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Regioselective Synthesis of Benzimidazolones via Cascade C–N Coupling of Monosubstituted Ureas

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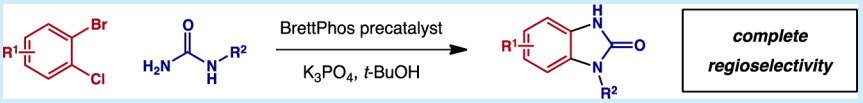
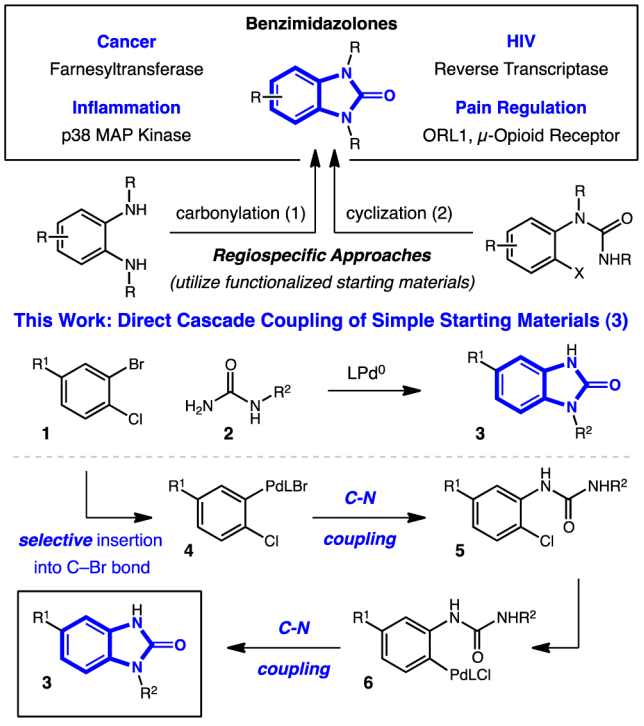
Supporting Information



ABSTRACT: A direct method for the regioselective construction of benzimidazolones is reported wherein a single palladium catalyst is employed to couple monosubstituted urea substrates with differentially substituted 1,2-dihaloaromatic systems. In this method, the catalyst is able to promote a cascade of two discrete chemoselective C–N bond-forming processes that allows the highly selective and predictable formation of complex heterocycles from simple, readily available starting materials.

The catalytic formation of carbon–nitrogen bonds is a central research focus in our laboratory,[1] and we have a longstanding interest in applying C–N cross-coupling methods to the selective construction or functionalization of valuable heterocycles.[2] Benzimidazolones are present in a range of biologically active small molecules that impact processes that are relevant to cancer,[3] inflammation,[4] HIV,[5] pain regulation,[6] and others.[7] There are methods that allow the direct benzimidazolone functionalization, but the reactivities of the two nitrogen atoms contained in the cyclic urea are very similar and, as a result, regioselectivity in these processes has typically been achieved through the use of protecting groups.[8] However, a number of regiospecific approaches have emerged that involve differentiation of the nitrogen atoms prior to heterocycle assembly. Two of the most commonly employed strategies involve carbonylation of phenylenediamine derivatives[3−7] (using phosgene or similar electrophiles, eq 1) or cyclization of functionalized phenylureas[9] (eq 2).

We recently described a regioselective approach to benzimidazole synthesis that operates through a cascade of C–N bond-forming reactions.[10] In this system, a single palladium catalyst mediates the selective coupling of bifunctional aryl electrophiles with two different nitrogen-based nucleophiles to afford the heterocyclic products. We questioned whether a similar approach could be developed to deliver complex benzimidazolones directly. More specifically, we understood that chemoselective oxidative addition[11] of a phosphine-ligated palladium(0) catalyst into *ortho*-bromochlorobenzene substrate **1** would give rise to the arylpalladium(II) bromide complex **4** (as shown in eq 3). Preferential arylation of the primary urea[12] (contained in nucleophile **2**) would afford the 2-chloroaniline derivative **5**, and an intramolecular coupling sequence (via intermediate **6**) would deliver the benzimidazolone **3**. If successful, the outlined process would grant access to functionalized benzimidazolone structures in a single step from commercially available or readily accessible starting materials, potentially with high levels of regiocontrol.



