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VIP **Homogeneous Catalysis**

Transition-Metal-Catalyzed Alkylations of Amines with Alkyl Halides: Photoinduced, Copper-Catalyzed Couplings of Carbazoles**

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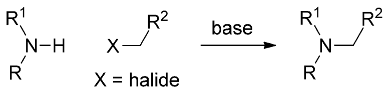
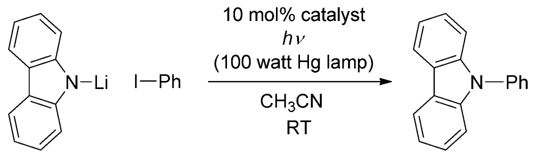
The development of new methods for the formation of carbon–nitrogen bonds is a central challenge in organic chemistry,[1] owing in part to the propensity of nitrogen-containing compounds to exhibit interesting bioactivity.[2] A variety of powerful approaches have been devised, including venerable processes such as reductive amination[3] and Ullmann coupling,[4,5] as well as the more recently developed Buchwald–Hartwig reaction.[6] Despite the utility of such processes, the discovery of novel methods for the formation of carbon–nitrogen bonds remains an important objective.[7]

Perhaps the most classic "textbook" approach to carbon–nitrogen bond construction is the reaction of an amine with an alkyl halide [Eq. (1)],[8] a transformation that continues to play a critical role in organic synthesis.[9] Because this process generally follows an S_N2 pathway, elevated reaction temperatures are typically employed for hindered primary and secondary electrophiles that are unactivated.[1] To our knowledge, there are virtually no examples of transition-metal-catalyzed variants of this method, which would enable carbon–nitrogen bond formation to proceed under milder conditions.[10]



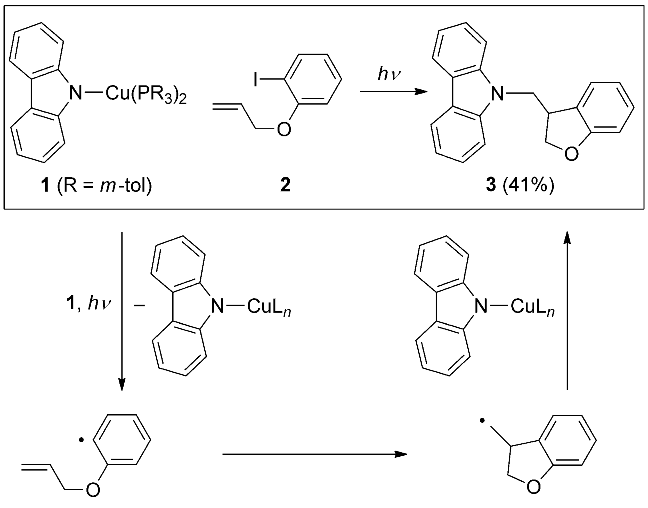
(1)

We recently reported that Ullmann C–N couplings of carbazole with aryl halides can be accomplished at room temperature through photolysis (for example, [Eq. (2)]).[11] As part of a mechanistic investigation of this process, we determined that irradiation of a mixture of copper–carbazolide complex **1** and aryl iodide **2** leads to cyclized coupling product **3** (Scheme 1). The formation of a C_{sp^3}–N bond in the product suggested to us that it might be possible to develop a method whereby a transition metal would catalyze the coupling of an amine with an alkyl halide. Herein, we describe the achievement of this objective, specifically, a photoinduced, copper-catalyzed coupling of carbazoles with alkyl iodides that occurs under very mild conditions (0 °C) [Eq. (3)].

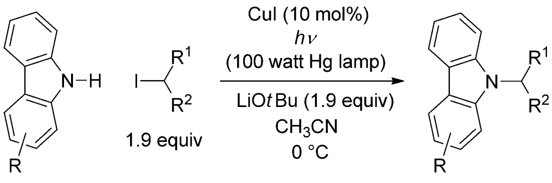


(2)

Catalyst	Yield [%]
[{(m-tol)$_3$P}$_2$Cu(carbazolide)] (**1**)	64
CuI	65



Scheme 1. Previous mechanistic study of photoinduced Ullmann couplings of aryl halides: Observation of C_{sp^3}–N bond formation.



