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# Synthesis of Benzofuro[3,2-*b*]pyridines via Palladium-Catalyzed Dual C−H Activation of 3-Phenoxypyridine 1-Oxides

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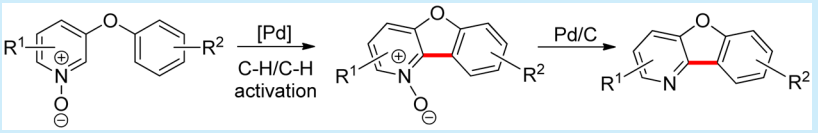
Supporting Information



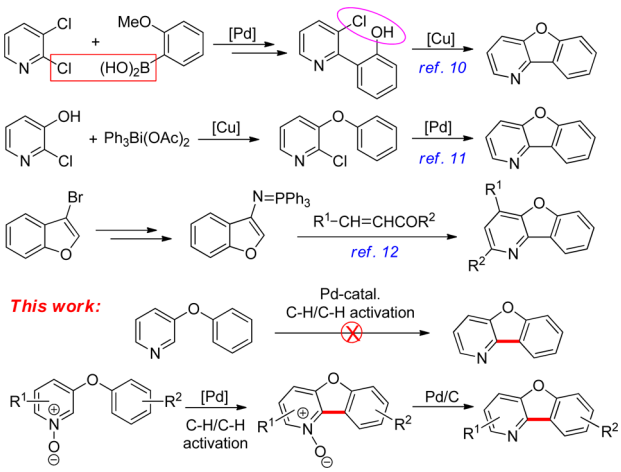

**ABSTRACT:** An efficient oxidative cyclization to straightforward synthesis of benzofuro[3,2-*b*]pyridine 1-oxides with high regioselectivity via Pd-catalyzed intramolecular dual C−H activation was developed. The resulting products could be deoxygenated easily to the corresponding benzofuro[3,2-*b*]pyridines in excellent yields.

Fused benzofuroheterocycles are usually key core motifs in many natural products, pharmaceuticals, and optoelectronically and biologically active compounds.[1] Numerous methods for their synthesis have been reported, including C−O cyclization of 2-halobipheny-ols[2] and 2-arylphenols,[3] C−C cyclization of 1-halo-2-phenoxybenzenes[4] and diaryl ethers,[5] and intramolecular decarboxylative[6] and decarbonylative[7] C−H arylation of 2-phenoxybenzoic acids. Among these methodologies, transition-metal-catalyzed intramolecular dehydrogenative C−C coupling of diphenyl ethers through C−H/C−H double activation represents an extremely attractive approach, which avoids the steps for installation of preactivated functional groups and is highly efficient to target molecules from readily available and environmentally benign starting materials.

Many heterocyclics bearing a benzofuro[3,2-*b*]pyridine moiety have been found with various pharmaceutical and biological activities, such as antiallergic, anti-inflammatory, antimicrobial, and analgesic activity,[8] cyclin-dependent kinase inhibitors, and topoisomerase inhibitors.[9] Therefore, development of efficient methods for their preparation have received great attention. Liu[10] and Li[11] described Pd/Cu-catalyzed preparation of benzofuro[3,2-*b*]pyridine from dichloropyridine or 2-chloro-3-pyridinol, but in limited examples (Scheme 1). In 2010, Funicello reported a multistep synthesis of benzofuro[3,2-*b*]pyridines from 3-bromobenzofuran via (benzofuran-3-yl)iminotriphenylphosphorane through an aza-Wittig−electrocyclization process (Scheme 1).[12] However, the preactivation of pyridine ring with metal-containing functionalities or halides could involve multistep procedures due to its low reactivity and poor regioselectivity, which is neither atom-economical nor environmentally friendly. In addition, the existing methods have limitations as to the functional group tolerance and narrow substrate scope.

