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Palladium-Catalyzed Sequential C–N/C–O Bond Formations: Synthesis of Oxazole Derivatives from Amides and Ketones

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Supporting Information

ABSTRACT: A highly efficient method for the synthesis of oxazole derivatives from simple amides and ketones has been established via a Pd(II)-catalyzed sp^2 C–H activation pathway in one step. The reaction is supposed to proceed through a C–N bond formation followed by a C–O bond formation closing the ring. Because of the simple and readily available starting materials, easy operation, and high bioactivity of oxazoles, this strategy can be broadly applied to medical chemistry.

The activation of a C–H bond by transition-metal catalysis has received increasing attention recently and constitutes one of the most significant arenas of modern organic chemistry.[1] In this regard, various metals, such as Rh,[2a] Ru,[2b] Fe,[2c] Cu,[2d] Ag,[2e] and Pd[2f] have made tremendous contributions. However, much less work has been reported for the preparation of oxygen-containing heterocycles via palladium-catalyzed C–H activation/C–O cyclization compared with that of C–H activation/C–N cyclization.[3] For example, the Yu group reported the first example for Pd-catalyzed aliphatic alcohol-directed C–H activation/C–O cyclization for the synthesis of dihydrobenzofurans.[3d] Herein, we present a new method for the synthesis of 2,4-disubstituted or 2,4,5-trisubstituted oxazoles using palladium acetate as the catalyst, $K_2S_2O_8$ as the stoichiometric oxidant, and $CuBr_2$ additive as the crucial promoter via Pd-catalyzed sp^2 C–H activation, followed by C–O bond cyclization of the condensation resulting in enamide in one pot.

Oxazoles are one of the common substructures in a wide variety of biologically active compounds, synthetic intermediates, and pharmaceuticals (Figure 1).[4] Therefore, various synthetic methods have been developed for the concise and efficient synthesis of highly substituted oxazole structures.[5] Classical synthetic methods for oxazoles can be typically classified into three aspects: the cyclization of acyclic precursors,[6] oxidation of oxazolines,[7] and the C–C coupling of oxazoles with other reagents.[8] In regard to the annulation of acyclic reaction, however, this methodology suffers from some disadvantages, such as the requirement of Brønsted acid catalysts, Lewis acid reagents, or previously prepared substrates, which limit the overall functional group tolerance of the transformation (Scheme 1 (1)).[9] For example, the Buchwald group reported a method for the cyclization of enamides to oxazoles, which is effective with preparation of enamide and equivalent loading of Cu catalyst (Scheme 1 (2)).[10] Therefore, the direct usage of stable and easily accessible starting materials can serve as a more direct and convenient method to afford oxazoles. In this context, we present a method for the synthesis of oxazole fragments using simple amides and ketones with great selectivity and a broad substrate scope.

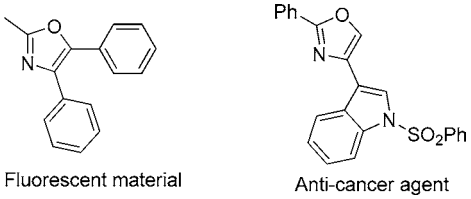
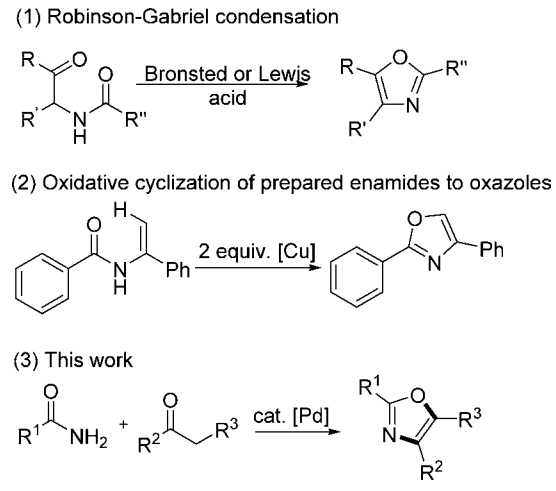


Figure 1. Selected examples for oxazole-containing fluorescent materials and pharmaceutical compounds.

