ORGANIC
LETTERS

2009
Vol. 11, No. 12
2511−2514

Heteroaryl Ethers by Oxidative Palladium Catalysis of Pyridotriazol-1-yloxy Pyrimidines with Arylboronic Acids

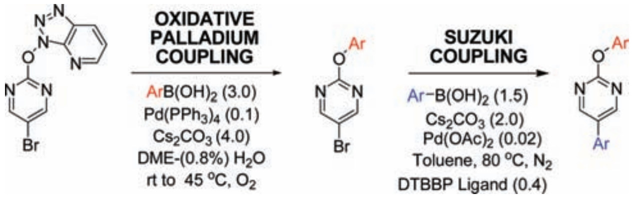
Sujata Bardhan, Sumrit Wacharasindhu, Zhao-Kui Wan, and Tarek S. Mansour*

Chemical Sciences, Wyeth Research, 401 North Middletown Road, Pearl River,
New York 10965 and 200 Cambridge Park Drive, Cambridge, Massachusetts 02140

mansout@wyeth.com

Received March 25, 2009

ABSTRACT



The oxidative palladium-catalyzed cross-coupling of pyrimidines containing pyridotriazol-1-yloxy (*O*Pt) as either a urea or an amide functional group with arylboronic acids in the presence of Cs_2CO_3 in DME containing 0.6−1.0% H_2O is described for the preparation of heteroaryl ethers. The bromo substitution in the case of 3-(5-bromo-pyrimidin-2-yloxy)-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine 1 could serve as a handle for further elaborations such as Suzuki coupling for attaching varied aryl groups.

Aryl ethers are an important class of biologically active compounds.[1] Recent synthetic methods that avoid the use of harsh conditions and result in better control over the classical methods have been reported. These methods include Mitsunobu reactions using immobilized triphenylphosphine for ease of purification,[1,2] reaction of aryl fluorides and silyl ethers,[3] and Ullman-type coupling reactions using CuI and [(dimethylamino)methyl]phosphonic acid derivatives.[4] These also include a variety of metal-mediated transformations involving Rh(I)-catalyzed [2 + 2 + 2] cycloaddition reactions,[5] Pd(0)-catalyzed enyne−diyne [4 + 2] cycloadditions,[6] Buchwald−Hartwig Pd-mediated couplings,[7] and Pd-catalyzed Heck reactions.[8]

Recently, we demonstrated the synthetic versatility of phosphonium-mediated S_NAr reactions with heterocycles[9] using benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphonium (BOP)[10] or (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP)[11] reagents. Phosphonium intermediates of pyrimidines could also be intercepted as partners in Suzuki cross-coupling reactions, resulting in the formation of C−C bonds.[10c] In the S_NAr reactions involving BOP reagents, mechanistic studies regarding the nature of the intermediates are consistent with a pathway involving stepwise formation of HOBt adducts from the

---

[1] (a) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T. Y.; Li, H.; Brase, S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421–3422. (b) Xu, B.; Xue, J.; Zhu, J.; Li, Y. *Chem. Lett.* **2008**, *37*, 202–203. (c) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; In Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1097−1106. (d) Hartwig, J. F. *Synlett* **2006**, *9*, 1283–1294.

[2] Valeur, E.; Roche, D. *Tetrahedron Lett.* **2008**, *49*, 4182–4185.

[3] Wang, T.; Love, J. A. *Synthesis* **2007**, *15*, 2237–2239.

[4] Jin, Y.; Liu, J.; Yin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Synlett* **2006**, *10*, 1564–1568.

[5] Clayden, J.; Moran, W. J. *Org. Biomol. Chem.* **2007**, *5*, 1028–1030.

[6] Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 568–572.

[7] (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396. (b) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 643–646.

[8] (a) He, T.; Tao, X.; Wu, X.; Cai, L.; Pike, V. W. *Synthesis* **2008**, *6*, 887–890. (b) Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340–4343. (c) Berthiol, F.; Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002**, *43*, 5625–5628.

10.1021/ol900592b CCC: $40.75

phosphonium intermediates.[9,12] Indeed, benzotriazol-yloxy quinazoline readily reacted with various nucleophiles in S_NAr fashion. Further investigations led to the discovery of an oxidative palladium-catalyzed S_NAr reaction of pyridotriazol-yloxy quinazoline (*O*Pt) adducts involving arylboronic acids and dioxygen under Pd catalysis without direct involvement of phenols.[13] This reaction is especially valuable when phenols are not readily available and is distinct compared to the homocoupling reactions in oxidative palladium reactions.

