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Palladium-Catalyzed Direct Arylation of Imidazolone *N*-Oxides with Aryl Bromides and Its Application in the Synthesis of GSK2137305

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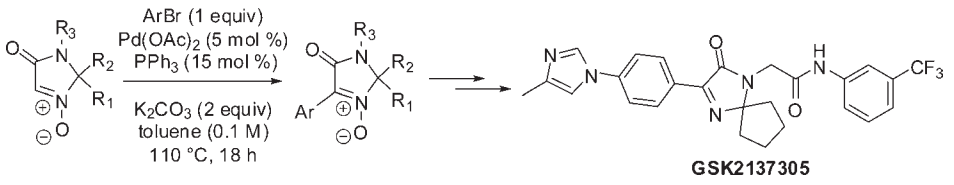
ABSTRACT



The palladium-catalyzed direct arylation of imidazolone *N*-oxides with aryl bromides to afford the corresponding 4-aryl imidazolone *N*-oxides is described. This method has been successfully used for the synthesis of GSK2137305.

The imidazolone skeleton is an important structural motif found in both synthetic and natural products such as GSK2137305 (**1**) and Kottamides A−D (Figure 1).[1] These specific natural product alkaloids exhibit a range of biological activities including anti-inflammatory, antitumor, and antimetabolic properties. Additionally, researchers at GlaxoSmithKline prepared a number of imidazolone-containing derivatives leading to the discovery of the developmental candidate GSK2137305 (**1**), a potent and selective Glycine transporter type-1 (GlyT1) inhibitor for potential treatment of neurological and neuropsychiatric disorders.[2] Merck scientists have also explored the imidazolone core structure and identified many synthetic analogues which show antagonist activities against the glucagon receptor, a biological target for type 2 diabetes.[3] Despite its importance, imidazolones have received less attention regarding their chemical reactivity and properties than other more common heterocycles.

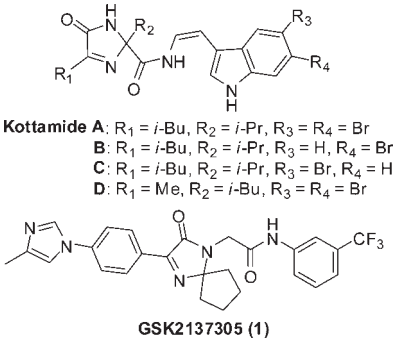


Figure 1. Biologically active imidazolone compounds.

In the past two decades, the field of transition-metal-catalyzed direct arylation of (hetero)arenes has grown rapidly.[4] However, the direct arylation reaction of π-electron-deficient heterocycles including pyridines and pyriding *N*-oxides remained challenging until a few years ago.

(1) Appleton, D. R.; Page, M. J.; Lambert, G.; Berridge, M. V.; Copp, B. R. *J. Org. Chem.* **2002**, *67*, 5402.

(2) (a) Graham, J. P.; Langlade, N.; Northall, J. M.; Roberts, A. J.; Whitehead, A. *J. Org. Process Res. Dev.* **2011**, *15*, 44. (b) Ueda, S.; Su, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 700. (c) Blunt, R.; Cooper, D. G.; Porter, R. A. WO 2009034061, 2009. (d) Ahmad, N. M.; Lai, J. Y. Q.; Andreotti, D. WO 2008092876, 2008. (e) Coulton, S.; Porter, R. A. WO 2008092872, 2008

(3) (a) Demong, D. E.; Miller, M. W.; Dai, X.; Wong, M. K.; Lavey, B. J.; Yu, W.; Zhou, G.; Stamford, A. W.; Kozlowski, J. A.; Greenlee, W. J.; Zhao, H.; Chen, P.; Lin, P.; Dai, P.; Davis, J. L. WO 2011119541, 2011. (b) Stamford, A.; Miller, M. W.; Demong, D. E.; Greenlee, W. J.; Kozlowski, J. A.; Lavey, B. J.; Wong, M. K. C.; Yu, W.; Dai, X.; Yang, D.-Y.; Zhou, G. WO 2010039789, 2010.

