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Copper-Catalyzed Regiospecific Synthesis of *N*-Alkylbenzimidazoles

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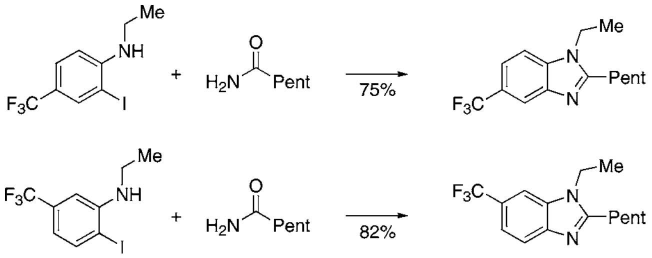
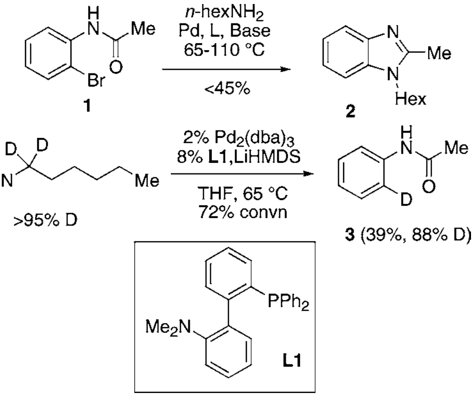
ABSTRACT



A copper-catalyzed method is described for the preparation of *N*-alkylbenzimidazoles in regioisomerically pure form starting from *o*-haloanilines. The method utilizing CuI and *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine allows the preparation of *N*-alkylbenzimidazoles in good to excellent yields.

Benzimidazoles are an important class of heterocycles with a wide range of applications.[1−4] Although numerous methods for their synthesis have been disclosed,[5] it remains difficult to access regioisomerically pure *N*-substituted benzimidazoles. We have recently disclosed a palladium-catalyzed method that allows access to *N*-arylbenzimidazoles in regioisomerically pure form.[6] However, the catalyst system used in the method failed to provide *N*-alkylbenzimidazoles (e.g., **2**) in acceptable yield when primary aliphatic amines were used as substrates (Scheme 1). Despite extensive effort made in the screening of ligands, bases, and solvents, only a modest yield of the product (**2**) could be realized. The desired coupling reaction was plagued by competing reduction of **1** to acetanilide. The problem was traced to a β-hydride elimination process from the intermediate Pd(aryl)amide through the use of 2,2-dideuterohexylamine (Scheme 1). This result demonstrates a major difference in the efficiency of the Pd-catalyzed coupling of *o*-haloanilides with primary aliphatic amines and with anilines. We reasoned that an analogous copper-catalyzed transformation might be more effective with amines possessing β-hydrogen atoms. Herein we describe a complementary copper-based catalytic method

Scheme 1. Pd-Catalyzed Amination with Aliphatic Amines



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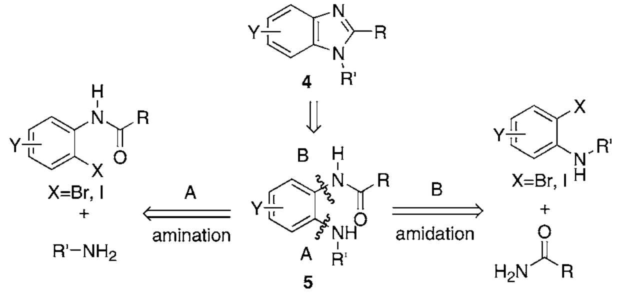
that enables us to prepare *N*-alkylbenzimidazoles in regioisomerically pure form.[7]

