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1,3,4-oxadiazol-2-amines and 1,3,4-thiadiazol-2-amines  
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Longjia Yan, Mingguo Deng, Anchao Chen, Yongliang Li, Wanzheng Zhang, et al.. Synthesis of N-pyrimidin[1,3,4]oxadiazoles and N-pyrimidin[1,3,4]-thiadiazoles from 1,3,4-oxadiazol-2-amines and 1,3,4-thiadiazol-2-amines via Pd-catalyzed heteroarylamination. *Tetrahedron Letters*, 2019, 60 (20), pp.1359-1362. 10.1016/j.tetlet.2019.04.022 . hal-02338726

**HAL Id: hal-02338726**

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Submitted on 22 Oct 2021

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# Synthesis of *N*-pyrimidin[1,3,4]oxadiazoles and *N*-pyrimidin[1,3,4]-thiadiazoles from 1,3,4-oxadiazol-2-amines and 1,3,4-thiadiazol-2-amines via Pd-catalyzed heteroarylation

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## ARTICLE INFO

### Article history:

Received

Received in revised form

Accepted

Available online

## ABSTRACT

An efficient and practical procedure was developed to prepare various *N*-pyrimidin[1,3,4]oxadiazole and thiadiazole scaffolds using a Buchwald-type coupling. The products of this reaction are otherwise difficult to access and could be used as building blocks in drug design.

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### Keywords:

1,3,4-oxadiazole

1,3,4-thiadiazole

pyrimidine

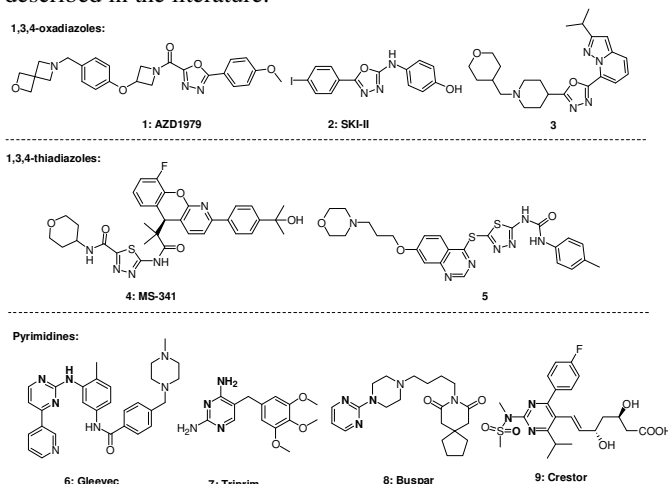
C-N cross-coupling

## Introduction

Five-membered aromatic rings with three heteroatoms are a type of aromatic compound in which the various heteroatoms contribute very differently to the formation of aromatic conjugation.<sup>1</sup> Among them, 1,3,4-oxadiazole and 1,3,4-thiadiazole scaffolds constitute an important core structure in chemotherapeutic agents and have attracted significant attention due to their interesting biological activities and medicinal properties (Fig. 1),<sup>2-5</sup> including as a melanin-concentrating hormone receptor 1 (MCHR1) antagonist (1: AZD1979),<sup>6-7</sup> sphingosine kinase (SK) inhibitor (2: SKI-II),<sup>8</sup> 5-HT<sub>4</sub> receptor partial agonists (3),<sup>9</sup> glucocorticoid receptor modulator (4: BMS-341),<sup>10</sup> and FMS-like tyrosine kinase 3 (FLT3) inhibitor (5).<sup>11</sup> In addition, these compounds also play a fundamental role in bioorganic chemistry and material science.<sup>12-15</sup>

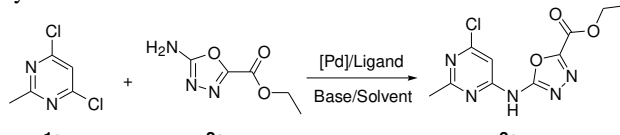
Pyrimidine, a six membered heterocyclic compound bearing two *N*-atoms in the ring, constitutes an important component of nucleic acid and is widespread in Nature.<sup>16-17</sup> The pyrimidine system is an important pharmacophore endowed with druglike properties (Fig. 1), which is present in the BCRABL tyrosine kinase inhibitor imatinib (Gleevec, 6),<sup>18</sup> a dihydrofolate reductase inhibitor (Trimethoprim, 7),<sup>19</sup> a 5-HT<sub>1A</sub> receptor agonist (Buspirone, 8),<sup>20</sup> and the HMG-CoA reductase inhibitor

Rosuvastatin (Crestor, 9).<sup>21</sup> However, the synthesis of pyrimidine derivatives containing a 1,3,4-oxadiazole ring or 1,3,4-thiadiazole ring, as well as their biological activities are seldom described in the literature.<sup>22-23</sup>



**Figure 1.** Representative bioactive skeletons containing 1,3,4-oxadiazole, 1,3,4-thiadiazole or pyrimidine frameworks.