(3)

Because we had established that carbazole readily engages in photoinduced Ullmann C–N couplings with aryl halides,[11] it represented a natural starting point from which to explore the proposed alkylation process. Furthermore, the development of a mild, versatile method for functionalizing this heterocycle through N-alkylation would represent

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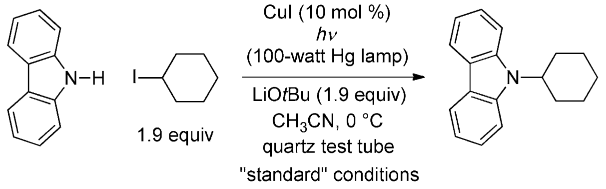
a useful proof-of-concept, given that the carbazole subunit is found in an array of natural and unnatural products that are of interest in fields ranging from biology to medicinal chemistry to materials science.[12,13]

In an initial study, we determined that our reported conditions for photoinduced, copper-catalyzed Ullmann N-arylation [Eq. (2)] do indeed also effect N-alkylation of carbazole by cyclohexyl iodide; however, the yield of the desired product was modest. Nevertheless, through optimization of the appropriate reaction parameters, we were able to develop a method that furnishes *N*-cyclohexylcarbazole in good yield at 0 °C (Table 1, entry 1).

Table 1: Photoinduced, copper-catalyzed N-alkylation: Coupling of carbazole with cyclohexyl iodide at 0 °C.



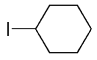
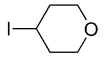
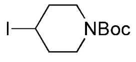
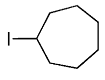
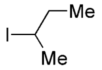
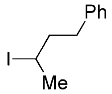
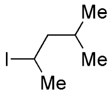
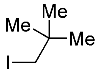
Entry	Change from "standard" conditions	Yield [%][a]
1	none	76
2	no CuI	16
3	no *hν*	1
4	no CuI and no *hν*	1
5	no LiO*t*Bu	<1
6	NaO*t*Bu instead of LiO*t*Bu	36
7	KO*t*Bu instead of LiO*t*Bu	21
8	Cs_2CO_3 instead of LiO*t*Bu	28
9	K_3PO_4 instead of LiO*t*Bu	9
10	$[\{(m\text{-tol})_3P\}_2Cu(\text{carbazolide})]$ instead of CuI	76
11	$Cu(OTf)_2$ instead of CuI	66
12	Cu powder instead of CuI	26
13	1.2 equiv of CyI and 1.2 equiv of LiO*t*Bu	37
14	5 mol % CuI	65
15	1 mol % CuI	43
16	30 °C instead of 0 °C	58
17	borosilicate, instead of quartz, test tube	65
18	under air instead of under nitrogen	41
19	0.1 equiv of H_2O	61

[a] The yield was determined by GC analysis versus a calibrated internal standard (average of two runs).

Under otherwise identical conditions in the absence of CuI, light, or both CuI and light, little or no carbon–nitrogen bond formation is observed (Table 1, entries 2–4).[14] Similarly, no coupling occurs if LiO*t*Bu is omitted (Table 1, entry 5), and the other Brønsted bases that we have investigated are significantly less effective (including NaO*t*Bu, KO*t*Bu, Cs_2CO_3, and K_3PO_4: Table 1, entries 6–9). Among the copper sources that we have examined, CuI is the most useful from the standpoints of convenience, cost, and efficiency (e.g., Table 1, entries 10–12). If less electrophile (Table 1, entry 13) or less CuI (entries 14 and 15) is employed, then a lower yield is obtained; nevertheless, the formation of the C–N coupling product in 43 % yield in the presence of 1 % CuI establishes that a substantial turnover number can be achieved. This photoinduced, copper-catalyzed N-alkylation proceeds with diminished efficiency at higher temperature (Table 1, entry 16) or in a borosilicate reaction vessel (entry 17). The reaction is modestly air- and moisture-sensitive (Table 1, entries 18 and 19).