In this letter, we report that pyrimidines carrying an *O*Pt functional group[12] (Figure 1) are good substrates for the oxidative Pd-catalyzed reaction resulting in the synthesis of heteroaryl ethers from pyridotriazol-l-yloxy pyrimidines, arylboronic acids, and dioxygen.

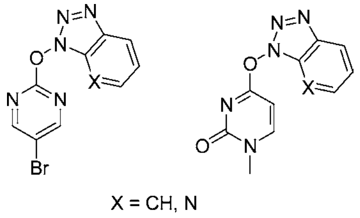
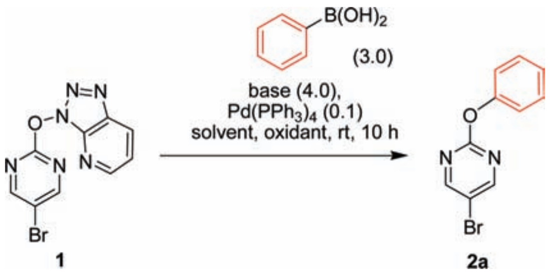


Figure 1. Oxidative Pd(0) reaction on representative cyclic OPt heterocycles.

Optimization studies were initially performed on 3-(5-bromo-pyrimidin-2-yloxy)-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine **1** with phenylboronic acid by evaluating various metals, ligands, solvents, and bases. The desired 2-phenoxy-5-bromopyrimidine product **2a** (Table 1) was observed without the detection of 2-phenyl-5-bromopyrimidine as the Suzuki cross-coupling product.

Table 1. Optimization Conditions of 3-(5-Bromo-pyrimidin-2-yloxy)-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine **1** Coupling with Phenylboronic Acids



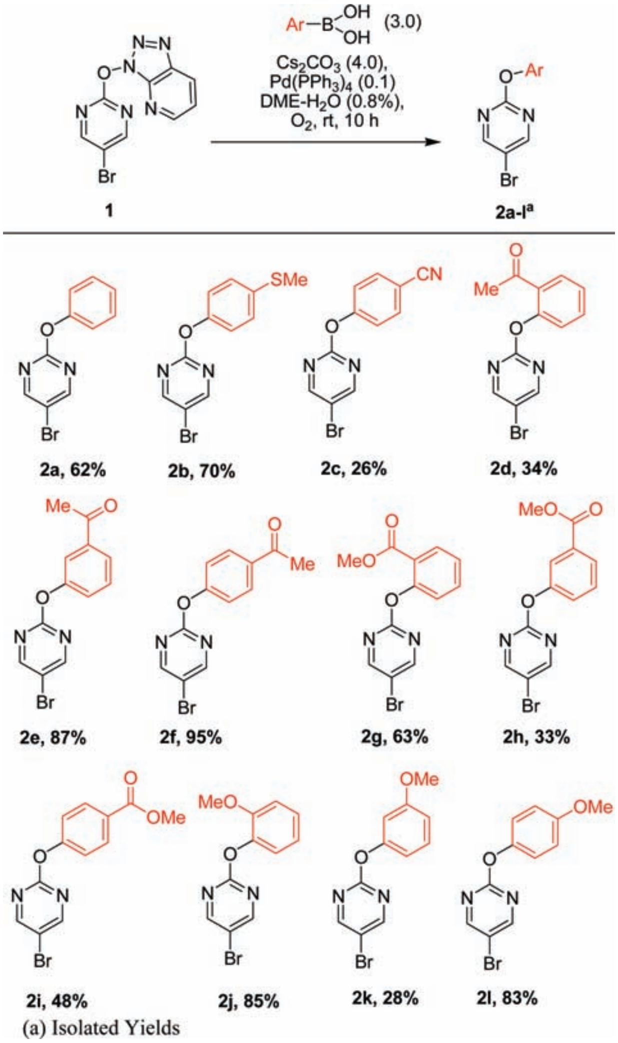
entry	base	solvent	oxidant	yield (%)[a]
1	Cs_2CO_3	DME	UHP	18
2	Cs_2CO_3	DME	H_2O_2 (10%)[b]	0[c]
3	No Base	DME	O_2	0
4	Cs_2CO_3	DME	N_2	35[d]
5	Cs_2CO_3	DME	O_2	25
6	Cs_2CO_3	DME−H_2O (0.8%)	O_2	62

[a] Isolated yields. [b] 30% w/w H_2O_2 [c] **2a** was not observed. Instead a polar and unidentified compound was formed. [d] Slightly wet batch of Cs_2CO_3 used.

