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Direct Heteroarylation of Tautomerizable Heterocycles into Unsymmetrical and Symmetrical Biheterocycles via Pd/Cu-Catalyzed Phosphonium Coupling

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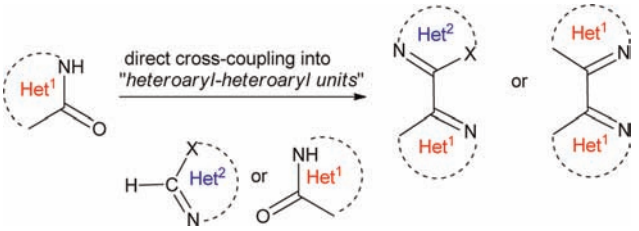
ABSTRACT



The direct cross-coupling of tautomerizable heterocycles with various unfunctionalized heteroarenes has been achieved through PyBroP-mediated and Pd/Cu-catalyzed sequential C–OH/C–H activation. The methodology allows a facile entry into novel diazine-azole biheterocyclic frameworks. Moreover, an unprecedented Pd-catalyzed phosphonium homocoupling of tautomerizable heterocycles was also developed to afford a direct synthetic route to symmetrical 1,2-, 1,3-, and 1,4-bidiazine units.

The heterobiaryl framework is an important constituent of various biologically active compounds and functional materials.[1] The synthesis of such biaryl units via transition metal catalyzed direct C–H arylation of heteroarenes has received increased attention due to several inherent benefits.[2] Thus, considerable progress has been achieved in the formation of "*heteroaryl–aryl*" units[2,3] via C–H arylation using various aryl halides and pseudohalides including C–O electrophiles.[3i–m,4] In contrast, similar strategies for the construction of "*heteroaryl–heteroaryl*" *scaffolds*[5] such as diazine-azoles or bidiazines remain far less explored.

On the other hand, tautomerizable heterocycles are widely distributed in naturally occurring compounds and

(1) For reviews, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(2) For leading reviews on C–H arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(3) For selected examples, see: (a) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (b) Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 7863. (c) Ohnmacht, S. A.; Culshaw, A. J.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 224. (d) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (e) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674. (f) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (g) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072. (h) Wagner, A. M.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 288. (i) Molander, G. A.; Beaumard, F. *Org. Lett.* **2010**, *12*, 4022. (j) Ackermann, L.; Althammer, A. S.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (k) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043. (l) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430. (m) Fan, S.; Yang, J.; Zhang, X. *Org. Lett.* **2011**, *13*, 4374.

(4) Li, B. J.; Yu, D. G.; Sun, C. L.; Shi, Z. J. *Chem.—Eur. J.* **2011**, *17*, 1728.

(5) (a) Steel, P. J. *Adv. Heterocycl. Chem.* **1996**, *67*, 1–117 and references therein. (b) Zhao, D.; You, J.; Hu, C. *Chem.—Eur. J.* **2011**, *17*, 5466. (c) Hughes, R. A.; Moody, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7930. For selected examples, see: (d) Duric, S.; Tzschucke, C. C. *Org. Lett.* **2011**, *13*, 2310. (e) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717. (f) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, *46*, 2471. (g) Truong, J.; Alvarado, L.; Tran, D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200. (h) Zhu, M.; Fujita, K.; Yamaguchi, R. *Chem. Commun.* **2011**, *47*, 12876. (i) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2010**, *76*, 8138.

(6) *The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals*, 13th ed.; Merck & Co., Inc.: Whitehouse Station, NJ, 2001.

