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Ligand-Free Copper-Manganese Spinel Oxide-Catalyzed Tandem One-Pot C–H Amidation and *N*-Arylation of Benzylamines: A Facile Access to 2-Arylquinazolin-4(3*H*)-ones

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Abstract: An efficient ligand-free copper-manganese (Cu-Mn) spinel oxide-catalyzed direct tandem C–H oxygenation and *N*-arylation of benzylamines has been developed. The method has been utilized for the synthesis of medicinally important 2-arylquinazolin-4(3*H*)-ones. Salient features of this method include recyclable catalyst, no ligand, excellent product yields, shorter reaction times and a broad substrate scope.

Keywords: *N*-arylation; 2-arylquinazolin-4(3*H*)-ones; C–H oxygenation; copper-manganese (Cu-Mn) bimetallic catalyst; recyclable catalyst

Amide bonds are not limited to biological systems and are present in a huge array of chemical compounds, including marketed drugs,[1] polymers,[2] and natural products.[3] Therefore the synthesis of amide bonds continues to be important task in organic chemistry. Amide bonds are typically synthesized by the condensation of carboxylic acids with amines; however, this coupling does not happen spontaneously at ambient temperature, and it typically requires higher temperatures. Therefore, usually it is necessary to first activate the carboxylic acid using coupling reagents. Moreover, this approach lacks atom-economy.[4,2b] Therefore, over the years several new methods have been reported for amide synthesis, including aminocarbonylation of aryl halides,[5] coupling of amines and alcohols through dehydrogenation,[6] and oxime rearrangement,[7] as well as direct coupling of alcohols and nitroarenes,[8] oxygenation of benzylamines[9] and many more. One of the straightforward approaches for amide synthesis is the direct oxygenation of benzylamines;[9] however, oxygenation of the α-methylene group of an amine has been a challenging task and it requires transition metal catalysts.[9b] Furthermore, the direct synthesis of *N*-arylamides *via* coupling of benzylamines with aryl halides in one-pot requires a metal catalyst, a base and a ligand.[10] The *N*-arylation of amides with aryl halides/nonaflates[11] has been reported. However, for a one-pot synthesis of *N*-arylated amides directly from benzylamine and aryl iodide, only one report is available in the literature which requires harsh reaction conditions (high temperature, long reaction time) and use of the ligand 1,10-phenanthroline (shown in Figure 1).[10]

In recent years, bimetallic catalysts have been extensively used in various organic transformations[2a] such as bimetallic palladium(III) for carbon-heteroatom bond formation,[12] Ru-Ce for dihydroxylation of glycals,[13] Ni-Pd for cross-coupling of two different aryl electrophiles,[14] Cu-Mn for Huisgen [3+2]-cycloadditions,[15] for the synthesis of imidazopyridines,[16] regioselective halogenations of phenol,[17] and for C–N bond formation from arylboronic acids and amines.[18] In continuation of our interest in the development of new protocols for the synthesis of amides[19] and quinazolinones,[20] herein we have developed the bimetallic Cu-Mn spinel oxide-catalyzed synthesis of *N*-arylated amides **1** directly *via* coupling of benzylamines **3** with aryl halides **2** without use of a ligand under mild reaction conditions (Figure 1). The utility of the developed protocol for the construction of medicinally important quinazolinones **6** has also been demonstrated.

Our work started with the reaction of aryl iodide **2a** with benzylamine **3a** in the presence of various catalysts, bases and solvents. To our surprise, in the presence of Fe_2O_3, the desired *N*-phenylbenzamide **1a** was formed in 30% yield (Table 1, entry 1). After screening various other catalysts available with us, a bimetallic Cu-Mn B (Cu: Mn = 1:0.25)[16] was found to pro-

