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Synthesis of Indoles by Conjugate Addition and Ligand-Free Copper-Catalyzed Intramolecular Arylation of Activated Acetylenes with *o*-Haloanilines

Detian Gao, Masood Parvez, and Thomas G. Back*[a]

The indole moiety is ubiquitous in both nature and pharmacology, and comprises the core structure of numerous alkaloids and other biologically important compounds.[1] Considerable effort has been expended in the development of versatile, efficient and economical synthetic routes to such compounds. Many modern approaches are based on Pd-catalyzed coupling reactions, which have been extensively investigated and can provide highly selective routes to variously substituted indole derivatives.[2]

Our earlier studies of palladium-catalyzed syntheses of related carbazoles[3a,b] and quinolones[3c] from readily available *o*-iodoanilines and dienyl or acetylenic sulfones[4] prompted us to investigate conjugate additions of *o*-iodoanilines to activated acetylenes, followed by intramolecular Pd-catalyzed arylations to afford indole products. However, the capricious nature of the process in our initial experiments and the high cost of palladium compounds prompted us to search for cheaper and more efficient catalysts for the cyclization step. We now report a more successful protocol based on a ligand-free copper-catalyzed intramolecular arylation reaction.

Since the discovery of the Ullman–Goldberg reaction[5] more than a century ago, a variety of other copper-catalyzed cross-coupling reactions of aryl halides leading to heteroatom–aryl and *C*-aryl products have been investigated.[6] Most such procedures rely upon Cu^I catalysts coordinated to various ligands, which can profoundly affect the reactivity of the catalyst. The mechanisms and ligand requirements of *O*-aryl[7a] and *N*-aryl[7b,c] coupling reactions have been particularly well-investigated. Copper-mediated *C*-arylations of active methylene compounds with aryl halides were first reported by Hurtley[8] and arylations of other substrates containing sp^3-hybridized activated C–H bonds are also well-known.[6b,d] Numerous procedures for the coupling of aryl groups with sp^2-hybridized carbon centers have been reported,[6c] while acetylenic substrates lead to aryl-substituted alkynes.[6a–c,9] A palladium-catalyzed aza-Heck hydroamination reaction of *o*-haloanilines and alkynes has been shown to afford indole products.[10]

In earlier work,[3c] we demonstrated that the conjugate additions of *o*-iodoaniline derivatives to acetylenic sulfones containing γ-hydrogens generally proceed via prior isomerization of the latter to the corresponding allenic sulfones and not by direct addition to the acetylenes, to afford the observed allylic sulfone products **3** as mixtures of geometrical isomers. We now report that these unseparated mixtures smoothly undergo intramolecular copper-catalyzed coupling to afford variously substituted 3-(*p*-toluenesulfonyl)indoles **4**. The cyclizations were conducted in the presence of Cs_2CO_3 and catalytic $Cu(OAc)_2$ in DMF at 125 °C, without protection from the atmosphere. The results are shown in Scheme 1 and Table 1. *N*-Deformylation occurred simultaneously under the basic conditions of the reaction. This ap-

Table 1. Preparation of indoles **4** and **7** from adducts **3** and **6**.[a,b]

Entry	Product	R	R′	Yield [%]
1	**4a**	H	*n*Pr	66
2	**4b**	H	$(CH_2)_{10}Me$	73
3	**4c**	H	$(CH_2)_2OBn$	78
4	**4d**	H	$(CH_2)_4CO_2Me$	75
5	**4e**	CO_2Me	*n*Pr	81
6	**4f**	CO_2Me	$(CH_2)_{10}Me$	78
7	**4g**	CO_2Me	$(CH_2)_2OBn$	80
8	**4h**	CO_2Me	$(CH_2)_4CO_2Me$	82
9	**4i**	CN	$(CH_2)_{10}Me$	77
10	**4j**	Me	$(CH_2)_{10}Me$	89
11	**7a**	H	H	68
12	**7b**	H	Ph	71

[a] The conjugate additions were performed as reported in ref. [3c]. [b] Enamine **3**, $Cu(OAc)_2$ (0.3 equiv), and Cs_2CO_3 (2 equiv) were heated in DMF for 3 h at 125 °C.

