Organic LETTERS

Letter

pubs.acs.org/OrgLett

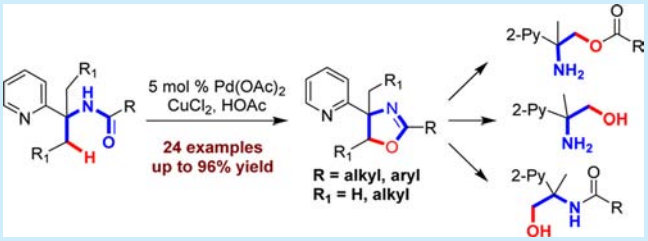
Synthesis of Oxazolines from Amides via Palladium-Catalyzed Functionalization of Unactivated C(sp^3)−H Bond

Bo Li, Si-Qing Wang, Bin Liu, and Bing-Feng Shi*

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

Supporting Information

ABSTRACT: A complementary method that enables the expeditious synthesis of oxazolines from amides via Pd-catalyzed C(sp^3)−H functionalization has been described. Preliminary studies indicate that the reaction might go through a chlorination/nucleophilic cyclization sequence, and the high efficiency of this sequence is enhanced by the *in situ* cyclative capture of the chlorinated intermediate. The resulting oxazolines can be further converted into the corresponding *β*-amino alcohols without chromatography.



Oxazoline is a prevalent structural motif found in natural products, pharmaceuticals, and advanced materials. It has also been widely applied in organic synthesis as versatile synthetic intermediates, protecting groups, chiral auxiliaries, and privileged ligands.[1] In addition, the oxazoline scaffold has been recognized as an effective directing group (DG) in transition-metal-catalyzed C−H activation reactions.[2] Therefore, various strategies have been developed for the synthesis of oxazolines.[3] While these strategies are effective, the development of a new complementary method for the synthesis of oxazolines is still highly desirable.

In the past decade, transition-metal-catalyzed C−H functionalization has emerged as an attractive and powerful strategy for the synthesis of heterocycles.[4] A variety of highly functionalized heterocycles, such as carbazoles, indazoles, indoles, pyrrolidines, indolines, and furans, have been accessed by this process.[4] However, to the best of our knowledge, there are no examples of preparation of oxazolines via C−H activation, due to the low reactivity of C(sp^3)−H bonds[5] and the relative reluctance of C(sp^3)−O reductive elimination from the metal center.[6−8] In our continuing interest in the Pd-catalyzed functionalization of unactivated C(sp^3)−H bonds, we report herein the efficient and highly functional group compatible synthesis of oxazolines via Pd-catalyzed C(sp^3)−H functionalization. Preliminary studies indicate that the reaction might go through a C(sp^3)−H activation/chlorination/nucleophilic cyclization sequence[10,11] and the high efficiency of this sequence is enhanced by the *in situ* cyclative capture of the chlorinated intermediate. Notably, the oxazolines can be transferred to *β*-amino alcohols without chromatography (Scheme 1).

Our synthetic attempts commenced with the conversion of *N*-(1-methyl-1-pyridin-2-yl-ethyl)butyramide **1a** to the corresponding oxazoline **2a** using $Pd(OAc)_2$ as the catalyst and $CuCl_2$ as the chloride source.[12] We were pleased to find that the desired oxazoline **2a** was obtained in 75% yield when the reaction was conducted in toluene under air (Table 1, entry 1). The addition of silver salts as the oxidant inhibited the reaction (entry 2). The reaction was very efficient when 5 equiv of HOAc were used (entry 3, 90% yield). Further investigations

Scheme 1. Oxazoline Synthesis via C(sp^3)−H Activation

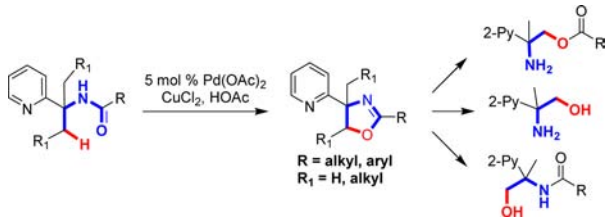
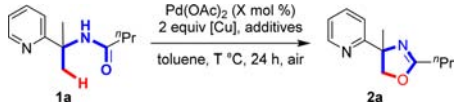


