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Isolation and characterization of 2-alkylaminobenzo[*b*]furans. Evidence for competing O-arylation in Cu-catalyzed intramolecular amidation

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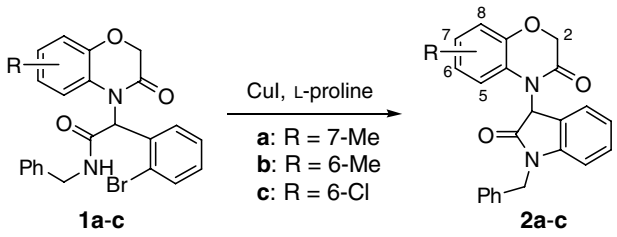
Abstract—2-Alkylaminobenzo[*b*]furans were isolated and characterized by X-ray crystal structural analysis, for the first time, from the Cu-catalyzed intramolecular amidation of hindered secondary amides under controlled microwave heating. A mechanism was proposed to account for competing Cu-catalyzed intramolecular N- and O-arylation pathways, which were controlled by the bulkiness of substituents on the nitrogen atom of secondary amides.

The Cu-mediated C_{Ar}–heteroatom bond formation[1] has been known in the literature and practiced in synthetic laboratories since the Ullmann era over 100 years ago. The catalytic versions of these transformations, in particular, the Cu-catalyzed N-arylation of amines (Ullmann reaction)[2] and amides (Goldberg reaction)[3], have been developed recently with the introduction of various types of enabling ligands to Cu.[1] For example, amino acids,[4] 1,2-diamines,[5] *N*,*N*-diethylsalicylamide,[6] and 1,10-phenanthrolines[7] have been reported for N-arylation of amides at relatively lower temperatures (80–120 °C for aryl halides). Despite significant advance witnessed in Cu-catalyzed transformations, a survey on the current literature reveals that the Cu-catalyzed amidation of aryl or vinyl bromides and iodides has been limited to primary amides, anilides, and lactams.[1] Except for *N*-cyclohexylformamide,[5] there is no prior report on the Cu-catalyzed N-arylation of sterically hindered acyclic secondary amides such as *N*-cyclohexyl and *N*-*t*-butyl carboxamides.[8] As a matter of steric hindrance,[9] the acyclic secondary amides possessing an *N*-bulky substituent might be difficult in coordination with the metal via the deprotonated amide nitrogen, rendering alternative reaction pathways such as O-arylation of amides possible.[10] We report here the isolation and structural characterization of 2-alkylaminobenzo[*b*]furans and propose a competing O-arylation pathway for Cu-catalyzed intramolecular N-arylation of bulky acyclic secondary amides.

We initiated our investigation with the *N*-benzyl (2-bromophenyl)acetamides **1a–c** (Scheme 1). The substrates were easily prepared from 2-aminophenols, 2-bromobenzaldehyde, 2-bromoacetic acid, and benzyl isocyanide through the microwave-assisted one-pot U-4CR and intramolecular O-alkylation approach recently reported in our laboratories.[11] Upon treating **1a–c** with CuI and L-proline[4] in the presence of a base in a protic polar solvent, the 2-oxindoles **2a–c** were produced (Table 1). As compared to the conventional heating at 100 °C for 20 h in DMSO, microwave heating[11,12] at



Scheme 1. Cu-catalyzed intramolecular amidation to 2-oxindoles.

Keywords: Amidation; Benzo[*b*]furan; Cu catalysis; 2-Oxindole.
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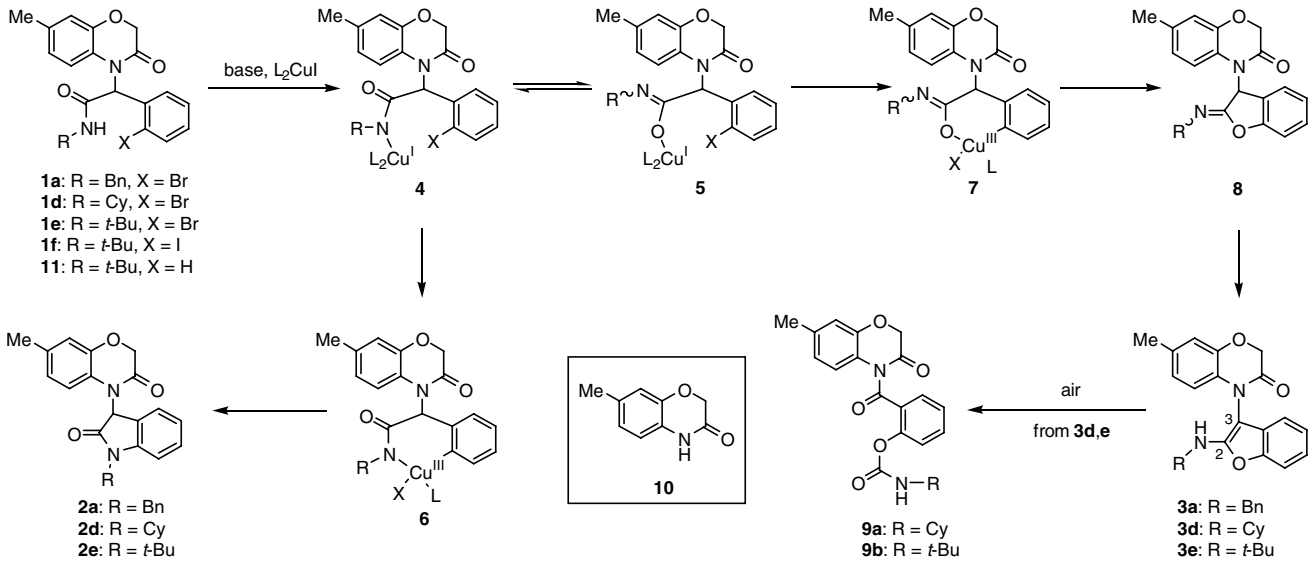
Table 1. Cu-catalyzed intramolecular amidation with microwave heating[a]