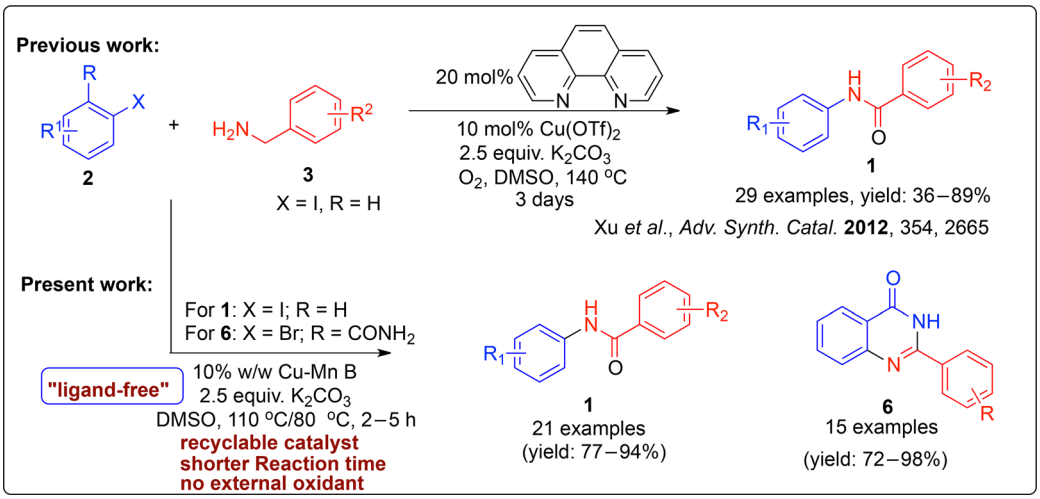
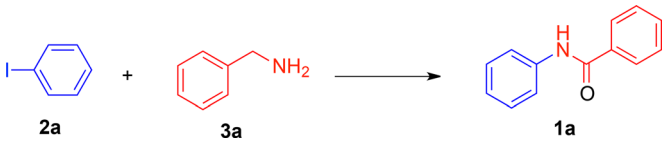


Figure 1. Previous and present work on metal-catalyzed tandem C–H oxygenation/*N*-arylation of benzylamines to produce *N*-arylamides.

Table 1. Optimization of the reaction conditions for amidation followed by *N*-arylation.[a,b]



