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PII: S0040-4039(19)30390-9
DOI: https://doi.org/10.1016/j.tetlet.2019.04.041
Reference: TETL 50756

To appear in: *Tetrahedron Letters*

Received Date: 12 March 2019
Revised Date: 22 April 2019
Accepted Date: 25 April 2019

Please cite this article as: Ranjith, J., Krishna, P.R., Copper-Catalyzed Oxidative C-H Bond Functionalization of *N*-Allylbenzamide for C-N and C-C Bond Formation, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.04.041

Graphical Abstract

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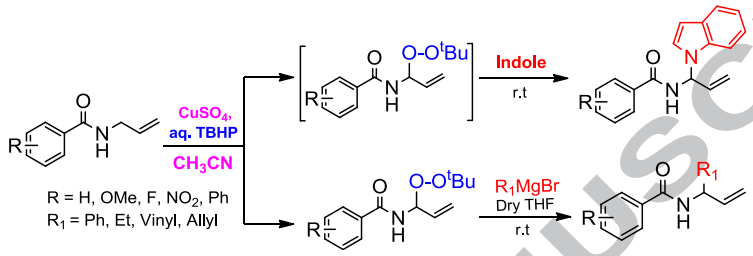

Tetrahedron Letters
journal homepage: www.elsevier.com

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

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Copper-catalyzed
Oxidative coupling
CDC coupling
Grignard reaction

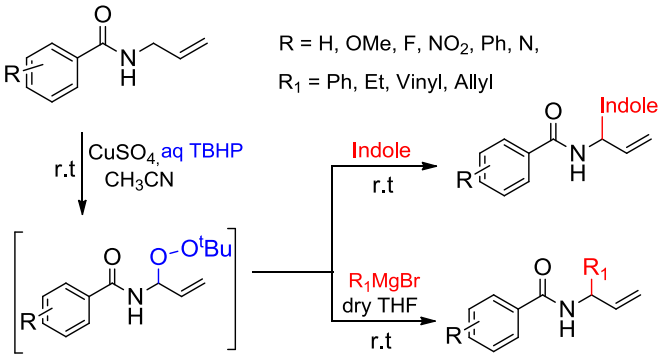
ABSTRACT

C-H Bond functionalization for C-N and C-C bond formations via cross-dehydrogenative coupling (CDC) of *N*-allylbenzamides with indole as amine source has been developed under a copper-catalyzed condition. 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 ($CuSO_4$/TBHP) system. Further, it was applied for the synthesis of α-substituted *N*-allylbenzamides by using Grignard reagent as nucleophiles

1. Introduction

The activation of C-H bonds for coupling reactions is a great importance in organic synthesis since nitrogen-containing compounds such as amide[1] and indole aminal[2] moieties are present in a variety of biologically and medicinally active compounds, and their synthesis and functionalization have received great attention. However, transition-metal-catalyzed C(sp^2)-N bond formation has been intensively studied,[3] C(sp^3)-H bonds which are naturally more abundant, still face great challenges in C-N bond formation.[4] Methodologies for direct α-C-H oxidation when the carbon adjacent to the nitrogen and oxygen atoms were developed under transition metals such as iron, copper and metal-free conditions.[5] Transition-metal-catalyzed cross-dehydrogenative coupling (CDC) reactions have emerged as powerful tools for organic synthesis. Besides being highly atom- and step-economic way of constructing C-C,[6] C-O[7] and C-N[8] bonds, such methods allow introduction of other functional groups directly through oxidative sp^3 C-H bond activation, in particular for amines or amides when the carbon adjacent to the nitrogen atom is the point of activation.

Further, copper catalyst in combination with TBHP oxidant is now emerging as a more powerful tool to functionalize C(sp^3)-H bonds followed by cross-coupling (CDC).[9] Herein we disclose an efficient and practical approach for the oxidative coupling of *N*-allylbenzamides with indoles and Grignard reagent as an nucleophile source into the α-substituted *N*-allylbenzamides 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).

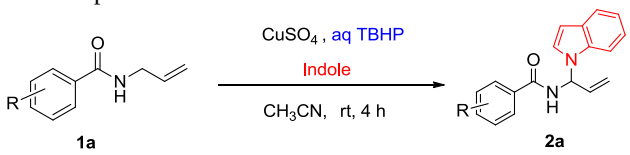


Scheme 1. C-H bond functionalization of allylbenzamides

The required substrates *N*-allylbenzamides were readily prepared from the corresponding benzoyl chloride and allylamine as per our earlier method.[10] At the outset, *N*-allylbenzamide **1a** was chosen as the model substrate to optimize reaction conditions including the oxidant equivalents, catalyst type and solvent 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 TBAI (10 mol %) was dissolved in CH_3CN (2 mL) at room temperature. Then indole (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 indole aminal (**2a**) in low yield (Table 1, entry 1). Next, the replacement of TBAI with other catalysts, including I_2, NIS and CuBr resulted in no improvement (Table 1, entries 2, 3 and 4). Then, the replacement of catalyst with $CuSO_4$ (2.5 mol %), the reaction proceeded to

