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Suzuki−Miyaura and Sonogashira Coupling of 6-Chloropurines and -Nucleosides in Water

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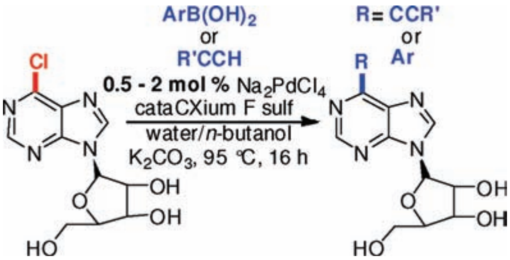
ABSTRACT



A general protocol is reported for the efficient Suzuki−Miyaura and the copper-free Sonogashira coupling of unprotected 6-chloropurines and unprotected *β*-D-ribofuranosyl-6-chloropurine in water or in water/*n*-butanol utilizing Na_2PdCl_4 and a disulfonated and highly water-soluble fluorenylphosphine (cataCXium F sulf).

The enormous progress in catalyst development has enabled the routine use of aryl chlorides in Pd-mediated cross-coupling chemistry.[1] Nonetheless, a number of difficult and potentially coordinating heteroatom-containing functional groups such as N- or S-heterocycles, amino, and hydroxy groups remain challenging, and the respective aryl chloride reactions require relatively high catalyst loading.[2] Chloropurines and the related chloropurine nucelosides contain several of these problematic functional groups. Thus, despite the interest in purine chemistry[3] (especially with 6-aryl and 6-ethynyl-substituted purines due to their cytostatic activity),[4,5] in the Suzuki and the Sonogashira couplings of chloropurines protective groups are normally employed, while coupling reactions of unprotected chloropurines are rare.[6−8] With chloropurine nucleoside coupling, normally protective groups are employed:[9,10] only Hocek briefly reported on the Suzuki coupling of unprotected nucleosides.[7] More often, the respective aryl bromides or iodides with[11−14] or without protective groups[15,16] were employed. As a consequence of these deficits, Kang et al. developed a method for the Suzuki coupling of tautomerizable purines via enolate

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(2) Hartwig, J. F. *Synthesis* **2006**, 1283.
(3) Legraverend, M.; Grierson, D. S. *Bioorg. Med. Chem. Lett.* **2006**, *14*, 3987.
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(5) Hocek, M.; Stepnicka, P.; Ludvik, J.; Cisarova, I.; Votruba, I.; Reha, D.; Hobza, P. *Chem.−Eur. J.* **2004**, *10*, 2058.
(6) Capek, P.; Vrábel, M.; Hasník, Z.; Pohl, R.; Hocek, M. *Synthesis* **2006**, 3515.
(7) Capek, P.; Pohl, R.; Hocek, M. *Org. Biomol. Chem.* **2006**, *4*, 2278.
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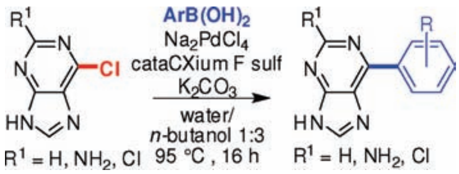
10.1021/ol9007475 CCC: $40.75

Table 1. Suzuki−Miyaura Coupling of 6-Chloropurines with Pd/cataCXium F sulf[c]



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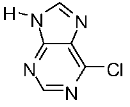
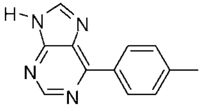
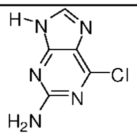
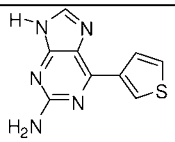
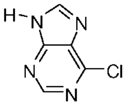
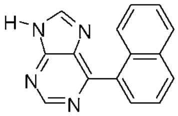
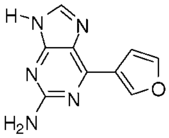
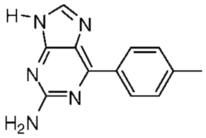
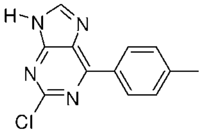
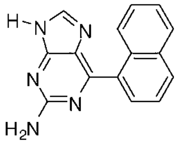
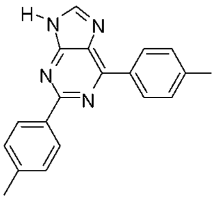
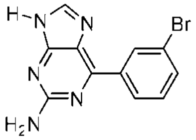
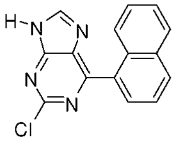
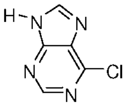
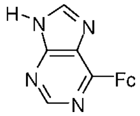
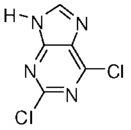
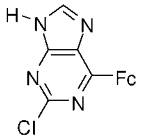
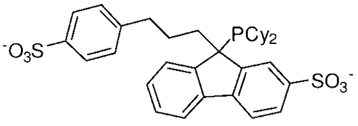
1			0.5 0.5 0.5[a] 0.25	90 87 79 78	7			1.0 0.5	83 9
2			1.0 0.5	88 67	8			1.0 0.5	75 12
3			2.0 2.0[a]	91 81	9			1.0 0.5	90 23
4			2.0	73	10			1.0[b]	88
5			2.0 0.5	76 44	11			1.0 0.5	76 8
6			2.0	84	12			2.0	77

