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Atom-Economical Transformation of Diaryliodonium Salts: Tandem C−H and N−H Arylation of Indoles

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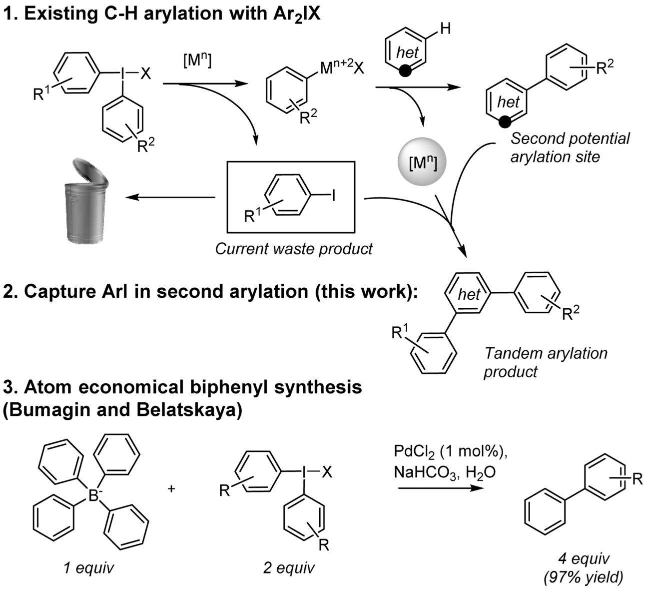
Supporting Information

ABSTRACT: Arylation using diaryliodonium salts generates one equivalent of an iodoarene as a side-product, a significant waste of atom economy. Here, we show that diaryliodoniums can undergo Cu-catalyzed tandem C−H/N−H arylation, producing novel indoles that incorporate both aryl groups from the reagent.

Diaryliodonium salts are receiving increasing attention as versatile arylating reagents.[1] They offer the appealing combination of excellent usability, being stable crystalline solids that are readily prepared using simple procedures, and high reactivity that can access novel reaction pathways. Recent applications have centered on metal-catalyzed arylation under mild conditions,[2] aryl radical chemistry using photoredox catalysis,[3] as well as metal-free arylation with simple nucleophiles under Friedel−Crafts or S$_N$-type mechanisms.[4] Despite these advances, diaryliodonium arylation is characterized by poor atom economy. The aryl iodide nucleofuge, weighing a minimum of 204 Da, is jettisoned on transfer of the reacting aryl group to the substrate or catalyst (Scheme 1). Nearly all iodonium arylation reactions to date, across all reaction classes, generate one equivalent of an iodoarene as waste that must be separated from the desired product.[5]

Our interest in arylation chemistry[6] led us to question whether this hitherto extraneous aryl iodide moiety could be captured in a second arylation reaction, such that both iodonium aryl groups underwent incorporation in a single operation. In particular, if the aryl iodide underwent a second arylation distinct from the first, we could achieve dual arylation at separate sites in a substrate in one step, with no wastage of arene residues. Literature precedent for atom economical use of iodoniums is very limited; Bumagin, Belatskaya et al. showed that 2 equiv of Ar$_2$IX underwent Suzuki−Miyaura cross-coupling with Ph$_4$BNa to yield 4 equiv of Ar-Ph in 97% yield, i.e., near-perfect utilization of aryl residues.[7] More recent work from the Nachtscheim and Wen groups has used cyclic iodonium salts to form tricyclic compounds (via intramolecular reaction of the incipient aryl iodide), a novel approach but one limited to the synthesis of tricyclic aromatics.[8] Harnessing discrete aryl groups in a diaryliodonium for two different bond-forming events has, to the best of our knowledge, not been reported.

Scheme 1. Transition-Metal-Catalyzed Activation of Diaryliodonium Salts



We chose to explore this idea through the double arylation of indole (**1a**), as arylated indoles are fundamental building blocks of biologically active compounds and functional materials.[9] We planned an initial C−H-arylation under copper catalysis, followed by N-arylation using the *in situ*-generated aryl iodide and the same metal catalyst. Gaunt's iodonium Cu-catalyzed indole arylation system appeared particularly well-suited for the first C−H activation,[9b] as it proceeds efficiently under mild conditions for a range of iodonium salts. For indole N-arylation, Buchwald has reported effective Cu-catalysis using chelating diamines and aryl iodides.[10]

Early trial reactions established, not unexpectedly, that the C- and N-arylation conditions were orthogonal to one another, e.g., indole arylation with Ph$_2$IOTf using Gaunt's conditions of Cu(OTf)$_2$ catalysis in DCM using di-*tert*-butylpyridine (dtbpy) as base gave the C-arylated product **3a** in 82% yield (Table 1, entry 1), with no N-arylation detected. Whereas indole arylation using ArI under Buchwald's conditions in dioxane gave *N*-phenyl indole in high yield, with no sign of C-arylation (entry 2).[11] To overcome this dichotomy and merge the two processes, we first needed a common solvent. The N-arylation was ineffective in DCM or DCE used in C−H arylation, but the C−H arylation could proceed using dioxane (65% yield of **3a**, entry 4). Next, we established that CuI could be used as the catalyst for both steps (entry 5), requiring a higher temperature