Pyridine or other heteroarene *N*-oxides belong to an important class of heteroaromatic motifs with distinctive reactivity. Since 2005, a significant breakthrough was reported by Fagnou in Pd-catalyzed direct regioselective C-2 arylation of pyridine *N*-oxides with aryl bromides.[13] Subsequently, various efforts have been devoted to the functionalization of *N*-oxides, including (hetero)arylation,[14] alkynylation,[14c,15] alkenylation,[14a,b,d,16] alkylation,[14b,c,15,17] amination/amidation,[18] acyloxylation,[19] acylation,[20] sulfonylation,[21] et al.[17c,22] via C−H bond activation. Nonetheless, intramolecular oxidative C−H/C−H cyclization for the construction of pyridine *N*-oxide fused heterocycles has been not addressed so far. In a continuation of our work on the C−H activation and cyclization,[23] herein we wish to illustrate an efficient and site-selective synthesis of benzofuro[3,2-*b*]pyridine *N*-oxides from readily available and stable 3-phenoxypyridine 1-oxides by Pd-catalyzed C−H/C−H oxidative cyclization. The reaction exhibits excellent functional group tolerance and is compatible with electron-donating or

**Scheme 1. Synthesis of Benzofuro[3,2-*b*]pyridines**

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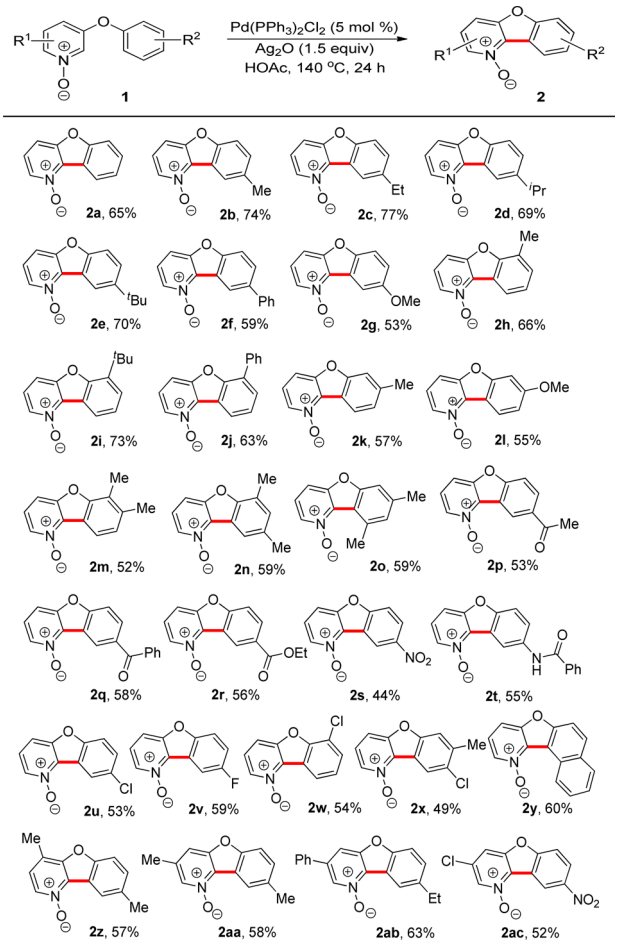
electron-withdrawing groups on the aromatic rings of 3-phenoxypyridine 1-oxides. It is important to note that no reaction was occurred for 3-phenoxypyridine. The obtained benzofuro[3,2-*b*]pyridine *N*-oxides are easy to be transferred into the corresponding benzofuro[3,2-*b*]pyridines by deoxygenation under Pd/C reduction conditions (Scheme 1).