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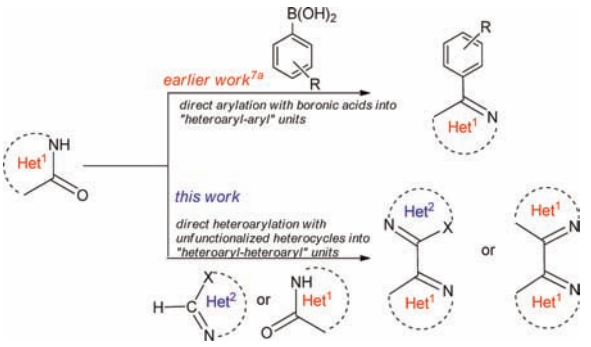
offer a convenient source of various heterocyclic building blocks.[6] Recently, these have also emerged as an attractive class of substrates for Pd-catalyzed cross-couplings via *in situ* C−OH activation using phosphonium salts.[7] In particular, the pioneering work of Kang et al. allowed the direct arylation of tautomerizable heterocycles using boronic acids as coupling partners (Scheme 1).[7a] However, it would be highly beneficial if *unfunctionalized heteroarenes*[2] could be utilized as a latent source of heterocyclic coupling partners for tautomerizable heterocycles. Such a combination of two complementary C−C bond forming approaches[2,7] would give a direct access to a wide range of biologically important *biheterocyclic scaffolds*. In the course of our continued interest in the development of catalytic approaches for the synthesis of novel biaryl frameworks,[7e,8] we became interested in exploring the utility of tautomerizable heterocycles for the synthesis of varied *heteroaryl−heteroaryl units*. Herein, we report the *Pd-catalyzed direct heteroarylation of tautomerizable heterocycles into diazine-azoles and bidiazines* respectively via PyBroP-mediated cross-coupling with azoles or phosphonium homocoupling (Scheme 1).

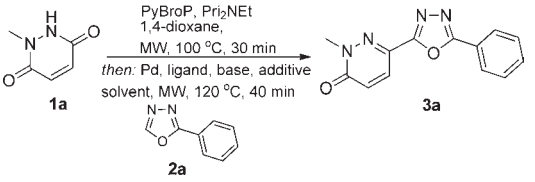
Scheme 1. Strategies for Arylation/Heteroarylation of Tautomerizable Heterocycles Using Phosphonium Coupling



Initially, the direct heteroarylation was explored using 2-methyl-1*H*-pyridazine-3,6-dione (**1a**) and 2-phenyl-1,3,4-oxadiazole (**2a**) as substrates (Table 1). Thus, a mixture of **1a** (0.3 mmol), PyBroP (1.2 equiv), and Pri_2NEt (3 equiv) in 1,4-dioxane[7] was irradiated with microwaves (MW) at 100 °C for 30 min to form the phosphonium salt. Thereafter, $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (3 equiv), and **2a** (1.5 equiv) were added, and the resulting mixture was further irradiated at 120 °C for 40 min (Table 1, entry 1).

However, these conditions afforded the desired product only in traces. This led us to hypothesize that the direct coupling of the heterocycle-phosphonium salt with heteroarenes might not be feasible using dioxane as the sole solvent. Therefore, after the initial formation of the phosphonium salt, DMA was also added to the reaction mixture while keeping the rest of the conditions unchanged (Table 1, entry 2). This modification provided the desired biheterocyclic product **3a** in 20% yield. A further optimization of this cross-coupling reaction (Table 1) indicated that other solvents such as DME (Table 1, entry 3) and DMF (entry 4) or another base (Cs_2CO_3, Table 1, entry 5) were not beneficial. Interestingly, the use of CuI (Table 1, entries 6−7) as an additive led to a significant improvement of the yield (65%, Table 1, entry 7), while addition of pivalic acid[3d] proved unsuitable under our conditions (21% yield, entry 8). The various other

Table 1. Optimization of the Cross-Coupling between 2-Methyl-1*H*-pyridazine-3,6-dione and 2-Phenyl-1,3,4-oxadiazole[a]