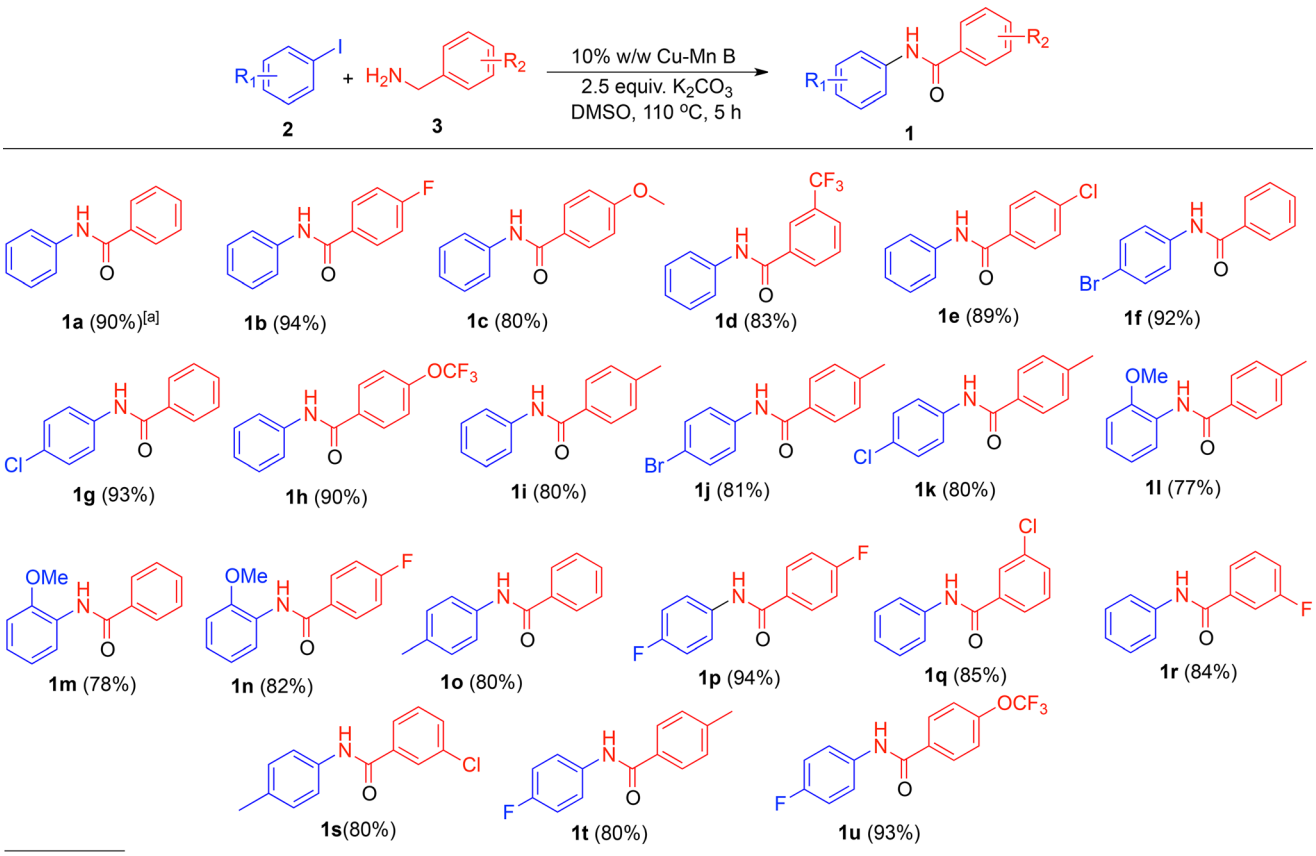
Entry	Catalyst (% w/w)	Temp. [°C]	Base (equiv.)	Ligand (equiv.)	Time [h]	Yield [%]of **1a**[c]
1	Fe_2O_3 (10)	110	K_2CO_3 (2)	none	6	30
2	Cu-Mn B (10)	110	none	none	10	0
3	Cu-Mn B (10)	110	K_3PO_4 (2)	none	12	60
4	Cu-Mn B (10)	110	NaOBt (2)	none	10	traces
5[d]	**Cu-Mn B (10)**	**110**	**K_2CO_3 (2)**	**none**	**5**	**94**
6	Cu-Mn B (5)	110	K_2CO_3 (2)	none	5	50
7	Cu-Mn B (10)	80	K_2CO_3 (2)	none	5	30
8	Cu-Mn A (10)	110	K_2CO_3 (2)	none	10	5
9	Cu-Mn C (10)	110	K_2CO_3 (2)	none	10	traces
10	CuO (10)	110	K_2CO_3 (2)	none	10	0
11	$MnCl_2$ (10)	110	K_2CO_3 (2)	none	10	0
12	$CuCl_2$ (10)	110	K_2CO_3 (2)	none	10	10
13[e]	Cu-Mn B (10)	110	K_2CO_3 (2)	L-proline (2)	10	90
14	CuO (I) (10)	110	K_3PO_4 (2)	none	10	10
15	$MnCl_2$ (10)	110	K_3PO_4 (2)	none	10	5
16[e]	Cu-Mn B (10)	110	K_2CO_3 (2)	none	5	85
17	$Cu(OAc)_2$ (10)	110	K_2CO_3 (2)	none	10	trace

[a] For a 100 mg scale (of **2a**) reaction, 5 mL of solvent DMSO were used.
[b] All reactions were carried out under an air atmosphere.
[c] Isolated yields.
[d] Optimized reaction conditions.
[e] Reaction under an N_2 atmosphere.

duce an excellent yield of desired product **1a** (entry 5). Two other bimetallic catalysts Cu-Mn A (2:0.25) and Cu-Mn C (Cu: Mn = 3:0.25) produced product **1a** only in traces (entries 8 and 9). The higher yield in the presence of Cu-Mn B was presumed to be due to its higher surface area compared to Cu-Mn A and C. When an SEM of Cu-Mn B was recorded, it showed the presence of a large number of adsorption sites in the materials which in part contribute to the high catalytic activity.[15–18] Furthermore, in order to understand the efficiency of the catalytic activity of Cu-Mn B catalyst over Cu-Mn A, Cu-Mn C and indi-