[a] D. Gao, Dr. M. Parvez, Prof. Dr. T. G. Back
Department of Chemistry, University of Calgary
Calgary, AB, T2N 1N4 (Canada)
Fax: (+1) 403-289-9488
E-mail: tgback@ucalgary.ca

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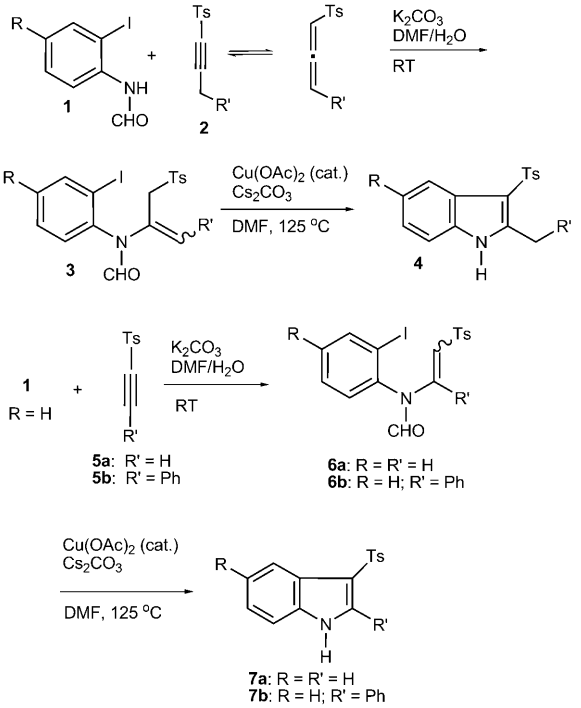
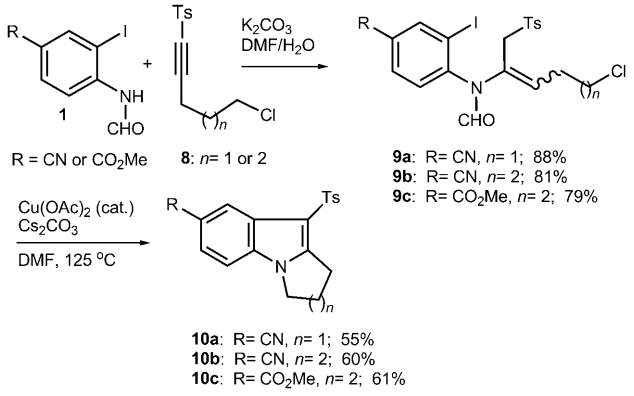


Scheme 1. Synthesis of indoles from *o*-iodoanilines and acetylenic sulfones **2** and **5**.

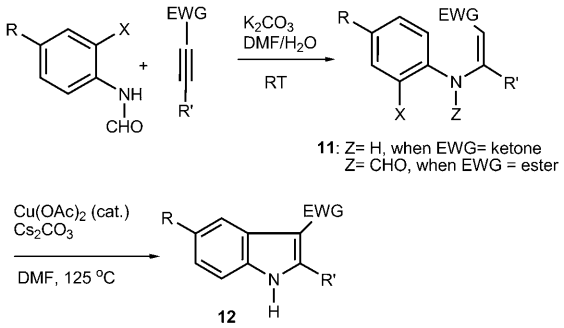
proach proved more effective than the use of CuI as the catalyst, as the latter required longer reaction times of ca. 16 h at 150 °C, even in the presence of 1.0–1.2 equiv of the catalyst, when applied to **3a–c** and **3e–h**.

Furthermore, the terminal acetylenic sulfone **5a** and its phenyl derivative **5b**, where isomerization to the corresponding allenic sulfones is not possible, also afforded the indoles **7a** and **7b** via the vinyl sulfones **6a** and **6b**, respectively (Scheme 1 and Table 1), while the conjugate addition products of chloroalkyl-substituted acetylenic sulfones **9a–c** underwent deformylation and cyclization, followed by intramolecular *N*-alkylation to afford the tricyclic products **10a–c** in a one-pot reaction (Scheme 2).[11] The sulfone moiety has the potential for further transformation via a variety of reductive, oxidative and cross-coupling methods,[12] and certain other 3-sulfonylindoles display anti-HIV activity.[13]



Scheme 2. Tandem cyclizations with acetylenic sulfones **8**.

We also report that similar conjugate additions to alkynoate esters and alkynones afforded **11**, which underwent copper-mediated cyclizations to indoles **12** (Scheme 3 and Table 2) in shorter reaction times and with less catalyst than



Scheme 3. Synthesis of indoles from *o*-iodoanilines and ynoates or ynones.