Table 1. Optimization of the Initial Screening Results[a]



entry	$Pd(OAc)_2$ (*X* mol %)	[Cu]	additive (equiv)	temp (°C)	yield (%)[b]
1	10	$CuCl_2$	–	120	75
2	10	$CuCl_2$	Ag_2CO_3 (2)	120	trace
3	10	$CuCl_2$	HOAc (5)	120	90
4	10	–	HOAc (5)	120	0
5	–	$CuCl_2$	HOAc (5)	120	0
6	10	CuCl	HOAc (5)	120	65
7	10	$CuBr_2$	HOAc (5)	120	40
8	10	CuI	HOAc (5)	120	0
9	10	$CuCl_2$	HOAc (5)	100	50
10	**5**	**$CuCl_2$**	**HOAc (5)**	**120**	**85**[c]

[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (*X* mol %), [Cu] (2.0 equiv), additive, in toluene (2 mL) at temp °C for 24 h under air. [b]^{1}H NMR yields using CH_2Br_2 as the internal standard. [c]Isolated yield.

Received: January 16, 2015
Published: February 16, 2015

DOI: 10.1021/acs.orglett.5b00151
Org. Lett. 2015, 17, 1200−1203

revealed that both $Pd(OAc)_2$ and $CuCl_2$ were crucial for the reaction (entries 5 and 6). Different halogen sources, such as CuCl, $CuBr_2$, and CuI, were examined and $CuCl_2$ was optimal (entries 6–8). Finally, we found that 5 mol % $Pd(OAc)_2$ was sufficient to deliver the desired oxazoline **2a** in a comparable yield (entry 10).

With the optimized conditions in hand, we next explored the generality and scope of the process. In general, substrates bearing various side chains were smoothly converted to the corresponding oxazolines in moderate to high yields as shown in Figure 1. A variety of functional groups, such as acetoxyl,

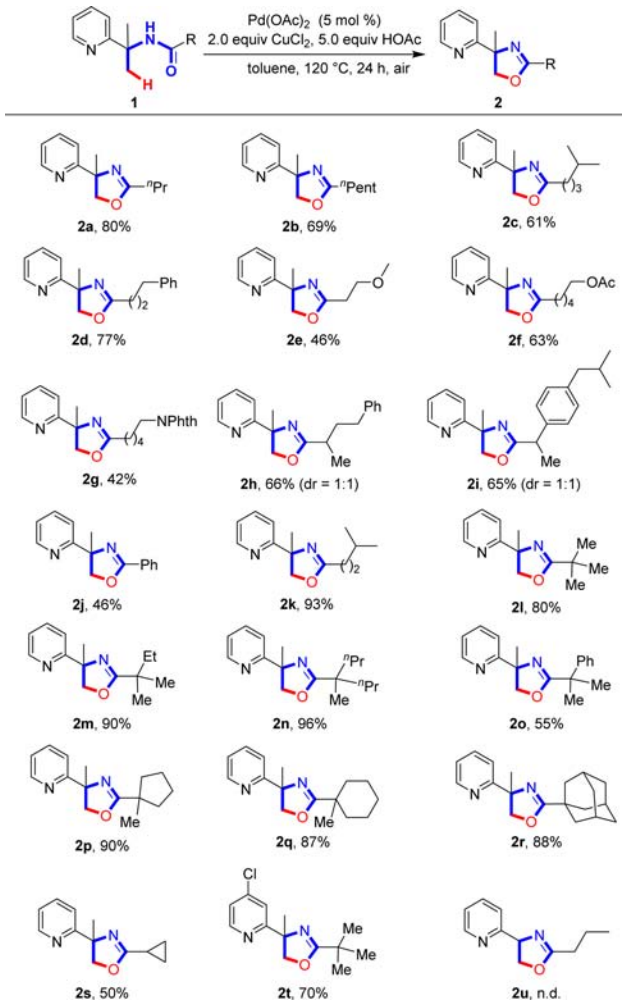
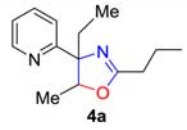
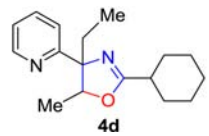