Scheme 1. Synthesis of Oxazoles via Prepared Amides



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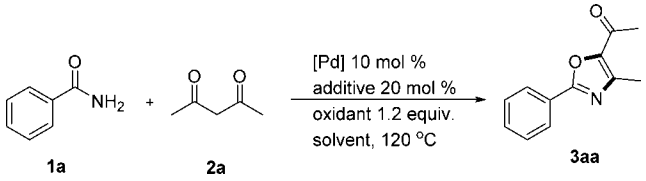
We began our studies by subjecting benzamide (**1a**) and acetyl acetone (**2a**) to a catalytic amount of $PdCl_2$ and 1.2 equiv of copper(II) bromide as an oxidant in DCE at 120 °C for 24 h (Table 1, entry 1). However, most of the **1a** remained,

Table 1. Optimization of Reaction Conditions[a]



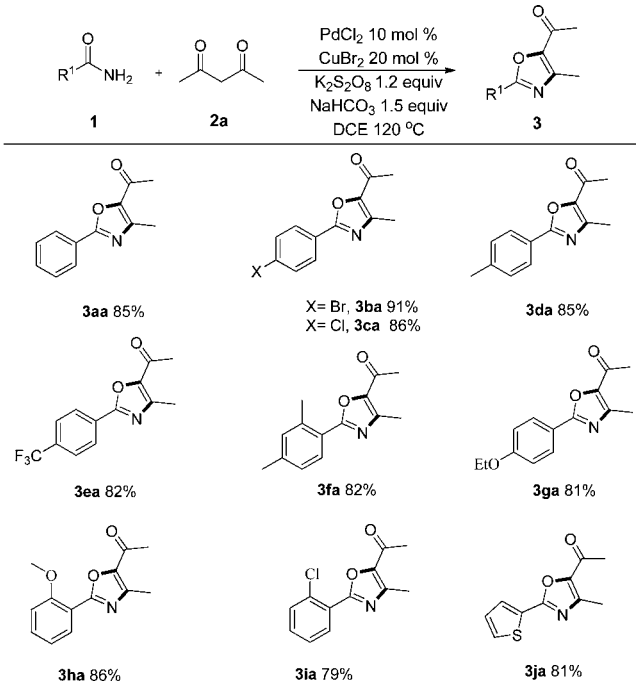
entry[a]	catalyst	additive	oxidant	solvent	yield[b] (%)
1	$PdCl_2$	$CuBr_2$		DCE	10
2	$PdCl_2$	$CuBr_2$	DBTP	DCE	60
3	$PdCl_2$	$CuBr_2$	TBHP	DCE	33
4	$PdCl_2$	$CuBr_2$	$PhI(OAc)_2$	DCE	34
5	$PdCl_2$	$CuBr_2$	DDQ	DCE	trace
6	$PdCl_2$	$CuBr_2$	$K_2S_2O_8$	DCE	76 (73)[c]
7	$PdCl_2$	$CuBr_2$	Ag_2O	DCE	55
8	$PdCl_2$	$CuBr_2$	BQ	DCE	24
9[d]	$PdCl_2$	$CuBr_2$	O_2	DCE	34
10[e]	$PdCl_2$	$CuBr_2$	$K_2S_2O_8$	DCE	12
11	$PdCl_2$	LiBr	$K_2S_2O_8$	DCE	15
12		$CuBr_2$	$K_2S_2O_8$	DCE	trace
13	$PdCl_2$		$K_2S_2O_8$	DCE	13
14[f]	$PdCl_2$	$CuBr_2$	$K_2S_2O_8$	DCE	86 (82)[c]

[a]Reaction conditions: Unless otherwise noted, the reaction was carried out with 0.5 mmol of benzamide and 1.2 equiv of acetyl acetone in solvent (1 mL) at 120 °C for 24 h. [b]Determined by GC−MS based on **1a**. [c]Isolated yield. [d]Reaction was carried at 80 °C. [e]1 mol % $PdCl_2$ was added. [f]0.75 mmol $NaHCO_3$ was added.

and only a trace amount of 2-methyl-3-acetyl-5-phenyloxazole (**3aa**) was detected. Later, extra oxidants such as di-*tert*-butyl peroxide (DBTP) and *tert*-butyl hydroperoxide (TBHP) were used. To our delight, 60% yield and 33% yield of the desired product were obtained, respectively (entries 2 and 3). Further investigation revealed that using $K_2S_2O_8$ as an oxidant gave the best results (entries 2−9). When LiBr was added instead of Cu catalyst, 15% yield of **3aa** was detected (entry 11). However, the reaction still resulted in 13% yield even without $CuBr_2$ (entry 13), and no **3aa** was detected without Pd catalyst (entry 12). Interestingly, upon addition of 1.5 equiv loading of $NaHCO_3$, a slightly better yield was achieved (entry 14).

