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Expanding the diversity of purine libraries

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Abstract—In recent years, there has been a resurgence of interest in the synthesis of purine derivatives due to the discovery of purine-derived ligands for a variety of nucleotide dependent enzymes. The majority of chemistry has focused on substitution of the purine core structure by alkylation at N9 and nucleophilic–aromatic substitution reactions at C2 and C6. Here we report the syntheses of aryl, *N*-aryl, *O*-aryl substituted purine libraries by the palladium-mediated coupling of boronic acids, anilines or phenols at the C2 position, and copper(II)-mediated *N*-arylation with boronic acids at the N9 position. The chemistry described here greatly expands our ability to introduce different functionality and create new purine scaffolds. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The purine ring is a ubiquitous recognition motif in biological systems. Guanosine and adenosine, two of the most common purines, serve as key recognition and anchoring elements in a variety of cofactors and signaling molecules (e.g. ATP, GTP, cAMP, cGMP, adoMet, adenosine and NADH). Correspondingly, an enormous number of proteins have evolved to recognize the purine motif including reductases, polymerases, G-proteins, methyltransferases, and protein kinases. Despite the abundance of protein kinases[1] (estimated to be encoded by 2–5% of the eukaryotic genome) and the high degree of conservation of active site residues, ATP-binding site directed inhibitors have been designed that are highly specific. For example, STI571[2] has been developed as a potent and selective Abl kinase inhibitor, and is in use for the treatment of chronic myelogenous leukemia (CML). Screens of purine libraries[3] have resulted in the identification of diverse purines that inhibit mitosis, alter cellular morphology, and induce apoptosis. By constructing new purine derivatives, we hope to develop inhibitors of different ATP-dependent proteins, which will be useful for elucidating function and potentially provide starting points for the development of new therapeutics.

Previous syntheses of purine libraries have relied on nucleophilic–aromatic substitution and alkylation chemistry to derivatize the 2-, 6- and 9-positions of the purine ring. One of the primary limitations of this chemistry is the inability to access a large number of pharmacologically relevant derivatives bearing aryl, anilino or phenolic substituents. In addition, the sluggish aromatic substitution of 2-fluoro or 2-chloro substituted purine compounds precludes the introduction of sterically hindered amines or anilines.[3c,3d] Here we report our efforts to expand the types of reactions that can be used to modify the purine ring to include transition metal-catalyzed coupling reactions.

2. Results and discussion

2.1. Derivatization at the C2 position with boronic acids, anilines or phenols by palladium-catalyzed cross-coupling reactions using a 'carbene' ligand

Recently, there have been significant advances in methodology for performing palladium-catalyzed C–C, C–N and C–O bond formation reactions with a wide variety of substrates. For example, new phosphine ligands[4] have allowed palladium-mediated functionalization of inexpensive chloroarenes with boronic acids and amines at room temperature. 1,3-Dimesityl-imidazolin-2-ylidene and its saturated analog, originally developed by Grubbs as carbene ligands for ruthenium-based olefin metathesis catalysts,[5] have also been found to be highly effective ligands. We sought to investigate

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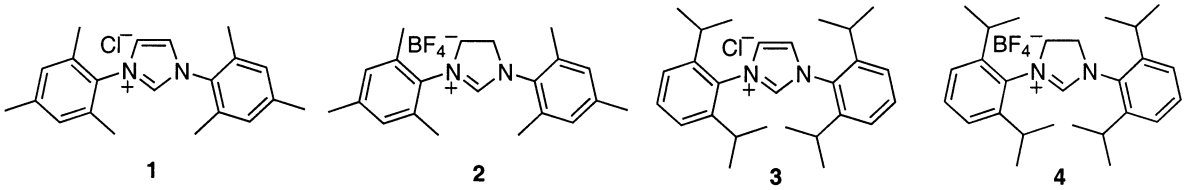
whether a 2-chloropurine would react with boronic acids, anilines and phenols under palladium-catalyzed cross-coupling conditions using the sterically demanding *N*-heterocyclic 'carbene' ligands **1** and **2**. Nolan (ligand **3**)[6] and Hartwig (ligand **4**)[7] have also explored the use of similar carbene ligands system for a variety of cross-coupling reactions.

