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Copper-Catalyzed Oxidative C-H Bond Functionalization of *N*-Allylbenzamide for Regioselective C-N and C-O Bond Formation

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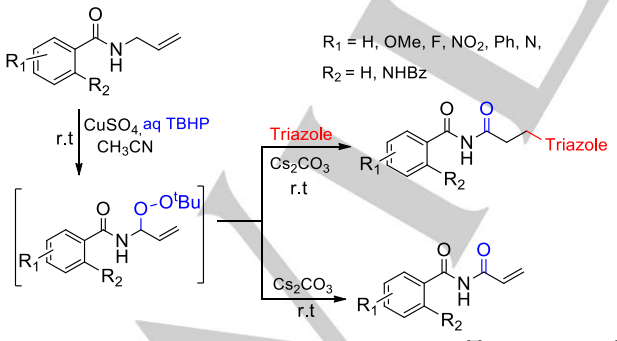
Abstract: Novel copper-catalyzed oxidative couplings of *N*-allylbenzamides via C-H bond functionalization for C-N and C-O bond formations have been developed. To demonstrate the utility of this approach, it was applied for the synthesis of β-aminoimides and Imides. To the best of our knowledge, these are the first examples in which different classes of *N*-containing compounds were directly prepared from the readily available *N*-allylbenzamides using an inexpensive catalyst-oxidant-base ($CuSO_4$/TBHP/Cs_2CO_3) system.

The immense potential of C-H bond activation for organic transformations using transition metal catalysts has been realized in robust and efficient methods for C-C, C-O and C-N bond formations over the decades.[1] Although different transition metals are known to catalyze the C-H oxidations,[2] among them copper is particularly advantageous because it is less expensive, low toxicity with broad tolerance. Recently, the copper catalyzed C-H oxidations for C(sp)-, C(sp^2)- and C(sp^3)-X (X = C, N, and O) bond formations have been described.[3] Also, the direct functionalization of allylic C-H bond of terminal alkenes has received a great deal of interest, leading to the frequent appearance of new protocols.[4] In particular, transition-metal catalyzed direct difunctionalization of allyl moiety is an important strategy for the synthesis of complex molecules.[5] In this context, very recently, Zhao et al. reported nickel-catalyzed 1,3 difunctionalization of allylamine moieties.[6]

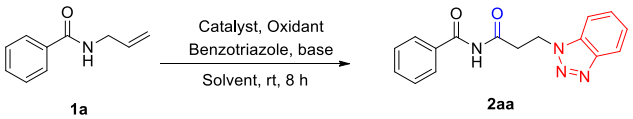
Scheme 1. C-H bond functionalization of allylbenzamides.



N-Containing compounds such as imides[7] and triazole[8] moieties are present in a variety of biologically and medicinally active compounds, and their synthesis and functionalization have received great attention. Traditionally, the synthesis of imides have relied primarily on amides with carbonyl chlorides, aldehydes, and acetic anhydride.[9] Notwithstanding these advancements, current trends on imide syntheses focus on the direct oxidation of sp^3 C-H bond adjacent to the nitrogen atom.[10] Herein we disclose an efficient and practical approach for the oxidative coupling of *N*-allylbenzamides with triazoles as an amine source into the corresponding β-aminoimides, using $CuSO_4$-TBHP as the system. To the best of our knowledge, no report exists in the literature on these oxidative transformations (Scheme 1).

