Copper-Catalyzed facile Synthesis of *N*-Benzylbenzamides from Benzylamines and Aldehydes by Oxidative C-H Bond Activation

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Abstract: *A versatile approach for the synthesis of N-Benzylbenzamides has been demonstrated by treating benzylamines with benzaldehydes under mild conditions, using CuI as a catalyst and TBHP as an oxidant at 90 °C. The reaction proceeds through direct oxidative C-H bond activation of the aldehyde C-H group. Both benzylamine and aldehyde substrates were tolerated well to obtain the desired products in good to excellent yields. The amide scaffold acts as a basic skeletal linkage in the peptide chain of proteins, pharmaceuticals, and bioactive organic molecules. Because of the relatively inert nature of the amide group, the nucleophiles need either harsh reaction conditions or extra steps, which lead to the transamidation of amide with amines under high thermal conditions. Therefore, the catalytic approach is in high demand to improve the method for the synthesis of amide derivatives.*

Key words: *N-Benzylbenzamides, TBHP, amide group, bioactive organic molecules, skeletal linkage, transamidation.*

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INTRODUCTION

In modern organic synthesis, the construction of the C-N bond is an important development to synthesize a variety of biologically and industrially applicable organic molecules, in which the formation of the amide bond has acquired a phenomenal significance for its existence as the basic linkage in natural products, pharmaceuticals, synthetic polymers, agrochemicals, peptides, and proteins.[1] It has been found that about 25% of renowned drug molecules contain an amide as a core functional group.[2] The *N*-Benzylbenzamides moiety possessing –CONH-, –CONHR, or –$CONR_2$ groups is a very stable molecule. They held together by intermolecular hydrogen bonding between the CO oxygen atom of one amide molecule and the NH hydrogen atom of another amide molecule.[3] There are a huge number of drug molecules bearing the benzamide functional group. Some of the examples of major marketed drugs that contain –CONH functional group include: Lidocaine,[4] a local anesthetic; Picotamide,[5] an antithromboxane agent; Butyrylcholinesterase (BChE) metabolites, Alzheimer's Disease[6]; Hsp90 inhibitor, Cancer chemotherapy[7]; 3D-PhaM melanogenesis inhibitor[8].

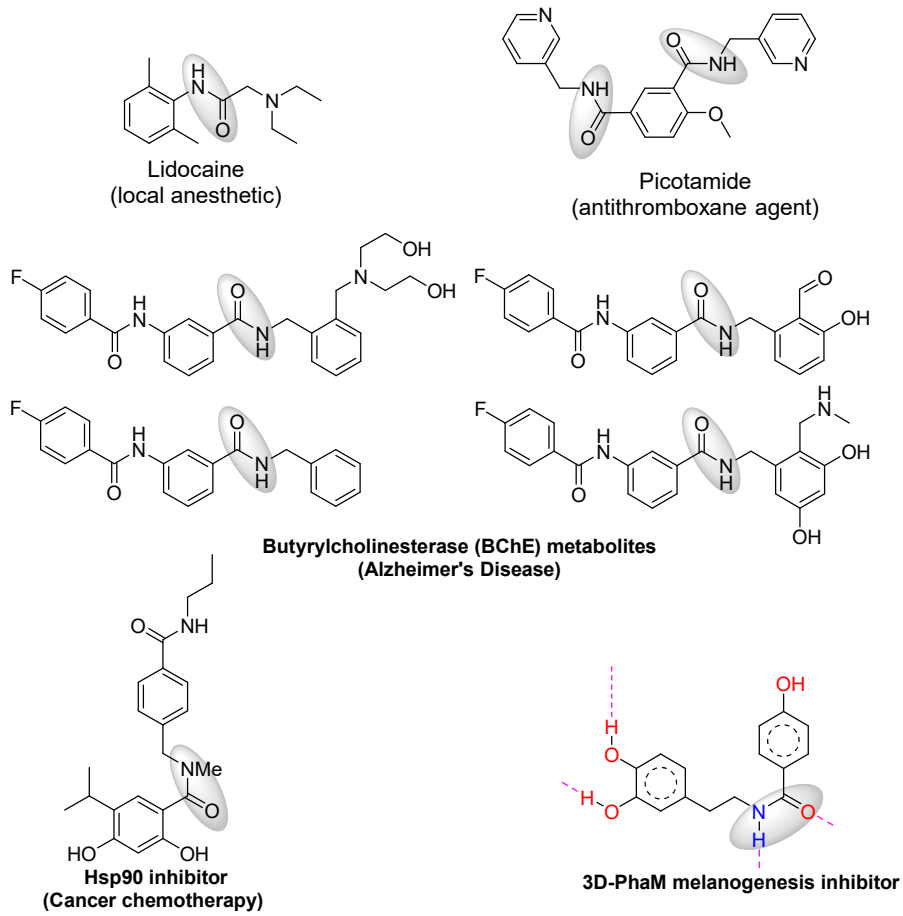


Figure 1: Selected examples of biologically/industrially important *N*-Benzylbenzamide scaffolds