vidual metals (Cu and Mn), the powder X-ray diffraction (XRD) spectra of the samples were recorded (Figure S1 in the Supporting information). Cu-Mn B catalyst showed tenorite (CuO), copper manganese oxide ($Cu_{1.4}Mn_{1.6}O_4$), hausmannite, (Mn_3O_4), manganese chloride hydrate ($MnCl_2{\cdot}2H_2O$) and crednerite ($CuMn_2O_4$) phases. However, the activity of the catalyst was primarily due to the surface interaction of two bimetallic spinel oxides such as $CuMn_2O_4$ (crednerite) and $Cu_{1.4}Mn_{1.6}O_4$ which are present in this Cu-Mn B catalyst. Particularly, the copper manganese oxide (M-C) phases are essential for the catalytic activity. Cu-Mn C showed a very small amount of M-C phases, and thus has poor catalytic activity. On the other hand, Cu-Mn B has distinct M-C phases with a comparatively lower intensity of tenorite; and thus it displayed excellent catalytic activity. However, a small increase in the amount of Cu results in lower activity (as observed with Cu-Mn A catalyst – Cu: Mn = 2:0.25), which may be due to blocking of the active sites of the spinel.[21] Furthermore, the specific surface area of the Cu-Mn B catalyst was higher (49.79 $m^2 g^{-1}$) compared with Cu-Mn A (42.07 $m^2 g^{-1}$) and Cu-Mn C (46.62 $m^2 g^{-1}$). The oxidation states of both metals in Cu-Mn catalyst B were determined by XPS analysis (Supporting Information, Figure S2). The XPS analysis indicated that the Cu exists in the Cu^{2+} oxidation state and Mn in the multi-states (Mn^{2+}, Mn^{3+} and Mn^{4+}). Thus, the improved efficiency of Cu and Mn metals when combined as a bimetallic catalyst, over individual metals, could be attributed to the existence of these metals in multiple oxidation states (Cu^{+2}, Mn^{+2}, Mn^{+3} and Mn^{+4}) in bimetallic Cu-Mn catalyst. In a nutshell, the distinct M-C phases and Cr phases (of Cu-Mn oxides) along with higher surface area, and phases with less ordered arrangements in Cu-Mn B catalyst resulted in the higher reactivity.

To know the catalytic activity of individual copper and manganese metals, we conducted control experiments by using Cu(I)O and $MnCl_2$ (Table 1, entries 10–12, 14,15, and 17) but the desired product was not formed. The individual metals were ineffective, thus bimetallic Cu-Mn spinel oxides (such as $CuMn_2O_4$) were found to be important for the catalytic activity. When the reaction was performed under



[a] The reaction of 1 g aryl iodide **2a** with 632 mg benzylamine **3a** under the optimized conditions also afforded *N*-phenylbenzamide **1a** in excellent (95%) yield.

Figure 2. Substrate scope of various substituted aryl halides and substituted benzylamines for the synthesis of substituted *N*-phenylbenzamides. *Reagents and conditions:* (a) aryl iodide (1 equiv.), benzylamine (1.2 equiv.), 10% w/w Cu-Mn, 2.5 equiv. K_2CO_3, DMSO, 110 °C, 5 h, 77–94%. All reactions were carried out on a 100 mg scale (of precursor **2**).

the optimized conditions (entry 5) but under a nitrogen atmosphere (entry 16), the product was still obtained in good yields. Among various bases investigated (entries 3–5), K_2CO_3 gave good results. DMSO as solvent was found to be best among toluene, 1,4-dioxane, 1,2-dichloroethane. Only up to 5% yield of desired product could be obtained with 1,4-dioxane and 1,2-dichloroethane as solvents. The reason for DMSO showing the best results might be due to the fact that DMSO must be acting as a source of oxygen for the reaction.

With the optimized reaction conditions in our hand, we tested various substituted aryl iodides and benzylamines bearing various functional groups (Figure 2). Aryl iodides with electron-donating groups such as OMe (**1l**, **1m**, **1n**), methyl (**1o**, **1s**) and electron-withdrawing groups such as bromo (**1f, 1j**), chloro (**1g**, **1k**) and fluoro (**1p**, **1t**, **1u**) gave the desired products in good yields (Figure 2). In the case of substituted benzylamines, the reaction proceeded well with electron-donating groups such as OMe (**1c**), methyl (**1i**, **1j**, **1k**, **1l**, **1t**) as well as electron-withdrawing groups such as chloro (**1e**, **1q**, **1s**), fluoro (**1b**, **1n**, **1p**), OCF_3 (**1h**, **1u**) and CF_3 (**1d**). Slightly better yields were obtained in electron-withdrawing group-containing aryl iodides/benzylamines compared to electron-donating group-containing aryl iodides or benzylamines.