With the optimal reaction conditions in hand, we subsequently explored the reaction scope. To explore the scope of the oxidative cyclization reaction, we examined the steric and electronic effects of the aryl substituents adjacent to the amide group **1** using 2,4-pentanedione (**2a**) as the model substrate (Table 2). The results indicated that reactions of amides with electron-donating groups, such as methoxy, methyl, and alkyl at the aryl ring, proceeded well with moderate to good yields (**3da**−**3ha**). For example, addition of 4-methylphenylamide in the reaction system led to 85% yield of 4-methyl-5-acetyl-2-(2,4-dimethylphenyl)oxazole (**3da**). Moreover, substituents at different positions of reactions of chloro- and bromo-substituted benzamides with **2a** proceeded well and gave the corresponding oxazole derivatives **3ba**, **3ca**, and **3ia** in 91%, 86%, and 79% yields, respectively. Specifically, the desired product **3ea** was obtained in 82% yield when 4-(trifluoromethyl)benzamide was used as the substrate. Other

Table 2. Pd-Catalyzed Synthesis of Substituted Oxazoles from Amides and 2,4-Pentanedione[a]



[a]Reaction conditions: unless otherwise noted, the reaction was carried out with 0.5 mmol of amide, 10 mol % of $PdCl_2$, 20 mol % of $CuBr_2$, 0.6 mmol of $K_2S_2O_8$, 0.75 mmol of $NaHCO_3$, and 0.6 mmol of acetyl acetone in DCE (1 mL) at 120 °C for 24 h.

aryl-functionalized amides could undergo the transformation smoothly, and thiophene-2-carboxamide could be tolerated in this transformation, generating **3ja** in good yield.

This aerobic Pd-catalyzed oxidative annulation was further expanded to a range of substituted ketones. A series of oxazoles could be obtained in good to excellent yields from different ketones (Table 3). We examined the reaction with a series of 1,3-dicarbonyls, and it was found that various substrates were converted into the corresponding products in moderate to good yields under the optimized conditions. For example, *β*-keto esters with different alkyl substitutes could provide the corresponding products with high yields regardless of the difference of the substituent (**3ab** to **3ad** and **3ai**), which means steric effects and electronic effects had little influence on the reaction. When the substrates were switched to *β*-keto amide (*N*,*N*-diethyl-3-oxobutanamide), the reaction gave the product with a lower yield of 31% (**3aj**). Furthermore, simple ketones could be smoothly transformed into the desired products with good yields (**3ae**−**ah**,**ak**). Specifically, with the substrate benzylacetone, 65% yield of 2,4-diphenyloxazole (**3ah**) was obtained.[11] The present method provides a simple and easily operable protocol for the preparation of 2,4-di or 2,3,5-trisubstituted oxazoles from simple and readily available starting materials.

To further demonstrate the synthetic application of our developed protocol (Scheme 2), benzothioamide was subjected to the system instead of benzamide, and excellent results were obtained under the standard conditions. 1-(4-Methyl-2-phenylthiazol-5-yl)ethan-1-one **4** was obtained in 56% yield. Naturally occurring and synthetic thiazole rings are both biologically active and pharmaceutically useful.[12] In addition, we applied the method to the synthesis of a fluorescent material **5** as the target

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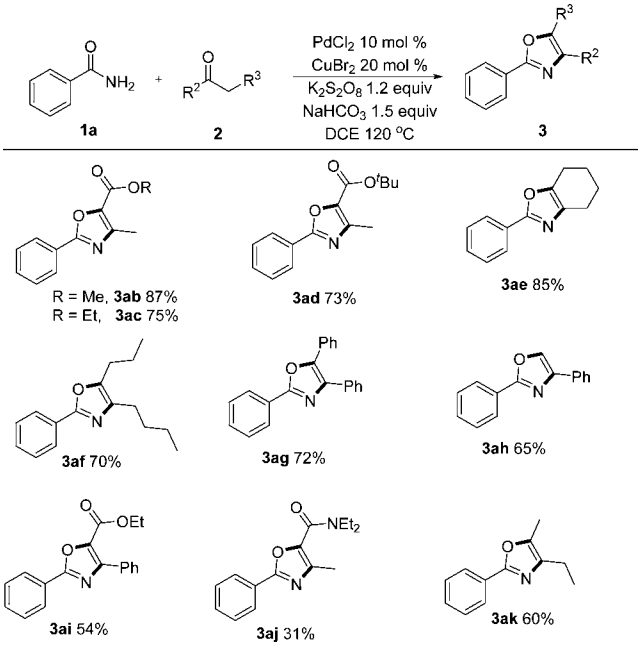
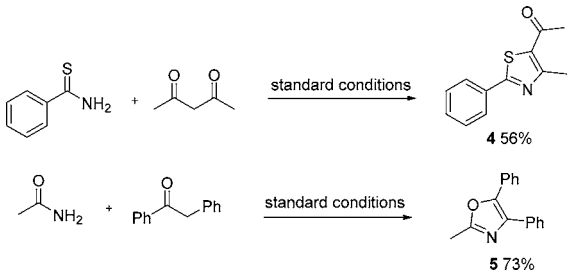
Table 3. Pd-Catalyzed Synthesis of Substituted Oxazoles from Benzamide and Ketones[a]