This metal-catalyzed N-alkylation process can be applied to couplings of a wide range of secondary and hindered primary alkyl iodides (Table 2), thereby complementing the S_N2 reaction;[15] for each coupling (entries 2–8), in the absence of CuI and/or light, essentially no C–N bond formation is observed ($\leq 10\%$). Thus, photoinduced, copper-catalyzed alkylations of carbazole with cyclic, including heterocyclic, electrophiles occur in uniformly good yield at 0 °C (Table 2, entries 1–4). Furthermore, acyclic secondary iodides are suitable coupling partners (Table 2, entries 5–7). Neopentyl iodide is a prototypical example of a poor electrophile for an S_N2 reaction,[16] yet the copper-catalyzed N-alkylation of carbazole proceeds smoothly with this substrate (61 % yield; Table 2, entry 8).

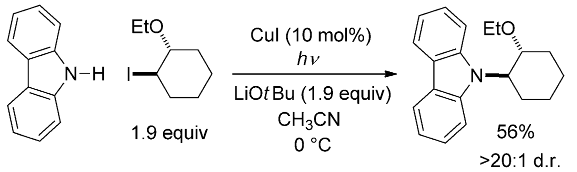
Table 2: Photoinduced, copper-catalyzed N-alkylation of carbazole: Scope with respect to the alkyl iodide (for the reaction conditions, see [Eq. (3)]).

Entry	Electrophile	Yield [%][a]
1		68
2		62
3		61
4		70
5		69
6		80
7		64
8		61

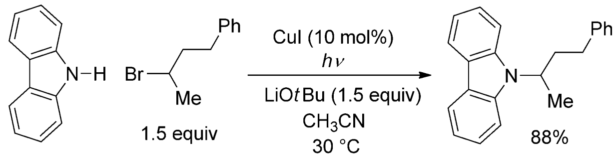
All data are the average of two experiments. [a] Yield of purified product.

We have also examined the scope of this metal-catalyzed N-alkylation process with respect to the carbazole coupling partner. Although the reaction of 1-fluorocarbazole occurs in modest yield (Table 3, entry 1), both 2- and 3-substituted carbazoles undergo photoinduced N-alkylation with cycloheptyl iodide in fairly good yield (Table 3, entries 2–4).

Furthermore, we have explored a stereoselective copper-catalyzed N-alkylation process. Thus, reaction of carbazole with a *trans*-2-substituted cyclohexyl iodide leads to the *trans* coupling product with excellent diastereoselectivity (>20:1; [Eq. (4)]). This highlights the potential stereochemical complementarity between our photoinduced method versus

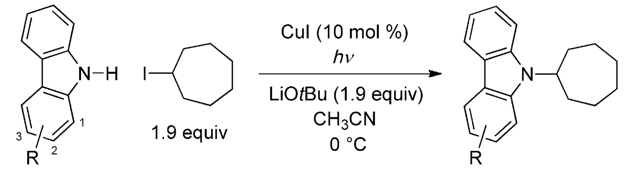


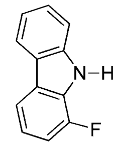
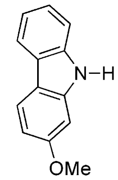
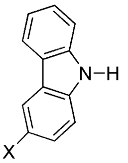
(4)



(6)

Table 3: Photoinduced, copper-catalyzed N-alkylation of substituted carbazoles.

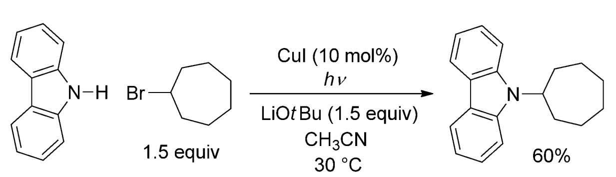


Entry	Carbazole		Yield [%][a]
1			45
2			73
3		X = OMe	59
4		Et	67

All data are the average of two experiments. [a] Yield of purified product.

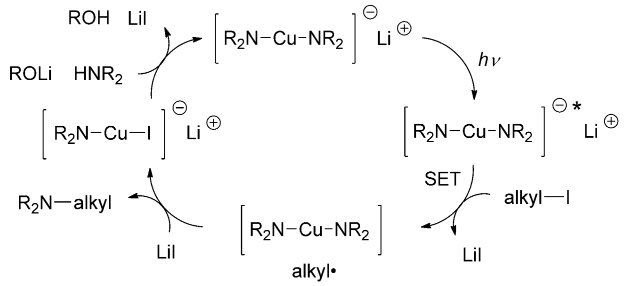
a traditional S_N2 approach to N-alkylation, which would proceed with inversion. In practice, however, our attempts to achieve this particular coupling through an S_N2 pathway (NaH/DMF) led to complete consumption of the electrophile without any appreciable C−N bond formation (< 1%).