The scope of this reaction was further extended for the synthesis of 2-arylquinazolin-4(3*H*)-one derivatives, which are of tremendous medicinal importance.[22] Although numerous methods are available in the literature for the synthesis of quinazolin-4(3*H*)-ones, only few reports are available *via* direct oxidative C–H amidation in an air atmosphere.[23] Using our method, quinazolin-4(3*H*)-ones **6a–o** were prepared in 2 h in 72–98%. Interestingly, after work-up of the organic layer followed by evaporation under vacuum, pure products were obtained without the need for column chromatography. A series of substituted 2-phenylquinazolin-4(3*H*)-ones with various substituted benzylamines were prepared as depicted in Figure 3. A wide range of functional groups were well tolerated on the benzylamines including electron-withdrawing, electron-donating and neutral substituted benzylamines; all producing good yields of the corresponding 2-phenylquinazolin-4(3*H*)-ones. In order to know the role of oxygen in this reaction, a control reaction in the presence of a nitrogen atmosphere was also performed, wherein the desired product **6a** was formed in 80% yield. This clearly indicated that oxygen is not required for this reaction; and the source of oxygen is DMSO.

Next, we investigated the catalytic efficiency of Cu-Mn B catalyst for multiple use. The catalyst was recovered by filtration after every reaction and reused for five successive reactions for the synthesis of *N*-phenylbezamide **1a** without loss of significant activity. The % yields over 5 cycles were 95, 94, 92, 92 and 90%. SEM analysis of the catalyst before (unused) and after use (after 5 cycles) showed that the surface