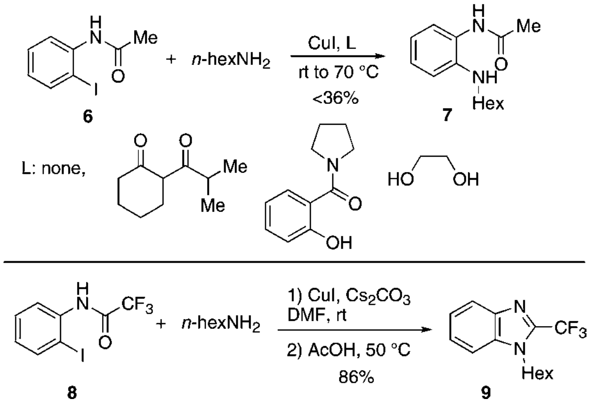
Retrosynthetically, there are two clear carbon−nitrogen bond disconnections for the synthesis of **5**, the precursor to *N*-alkylbenzimidazoles **4** (Scheme 2). Each requires a different type of coupling reaction (the amination or amidation of an aryl bromide or iodide). Using copper catalysts, both processes are well precedented in the literature.[8]

Scheme 2. Possible Bond Disconnections for the Synthesis of *N*-Alkylbenzimidazoles



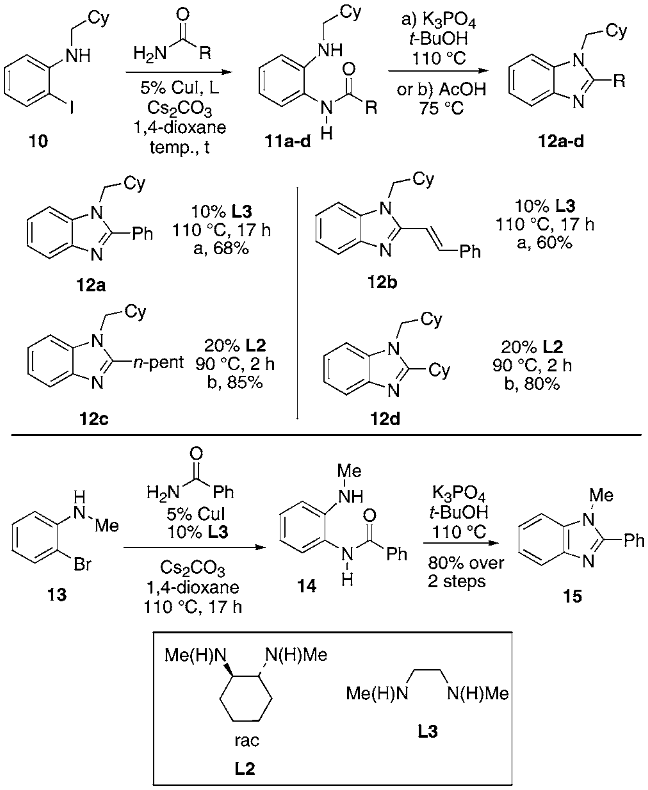
Bond disconnection A was investigated first using the model reaction that combined aryl iodide **6** and *n*-hexylamine (Scheme 3). Under the conditions screened, none of the ligands provided amination product **7** in acceptable yield. Considering that the acidity of the amide proton is known to have a substantial effect on the rate of amination,[9] we examined the combination of aryl iodide **8** and *n*-hexylamine, which proceeded smoothly at room temperature, not necessitating the use of added ligand. The nascent coupling product spontaneously cyclized under the reaction conditions to provide benzimidazole **9** in 82% yield.[7] Unfortunately, the process only worked well for trifluoroacetamide substrates (**5**, R = CF_3) and hence lacked generality.

