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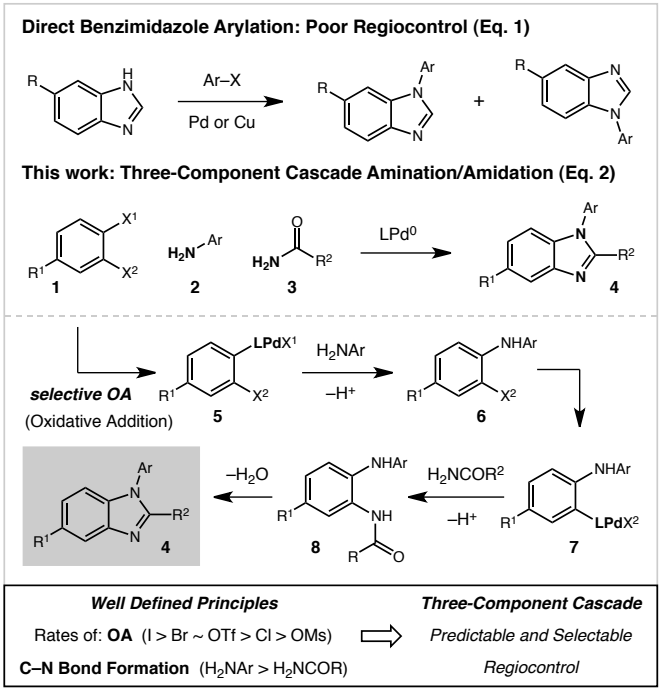
Cascade Palladium Catalysis: A Predictable and Selectable Regiocontrolled Synthesis of *N*-Arylbenzimidazoles**

*Nathan T. Jui and Stephen L. Buchwald**

This manuscript is dedicated to Professor Irina Beletskaya in recognition of her contributions to the field of metal-catalyzed reactions.

Nitrogen-containing heterocyclic groups are pervasive structural elements in natural products, medicines, agricultural chemicals, and functional materials. As a result, the construction and functionalization of these is a central focus in organic synthesis. Our group, among others, has a long-standing interest in developing catalytic methods that enable the efficient and selective formation of carbon–nitrogen bonds,[1] and we seek to apply these technologies to the preparation and/or modification of a broad array of heterocyclic scaffolds, including benzimidazoles. Regioselective benzimidazole alkylation or arylation is challenging due to the relatively similar electronic properties exhibited by the non-equivalent nitrogen atoms contained within the imidazole moiety.[2]

While transition-metal catalysts have evolved to efficiently install aryl units directly onto benzimidazole substrates,[3] regioisomeric mixtures are formed in the absence of significant steric differentiation of the two nitrogen atoms (equation 1).[4] As a result, a number of methods have been developed to overcome this issue.[5] The most commonly utilized strategy involves intramolecular cyclization of arylamidine structures,[6] and both cross-coupling[6a-h] and oxidative cyclization[6i,j] technologies have been explored extensively. In addition, a number of elegant cascade processes have emerged that enable *in situ* arylamidine formation followed by cyclization.[7] In addition to the laboratories of Ma[8a,c] and Clark,[9b,c] we have developed an alternative approach wherein catalytic amination[8] or amidation[9] of 2-chloroaniline derivatives and subsequent condensation delivers the desired azole products. We envisioned a complimentary strategy for the direct construction of benzimidazoles via a regio- and chemo-selective cascade of palladium-catalyzed C–N bond-forming reactions involving a 2-chloroaryl sulfonate (or similar) substrate and two discrete nitrogen-based nucleophiles that are added at the same time (equation 2). The outlined three-component coupling method represents a potentially powerful alternative approach to heterocycle synthesis that would provide modular access to a broad range of functionalized



benzimidazoles with predictable and potentially *selectable* regiocontrol.