[a] Solvent water. [b] 3.0 equiv of boronic acid were used. [c] Reaction conditions: 1.0 equiv of chloropurine, 1.5 equiv of boronic acid, 2.5 equiv of K_2CO_3, degassed water (1.5 mL), *n*-butanol (4.5 mL), 100 °C, reaction time 16 h, catalyst stock solution in water (c Pd = 1.0 mol %/mL, Na_2PdCl_4/cataCXium F sulf L/Pd 2:1. Yields correspond to isolated material after column chromatography (silica), CH_2Cl_2/MeOH/NEt_3 = 5/1/1.

activation, which was also applied to an unprotected purine nucleoside.[17] The Sonogashira coupling of chloropurines is also challenging and requires protective groups[5,18−20] or the use of more reactive bromo- or iodopurines.[21−23]



cataCXium F sulf

We report here a simple Pd-based protocol for both the Suzuki and the Sonogashira coupling of unprotected chloropurine nucleosides using Na_2PdCl_4 and the water-soluble and commercially available fluorenylphosphine (cataCXium F sulf) recently reported by us.[24,25] This ligand already

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(20) Volpini, R.; Costanzi, S.; Lambertucci, C.; Taffi, S.; Vittori, S.; Klotz, K.-N.; Cristalli, G. *J. Med. Chem.* **2002**, *45*, 3271.

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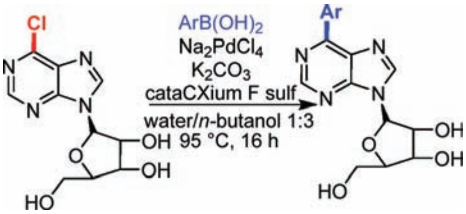
Table 2. Suzuki−Miyaura Coupling of 6-Chloropurine Nucleosides with Pd/cataCXium F sulf[b]



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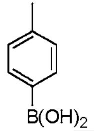
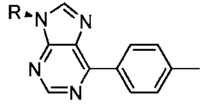
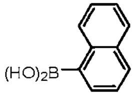
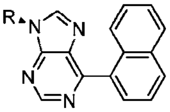
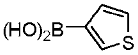
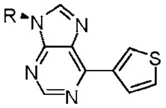
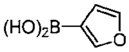
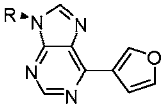
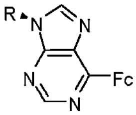
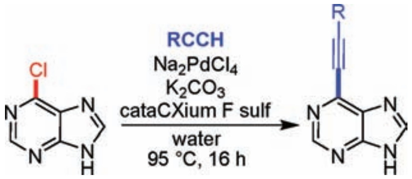
1			0.5 0.1	91 47
2			2.0 0.5	77 12
3			2.0 2.0[a] 0.5	78 69 22
4			2.0 2.0[a] 0.5	87 81 21
5	FcB(OH)2		2.0 2.0[a] 0.5	81 76 10

[a] Solvent water. [b] Reaction conditions: see legend of Table 1.

Table 3. Sonogashira Coupling of 6-Chloropurine with Pd/cataCXium F sulf[a]



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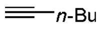
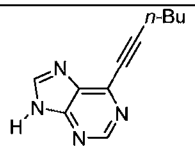
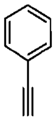
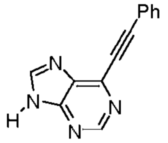
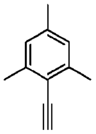
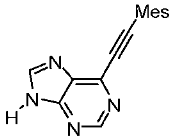
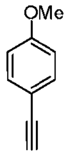
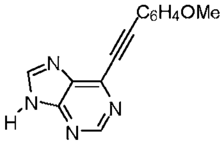
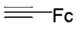
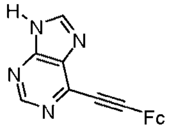
1			2.0	75
2			2.0 1.0	99 89
3			2.0 1.0	78 43
4			2.0 1.0	96 76
5			2.0	71

[a] Reaction conditions: 1.0 equiv of chloropurine, 1.13 equiv of acetylene, 1.33 equiv of K_2CO_3, water, 95 °C, reaction time 16 h, catalyst stock solution in water (c Pd = 1.0 mol %/mL, Na_2PdCl_4/CataCXium F sulf L/Pd 2:1. Yields correspond to isolated material after column chromatography (silica), cyclohexane/EtOAc/NEt_3 = 9/1/1.

demonstrated its high efficiency in aqueous cross-coupling chemistry.[26−28]

We first expanded on the known Suzuki coupling of unprotected 6-chloropurine (Table 1).[8] The reaction of 6-chloropurine and tolylboronic acid (Table 1, entry 1) gives respectable yields (78%) with as little as 0.25 mol % [Pd]. This compares favorably with the use of 5 mol % of $Pd(OAc)_2$, 12.5 mol % of phosphine, and microwave irradiation needed to afford good yields of closely related coupling products.[7]

With sterically demanding boronic acids (Table 1, entries 2, 4, and 6), 1−2 mol % is needed. The use of water/*n*-butanol 1:3 in the presence of K_2CO_3 gives only slightly better yields than with water alone (Table 1, entries 1 and 3). Employment of a biphasic system facilitates the isolation of product. The simple separation of the aqueous layer leads to the removal of the salts as well as of excess boronic acid, while the products are isolated from the *n*-butanol solution. It is important to note that the formation of butyl ethers was never observed in such reactions.

