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Application of Daugulis Copper-Catalyzed Direct Arylation to the Synthesis of 5-Aryl Benzotriazepines

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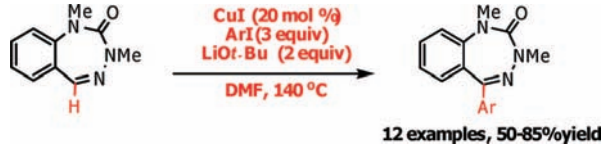
ABSTRACT



A method for the direct arylation of benzotriazepines is reported, employing an aryl iodide as the coupling partner, copper iodide as the catalyst, and lithium *tert*-butoxide as the base. A variety of electron-rich, electron-poor, and sterically hindered aryl iodides are compatible with the reaction conditions. The arylation reaction can also be performed outside a glovebox in air without a significant decrease in yield. Furthermore, convenient microwave conditions for carrying out this transformation are reported.

Benzodiazepines and benzotriazepines are classes of non-aromatic heterocycles that have emerged as privileged pharmacophore stuctures due to their wide-ranging biological activities.[1] Examples of well-known benzodiazepines include Valium (diazepam), Librium (chlordizepoxide), Xanax (alprazolam), and Ativan (lorazepam).[2] In addition, a number of benzotriazepines are currently being evaluated in clinical trials.[3] As a consequence, strategies for the rapid synthesis and functionalization of these classes of compounds are of considerable interest to both academic and industrial researchers.[4]

We have previously reported on the Rh-catalyzed direct functionalization of a range of nitrogen heterocycles,[5] with many of these transformations documented to proceed via Rh-bound N-heterocyclic carbene (NHC) intermediates. We speculated that benzodiazepines and triazepines should be capable of forming NHC−metal complexes and were able to isolate and characterize a 1,4-benzodiazepine NHC−Rh complex.[6] However, we were not able to achieve the Rh-catalyzed direct arylation of either 1,4-benzodiazepines or triazepines under a wide range of reaction conditions and therefore focused on alternative transition metal catalysts for the direct arylation of these classes of heterocycles. Herein we report that benzotriazepines can be efficiently arylated via Cu-catalysis.[7,8]

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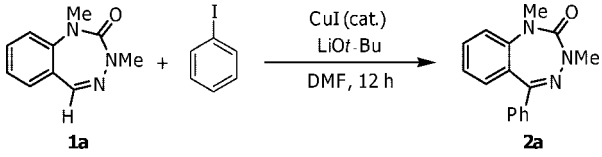
The direct arylation of benzotriazepine **1a** was intially explored using copper catalysts according to the conditions reported by Daugulis and co-workers for the direct arylation of aromatic C−H bonds, CuI (10 mol %), LiO*t*Bu (2 equiv), and PhI (3 equiv) in DMF at 140 °C.[9,10] Under these conditions arylated product **2a** was obtained in a promising 40% isolated yield (Table 1), although the reaction time

Table 1. Effect of Catalyst Loading and Temperature[a]



1a **2a**

entry	catalyst loading	temperature (°C)	% yield
1	10%	140	36 (40[b])
2	10%	140	5[c]
3	1.0 equiv	140	19[c]
4	1.0 equiv	140	99 (98[b])
5	2.0 equiv	140	100
6	20%	140	79 (75[b])
7	20%	100	16
8	20%	rt	5

[a] Conditions: benzotriazepine substrate (1 equiv), PhI (3 equiv), LiO*t*Bu (2 equiv). Yields were determined by GC integration relative to hexamethylbenzene as an internal standard. [b] Isolated yield. [c] Reaction time = 30 min.

necessary for complete conversion (12 h) (entry 1) was longer than that reported by Daugulis for the arylation of azoles (10−30 min) (entry 2).

To increase product yield, we first examined catalyst loading and temperature (Table 1). The use of stoichiometric CuI resulted in quantitative conversion of the benzotriazepine **1a** to the arylated product **2a** (entries 4 and 5). Decreasing the amount of CuI negatively affects the yield of the arylated product, as does lowering the reaction temperature (entries 6−8). With the aim of developing a catalytic direct arylation, we chose 20 mol % of the copper catalyst and 140 °C for further evaluation of reaction parameters.

In this survey, we first examined the effect of copper source and the electrophilic coupling partner (Table 2).