As in the case with quinazoline *O*Pt,[13] $Pd(PPh_3)_4$ in DME proved to be advantageous over $Pd(OAc)_2$. Further screening of base effects identified Cs_2CO_3 and Na_2CO_3 as suitable bases for this transformation. With Cs_2CO_3 as the base of choice, dioxygen proved to be the best oxidant in comparison to H_2O_2[14] or anhydrous urea hydrogen peroxide (UHP) (Table 1). The presence of water 0.6−1.0% in DME was necessary to achieve good yields of **2a**. The *O*Bt analogue of **1** is also a good substrate for this transformation, although heteroaryl ethers are formed at a slower reaction rate.

Arylboronic acids containing diverse functional groups underwent transformation to heteroaryl ethers **2a**−**l** readily under mild conditions (Scheme 1). The presence of a thiomethyl moiety in **2b** did not result in any complications due to potential sulfoxide or sulfone formation. The electronic and steric effects were evaluated using three arylboronic acids carrying acetyl, carbomethoxy, and methoxy substituents at the o, m, and p positions. Boronic acids with electronic withdrawing (acetyl, carbomethoxy) and donating groups (methoxy) gave moderate to excellent yields of

Scheme 1. Coupling Reaction of **1** with Arylboronic Acids

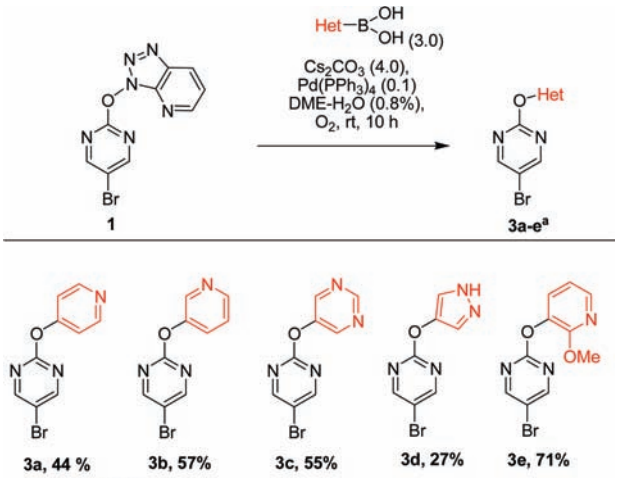


(a) Isolated Yields

isolated heteroaryl ethers **2d**−**i** and **2j**−**l**, respectively. It is unclear why the yield of **2d** is low especially in comparison to **2g** and **2j**, and this does not suggest electronic reasons since the latter compounds were formed in good yields.

Boronic acids derived from a variety of heterocycles produce heteroaryl ethers under the oxidative palladium coupling conditions (Scheme 2). In the case of **3d** no protection of the nitrogen moiety is required. A limitation of the scope of this reaction was realized with boronic acids containing a heteroatom in the α position as the reaction was too slow to form the desired product in a synthetically useful manner. The use of excess arylboronic acids is necessary to compensate for the homocoupling products under the oxidative Pd(0) reaction conditions.[15]

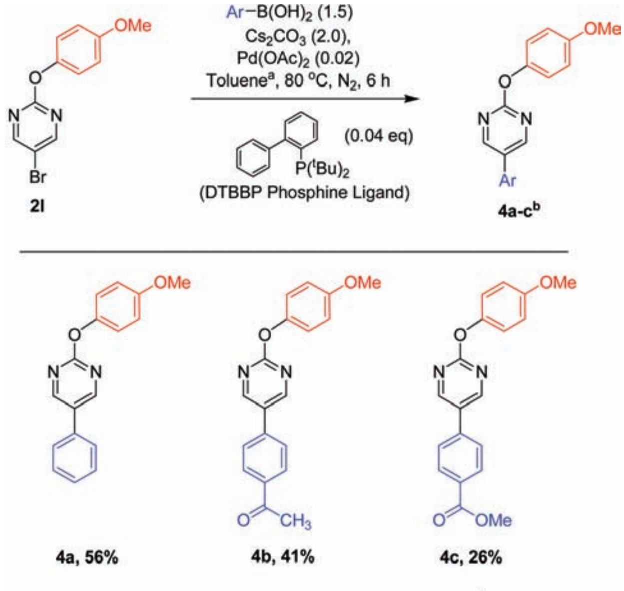
Scheme 2. Coupling Reaction of **1** with Heteroarylboronic Acids



(a) Isolated Yields.