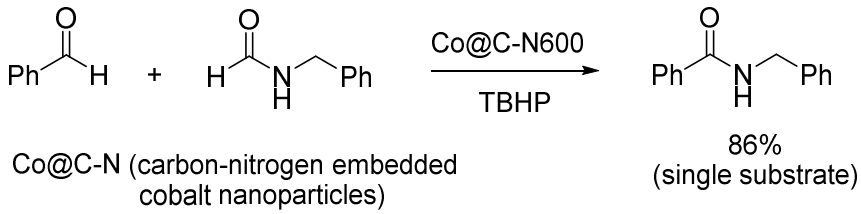
As a prerequisite to these priorities, the American Chemical Society (ACS), the Green Chemistry Institute (GCI), and leading global pharmaceutical companies organized the ACS GCI Pharmaceutical Roundtable (ACS GCIPR) meeting in 2005 and voted top for 'amide formation evading poor atom economy reagents' by integrating green chemistry and green engineering in drug synthesis.[9] Krause and co-workers disclosed the amidation of carboxylic acids and ethoxyacetylene with amines using organoruthenium chlorides. Conceivably, a good number of functional groups were tolerated, producing moderate to excellent yields.[10] Ru-catalyst and *N*-heterocyclic carbene (NHC) precursor mediated *N*-Benzylbenzamides synthesis from aldehydes and primary amines was performed by Chen and co-workers. Substrate scope was examined by preparing a range of *N*-Benzylbenzamides with moderate to good yields.[12] Kumar et al. developed an *in situ* generated catalyst from readily available *N*-heterocyclic carbene (NHC) precursor, $RuH_2(PPh_3)_4$, CH_3CN, and NaH to examine its activity in the synthesis of *N*-Arylarylamides directly either from aldehydes or alcohols with amines. The catalyst produced moderate to high yields by reacting several benzylamines with aldehydes or alcohols.[13] Construction of amides from in-situ generated acid chlorides with $Ru(bpy)_3Cl_2$ as photocatalyst and TBHP as oxidant under visible-light (blue LEDs) irradiation;[14] Kulkarni and co-workers base-mediated *N*-Arylbenzamides synthesis from benzylazides and aromatic aldehydes with moderate to good yields.[15] In the course of synthesizing several amides, Bai and co-workers reported *N*-benzylbenzamide by oxidative amidation of aldehydes using a heterogeneous Co@C-Nbased catalytic system (Scheme 1.1).[16] While synthesizing the basic amides, Ghosh et al. reported the synthesis of *N*-benzylbenzamide from benzyl alcohol and benzylamines using $[Ru(benzene)Cl_2]_2$ and NHC precursor.[17] Renuka and Gayathri reported the oxidative amidation of benzylalcohol and aryl/alkyl amines for the synthesis of

N-aryl/alkyl benzamides using polymer-supported 2,6-bis(benzimidazolyl)pyridine copper(II) chloride complex [Cu(PS-BBP)Cl_2] in TBHP and water with good to excellent yields.[18] Very recently, oxidative amidation of benzylamines for the synthesis of *N*-benzylbenzamides employing sodium hypochlorite (NaOCl) and water has been reported by Salles and co-workers (Scheme 1.2).[19]

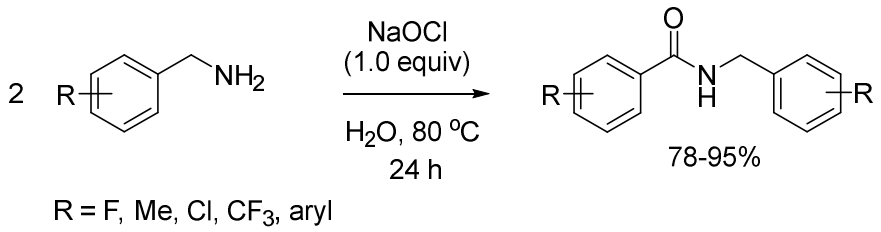
Although the above methodologies are well contributed for the synthesis of *N*-Benzylbenzamides, nonetheless, they encounter certain interpolations such as bleak atom efficiency, application of stoichiometric amounts of reagents, excessive generation of wastes, tedious workup procedures, usage of amine salts, perilous catalysis, strong additive usage, or extremely high temperature conditions. Consequent to these deterrents, the exploration of a simple, atom-efficient and greener synthetic approach for the synthesis of *N*-Benzylbenzamides has become a great deal of task. Herein, we report a facile method for the synthesis of *N*-Benzylbenzamides from benzylamines and arylaldehydes by C-H activation using copper(I) iodide catalyst and TBHP oxidant under moderate temperature conditions (Scheme 1). Pragmatically, this protocol is particularly significant in the context that the reaction between primary amine and aldehyde has every chance to undergo Schiff base formation.