We initially investigate the reaction conditions for the dehydrogenative cyclization of 3-(*p*-tolyloxy)pyridine 1-oxide (**1b**) as model substrate, which was prepared from *p*-cresol and 3-bromopyridine.[24] The results are listed in Table S1 in the Supporting Information. The effect of solvent was examined, and HOAc was found to be the best one among the tested solvents (Table S1, entries 1−11). When the model reaction was performed in the presence of $Pd(OAc)_2$ (5.0 mol %) and HOAc as solvent at 140 °C for 24 h, $Ag_2O$ is the most effective oxidant among AgOAc, $Ag_2CO_3$, $AgNO_3$, $K_2S_2O_8$, BQ (1,4-benzoquinone), $Cu(OA)_2$, and $PhI(OA)_2$ (Table S1, entries 12−18). To our delight, when $Pd(PPh_3)_2Cl_2$ was employed instead of $Pd(OAc)_2$, the desired product **2b** was obtained in 74% yield (Table S1, entry 19). Other Pd catalysts, $PdCl_2$ and $Pd_2(dba)_3$, afforded poor results, and no reaction was observed in the absence of Pd. The optimized reaction conditions consist of $Pd(PPh_3)_2Cl_2$ (5.0 mol %), $Ag_2O$ (1.5 equiv), and HOAc (solvent) at 140 °C for 24 h under air.

With the optimized reaction conditions in hand, the scope of this dual C−H/C−H oxidative cyclization was investigated, as shown in Scheme 2. A variety of 3-phenoxypyridine 1-oxides were subjected to the reaction, and the desired products were obtained in fair to good yields with excellent functional-group tolerance. 3-Phenoxypyridine 1-oxide (**1a**) was underwent the reaction to generate the corresponding product benzofuro[3,2-*b*]pyridine 1-oxide (**2a**) in 65% yield. 3-Phenoxypyridine 1-oxides containing an electron-donating substituent (Me, Et, $^i$Pr, or $^t$Bu) in the *ortho*- or *para*-position of phenyl rings occurred smoothly to give the desired products (**2b−e,h,i**) in 66−77% yields. 3-Phenoxypyridine 1-oxides bearing phenyl in the *ortho*- and *para*-position of the aryl rings gave the products **2f** and **2j** in 59 and 63% yields. 3-Phenoxypyridine 1-oxides with a strong electron-rich or electron-deficient substituent, such as methoxyl, acetyl, benzoyl, ester, nitro, or amide groups on the benzene rings, afforded the moderate yields of the desired products (**2g,l,p−t**), inferior to that of those with non- or alkyl-substituted 3-phenoxypyridine 1-oxides. For example, 3-(4-methoxyphenoxy)pyridine 1-oxide (**1g**) and 3-(4-acetylphenoxy)pyridine 1-oxide (**1p**) resulted in the desired products **2g** and **2p** in 53% yield. For substrates **1k** and **1l** in which methyl and methoxyl groups were located at the *meta*-position possessing two nonequivalent *ortho*-hydrogen on the phenyl ring, interestingly, C−C bond formations occurred at the less sterically hindered site in exclusive regioselectivity (**2k** and **2l**). Dimethyl-substituted products (**2m−o**) were also obtained in moderate yields from the corresponding starting materials (**1m−o**).

Remarkably, the catalytic system could tolerate C−Cl and C−F bonds, which can provide further transformation (**2u−x**). It should be noted that 3-(2-chlorophenoxy)pyridine 1-oxide (**1w**) underwent exclusively oxidative C−H/C−H cyclization rather than oxidative C−H/C−Cl coupling reaction, providing **2w** in 54% yield. Furthermore, when 3-(naphthalen-2-yloxy)-pyridine 1-oxide (**1y**) was employed, the cyclization occurred at α-C−H position, showing excellent regioselectivity and good reactivity (**2y**, 60% yield, the structure of **2y** was confirmed by X-ray diffraction analysis, shown in the Supporting Information). Subsequently, substrates possessing methyl and phenyl in pyridine rings were examined for their reactivity. Gratifyingly, 4-methyl-3-(*p*-tolyloxy)pyridine 1-oxide (**1z**), 3-methyl-5-(*p*-tolyloxy)pyridine 1-oxide (**1aa**), 3-(4-ethylphenoxy)-5-phenylpyridine 1-oxide (**1ab**), and 3-chloro-5-(4-nitrophenoxy)-pyridine 1-oxide (**1ac**) also underwent the reaction to afford the expected products **2z**, **2aa**, **2ab**, and **2ac** in moderate yields. An attempt was made to prepare 3-pyridinyloxypyridine 1-oxides, but failed.