In a preliminary investigation, we have established that this copper-catalyzed N-alkylation is not limited to alkyl iodides as the electrophilic partner: alkyl bromides can also be employed. For example, upon irradiation at 30 °C in the presence of CuI and base, carbazole couples with cyclic and acyclic bromides to form the desired carbon–nitrogen bond in moderate to very good yield ([Eq. (5)] and [Eq. (6)]).



(5)

With respect to the mechanism of the present reaction, we hypothesize that Li[Cu(carbazolide)$_2$] is formed under the reaction conditions and may be an intermediate in the alkylation pathway (for an outline of a possible mechanism, see Scheme 2).[17] When we examine the electrospray mass spectra of coupling reactions in progress, we do indeed detect substantial quantities of ions with molecular weights of 395 and 397 (and the ratio is approximately constant), which correspond to the masses of $[^{63}\mathrm{Cu(carbazolide)_2}]^-$ and $[^{65}\mathrm{Cu(carbazolide)_2}]^-$. We were able to synthesize Li[Cu(carbazolide)$_2$] as its $[\mathrm{Li(CH_3CN)_4}]^+$ (**4**) and $[\mathrm{Li([12]crown\text{-}4)_2}]^+$ (**5**) adducts, and we obtained an X-ray crystal structure of the latter (Figure 1 a). In the solid state, this two-coordinate copper complex adopts a linear geometry (∡N-Cu-N = 178°) with a dihedral angle of 89° between the two carbazolide planes. The excitation and emission profiles of complex **5** are shown in Figure 1 b.



Scheme 2. A possible pathway for photoinduced, copper-catalyzed N-alkylation of carbazole. SET = single-electron transfer.

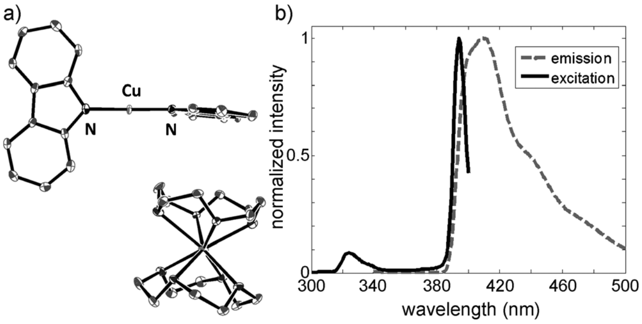
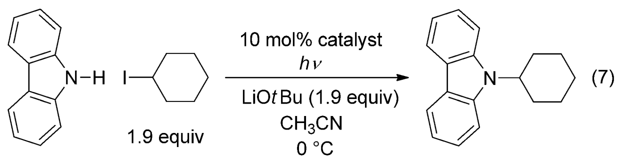


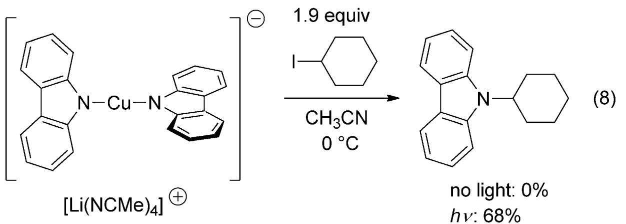
Figure 1. $[\mathrm{Li([12]crown\text{-}4)_2}][\mathrm{Cu(carbazolide)_2}]$ (**5**): a) X-ray structure (thermal ellipsoids drawn at 50% probability and H atoms omitted for clarity). b) Excitation (emission wavelength: 410 nm) and emission (excitation wavelength: 325 nm) spectra in CH_3CN.