Previous Methods:

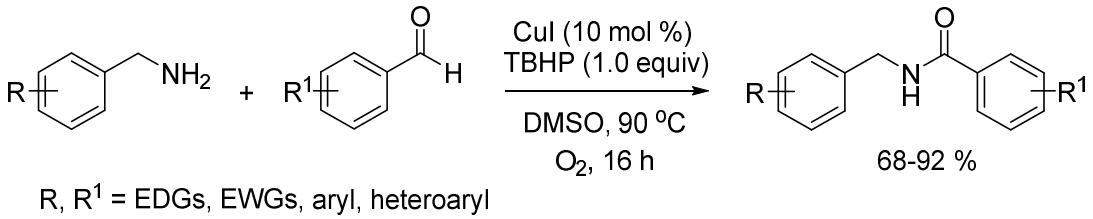
1.



2.



Our Method:



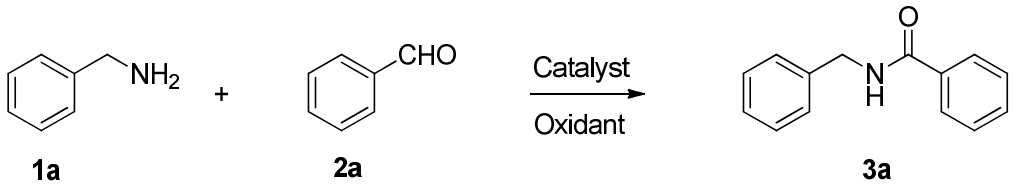
Scheme 1: CuI-catalyzed synthesis of *N*-benzylbenzamides from benzylamines and aromatic aldehydes

Optimization of Reaction Conditions:

The screening for *N*-Benzylbenzamides formation has been initiated by the reaction of benzylamine (**1a**, 1.0 mmol) and benzaldehyde (**2a**, 1.2 mmol) with a range of copper(II) as well as copper(I) catalysts

in the presence of *tert*-butyl hydroperoxide (TBHP) using polar aprotic or selective non-polar solvents at 90 °C under air atmospheric conditions (Table 1). Initially, the reaction has been commenced with copper(II) salts such as $Cu(OAc)_2$, CuO, $CuCl_2$and $CuBr_2$ (Table 1, entries 1-4). These catalysts supported scanty yields of the desired product **3a** from 30-43%. This may be due to the unfavourable redox conditions for Cu(II) salts. Subsequently, we conducted the reaction with Cu(I) salts such as CuCl, CuBr, and CuI under the same reaction conditions (Table 1, entries 5-7). Delightfully, copper(I) iodide produced a substantially higher yield (76%) than either copper(I) chloride (36%) or copper(I) bromide (45%), which are in turn higher than the yields obtained from Cu(II) salts. These results inspired us to explore further for higher yields of the desired product. Very quickly, when the reaction was performed with copper(I) iodide under an oxygen atmosphere, surprisingly, the yields of the desired product dramatically increased to 89% (Table 1, entry 8). The increase in yield suggests that an oxygen-rich atmospheric condition promotes the oxidant TBHP action towards the production of higher yield. Further, a decrease in catalyst loading from 10 mol% to 5.0 mol% abruptly decreased the product yield from 89% to 61% (Table 1, entry 9). In order to optimize for higher yields, other oxidants such as DTBP (di-tertiary butyl peroxide), H_2O_2, and Oxone were examined. However, these oxidants produced disappointing yields (Table 1, entries 10-12). Ostensibly, the product yield was detrimental (55%) under an N_2 atmosphere (Table 1, entry 13). Moreover, the progress of the reaction was also studied by altering the solvent medium under the same oxygen atmospheric conditions (Table 1, entries 14-16). Notably, the reaction did not proceed to give the desired product **3a** in the absence of a catalyst (Table 1, entry 17). Altogether, the conditions observed in entry 8 in Table 1 have been considered as optimal reaction conditions to study the substrate scope.

Table 1. Optimization of Reaction Conditions[a]



