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**Titel:** The Directed Metalation Group Dance. Regioselective Iterative Functionalization of 7-Azaindole by Controlled Annular Isomerism

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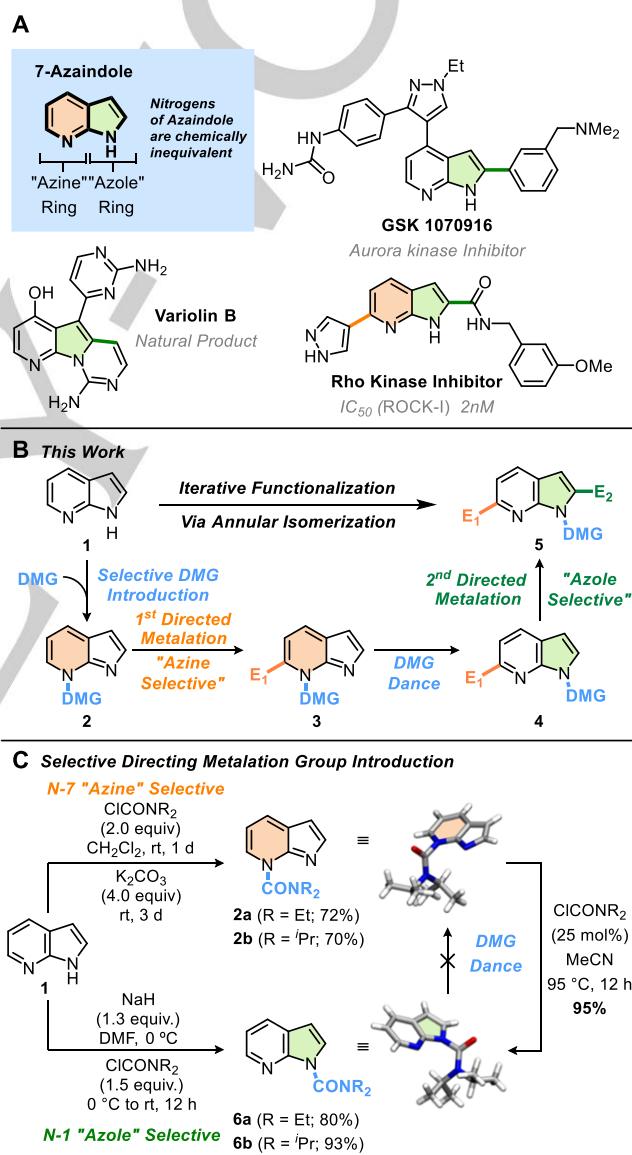
# The Directed Metalation Group Dance. Regioselective Iterative Functionalization of 7-Azaindole by Controlled Annular Isomerism

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*Ted Taylor In Memoriam, a man for all heterocycles*

**Abstract:** The regioselective functionalization of 7-azaindole by controlled annular directed metalation group isomerism is reported. The N-7 carbamoyl azaindoles **2a–b** undergo regioselective metalation and electrophile quench to furnish C-6 substituted derivatives **3** which, in the presence of catalytic amount of CICONR<sub>2</sub> afford products **4** by an N-7 to N-1 carbamoyl group dance. A second directed metalation-electrophile quench sequence leads to 2,6-substituted azaindoles **5**. Optimization of metalation conditions for C-2 and C-6, separately and iteratively, is presented. Using the directed metalation group dance strategy, a late-stage deuteration of an antipsychotic drug is described. Overall, the controlled annular isomerism of a carbamoyl directing group allows multiple functionalization events of the bioactive azaindole scaffold.