The proposed proccess, shown in equation 2, involves selective oxidative addition of a palladium catalyst into the C–X^1 bond of the di-activated arene **1** to form the organopalladium intermediate **5**. Arylation of an arylamine substrate (**2**), in preference to the amide nucleophile, would provide the *ortho*-haloaniline **6**. A second palladium insertion followed by coupling with amide **3** would yield the *o*-phenylenediamine derivative **8** that, after condensation, would convert to the desired benzimidazole **4**. While the outlined process would require two different fundamental steps to occur with high levels of chemoselectivity, namely oxidative addition to X^1 and C–N coupling, we anticipated that both elements would be possible because (i) relative rates of oxidative addition to aryl electrophiles are understood to generally follow the pattern: I > OTf ~ Br > Cl > OMs,[10] and (ii) it has been demonstrated that arylamines can react preferentially with aryl palladium complexes in the presence of amides.[11] Herein, we describe the realization of this design and its application to a process that exploits the orthogonal reactivity of aryl triflates and aryl mesylates to produce either of the two possible benzimidazole regioisomers in a selectable manner from a single 2-chlorophenol precursor.

We have developed a family of dialkylbiaryl phosphines that are highly efficient ligands for a number of palladium-catalyzed processes,[12] including amination[13] and amidation[14] reactions. From the outset, we recognized that the identification of a single catalyst that could perform the chemo- and regioselective coupling of both aniline and amide nucleophiles was critical and we expected

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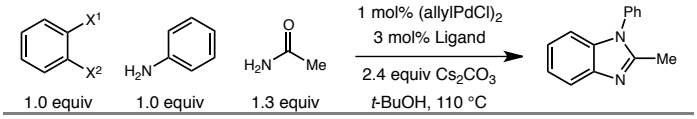
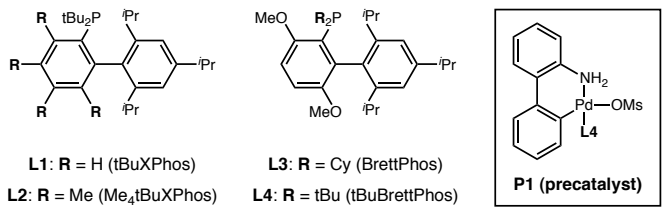
that the ligand would be key to the success of this method. Given the facile access to 2-chlorophenols, we were first interested in developing this cascade reaction using 2-chlorophenyl triflate, one equivalent of aniline, and a slight excess of acetamide (Table 1). When treated with $(allylPdCl)_2$ (1 mol%), phosphine ligand (3 mol%), 2.4 equivalents of cesium carbonate, and *tert*-butanol at 110 °C for 12 hours, the desired benzimidazole was provided in varying amounts (Table 1, entries 1–7). Although the use of triphenyl-, tricyclohexyl-, or tri-*tert*-butyl phosphine was unsuccessful in this context (entries 1–3), catalysts based on biarylphosphine ligands did result in formation of the desired product. While tBuXPhos (**L1**), Me_4tBuXPhos (**L2**), or BrettPhos (**L3**)—phosphines that have been employed in amination or amidation reactions of aryl chlorides—were less effective supporting ligands in this cascade (entries 4–6, up to 63% yield), the catalyst based on tBuBrettPhos (**L4**) provided the desired benzimidazole in 77% yield (entry 7). The yield was further improved by employing the recently described 4-aminobiphenyl-derived tBuBrettPhos mesylate precatalyst (**P1**),[15] which delivered the desired product in 88% GC yield (86% isolated; Table 1, entry 8). Additionally, we found that 2-chloro-1-bromobenzene and 1,2-dichlorobenzene can also function as the electrophilic component of this system, further demonstrating the utility of this process.

Table 1. Cascade amination/amidation: Catalyst identification.[a]