[a]Reaction conditions: unless otherwise noted, the reaction was carried out with 0.5 mmol of benzylamide, 10 mol % of $PdCl_2$, 20 mol % of $CuBr_2$, 0.6 mmol of $K_2S_2O_8$, 0.75 mmol of $NaHCO_3$, and 0.6 mmol of ketone in DCE (1 mL) at 120 °C for 24 h.

Scheme 2. Application of Our Methodology

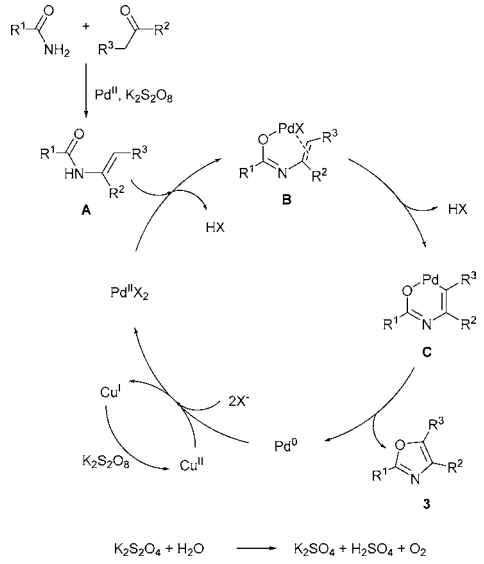


molecule.[13] The reaction of acetamide with 1,2-diphenylethan-1-one gave 73% yield of **5** in one operation.

To gain a deeper insight into the mechanism of this cascade oxidative cyclization, several control experiments were conducted (see the Supporting Information for details).[14] The desired product **3aa** was obtained only in relative low yield when TEMPO or BHT was added.[15] With the addition of $PdCl_2$ and $K_2S_2O_8$, amide and ketones would undergo dehydration followed by imine and enamine isomerization, and an 80% yield of **3aa′** *N*-(4-oxopent-2-en-2-yl)benzamide was obtained.[16] In addition, starting material benzamide totally remained in the absence of Pd or Cu catalyst, which suggested the role of Pd catalyst (as well as shown in Table 1, entries 11 and 13). Moreover, the intermediate **3aa′** was stable in the system without Cu catalyst. However, 40% of intermediate **3aa′** would be recovered to benzamide, and no **3aa** was detected in the standard conditions without Pd catalyst.

On the basis of the experimental results and previous reports,[3d,12−14,17] a plausible mechanism for this transformation is proposed in Scheme 3. First, in the presence of Pd catalyst and $K_2S_2O_8$, amide and ketones would undergo dehydration condensation to form the intermediate **A**. The interaction of **A** and Pd(II) presumably led to a Pd−O adduct, which would coordinate with C−C double bond to give intermediate **B**. Followed by insertion of C−C double bond, metallacycle **C** was obtained by sp^2 C−H activation of intermediate **B**.[3d,18] Subsequent reductive elimination from intermediate **C** resulted in the target product **3aa** and the reduced Pd(0) species was oxidized to Pd(II) to complete the catalytic cycle. Alternatively, it is possible to undergo an electrophilic C−H palladation from B to C.[19]

Scheme 3. Possible Catalytic Cycle



In conclusion, a novel and effective method has been developed to construct highly substituted oxazoles via a palladium-catalyzed dehydration/C−H functionalization/C−O bond-forming reaction between amides and ketones. This process requires only inexpensive reagents and a wide range of functionalities could be tolerated, and it may find applications in natural product synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selective reviews of metal-catalyzed reactions: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335−344. (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023−2035. (c) Xiao, Q.; Zhang, Y.; Wang, J. B. *Acc. Chem. Res.* **2013**, *46*, 236−247. (d) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2018. (e) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (f) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736−1748.

(2) (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013−1025. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (c) Zhao, B. G.; Han, Z. B.; Ding, K. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 4744−4788. (d) Sakakura, A.; Ishihara, K. *Chem. Soc. Rev.* **2011**, *40*, 163−172. (e) Pati, K.; Liu, R.-S. *Chem. Commun.* **2012**, *48*, 6049−6051. (f) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453−3516.