**Scheme 2. Scope of C−H/C−H Oxidative Cyclization of 3-Phenoxypyridine 1-Oxides**[a,b]




[a]Reaction conditions: **1** (0.20 mmol), $Pd(PPh_3)_2Cl_2$ (0.01 mmol), $Ag_2O$ (1.5 equiv), HOAc (0.50 mL), air, 140 °C, 24 h. [b]Isolated yield.

With the obtained benzofuro[3,2-*b*]pyridine 1-oxides in hand, they were easily reduced to the corresponding benzofuro[3,2-*b*]pyridines in the presence of Pd catalyst on charcoal.[25] A variety of benzofuro[3,2-*b*]pyridine 1-oxides with both electron-donating and electron-withdrawing groups on the aromatic rings of substrates underwent the deoxygenation smoothly to generate the corresponding products in good to excellent yields (81−93% yields, Scheme 3), indicating the reduction is not sensitive to the electronic and steric effect of substituted groups. It should be noted that **2s** and **2ac** were reduced into **3s** and **3ac** in high yields through the deoxygenation and the reduction of nitro to amine processes. It provides a practical and alternative route to a variety of benzofuro[3,2-*b*]pyridines.

To gain insight into the reaction mechanism, an H/D exchange experiment was conducted. When 3-([1,1′-biphenyl]-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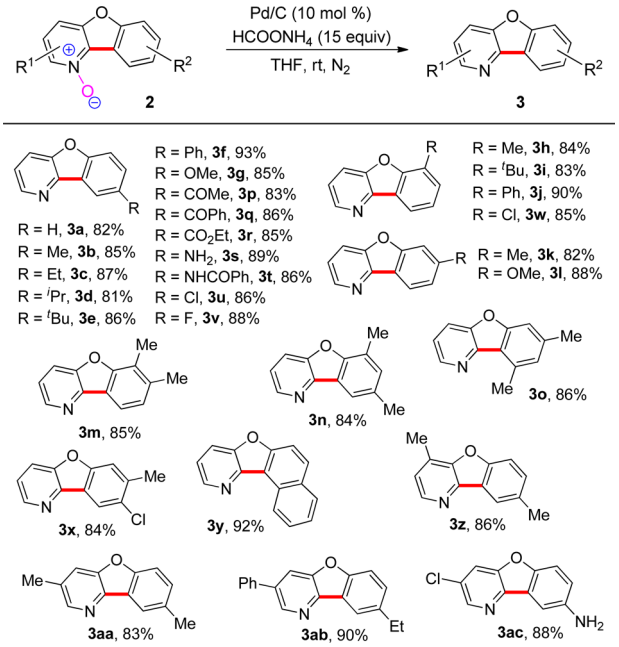
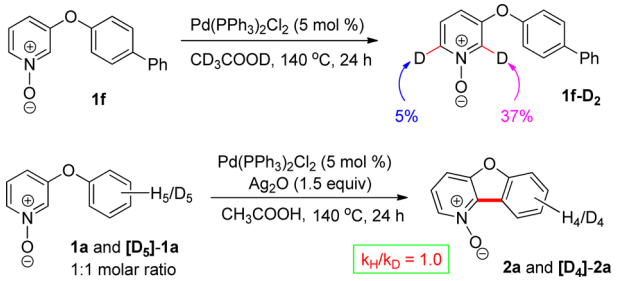
**Scheme 3. Deoxygenation of Benzofuro[3,2-*b*]pyridine *N*-Oxides to Benzofuro[3,2-*b*]pyridine**[a,b]




[a]Reaction conditions: **2** (0.30 mmol), Pd/C (0.03 mmol), THF (1.0 mL), $HCOONH_4$ (15 equiv), $N_2$, rt, 12 h. [b]Isolated yield.