Azaindoles occupy a prominent position in drug discovery research due to their diverse bioactivities, especially in the area of protein kinase inhibition for the development of anti-cancer therapies. Among the four isosteres, the 7-azaindole scaffold, also present in a rare class of natural products,<sup>[1]</sup> has emerged as the key heterocycle for structural modification for provision of new bioactive molecules (Figure 1, A).<sup>[2]</sup> Among the synthetic routes for 7-azaindoles, metalation-based methodologies have achieved dominance over classical processes due to advantages of regioselectivity, multiple substitution and ready modification of the prototype nucleus.<sup>[3,4]</sup> In previous efforts, we have demonstrated the power of the directed *ortho* metalation (DoM) reaction in new halogen dance strategies,<sup>[5]</sup> anionic *ortho*-Fries rearrangement processes,<sup>[6]</sup> latent directed metalation group (DMG) protocols,<sup>[7]</sup> and, as demonstrated on the 7-azaindole framework, “walk-around-the-ring” sequences.<sup>[4a,4b,8]</sup> Whilst synthetically powerful, these metalation based approaches involve several steps: DMG introduction, its use to direct the functionalization event, and its subsequent removal or modification.



**Figure 1.** A) 7-Azaindole in natural and bioactive molecules and drugs with azine and azole ring functionalization. B) Selective iterative functionalization through DMG controlled annular isomerization. C) Regioselective introduction and migration studies on 7-azaindole.

Inspired by the work of Sames on silyl migration,<sup>[9]</sup> we hypothesized that the N-7 DMG azaindoles **2** would undergo DoM-mediated C-6 functionalization (Figure 1, B) and, by azine to azole ring DMG dance to the thermodynamically more stable

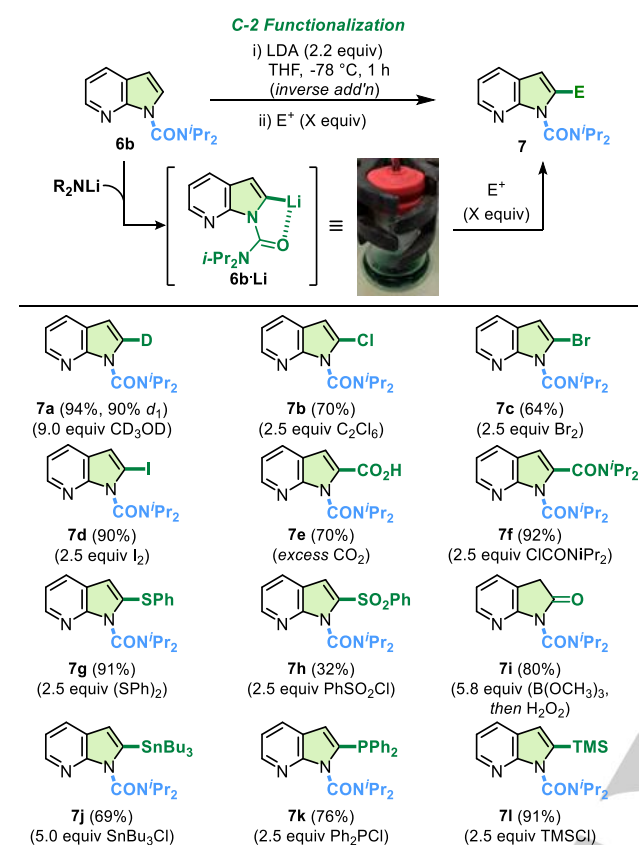
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isomer (**3**→**4**), would allow C-2 functionalization to afford 2,6-



disubstituted azaindoles **5**. Such a migration sequence

**Figure 2.** Regioselective synthesis of C-2 substituted 7-azaindoles. Reactions were performed on a 0.41 mmol scale. Reaction conditions: **6b** (0.41 mmol, 1.0 equiv), LDA (0.90 mmol, 2.2 equiv), THF (0.10 M), -78 °C, 1 h; then E<sup>+</sup> (1.0–3.7 mmol, 2.5–9.0 equiv), -78 °C (1 h) to 23 °C (12 h). Yields of isolated products.

circumvents the removal and introduction of the DMG and would allow the same group to direct functionalization at a new, remote location. In continuing efforts to invent new DoM-founded chemistry,<sup>[10]</sup> we now report the successful attainment of the DMG dance concept (**3**→**4**), which establishes a regioselective route to 7-azaindoles bearing diverse C-2 (**Table 1**) and C-2 and C-6 (**Figure 3**) substitution patterns.