The required substrates *N*-allylbenzamides were readily prepared from the corresponding benzoyl chloride and allylamine as per our earlier method.[11] At the outset, *N*-allylbenzamide **1a** was chosen as the model substrate to optimize reaction conditions including the oxidant equivalents, catalyst type, base, solvent, and time as disclosed in Table 1. Accordingly, a preformed solution of *N*-allylbenzamide **1a** (1.0 equiv), TBHP (70% solution in water, 2.0 equiv) and $CuSO_4$ (2.5 mol %) was dissolved in CH_3CN (2 mL) at room temperature. Then, Cs_2CO_3 (2.0 equiv) and 1*H*-benzotriazole (1.0 equiv) as a nucleophilic amine source was added and the resultant solution was stirred for 10 h at same temperature, the reaction proceeded to afford the desired product β-aminoimide (**2aa**) in low yield (Table 1, entry 1). In order to improve the efficiency, we studied the amount of $CuSO_4$, to our delight, 10 mol% of catalyst provided an 89% yield of the desired product **2aa** (Table 1, entries 2, 3 and 4). Moreover, during the optimization study, the required TBHP was reduced to 1.0 equiv and 1.5 equiv and the yield of **2aa** correspondingly decreased to 52% and 67% respectively (Table 1, entries 5 and 6). In the absence of the catalyst no product was formed (Table 1, entry 7). Next, the replacement of $CuSO_4$ with other catalysts, including CuBr, TBAI, I_2, and NIS resulted in no improvement (Table 1, entries 8, 9, 10 and 11). The replacement of TBHP with *m*-CPBA and oxone, the product was undetected (Table 1, entries 12 and 13). In the absence of the base no product formation was identified (Table 1, entry 14). Also, we optimized the reaction conditions with various bases such as K_2CO_3, Na_2CO_3, and $CaCO_3$ which resulted in a decreased yield of **2aa** (Table 1, entries 15, 16 and 17). Further optimization using other solvents such as CH_2Cl_2, 1, 2-dichloroethane (DCE), and THF resulted in the formation of **2aa** in lower yields (Table 1, entries 18, 19 and 20). Through, these results we concluded that $CuSO_4$ (10 mol %), TBHP (70% solution in water, 2.0 equiv) and Cs_2CO_3 (2.0 equiv) in CH_3CN (2 mL) at room temperature are the optimal conditions for the synthesis of β-aminoimide **2aa** (Table 1, entry 4).

Table 1. Optimization of the reaction conditions[a,b].



1a **2aa**

Entry	Catalyst (mol%)	oxidant (equiv.)	Base (2equiv.)	Solvent	Yield (%)[b]

1	$CuSO_4$(2.5)	TBHP (2)	Cs_2CO_3	CH_3CN	26
2	$CuSO_4$ (5)	TBHP (2)	Cs_2CO_3	CH_3CN	44
3	$CuSO_4$(7.5)	TBHP (2)	Cs_2CO_3	CH_3CN	76
4	**$CuSO_4$(10)**	**TBHP (2)**	**Cs_2CO_3**	**CH_3CN**	**89**
5	$CuSO_4$ (10)	TBHP (1)	Cs_2CO_3	CH_3CN	52
6	$CuSO_4$ (10)	TBHP(1.5)	Cs_2CO_3	CH_3CN	67
7	-	TBHP (2)	Cs_2CO_3	CH_3CN	0
8	CuBr (10)	TBHP (2)	Cs_2CO_3	CH_3CN	38
9	TBAI (10)	TBHP (2)	Cs_2CO_3	CH_3CN	32
10	I_2 (10)	TBHP (2)	Cs_2CO_3	CH_3CN	Trase
11	NIS (10)	TBHP (2)	Cs_2CO_3	CH_3CN	10
12	$CuSO_4$ (10)	*m*-CPBA (2)	Cs_2CO_3	CH_3CN	0
13	$CuSO_4$ (10)	Oxone (2)	Cs_2CO_3	CH_3CN	0
14	$CuSO_4$ (10)	TBHP (2)	-	CH_3CN	0
15	$CuSO_4$ (10)	TBHP (2)	K_2CO_3	CH_3CN	34
16	$CuSO_4$ (10)	TBHP (2)	Na_2CO_3	CH_3CN	Trase
17	$CuSO_4$ (10)	TBHP (2)	$CaCO_3$	CH_3CN	0
18	$CuSO_4$ (10)	TBHP (2)	Cs_2CO_3	CH_2Cl_2	56
19	$CuSO_4$ (10)	TBHP (2)	Cs_2CO_3	DCE	20
20	$CuSO_4$ (10)	TBHP (2)	Cs_2CO_3	THF	0

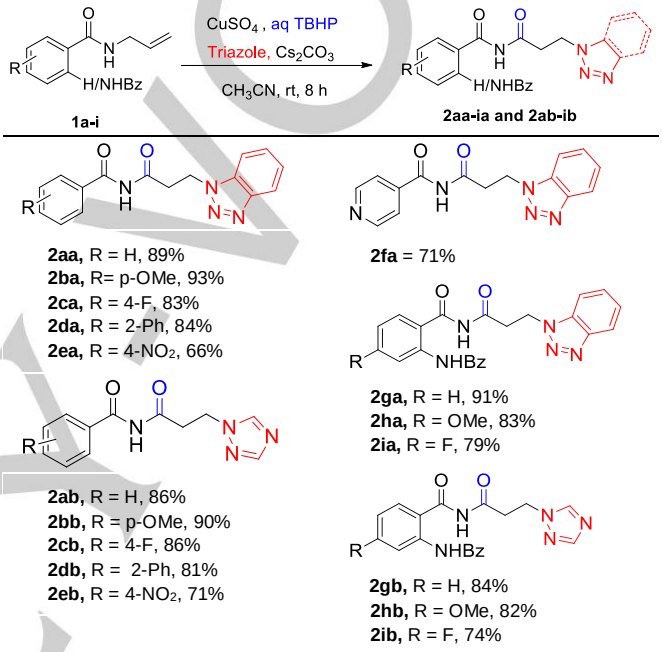
[a] Reaction conditions: *N*-allylbenzamide (0.62 mmol), aq. TBHP (1.24 mmol), $CuSO_4$ (10 mol%), Cs_2CO_3 (1.24 mmol), benzotriazole (0.6 mmol, 1.0 equiv.), solvent (2 mL), temperature (rt) under nitrogen atmosphere.

