Homogeneous Catalysis

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

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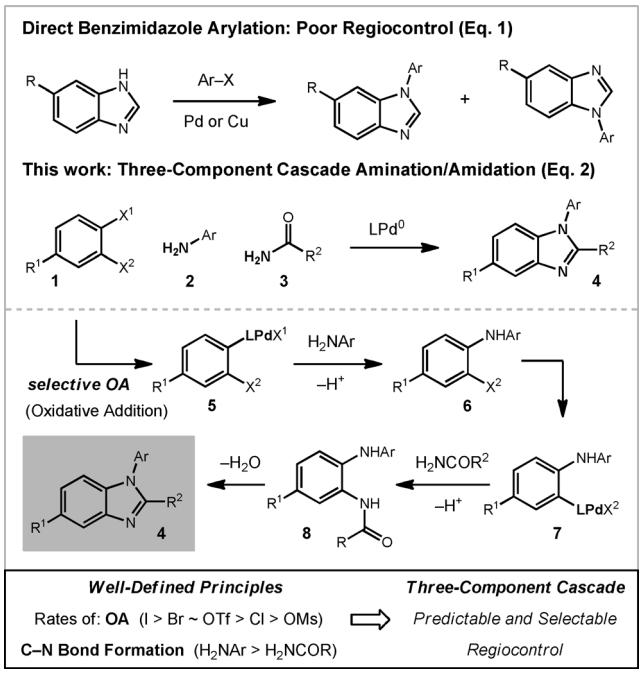
Dedicated to Professor Irina Beletskaya

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 which enable the efficient and selective formation of carbon–nitrogen bonds,[1] and we seek to apply these technologies to the preparation or modification of a broad array of heterocyclic scaffolds, including benzimidazoles. Regioselective benzimidazole alkylation or arylation is challenging because of 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 [Eq. (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 and enable in situ arylamidine formation with subsequent cyclization.[7] In addition to the groups 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 by a regio- and chemoselective cascade of palladium-catalyzed C–N bond-forming reactions involving a 2-chloroaryl sulfonate (or similar) substrate and two discrete nitrogen-based nucleophiles which are added at the same time [Eq. (2)]. The outlined three-component coupling method represents a potentially powerful alternative approach to heterocycle synthesis and 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 diactivated 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 and subsequent coupling with the amide **3** would yield the *o*-phenylenediamine derivative **8** which, after condensation, would convert into 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 1) relative rates of oxidative addition to aryl electrophiles are understood to

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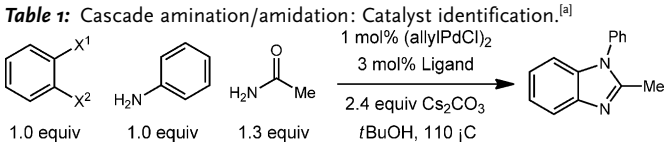
generally follow the pattern: I > OTf ≈ Br > Cl > OMs,[10] and 2) it has been demonstrated that arylamines can react preferentially with aryl palladium complexes in the presence of amides.[11] Herein, we describe the realization of this design and its application to a process which exploits the orthogonal 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 which 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 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 tripheny-, tricyclohexyl-, or tri-*tert*-butylphosphine was unsuccessful in this context (entries 1–3), catalysts based on biarylphosphine ligands did result in formation of the desired product. While *t*BuXPhos (**L1**), Me$_4$*t*BuXPhos (**L2**), or BrettPhos (**L3**), phosphines which 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 *t*BuBrettPhos (**L4**) provided the desired benzimidazole in 77% yield (entry 7). The yield was further improved by employing the recently described 4-aminobiphenyl-derived *t*BuBrettPhos mesylate precatalyst **P1**,[15] which delivered the desired product in 88% GC yield (86% yield of isolated product; 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.

