White solid (61 mg, 70%). **4-Methylbenzamide**[4d] **(5c):** White solid (49 mg, 65%). **4-(trifluoromethoxy)benzamide**[4c] **(5d):** White solid (69 mg, 60%). **4-(dimethylamino)benzamide**[5] **(5e):** White solid (60 mg, 65%). **4-Fluorobenzamide**[8c] **(5f):** White solid (45 mg, 58%). **4-(trifluoromethyl)benzamide**[8f] **(5g):** White solid (53 mg, 50%). **2-Chlorobenzamide**[5] **(5h):** White solid (52 mg, 60%). **2-Fluorobenzamide**[6g] **(5i):** White solid (43 mg, 55%). **3-Bromobenzamide**[5] **(5j):** White solid (56 mg, 50%). **3-Methoxybenzamide**[8c] **(5k):** White solid (47 mg, 55%). **3,4-Dimethoxybenzamide**[5] **(5l):** White solid (66 mg, 65%). **3,4,5-Trimethoxybenzamide**[5] **(5m):** White solid (72 mg, 60%). **3,4-Dichlorobenzamide**[17c] **(5n):** White solid (68 mg, 54%). **2,4-Dichlorobenzamide**[5] **(5o):** White solid (67 mg, 63%). **1-Naphthamide**[4d] **(5p):** White solid (48 mg, 50%). **Picolinamide**[4d] **(5q):** White solid (38 mg, 56%). **Furan-2-carboxamide** [5] **(5r):** White solid (44 mg, 70%).

**General procedure for the synthesis of primary aliphatic amides from primary amines (GP II):** Primary amine (0.56 mmol) was added to a solution of 9*H*-fluoren-9-imine (1 equiv) in toluene (2 mL) and the mixture was refluxed for 60 h. After the disappearance of the starting material indicated from TLC, solvent was evaporated in vacuum and crude product was subjected to silica gel chromatography (EtOAc: hexane, 1:1) to afford the analytically pure amides.

**Octanamide**[11c] **(6a):** White solid (32 mg, 40%). **Decanamide**[17e] **(6b):** White solid (46 mg, 48%). **Dodecanamide**[11c] **(6c):** White solid (62 mg, 55%). **Tetradecanamide**[17a] **(6d):** White solid (69 mg, 54%).

**Palmitamide (6e):** According to general procedure II, hexadecylamine (0.14 mL, 0.56 mmol) and 9*H*-fluoren-9-imine **2b** (0.10 g, 0.56 mmol) in toluene (2 mL) were refluxed for 60 h and

column chromatography (silica gel; EtOAc: hexane, 1:1) of the crude product gave **6e** as white solid (76 mg, 53%). Mp 103-104 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$) δ = 5.48 (s, 1H), 5.42 (s, 1H), 2.21 (t, *J* = 7.8 Hz, 2H), 1.65 – 1.60 (m, 2H), 1.33 – 1.24 (m, 24H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$) δ = 175.8, 36.2, 32.1, 29.89, 29.87, 29.85, 29.80, 29.7, 29.6, 29.5, 29.4, 25.7, 22.9, 14.3 ppm. (Reduced numbers of $^{13}$C signals is observed due to overlapping). HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{16}H_{34}NO$ 256.2635; Found 256.2638.

**Stearamide (6f):** According to general procedure II, octadecylamine (0.15 mL, 0.56 mmol) and 9*H*-fluoren-9-imine **2b** (0.10 g, 0.56 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 1:1) of crude gave **6f** as white solid (82 mg, 51%). Mp 106-107 $^{o}$C. $^{1}$H NMR (600 MHz, $CDCl_3$) δ = 5.51 (s, 1H), 5.42 (s, 1H), 2.21 (t, *J* = 7.8 Hz, 2H), 1.65 – 1.60 (m, 2H), 1.34 – 1.22 (s, 28H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$) δ = 175.8, 36.1, 32.1, 29.9, 29.83, 29.78, 29.65, 29.5, 29.4, 25.7, 22.9, 14.3 ppm. (Reduced numbers of $^{13}$C signals is observed due to overlapping). HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{18}H_{38}NO$ 284.2948; Found 284.2946.

**General procedure for the synthesis of Secondary Amides or lactams from secondary acyclic or cyclic amines (III):**

Secondary acyclic or cyclic amine (0.56 mmol) was added to a solution of 9*H*-fluoren-9-imine (0.56 mmol) in toluene (2 mL) and the mixture was refluxed for 24 h. After the disappearance of the starting material indicated from TLC, solvent was evaporated in vacuum and crude product was subjected to silica gel chromatography (silica gel; EtOAc: hexane, 1:1) to afford the analytically pure amides and lactams.