4-yloxy)pyridine 1-oxide (**1f**) was subjected to the dual C−H/C−H activation in $CD_3COOD$ in the presence $Pd(PPh_3)_2Cl_2$ without $Ag_2O$, a significant deuterium incorporation (37%) was observed at the 2-position of pyridine ring, and only 5% deuterium at the 6-position was incorporated (Scheme 4). In

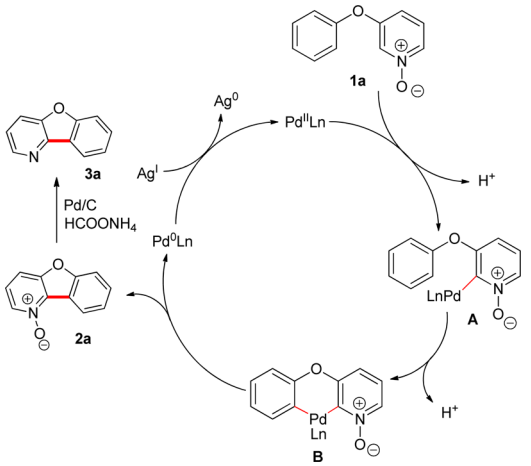
**Scheme 4. H/D Exchange and Kinetic Isotope Effect**




contrast, no deuterium incorporation was found at the phenyl ring. According to this result, the first C−H activation occurred at the more steric demanding C2-position of the pyridine oxide ring. In addition, an intermolecular isotope kinetic experiment was performed. When **1a** and its deuterated analogue [D5]-**1a** in 1:1 molar ratio were subjected to the reaction a kinetic isotope effect ($k_H/k_D$ = 1.0) was obtained (Scheme 4), implicating that C−H bond cleavage of arenes is not the rate-determining step in the reaction.

A possible reaction mechanism is proposed in Scheme 5 on the basis of the above experiments and the previous investigation.[16b,22a] First, $Pd^{II}$ catalyst reacted with 3-phenoxypyridine 1-oxide (**1a**) via C−H bond activation to afford a C2-palladated species **A**, which further underwent an intramolecular cyclization to form bis-arylpalladium species **B** via another C−H bond activation. The obtained **B** underwent reductive elimination to afford the product **2a** and Pd(0)

**Scheme 5. Possible Mechanism for the Reactions**




species, which was oxidized by Ag(I) to regenerate Pd(II) species to complete the catalytic cycle. Finally, **2a** was deoxidized in the presence of Pd/C to give the deoxygenation product **3a**.

In summary, we have developed an efficient, novel, and regioselective oxidative cyclization to straightforward synthesis of benzofuro[3,2-*b*]pyridine 1-oxides via Pd-catalyzed intramolecular dual C−H activation. This catalytic system shows excellent compatibility with numerous synthetically relevant functional groups, thus affording a practical tool for the preparation of a variety of substituted benzofuro[3,2-*b*]pyridine 1-oxides. The resulting products can be deoxygenated easily to the corresponding benzofuro[3,2-*b*]pyridines in excellent yields. Further investigations of the detailed reaction mechanism and the application of this methodology are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Full experimental details and characterization data 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) (a) Oliveira, A. M. A. G.; Raposo, M. M. M.; Oliveira-Campos, A. M. F.; Machado, A. E. H.; Puapairoj, P.; Pedro, M.; Nascimento, M. S. J.; Portela, C.; Afonso, C.; Pinto, M. *Eur. J. Med. Chem.* **2006**, *41*, 367. (b) Teng, H.; Thakur, G. A.; Makriyannis, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5999.

(2) Kawaguchi, K.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2007**, *72*, 5119.

(3) (a) 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. (b) Wei, Y.; Yoshikai, N.