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**Table 1.** Optimization of the heteroarylamination reaction.<sup>a</sup>


Entry	[Pd]	Ligand	Base	Solvent	T(°C)	Yield <b>3a</b> (%) <sup>b</sup>
1	Pd(OAc) <sub>2</sub>	BINAP	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	100	36
2	Pd(OAc) <sub>2</sub>	dppf	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	100	24
3	Pd(OAc) <sub>2</sub>	xphos	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	100	trace
4	Pd(OAc) <sub>2</sub>	P( <i>t</i> -Bu) <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	100	15
5	Pd(OAc) <sub>2</sub>	Sphos	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	100	trace
6	Pd(OAc) <sub>2</sub>	xantphos	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	100	45
7	Pd <sub>2</sub> dba <sub>3</sub>	xantphos	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	100	44
8	Pd(OAc) <sub>2</sub>	xantphos	K <sub>2</sub> CO <sub>3</sub>	Dioxane	100	26
9	Pd(OAc) <sub>2</sub>	xantphos	LiHMDS	Dioxane	100	40
10	Pd(OAc) <sub>2</sub>	xantphos	NaO <sup>t</sup> Bu	Dioxane	100	56
11	Pd(OAc) <sub>2</sub>	xantphos	NaO <sup>t</sup> Bu	Toluene	100	14
12	Pd(OAc) <sub>2</sub>	xantphos	NaO <sup>t</sup> Bu	THF	100	46
13	Pd(OAc) <sub>2</sub>	xantphos	NaO <sup>t</sup> Bu	DMF	100	68
14	Pd(OAc) <sub>2</sub>	xantphos	NaO <sup>t</sup> Bu	DME	80	34
15	Pd(OAc) <sub>2</sub>	xantphos	NaO <sup>t</sup> Bu	DMF	110	71
16	Pd(OAc) <sub>2</sub>	xantphos	NaO <sup>t</sup> Bu	DMF	120	68
17	Pd(OAc) <sub>2</sub>	xantphos	NaO <sup>t</sup> Bu	DMF	110	65 <sup>c</sup>

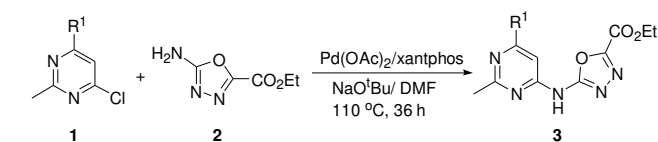
<sup>a</sup> Reagents and conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Pd] (0.02 mmol), ligand (0.04 mmol), base (0.3 mmol), solvent (2 mL), 36 h. <sup>b</sup> Isolated yield. <sup>c</sup> microwave (MW) irradiation, 1 h.

During the course of a medicinal chemistry program, the synthesis of a pyrimidine intermediate containing a 1,3,4-oxadiazole ring **3a** (Table 1) became important for further transformations. Despite the simple structural features of this compound, our synthetic efforts towards **3a** were met with significant setbacks, due to the low reactivity of the five-membered ring. Herein, we report optimized conditions, substrate scope, and applications of the Pd-catalyzed C-N cross-coupling of 4-chloro-2-methylpyrimidines and 1,3,4-oxadiazol-2-amines or 1,3,4-thiadiazol-2-amines, which provide facile access to these compounds and their derivatives.