In order to test the DMG dance concept, the regioisomeric N-7 (**2a,b**) and N-1 (**6a,b**) carbamoyl azaindoles were prepared (**Figure 1, C**, for optimization see SI).<sup>[11]</sup> The choice of the CONR<sub>2</sub> as DMG was dictated by its previous efficacy in DoM chemistry.<sup>[4b,12]</sup> Although N-1 DMG 7-azaindoles have been synthesized previously,<sup>[4b,13]</sup> to the best of our knowledge, N-7 DMG-bearing 7-azaindole isomers are unknown. The identity of the two isomers was unambiguously confirmed by X-ray crystallography. To assess the expected thermodynamically driven DMG dance, compound **2b** was subjected to a catalytic quantity of di-isopropyl carbamoyl chloride which led, under optimized conditions (see SI, Table 1), to the isomeric derivative **6b** in 95% yield.

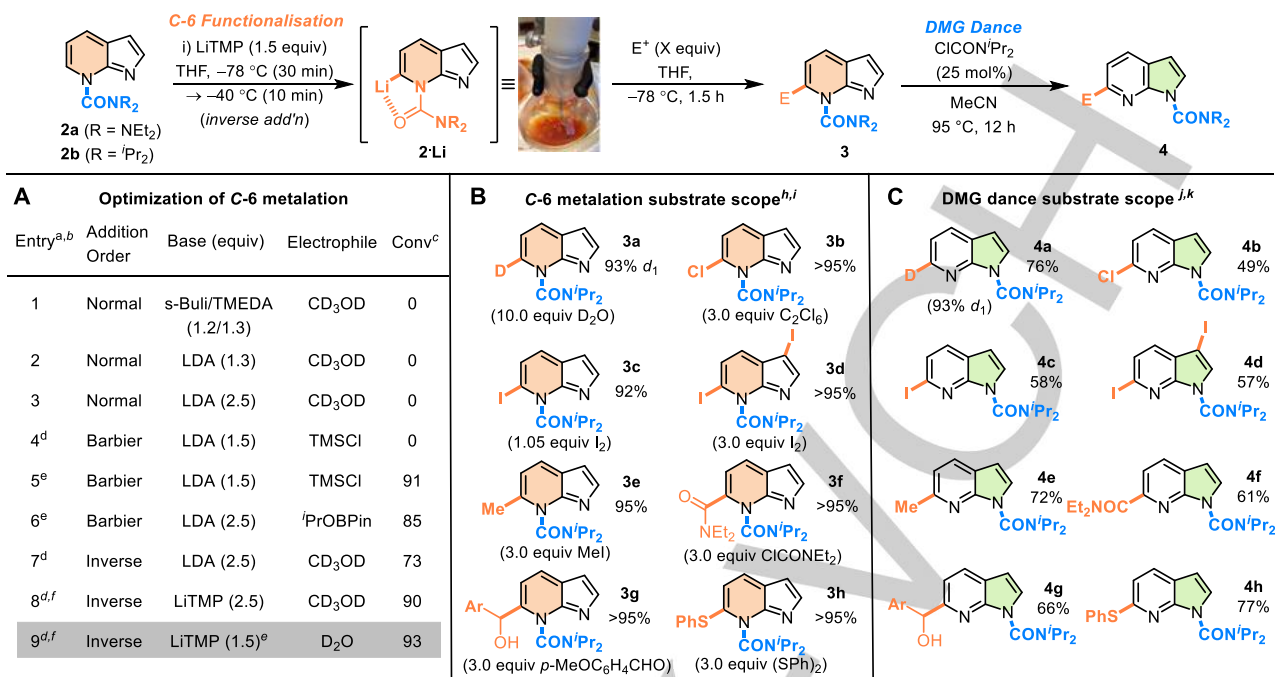
With conditions for the introduction and migration of the DMG in place, selective functionalization of each ring in the azaindole scaffold was undertaken. Firstly, the DoM route to 2-substituted 7-azaindoles **7** was investigated (**Figure 2**). After considerable optimization (see SI), treatment of **6b** with LDA using an inverse addition protocol led to efficient C-2 metalation affording **7a** (90% *d*<sub>1</sub> by <sup>1</sup>H NMR). A comprehensive study of the reaction scope was undertaken, leading to the preparation of a variety of carbon, halogen, sulfur, and phosphorus 2-substituted derivatives **7b–l**. Of particular note is the oxidative conversion of the B(OR)<sub>2</sub> derivative into the azaoxindole **7i**<sup>[14]</sup> and the availability of substrates for further useful metalation (**7e, f, h, j**) and cross-coupling (**7b–d, g, i, j, l**) chemistry.