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*Org. Lett.* XXXX, XXX, XXX−XXX

*Org. Lett.* **2011**, *13*, 5504. (c) Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078.
(4) (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739.
(5) (a) Shiotani, A.; Itatani, H. *Angew. Chem., Int. Ed.* **1974**, *13*, 471. (b) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022. (c) Trosien, S.; Böttger, P.; Waldvogel, S. R. *Org. Lett.* **2014**, *16*, 402. (d) Niu, L.; Yang, H.; Jiang, Y.; Fu, H. *Adv. Synth. Catal.* **2013**, *355*, 3625. (e) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 5340. (f) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251. (g) Hagelin, H.; Oslob, J. D.; Åkermark, B. *Chem.—Eur. J.* **1999**, *5*, 2413.
(6) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194.
(7) Maetani, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 2754.
(8) (a) Khan, I. A.; Kulkarni, M. V.; Gopal, M.; Shahabuddin, M. S.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3584. (b) Deady, L. W.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C.; Denny, A. W. *J. Med. Chem.* **1997**, *40*, 2040.
(9) Voigt, B.; Meijer, L.; Lozach, O.; Schächtele, C.; Totzke, F.; Hilgeroth, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 823.
(10) Liu, J.; Fitzgerald, A. E.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2951.
(11) Yue, W. S.; Li, J. J. *Org. Lett.* **2002**, *4*, 2201.
(12) Funicello, M.; Laboragine, V.; Pandolfo, R.; Spagnolo, P. *Synlett* **2010**, 77.
(13) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.
(14) (a) Liu, W.; Li, Y.; Xu, B.; Kuang, C. *Org. Lett.* **2013**, *15*, 2342. (b) Larionov, O. V.; Stephens, D.; Mfuh, A.; Chavez, G. *Org. Lett.* **2014**, *16*, 864. (c) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (e) Liu, W.; Yu, X.; Li, Y.; Kuang, C. *Chem. Commun.* **2014**, *50*, 9291. (f) Gong, X.; Song, G.; Zhang, H.; Li, X. *Org. Lett.* **2011**, *13*, 1766. (g) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822. (h) Wang, Z.; Song, F.; Zhao, Y.; Huang, Y.; Yang, L.; Zhao, D.; Lan, J.; You, J. *Chem.—Eur. J.* **2012**, *18*, 16616. (i) Campeau, L.-C.; Stuart, D.-R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (j) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296.
(15) Jeong, J.; Patel, P.; Hwang, H.; Chang, S. *Org. Lett.* **2014**, *16*, 4598.
(16) (a) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (b) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888.
(17) (a) Ryu, J.; Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3677. (b) Wu, Z.; Pi, C.; Cui, X.; Bai, J.; Wu, Y. *Adv. Synth. Catal.* **2013**, *355*, 1971. (c) Yao, B.; Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H.; Wang, M.-K.; Tang, R.-Y.; Zhang, X.-G.; Deng, C.-L. *Adv. Synth. Catal.* **2012**, *354*, 1890. (d) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. *Chem.—Eur. J.* **2009**, *15*, 333. (e) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616.
(18) (a) Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. *Org. Lett.* **2014**, *16*, 1840. (b) Li, G.; Jia, C.; Sun, K. *Org. Lett.* **2013**, *15*, 5198.
(19) Chen, X.; Zhu, C.; Cui, X.; Wu, Y. *Chem. Commun.* **2013**, *49*, 6900.
(20) Suresh, R.; Kumaran, R. S.; Senthilkumar, V.; Muthusubramanian, S. *RSC Adv.* **2014**, *4*, 31685.
(21) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y. *Org. Lett.* **2013**, *15*, 1270.
(22) (a) Liu, W.; Li, Y.; Wang, Y.; Kuang, C. *Org. Lett.* **2013**, *15*, 4682. (b) Huckins, J. R.; Bercot, E. A.; Thiel, O. R.; Hwang, T.-L.; Bio, M. M. *J. Am. Chem. Soc.* **2013**, *135*, 14492. (c) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Org. Lett.* **2013**, *15*, 792.
(23) Li, C.; Zhang, Y.; Li, P.; Wang, L. *J. Org. Chem.* **2011**, *76*, 4692.
(24) (a) Yang, S.; Wu, C.; Zhou, H.; Yang, Y.; Zhao, Y.; Wang, C.; Yang, W.; Xu, J. *Adv. Synth. Catal.* **2013**, *355*, 53. (b) Stolle, W. T.; Sih, J. C.; Hsi, R. S. P. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 891.
(25) Balicki, R. *Synthesis* **1989**, 645.



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