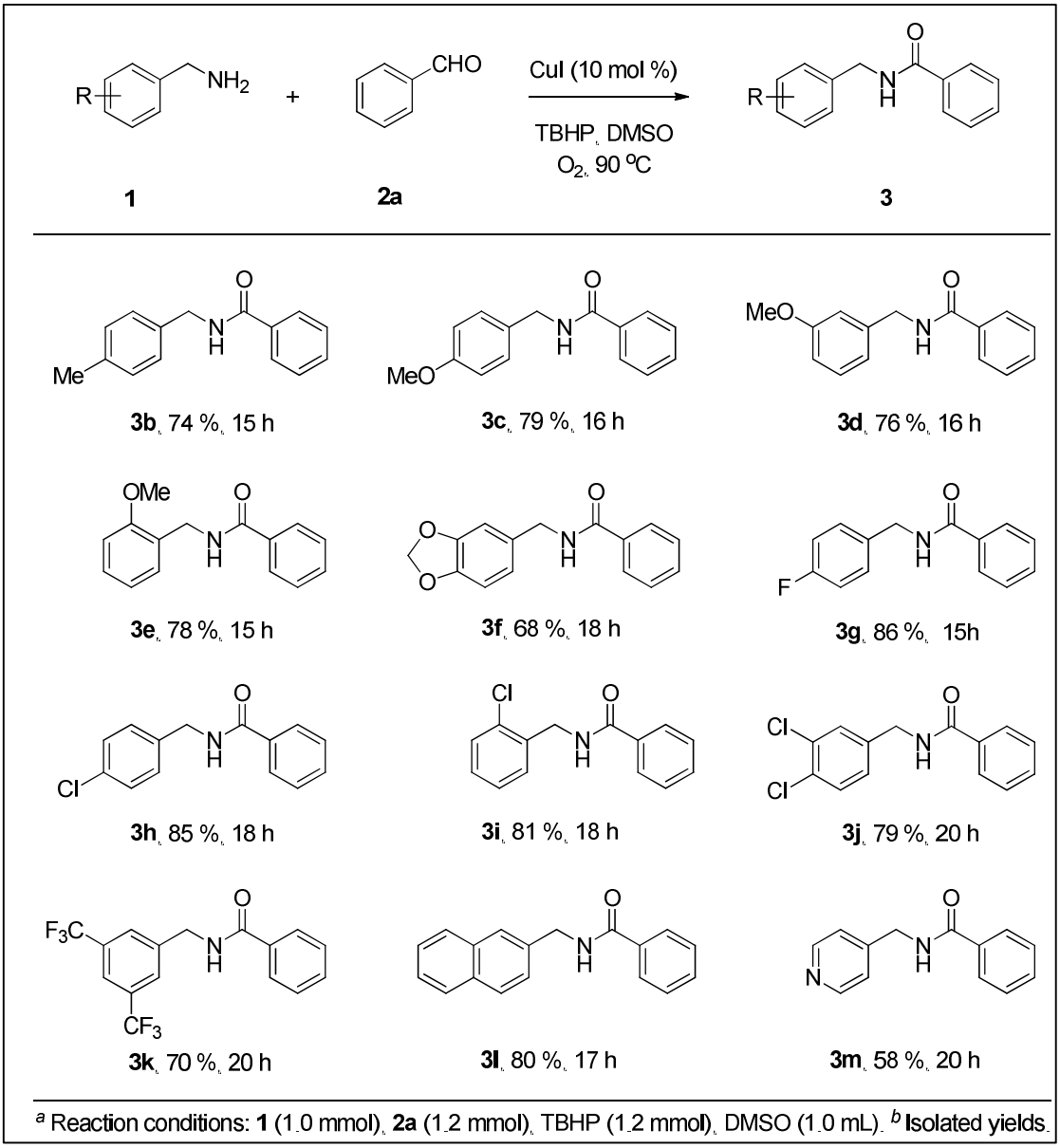
1a **2a** **3a**

Entry	Catalyst	Solvent	Oxidant	Yield (%)[b]
1	$Cu(OAc)_2$	DMSO	TBHP	32
2	CuO	DMSO	TBHP	30
3	$CuCl_2$	DMSO	TBHP	31
4	$CuBr_2$	DMSO	TBHP	43
5	CuCl	DMSO	TBHP	36
6	CuBr	DMSO	TBHP	45
7	CuI	DMSO	TBHP	76
8[c]	**CuI**	**DMSO**	**TBHP**	**89**
9[c,d]	CuI	DMSO	TBHP	61
10[c]	CuI	DMSO	DTBP	54
11[c]	CuI	DMSO	H_2O_2	45
12[c]	CuI	DMSO	Oxone	41
13[c,f]	CuI	DMSO	TBHP	55
14[c]	CuI	toluene	TBHP	15
15[c]	CuI	DMF	TBHP	54
16[c]	CuI	NMP	TBHP	49
17[c]	–	DMSO	TBHP	n.r

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), Solvent (2.0 mL), 90 °C, 24 h. [b] Isolated yield. [c] Oxygen. [d] Using 5.0 mol % of CuI. [e] Reaction performed at 50 °C. [f] Under N_2 balloon.