[b] Isolated yield.

Having optimized reaction conditions in hand, we investigated the scope and generality of the oxidative synthesis of β-aminoimide **2**. As illustrated (Scheme 2), all the substrates **1a-i** well tolerated the optimized conditions to furnish the corresponding β-aminoimide derivatives **2** in good to excellent yields. Interestingly, the reaction shows excellent regioselectivity. The electron rich substrate p-OMe (**1b**) also underwent the reaction to give the desired product **2ba** in 93% yield. Subsequently, we next probed the feasibility of electron-withdrawing substituent such as (F, Ph, and NO_2) **1c-1e** on the phenyl ring. Of note, all the reactions proceeded smoothly, affording the corresponding β-aminoimide products **2ca-2ea** in 66-84% yields. Noteworthy, a heterocyclic bearing allylamide such as *N*-allylisonicotinamide **1f** performed well under oxidative coupling process to generate **2fa** in 71% yield. Notably, the oxidative addition reaction of sterically hindered substrate *N*-allyl-2-benzamidobenzamide **1g** and their substituent such as methoxy **1h** and fluoro **1i** moieties are accomplished successfully to obtain the β-aminoimide derivatives **2ga**, **2ha** and **2ia** in 91%, 83% and 79% yields respectively.

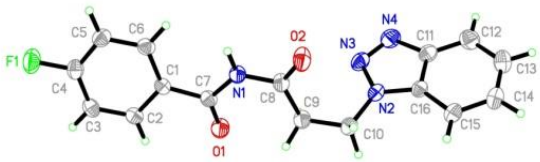
Interestingly, by switching the nucleophilic amine source to 1,2,4 triazole, oxidative coupling reaction of **1a** proceeded smoothly to afford the corresponding aminoimide **2ab** in 86% yield (Scheme 2). Likewise, a range of *N*-allylbenzamides (**1b-e**) and sterically hindered substrates (**1g**-**1i**) bearing electronically varied groups (e.g. OMe, F, Ph, NO_2) on the phenyl ring were found to be tolerant in these transformations, and the corresponding products (**2ab**-**2eb** and **2gb**-**2ib**) were obtained in moderate to good yields in highly regioselective manner. Further structural confirmation of 2ca and 2ab was ascertained by X-ray studies (see SI). Other *N*-containing nucleophiles did not yield the respective products.

Scheme 2. Synthesis of β-amino imides [a,b].



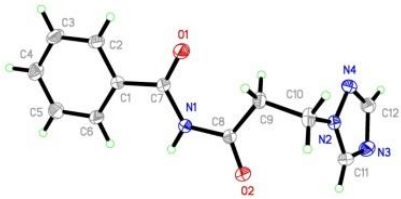
[a] Reaction conditions: **1a** (1.0 equiv), $CuSO_4$ (10 mol%), aq. TBHP (2.0 equiv), triazole (1.0 equiv) and Cs_2CO_3 (2.0 equiv) in CH_3CN (2 mL) solvent at rt. [b] Isolated yield.

Figure 1. ORTEP representation of Compound **2ca** (CCDC 1837199).



X-ray crystal structure of **2ca** showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii.

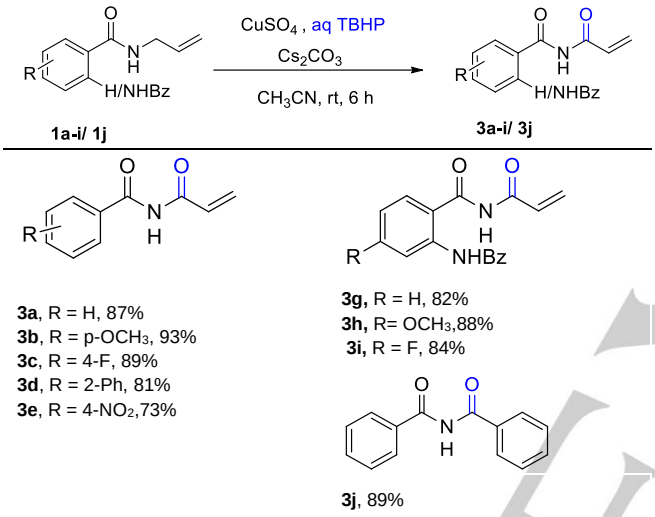
Figure 2. ORTEP representation of Compound **2ab** (CCDC 1837198).