With conditions for C-2 functionalization in hand, investigation of the C-6 metalation process was conducted (**Table 1, A**). Metalation of **2a** using *s*-BuLi/TMEDA or LDA followed by CD<sub>3</sub>OD quench resulted in product with undetectable *d*-incorporation, suggesting lower C-6 H acidity compared to that of the pyridine C-2 acidity.<sup>[15]</sup> Using Barbier conditions (LDA/TMSCl)<sup>[16]</sup> led to quantitative conversion to **3** (E = TMS) by GC-MS analysis of crude product (entry 4) but normal aqueous work-up resulted in desilylation to starting material **2a**. Switching to anhydrous work-up conditions resulted in formation of products **3** (E = TMS and Bpin) in excellent conversion by <sup>1</sup>H NMR (entries 5 and 6) but subjection to normal work-up also resulted in isolation of starting material **2a**, undoubtedly the result of *ipso*-protodesilylation and *ipso*-protodeboronation.<sup>[17]</sup> In view of the limited electrophile-base compatible combinations for the Barbier and Martin procedures, we returned to examine C-6 metalation of **2b** using inverse addition-electrophile quench procedures. Gratifyingly, 2.5 equiv of LDA under inverse addition conditions gave product **3a** with modest *d*-incorporation (entry 7, 73% *d*<sub>1</sub>). Switching to the more sterically hindered LiTMP and modification of reaction temperature improved the level of anion formation considerably (entries 8 and 9, 90% and 93% *d*<sub>1</sub>, respectively).

Under the optimized conditions, the C-6 DoM chemistry of **2b** was generalized (**Table 1, B**). As shown, the methodology allows the synthesis of halogen containing **3b–d**, carbon-based **3e–g**, and heteroatom-based **3h** azaindole derivatives. A potentially useful finding is the observation of controlled mono-/bis-iodination of **2b** simply by modification of the I<sub>2</sub> stoichiometry (**3c** vs **3d**). Although high levels of conversion (>92%) were observed in all cases (<sup>1</sup>H NMR analysis), yields of isolated products were compromised due to their instability to column chromatography. Fortunately, simple exposure of the crude reaction products to the optimized DMG dance conditions afforded 6-substituted azaindoles **4** which proved readily separable. In this manner, methyl, carbamoyl, carbinol, and sulfide substituted products **4a–h** (**Table 1, C**) were readily accessible in good to excellent yields.

To fully establish the DMG dance strategy for general regioselective C-2 and C-6 functionalization of the 7-azaindole scaffold, C-2 DoM reactions of substrate **4** were undertaken. Application of the optimized C-2 metalation conditions on **4**, followed by electrophile quench, afforded products