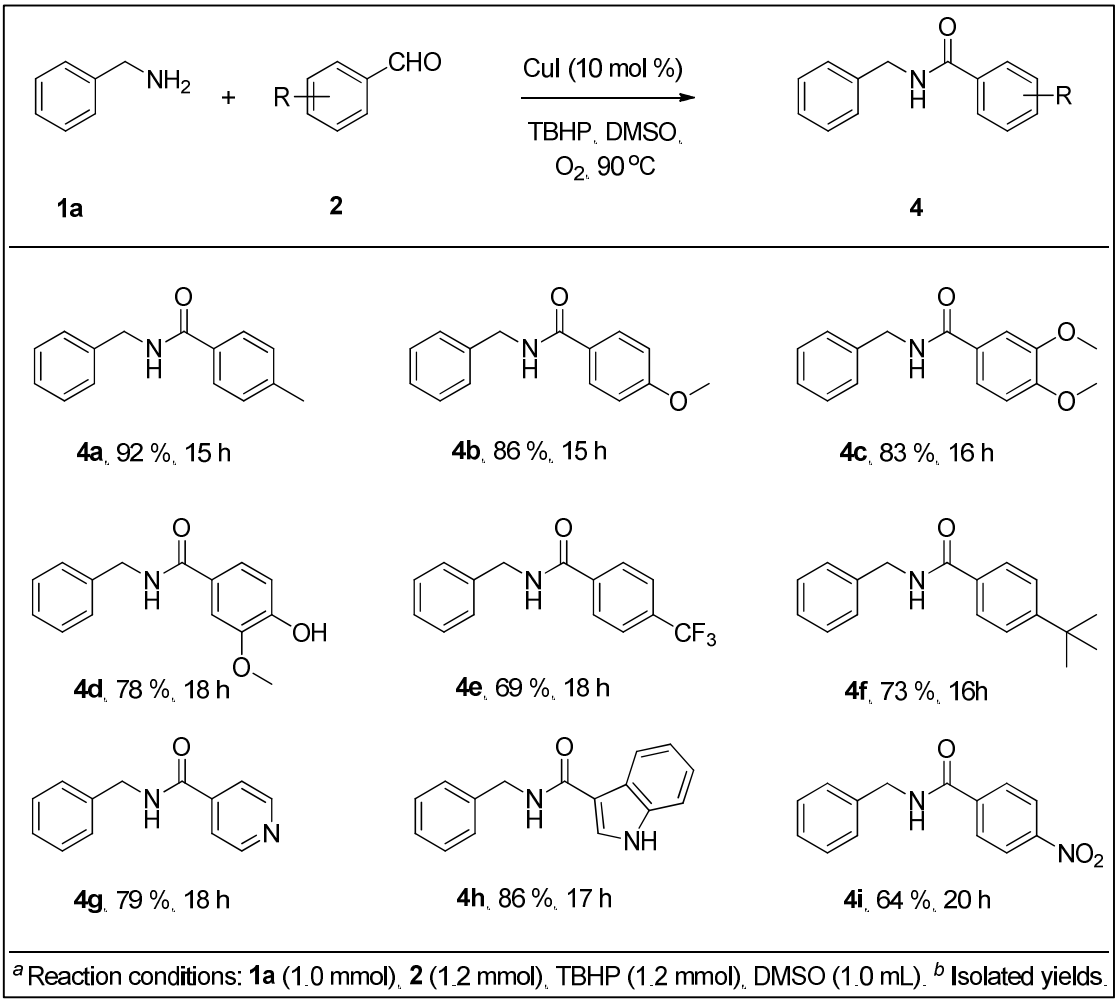
After establishing the optimized reaction conditions, we proceeded to study the scope of benzylamines (**1**) with benzaldehyde (**2a**) under the standard reaction conditions (Scheme 2). Primarily, when the reaction was executed with electron-donating groups such as Me, OMe, and piperonyl, the corresponding desired products **3b-3f** were resulted in moderate to good yields (68-79%). The maximum and the minimum yields supported among the electron-rich species are *p*-OMe(**3c**) and piperonyl (**3f**), respectively. Noteworthily, the electron-deficient species were tolerated better than the electron-rich species, giving the respective desired products **3g-3i** in good yields (86-81%). However, the disubstituted electron withdrawing groups such as 3,4-dichloro- (**3j**) and 3,5-bis(trifluoromethyl)- (**3k**) gave moderately lower yields than the monosubstituted electron withdrawing groups. This may be due to the competitive influence of disubstituted electron-deficient groups on the phenyl ring. Furthermore, the naphthyl fused ring system tolerated well to give the corresponding product **3l** in good yield (80%). Likewise, the pyridyl hetero ring system also endured to produce the desired product **3m** with moderate yield (58%).

Scheme 2. Scope of Benzylamines[a,b]



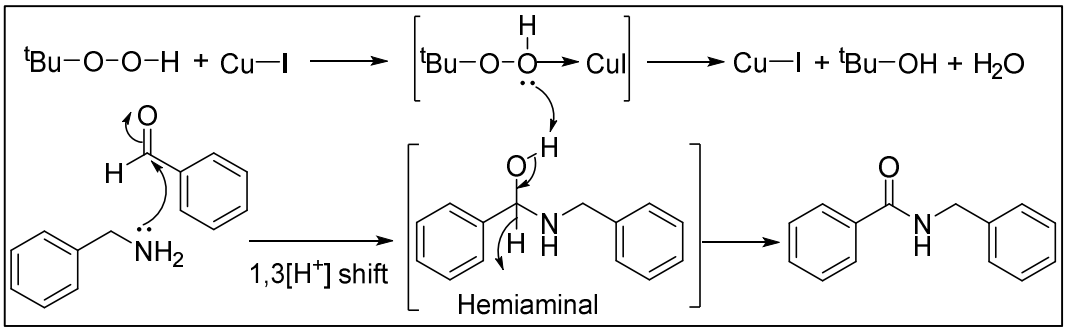
Thereafter, the substrate scope of benzaldehydes **2** was examined with benzylamine (**1a**) under the optimized reaction conditions (Scheme 3). Broadly, the electron-rich functionalities of benzaldehydes, such as Me, OMe, and 3,4-dimethoxy, delivered perceptibly higher yields (**4a-4c**) than the electron-rich species of benzylamines (Scheme 3, **3b-3f**). In contrast to benzylamines, the electron-deficient species of benzaldehydes produced higher yields than the electron-rich species, suggesting that the electron-rich functionalities on the phenyl ring of benzaldehyde afforded well for C-H activation to produce the desired compounds. In addition, vanillin also tolerated well to afford the desired product **4d** in 78% yield. However, 4-tert-butylbenzaldehyde gave *N*-benzyl-4-(tert-butyl)benzamide (**4e**) in 73% yield, which is lower than the other electron-donating groups (**4a-4d**). This was possibly due to the bulkiness of the methyl groups, which eventually diminishes their characteristic electron-donating nature. Conversely, electron-withdrawing groups such as -CF_3, -NO_2 groups afforded weakly to produce the corresponding products **4f** and **4g**in 69% and 64% respectively. Furthermore, indole-3-carboxaldehyde and 4-pyridinecarboxaldehyde (isonicotinaldehyde) produced the desired products **4h** and **4i** in 85% and 66%yields.