## Results and Discussion

For this study, we chose 4,6-dichloro-2-methylpyrimidine **1a** and ethyl 5-amino-1,3,4-oxadiazole-2-carboxylate **2a** as model starting materials. Compound **2a** can be prepared *via* oxidative cyclization from the corresponding acyhydrazone in good yields.<sup>24-25</sup> We first examined the reaction of **2a** with 4,6-dichloro-2-methylpyrimidine in the presence of different bases (Cs<sub>2</sub>CO<sub>3</sub>, NaH, NaO<sup>t</sup>Bu and LiHMDS) in 1,4-dioxane under conventional thermal heating conditions, which failed to effectively produce product **3a**. In order to access **3a**, we next examined the Pd-catalyzed Buchwald–Hartwig-type heteroarylamination procedure. Under classical conditions using 10 mol% Pd(OAc)<sub>2</sub>, 20 mol% BINAP and 1.5 equiv. of Cs<sub>2</sub>CO<sub>3</sub> in 1,4-dioxane, the reaction proceeded and product **3a** was obtained in 36% yield (Table 1, entry 1). We subsequently investigated the effect of various ligands on the yield. Xantphos ligand gave better results (Table 1, entry 6). A similar yield was obtained when Xantphos ligand was replaced by Pd<sub>2</sub>dba<sub>3</sub> (Table 1, entry 7). Replacement of Cs<sub>2</sub>CO<sub>3</sub> by K<sub>2</sub>CO<sub>3</sub> or LiHMDS led to lower yields and NaO<sup>t</sup>Bu gave a satisfactory yield (Table 1, entries 8–10). Next, we screened different organic solvents and identified DMF as the most effective solvent (Table 1, entry 13), while toluene resulted in a poor yield (Table 1, entry 11). The yield could be further improved by increasing the temperature to a maximum of 110 °C (Table 1, entry 15), whereas higher

temperatures led to partial decomposition (Table 1, entry 16). Various studies have indicated that microwave irradiation (MW) could accelerate the Pd-catalyzed C-N reaction.<sup>26-27</sup> However, attempts to increase the yield of **3a** by performing the reaction under MW condition were not successful (Table 1, entry 17).

**Table 2.** Preparation of *N*-pyrimidin[1,3,4]oxadiazoles **3a-f**.<sup>a</sup>

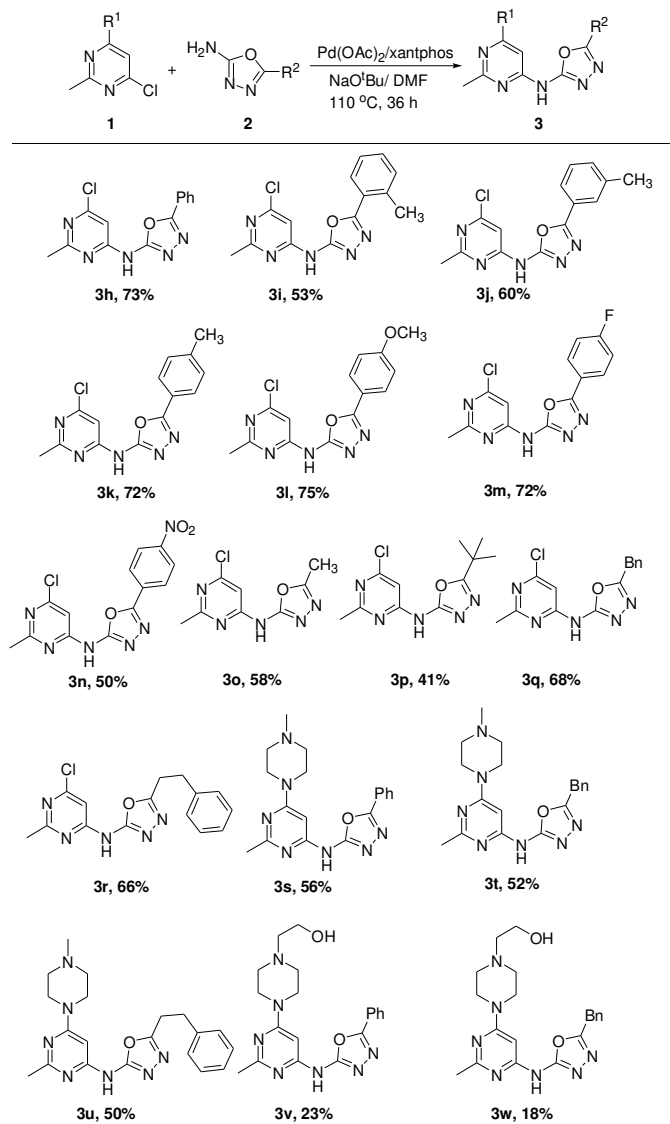
Entry	R <sup>1</sup>	Product	Yield (%) <sup>b</sup>
1	Cl	<b>3a</b>	71
2	Ph	<b>3b</b>	70
3	3-NO <sub>2</sub> Ph	<b>3c</b>	61
4	4-NO <sub>2</sub> Ph	<b>3d</b>	66
5	<i>N</i> -methylpiperazine	<b>3e</b>	55
6	<i>N</i> -acetylpiperazine	<b>3f</b>	36
7	<i>N</i> -(2-hydroxyethyl)piperazine	<b>3g</b>	20