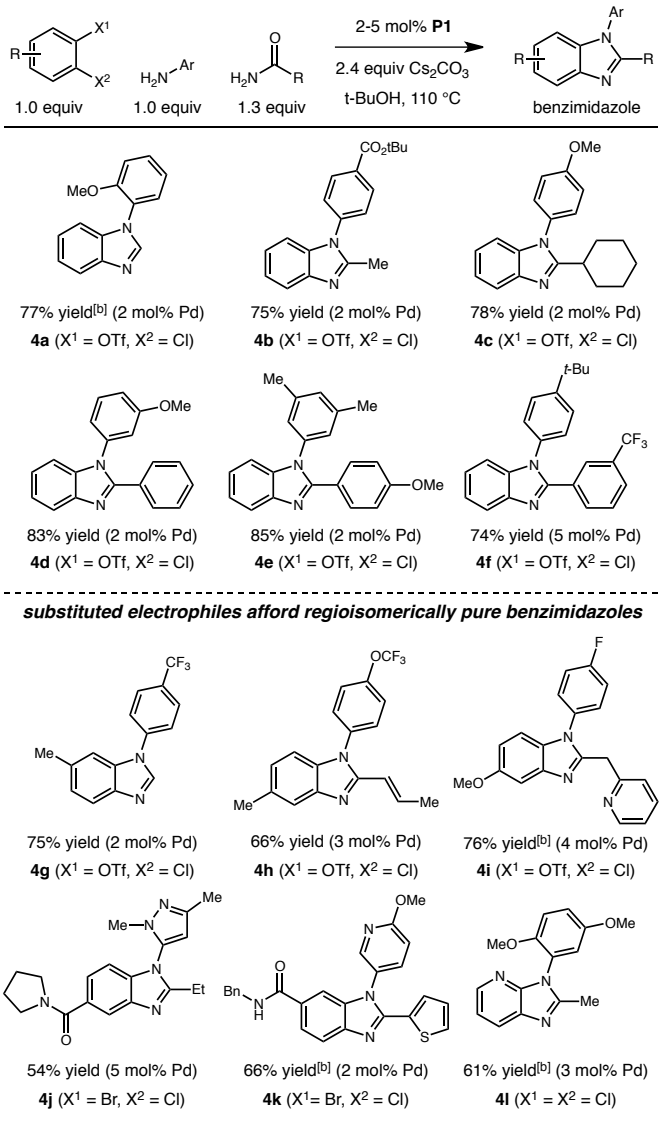
Entry	X^1	X^2	Ligand	Yield[b]
1	OTf	Cl	PPh_3	0%
2	OTf	Cl	PCy_3	0%
3	OTf	Cl	$PtBu_3$	0%
4	OTf	Cl	**L1**	trace
5	OTf	Cl	**L2**	47%
6	OTf	Cl	**L3**	63%
7	OTf	Cl	**L4**	77%
8	OTf	Cl	**2 mol% P1**[c]	88% (86%)
9	Br	Cl	**2 mol% P1**[c]	87%
10	Cl	Cl	**2 mol% P1**[c]	70%

[a] Reaction conditions: aryl halide (0.5 mmol), aniline (0.5 mmol), acetamide (0.65 mmol), $(allylPdCl)_2$ (3 mol%), ligand (3 mol%), Cs_2CO_3 (1.2 mmol), tBuOH (1.0 mL), 110 °C, 12 h. [b] Yield determined by GC using tetradecane as internal standard, isolated yield in parenthesis. [c] Precatalyst **P1** was used instead of $(allylPdCl)_2$ and ligand.