required in the case of the acetylenic sulfones. While this work was in progress, Cacchi et al.[14] reported cyclizations of *N*-(2-iodoaryl)enaminones, catalyzed by CuI in the presence of the ligand 1,10-phenanthroline. The products were 3-aroyl-2-arylindoles, along with one example of a 2-alkyl derivative. Our results indicate that a 2-alkyl group can be readily incorporated into variously substituted indole products (Table 2, entries 1–5 and 7–16) as well as in the acyl moiety at C-3 (entries 15–16). Both electron-withdrawing and -donating substituents are tolerated at the 4-position of the aniline, including 4-halo substituents (entries 3, 4, 10, 11 and 16), and remain intact in the final products **12**. Moreover, the corresponding 2-bromoaniline (entry 9; X = Br instead of I) was also successfully cyclized, while preliminary

Table 2. Preparation of indoles **12** from adducts **11**.[a,b]

Entry	Product	R	R′	X	EWG	Yield [%]
1	**12a**	H	Me	I	CO_2Et	81
2	**12b**	H	nC_5H_{11}	I	CO_2Me	80
3	**12c**	Cl	nC_5H_{11}	I	CO_2Me	83
4	**12d**	I	nC_5H_{11}	I	CO_2Me	83
5	**12e**	Me	nC_5H_{11}	I	CO_2Me	81
6	**12f**	CN	Ph	I	CO_2Me	81
7	**12g**	H	*n*Bu	I	PhCO	87
8	**12h**	CN	*n*Bu	I	PhCO	85
9	**12h**	CN	*n*Bu	Br	PhCO	69
10	**12i**	Cl	*n*Bu	I	PhCO	92
11	**12j**	I	*n*Bu	I	PhCO	85
12	**12k**	Me	*n*Bu	I	PhCO	86
13	**12l**	CO_2Me	*n*Bu	I	PhCO	81
14	**12l**	CO_2Me	*n*Bu	Cl	PhCO	–
15	**12m**	CN	*n*Bu	I	*n*PrCO	76
16	**12n**	I	*n*Bu	I	*n*PrCO	91

[a] Products **11** were chiefly the *Z* isomers, but in entries 2–5 small amounts of the regioisomeric β,γ-unsaturated esters were detected. [b] Enamine **11**, $Cu(OAc)_2$ (0.15 equiv), and Cs_2CO_3 (1–2 equiv) were heated in DMF for 0.5–3 h at 125 °C.

experiments with the 2-chloro derivative were unsuccessful (entry 14; X = Cl instead of I). The conjugate addition and cyclization steps in entries 8 and 10 were also performed in one pot, whereby the conjugate additions were conducted in the usual manner (DMF/K_2CO_3/room temperature), followed by the addition of $Cu(OAc)_2$ and heating at 125 °C for 45–60 min, affording the products in 63 and 60 %, yield, respectively.

Further investigations of the reaction in entry 8 revealed that the Cu^{II} species **14**, containing two enaminone ligands, was formed in the initial stages of the reaction. It was isolated in high yield when the reaction was performed at room temperature and its structure was determined unequivocally by X-ray crystallography (Figure 1). Since the enaminone functions as both ligand and substrate in this process, an added ligand is not required. We propose that subsequent reduction of **14** to the required Cu^{I} species **15**, likely accompanied by dissociation of one enaminone ligand, is followed by oxidative addition of the aryl–iodine bond of **15** to the metal center to form the Cu^{III} intermediate **16**, and finally reductive elimination to afford the indole product (Scheme 4). The latter two steps are based on those indicated by Evindar and Batey[7a] in their Cu^{I}-catalyzed intramolecular *O*-arylation of *o*-haloanilides, and by Cacchi et al.[14] in their enaminone cyclizations. The initial reduction of Cu^{II} to Cu^{I} is very likely effected by the solvent DMF.[15] This is supported by the observation that $Cu(OAc)_2$ failed to catalyze the cyclization in other polar solvents such as water or HMPA, while CuI afforded the same indole products in neat HMPA or DMF, in comparable and poorer yields, respectively. The intermediates **3**, **6**, **9** and **11**, derived from acetylenic sulfones and ynoates, undergo deformylation in situ prior to cyclization under the higher temperatures (125 °C) of the latter step. The mechanisms of the cyclizations of the ynoates are likely similar to those of the ynones