To evaluate the feasibility of the proposed cascade process, we treated 2-bromo-1-chloro-4-fluorobenzene with 1.2 equiv of benzylurea, 2.4 equiv of an inorganic base, and a series of palladium precatalysts (a selection of which are shown in Table 1) at 110 °C for 14 h. Although *t*-BuBrettPhos[13] and XantPhos[12] are capable supporting ligands for palladium-mediated urea arylation, we found that the catalyst based on BrettPhos was uniquely able to perform both coupling steps of the detailed cascade. In the presence of 5 mol % BrettPhos

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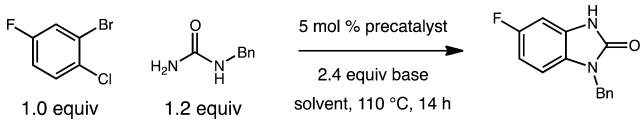
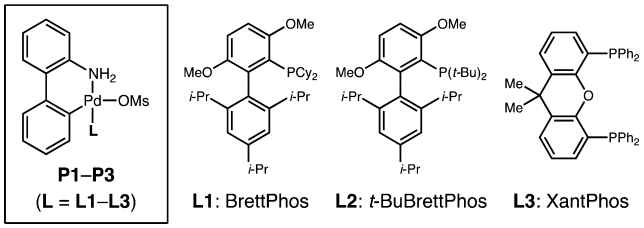
Table 1. Optimization of the Reaction Conditions[a]



entry	precatalyst	solvent	base	NMR yield
1	**P3**	*t*-BuOH	K_3PO_4	0%
2	**P2**	*t*-BuOH	K_3PO_4	0%
3	**P1**	*t*-BuOH	K_3PO_4	85%
4	**P1**	*t*-BuOH	K_2CO_3	77%
5	**P1**	*t*-BuOH	Cs_2CO_3	68%
6	**P1**	dioxane	K_3PO_4	75%
7	**P1**	PhMe	K_3PO_4	0%

[a]Reactions were performed on a 0.2 mmol scale; yield was determined by ^{19}F NMR using 1-fluoronaphthalene as an internal standard; complete regioselectivity was observed in all cases.

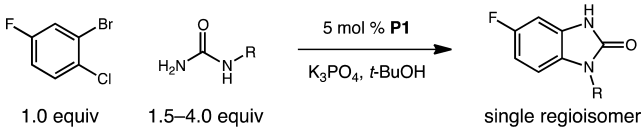


palladium(II) mesylate precatalyst (**P1**),[14] the substrates reacted smoothly to provide the corresponding 5-fluoro-substituted benzimidazolone as a *single regioisomer* with good efficiency (entry 3, 85% ^{19}F NMR yield). While inorganic carbonate bases were also capable of promoting this transformation (entries 4 and 5), a decrease in product yield was observed when dioxane or toluene were used as solvent (entries 6 and 7).

To assess the substrate scope of this cascade transformation, 2-bromo-1-chloro-4-fluorobenzene was coupled with a range of ureas under standard conditions. As shown in Table 2, a number of alkyl-substituted ureas, including electronically diverse benzylurea derivatives, gave rise to the corresponding 5-fluoro-1-alkylbenzimidazolones in good yield (Table 2, entries 1–5). Unfortunately, we found that the incorporation of electron-rich arylurea systems was inefficient under these conditions (presumably due to instability of the intermediate 2-chloroarylurea),[15] but electron-neutral substrates could be employed to give the desired heterocycles in synthetically acceptable yields (entries 6 and 7). Notably, the outlined conditions afforded the desired heterocycles with complete regioselectivity.

We then turned our attention to evaluating the scope of the electrophile in this process. As shown in Scheme 1, these