<sup>a</sup> Reagents and conditions: **1** (0.2 mmol), **2** (0.3 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), xantphos (0.04 mmol), NaO<sup>t</sup>Bu (0.3 mmol), DMF (2 mL), 36 h. <sup>b</sup> Isolated yield.

Having determined the optimal reaction conditions (Table 1, entry 15), the scope of the reaction was explored with different substituted pyrimidine derivatives **1** (Table 2), which were prepared by the reaction of 4,6-dichloro-2-methylpyrimidine **1a** with arylamines or substituted piperazines, to afford various functionalized *N*-pyrimidin[1,3,4]oxadiazoles **3**. 4-Chloro-2-methylpyrimidine substituted by a phenyl group provided the desired product in good yield (Table 2, entry 2). 4-Chloro-2-methylpyrimidine substituted by phenyl groups with electron withdrawing NO<sub>2</sub> substituents were also tolerated, leading to the

desired products **3c-d** (Table 2, entries 3-4). Conversely, 4-chloro-2-methylpyrimidine substituted by piperazine groups, resulted in decreased yields (Table 2, entries 5-7), especially for 2-(4-(6-chloro-2-methylpyrimidin-4-yl)piperazin-1-yl)ethan-1-ol (Table 2, entry 7).

**Table 3.** Preparation of *N*-pyrimidin[1,3,4]oxadiazoles **3h-w**.<sup>a</sup>



<sup>a</sup> Reagents and conditions: **1** (0.2 mmol), **2** (0.3 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), xantphos (0.04 mmol), NaO<sup>t</sup>Bu (0.3 mmol), DMF (2 mL), 36 h.

Next, we extended the Pd-catalyzed heteroarylamination to 1,3,4-oxadiazol-2-amines bearing various substituents at the 5-position (Table 3). The reaction conditions were compatible with phenyl (**3h**), benzyl (**3q**) and electron-donating substituents at the aryl moieties, such as methyl and methoxy groups (**3k-l**). In addition to electron-donating substitution, halogens such as F were also tolerated (**3m**). However, aryl groups with an electron deficient substituent led to a modest yield (**3n**). Additionally, aliphatic groups afforded the corresponding products with reduced yields (**3o-p**). On the other hand, and similar to the results observed in Table 2, 1,3,4-oxadiazol-2-amines bearing phenyl and benzyl groups did not react well with 4-chloro-2-methyl-6-(4-methylpiperazin-1-yl)pyrimidine **1e** and 2-(4-(6-chloro-2-methylpyrimidin-4-yl)piperazin-1-yl)ethan-1-ol **1g**

under these conditions, providing the corresponding products in lower yields (**3t-w**).

**Table 4.** Preparation of *N*-pyrimidin[1,3,4]thiadiazoles **5a-g**.<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%) <sup>b</sup>
1	Cl	COOEt	<b>5a</b>	50
2	Cl	Me	<b>5b</b>	38
3	Cl	<i>i</i> -Pr	<b>5c</b>	35
4	<i>N</i> -methylpiperazine	Ph	<b>5d</b>	41
5	<i>N</i> -methylpiperazine	COOEt	<b>5e</b>	33
6	<i>N</i> -methylpiperazine	Me	<b>5f</b>	25
7	<i>N</i> -methylpiperazine	<i>i</i> -Pr	<b>5g</b>	16

<sup>a</sup> Reagents and conditions: **1** (0.2 mmol), **4** (0.3 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), xantphos (0.04 mmol), NaO<sup>t</sup>Bu (0.3 mmol), DMF (2 mL), 36 h.

<sup>b</sup> Isolated yields.