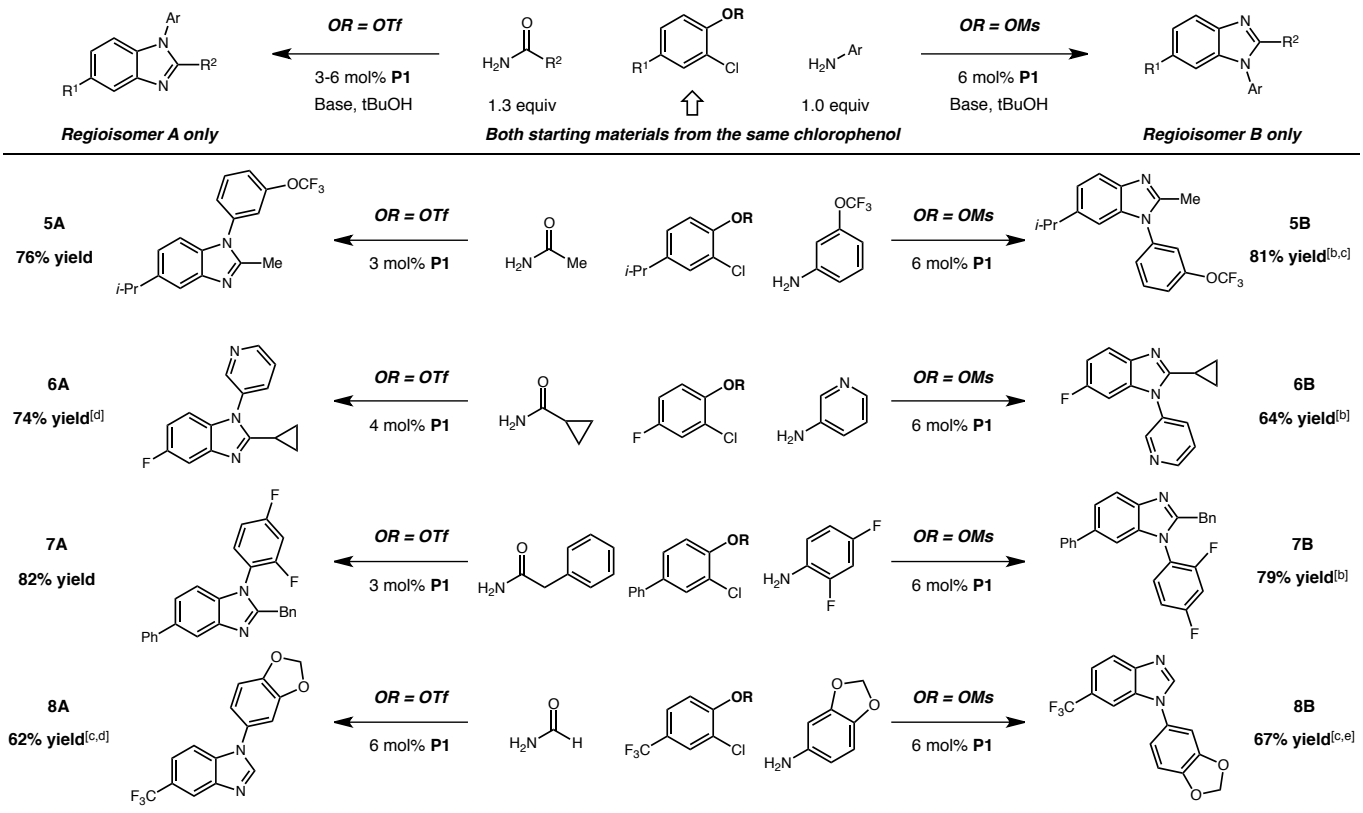
Having identified conditions that enable this cascade process, we evaluated the substrate scope of this transformation. As highlighted in Table 2, a range of substituted arylamines bearing electron-donating or electron-withdrawing substituents readily participate in this process as do aminopyridine and aminopyrazole substrates. In addition to formamide, simple straight-chain alkyl-, branched alkyl-, vinyl-, and aryl-substituted amides react smoothly under standard conditions (54–85% yield), although some substrate combinations require slightly elevated catalyst loading to proceed to completion in the 12-hour period (up to 5 mol%). Moreover, we found that a range of 4- or 5-substituted 2-chloroaryl triflates provide access to the corresponding benzimidazoles in moderate to good yield as single regioisomers. While 2-chloroaryl triflates are generally the best substrates in this chemistry, competitive hydrolysis of the triflate function was observed in the presence of electron-withdrawing substituents. However, the corresponding 2-chloroaryl bromides could be used to circumvent this issue (Table 2, **4j, 4k**). In all of the cases examined, selective amination of the aryl triflate (or bromide) was observed but, in some cases, significant amounts of diaminated electrophile was observed. We found that the yield of the desired product in these examples was increased by stirring the reaction mixture for 1 hour at 45 °C followed by 12 hours at 110 °C (Table 2, **4a**, **4i**, **4k**). While this process is efficient for a range of 4- or 5-substituted deactivated electrophiles,

Table 2. Complex benzimidazole synthesis via Pd-cascade.[a]



[a] Reaction conditions: aryl halide (1.0 mmol), arylamine (1.0 mmol), amide (1.3 mmol), **P1** (2–5 mol%), Cs_2CO_3 (2.4 mmol), tBuOH (1.5 mL), 110 °C, 12 h; Isolated yields are shown (average of two runs). [b] Reaction was conducted at 45°C for 1 h then at 110 °C for 12 h.

Table 3. Selectable regiocontrolled synthesis of either benzimidazole isomer from starting materials derived from the same chlorophenol.[a]



[a] Isolated yields on a 1.0 mmol scale (average of two runs); regiochemical assignments were made by steady-state nOe difference spectra or by analogy. [b] Reaction was conducted for 24 h. [c] 3.0 mmol K_3PO_4 was used as base. [d] Reaction was conducted at 45°C for 1 h then at 110 °C for 12 h. [e] Reaction was conducted at room temperature for 2 h then at 110°C for 24 h.

substitution at the 3- or 6-positions was not well tolerated, presumably due to the bulky nature of the palladium catalyst. In addition, selective amination of the more activated 2-position of 2,3-dichloropyridine was possible under the same treatment to finally give rise to the imidazo[4,5,*b*]pyridine product **4l** in useful yield (61%) with complete regiocontrol.