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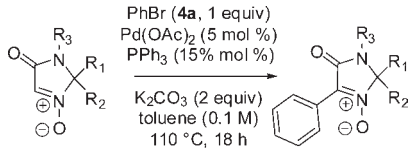
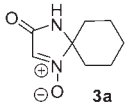
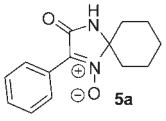
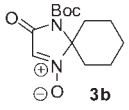
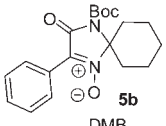
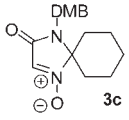
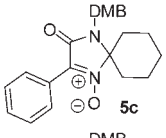
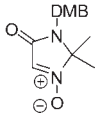
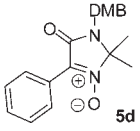
In 2005, Fagnou and co-workers first reported that pyridine *N*-oxides undergo direct ortho arylation in synthetically useful yields.[5] The resulting arylated derivatives were then converted to 2-arylpyridines by hydrogenolysis. Since then the *N*-oxide strategy has been further explored and quickly extended to many other heterocycles.[6,7]

To the best of our knowledge, imidazolone *N*-oxides have not been investigated in the context of metal catalyzed cross-coupling reactions. With our interests in palladium-catalyzed coupling reactions,[8] we selected imidazolone *N*-oxides as substrates and systematically studied their direct arylation reactions. Subsequently, we applied our results to the synthesis of GSK2137305 (**1**).

Table 1. Influence of *N*-Substitition and 2-Substitution



entry	substrate	product	yield[a]
1	 3a	 5a	49%
2	 3b	 5b	88%
3[b]	 3c	 5c	91%
4[b]	 3d	 5d	94%

[a] Isolated yields. [b] DMB = 2,4-dimethoxybenzyl.

In our initial exploration, we used similar palladium-catalyzed direct coupling conditions to those reported by Fagnou et al.[7g] for our imidazolone *N*-oxide substrates; using only 1 equiv of phenyl bromide **4a** in order to achieve an economic and efficient method. The starting imidazolone *N*-oxide substrate **3a** was easily prepared by a reported procedure.[9] Upon treating **3a** with phenyl bromide (**4a**, 1 equiv) in the presence of $Pd(OAc)_2$ (5 mol %), triphenylphosphine (15 mol %), and K_2CO_3 (2 equiv) in toluene, and heating in a sealed tube for 18 h at 110 °C, the desired coupling product **5a** was obtained in reasonable yield (Table 1, entry 1). Upon changing the solvent to dioxane, the yield was only slightly improved from 49% to 53%. With these encouraging results, we decided to mask the NH with Boc and 2,4-dimethoxybenzyl protecting groups[10] to determine the effect on overall reaction yield. As expected, Boc protected imidazolone *N*-oxide **3b**[9] showed a significant increase in yield to 88% (Table 1, entry 2). A drawback for the Boc protecting group is that a minor amount of deprotected product **5a** (6%) was also formed during the reaction. In contrast, the 2,4-dimethoxybenzyl imidazolone *N*-oxide **3c**[11] yielded **5c** in 91% yield without any observed **5a** formation. In addition, we coupled **4a** with 2,4-dimethoxybenzyl imidazolone *N*-oxide **3d** giving the desired product **7** in 94% yield. Based on the similar yields for the dimethyl and spirocyclohexyl analogues, we conclude that substituents at the 2-position on the core ring are too far away from the reactive site at the 4-position to impose any steric effects on the observed reaction yield. Therefore, we selected **3c** as the substrate to explore the scope of reaction and establish a general and practical method for the preparation of 4-substituted imidazolones.