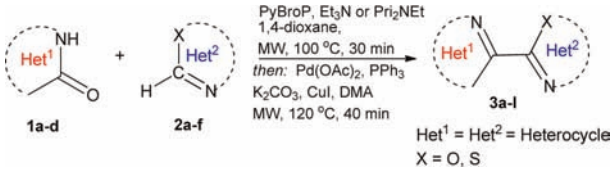
entry	solvent	base	Pd/ligand	additive	yield[b] (%)
1	Dioxane	K_2CO_3	$Pd(OAc)_2$/PPh_3	–	traces
2	DMA	K_2CO_3	$Pd(OAc)_2$/PPh_3	–	20
3	DME	K_2CO_3	$Pd(OAc)_2$/PPh_3	–	traces
4	DMF	K_2CO_3	$Pd(OAc)_2$/PPh_3	–	10
5	DMA	Cs_2CO_3	$Pd(OAc)_2$/PPh_3	–	15
6	DMA	K_2CO_3	$Pd(OAc)_2$/PPh_3	CuI[c]	51 (30)[d]
7	DMA	K_2CO_3	$Pd(OAc)_2$/PPh_3	CuI	65
8	DMA	K_2CO_3	$Pd(OAc)_2$/PPh_3	Pivalic acid[e]	21
9	DMA	K_2CO_3	$Pd(OAc)_2$/XPhos	CuI	traces
10	DMA	K_2CO_3	$Pd(OAc)_2$/Xantphos	CuI	55
11	DMA	K_2CO_3	$Pd(OAc)_2$[e]/PPh_3	CuI	77(nd,[g,h] 72[i])
12	DMA	K_2CO_3	$Pd(PPh_3)_4$[f]	CuI	66
13	DMA	K_2CO_3	$Pd(PPh_3)_2Cl_2$[f]	CuI	62

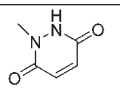
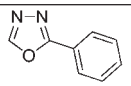
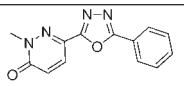
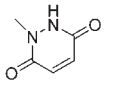
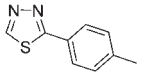
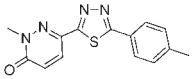
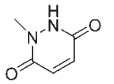
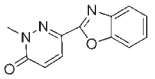
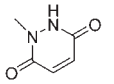
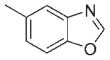
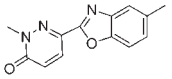
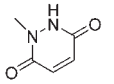
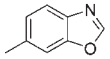
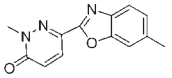
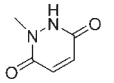
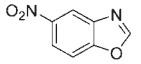
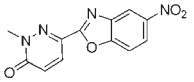
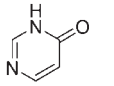
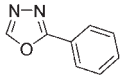
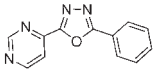
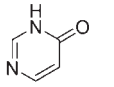
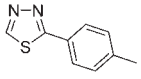
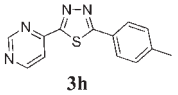
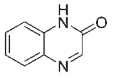
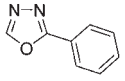
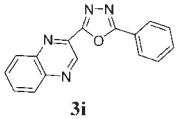
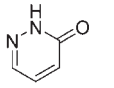
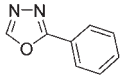
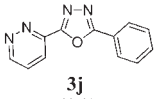
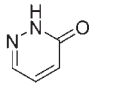
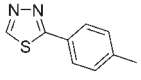
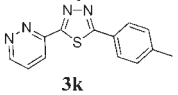
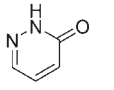
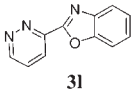
[a] General conditions: **1a** (0.27 mmol), PyBroP (1.2 equiv), Pri_2NEt (3 equiv), in 1,4-dioxane (1.5 mL), MW, 100 °C, 30 min; then $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), base (3 equiv), additive (50 mol %), **2a** (1.5 equiv), DMA (1.5 mL), MW, 120 °C, 40 min. [b] Yield of pure isolated product (single run). [c] 30 mol %. [d] Yield using Et_3N in place of Pri_2NEt. [e] $Pd(OAc)_2$ (7 mol %)/PPh_3 (14 mol %). [f] (7 mol %). [g] Not detected. [h] Reaction without Pd catalyst. [i] Reaction under conventional heating at 120 °C, 16 h

(7) (a) Kang, F.-A.; Sui, Z.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300. (b) Kang, F.-A.; Sui, Z.; Murray, W. V. *Eur. J. Org. Chem.* **2009**, 461. (c) Kang, F.-A.; Lanter, J. C.; Cai, C.; Sui, Z.; Murray, W. V. *Chem. Commun.* **2010**, *46*, 1347. (d) Shi, C.; Aldrich, C. C. *Org. Lett.* **2010**, *12*, 2286. (e) Mehta, V. P.; Modha, S. G.; Van der Eycken, E. *J. Org. Chem.* **2010**, *75*, 976. (f) Li, S.-M.; Huang, J.; Chena, G.-J.; Han, F.-S. *Chem. Commun.* **2011**, *47*, 12840.