**4-Methoxy-*N*-methylbenzamide**[5] **(7a):** White solid (37 mg, 40%).

***N*-ethyl-4-methoxybenzamide**[5] **(7b):** Column chromatography (silica gel; EtOAc: hexane, 1:2) gave **7b** as an oil (50 mg, 50%).

**4-Methoxy-*N*-propylbenzamide**[5] **(7c):** Column chromatography (silica gel; EtOAc: hexane, 1:3) gave **7c** as an oil (60 mg, 55%).

***N*-butyl-4-methoxybenzamide**[5] **(7d):** Column chromatography (silica gel; EtOAc: hexane, 1:3) gave **7d** as an oil (50 mg, 40%).

**4-Chloro-*N*-methylbenzamide**[5] **(7e):** White solid (48 mg, 50%).

***N*-(2-hydroxyethyl)benzamide**[17f] **(7f): C**olumn chromatography (silica gel; EtOAc: hexane, 2:1) gave **7f** as an oil (50 mg, 54%).

**Pyrrolidin-2-one**[8a] **(7g):** Oil (36 mg, 75%).

**Isoindolin-1-one**[17b] **(7h):** White solid (43 mg, 57%).

**3,4-Dihydroisoquinolin-1(2H)-one**[9d] **(7i):** Oil (71 mg, 82%).

**3,4-Dihydro-6,7-dimethoxyisoquinolin-1(2H)-one**[17d] **(7j):** Column chromatography (silica gel; EtOAc: hexane, 2:1) gave **7j** as white solid (88 mg, 76%).

**2-(5-allyl-2,3-dimethoxybenzylamino)ethanol (18a):** 5-allyl-2-hydroxy-3-methoxybenzaldehyde (0.28 g, 1.43 mmol), dimethyl sulphate (0.54 g, 4.30 mmol ) and potassium carbonate (0.59 g, 4.30 mmol) in acetone (5 mL) were refluxed for 12 h. After completetion of the starting materials (indicated from TLC), solvent was evaporated and residue was purified by coloum chromatography (silica gel; EtOAc: hexane, 1:20) to afford 5-allyl-2,3-dimethoxybenzaldehyde as an oil (0.27 g, 90%). Then 5-allyl-2,3-dimethoxybenzaldehyde (0.10

g, 0.49 mmol) and ethanolamine (30 mg, 0.49 mmol) were dissolved in dichloromethane (3 mL) and the mixture was stirred at room temperature for 12 h in the presence of 4Å MS (0.1 g). After consumption of starting material, molecular sieves were filtered out and the solvent was evaporated to give 2-(5-allyl-2,3-dimethoxybenzylideneamino)ethanol (0.10 g, 85%). 2-(5-allyl-2,3-dimethoxybenzylideneamino)ethanol (0.10 g, 0.40 mmol) was treated with sodium cyanoborohydride (51 mg, 0.80 mmol ) in MeOH (3 mL) at 40 °C for 4 h. MeOH was then evaporated and residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (20 mL of brine and 20 mL of water), dried ($Na_2SO4$) and concentrated in vaccua. Colum chromatography (silica gel; EtOAc: hexane, 1:3) of the residue gave **18a** as an oil (94 mg, 95%). $^1$H NMR (400 MHz, $CDCl_3$) δ = 6.77 (s, 1H), 6.64 (s, 1H), 5.94 – 5.89 (m, 1H), 5.10 – 5.05 (m, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.62 – 3.57 (m, 4H), 3.32 (d, *J* = 6.5 Hz, 2H), 2.63 – 2.60 (m, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$) δ = 152.5, 146.1, 137.4, 135.6, 132.4, 122.5, 115.8, 111.6, 60.7, 58.9, 55.7, 54.9, 52.3, 40.1 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{14}H_{22}NO_3$ 252.1594; Found 252.1594.

**5-Allyl-*N*-(2-hydroxyethyl)-2,3-dimethoxybenzamide (19a)**: According to general procedure III, 2-(5-allyl-2,3-dimethoxybenzylamino)ethanol (**18a**) (75 mg, 0.30 mmol) and 9*H*-fluoren-9-imine, **2b** (80 mg, 0.45 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 2:1) of the crude product gave **19a** as an oil (30 mg, 38%) along with starting material **18a** (23 mg, 30%). $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.45 (s, 1H), 7.52 (s, 1H), 6.87 (s, 1H), 6.01 – 5.88 (m, 1H), 5.12 – 5.07 (m, 2H), 3.88 (s, 6H), 3.84 – 3.81 (m, 2H), 3.65 – 3.61 (m, 2H), 3.37 (d, *J* = 6.8 Hz, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$) δ = 166.7,

152.5, 145.9, 136.8, 136.6, 125.8, 122.4, 116.4, 115.9, 62.9, 61.4, 56.1, 42.9, 40.0 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{14}H_{20}NO_4$ 266.1387; Found 266.1398.