Having identified reaction conditions which 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-

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	**P1**[c] (2 mol%)	88 (86)
9	Br	Cl	**P1**[c] (2 mol%)	87
10	Cl	Cl	**P1**[c] (2 mol%)	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), *t*BuOH (1.0 mL), 110°C, 12 h. [b] Yield determined by GC using tetradecane as an internal standard. Yield of isolated product given within parentheses. [c] The precatalyst **P1** was used instead of [(allylPdCl)$_2$] and ligand. TF = trifluoromethanesulfonyl.

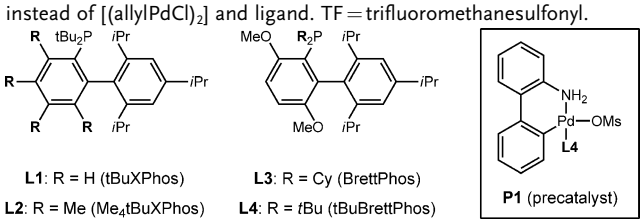
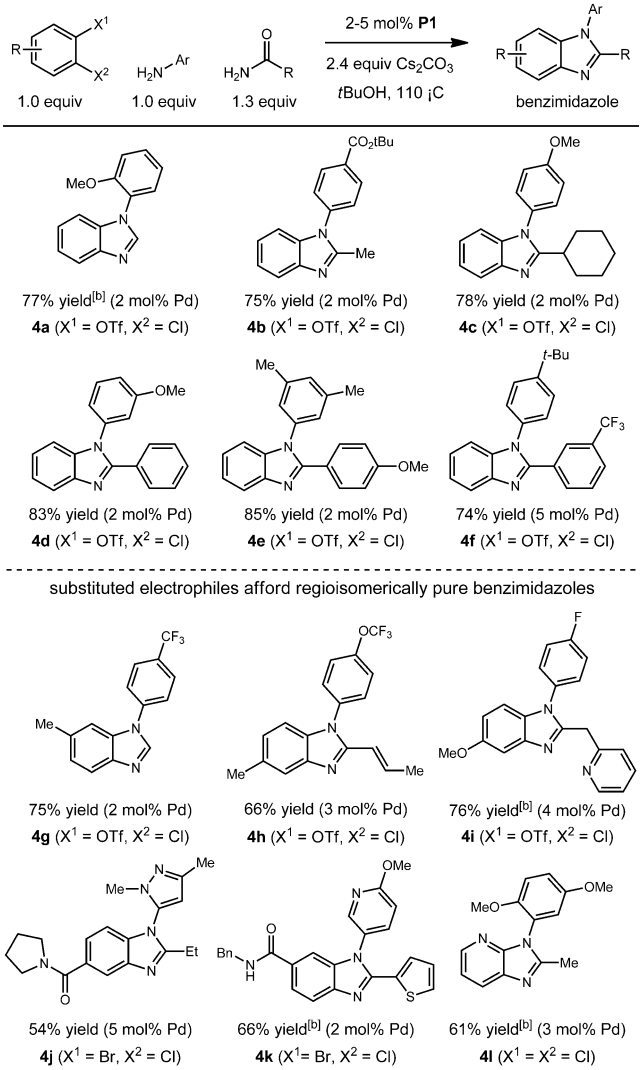


Table 2: Complex benzimidazole synthesis by a palladium-cascade.[a]