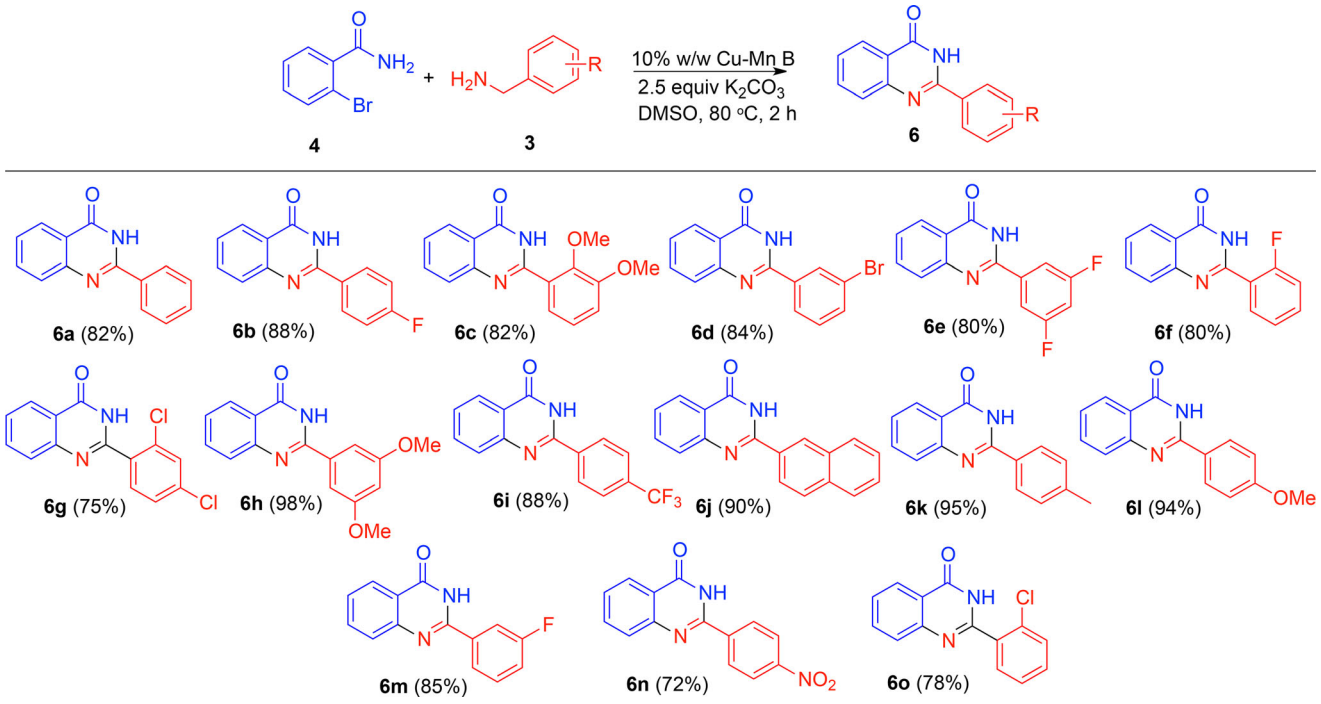


Figure 3. Substrate scope of substituted benzylamines for the synthesis of substituted 2-phenylquinazolin-4(3*H*)-ones. *Reagents and conditions:* (a) 10% w/w Cu-Mn B, 2.5 equiv. K_2CO_3, DMSO, 80 °C, 2 h, 75–98%. All reactions were carried out on a 100 mg scale (of precursor **4**).

morphology of catalyst remains unchanged even after 5 runs (Figure 4). This indicated the potential of this catalyst for the commercial and economical synthesis of this class of medicinally important heterocycles. Next in order to check the metal leaching, we analyzed the recycled catalyst by ICP-MS. The Cu and Mn contents of the fresh catalyst were found to be 612306 and 49181 mg kg^{-1}. The catalyst recycled after 5 runs showed similar metal contents (606179 and 45045 mg kg^{-1} of Cu and Mn, respectively). This clearly indicated that even after recycling the catalyst for 5 times, there was no leaching of metals from the bimetallic spinel catalyst.

Towards elucidating the reaction mechanism, we conducted a few control experiments. The reaction of aryl iodide **2a** with benzylamine **3a** under the optimized reaction conditions under a nitrogen atmosphere gave the corresponding product **1a** in 85% yield (Figure 5a and entry 16 of Table 1). This shows that external O_2 is not required for the reaction and DMSO could be the possible source of oxygen. Furthermore, we conducted a reaction without taking the aryl iodide under the optimized condition which led to the formation of benzamide **7** (Figure 5b). After synthesis of amide **7**, we then reacted it with aryl

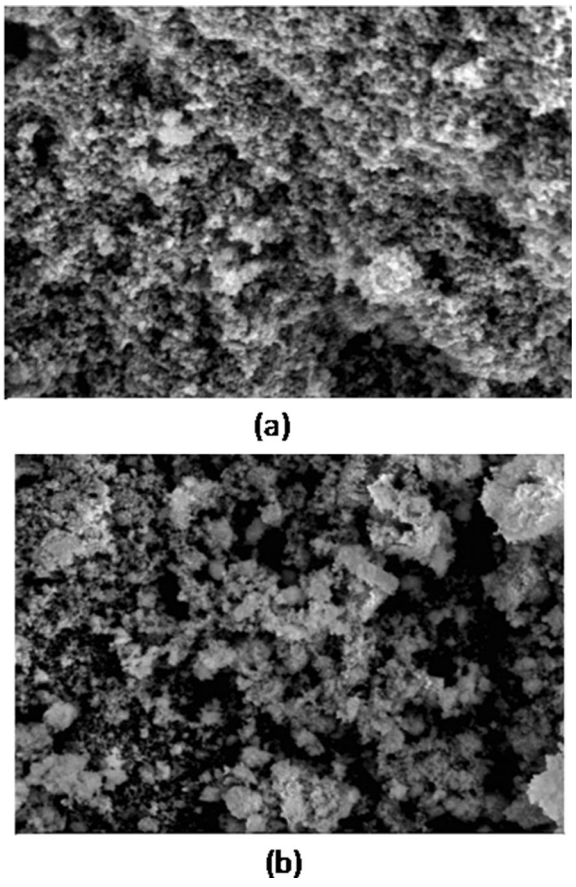


Figure 4. SEM images for catalyst before (**a**) and after 5 cycles of use (**b**).