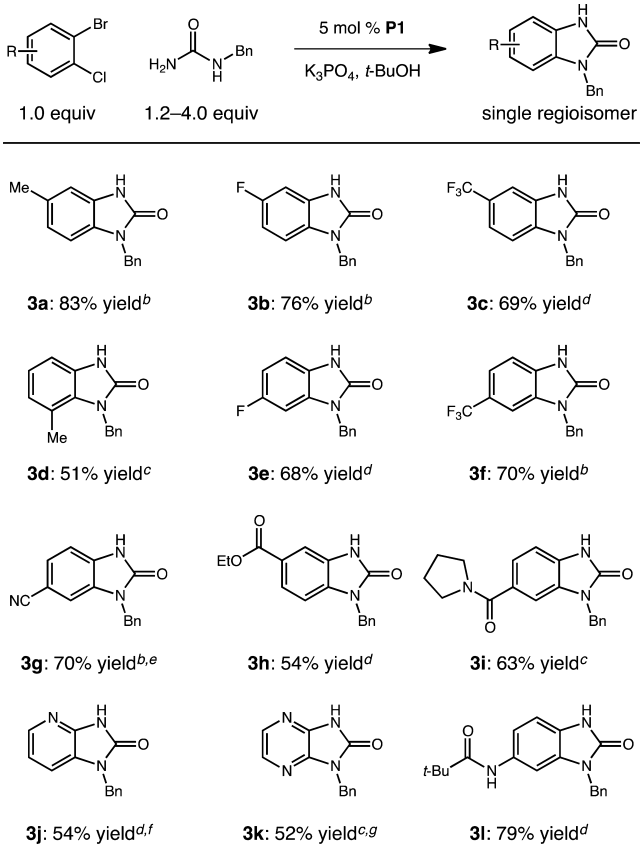
Table 2. Regioselective Benzimidazolone Synthesis: Scope of the Urea Coupling Partner[a]



entry	R	equiv urea	yield[b]
1	Me	2.5	76%
2	Bu	2.5	85%
3	2-F-Bn	1.5	75%
4	4-CF_3-Bn	4.0	76%
5	4-MeO-Bn	1.5	78%
6	Ph	4.0	70%
7	4-F-C_6H_4	4.0	59%

[a]Reaction conditions: ArBr (1.0 mmol), urea (1.5–4.0 mmol), K_3PO_4 (2.4 mmol), precatalyst **P1** (0.05 mmol), *t*-BuOH (4.0 mL), 110 °C, 14 h. [b]Isolated yield (average of two runs).

Scheme 1. Cascade Approach to Benzimidazolones: Scope of the Electrophile[a]



[a]Reaction conditions: ArBr (1.0 mmol), benzylurea (1.5–4.0 mmol), K_3PO_4 (2.4 mmol), precatalyst **P1** (0.05 mmol), *t*-BuOH (4.0 mL), 110 °C, 14 h; isolated yields (average of two runs). [b] 1.2 equiv of benzylurea. [c] 2.5 equiv of benzylurea. [d] 4.0 equiv of benzylurea. [e] Reaction conducted with 3 mol % **P1**. [f] 2,3-Dichloropyridine used as starting material. [g] 2,3-Dichloropyrazine used as starting material.

catalytic conditions allowed us to unite a collection of substituted 2-bromochlorobenzene derivatives with benzylurea to give the corresponding complex heterocycles. In addition to methyl groups (**3a** and **3d**), electron-withdrawing substituents, including trifluoromethyl (**3c** and **3f**), cyano (**3g**), ester (**3h**), and amide (**3i**) groups, were tolerated in this process (51–83% yield) and again the products were obtained in regioisomerically pure form. Furthermore, we found that the selective coupling of 2,3-dichloropyridine could be achieved under standard conditions to afford exclusively the 1-substituted imidazo[4,5-*b*]pyridin-2-one in moderate yield.

In summary, we describe a novel approach to regioselective benzimidazolone construction that operates through a cascade of two discrete palladium-catalyzed C–N bond-forming reactions. In this process, the heterocyclic products are formed with complete regiocontrol that stems from the chemoselective

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nature of two different fundamental catalytic operations, namely oxidative addition of the palladium catalyst to Ar−Br bonds in the presence of Ar−Cl bonds and preferential C−N bond formation of primary urea nitrogen atoms. Finally, this method utilizes a commercially available palladium precatalyst and simple starting materials to provide direct and selective access to a collection of complex benzimidazolones in a single step.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and data in addition to spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): MIT has or has filed patents on the ligands/precatalysts that are described in this paper from which S.L.B. and former/current coworkers receive royalty payments.

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(15) When 4-methoxyphenylurea was used as a substrate under the described conditions, a low yield of the desired benzimidazolone was obtained and decomposition products (*p*-anisidine and 4-methoxyphenylisocyanate) were observed by GCMS.