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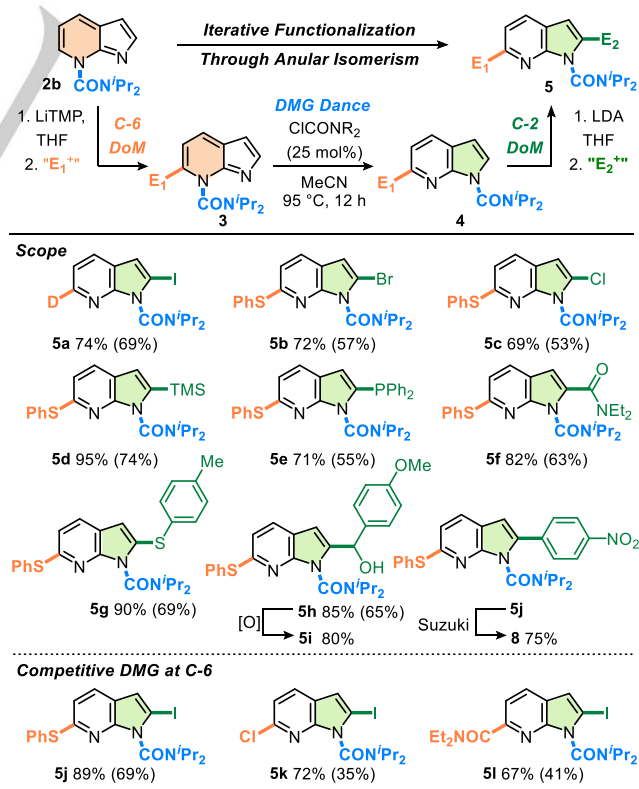


**Table 1.** Optimization of C-6 metalation, substrate scope and DMG migration from N-7 to N-1. A: [a] All reactions were performed on a 0.41 mmol scale. [b] Entries 1–6: **2a** as starting material; entries 7–9: **2b** as starting material. [c] % deuteration / conversion was determined by 400 MHz <sup>1</sup>H NMR analysis on the crude reaction mixture. [d] Aqueous workup. [e] Anhydrous workup. [f] The reaction was stirred at -78 °C for 30 mins before being warmed to -40 °C for 10 min. Electrophile was added at -78 °C, and the reaction was stirred for 1.5 h at this temperature. [g] LiTMP was prepared using 1.6 equiv 2,2,6,6-tetramethylpiperidine and 1.5 equiv t-BuLi in THF solution. B: [h] Reaction conditions: **2b** (0.41 mmol, 1.0 equiv), LiTMP (0.62 mmol, 1.5 equiv), THF (0.10 M), -78 °C (30 min) to -40 °C (10 min); then E+ (0.43–4.1 mmol, 1.05–10.0 equiv), -78 °C, 1.5 h. [i] All % yields represent conversion as determined by 400 MHz <sup>1</sup>H NMR on the crude reaction mixture. C: [j] Reaction conditions: **2b** (0.41 mmol, 1.0 equiv), LiTMP (0.62 mmol, 1.5 equiv), THF (0.10 M), -78 °C (30 min) to -40 °C (10 min); then E+ (0.43–4.1 mmol, 1.05–10.0 equiv), -78 °C, 1.5 h. After subsequent work-up: **3** (assumed 0.41 mmol, 1.0 equiv), CICONPr<sub>2</sub> (0.10 mmol, 25 mol%), MeCN (0.04 M), 95 °C, 12 h. [k] All % yields are of isolated products over the two steps (i.e. from **2b**)

**5a–j** in good yields (67–89%) (Figure 3). Of particular note, the presence of the powerful N-1 DMG overrides any competitive metalation at C-5 aided by the potential DMGs present at C-6 (**5j,k**) including the powerful amide directing groups (**5l**). Given the prevalence of bioactive 2-arylated 7-azaindole variants (e.g. GSK 1070916, Figure 1, A), we explored the feasibility of the cross-coupling of **5j** with 4-nitrophenylboronic acid, two expectedly proficient coupling partners.<sup>[18]</sup> In a preliminary encouraging study, Suzuki-Miyaura coupling resulted in the formation of product **8** in good yield.