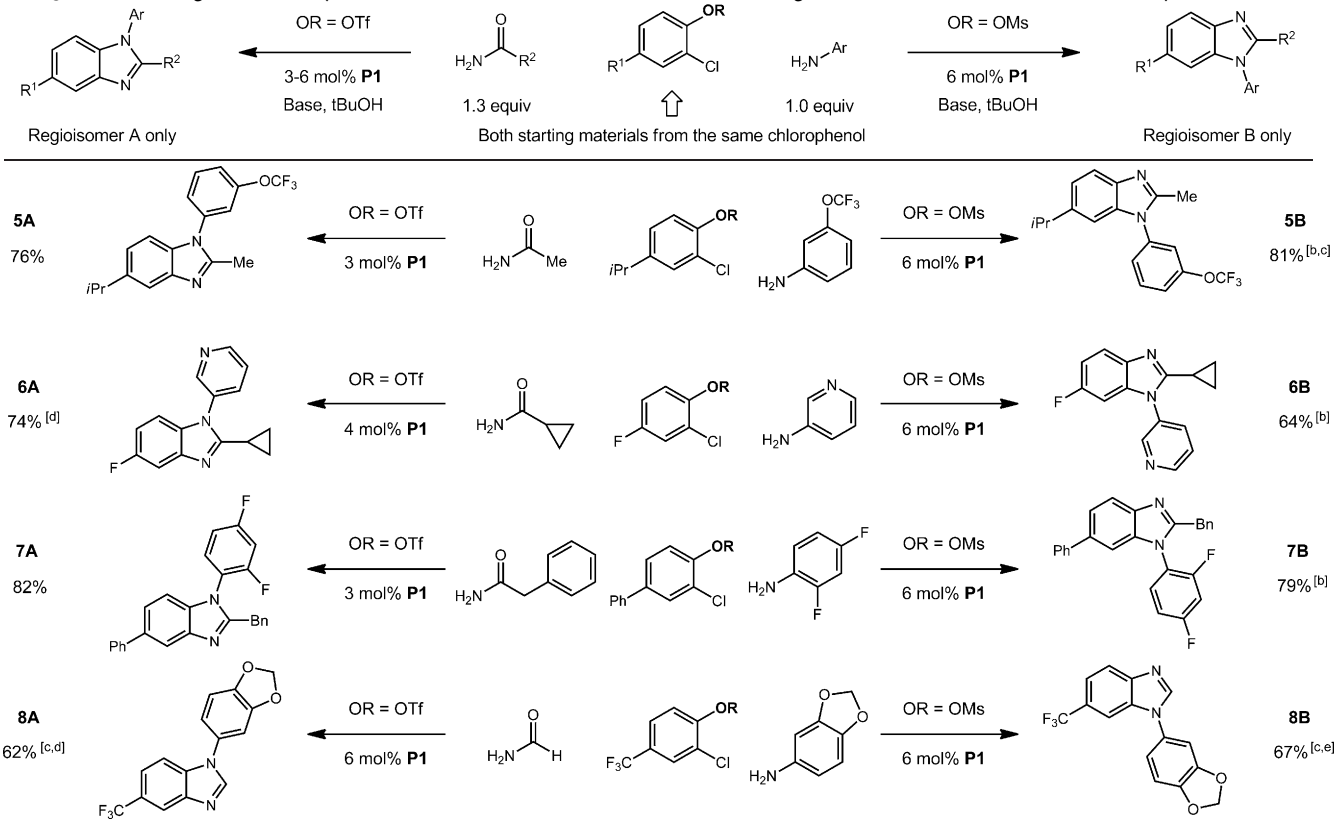


[a] Reaction conditions: aryl halide (1.0 mmol), arylamine (1.0 mmol), amide (1.3 mmol), **P1** (2–5 mol%), Cs_2CO_3 (2.4 mmol), *t*BuOH (1.5 mL), 110°C, 12 h. Yields are those of isolated product as an average of two runs. [b] Reaction was conducted at 45°C for 1 h then at 110°C for 12 h.

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 reaction 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 (**4j, 4k**; Table 2). 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 were 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 h at 110 °C (**4a**, **4i**, **4k**; Table 2). While this process is efficient for a range of 4- or 5-substituted deactivated electrophiles, substitution at the 3- or 6-positions was not well tolerated, presumably because of 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 which 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 reaction 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 (**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

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



[a] Yield of isolated product from reaction run 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. Ms = methanesulfonyl.

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 reaction conditions efficiently provided both regioisomers in the presence of electron-neutral (fluoro and phenyl) substituents on the difunctional electrophile (**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 the base enabled these processes to occur, thus 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 which involves cascade intermolecular amination and amidation reactions of 2-chloroaryl sulfonates (or halides). We found that a single catalyst, based on *t*BuBrettPhos, 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 versus mesylate), which are derived from the same chlorophenols, can be reacted under very similar reaction 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.