***N*-(4-chloro-2-methoxybenzyl)butan-1-amine (18b):** 4-chloro-2-hydroxybenzaldehyde (0.25 g, 1.61 mmol), dimethyl sulphate (0.61 g, 4.84 mmol ) and potassium carbonate (0.67 g, 4.84 mmol ) in acetone (5 mL) were refluxed for 12 h. After completetion of the starting materials (indicated from TLC), solvent was evaporated and the residue was purified by coloum chromatography (silica gel; EtOAc: hexane, 1:20) to afford 4-chloro-2-methoxybenzaldehyde as a white solid (0.22 g, 80%). Then 4-chloro-2-methoxybenzaldehyde (0.1 g, 0.59 mmol) and n-butylamine (43 mg, 0.59 mmol) were dissolved in dichloromethane (3 mL) and the mixture was stirred at room temperature for 12 h in the presence of 4Å MS (0.1 g). After consumption of starting material, molecular sieves were filtered out and the solvent was evaporated to give *N*-(4-chloro-2-methoxybenzylidene)butan-1-amine (0.12 g, 88%). *N*-(4-chloro-2-methoxybenzylidene)butan-1-amine (0.1 g, 0.44 mmol) was treated with sodium cyanoborohydride (56 mg, 0.89 mmol ) in MeOH (3 mL) at 40 °C for 4 h . MeOH was evaporated and residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (20 mL of brine and 20 mL of water), dried ($Na_2SO4$) and concentrated in vaccua. Colum chromatography (silica gel; EtOAc: hexane, 1:1) of the residue gave **18b** as an oil (91 mg, 90%). $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 2.8 Hz, 1H), 7.16 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 2H), 2.59 – 2.55 (m, 2H), 1.51 – 1.44 (m, 2H), 1.37 – 1.30 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$) δ = 156.2, 130.4, 129.5, 127.6, 125.3, 111.3, 55.6, 49.0, 48.8, 32.2, 20.5, 14.0 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{12}H_{19}ClNO$ 228.1150; Found 228.1155.

***N*-butyl-4-chloro-2-methoxybenzamide** (**19b**): According to general procedure III: (E)-N-(4-chloro-2-methoxybenzylidene)butan-1-amine (**18b**) (68 mg, 0.30 mmol) and 9*H*-fluoren-9-imine, **2b** (80 mg, 0.45 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 2:1) of the crude product gave **19b** as an oil (32 mg, 45%) along with starting material **18a** (14 mg, 21%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 2.8 Hz, 1H), 7.79 (s, 1H), 7.37 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 3.95 (s, 3H), 3.48 – 3.43 (m, 2H), 1.63 – 1.56 (m, 2H), 1.44 – 1.38 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 164.0, 156.0, 132.2, 132.1, 126.9, 123.3, 112.9, 56.4, 39.7, 31.7, 20.3, 13.9 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{12}H_{17}ClNO_2$ 242.0942; Found 242.0950.

***N*-(4-chlorobenzyl)-2-phenylethanamine (18c):** 4-chlorobenzaldehyde (0.20 g, 1.43 mmol) and 2-phenylethanamine (0.17 g, 1.43 mmol) were dissolved in dichloromethane (3 mL) and the mixture was stirred at room temperature for 12 h in the presence of 4Å MS (0.20 g). After consumption of starting material, molecular sieves were filtered out and the solvent was evaporated to obtain the imine *N*-(4-chlorobenzylidene)-2-phenylethanamine (0.30 g, 88%). *N*-(4-chlorobenzylidene)-2-phenylethanamine (0.10 g, 0.41 mmol) was treated with sodium cyanoborohydride (52 mg, 0.82 mmol) in MeOH (3 mL) at 40 °C for 4 h. MeOH was evaporated and residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (20 mL of brine and 20 mL of water), dried ($Na_2SO4$) and concentrated in vaccua. Colum chromatography (silica gel; EtOAc: hexane, 1:3) of the residue gave **18c** as an oil, (91 mg, 90%).$^{1}$H NMR (600 MHz, $CDCl_3$) δ = 7.37 – 7.32 (m, 4H), 7.29 – 7.26 (m, 5H), 3.81 (s, 2H), 2.96 – 293 (m, 2H), 2.89 – 2.87 (m, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$) δ = 140.0, 138.9, 132.6, 129.5, 128.8, 128.6, 128.5, 126.3, 53.1, 50.5,

36.4 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{15}H_{17}ClN$ 246.1044; Found 246.1038.