Finally, this procedure was applied to the preparation of *N*-pyrimidin[1,3,4]thiadiazoles **5**. As shown in Table 4, the Buchwald-Hartwig reaction could be used for the functionalization of 5-substituted 1,3,4-thiadiazol-2-amines by using 4-chloropyrimidine derivative **1** to provide the corresponding *N*-pyrimidin[1,3,4]thiadiazoles. Compared to the synthesis of *N*-pyrimidine[1,3,4]oxadiazoles, the decrease in yield may be due to poisoning of the Pd-catalyst by the S-atom in the 1,3,4-thiadiazole ring, which is consistent with other Buchwald-Hartwig amine arylation reactions with sulfur-containing reagents, using a (NHC)Pd(R-allyl)Cl complex as the catalyst.<sup>28</sup>

## Conclusion

We have successfully developed an efficient Buchwald-type coupling method for the synthesis of novel *N*-pyrimidin[1,3,4]oxadiazoles and *N*-pyrimidin[1,3,4]thiadiazoles using Pd(OAc)<sub>2</sub> as the catalyst and xantphos as the ligand. The method employs readily available reagents and possesses broad scope and good functional group tolerance. Further efforts to utilize these compounds as versatile building blocks for assembling interesting heterocyclic molecules which can be applied in medicinal chemistry research are currently underway in our laboratories.

## Acknowledgments

This project is supported by China Science Foundation (Grant No. 21672043).

## References and notes

- Majumdar, P.; Pati, A.; Patra, M.; Behera, R. K.; Behera, A. K. *Chem. Rev.* **2014**, 114, 2942-2977.
- Hamdy, R.; Ziedan, N. I.; Ali, S.; Bordoni, C.; El-Sadek, M.; Lashin, E.; Brancale, A.; Jones, A. T.; Westwell, A. D. *Bioorg. Med. Chem. Lett.* **2017**, 27, 1037-1040.
- Bajaj, S.; Roy, P. P.; Singh, J. *Anticancer Agents Med. Chem.* **2018**, 17, 1869-1883.
- Aliabadi, A. *Anticancer Agents Med. Chem.* **2016**, 16, 1301-1314.