Figure 1. Pd-catalyzed annulation of methyl C(sp^3)–H bonds. Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $CuCl_2$ (0.4 mmol) and HOAc (1.0 mmol) in toluene (2 mL) at 120 °C for 24 h under air. Isolated yields. For structure **2u**, n.d. = not detected.

alkoxy, and Phth-protected amine, were tolerated under the reaction conditions. Generally, amides bearing quaternary carbon centers at the α-position were converted to the corresponding oxazolines (**2l**–**2r**) more efficiently than amides with a linear chain (**2b**–**2j**), indicating that steric congestion around the amide improves the reaction efficiency. When benzamide **1j** and 2-phenyl-isobutyramide **1o** were subjected to the cyclization conditions, reduced yields were obtained, largely due to the side reaction of halogenation on the aromatic ring. Interestingly, the annulation of cyclopropanecarboxamide **1s** gave the oxazoline product **2s** in 50% yield without affecting the highly strained cyclopropane. It is worth noting that the substituent, such as chloro, on the pyridine ring was also tolerated and gave **2t** in moderate yield. The cyclization structure was unambiguously confirmed by X-ray analysis of compound **2r**.[13] A quaternary α-carbon was necessary for the success of the reaction, since no desired product was observed when amide **1u** was used as the substrate.

We were delighted to find that substrates with methylene C(sp^3)–H bonds also reacted efficiently to give the desired oxzalines in good yield (Table 2). Amides with linear chains

Table 2. Pd-Catalyzed Annulation of Methylene C (sp^3)–H Bonds[a]

entry	-R	product	yield (%)
1		 **4a**	69
2		 **4b**	91
3		 **4c**	73[b]
4		 **4d**	56[c]

[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $CuCl_2$ (0.4 mmol), and HOAc (1.0 mmol) in toluene (2 mL) at 120 °C for 24 h under air. Isolated yields. [b]2 mL of toluene. [c]2 mL of toluene, 32 h.

and cyclic rings were all found to be suitable. Consistent with our previous observations, the reactivity is enhanced if sterically demanding substrates are used (entry 2, pivalamide **4b**, 91% yield).

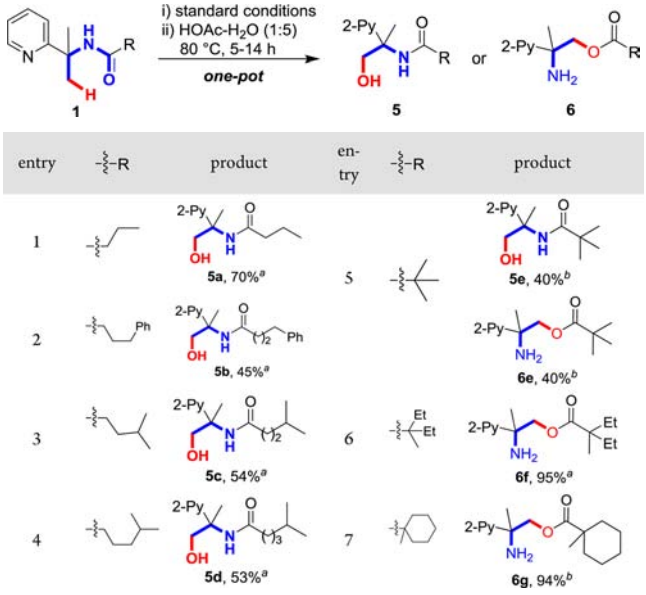
Finally, a one-pot Pd-catalyzed annulation/hydrolysis sequence was established for the synthesis of 2-hydroxy aminoacyls **5** and 2-aminoethyl acyloxys **6** from the corresponding amides **1**. As shown in Table 3, amides **1** reacted under the standard conditions followed by hydrolysis with acetic acid, to give the protected β-amino alcohols **5** or **6** in moderate to high yields. It is worth noting that the hydrolysis of amides with linear aliphatic chains provided 2-hydroxy aminoacyls **5** exclusively in reduced yields (45%–70% yield), while the hydrolysis of the amides with bulky quaternary carbon centers at the α-position proceeded more efficiently to give 2-aminoethyl acyloxys **6** in high yields (**6f**, 95%; **6g**, 94%). These results indicated that steric factor has significant influence on the type of products and reaction efficiency.