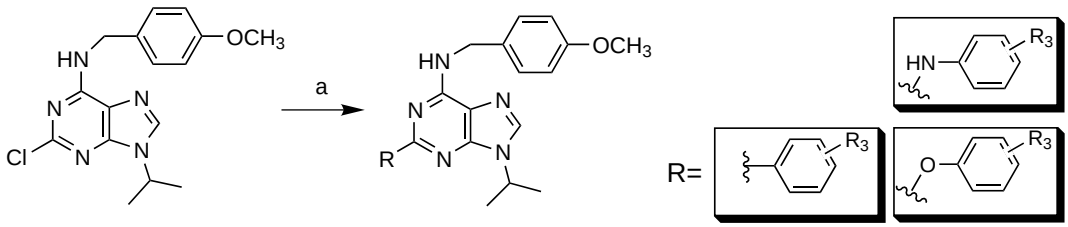


1 **2** **3** **4**

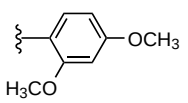
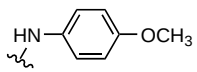
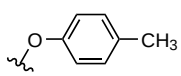
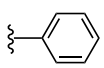
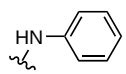
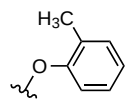
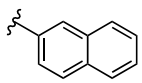
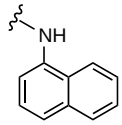
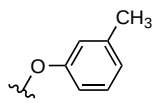
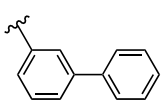
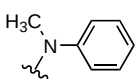
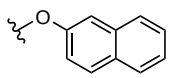
We found that all three substrates can be efficiently coupled to the purine core using either ligand **1** or **2**. The typical conditions involved reaction of the 2-chloropurine substrate with 1.5 equiv. of arylboronic acid in the presence of $Pd_2(dba)_3$ (1.5 mol%), carbene ligand **1** (3 mol%), and 2.0 equiv. of Cs_2CO_3 in anhydrous 1,4-dioxane under argon. The reactions are typically complete after stirring at 80°C for 12 h. For coupling reactions to anilines and phenols potassium *t*-butoxide was used as the base. Using these reaction conditions[8] 2-chloro-6-(4-methoxybenzylamino)-9-isopropylpurine was coupled with boronic acids, anilines and phenols (Table 1) with isolated final products over 90% yields. For the substrates bearing strong electron-withdrawing groups or sterically very hindered *ortho* substituents, the yields are relatively low. Not surprisingly, substrates with halogens, especially those with chloro or bromo substituents, usually result in complex mixtures. Only fluoro-substituted substrates can be coupled to purine in good yield.

While we chose to validate the palladium-catalyzed coupling reaction at the most unreactive position of the purine ring, namely C2, it was also of interest to determine whether boronic acids can be selectively coupled with 2,6-dichloropurine at the C6 position. Indeed, with 1 equiv. of boronic acid the C6 position can be selectively functionalized with only a trace quantity bis-functionalized product detected by LC–MS. The

Table 1. Palladium-catalyzed C2 substitution of purine



a. 1.5 equiv of boronic acids, 2.0 equiv of Cs_2CO_3 / 1.5 equiv of anilines, 2.0 equiv of KO^{t}Bu, / 1.5 equiv of phenols, 2.0 equiv of KO^{t}Bu, 1.5% of $Pd_2(dba)_3$, 3.0% of carbene ligand 1 or 2 , anhydrous dioxanes

Entry	R^1	Yield (%)	Entry	R^2	Yield (%)	Entry	R^3	Yield (%)
1		96	5		97	9		90
2		93	6		95	10		90
3		94	7		94	11		90
4		93	8		91	12		91

[1] via cross coupling with boronic acids; [2] via cross coupling with anilines; [3] via cross coupling with phenols

bulky phosphine ligands, 2-(di-*t*-butylphosphino)-biphenyl and 2-(di-cyclohexylphosphino)biphenyl, were also tested according to the conditions reported by Buchwald[4] and resulted in similar or lower yields for certain substrates compared to the 'carbene' ligand.

The choice of base has significant effects on the yield of the coupling reaction.[4] Although the precise details of the reaction are unclear,[6,7] it has been proposed that the imidazolium salts are first deprotonated to form to a carbene species which is then complexed with the transition metal. However, even a strong base such as potassium *tert*-butoxide cannot deprotonate the imidazolium ligand **2** at room temperature and is instead believed to add to the 2-position of the imidazolium salt to form the 2-alkoxy-adduct.[5b] It would be even more surprising if a much weaker base such as Cs_2CO_3 or $CsHCO_3$, which are employed for the Suzuki coupling reaction, can deprotonate the imidazolium salt at room temperature. Certainly, further mechanistic studies are required to clarify the real active catalyst for this palladium-catalyzed cross coupling reaction employing imidazolium salt as ligands.