$[\mathrm{Li(CH_3CN)_4}][\mathrm{Cu(carbazolide)_2}]$ (**4**) catalyzes the N-alkylation of carbazole by cyclohexyl iodide with a rate and efficiency similar to CuI [Eq. (7)]. When copper complex **4** is treated with cyclohexyl iodide at 0 °C in the absence of light,



Catalyst	Yield [%]
Complex **4**	81
CuI	74

no carbon–nitrogen bond formation occurs; on the other hand, if this mixture is irradiated, *N*-cyclohexylcarbazole is produced in 68 % yield [Eq. (8)], indicating that complex **4** is



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chemically competent for the catalytic process. Thus, the data that we have accumulated to date are consistent with the suggestion that Li[Cu(carbazolide)$_2$] may be an intermediate in this metal-catalyzed N-alkylation reaction.

In summary, we have developed a transition-metal-catalyzed variant of a classic process, the N-alkylation of an amine with an alkyl halide. Specifically, we have established that, upon photolysis, a range of N-alkylations of carbazoles can be achieved with secondary and hindered primary alkyl iodides (thereby complementing S$_N$2 reactions of unhindered primary electrophiles) under mild conditions (0 °C) with a simple precatalyst (CuI) in the presence of a Brønsted base. Our data are consistent with the formation of Li[Cu(carbazolide)$_2$] under the coupling conditions and a possible role for this complex in the catalytic cycle. Additional studies of photoinduced, copper-catalyzed processes, including mechanistic investigations (e.g., of the C–N bond-forming step), are underway.

Experimental Section

Representative procedure: The carbazole (1.00 mmol), LiO*t*Bu (152 mg, 1.90 mmol), and CuI (19.5 mg, 0.10 mmol) were added to an oven-dried 10 mL quartz test tube that contained a stir bar. The test tube was fitted with a rubber septum, the joint was wrapped with electrical tape, and the test tube was evacuated and backfilled with nitrogen (3 cycles). Acetonitrile (4.0 mL) and the alkyl iodide (1.90 mmol) were added in turn by using a syringe, and then the test tube was detached from the nitrogen line, and the puncture holes of the septum were covered with vacuum grease. The resulting mixture was stirred for 5 min, and then the test tube was suspended in an ice-filled dewar. The stirred mixture was irradiated with a 100 watt Hg lamp, positioned directly above the dewar, for 10 h. Next, the mixture was passed through a long plug of silica gel (eluant: hexanes; monitored by TLC), the solvent was removed, and the residue was loaded onto a silica-gel column using hexanes and purified by chromatography.

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[1] a) E. Schaumann, *Sci. Synth.* **2008**, *40a*, 7–22; b) H. Butenschön, *Sci. Synth.* **2008**, *40a*, 157–201; c) S. A. Lawrence, *Sci. Synth.* **2008**, *40a*, 501–577; d) U. Scholz, B. Schlummer, *Sci. Synth.* **2007**, *31b*, 1565–1678.

[2] For some leading references, see: *The Alkaloids: Chemistry and Biology*, *Vol. 70* (Ed.: H.-J. Knölker), Elsevier, San Diego, **2011**.

[3] For leading references, see: P. Margaretha, *Sci. Synth, Knowledge Updates* **2010/01**, 405–442.

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[5] For recent reviews and leading references, see: a) J. D. Senra, L. C. S. Aguiar, A. B. C. Simas, *Curr. Org. Synth.* **2011**, *8*, 53–78; b) Y. Jiang, D. Ma in *Catalysis without Precious Metals* (Ed.: R. M. Bullock), Wiley-Blackwell, Weinheim, **2010**, pp. 213–233; c) L. Penn, D. Gelman in *Chemistry of Organocopper Compounds*, *Part 2* (Ed.: Z. Rappoport, I. Marek), Wiley, Chichester, **2009**, pp. 881–990.

[6] For example, see: a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50; b) J. F. Hartwig, S. Shekhar, Q. Shen, F. Barrios-Landeros in *Chemistry of Anilines*, *Vol. 1* (Ed.: Z. Rapaport), Wiley, New York, **2007**, pp. 455–536.

[7] For examples of very recent approaches, see: a) R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *J. Am. Chem. Soc.* **2012**, *134*, 6571–6574; b) T. J. Barker, E. R. Jarvo, *Angew. Chem.* **2011**, *123*, 8475–8478; *Angew. Chem. Int. Ed.* **2011**, *50*, 8325–8328.