(3) (a) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149−8150. (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790−6791. (c) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411−6413. (d) Wang, X. S.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203−12205. (e) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250−9253.

(4) (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115−2134. (b) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584−605. (c) Palmer, D. C.; J. Wiley & Sons: New York, 2003; Vol. *60*, pp 907−1061. (d) McGovern, S. L.; Caselli, E.; Grigorieff, N.; Shoichet, B. K. *J. Med. Chem.* **2002**, *45*, 1712−1722. (e) Murcia-Soler, M.; Perez-Gimenez, F.; Garcia-March, F. J.; Salabert-Salvador, M. T.; Diaz-Villanueva, W.; Castro-Bleda, M. J.; Villanueva-Pareja, A. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1031−1041.

(5) (a) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389−437. (b) Turchi, I. J. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 32−76. (c) Shi, B.; Blake, A. J.; Lewis, W.; Campbell, I. B.; Judkins, B. D.; Moody, C. J. *J. Org. Chem.* **2010**, *75*, 152−161. (d) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979−981. (e) Xue, W.-J.; Li, Q.; Zhu, Y.-P.; Wang, J.-G.; Wu, A.-X. *Chem. Commun.* **2012**, *48*, 3485−3487.

(6) For selective examples of the cyclization of enamides: (a) Ferreira, P. M. T.; Monteiro, L. S.; Pereira, G. *Eur. J. Org. Chem.* **2008**, *27*, 4676−4683. (b) Ferreira, P. M. T.; Castanheira, E. M. S.; Monteiro, L. S.; Pereira, G.; Vilaça, H. *Tetrahedron.* **2010**, *66*, 8672−8680. (c) Misra, N. C.; Ila, H. *J. Org. Chem.* **2010**, *75*, 5195−5202. (d) Martin, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521−5524. (e) Zhou, H.; Chung, W.-J.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2009**, *45*, 3472−3474.

(7) Meyers, A. I.; Tavares, X. *J. Org. Chem.* **1996**, *61*, 8207-−8215. (b) Huang, Y.; Ni, L. J.; Gan, H. F.; He, Y.; Xu, J.; Wu, X. M.; Yao, H. Q. *Tetrahedron.* **2011**, *67*, 2066−2071.

(8) (a) Alberico, D.; Scott, M. K.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (b) Zhang, M. L.; Zhang, S. H.; Liu, M. C.; Cheng, J. *Chem. Commun.* **2011**, *47*, 11522−11524. (c) Shen, X.-B.; Zhang, Y.; Chen, W.-X.; Xiao, Z.-K.; Hu, T.-T.; Shao, L.-X. *Org. Lett.* **2014**, *16*, 1984−1987.

(9) (a) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167−2168. (b) Nguyen, T. X.; Dakanali, M.; Trzoss, L.; Theodorakis, E. A. *Org. Lett.* **2011**, *13*, 3308−3311.

(10) (a) Cheung, C. W.; Buchwald, S. L. *J. Org. Chem.* **2012**, *77*, 7526−7537. (b) Wendlandt, A. E.; Stahl, S. S. *Org. Biomol. Chem.* **2012**, *10*, 3866−3870.

(11) Xu, Z. J.; Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11367−11370.

(12) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685−714.

(13) Hashimoto, H.; Imamura, K.; Haruta, J.; Wakitani, K. *J. Med. Chem.* **2002**, *45*, 1511−1517.

(14) For details, the results of control experiments are provided in the Supporting Information.

(15) Giglio, B. C.; Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 13320−13322.

(16) (a) Chen, C.; Hong, L.; Xu, Z.-Q.; Liu, L.; Wang, R. *Org. Lett.* **2006**, *8*, 2277−2280. (b) Basa, P. N.; Bhowmick, A.; Horn, L. M.; Sykes, A. G. *Org. Lett.* **2012**, *14*, 2698−2701. (c) Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed.* **1968**, *7*, 7−14.

(17) (a) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717−4720. (b) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141−1143.

(18) (a) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931−2934. (b) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561.

(19) (a) Nishikata, T.; Abela, A. R.; Huang, S. L.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978−4979. (b) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781−784. (c) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586−1587. (d) Zheng, M.; Huang, L.; Wu, W.; Jiang, H. *Org. Lett.* **2013**, *15*, 1838−1841.

NOTE ADDED AFTER ASAP PUBLICATION

The toc/abstract graphic was replaced on November 13, 2014.