Scheme 3. Scope of Benzaldehydes[a,b]



Plausible reaction mechanism:

Based on the optimized reaction conditions and available literature,[18] we propose a plausible reaction mechanism for the amidation of aldehydes with amines using CuI catalyst and TBHP as an oxidant. It has been predicted that C−H activation of aldehyde occurs through the formation of a hemiaminal intermediate from aldehyde and benzylamine. The hemiaminal intermediate thus formed would undergo further oxidation through proton abstraction by the peroxy-oxygen of TBHP from TBHP-CuI complex to produce *N*-Benzylbenzamides with the consequent expulsion of water and *t*-butanol (Scheme 4).



Scheme 4: Proposed mechanistic route for *N*-Benzylbenzamides formation from benzylamine and aldehyde

CONCLUSIONS

In conclusion, we have proved a facile method for the synthesis of secondary *N*-Benzylbenzamides from benzylamines and aromatic aldehydes through copper(I) iodide-catalyzed oxidative amidation using TBHP as the oxidant. This protocol is afforded for a wide variety of substrates bearing EDGs, EWGs, as well as fused and heteroaryl systems, with 22 examples proving its versatility. These secondary *N*-Benzylbenzamides are the building blocks for the synthesis of biologically important and industrially applicable compounds. This method edges over the previous methods wherein higher metal complexes and harsh reaction conditions have been employed. The mechanistic aspects suggest that the C-H activation of aldehydes occurs through a hemiaminal intermediate. Experiments are in progress to explore the possible route for *N*-Benzylbenzamides formation.

EXPERIMENTAL SECTION

General Information:

All reactions were performed with oven-dried round-bottom flasks using dry solvents under a molecular O_2 balloon unless stated otherwise. CuI was acquired from Sigma-Aldrich and used as received. Other substrates were used as received from commercial vendors. Reaction progress was observed by TLC on 0.25-mm Merck silica gel plates (60 F_{254}) and UV light for visualization. Purification was made with column chromatography using silica gel 100-200 mesh. Melting points were recorded on a Büchi melting point apparatus and were uncorrected. IR spectra were recorded on an RX1 FT-IR spectrophotometer. NMR was recorded on a JEOL ECX-400P spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz), with $CDCl_3$ as the solvent by setting TMS as the internal standard. Compounds Mass was recorded on a 6530 Accurate-Mass Q-TOF LC/MS using Agilent Technologies.

General Procedure for the Synthesis of *N*-Benzylbenzamides:

To a clean and oven-dried 10 mL round-bottomed flask, benzylamine (1.0 mmol), benzaldehyde (1.2 mmol), CuI, and DMSO (2.0 mL) were added under a molecular oxygen atmosphere. The contents were brought to ice-cold temperature, and TBHP (1.2 mmol) was added slowly drop by drop with constant stirring with a magnetic stirrer. After complete addition of TBHP, the temperature of the reaction mixture was slowly raised to 90 ^{o}C and continued till the complete consumption of reactants by checking with TLC at regular intervals. Then the crude reaction mixture was cooled to room temperature and extracted with EtOAc/ Hexane, maintaining the pH with $NaHCO_3$, followed by thorough washings with brine. Then the ethyl acetate layer was dried with anhydrous Na_2SO_4 salt and filtered. The filtrate was further concentrated with rotavapor under reduced pressure. The residue was dried with silica gel and purified by column chromatography. The purified compounds were used for physical constants and spectral characterization.

Compounds characterization:

N-benzylbenzamide **(3a).** Yield: 89%, white solid, M.P. 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 7.6 Hz, 2H), 7.46-7.43 (m, 1H), 7.38-7.34 (m, 2H), 7.29-7.24 (m, 5H), 6.72 (br s, 1H), 4.57 (d, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 138.2, 134.3, 131.4, 128.6, 128.5, 127.7, 127.4, 126.9, 43.9; IR: 3059, 2923, 2854, 1726.39, 1603.56, 698.73; HRMS (ESI, m/z): calcd for $C_{14}H_{13}NO$ $[M + H]^+$ 212.0917, found 212.0920.