afford the desired product indole aminal (**2a**) in 36% (Table 1, entry 5). In order to improve the efficiency, we studied the amount of $CuSO_4$, to our delight, 10 mol% of catalyst provided an 84% yield of the desired product **2a** for 4 h at same temperature (Table 1, entries 6, 7 and 8). Moreover, during the optimization study, the required TBHP was reduced to 1.0 equiv and 1.5 equiv and the yield of **2a** correspondingly decreased to 50% and 67% respectively (Table 1, entries 9 and 10). In the absence of the catalyst no product was formed (Table 1, entry 11). The replacement of TBHP with *m*-CPBA and oxone, the product was undetected (Table 1, entries 12 and 13). Further optimization using other solvents such as CH_2Cl_2, 1, 2-dichloroethane (DCE), and THF resulted in the formation of **2a** in lower yields (Table 1, entries 14, 15 and 16). Through, these results we concluded that $CuSO_4$ (10 mol %) and TBHP (70% solution in water, 2.0 equiv) in CH_3CN (2 mL) at room temperature are the optimal conditions for the synthesis of indole aminal **2a** (Table 1, entry 8).

Table 1. Optimization of reaction conditions[a]

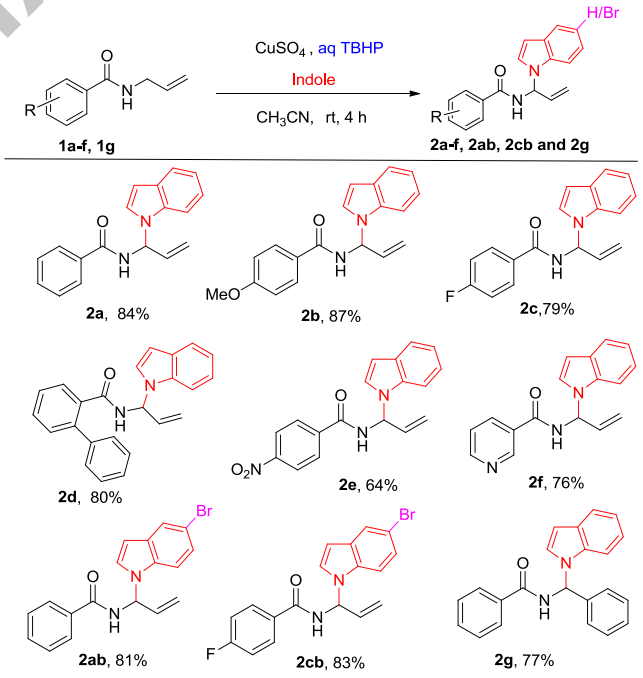


Entry	Catalyst (mol%)	oxidant (equiv.)	Solvent	Yield (%)[b]
1	TBAI (10)	TBHP (2)	CH_3CN	15
2	I_2 (10)	TBHP (2)	CH_3CN	Trace
3	NIS (10)	TBHP (2)	CH_3CN	10
4	CuBr (10)	TBHP (2)	CH_3CN	32
5	$CuSO_4$(2.5)	TBHP (2)	CH_3CN	36
6	$CuSO_4$ (5)	TBHP (2)	CH_3CN	52
7	$CuSO_4$(7.5)	TBHP (2)	CH_3CN	76
8	**$CuSO_4$(10)**	**TBHP (2)**	**CH_3CN**	**84**
9	$CuSO_4$ (10)	TBHP (1)	CH_3CN	50
10	$CuSO_4$ (10)	TBHP(1.5)	CH_3CN	67
11	-	TBHP (2)	CH_3CN	0
12	$CuSO_4$ (10)	*m*-CPBA (2)	CH_3CN	0
13	$CuSO_4$ (10)	Oxone (2)	CH_3CN	0
14	$CuSO_4$ (10)	TBHP (2)	CH_2Cl_2	56
15	$CuSO_4$ (10)	TBHP (2)	DCE	20
16	$CuSO_4$ (10)	TBHP (2)	THF	0

[a] Reaction conditions: *N*-allylbenzamide (0.62 mmol), $CuSO_4$ (10 mol%), aq. TBHP (1.24 mmol), indole (0.6 mmol, 1.0 equiv.), solvent (2 mL), temperature (rt) under nitrogen atmosphere.
[b] The yields refer to isolated products purified by column chromatography.