Suzuki reactions of 2-amino-6-chloropurine also require 1−2 mol % [Pd] (Table 1, entries 3− 5 and 7). The reaction of 2-amino-6-chloropurine with 3-bromophenylboronic acid (Table 1, entry 5) is highly instructive since it is the purine C−Cl bond which undergoes the Suzuki reaction and not the C−Br bond in the boronic acid. This points toward the strongly activating nature of the purine ring[15] and shows that the difficulties in the cross-coupling of chloropurines result from the overall inhibition of the catalyst and not from lack of reactivity of the C−Cl bond. In 2,6-dichloropurine, it is possible to introduce aryl groups selectively, first at the

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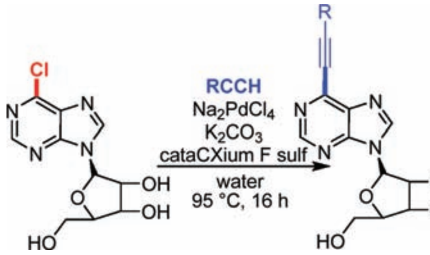
Table 4. Sonogashira Coupling of a 6-Chloropurine Nucleoside with Pd/cataCXium F sulf[a]



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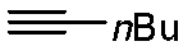
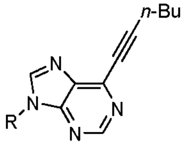
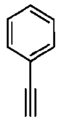
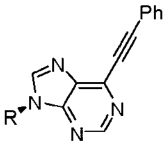
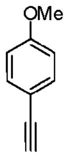
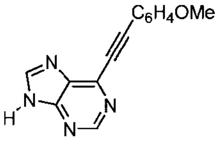
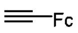
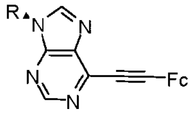
1			2.0	67
2			2.0	82
3			2.0	90
4			2.0	69

[a] Reaction conditions: see legend of Table 3.

6-position and then at the 2-position (Table 1, entries 9−12). Protodeboronation reactions of thiophene- and furanboronic acids are not of relevance in the present context.[27]

The protocol developed for the 6-chloropurine coupling was also applied to β-D-ribofuranosyl-6-chloropurine (Table 2). We tested a normal (Table 2, entry 1), a sterically demanding (entry 2), two heterocyclic (entries 3 and 4), and an electrochemically active boronic acid (Table 2, entry 5) useful as a marker.[29] In the absence of protective groups, a catalyst loading of between 0.5 and 2 mol % [Pd] is sufficient to obtain isolated yields after chromatography of between 77 and 91% yield. All of these reactions can also be conducted in pure water as the reaction solvent. The yields are only slightly lower than in *n*-butanol/water (Table 1, entries 1 and 3, Table 2, entries 3−5).

The same catalyst recipe was applied in the copper-free Sonogashira coupling of unprotected chloropurines (Table 3). Amounts of 2 mol % of Na_2PdCl_4 and 4 mol % of cataCXium F sulf are sufficient to synthesize the respective 6-ethinylpurines in isolated yields of between 71 and 99% after chromatography. These coupling reactions work for aryl acetylene and also for the more difficult ferrocenyl (Fc = ferrocenyl) and alkyl acetylenes.

The same protocol was applied to the copper-free Sonogashira coupling of unprotected β-D-ribofuranosyl-6-chloropurine (Table 4). The isolated yields are only slightly lower than with chloropurine, and the respective ethynylated products were isolated in 67−90% yield. With respect to the yield, it does not make any difference whether the Sonogashira reactions are carried out in water/*n*-butanol 1:3 or in pure water. Finally, it is interesting to note that the catalyst loadings in the Sonogashira and Suzuki reactions of chloropurines are in the same range as for Sonogashira reactions of aryl chlorides,[30] while drastically less [Pd] is required in the Suzuki reactions of “normal” aryl chlorides.[31]

In conclusion, we have developed a simple Suzuki and copper-free Sonogashira coupling protocol for the reactions of unprotected 6-chloropurines and β-D-ribofuranosyl-6-chloropurine with various arylboronic acids and aryl- or alkylacetylenes. Catalyst loadings between 0.25 and 2 mol % Na_2PdCl_4 and twice as much of the disulfonated fluorenylphosphine (cataCXium F sulf) in water or *n*-butanol/water used a simple base (K_2CO_3) to produce excellent yields of cross-coupling products.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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