N-(4-methylbenzyl)benzamide **(3b).** Yield: 74%, White solid, M.P. 136-137 °C (Lit. 132–134 ^{o}C);[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.6 Hz, 2H), 7.52-7.41 (m, 3H), 7.18-7.16 (m, 3H), 7.25-7.22 (m, 1H), 6.32 (br s, 1H), 4.62 (d, J = 7.6 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 137.4, 135.1, 134.5, 131.5, 129.4, 128.6, 127.9, 126.9, 43.9, 21.1; I.R (neat): 3311, 2920, 1639, 1546, 1420, 1317, 783, 694 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{15}H_{15}NO$ $[M + H]^+$ 226.1226, found 226.1228.

N-(4-methoxybenzyl)benzamide **(3c).** Yield: 79%, white solid, M.P. 88-91 °C (Lit. 95–97 °C);[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 6.8 Hz, 2H), 7.38-7.29 (m, 3H), 7.26-7.17 (m, 2H), 6.86-6.79 (m, 2H), 6.69 (br s, 1H), 4.57 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 159.1, 134.4, 131.4, 130.2, 129.2, 128.5, 126.9, 114.1, 55.3, 43.6; IR: 3311, 2922, 2851, 1696, 1642, 1604, 1248, 744, 712; HRMS (ESI, m/z): calcd for $C_{15}H_{15}NO_2$ $[M + H]^+$ 242.1176, found 242.1178.

N-(2-methoxybenzyl)benzamide **(3e).** Yield: 78%, white semi solid, M.P. 139-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.47-7.37 (m, 3H), 7.26-7.24 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.58 (br s, 1H), 4.54 (d, *J* = 5.2 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 157.5, 134.7, 131.1, 130.1, 129.9, 129.8, 129.7, 129.1, 128.7, 128.6, 128.3, 128.1, 126.9, 126.1, 120.9, 120.5, 55.4, 40.0; IR: 3332, 2924, 2850, 1648, 1599, 1548, 1241, 749; HRMS (ESI, m/z): calcd for $C_{15}H_{15}NO_2$ $[M + H]^+$ 242.1176, found 242.1188.

N-(benzo[d][1,3]dioxol-5-ylmethyl)benzamide **(3f).** Yield: 68%, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.51-7.46 (m, 1H), 7.42-7.39 (m, 2H), 6.83 (d, *J* = 1.6 Hz, 1H), 6.81-6.74 (m, 2H), 6.38 (br s, 1H), 5.93 (s, 2H), 4.53 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 147.9, 146.9, 134.2, 131.9, 131.5, 128.5, 127.9, 126.9, 121.2, 108.5, 108.3, 101.0, 43.9; IR: 3326, 3064, 2922, 2852, 1725, 1638, 1539, 1488, 1250, 768; HRMS (ESI, m/z): calcd for $C_{15}H_{13}NO_3$ $[M + H]^+$ 256.0930, found 256.0935.

N-(4-flourobenzyl)benzamide **(3g).** Yield: 86%, white solid, M.P. 123-125 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.75 (m, 2H), 7.50-7.47 (m, 1H), 7.43-7.39 (m, 1H), 7.32-7.28 (m, 2H), 7.10-7.06 (m, 1H), 7.03-6.99 (m, 2H), 6.44 (br s, 1H), 4.59-4.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 134.2, 133.9, 131.7, 129.6, 129.5, 128.6, 126.9, 115.7, 115.5, 43.4; IR: 3297, 2925, 2854, 1635, 1600, 1503, 1224, 696; HRMS (ESI, m/z): calcd for $C_{14}H_{12}FNO$ $[M + H]^+$ 230.1910, found 230.1920.

N-(4-chlorobenzyl)benzamide **(3h).** Yield: 85%, white solid, M.P. 132-134 °C (Lit. 133– 134 °C);[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.51-7.48 (m, 1H), 7.44-7.38 (m, 2H), 7.31-7.28 (m, 4H), 6.83 (br s, 1H), 4.59 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 136.7, 134.1, 131.7, 129.2, 128.9, 128.6, 126.9, 43.9; IR: 3315, 2922, 2855, 1693, 1639, 1595, 1274, 715; HRMS (ESI, m/z): calcd for $C_{14}H_{12}ClNO$ $[M + H]^+$ 246.0680, found 246.0653.

N-(3,4-dichlorobenzyl)benzamide **(3j).** Yield: 79%, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.64 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.41-7.39 (m, 3H), 7.16 (d, *J* = 8.4, 1.6 Hz, 1H), 6.72 (br s, 1H), 4.56 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 137.9, 136.3, 133.6, 130.7, 129.7, 129.2, 127.2, 126.1, 43.1; HRMS (ESI, m/z): calcd for $C_{14}H_{11}Cl_2NO$ $[M + H]^+$ 281.0186, found 281.0190.