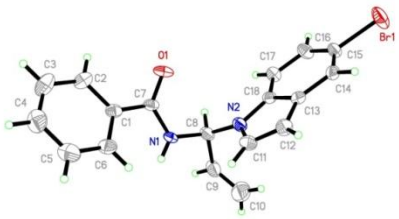
Having optimized reaction conditions in hand, we investigated the scope and generality of the oxidative C-H/N-H cross-coupling adjacent to an amide nitrogen atom, affording the cross dehydrogenative coupling (CDC) product **2**. As illustrated (Scheme 2), all the substrates **1a-g** well tolerated the optimized conditions to furnish the corresponding indole aminal derivatives **2** in good to excellent yields. Alerted, we quickly sought to broaden the scope of the *N*-allylbenzamide derivatives with electron-donating, electron-withdrawing groups on phenyl ring was investigated. The reaction with electron-donating derivatives showed higher yields than electron-withdrawing derivatives (**2b-2e**). Pleasingly, a heterocyclic bearing allylamide such as *N*-allylisonicotinamide (**1f**) also underwent smooth reaction to furnish the product **2f** in 76% yield. Notably, the oxidative CDC reaction was applicable to a bromoindole with *N*-allylbenzamide (**1a**), *N*-allyl-4-fluorobenzamide (**1c**), when evaluated under the established conditions to obtain the anticipated cross-coupling products **2ab** and **2cb** in 81% and 83% yields respectively. Also, the *N*-benzylbenzamide **1g** could be employed in the reaction to give the desired product **2g** in 77% yield. Further, structural confirmation of **2ab** was ascertained by X-ray studies (see SI).

Scheme 2. Synthesis of Indol Aminals[a,b]



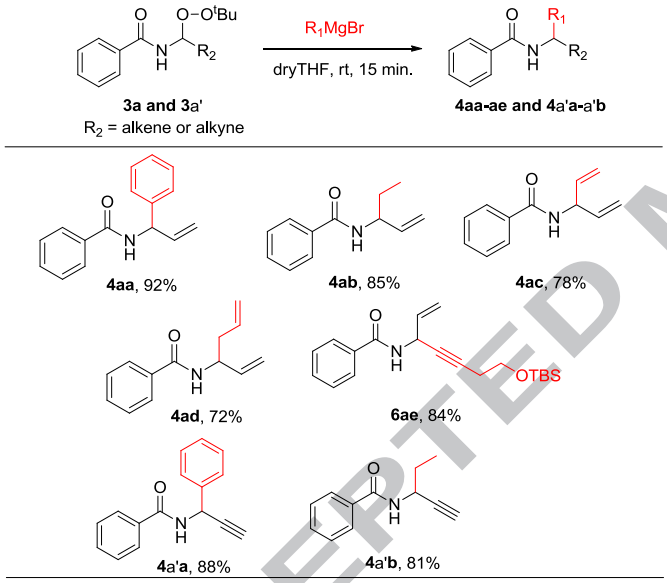
[a]Reaction conditions: **1a** (1.0 equiv), $CuSO_4$ (10 mol%), aq. TBHP (2.0 equiv), indole (1.0 equiv.), solvent (2 mL), temperature (rt) under nitrogen atmosphere. [b]Isolated yields.

Figure 1. ORTEP representation of Compound **2ab** (CCDC 1837200)



After successful C-H/N-H oxidative coupling reaction, we explored the protocol for C-C bond formation through oxidative functionalization of C-H bond activation (Scheme 3). Since **3a** or **3a'** were the presumable intermediates, we isolated them independently and conducted the next set of reactions. Thus, the *N*-allylbenzamide **1a** when treated with aq. TBHP and $CuSO_4$ in CH_3CN, gave the desired product *N*-(1-(*tert*-butylperoxy)allyl)benzamide (**3a**) in good yield. Peroxide **3a** when exposed to 3.0 equiv of PhMgBr in dryTHF, *N*-(1-phenylallyl) benzamide **4aa** was obtained in 92% yield within 15 min at room temperature (Scheme 3). Encouraged by these findings, we next examined the scope of aliphatic Grignard reagents such as EtMgBr, vinylMgBr, allylMgBr, and (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilaneMgBr which an oxidative functionalization successfully on **3a** furnished the corresponding products (**4ab-4ae**) in good to excellent yields. Moreover, *N*-(1-(*tert*-butylperoxy) prop-2-yn-1-yl) benzamide **3a'** was prepared the same way as compound **3a** by using *N*-propargylbenzamide. Similarly, peroxide **3a'** on exposure to PhMgBr and EtMgBr afforded the desired compounds **4a'a** and **4a'b** in good yields.