Scheme 3. Synthesis of *N*-Alkylbenzimidazoles via Bond Disconnection A



We next turned our focus to a route based on bond disconnection B (Scheme 4). Using conditions for the copper-catalyzed amidation (5 mol % of CuI, 20 mol % of diamine ligand, 1.5 equiv of Cs_2CO_3 in 1,4-dioxane) previously reported by our group, aryl iodide **10** was allowed to react with benzamide to provide the desired amidation product **11a**; these coupling conditions proved to be quite general. In addition to benzamide, hexanamide, cyclohexanecarboxamide, and (*E*)-cinnamamide were all successfully coupled with **10**. In contrast to the synthesis of *N*-arylbenzimidazoles, the amidation products **11a**−**d** did not spontaneously cyclize to provide *N*-alkylbenzimidazoles **12a**−**d** under the coupling conditions. Depending on the substrate, two protocols were developed to accomplish the dehydration process. Amides such as **11a**,**b** were converted to *N*-alkylbenzimidazoles **12a**,**b** by treatment with 1.5 equiv of K_3PO_4 in *t*-BuOH at 110 °C (8 h). The amidation and cyclodehydration steps were performed in a single reaction vessel. The cyclodehydration of amides **11c**,**d** to *N*-alkylbenzimidazoles **12c**,**d** was accomplished by heating the former in AcOH at 90 °C for 2 h. We were also able to extend this chemistry to an aryl bromide substrate, **13**, as shown for the preparation of **15**.

Scheme 4. Scope for Copper-Catalyzed Synthesis of *N*-Alkylbenzimidazoles



To address the issue of preparing regioisomerically pure *N*-alkylbenzimidazoles, the coupling reactions of two pairs

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[7] During the preparation of this manuscript, Ma et al. published a related Cu-catalyzed process for the preparation of *N*-alkylbenzimidazoles: Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598−2601.

[8] Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364.

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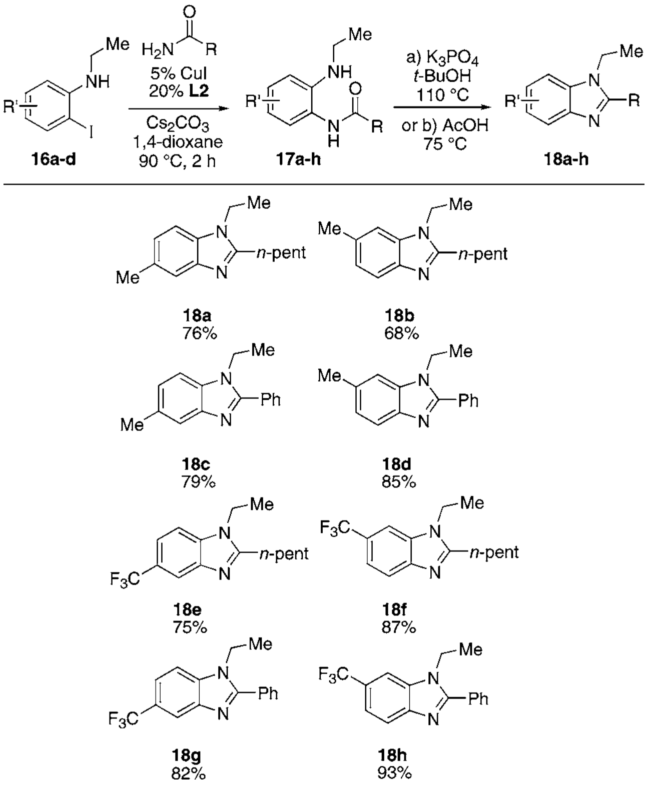
of isomeric aryl iodides **16a−d** and two amides (benzamide and hexanamide) were carried out (Scheme 5). Four pairs of regioisomeric *N*-alkylbenzimidazoles **18a−h** were synthesized in good yields using the conditions described above without need for further optimization. Compared to the palladium-catalyzed synthesis of *N*-arylbenzimidazoles,[6] this method appeared to be less sensitive to the substitution pattern of the aryl iodide substrates.

Scheme 5. Copper-Catalyzed Synthesis of Regioisomeric *N*-Alkylbenzimidazoles



In summary, we have developed a copper-catalyzed method for the synthesis of *N*-alkylbenzimidazoles. In conjunction with our palladium-catalyzed method for the synthesis of *N*-arylbenzimidazoles, these two complementary methods allow the synthesis of *N*-substituted benzimidazoles in regioisomerically pure form, an unmet need in the synthesis of benzimidazoles.

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Supporting Information Available: Experimental procedures 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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