[8] In introductory textbooks on organic chemistry, the alkylation of amines with alkyl halides is often the first reaction of amines that is described. For example, see: a) M. Loudon in *Organic Chemistry*, 5th ed., Roberts & Company, Greenwood Village, **2009**, chap. 23.7A; b) J. McMurry, *Organic Chemistry*, Brooks/Cole, Belmont, **2012**, chap. 24.7.

[9] In a recent "Analysis of the reactions used for the preparation of drug candidate molecules" (J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347), "Heteroatom alkylation & arylation" was the reaction category with the highest frequency use (19 %; Table 2). Within this category, "N-Substitution" was the most-often-used process (57 %; Table 10), and, within "N-Substitution", "N-Akylation with Alk-X" was the most frequently employed reaction (36 %; Table 11).

[10] There are isolated reports of N-alkylations of amines with unactivated alkyl halides that proceed in the presence of a substoichiometric quantity of a transition metal. For example, see: a) A. Aydın, I. Kaya, *Electrochim. Acta* **2012**, *65*, 104–114 (165 °C; primary alkyl bromide); b) X. Tu, X. Fu, Q. Jiang, Z. Liu, G. Chen, *Dyes Pigm.* **2011**, *88*, 39–43 (80 °C; primary alkyl bromide); c) M. Kozuka, T. Tsuchida, M. Mitani, *Tetrahedron Lett.* **2005**, *46*, 4527–4530 (83 °C; primary alkyl bromide).

[11] S. E. Creutz, K. J. Lotito, G. C. Fu, J. C. Peters, *Science* **2012**, *338*, 647–651.

[12] For two recent examples, see: a) T. Hirota, J. W. Lee, P. C. St. John, M. Sawa, K. Iwaisako, T. Noguchi, P. Y. Pongsawakul, T. Sonntag, D. K. Welsh, D. A. Brenner, F. J. Doyle III, P. G. Schultz, S. A. Kay, *Science* **2012**, *337*, 1094–1097; b) H. Uoyama, K. Goushi, K. Shizu, H. Nomura, C. Adachi, *Nature* **2012**, *492*, 234–238.

[13] For a few recent reviews, see: a) occurrence, biogenesis, and synthesis of biologically active carbazoles: A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193–3328; b) carbazole-based polymers: J. Li, A. C. Grimsdale, *Chem. Soc. Rev.* **2010**, *39*, 2399–2410.

[14] Our observation of C–N bond formation upon irradiation in the absence of CuI (entry 2 of Table 1) may be due to the photophysical properties of lithium carbazolide itself. For example, see: H. W. Vos, H. H. Blom, N. H. Velthorst, C. MacLean, *J. Chem. Soc. Perkin Trans. 2* **1972**, 635 – 639. For the excitation and emission spectra of lithium carbazolide in CH_3CN, see the Supporting Information.

[15] a) Under our standard conditions: an unactivated tertiary alkyl iodide and an unactivated secondary alkyl chloride were not suitable coupling partners; a small amount of hydrodehalogenation (reduction) of the electrophile was observed; CuBr and CuCl furnished slightly lower yields; at partial conversion, C–N bond formation stopped when the mercury lamp was turned off, and resumed when the lamp was turned back on; b) Cyclohexyl iodide is stable to photolysis in CH_3CN at 0 °C for 10 h (> 98% recovery); c) On a gram scale (1.15 g of product), the coupling of carbazole with cyclohexyl iodide at 30 °C proceeded in 58% yield.

[16] For example, see: T. H. Lowry, K. S. Richardson in *Mechanism and Theory in Organic Chemistry*, HarperCollins, New York, **1987**, pp. 377 – 378.

[17] We are not aware of previous investigations of $[Cu(carbazolide)_2]^-$ complexes. However, $[Cu(anilide)_2]^-$ complexes have been proposed as intermediates in nonphotochemical arylations of anilines (e.g.: C.-K. Tseng, C.-R. Lee, C.-C. Han, S.-G. Shyu, *Chem. Eur. J.* **2011**, *17*, 2716 – 2723). See also:R. Giri, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 15860 – 15863.