Scheme 3. Synthesis of α-substituted *N*-allylbenzamides with Grignard Reagents[a,b]



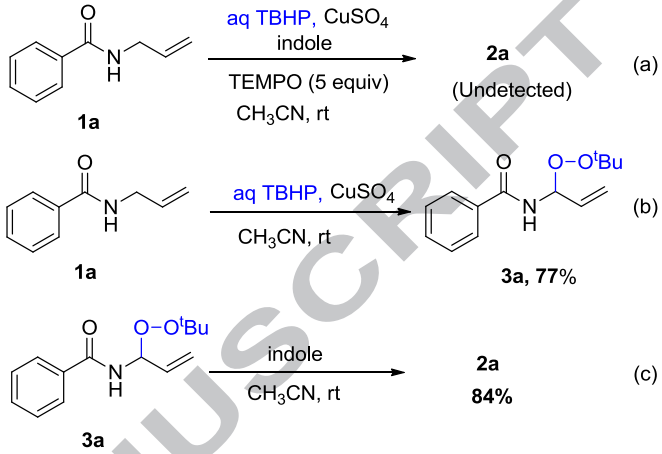
[a]Reaction conditions: **3a** (1.0 equiv), R_1MgBr (3.0 equiv), in dry THF (2 mL) solvent, temperature (rt) under nitrogen atmosphere. [b]Isolated yields.

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, **1**a was treated with aq.TBHP and $CuSO_4$, to afford the corresponding peroxide **3a** (Scheme 4b). Further, to learn the reaction path, *N*-(1-(tert-butylperoxy)allyl)benzamide **3a** was treated with indole under the optimized conditions, the desired indole aminal **2a** was obtained (Scheme 4c). It gives clear idea that the reaction goes through the tert-butylperoxy intermediate, indole would participate via CDC coupling reaction.

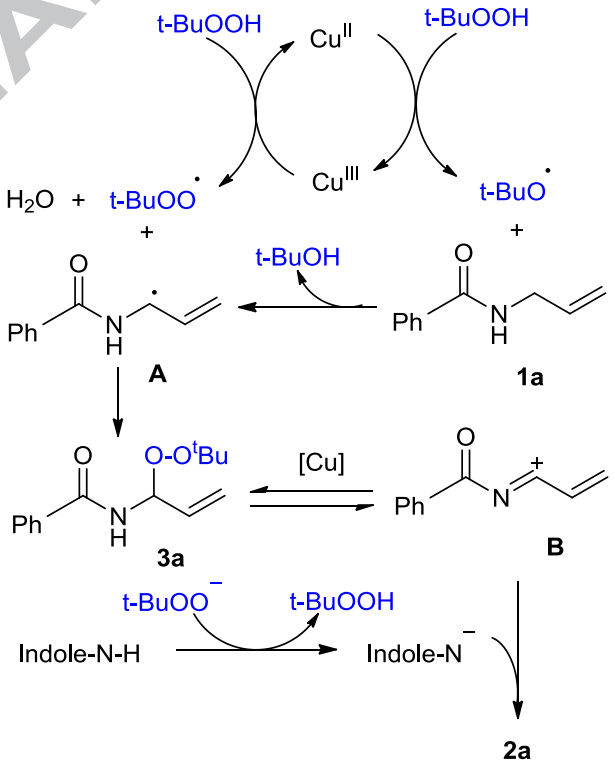
On the basis of the control experiments and previous reports, we propose a possible mechanism as shown in Scheme 5. Initially, the role of copper (II) species is to catalyze the decomposition of the oxidant tBuOOH into tBuO$^{\bullet}$ and tBuOO$^{\bullet}$.[11]

Then tert-butoxy radical can be hydrogen atom acceptor in reaction with **1a**, forming radical **A**. This reacts further to afford peroxide **3a**, which decomposes to the iminium intermediate **B** by copper catalysis. Finally, CDC coupling of iminium intermediate with indole nucleophile gave the desired product **2a**.

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 oxidative coupling of *N*-allylbenzamide with indoles furnished dehydrogenative C (sp^3)-N cross coupling products in mild conditions using TBHP as the oxidant, $CuSO_4$ as the catalyst. Likewise, we have obtained α-substituted amides by treating tert-butylperoxyallylbenzamide with Grignard reagents. Efforts to find newer applications of this protocol are currently underway in our laboratory.

Acknowledgments

J.R thanks CSIR New Delhi for research fellowship. I thank Dr. Balasubramanian Sridhar for X-ray analysis, Laboratory of X-ray Crystallography, CSIR-IICT. CSIR-IICT Commun. No. IICT/pubs./2019/057.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

1. C-H Bond functionalization
2. Cross-dehydrogenative coupling (CDC)
3. Grignard Reaction