To further evaluate the power of this modular cascade strategy, we questioned whether it could be employed to ultimately arrive at *either* of the possible benzimidazole regioisomers from the *same* 2-chlorophenol starting material. This would be especially interesting because, while a broad range of 3- or 4-substituted 2-chlorophenols are commercial or readily accessible, it is rare that both isomers are available. This strategy would allow one to generally access either product (in a selectable fashion) from the most convenient starting material, an appealing feature that is absent in current methods for regioselective benzimidazole synthesis. As described above (and shown in Table 3), 4-substituted-2-chloroaryl triflates react under standard conditions to provide the corresponding 5-substituted *N*-arylbenzimidazoles (denoted regioisomer A in Table 3) with complete regioselectivity. Given the relatively low reactivity of aryl mesylates toward oxidative addition, we reasoned that palladium insertion into Ar–Cl of the corresponding chloroaryl mesylate might preclude Ar–OMs insertion and that the reaction would deliver the opposite regioisomer (regioisomer B). We found that, although the mesylate cascade required higher catalyst loading and reaction time (6 mol% Pd and 24 h), generic access to 6-substituted benzimidazole products can be achieved in this manner. As shown in Table 3, this strategy was applied to 2-chlorophenols bearing alkyl-, fluoro-, aryl-, or trifluoromethyl-substitution to predictably access either of the corresponding regioisomeric benzimidazoles in a selectable manner. While the standard conditions efficiently provided both regioisomers in presence of electron-neutral (fluoro and phenyl) substituents on the difunctional electrophile (to give benzimidazoles **6A**, **6B** and **7A**, **7B**), significant sulfonate hydrolysis was observed with the 4-isopropyl-substituted 2-chlorophenyl mesylate and both of the 4-trifluoromethyl-2-chlorophenyl sulfonates. We found that replacing Cs_2CO_3 with K_3PO_4 as base enabled these processes to occur, delivering the desired products with acceptable levels of chemical efficiency (62–81% yield).

In summary, we have developed a novel approach to regioselective *N*-arylbenzimidazole synthesis that involves cascade intermolecular amination and amidation reactions of 2-chloroaryl sulfonates (or halides). We found that a single catalyst, based on tBuBrettPhos, is able to selectively perform both catalytic elements of this process for a broad range of arylamine (or heteroarylamine), amide, and bifunctional electrophile substrates to afford the corresponding benzimidazole products with complete regioselectivity. Moreover, we have demonstrated that different 2-chloroaryl sulfonates (triflate vs. mesylate) that are derived from the same chlorophenols can be reacted under very similar conditions to exclusively afford the opposite regioisomeric heterocycles. In addition to offering a complementary method for regioselective benzimidazole synthesis, we anticipate that the described cascade strategy represents a potentially powerful approach to streamlining chemical synthesis, particularly within the realm of palladium-catalyzed reactions.

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[16] MIT holds or has filed patents on the ligands and precatalysts used in this work for which S.L.B. receives royalty payments.

Cascade Catalysis

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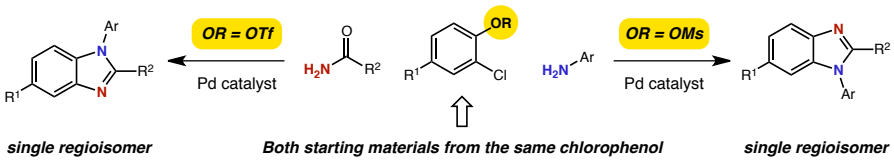

single regioisomer ***Both starting materials from the same chlorophenol*** ***single regioisomer***

The choice is yours: The palladium-catalyzed cascade reaction of 2-chloroaryl sulfonates with arylamine and amide nucleophiles provides direct access to *N*-arylbenzimidazoles in a single step with complete regiocontrol. This strategy selectively produces the heterocycles based on chemoselective oxidative addition; 2-chloroaryl triflates produce one regioisomer and the corresponding 2-chloroaryl mesylates deliver the other in a selectable manner.