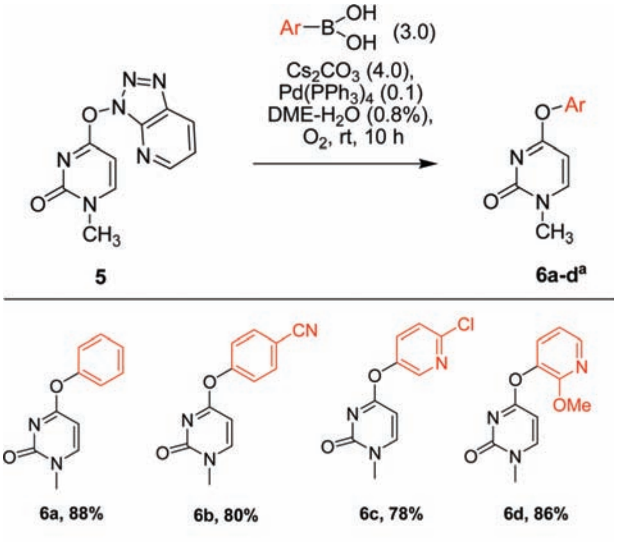
The choice of the 5-bromo substituent in **1** was deliberately made to evaluate the chemo- and regioselectivity of an oxidative Pd coupling reaction at C2 with a possible Suzuki-type reaction at C5. In all cases reported (in Scheme 1), Suzuki coupling at the C5 position was not observed. This observation leaves the opportunity to exploit further chemistry by using the 5-bromo group as a chemical handle. Toward this end, a few 5-aryl pyrimidines were synthesized through Suzuki coupling as shown in Scheme 3. Heteroaryl ethers such as **2l** readily underwent cross-coupling reactions with a variety of arylboronic acids to provide the desired products using the Buchwald ligand DTBBP (Scheme 3) under Pd(II) catalysis.[16]

Scheme 3. Suzuki Cross-Coupling Reaction of 5-Bromo-2-(4-methoxyphenoxy)pyrimidine **2l**



(a) Distilled over calcium hydride and stored over 4 Å Molecular Sieves. (b) Unoptimized Yields.

Scheme 4. Oxidative Palladium Coupling Reaction of 4-(3*H*-[1,2,3]Triazolo[4,5-*b*]pyridin-3-yloxy)-1-methylpyrimidin-2(1*H*)-one **5** with Arylboronic Acids



(a) Isolated Yields

Pyrimidine bases are important biologically. Therefore, extension of this transformation to 4-(3*H*-[1,2,3]triazolo[4,5-*b*]-pyridine-3-yloxy)-1-methylpyrimidin-2(1*H*)-one **5** was attempted since this heterocycle has an N3 substituent different from that of **1** or the quinazoline analogue in both basicity and electronic factors. The oxidative palladium reaction followed by an S_NAr reaction, indeed, proceeded very well with **5** producing excellent isolated yields of heteroaryl ethers **6a**−**d** (Scheme 4). The excellent yields derived from pyrimidines **1** and **5** demonstrate good potential and broaden the scope for an effective *O*-arylation reaction (Schemes 1 and 4). Consistent with our earlier findings on the lack of reactivity of the 5-bromo moiety in **1**,[13] the 2-chloro moiety in **6c** did not cause any complications. In conclusion, the expanded scope of the oxidative palladium coupling reactions of heterocyclic *O*Pt derivatives[17] with arylboronic acids provides an efficient synthesis of heteroaryl ethers of biologically important pyrimidine heterocycles. This transformation amounts to the S_NAr reaction[12] of phenols with the *O*Pt heterocycles but offers the advantage of not using phenols when they are not readily available or are unstable. Additionally, the reaction conditions are mild and apply to *O*Pt derivatives of amides and ureas. The formation of heteroaryl ethers by this method complements earlier reports on the potential of using stable *O*Pt adducts of heterocycles in novel synthetic transformations. Mechanistic studies likely involving the formation[13,18] of $(\eta^2\text{-O}_2)\text{Pd}(\text{PPh}_3)_2$ and its reaction with aryl boronic acids are under investigation and will be reported elsewhere.[19]