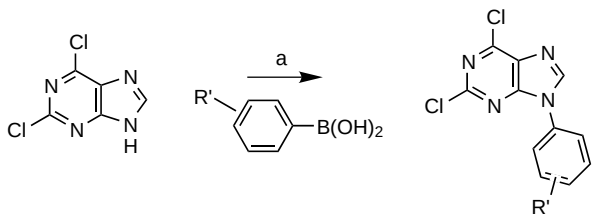
2.2. Derivatization of the purine N9 position with boronic acids via cupric acetate catalyzed cross-coupling reaction

The most commonly used methods to modify the purine N9 position include anionic alkylation with an alkyl halide and strong base, Mitsunobu alkylation, and various glycosylation reactions. None of these methods allow synthesis of N9-aryl substituted purines. Previously, N9-aryl purines were constructed by aniline addition to 5-amino-6-chloro-pyrimidine followed by cyclization with triethylorthoformate (or equivalent) to afford the 9-arylpurine.[9] While this procedure offers the opportunity to simultaneously derivatize the C8 position with select alkyl groups, it would be difficult to prepare a N9-focused combinatorial library by this method. The copper(II) mediated *N*-arylation of heterocycles[10] such as imidazole offers the possibility of direct arylation of the purine N9 position. Here, we demonstrate that 9-arylpurines can be prepared by cupric acetate-mediated coupling of purine N9 with arylboronic acids.

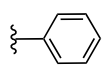
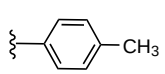
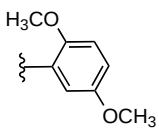
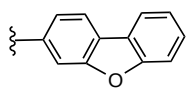
Reaction of 2,6-dichloropurine with boronic acids in the presence of cupric acetate and triethylamine resulted in the desired N9-aryl product[11] (Table 2). While the reaction appears to proceed to completion as judged by LC–MS, isolation of the product from the reaction mixture is difficult, presumably due to the strong surface absorption of product to the crude reaction materials. Although the purine is capable of forming regioisomers (N9/N7), it was found in each case that the N9 arylated product is the major regioisomer (>90%) with the N7 regioisomer being produced in low yield.

In summary, we have demonstrated the versatility of palladium and copper(II)-mediated coupling reactions to expand the diversity of purine libraries. Focused collections of purine compounds bearing C–C(sp^2), C–N-aryl and C–O-aryl bonds were synthesized by palladium-mediated coupling of boronic acids, anilines and phenols at the C2 position, and copper(II)-mediated *N*-arylation with boronic acids at the N9 position. The chemistry described here greatly expands our ability to introduce different functionality and create hybrid aryl-purine scaffolds.

Table 2. N9-arylation of purine



a. anhydrous cupric acetate, 4 Å activated molecular sieves, triethylamine,DCM.

Entry	N9 aryl substituents	Yield (%)	Entry	N9 aryl substituents	Yield (%)
1		45	3		47
2		43	4		44