First, we continued to use the current method for the exploration of aryl halides and trifluoromethanesulfonate on the directed arylation. As shown in Table 2, all but phenyl bromide displayed poor reactivity. For example, phenyl iodide gave only a 32% yield (Table 2, entry 1) compared to 91% from phenyl bromide. Phenyl chloride gave the desired product in only a 4% yield with unreacted

(4) For recent reviews on direct arylation, see: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Han, W.; Ofial, A. R. *Synlett* **2011**, 1951. (c) Hirano, K.; Miura, M. *Synlett* **2011**, 294. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (g) Chen, X.; Engle, K.-M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (h) Ackermann, L. *Pure Appl. Chem.* **2009**, *82*, 1403. (i) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (j) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (k) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rew.* **2007**, *36*, 1173. (l) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200.

(5) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(6) For selected reviews containing *N*-oxide substrates, see: (a) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (b) Ackermann, L.; Vicente, R.; Kapai, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35.

(7) For recent examples of palladium-catalyzed direct arylation with *N*-oxide, see: (a) Duric, S.; Tzschucke, C. C. *Org. Lett.* **2011**, *13*, 2310. (b) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430. (c) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180. (d) Schipper, D. J.; Mohamed, E.-S.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977. (e) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155. (f) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357. (g) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Megan, B.-L.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (h) Campeau, L.-C.; Megan, B.-L.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. (i) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (j) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781.

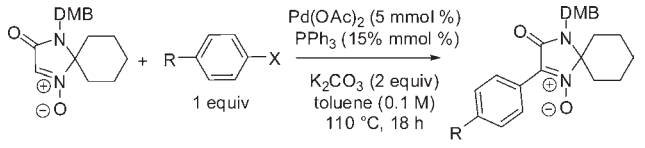
(8) Bliss, B. I.; Ahmed, F.; Iyer, S.; Lin, W.; Walker, J.; Zhao, H. *Tetrahedron Lett.* **2010**, *51*, 3259.

(9) Cheng, S.; Wu, H.; Hu, X. *Synth. Commun.* **2007**, *37*, 297.

(10) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 639–640.

(11) Compound **3c** was prepared according to a similar procedure reported in the reference: Dai, X.; Miller, M. W.; Stamford, A. W. *Org. Lett.* **2010**, *12*, 2718. See Supporting Information for detailed experimental.

Table 2. Reactivities of Phenyl Halides and Triflate



entry	substrate	product[b]	yield[a]
1	**4b** X = I	**5c**	32%
2	**4c** X = Cl	**5c**	4%
3	**4d** X = OTf	**5c**	11%
4	**6a** X = Br	**7**	80%
5	**6b** X = I	**7**	13%
6	**6c** X = Cl	**7**	0%

[a] Isolated yields. [b] DMB = 2,4-dimethoxybenzyl.

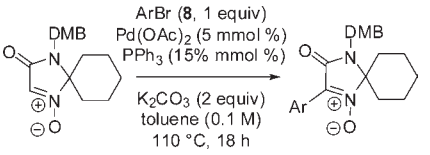
starting materials remaining. When the 4-methoxyphenyl halogen reagents were used, the yields of the coupling reactions were slightly lower than their corresponding phenyl halides. However, the reactivity pattern remained the same: Br > I > Cl. Thus, we focused on aryl bromides for our studies on palladium-catalyzed direct arylation.

A range of substituted phenyl bromides with diverse functional groups including alkyl (ortho, meta, and para), ester, trifluoromethyl, and cyano groups were evaluated, and all afforded the desired products in modest to high yields (Table 3, entries 1–6). Other aryl bromides, in particular 3-pyridyl bromide (**8g**) and imidazole-substituted aryl bromide (**8i**), also gave good isolated yields (entries 7–9). The reaction tolerates both electron-withdrawing and -donating substitution on the aryl bromides. This proves that imidazolone *N*-oxides can undergo palladium-catalyzed direct arylation in synthetically useful yields under current reaction conditions.

Next, we investigated deoxygenation and removal of the 2,4-dimethoxybenzyl group. Although deoxygenation of *N*-heteroarene *N*-oxides has been well documented,[12] there is no available procedure for the conversion of imidazolone *N*-oxides to the corresponding imidazolones from a literature search.