Entry	Substrate	Solvent	Base[c]	T (°C)	t (min)	Isolated yield (%)
1[b]	**1a**	DMSO	K_2CO_3	100	1200	**2a**: 71
2	**1a**	DMSO	K_2CO_3	150	30	**2a**: 90
3	**1a**	MeCN	K_2CO_3	150	35	**2a**: 88
4	**1a**	MeCN	$K_3PO_4{\cdot}3H_2O$	150	35	**2a**: 90
5	**1b**	MeCN	$K_3PO_4{\cdot}3H_2O$	150	50	**2b**: 85
6	**1c**	MeCN	$K_3PO_4{\cdot}3H_2O$	150	50	**2c**: 59

[a] Except for entry 1, all reactions were carried out in closed pressurized vials with the reaction temperature measured by an IR sensor. CuI (10 mol %) and L-proline (20 mol %) were used as the catalyst.
[b] Entry 1 was performed in an oil bath with 23 mol % CuI and 37 mol % L-proline.
[c] 2 equiv of the base was used.

150 °C for 30 min afforded an improved yield of 90% for product **2a** (Table 1, entries 1 and 2). Similar efficiency of the microwave-heated amidation in MeCN was obtained (Table 1, entry 3). We also found that a mild base, $K_3PO_4{\cdot}3H_2O$, could be used to furnish **2a–c** in 59–90% yields (Table 1, entries 4–6). By using DMF as the solvent, the same Cu-catalyzed intramolecular amidation of **1a–c** could occur in the absence of L-proline.[11]

Scheme 2 and Table 2 summarize our results on the microwave-assisted Cu-catalyzed intramolecular amidation of **1d–f**. We carried out the amidation of **1d** at 150 and 180 °C for 80 min, the desired 2-oxindole **2d** was isolated in up to 40% yield along with 2-(cyclohexylamino)benzo[*b*]furan **3d** (Table 2, entries 1 and 2).[13] The structures of **2d** and **3d** were assigned spectroscopically and **2d** was further confirmed by X-ray crystallographic analysis (Fig. 1).[14] As expected, reaction of the *N*-*t*-Bu-substituted **1e** by using 10 mol % CuI and 20 mol % L-proline at 180 °C for 60 min afforded only 3% of **2e** and 17% of **3e** along with 60% recovery of **1e** (Table 2, entry 6). During recrystallization of **3e**, a new compound **9b** was obtained. The structures of both **3e** and **9b** were proved by X-ray crystal structural analysis as shown in Figures 2 and 3.[14] Clearly, **9b** was formed by oxidative cleavage of the C2–C3 double bond upon exposure to air.[15,16] Formation of **9b** could be suppressed by recrystallization of **3e** under an inert atmosphere. On the other hand, **9a** could be obtained by bubbling a stream of oxygen gas into a solution of **3d** in EtOAc–hexane at room temperature. In order to optimize the amidation conditions, we varied the catalyst loading and base for the reaction of **1d** and no better results were obtained (Table 2, entries 3–5). Extension of the reaction time of **1e** to 120 min with 15 mol % CuI and 30 mol % L-proline led to formation of a decomposed byproduct **10** (10%, Table 2, entry 7). Change of MeCN to DMF as the solvent gave only **2e** (13%, Table 2, entry 8), while replacement of the base $K_3PO_4{\cdot}3H_2O$ by K_2CO_3 furnished similar product distribution (Table 2, entry 9). When a stoichiometric CuI or *N*,*N*′-dimethyl-1,2-ethylenediamine[5] was used, almost no reaction took place (Table 2, entries 10 and 11). We also examined amidation of iodide **1f** and obtained both 2-oxindole **2e** and benzo[*b*]furan **3e** but in favor of the N-arylation product **2e** (Table 2, entries 12 and 13). A deiodination byproduct **11** was isolated in the reaction of **1f** even at 130 °C and it became the major component (45%) when heating **1f** in an oil bath in MeCN at 80 °C for 48 h (Table 2, entry 14). Byproduct **10** was produced at 80 °C in 35% yield as well. In contrast to the Cu-cat-