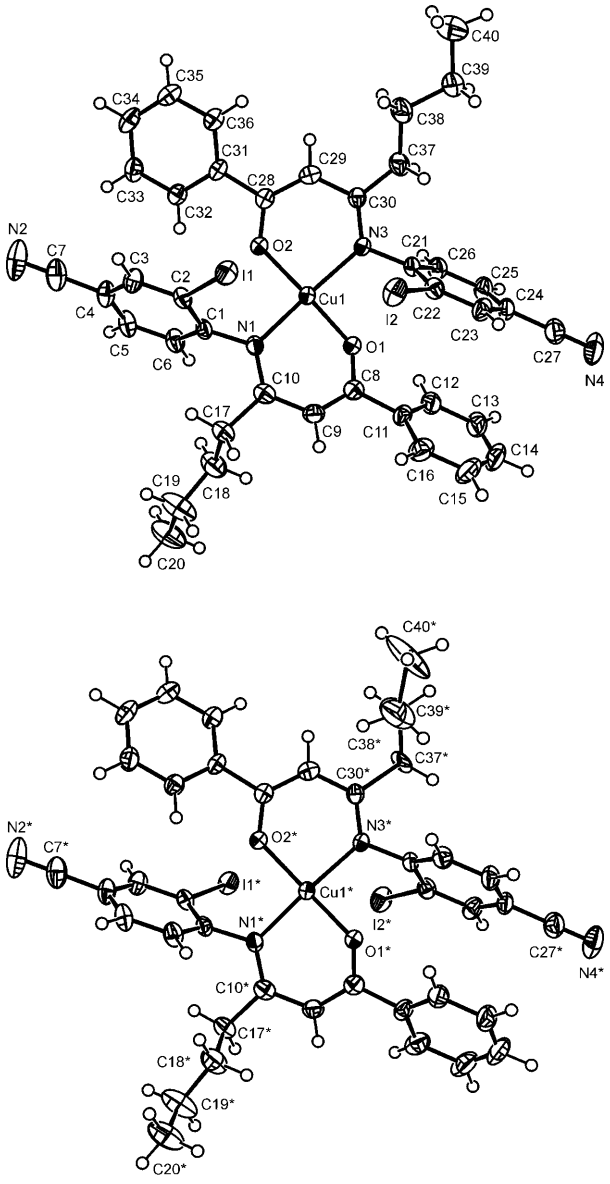
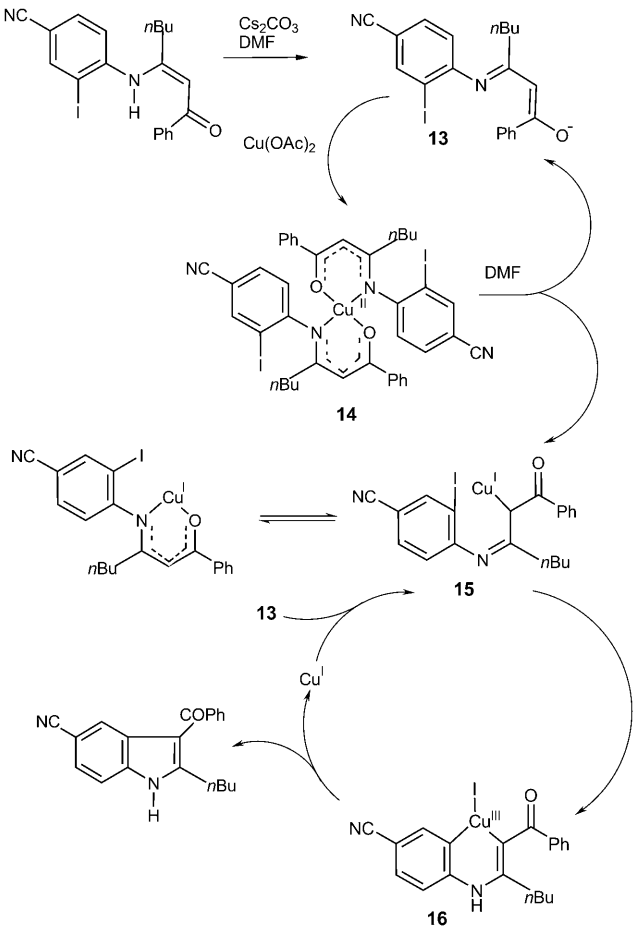


Figure 1. ORTEP diagrams (50 % probability) of the two conformations of **14** (see Supporting Information for details).[16]



Scheme 4. $Cu(OAc)_2$-mediated enaminone cyclization.

shown in Scheme 4, while those of the acetylenic sulfones require further study and may follow different pathways.

In conclusion, we have demonstrated that the conjugate addition products of *o*-haloanilines to acetylenic sulfones, ynoates or ynones can be effectively cyclized to afford variously substituted indoles by means of a novel ligand-free $Cu(OAc)_2$-mediated intramolecular arylation step. The unexpected formation of **14** in the initial stages of the reaction in the ynone series indicates that the corresponding enaminone serves as both the ligand and the substrate in the catalytic cycle, and that formation of the complex precedes the reduction of Cu^{II} to a catalytically active Cu^{I} species.

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Keywords: acetylenes · copper · cyclization · indoles

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[16] CCDC-786127 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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