Acknowledgements

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8. Representative experimental procedure of C–C, C–N and C–O bond formation at C2/C6 of purine via palladium-catalyzed cross-coupling reactions:
   (a) Boronic acid coupling reactions: A 10 mL flame-dried Schlenk flask equipped with a magnetic stir bar was charged with 2-chloro-6-(4-methoxybenzylamino)-9-isopropylpurine (0.193 g, 0.5 mmol, 1.0 equiv.), 2,4-dimethoxyphenylboronic acid (0.136 g, 0.75 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (0.0069 g, 0.0075 mmol, 0.015 equiv.), ligand **1** (0.0051 g, 0.015 mmol, 0.03 equiv.) and Cs_2CO_3 (0.326 g, 1.0 mmol, 2.0 equiv.). The Schlenk flask was evacuated and backfilled with argon and charged with anhydrous 1,4-dioxane (2.0 mL). The reaction was stirred under argon at 80°C and monitored by TLC. When the reaction was complete after 8 h, the solvent was removed in vacuo and the reaction crude was purified by flash column chromatography (3% methanol in dichloromethane) to afford desired 2-(2,4-dimethoxyphenyl)-6-(4-methoxybenzylamino)-9-isopropylpurine (207 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, 6H, $J=6.8$ Hz), 3.79 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.87–4.96 (m, 3H), 6.14 (br, 1H), 6.57–6.60 (m, 2H), 6.85 (d, 2H, $J=8.6$ Hz), 7.34 (d, 2H, $J=8.6$ Hz), 7.73 (s, 1H), 7.78 (d, 1H, $J=8.2$ Hz); HRMS (MALDI-FTMS) [MH^+] $C_{24}H_{28}N_5O_3$ 434.2187, found: 434.2168.
   (b) Aniline coupling: A 10 mL flame-dried Schlenk flask equipped with a magnetic stir bar was charged with 2-chloro-6-(4-methoxybenzylamino)-9-isopropylpurine (0.193 g, 0.5 mmol, 1.0 equiv.), 4-methoxyaniline (0.092 g, 0.75 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (0.0069 g, 0.0075 mmol, 0.015 equiv.), ligand **1** (0.0051 g, 0.015 mmol, 0.03 equiv.) and KO^{t}Bu (0.112 g, 1.0 mmol, 2.0 equiv.). The Schlenk flask was evacuated and backfilled with argon and charged with anhydrous 1,4-dioxane (2.0 mL). The reaction was stirred under argon at 80°C and monitored by TLC. When the reaction was complete after 8 h, the solvent was removed in vacuo and the reaction crude was purified by flash column chromatography (3% methanol in dichloromethane) to afford desired 2-(4-methoxyphenylamino)-6-(4-methoxybenzylamino)-9-isopropylpurine (203 mg, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (d, 6H, $J=6.6$ Hz), 3.76 (s, 3H), 3.78 (s, 3H), 4.66 (m, 1H, $J=6.6$ Hz), 4.72 (br, 2H), 6.06 (br, 1H), 6.60 (br, 1H), 6.82 (d, 2H, $J=13$ Hz), 6.84 (d, 2H, $J=13$ Hz), 7.09 (s, 1H), 7.26 (d, 2H, $J=8.8$ Hz), 7.42 (s, 1H), 7.56 (d, 2H, $J=8.8$ Hz); HRMS (MALDI-FTMS) [MH^+] $C_{23}H_{27}N_6O_2$ 419.2195, found: 419.2209.
   (c) Phenol coupling: A 10 mL flame-dried Schlenk flask equipped with a magnetic stir bar was charged with 2-chloro-6-(4-methoxybenzylamino)-9-isopropylpurine (0.193 g, 0.5 mmol, 1.0 equiv.), 4-methylphenol (0.081 g, 0.75 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (0.0069 g, 0.0075 mmol, 0.015 equiv.), ligand **1** (0.0051 g, 0.015 mmol, 0.03 equiv.) and KO^{t}Bu (0.112 g, 1.0 mmol, 2.0 equiv.). The Schlenk flask was evacuated and backfilled with argon and charged with anhydrous 1,4-dioxane (2.0 mL). The reaction was stirred under argon at 90°C and monitored by TLC. When the reaction was complete after 8 h, the solvent was removed in vacuo and the reaction crude was purified by flash column chromatography (2% methanol in dichloromethane) to afford desired 2-(4-methylphenoxy)-6-(4-methoxy-benzylamino)-9-isopropylpurine (180 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, 6H, $J=6.8$ Hz), 2.37 (s, 3H), 3.79 (s, 3H), 4.54 (br, 2H), 4.71 (m, 1H, $J=6.8$ Hz), 6.35 (br, 1H), 6.81 (d, 2H, $J=8.4$ Hz), 7.10–7.18 (m, 6H), 7.65 (s, 1H); HRMS (MALDI-FTMS) [MH^+] $C_{23}H_{26}N_5O_2$ 404.2081, found: 404.2080.
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11. **Purine N9 arylation via boronic acids/cupric acetate**: A 20 mL glass vial equipped with a magnetic stir bar was charged with 2,6-dichloropurine (0.200 g, 1.06 mmol, 1.0 equiv.), 4-methylphenylboronic acid (0.288 g, 2.12 mmol, 2.0 equiv.), anhydrous cupric acetate (0.384 g, 2.12 mmol, 2.0 equiv.), 4 Å activated molecular sieves (0.500 g), triethylamine (0.443 mL, 3.18 mmol, 3.0 equiv.) and dichloromethane (5.0 mL). The reaction was stirred under air at ambient temperature and monitored by TLC. When the reaction was complete after 24 h, it was filtered through Celite, washed with methanol and purified by flash column chromatography (1% methanol in dichloromethane) to afford desired 2,6-dichloro-9-(4-methylphenyl)-purine (0.136 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.41 (d, 2H, $J=8.1$ Hz), 7.54 (d, 2H, $J=8.1$ Hz), 8.35 (s, 1H); HRMS (MALDI-FTMS) $C_{12}H_8Cl_2N_4$ [MH^+] 279.0199, found: 279.0208.