Scheme 2. Competitive reaction pathways for Cu-catalyzed intramolecular O- and N-arylation of secondary amides.

Table 2. Cu-catalyzed intramolecular O- and N-arylation of amides **1d–f**[a]

Entry	Substrate	Catalyst (mol %)	Base[b]	T (°C)	t (min)	Isolated yields (%)
1	**1d**	CuI (10), L-prolin (20)	$K_3PO_4{\cdot}3H_2O$	150	80	**2d**: 19; **3d**: 5
2	**1d**	CuI (10), L-prolin (20)	$K_3PO_4{\cdot}3H_2O$	180	80	**2d**: 40; **3d**: 11
3	**1d**	CuI (20), L-prolin (40)	$K_3PO_4{\cdot}3H_2O$	180	80	**2d**: 40; **3d**: 11
4	**1d**	CuI (20), L-prolin (40)	Cs_2CO_3	180	50	**2d**: 27
5	**1d**	CuI (10), L-prolin (20)	NaO*t*-Bu	180	50	**2d** + **3d**: Trace
6	**1e**	CuI (10), L-prolin (20)	$K_3PO_4{\cdot}3H_2O$	180	60	**1e**: 60; **2e**: 3; **3e**: 17
7	**1e**	CuI (15), L-prolin (30)	$K_3PO_4{\cdot}3H_2O$	180	120	**1e**: 52; **2e**: 2; **3e**: 17; **10**: 10
8[c]	**1e**	CuI (10), L-prolin (20)	$K_3PO_4{\cdot}3H_2O$	180	60	**2e**: 13; **3e**: 0
9	**1e**	CuI (10), L-prolin (20)	K_2CO_3	180	60	**2e**: 5; **3e**: 14
10	**1e**	CuI (100), L-prolin (200)	$K_3PO_4{\cdot}3H_2O$	180	60	**1e**: 80; No other products
11	**1e**	CuI (10), DA[d] (20)	$K_3PO_4{\cdot}3H_2O$	180	60	**2e** + **3e**: Trace
12	**1f**	CuI (10), L-prolin (20)	$K_3PO_4{\cdot}3H_2O$	180	60	**2e**: 25; **3e**: 15; **11**: 22
13	**1f**	CuI (10), L-prolin (20)	$K_3PO_4{\cdot}3H_2O$	130	120	**2e**: 18; **3e**: 12; **11**: 23
14[e]	**1f**	CuI (10), L-prolin (20)	$K_3PO_4{\cdot}3H_2O$	80	2880	**2e**: 9; **3e**: Trace; **10**: 35; **11**: 45

[a] Except for entries 8 and 14, all reactions were carried out in MeCN in closed pressurized vials with the reaction temperature measured by an IR sensor.
[b] 2 equiv of the base were used.
[c] In DMF.
[d] DA = *N*,*N*′-dimethyl-1,2-ethylenediamine.
[e] In MeCN using an oil bath.

alyzed amidation described above, the 2-oxindoles **2d** and **2e** could be synthesized from **1d**,**e** in 88–90% yields by using 5 mol% $Pd(OAc)_2$, 5 mol% BINAP and 2 equiv of K_2CO_3 with microwave heating in PhMe at 150 °C for 40–45 min.[8b]

The Cu-catalyzed intramolecular amidation of hindered substrates as disclosed above has not reached the stage for efficient synthetic application but the results are of interest in elaborating the reaction mechanism. As outlined in Scheme 2, coordination of Cu^I with the deprotonated amide could give two equilibrating species **4** and **5**. With a less bulky R, the N-ligated **4** should be favored, leading to formation of the N-arylation products **2** via the Cu^{III} species **6**. On the other hand, with a bulky R at the nitrogen atom, the *O*-complexed Cu^I