5. Haider, S.; Alam, M. S.; Hamid, H. *Eur. J. Med. Chem.* **2015**, *92*, 156-177.
6. Ploj, K.; Benthem, L.; Kakol-Palm, D.; Gennemark, P.; Anderesson, L.; Bjursell, M.; Börjesson, J.; Kärrberg, L.; Månsson, M.; Antonsson, M.; Johansson, A.; Iverson, S.; Carlsson, B.; Turnbull, A.; Lindén, D. *Br. J. Pharmacol.* **2016**, *173*, 2739-2751.
7. Johansson, A.; Löfberg, C.; Antonsson, M.; Unge, von. S.; Hayes, M. A.; Judkins, R.; Ploj, K.; Benthem, L.; Lindén, D.; Brodin, P.; Wennerberg, M.; Fredenwall, M.; Li, L.; Persson, J.; Bergman, R.; Pettersen, A.; Gennemark, P.; Hogner, A. *J. Med. Chem.* **2016**, *59*, 2497-2511.
8. Aurelio, L.; Scullino, C. V.; Pitman, M. R.; Sexton, A.; Oliver, V.; Davies, L.; Rebello, R. J.; Furic, L.; Creek, D. J.; Pitson, S. M.; Flynn, B. L. *J. Med. Chem.* **2016**, *59*, 865-984.
9. Niroqi, R.; Mohammed, A. R.; Shinde, A. K.; Gaqqinapally, S. R.; Kancharla, D. M.; Middekadi, V. R.; Boqaraju, N.; Ravella, S. R.; Singh, P.; Birangal, S. R.; Subramanian, R.; Palacharla, R. C.; Benade, V.; Muddana, N.; Jayarajan, P. *J. Med. Chem.* **2018**, *61*, 4993-5008.
10. Yang, M. G.; Dhar, T. G.; Xiao, Z.; Xiao, H. Y.; Duan, J. J.; Jiang, B.; Galella, M. A.; Cunningham, M.; Wang, J.; Habte, S.; Shuster, D.; McIntyre, K. W.; Carman, J.; Holloway, D. A.; Somerville, J. E.; Nadler, S. G.; Salter-Cid, L.; Barrish, J. C.; Weinstein, D. S. *J. Med. Chem.* **2015**, *58*, 4278-4290.
11. Li, W. W.; Wang, X. Y.; Zheng, R. L.; Yan, H. X.; Cao, Z. X.; Zhong, L.; Wang, Z. R.; Ji, P.; Yang, L. L.; Wang, L. J.; Xu, Y.; Liu, J. J.; Yang, J.; Zhang, C. H.; Ma, S.; Feng, S.; Sun, Q. Z.; Wei, Y. Q.; Yang, S. Y. *J. Med. Chem.* **2012**, *55*, 3852-3866.
12. Khalilullah, H.; Ahsan, M. J.; Hedaitullah, M.; Khan, S.; Ahmed, B. *Mini-Rev. Med. Chem.* **2012**, *12*, 789-801.
13. Li, Z.; Zhan, P.; Liu, X. *Mini-Rev. Med. Chem.* **2011**, *11*, 1130-1142.
14. Guin, S.; Ghosh, T.; Rout, S. K.; Banerjee, A.; Patel, B. K. *Org. Lett.* **2011**, *13*, 5976-5979.
15. Hu, Y.; Li, C. Y.; Wang, X. M.; Yang, Y. H.; Zhu, H. L. *Chem. Rev.* **2014**, *114*, 5572-5610.
16. Seio, K.; Kanamori, T.; Masaki, Y. *Tetrahedron Lett.* **2018**, *59*, 1977-1985.
17. Prachayasittikul, S.; Pingaew, R.; Worachartcheewan, A.; Sinthupoom, N.; Prachayasittikul, V.; Ruchirawat, S.; Prachayasittikul, V. *Mini-Rev. Med. Chem.* **2017**, *17*, 869-901.
18. Campiotti, L.; Suter, M. B.; Guasti, L.; Piazza, R.; Gambacorti-Passerini, C.; Grandi, A. M.; Squizzato, A. *Eur. J. Cancer.* **2017**, *77*, 48-56.
19. Palomino, J. C.; Martin, A. *Future Microbiol.* **2016**, *11*, 539-547.
20. Mula, M. *Expert Opin. Pharmacother.* **2018**, *19*, 1867-1874.
21. Leea, Y. H.; Vijia, M.; Leeb, E.; Joa, H.; Yoob, K.; Sima, J.; Leeb, S.; Leec, K.; Leea, H.; Junga, J. K. *Tetrahedron Lett.* **2017**, *58*, 2614-2617.
22. Li, C.; Rosenau, A. *Tetrahedron Lett.* **2009**, *50*, 5888-5893.
23. Stewart, A.O.; Bhatia, P. A.; McCarty, C. M.; Patel, M. V.; Staeger, M. A.; Arendsen, D. L.; Gunawardana, I. W.; Melcher, L. M.; Zhu, G. D.; Boyd, S. A.; Fry, D. G.; Cool, B. L.; Kifle, L.; Lartey, K.; Marsh, K. C.; Kempf-Grote, A. J.; Kilgannon, P.; Wisdom, W.; Meyer, J.; Gallatin, W. M.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 988-1002.
24. Reddy, G. D.; Mo, C. H.; Euy, L. M. *RSC Advances.* **2013**, *3*, 7684-7687.
25. Niu, P. F.; Kang, J. F.; Tian, X. H.; Song, L. N.; Liu, H. X.; Wu, J.; Yu, W. Q.; Chang, J. B. *J. Org. Chem.* **2015**, *80*, 1018-1024.
26. Yang, J.; Li, P. H.; Zhang, Y. C.; Wang, L. *J. Organomet. Chem.* **2014**, *766*, 73-79.
27. Farard, J.; Loge, C.; Pferffer, B.; Lesur, B.; Duflos, M. *Tetrahedron Lett.* **2009**, *50*, 5729-5732.
28. Cawley, M. J.; Cloke, F. G. N.; Fitzmaurice, R. J.; Pearson, S. E.; Scott, J. S.; Caddick, S. *Org. Biomol. Chem.* **2008**, *6*, 2820-2825.

### Supplementary Material

Experimental details and NMR spectra for all reported compounds can be found in supplementary material.

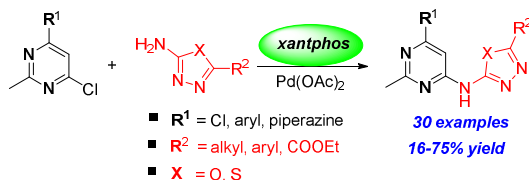
## Graphical Abstract

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