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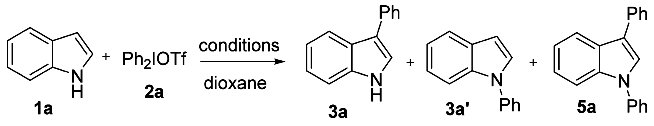
Table 1. Reaction Optimization



entry	catalyst/ligand	base	temp (°C)	time (h)	yield (%)[a] (3a:3a′:5a)
1[b]	Cu(OTf)$_2$ (10 mol %)	dtbpy (1.1 equiv)	rt	24	82:0:0
2[c]	CuI (5 mol %), DMEDA (10 mol %)	K_3PO_4 (2 equiv)	110	12	0:96:0
3[d]	CuI (5 mol %), DMEDA (10 mol %)	K_3PO_4 (2 equiv)	110	12	0:0:86
4	Cu(OTf)$_2$ (10 mol %)	dtbpy (1.1 equiv)	rt	24	65:0:0
5	CuI (5 mol %)	dtbpy (1.1 equiv)	60	24	78:0:0
6	CuI (5 mol %)	dipea (1.1 equiv)	60	24	0:0:0
7[e]	CuI (5 mol %)	K_3PO_4 (1.5 equiv)	rt	24	30:25:0
8[e]	CuI (5 mol %), DMEDA (10 mol %)	K_3PO_4 (1.5 equiv)	110	16	0:30:0
9[c]	CuI (5 mol %), DMEDA (10 mol %)	K_3PO_4 (2 equiv), dtbpy (1.1 equiv)	110	12	0:94:0
10[e]	CuI (5 mol %); then CuI (5 mol %), DMEDA (10 mol %)	dtbpy (1.1 equiv); then K_3PO_4 (2 equiv)	60, then 110	24, then 16	40:0:20
11	CuI (5 mol %); then CuI (50 mol %), DMEDA (100 mol %)	dtbpy (1.1 equiv); then K_3PO_4 (2 equiv)	60, then 110	24, then 16	0:0:65
12[f]	CuI (20 mol %); then DMEDA (30 mol %)	dtbpy (1.1 equiv); then K_3PO_4 (2 equiv)	60, then 110	24, then 16	0:0:63

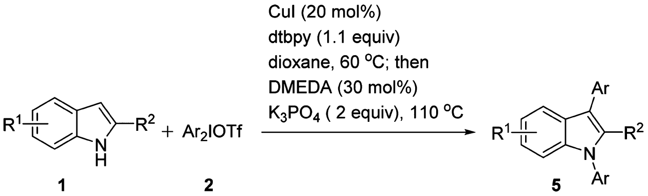
Unless otherwise noted, all reactions were run with **1a** (0.2 mmol) and **2a** (1.1 equiv) in a crimped cap glass vial under an inert atmosphere. [a]Isolated yields. [b]CH_2Cl_2 as solvent. [c]Iodobenzene used instead of **2a**. [d]3-Phenyl indole **3a** and iodobenzene used instead of **1a** and **2a**. [e]Reaction did not reach completion. [f]1.05 equiv of **2a** was used.

of 60 °C for C−H arylation relative to Cu(OTf)$_2$. The base/ligand requirements for each step, however, remained distinct (entries 6−8). While the DMEDA required for N-arylation was observed to completely suppress C-arylation (entry 8), we were pleased to find that the dtbpy required for C-arylation was well tolerated under the N-arylation conditions (entry 9). Accordingly, simple addition of an inorganic base and DMEDA to the reaction vessel on completion of the first arylation would in principle enable tandem arylation.

Initial efforts in this direction using two additions of CuI (5 mol %), however, gave low yields of **5a** (entry 10). It appeared that excess diphenyliodonium **2a** (~10 mol %) remaining in solution from the C-arylation was problematic, inhibiting the second N-arylation.[12] Increasing the CuI loading to 50 mol % successfully circumvented this problem, producing 1,3-diphenyl indole in 65% yield (entry 11). Optimally, we could lower the catalyst loading to 20 mol %, using 1.05 equiv of iodonium **2a**, to give **5a** in 63% overall yield.

We were pleased to find that the tandem C−H/N−H process was productive for a variety of diaryliodonium salts. Using 1.05 equiv of **2** in each case, the one pot, two-step protocol proved broadly applicable, with chlorine, fluorine, methyl, and methoxy-substituted aryl iodoniums all being tolerated (Table 2) for a variety of indoles. The di(*meta*-tolyl)iodonium was somewhat anomalous in producing 16% of indole C2 arylation (no N-arylation) as a byproduct (entry 11); all other iodoniums gave clean C3 selectivity. The reaction was not effective for 2-substituted indoles, with 2-methylindole giving a low yield of **5k** after prolonged heating.