To further demonstrate the synthetic versatility of our protocol, we successfully realized the conversion of amide **1a** into the corresponding β-amino alcohol **7** without chromatography [eq 1]. The resulting β-amino alcohol can act as a versatile building block for further transformation.

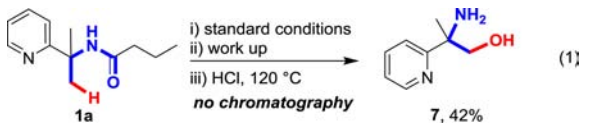
To gain greater insight into the mechanism of the annulation reactions, preliminary mechanistic studies were also conducted.

DOI: 10.1021/acs.orglett.5b00151
Org. Lett. 2015, 17, 1200–1203

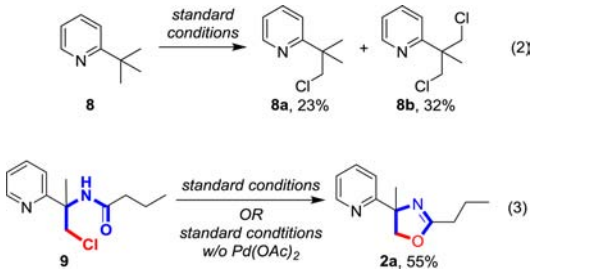
Table 3. One-Pot Synthesis of 2-Hydroxy Aminoacyls and 2-Aminoethyl Acyloxys



[a]5 h. [b]14 h.



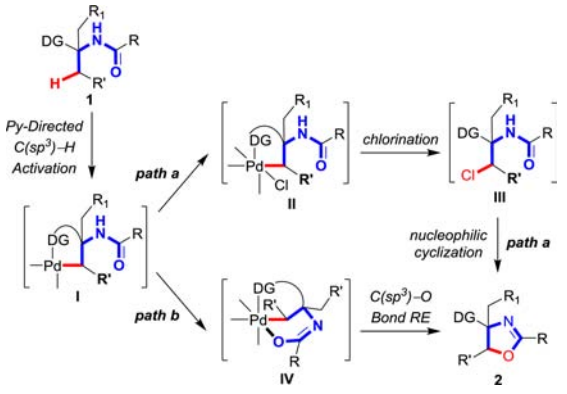
First, 2-(*tert*-butyl)pyridine **8** was subjected to the standard reaction conditions, and chlorinated products **8a** and **8b** were obtained [eq 2].[11d] Second, the chlorinated product *N*-(1-chloro-2-(pyridin-2-yl)propan-2-yl)butyramide **9** can be converted to oxazoline **2a** under the standard reaction conditions [eq 3].



Based on these observations, a C(sp^3)−H activation/chlorination/cyclization sequence pathway is proposed (Scheme 2, path a). First, pyridyl-directed C(sp^3)−H activation gives palladacyle **I**, which undergoes oxidative addition with $CuCl_2$ to give high-valent Pd(IV) intermediate **II**. Reductive elimination affords the chlorinated product **III**,[12] which undergoes nucleophilic cyclization to generate oxazoline **2**. The high efficiency of the whole sequence (up to 96% yield) and the relatively low reactivity of the chlorination of **8** partially indicate that the *in situ* cyclative capture of the chlorinated intermediate can facilitate the sequence.[15] It should be noted that a mechanism involving the intramolecular C(sp^3)−O reductive elimination[6] could not be completely excluded at this stage (Scheme 2, path b).