Having successfully demonstrated the direct arylation of the core ring, we now set out to continue the synthetic route toward the synthesis of GSK2137305 (**1**) by *N*-oxide deprotection. Three different deoxygenation reaction conditions are typically employed for a range of heteroarene

Table 3. Reactivities of Aryl Bromides



entry	aryl bromide		product[b]		yield[a]
1	**8a**		**9a**		92%
2	**8b**		**9b**		86%
3	**8c**	R = Me	**9c**		78%
4	**8d**	R = CO_2Et	**9d**		86%
5	**8e**	R = CF_3	**9e**		71%
6	**8f**	R = CN	**9f**		83%
7	**8g**		**9g**		68%
8	**8h**		**9h**		80%
9	**8i**		**9i**		65%

[a] Isolated yields. [b] DMB = 2,4-dimethoxybenzyl.

N-oxides.[7g] These include 10% Pd/C with ammonium formate,[13] Zn dust in aqueous ammonium chloride/THF,[14] and Fe dust in acetic acid.[15] Upon application of these conditions to our imidazolone *N*-oxides, the formation of undesired imidazolidinones occurred as a result of full or partial reduction. We next moved our attention to "non-hydrogen donor"-type deoxygenated reagents such as P(*n*-Bu)$_3$[16] and PCl_3.[17] However, the starting materials

(12) For recent examples on deoxygenation of heteroarene *N*-oxides, see: (a) Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. *J. Org. Chem.* **2011**, *76*, 7842. (b) Mikami, Y.; Noujima, A.; Mitsudome, T.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem.—Eur. J.* **2011**, *17*, 1768. (c) Gowda, N. B.; Rao, G. K.; Ramakrishna, R. A. *Tetrahedron Lett.* **2009**, *51*, 5690. (d) Caliskan, H.; Zaim, O. *Synth. Commun.* **2010**, *40*, 3078. (e) Reis, P. M.; Royo, B. *Tetrahedron Lett.* **2009**, *50*, 949. (f) Fuentes, J. A.; Clarke, M. L. *Synlett* **2008**, 2579. (g) Ponaras, A. A.; Zaim, O. *J. Heterocycl. Chem.* **2007**, *44*, 487. (h) Saini, A.; Kumar, S.; Sandhu, J. S. *Synlett* **2006**, 395.

(13) Balicki, R. *Synthesis* **1989**, 645.

(14) Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997**, 891.

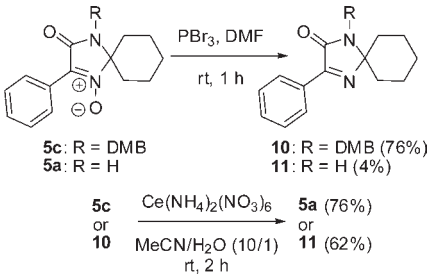
(15) Julemont, F.; deLeval, X.; Michaux, C.; Renard, J.-F.; Winum, J.-Y.; Montero, J.-L.; Damas, J.; Dogne, J.-M.; Pirotte, B. *J. Med. Chem.* **2004**, *47*, 6749.

(16) Cividino, P.; Dheu-Andries, M.-L.; Ou, J.; Milet, A.; Py, S.; Toy, P. H. *Tetrahedron Lett.* **2009**, *51*, 7038.

(17) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872.

still remained and survived these reaction conditions. Eventually we found that PBr_3[18] is a preferred reagent for deoxygenating imidazolone *N*-oxides, as exemplified in Scheme 1. Treatment of **5c** with PBr_3 (10 equiv) in DMF led to deoxygenated compound **10** in 76% yield.[19] In contrast, unprotected **5a** gave the desired product **11** in only 4% yield. As expected, ceric ammonium nitrate (CAN) cleaved the 2,4-dimethoxybenzyl (DMB) protecting group from both amides **5c** and **10** in good yields (Scheme 1).