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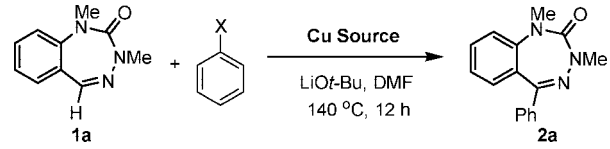
Table 2. Effect of Copper Source and Phenyl Halide Coupling Partner[a]



1a **2a**

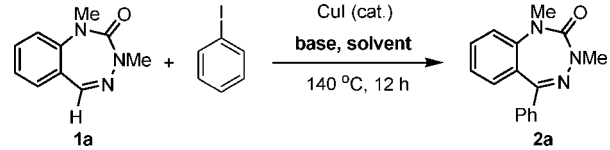
entry	Cu catalyst	PhX	% yield
1	None	PhI	0
2	$CuCl_2$	PhI	55
3	$CuBr_2$	PhI	57
4	$Cu(OAc)_2$	PhI	42
5	CuCl	PhI	65
6	CuBr	PhI	66
7	CuOAc	PhI	58
8	**CuI**	**PhI**	**79**
9	CuI	PhBr	5[b]
10	CuI	PhCl	0

[a] Conditions: benzotriazepine substrate (1 equiv), PhX (3 equiv), Cu catalyst (20 mol %), LiO*t*Bu (2 equiv). Yields determined by GC integration relative to hexamethylbenzene as an internal standard. [b] Reaction time = 24 h.

Without copper, no reaction was observed (entry 1). Interestingly, both Cu(I) and Cu(II) catalysts could be employed in this transformation. However, Cu(I) complexes tended to result in higher yields. Consistent with Daugulis's observations for the arylation of aromatic heterocycles, only aryl iodides are effective coupling partners, with aryl bromides and chlorides giving little or no product (entries 9 and 10). This result suggests that this method should be useful for the chemoselective arylation at iodide-substituted centers when other halogen substituents are present (vide infra).

Upon examining different bases and solvents (Table 3), LiO*t*Bu and DMF were found to be optimal. Stronger bases

Table 3. Effect of Base and Solvent[a]



1a **2a**

entry	base	solvent	% yield
1	**LiO*t*Bu**	**DMF**	**79**
2	NaO*t*Bu	DMF	15
3	KO*t*Bu	DMF	10
4	LDA	DMF	7
5	Na_2CO_3	DMF	0[b]
6	Cs_2CO_3	DMF	0[b]
7	K_3PO_4	DMF	15[b]
8	LiO*t*Bu	DMA	52
9	LiO*t*Bu	THF	60
10	LiO*t*Bu	dioxane	36[b]
11	LiO*t*Bu	toluene	8

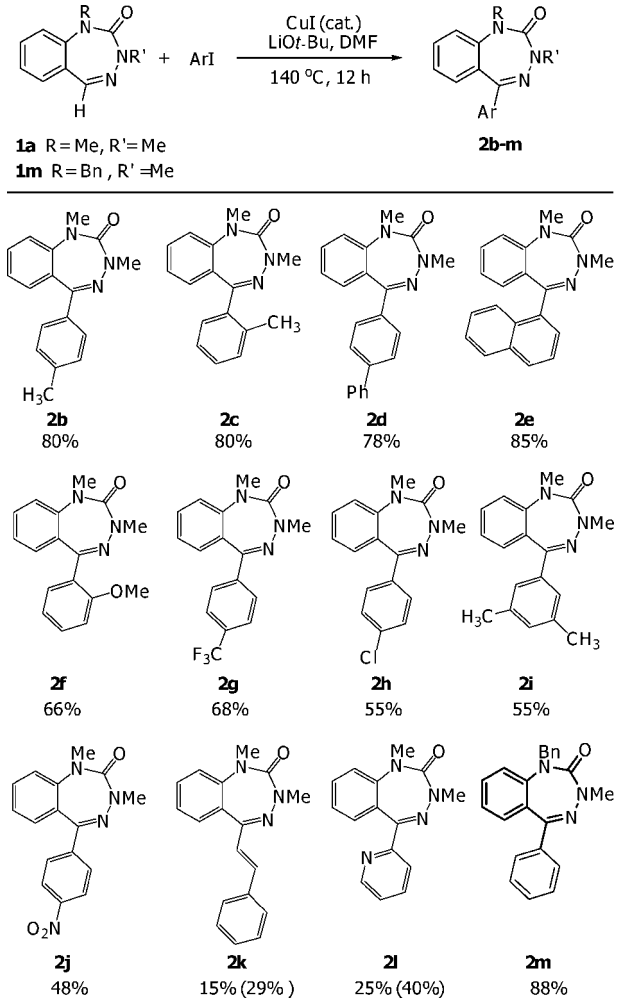
[a] Conditions: benzotriazepine substrate (1 equiv), PhI (3 equiv), CuI (20 mol %), base (2 equiv). Solvent (1.0 M benzotriazepine substrate). Yields were determined by GC integration relative to hexamethylbenzene as an internal standard. [b] Reaction time = 24 h.

resulted in significantly lower yields as well as starting material decomposition (entries 2−4). Either no reaction or low conversion was observed when weaker bases were employed (entries 5−7). The mechanism of this direct arylation reaction is likely to be similar to that previously reported by Daugulis and co-workers for the Cu-catalyzed arylation of aromatic C−H bonds, wherein the base is necessary for deprotonation/metalation.[9] Weaker bases such as K_3PO_4, which is effective for the direct arylation of azoles and polyfluoroarenes, did not work well for benzotriazepine substrates presumably because of the much higher pK_a value of the benzotriazepine sp^2 C−H bond. For this heterocycle class, the stronger base, LiO*t*Bu, as well as prolonged reaction times, are apparently necessary for deprotonation/metalation. A variety of solvents were evaluated with LiO*t*Bu as the base and in all cases resulted in much poorer conversion relative to DMF (entries 8−11).