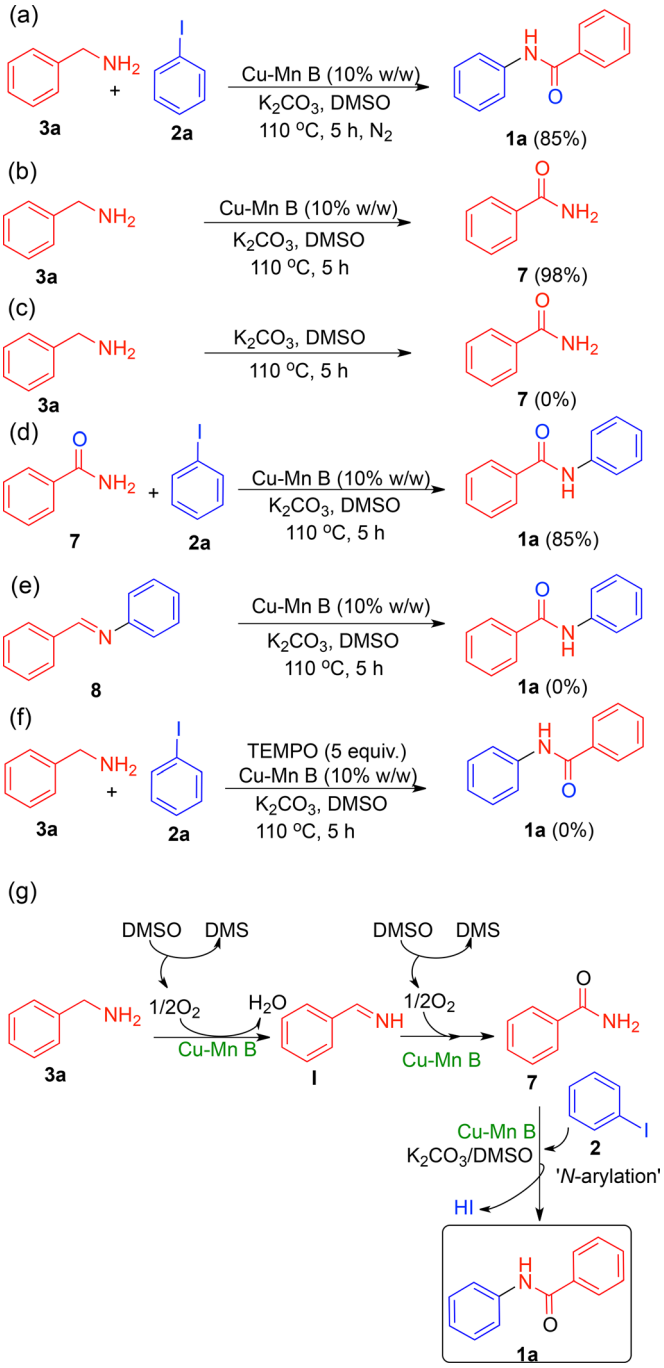


Figure 5. Control experiments (a)–(f) and proposed mechanism (g) for the synthesis of *N*-phenylbenzamide **1a**.

iodide under the optimized reaction conditions, which resulted in the formation of product **1a** in 85% yield (Figure 5d). Furthermore, we also conducted the reaction of *N*-benzylidenebenzenamine (*N*-benzylated aniline) **8** under the optimized reaction conditions in order to exclude the possibility of other reaction pathways (*N*-arylation followed by oxidation) (Figure 5e). In order to check whether DMSO auto-decomposition follows a radical pathway, the reaction of **3a** with

2a was performed in the presence of the free-radical quencher TEMPO (Figure 5f), wherein the product **1a** was not formed, indicating that the reaction process involves a free-radical mechanism.