(8) (a) Beryozkina, T.; Appukkuttan, P.; Mont, N.; Van der Eycken, E. *Org. Lett.* **2006**, *8*, 487. (b) Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Chem.—Eur. J.* **2007**, *13*, 6452.

Table 2. Pd-Catalyzed Direct Heteroarylation of Tautomerizable Heterocycles with Heteroarenes Using Phosphonium Coupling[a,b]



entry	het[1]	het[2]	product	yield[c] (%)
1			 **3a**	77[a]
2			 **3b**	62[a]
3			 **3c**	70[b]
4			 **3d**	72[b]
5			 **3e**	68[b]
6			 **3f**	74[b]
7			 **3g**	65[a,d]
8			 **3h**	51[a,d]
9			 **3i**	66[a]
10			 **3j**	75[a]
11			 **3k**	60[a]
12			 **3l**	71[b]

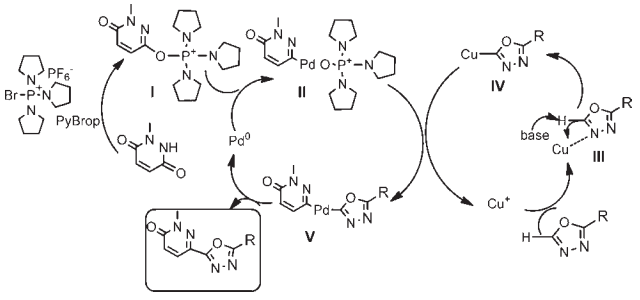
[a] Condition A: Het[1] (0.27 mmol), PyBroP (1.2 equiv), Pri_2NEt (3 equiv) in 1,4-dioxane (1.5 mL), MW, 100 °C, 30 min; then $Pd(OAc)_2$ (7 mol %), PPh_3 (14 mol %), K_2CO_3 (3 equiv), CuI (50 mol %), Het[2] (1.5 equiv), DMA (1.5 mL), MW, 120 °C, 40 min. [b] Condition B: this is the same as condition A, except that Pri_2NEt is replaced by Et_3N (3 equiv) and 2 equiv of Het[2] were used. [c] Yield of pure isolated product (single run). [d] 5 equiv of Pri_2NEt were used.

Pd-catalysts/ligands (entries 9, 10, 12, and 13) did not result in a substantial amelioration of the yield. However, an increase in catalyst loading of $Pd(OAc)_2$ up to 7 mol % (entry 11) further enhanced the yield of **3a** (77%).

With the optimized conditions (A) in hand (Table 1, entry 11), the substrate scope with respect to both coupling partners was explored (Table 2). Interestingly, the above heteroarylation also proceeded well with other biologically important[9] heteroarene[10] cores such as 1,3,4-thiadiazole (entry 2) and benzoxazoles (entries 3−6). However, a slight modification (condition B) employing Et_3N (3 equiv) instead of Pri_2NEt was found to be beneficial in the case of benzoxazoles. Similarly, the protocol was also applicable to various tautomerizable heterocycles, thereby, allowing an unprecedented direct linkage of 1,3-, (entries 7−8), 1,4-, (entry 9) and 1,2-diazine units (entries 10−12) with diverse azoles. Such diazine-azole biheterocyclic scaffolds are expected to possess important applications in medicinal[9,11] and materials chemistry.[12]

The above transformation plausibly proceeds through a sequential C−OH[7] and C−H activation pathway[2,3g] (Scheme 2). The phosphonium salt **I**, obtained by activation of the tautomerizable heterocycle with PyBroP, enters the Pd catalytic cycle via oxidative addition of Pd(0) to give a heterocycle-Pd(II)-complex **II**. Subsequently, the above Pd(II)-complex undergoes transmetalation with a Cu(I)-heteroaryl species **IV** (formed concurrently via C−H bond activation of heteroarene **III**) to give **V** which provides the desired biheterocycle upon reductive elimination (Scheme 2).