Using the optimal reaction conditions the scope of the catalytic direct arylation reaction was next examined (Scheme 1). Benzotriazepine **1a** could be successfully coupled to both electron-poor and electron-rich aryl iodides to give benzotriazepines **2g**, **2h**, and **2j** and benzotriazepines **2b**, **2c**, **2f**, and **2i**, respectively. *Ortho*-substituted aryl iodides could also be coupled in high yields (benzotriazepines **2c** and **2f**). Good functional group compatibility was observed with alkoxy (**2f**), chloro (**2h**), nitro (**2j**), and pyridyl (**2l**) groups all being compatible with the reaction conditions. Although 2-iodopyridine coupled in only modest yields with 20 mol % CuI, the yield of **2l** could be significantly improved by employing stoichiometric quantities of CuI. A vinyl iodide was also coupled (**2k**) with stoichiometric CuI resulting in a doubling of the yield relative to that obtained when 20 mol % CuI was used. The *N*-Bn-protected benzotriazepine substrate was also an effective reaction partner in this transformation (**2m**). In contrast, benzotriazepines with free N−H groups, e.g., **1** (R = H), are not effective substrates as a result of competitive N-arylation.

We also found that this reaction can be conducted outside of the glovebox in air without significantly decreasing the yield of product (Scheme 2). Moreover, microwave irradiation could be used to shorten reaction times (Table 4). With this method of heating, 1 equiv of CuI is optimal, and at this stoichiometry, complete conversion is observed within 1 h at 140 °C (entry 5).

Scheme 1. Benzotriazepine Direct Arylation Substrate Scope[a]



[a] Conditions: benzotriazepine substrate (1 equiv), aryl iodide (3 equiv), CuI (20 mol %), LiO*t*Bu (2 equiv). Reported yields are isolated yields. Yields in parentheses are isolated yield when employing 1 equiv of CuI.

Scheme 2. Arylation Reaction Outside of Glovebox

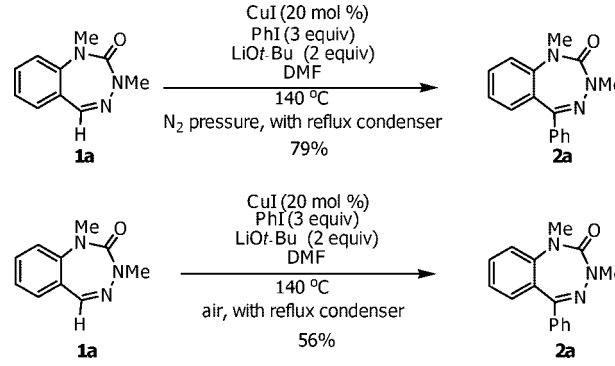
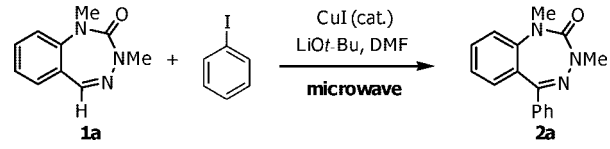


Table 4. Microwave-Assisted Benzotriazepine Arylation[a]



entry	catalyst loading	conditions	% yield[a]
1	20%	140 °C, 12 h	62
2	20%	150 °C, 6 h	57
3	20%	160 °C, 1 h	51
4	20%	200 °C, 30 min	33
5	**1 equiv**	**140, 1 h**	**98 (99[b])**

[a] Conditions: benzotriazepine substrate (1 equiv), PhI (3 equiv), LiO*t*Bu (2 equiv). Yields are GC yields determined by integration relative to hexamethylbenzene as an internal standard. [b] Isolated yield.

In conclusion, we have developed an efficient Cu-catalyzed protocol for the direct arylation of benzotriazepines, a class of heterocycles that are actively being investigated as drug candidates. This is the first example of the copper-mediated coupling of nonaromatic heterocycles. The transformation can be conducted either under inert atmosphere or in air and can be conveniently performed using microwave irradation. Further studies to expand substrate scope to benzodiazepines and other benzazepine derivatives are currently underway.

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Supporting Information Available: Full experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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