In conclusion, we have developed a complementary strategy to enable the expeditious synthesis of oxazolines via Pd-catalyzed C(sp^3)−H functionalization. The resulting oxazolines can be further converted into the corresponding *β*-amino alcohols without chromatography. Preliminary studies indicate the reaction might go through a chlorinated intermediate and the high efficiency of this sequence is enhanced by the *in situ* cyclative capture of this intermediate.

Scheme 2. Plausible Mechanism



■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data for all new compounds, and X-ray for **2r**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bfshi@zju.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Basic Research Program of China (2015CB856600), the NSFC (21422206, 21272206), and Zhejiang Provincial NSFC (LZ12B02001) is gratefully acknowledged.

■ REFERENCES

(1) (a) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (c) Gomez, M.; Muller, G.; Rocamora, M. *Coord. Chem. Rev.* **1999**, *193*, 769. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (e) Liao, S.; Sun, X. L.; Tang, Y. *Acc. Chem. Res.* **2014**, *47*, 2260.

(2) For an early example, see: Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112.

(3) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483.

(4) For selected reviews, see: (a) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* DOI: 10.1021/cr500410y. (b) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012**, *44*, 1778. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (c) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874.

(5) For selected reviews on C(sp^3)−H activation, see: (a) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (b) Zhang, Q.; Chen, K.; Shi, B.-F. *Synlett* **2014**, *25*, 1941. (c) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (d) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (e) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (f) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (g) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (h) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (i) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605.

DOI: 10.1021/acs.orglett.5b00151
Org. Lett. 2015, 17, 1200−1203

(6) For selected examples of heterocycle synthesis via intramolecular C(sp^2)−O formation, see: (a) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. (b) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203. (c) 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. (d) Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078. (e) Zhao, J.; Zhang, Q.; Liu, L.; He, Y.; Li, J.; Li, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 5362. (f) Gallardo-Donaire, J.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 9350. For a review, see: (g) Liu, B.; Shi, B.-F. *Tetrahedron Lett.* **2015**, *56*, 15 and references therein.

(7) For seminal examples of Pt(II)-catalyzed lactone synthesis via intramolecular C(sp^3)−O formation, see: (a) Kao, L.-C.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1242. (b) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149.

(8) For selected examples of intermolecular oxygenation of unactivated C(sp^3)−H, see: (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (b) Ren, Z.; Mo, F.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 16991. (c) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (d) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724. (e) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712. (f) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. (g) Zhou, L.; Lu, W. *Org. Lett.* **2014**, *16*, 508.

(9) (a) Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.-J.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. (b) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. (c) Zhang, Q.; Yin, X.-S.; Zhao, S.; Fang, S.-L.; Shi, B.-F. *Chem. Commun.* **2014**, *50*, 8353. (d) Chen, K.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 11950. (e) Chen, K.; Zhang, S.-Q.; Xu, J.-W.; Hu, F.; Shi, B.-F. *Chem. Commun.* **2014**, *50*, 13924.

(10) For an example of synthesis of *β*-lactam via a C(sp^3)−H chlorination−amination sequence, see: Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058.

(11) Pd-catalyzed halogenation of unactivated C(sp^3)−H is challenging, and few examples have been reported. For iodination, see: (a) Reference 2a. (b) Giri, R.; Wasa, M.; Brazzano, S. P.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 5685. For a recent example of bromination and chlorination, see: (c) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Shankar, M.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 5258. For an isolated example, see: (d) Stowers, K. J.; Kubota, A.; Sanford, M. S. *Chem. Sci.* **2012**, *3*, 3192.

(12) For early examples of Pd-catalyzed C−X bond formation with CuX_2 as oxidants and a chloride source, see: (a) Zhu, G.; Lu, X. *J. Organomet. Chem.* **1996**, *508*, 83. (b) El-Qisairi, A. K.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439. (c) Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, *45*, 1785. (d) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618.

(13) CCDC 1040923 (**2r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) For early examples of using pyridyl as a DG for C(sp^3)−H activation, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (c) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (d) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (e) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634.

(15) The nucleophilic cyclization of the chlorinated intermediate is very fast, and efforts to capture this intermediate were unsuccessful.

DOI: 10.1021/acs.orglett.5b00151
Org. Lett. 2015, 17, 1200−1203