**4-Chloro-*N*-phenethylbenzamide** (**19c**): According to general procedure III, *N*-(4-chlorobenzyl)-2-phenylethanamine (**18c**) (73 mg, 0.30 mmol) and 9*H*-fluoren-9-imine, **2b** (80 mg, 0.45 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 2:1) of the crude product gave **19c** as an oil (39 mg, 51%) along with starting material **18c** (29 mg 40%). $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.63 – 7.60 (m, 2H), 7.39 – 7.31 (m, 4H), 7.27 – 7.22 (m, 3H), 6.14 (s, 1H), 3.71 (q, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 2H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 166.5, 138.8, 137.7, 133.1, 128.9, 128.9, 128.9, 128.3, 126.8, 41.3, 35.7 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{15}H_{15}ClNO$ 260.0837; Found 260.0836.

***N*-(5-chloro-2-methoxybenzyl)-2-phenylethanamine (18d):** 5-chloro-2-hydroxybenzaldehyde (0.28 g, 1.77 mmol), dimethyl sulphate (0.67 g, 5.32 mmol ) and potassium carbonate (0.73 g, 5.32 mmol) in acetone (5 mL) were refluxed for 12 h. After completetion of the starting materials (indicated from TLC), solvent was evaporated and residue was purified by coloum chromatography (silica gel; EtOAc: hexane, 1:20) to afford 5-chloro-2-methoxybenzaldehyde as white solid (0.23 g, 78%). Then 5-chloro-2-methoxybenzaldehyde (0.12 mg, 0.71 mmol) and pnenylethanamine (85 mg, 0.71 mmol) were dissolved in dichloromethane (3 mL) and stirred at room temperature for 12 h in the presence of 4Å MS (0.12 g). After consumption of starting material, molecular sieves were filtered out and the solvent was evaporated to obtain the imine, *N*-(5-chloro-2-methoxybenzylidene)-2-phenylethanamine (0.16 g, 85%). *N*-(5-chloro-2-methoxybenzylidene)-2-phenylethanamine (0.15 g, 0.55 mmol) was treated with sodium cyanoborohydride (69 mg, 1.10 mmol) in MeOH (3 mL) at 40 °C for 4 h. MeOH was evaporated and

residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (20 mL of brine and 20 mL of water), dried ($Na_2SO4$) and concentrated in vaccua. Colum chromatography (silica gel; EtOAc: hexane, 1:2) of the residue gave **18d** as an oil (0.14 g, 90%).$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.27 (m, 2H), 7.22 – 7.15 (m, 5H), 6.73 (d, *J* = 8.8 Hz, 1H), 3.76 (s, 2H), 3.70 (s, 3H), 2.88 – 2.80 (m, 4H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$) δ = 156.1, 139.8, 129.63, 129.58, 128.7, 128.5, 127.8, 126.2, 125.3, 111.3, 55.4, 50.1, 48.7, 36.1 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{16}H_{19}ClNO$ 276.1150; Found 276.1157.

**5-Chloro-2-methoxy-*N*-phenethylbenzamide(19d)**: According to general procedure III, *N*-(5-chloro-2-methoxybenzyl)-2-phenylethanamine (**18d**) (82 mg, 0.30 mmol) and 9*H*-fluoren-9-imine, **2b** (80 mg, 0.45 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography of crude product (silica gel; EtOAc: hexane, 2:1) gave **19d** as an oil (38 mg, 44%) along with starting material **18d** (23 mg, 28%). $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 2.8 Hz, 1H), 7.83 (s, 1H), 7.36 – 7.32 (m, 3H), 7.27 – 7.24 (m, 3H), 6.84 (d, *J* = 8.8 Hz, 1H), 3.78 – 3.75 (m, 2H), 3.73 (s, 3H), 2.92 (t, *J* = 6.8 Hz, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$) δ = 163.9, 155.9, 139.2, 132.2, 132.0, 128.9, 128.6, 126.7, 126.5, 122.9, 112.7, 56.0, 40.9, 35.5 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{16}H_{17}ClNO_2$ 290.0942; Found 290.0949.

## ASSOCIATED CONTENT

### Supporting Information

Additional tables and copies of NMR spectra supplied as Supporting Information.

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**Notes**

The authors declare no competing financial interest.

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