Table 2. Scope of Cu(I)-Catalyzed Diarylation of Indole by Symmetrical Diaryliodonium Salts

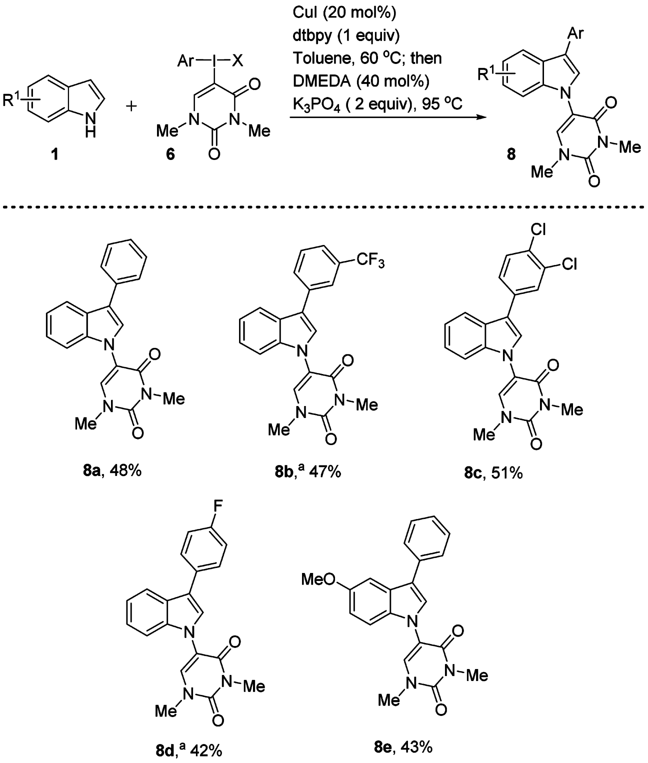


entry	R^1	R^2	Ar	yield (%)[a]
1	H	H	4-(Cl)C_6H_4	60 (**5b**)
2	H	H	4-(F)C_6H_4	58 (**5c**)
3	H	H	4-(Me)C_6H_4	67 (**5d**)
4	H	H	4-(OMe)C_6H_4	41 (**5e**)
5	5-OMe	H	C_6H_5	66 (**5f**)
6	5-OMe	H	4-(Me)C_6H_4	53 (**5g**)
7	5-OMe	H	4-(Cl)C_6H_4	55 (**5h**)
8	5-Me	H	4-(Me)C_6H_4	65 (**5i**)
9	5-F	H	4-(F)C_6H_4	57 (**5j**)
10[b]	H	Me	C_6H_5	20 (**5k**)
11[c]	H	H	3-(Me)C_6H_4	46 (**5l**)

[a]Isolated yields. [b]Step 1 at 75 °C and Step 2 at 150 °C. Reaction did not reach completion even after 48h at 150 °C. [c]2-Aryl indole isolated in 16% yield.

Having established the reaction for symmetrical diaryliodoniums, we were keen to extend it to unsymmetrical analogs. Controlling this reaction presented an immediate challenge, as selective aryl transfer in metal-catalyzed iodonium arylation is usually achieved via steric differentiation of the two arene units.[2b−i,13] The N-arylation step in our sequence is, however, very sensitive to steric hindrance in the aryl *ortho*-position, indicating that hindered aryl iodides will not be productive under the reaction conditions. Selectivity using electronic control, by contrast, is well-precedented for metal-free reactions,[14] but poorly exemplified for metal-mediated processes.[15] Trial reactions with simple electron-rich/-poor diaryliodoniums bore this out, producing regio-isomeric mixtures of 1,3-diarylated indoles. More promising results were obtained, however, using the phenyl dimethyluracil iodonium salts recently introduced by Gaunt et al. for the organocatalytic arylation of aldehydes.[16] Following some optimization studies (see Supporting Information), we were pleased to observe successful sequential C−H and N−H arylation with the phenyl-uracil iodonium triflate **6a**, producing the novel indoyl uracil **8a** in 48% yield (Scheme 2). The 5-iodouracil generated after the first arylation is productive in the N-arylation but somewhat unstable under the original reaction conditions. A solvent switch to toluene and a slight reduction in temperature for the second step enabled successful coupling. No regio-isomeric products were observed, although small amounts of the mono-C-arylated indoles were isolated as side-products in each case (see Supporting Information). Pleasingly, we could exemplify the chemistry on a small range of aryl uracil iodoniums to access the doubly arylated indole structures **8b−e** featuring a selection of functionality.

Scheme 2. Scope of Cu(I)-Catalyzed Diarylation of Indole by Unsymmetrical Diaryliodonium Salts[a]



8a, 48%
8b,[a] 47%
8c, 51%
8d,[a] 42%
8e, 43%

[a]No conversion was observed at 60 °C for step 1. Complete conversion at 80 °C.

In conclusion, we have shown, for the first time, that diaryliodonium salts can be utilized for tandem arylation reactions in one pot, avoiding the wastage of aryl residues that has up to now been characteristic of these reagents. The protocol exemplifies the versatility of Cu catalysis in C−H and N−H arylation, using the same metal catalyst to access novel indole heterocycles in a single operation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimization tables and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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