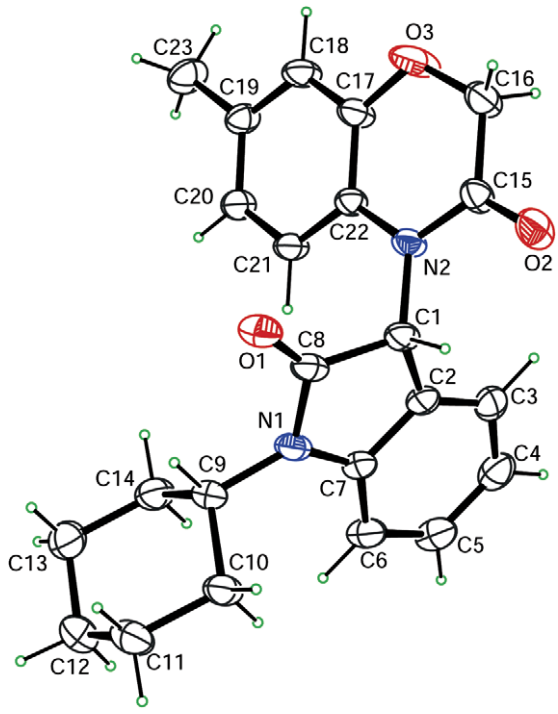


Figure 1. X-ray crystal structure of 2-oxindole **2d**.

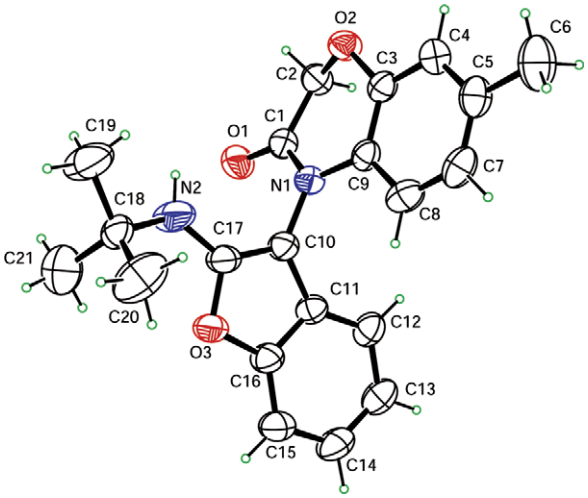


Figure 2. X-ray crystal structure of 2-(*tert*-butylamino)benzo[*b*]furan **3e**.

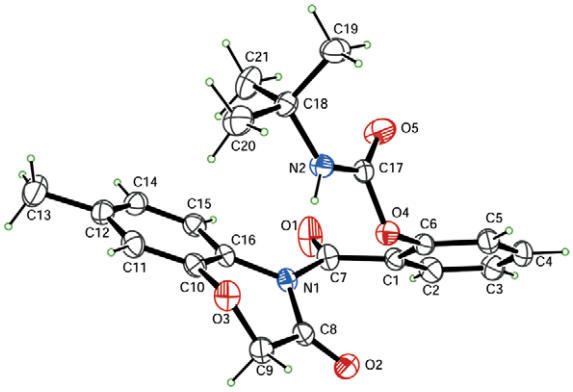


Figure 3. X-ray crystal structure of O-protected salicylamide **9b**.

species **5** might take part in the subsequent oxidative addition to form **7**, which transforms into the O-arylation products **8** via reductive elimination. A base-promoted rearrangement of **8** should afford 2-alkylaminobenzo[*b*]furans **3**. The determinant factor among the competing N- and O-arylation pathways is the size of the R group. For **1a** possessing an *N*-benzyl group, only lactam **2a** was formed. The selectivity is consistent with the intrinsic higher reactivity of **4** toward oxidative addition to form Cu^{III} species **6** as compared to that of **5**. At high reaction temperatures, Cu^{I} complex **5** becomes activated toward oxidative addition, eventually resulting in the formation of O-arylation products.

In summary, we have investigated the microwave-assisted Cu-catalyzed intramolecular amidation and found that the amide *N*-substituent played a determinant role in selectivity among N- and O-arylation. As reported in the literature, N-arylation is normally favored for Cu-catalyzed arylation of primary amides, anilides, and lactams.[1] At the temperatures below 130 °C, hindered secondary amides usually fail to react efficiently with Cu catalysts. For example, on the completion of this work, Zhu and co-workers[8d] reported that a combination of CuI and 1,2-diamines[5] failed to promote the formation of a 2-oxindole from the corresponding aryl iodide in refluxing PhMe. In our study using controlled microwave heating at high temperatures, the Cu-catalyzed O-arylation of hindered secondary amides took place, leading to the formation of 2-alkylaminobenzo[*b*]-furans. The O-arylation of amides is unique to Cu catalysts because exclusive formation of N-arylation products was observed for Pd-catalyzed reactions of similar hindered secondary amides.[8b] Finally, in order to render synthetic application possible, much more reactive Cu catalysts are needed for efficient O-arylation of hindered secondary amides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.084.

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