X-ray crystal structure of **2ab** showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii.

Further, *N*-allylbenzamides **1a** treated under optimized reaction conditions in the absence of nucleophilic amine source, afforded the corresponding α,β-unsaturated imides **3a** in 87% yield (Scheme 3). While the substrate with an electron-donating group (-OMe) **1b** gave the desired product **3b** in 93% yield. *N*-allylbenzamides with electron-withdrawing groups such as -F, -Ph and -NO_2, substrates **1c-e** were also applied in the reaction successfully to provide the corresponding imide compounds **3c-e** in 89%, 81% and 73% yields respectively. Further, the new series of sterically hindered substrate *N*-allyl-2-benzamidobenzamides **1g**, **1h** and **1i** proceeded smoothly to afford the corresponding products **3g**, **3h** and **3i** in good yields effectively. Noteworthy that *N*-benzylbenzamide **1j** also afforded product **3j** in good yield 89%.

Scheme 3. Synthesis of N-Acryloylbenzamides [a,b].



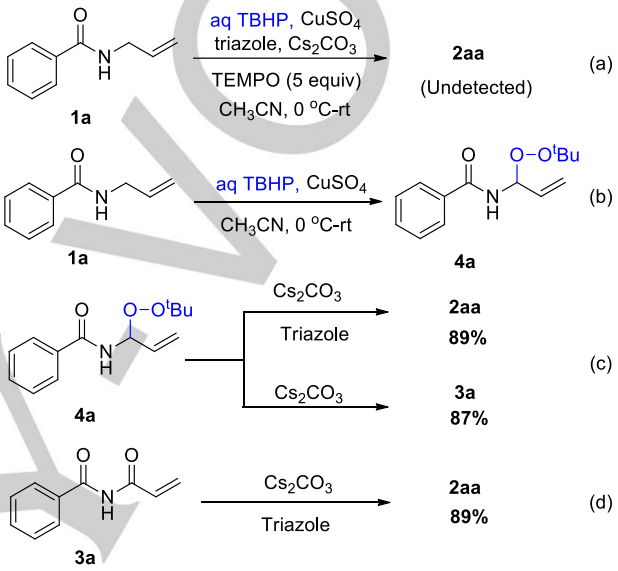
[a] Reaction conditions: **1a** (1.0 equiv), $CuSO_4$ (10 mol%), aq. TBHP (2.0 equiv) and Cs_2CO_3 (2.0 equiv) in CH_3CN (2 mL) solvent at rt.

[b] Isolated yield.

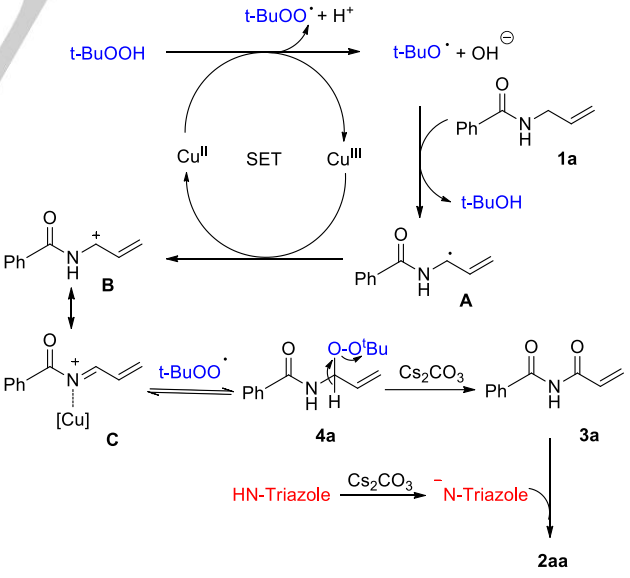
To gain insight into the mechanism of these oxidative coupling reactions some control experiments were carried out (Scheme 4). First, 5 equiv of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was added into the **1a** under standard conditions, and it was found that the reaction was completely inhibited. Thus, it indicates a radical nature of the mechanism (Scheme 4a). Next, **1a** was treated with aq.TBHP and $CuSO_4$, afforded the corresponding peroxide **4a** (Scheme 4b). Further, to learn the reaction path, *N*-(1-(tert-butylperoxy)allyl)benzamide **4a** was treated with triazole under the optimized conditions, the desired aminoimide **2aa** was obtained respectively, and the absence of nucleophilic amine source, afforded the corresponding imide **3a**. It gives clear idea that the reaction goes through the tert-butylperoxy intermediate (Scheme 4c). Also, *N*-acryloylbenzamide **3a** when subjected to the optimized conditions gave amino imide **2aa** (89%) with triazoles. It demonstrated that triazoles would participate via aza-Michael addition pathway (Scheme 4d).