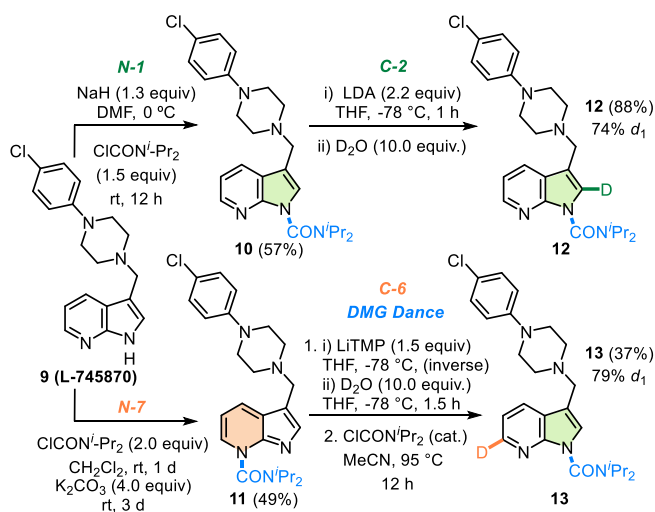
In consideration of the interest in deuterated molecules as new drug entities,<sup>[19]</sup> we undertook a deuteration study of the antipsychotic agent L-745870 (**9**, Figure 4). Thus, compound **10**, prepared (see SI) and subjected to deuteration using the standard LDA protocol afforded **12** (88% yield, 74% d<sub>1</sub>). Subjecting the isomeric N-7 carbamoyl derivative **11** to the LiTMP/D<sub>2</sub>O conditions as previously optimized (Table 1, A) followed by the catalytic DMG dance procedure afforded deuterated material **13** in 37% yield over two steps (79% d<sub>1</sub>).

In summary, we have demonstrated a new DMG dance concept and developed it for a general and highly regioselective synthesis of 2- and 6- and combined 2,6-substituted 7-azaindole derivatives. In addition, we have illustrated an application of this annular DMG isomerism concept in the regioselective synthesis of deuterated antipsychotic agent L-745870, a result which may anticipate late-stage derivatization of other commercial drugs.



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**Figure 3.** Iterative C-6 and C-2 functionalization of 7-azaindole by DoM and DMG dance reactions. [a] yield from **4**. [b] Yield from **2b** given in brackets over three step sequence. For **5h**→**5i** (Oxidation), **5j**→**8** (Suzuki coupling), see SI.



**Figure 4.** Regioselective deuteration of antipsychotic agent L-745870.

Aside from the viability of the DMG dance methodology for the construction of new and difficult to access 7-azaindoles, its adaption to similarly two-nitrogen related aza-heterocycles may be envisaged. Pertinent work is in progress and will be reported in due course.

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**Keywords:** Azaindole • DMG Dance • Iterative metalation • Regioselectivity • Lithiation

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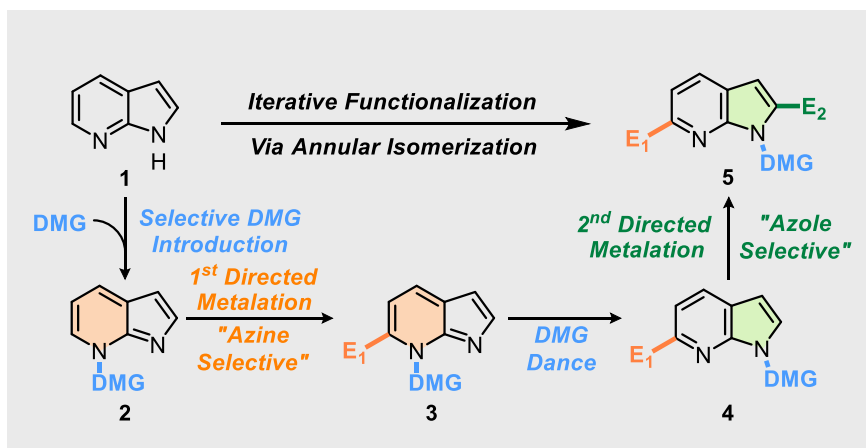
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The Directed Metalation Group  
Dance. Regioselective Iterative  
Functionalization of 7-Azaindole by  
Controlled Annular Isomerism

### The Directed Metalation Group Dance

A new Directed Metalation Group (DMG) dance concept is disclosed on the 7-azaindole framework. Azine selective (N-7) incorporation of the carbamoyl DMG allows C-6 functionalization via directed *ortho* metalation. The controlled annular DMG dance N-7 to N-1 generates the azole (N-1) DMG derivative. Second and iterative DoM reactions allow the synthesis of 2,6-substituted azaindoles in good yields. The DMG dance methodology is demonstrated in site selective deuteration of a drug scaffold.