Acknowledgment. The authors wish to thank Elwira Muszynska and Murthy Damarla of Wyeth Research for purification of **2j**.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900592B

---

(9) (a) Wan, Z.-K.; Binnum, E.; Wilson, D. P.; Lee, J. *Org. Lett.* **2005**, *7*, 5877–5880. (b) Wan, Z.-K.; Wacharasindhu, S.; Binnum, E.; Mansour, T. *Org. Lett.* **2006**, *8*, 2425–2428. (c) Levins, C. G.; Wan, Z.-K. *Org. Lett.* **2008**, *10*, 1755–1758.

(10) Synthetic utlility of BOP and related reagents: (a) Coste, J.; Frerot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967–1970. (b) Srivastava, T. K.; Haq, W.; Bhanumati, S.; Velmurugan, D.; Sharma, U.; Jagannathan, N. R.; Katti, S. B. *Protein Pept. Lett.* **2001**, *8*, 39–44. (c) Kang, F.-A.; Sui, Z.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300–11302.

(11) For PyAOP, see: Alsina, J.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **1996**, *37*, 4174–4175.

(12) Wan, Z.-K.; Wacharasindhu, S.; Levins, C.; Lin, M.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 10194–10210.

(13) Wacharasindhu, S.; Bardhan, S.; Wan, Z.-K.; Tabei, K.; Mansour, T. S. *J. Am. Chem. Soc.* **2009**, *131*, 4174–4175.

(14) Use of higher concentrations of H_2O_2 appears to inhibit the formation of **2a** (Table 1).

(15) (a) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829–6836. (b) Aramendia, M. A.; Lafont, F.; Moreno-Manas, M.; Pleixats, R.; Roglans, A. *J. Org. Chem.* **1999**, *64*, 3592–3594. (c) Hossain, K. M.; Kameyama, T.; Shibata, T.; Tagaki, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2415–2420. (d) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087–4089. (e) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541–1544. (f) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623–4625. (g) Yamamoto, Y.; Suzuki, R.; Hattori, K.; Nishiyama, H. *Synlett* **2006**, 1027−1030. (h) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (i) Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 2804–2805. (k) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384–16393.

(16) For the DTBBP ligand: Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378.

(17) For recent alternate use of benzotriazol-1-yl derivatives in organic synthesis, see: (a) Katritzky, A. R.; Tao, H.; Kirichenko, K. *ARKIVOC* **2007**, *10*, 142–151. (b) Katritzky, A. R.; Vakulenko, A. V.; Akue-Gedu, R.; Gromova, A. V.; Witek, R.; Rogers, J. W. *ARKIVOC* **2007**, *1*, 9–21. (c) Katritzky, A. R.; Todadze, E.; Angrish, P.; Draghici, B. *J. Org. Chem.* **2007**, *72*, 5794–5801. (d) Katritzky, A. R.; Le, K. N. B.; Khelashvili, L.; Mohapatra, P. P. *J. Org. Chem.* **2006**, *71*, 9861–9864. (e) Katritzky, A. R.; Tao, H.; Jiang, R.; Suzuki, K.; Kirichenko, K. *J. Org. Chem.* **2007**, *72*, 407–414.

(18) (a) Canty, A. J.; Jin, H.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **1998**, *37*, 3975–3981. (b) van Belzen, R.; Elsevier, C. J.; Dedieu, A.; Veldman, N.; Spek, A. L. *Organometallics* **2003**, *22*, 722−736. Insertion of O into a Pd(I)−Pd(I) dimer and subsequent C−O bond formation cannot be excluded, see: (c) Dura-Vila, V.; Mingos, D. M. P.; Vilar, R.; White, A. F. P.; Williams, D. J. *Chem. Commun.* **2000**, *16*, 1525–1526.

(19) Lower isolated yields <5% were obtained with 4-iodobenzeneboronic acid and 5-indolylboronic acid.