On the basis of the control experiments and previous reports, we propose a possible mechanism as shown in Scheme 5. Initially, the first step involves a TBHP cleavage initiated by a copper (II) species to give a tert-butoxy radical.[10f,12] The tert-butoxy radical abstracts an allylic hydrogen of **1a** providing allylic radical **A**. Single-electron transfer (SET) from **A** onto the generated copper (III) species leads to allylic cation **B**, which readily undergoes oxidation to yield imine intermediate **C**. *N*-acyliminium intermediate **C** may succumb to the nucleophilic addition of TBHP and generate an intermediate **4a**. Further, peroxide **4a** converted into the corresponding imide **3a** by Cs_2CO_3 via Kornblum-DeLaMare rearrangement.[13] Finally, Michael addition of **3a** with triazole nucleophile gave the desired product **2aa**.

Scheme 4. Control experiments.



Scheme 5. Proposed Mechanism.



In conclusion we have demonstrated C-H functionalization of *N*-allylbenzamide derivatives by an efficient novel copper catalyzed protocol in “one-pot” fashion. The direct oxo-amination of *N*-allylbenzamide derivatives into the β-aminoimide involved mild conditions using TBHP as the oxidant, $CuSO_4$ as the catalyst, Cs_2CO_3 as the base, and triazole as a nucleophilic amine source. Subsequently, the direct amidation of *N*-

allylbenzamide derivatives into the *N*-acryloylbenzamides under same oxidative conditions. Efforts to find newer applications of this protocol are currently underway in our laboratory.

Experimental Section

General procedure for the synthesis of β-amino imide 2aa

N-Allylbenzamide **1a** (0.1 g, 0.62 mmol.), TBHP (70 % in H_2O, 0.12 mL, 1.24 mmol.) and $CuSO_4$ (10 mol%, 0.01 g, 0.062 mmol.) was dissolved in CH_3CN (2 mL) room temperature. Then, Cs_2CO_3 (0.4 g, 1.24 mmol.) and Benzotriazole (73 mg, 0.62 mmol.) was added and the resultant solution was stirred for 8 h at same temperature. The reaction was monitored by TLC analysis until the starting material was consumed. After the reaction was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to get crude. The crude was purified by silica gel column chromatography using EtOAc: hexane as eluents to afford corresponding product **2aa**.

General procedure B for the synthesis of N-Acryloylbenzamide 3a

N-Allylbenzamide **1a** (0.1 g, 0.62 mmol.), TBHP (70 % in H_2O, 0.12 mL, 1.24 mmol.) and $CuSO_4$ (10 mol%, 0.01 g, 0.062 mmol.) was dissolved in CH_3CN (2 mL) at room temperature. Then, Cs_2CO_3 (0.4 g, 1.24 mmol.) was added and the resultant solution was stirred for 6 h at same temperature. The reaction was monitored by TLC analysis until the starting material was consumed. After the reaction was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to get crude. The crude was purified by silica gel column chromatography using EtOAc: hexane as eluents to afford corresponding product **3a**.

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Keywords: copper-catalyzed • oxidative coupling • oxo-amination • regioselectivity • imides

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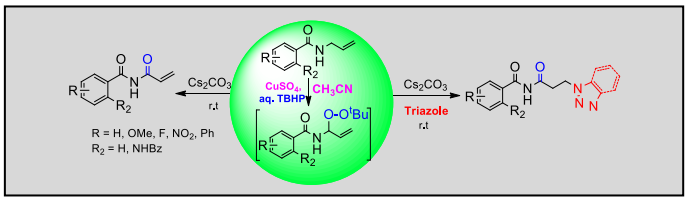
Entry for the Table of Contents



Difunctionalization of *N*-allylbenzamide with triazole as nucleophilic amine source under mild reaction conditions ($CuSO_4$/TBHP/Cs_2CO_3) provided β-aminoimides in excellent regioselectivity. Also, the direct amidation of *N*-allylbenzamide derivatives into the *N*-acryloylbenzamides.