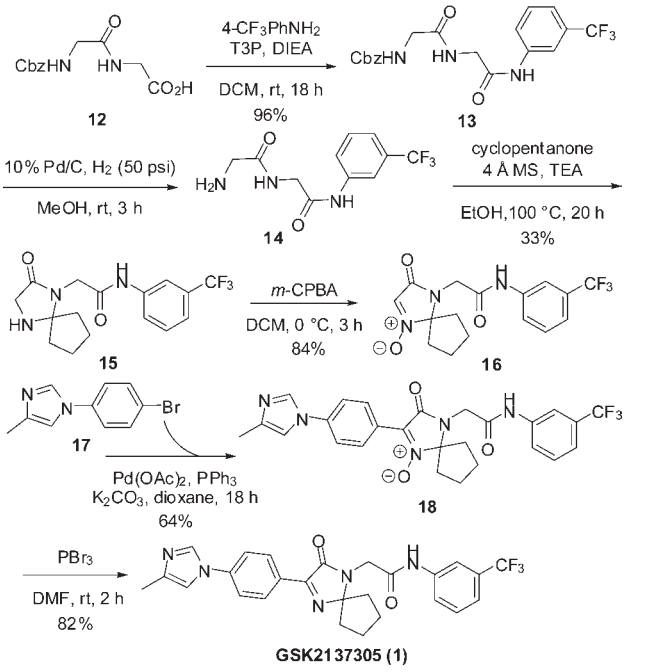
Scheme 1. Deoxygenation and Cleavage of DMB[a]



[a] DMB = 2,4-dimethoxybenzyl.

Finally, we applied our direct arylation method and strategy on the synthesis of GSK2137305 (**1**) as shown in Scheme 2. Commercially available glycylglycinamide **12** was coupled with 4-trifluoroaniline in the presence of propylphosphonic anhydride (T3P) and diisopropylethylamine (DIEA) in anhydrous DCM giving the desired product **13** in 96% isolated yield. After hydrogenolysis of the Cbz protecting group, aminoamide **14** was used directly in the next step to give the cyclized spiro imidazolidinone **15** in 33% yield over two steps. Imidazolone *N*-oxide **16** was obtained by the subsequent *m*-CPBA oxidation of **15**, which was then coupled with aryl bromide **17**[20] using the above established method affording the product **18** in 64% yield. Finally *N*-oxide removal with PBr_3 gave GSK2137305 (**1**) in 82% yield, which demonstrated identical analytical data to those reported.[2a]

Scheme 2. Synthesis of GSK2137305



Notably, the *N*-oxide **16** could be a useful intermediate to access analogues of compound **1** by direct arylations at the 4-position.

In conclusion, we have systematically investigated the direct arylaton of imidazolone *N*-oxides with aryl bromides and their equivalents, catalyzed by palladium, to afford the corresponding 4-aryl imidazolone *N*-oxides. Deoxygenation and cleavage of 2,4-dimethoxybenzyl (DMB) on imidazolones and imidazolone *N*-oxides were also discussed. We have successfully applied our synthetic method and strategy to the preparation of GSK 2137305 (**1**). Further investigation on imidazolone chemistry is in progress.

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Supporting Information Available. Experimental procedures, ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) For examples on deoxygenation of heteroarene *N*-oxides with PBr_3, see: (a) Familoni, O. B.; Klaas, P. J.; Lobb, K. A.; Pakade, V. E.; Kaye, P. T. *Org. Biomol. Chem.* **2006**, *4*, 3960. (b) Bremner, D. H.; Dunn, A. D.; Wilson, K. A.; Sturrock, K. R.; Wishart, G. *Synthesis* **1997**, 949.

(19) We noticed that bromonation of the DMB group occasionally formed during the workup process. We are continuing our efforts for a better deoxygenation method.

(20) Bruton, G.; Cooper, I. R.; Orlek, B. S. WO 2006040192, 2006

The authors declare no competing financial interest.