Scheme 2. Plausible Mechanism of the Pd/Cu-Catalyzed Direct Cross-Coupling of Tautomerizable Heterocycles with Heteroarenes



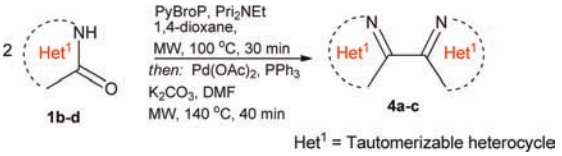
In the course of our above studies, some homocoupled product (10−15%) of the tautomerizable heterocycle was

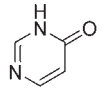
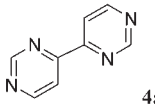
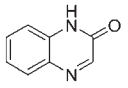
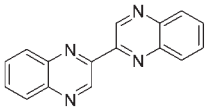
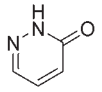
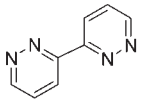
(9) (a) Koezen, J. E. M.; Timmerman, H.; Vollinga, R. C.; Kunzel, J. F. V. D.; Groote, M. D.; Visser, S.; IJzerman, A. P. *J. Med. Chem.* **2001**, *44*, 749. (b) Rao, A. U.; Shao, N.; Aslanian, R. G.; Chan, T.-Y.; Degrado, S. J.; Wang, L.; McKittrick, B.; Senior, M.; West, R. E.; Williams, S. M.; Wu, R.-L.; Hwa, J.; Patel, B.; Zheng, S.; Sondey, C.; Palani, A. *ACS Med. Chem. Lett.* **2012**, *3*, 198. (c) Yoshida, S.; Shiokawa, S.; Kawano, K.; Ito, T.; Murakami, H.; Suzuki, H.; Sato, Y. *J. Med. Chem.* **2005**, *48*, 7075. (d) Leung, D.; Du, W.; Hardouin, C.; Cheng, H.; Hwang, I.; Cravatt, B. F.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1423.

(10) The use of heteroarenes such as imidazoles, indoles, and benzothiazoles was also explored; however, these did not undergo cross-coupling under the above conditions.

(11) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.

Table 3. Pd-Catalyzed Homophosphonium Coupling of Tautomerizable Heterocycles into Symmetrical Bidiazines[a]



entry	het[1]	product	yield[b] (%)
1	 **1b**	 **4a**	72
2	 **1c**	 **4b**	70
3	 **1d**	 **4c**	71

[a] General conditions: Het[1] (0.36 mmol), PyBroP (1.2 equiv), Pri_2NEt (5 equiv) in 1,4-dioxane (1.5 mL), MW, 100 °C, 30 min; then $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (2 equiv), DMF (1.5 mL), MW, 140 °C, 40 min. [b] Yield of pure isolated product (single run).

detected. To the best of our knowledge, such homodimerization of tautomerizable heterocycles has so far not been reported in the case of palladium catalyzed phosphonium couplings.[13] Interestingly, the resulting symmetrical biheterocycles have important applications in photochemistry and as π-accepting ligands in coordination chemistry.[14] Moreover, such homodimeric scaffolds have been predominantly accessed via multiple steps or functionalized substrates.[15] Due to the above observations, the utility of this unprecedented homocoupling reaction was evaluated using 4(3*H*)-pyrimidinone (**1b**) as a model substrate. We found that the use of an increased amount of Pri_2NEt (5 equiv), $Pd(OAc)_2$ (10 mol %), and PPh_3 (20 mol %) and replacement of DMA with DMF as solvent at 140 °C led to a significant enhancement in yield (72%) of the desired symmetrical 4,4′-bipyrimidine (**4a**) (Table 3, entry 1). Importantly, the above condition also provided a novel access to the homodimers of other 1,4- and 1,2-diazines (Table 3, entries 2−3).

In conclusion, we have developed an elegant Pd-catalyzed phosphonium coupling of tautomerizable heterocycles with various unfunctionalized heteroarenes. The protocol enables a direct and unprecedented linkage of 1,2-, 1,3-, as well as 1,4-diazines with azoles using readily available substrates. Significantly, a direct approach for the synthesis of symmetrical bidiazines was also achieved via a novel Pd-catalyzed phosphonium homocoupling of tautomerizable heterocycles.

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Supporting Information Available. Complete experimental details and spectroscopic data of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.