On the basis of these control experiments, we propose a reaction mechanism as depicted in Figure 5g. Benzylamine **3a** gets converted to imine intermediate **I** which, on oxygenation in presence of DMSO under standard reaction conditions, produces amide **7**. A similar type of oxidation of benzylamines to the corresponding amides has been reported earlier using manganese dioxide as catalyst,[9c,24] and a Ru catalyst.[9b] Next, the benzamide **7** on reaction with aryl iodide (**2**) undergoes *N*-arylation through elimination of HI producing *N*-arylated benzamide **1a** (Figure 5g). Similarly, a reaction mechanism for the synthesis of 2-phenylquinazoline-4(3*H*)-ones **6** from 2-bromobenz->amide (**4**) is depicted in Figure 6.

In conclusion, we have developed an efficient, scaleable ligand-free Cu-Mn-catalyzed protocol for the synthesis of *N*-arylated amides directly from benzylamines. Its utility for the synthesis of medicinally important quinazolin-4(3*H*)-ones has also been demonstrated.

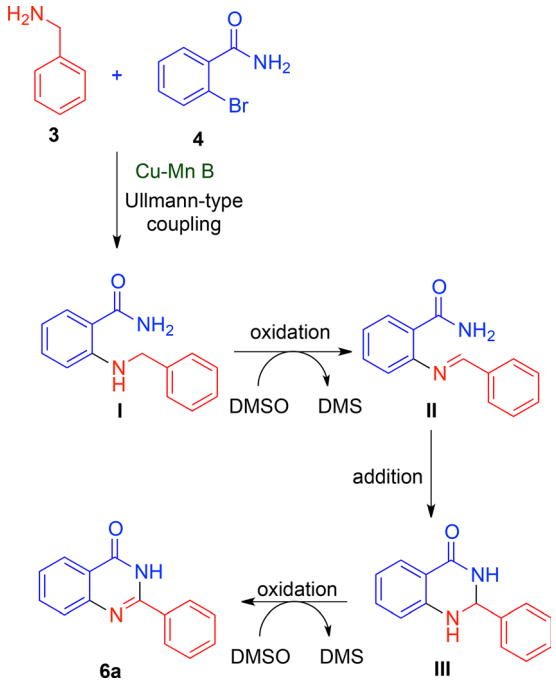


Figure 6. Proposed mechanism for the synthesis of 2-phenylquinazolin-4(3*H*)-ones.

Experimental Section

General Procedure for the Synthesis of *N*-Phenylbenzamides 1a–u and 2-Phenylquinazolin-4(3*H*)-ones 6a–p

To a solution of aryl iodide or 2-bromobenzamide (1 equiv.) in 5 mL of DMSO were added 10% w/w of Cu-Mn B, 2.5 equiv .of K_2CO_3 and 1.2 equiv. of amine and the mixture was heated at 80 °C or 110 °C for 2–5 h. After completion of the reaction, the mixture was filtered to recover the catalyst. Water was added to the filtrate and the product was extracted with EtOAc. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated to afford the crude product. Products **1a–u** were purified by silica gel column chromatography using EtOAc/hexane as eluent. Products **6a–p** were directly obtained as pure products after recrystallization with acetone.

Spectral data of the representative compound **1a** are provided below. Spectral data of the remaining compounds are provided in the Supporting Information.

***N*-Phenylbenzamide (1a):** White solid; HPLC: t_R = 6.84 min (100% purity); mp 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (brs, 1H), 7.87 (d, J = 8 Hz, 2H), 7.65 (d, J = 8 Hz, 2H), 7.54–7.45 (m, 3H), 7.38 (t, J = 8 Hz, 16 Hz, 2H), 7.17 (t, J = 8 Hz, 16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 137.9, 135, 131.8, 129.1, 128.8, 127, 124.6, 120.3; GC-MS (EI): m/z = 197 (M^+, 100), 181 (7), 180 (39); HR-ESI-MS: m/z = 198.0915 calcd for $C_{13}H_{11}NO$ + H^+: 198.0913; IR ($CHCl_3$): ν_{max} = 3343, 2923, 2852, 2108, 1654, 1598, 1588, 1525, 1437, 1322, 1216, 1075, 1018 cm^{-1}.

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8 Ligand-Free Copper-Manganese Spinel Oxide-Catalyzed Tandem One-Pot C–H Amidation and *N*-Arylation of Benzylamines: A Facile Access to 2-Arylquinazolin-4(3*H*)-ones

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