N-(3,5-bis(trifluoromethyl)benzyl)benzamide **(3k).** Yield: 70%, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.6 Hz, 1H), 7.82-7.78 (m, 4H), 7.54-7.50 (m, 1H), 7.44-7.41 (m, 2H), 7.08 (br s, 1H), 4.72 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 141.1, 133.5, 132.7, 132.1, 131.9, 131.7, 129.9, 128.7, 128.2, 127.7, 127.0, 124.5, 121.8, 121.4, 43.9; IR: 3309, 2922, 2853, 1709, 1644, 1537, 1279, 1133, 707; HRMS (ESI, m/z): calcd for $C_{16}H_{11}F_6NO$ $[M + H]^+$ 348.0687, found 348.0690.

N-benzyl-4-methylbenzamide **(4a).** Yield: 92%, yellow solid, M.P. 94-97 °C (95.2–98.1 °C),[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 6H), 7.16-7.09 (m, 3H), 4.43 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 141.9, 138.2, 131.5, 129.2, 128.8, 127.9, 127.6, 126.9, 44.1, 21.4; IR: 3277, 3059, 3029, 2920, 2859, 1634, 1548, 745, 698; HRMS (ESI, m/z): calcd for $C_{15}H_{15}NO$ $[M + H]^+$ 226.1228, found 226.1235.

N-benzyl-4-methoxybenzamide **(4b).** Yield: 86%, pale yellow solid, M.P. 144-147 °C (Lit. 146.6–148.8 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 4.0 Hz, 1H), 7.33-7.28 (m, 4H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.34 (br s, 1H), 4.64 (d, *J* = 5.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 162.2, 138.3, 128.7, 127.9, 127.6, 126.5, 113.7, 55.4, 43.9; HRMS (ESI, m/z): calcd for $C_{15}H_{15}NO_2$ $[M + H]^+$ 242.1179; Found: 242.1186.

***N-benzyl-3,4-dimethoxybenzamide* (4c).** Yield: 83%, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.4 Hz, 2H), 7.36 (d, *J* = 3.6 Hz, 4H), 7.33-7.27 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 2H) 6.35 (br s, 1H), 4.65 (d, *J* = 6.0 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 151.7, 148.9, 138.3, 128.7, 128.6, 127.9, 127.5, 126.9, 119.2, 110.6, 110.2, 55.9, 43.9; HRMS (ESI, m/z): calcd for $C_{16}H_{17}NO_3$ $[M + H]^+$ 272.1276, found 272.1279.

***N-benzyl-4-(trifluoromethyl)benzamide* (4e).** Yield: 69%, white solid, M.P. 165-166 ºC (Lit. 165–167 ºC);[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.39-7.31 (m, 5H), 6.43 (br s, 1H), 4.68-4.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 137.6, 137.6, 128.9, 127.9, 127.9, 127.4, 125.7, 125.7, 44.3; HRMS (ESI, m/z): calcd for $C_{15}H_{12}F_3NO$ $[M + H]^+$ 280.0940, found 280.0942.

***N-Benzyl-4-(tert-butyl)benzamide* (4f).** Yield: 73%, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.36−7.31 (m, 4H), 7.30−7.27 (m, 1H), 6.47 (bs, 1H), 4.63 (d, J = 6.0 Hz, 2H), 1.43 (s, 9H). 13C NMR (100 MHz, CDCl3) δ 167.3, 150.0, 138.2, 132.5, 129.0, 128.0, 127.7, 127.1, 126.4, 44.2, 40.2, 26.6; IR: 3317, 1731, 1707, 1539, 1151, 696, 642 cm^{-1}.

***N-benzylisonicotinamide* (4g).** Yield: 79%, white solid, M.P. 88-91 °C (Lit. 91.6 °C);[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68-8.66 (m, 2H), 7.63-7.61 (m, 2H), 7.38-7.29 (m, 5H), 6.95 (br s, 1H), 4.62 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 150.4, 141.4, 137.4, 128.8, 128.6, 127.9, 127.8, 127.3, 120.9, 44.2; HRMS (ESI, m/z): calcd for $C_{13}H_{12}N_2O$ $[M + H]^+$ 212.0948; found: 212.0954.

N-Benzyl-4-nitrobenzamide (**4i**). Yield: 64%, yellow solid. M.P. 114–116 °C; 1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.6 Hz, 2H), 7.94 (d, J = 7.6 Hz, 2H), 7.35 (brs, 5H), 6.79 (brs, 1H), 4.64 (d, J = 4.8 Hz, 2H); 13C NMR (100 MHz, $CDCl_3$) δ 165.6, 149.8, 140.1, 137.6, 129.1, 128.4, 128.1, 123.9, 44.6; HRMS Calcd for $C_{14}H_{12}N_2O_3$ (M + H+): 257.0919; Found: 257.0926.

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Conflict of Interest:

The authors declare no conflict of interest.

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