Organic LETTERS

Letter

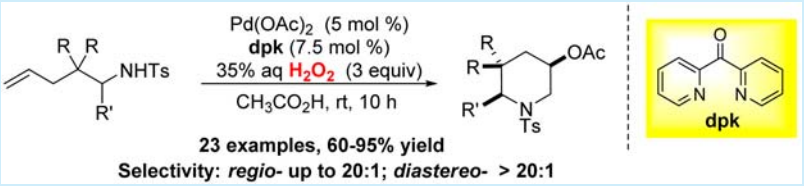
pubs.acs.org/OrgLett

Palladium-Catalyzed Intramolecular Aminoacetoxylation of Unactivated Alkenes with Hydrogen Peroxide as Oxidant

Haitao Zhu, Pinhong Chen, and Guosheng Liu*

State Key Laboratory of Organometallics Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, China 200032

Supporting Information

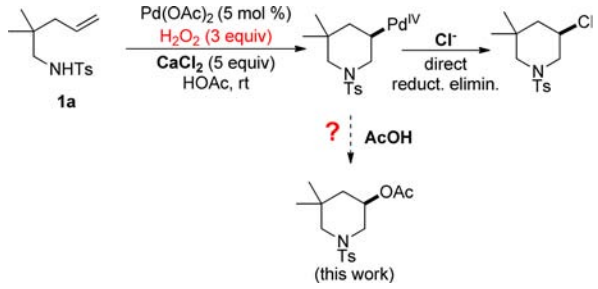


ABSTRACT: A palladium-catalyzed intramolecular aminoacetoxylation of unactivated alkenes was developed in which H_2O_2 was used as the sole oxidant. A variety of 3-acetoxylated piperidines were obtained in good yields with good to excellent regio- and diastereoselectivities. Mechanistic study revealed that the addition of di(2-pyridyl) ketone (dpk) ligand was crucial to promote the oxidative cleavage of the C−Pd(II) bond by H_2O_2 to give the C−OAc bond.

Oxygenated piperidine has been identified as an essential moiety in bioactive natural products and biologically active molecules such as veratramine, (+)-febrifugine, and (−)-cassine.[1] The exploration of efficient syntheses of piperidines has received much attention.[2] Among the syntheses, palladium-catalyzed amination of alkenes presented an efficient strategy for the construction of these heterocycles.[3] Recently, Sorensen,[4a] Stahl,[4b] Sanford,[4c] Muñiz,[4d−f] Michael,[4g] and our group[4h] independently discovered the palladium-catalyzed aminooxygenation of alkenes[4] in which $PhI(OAc)_2$ and NFSI were used as strong oxidants to cleavage sp^3 C−Pd bond via a high-valent palladium intermediate. However, these reactions generally undergo 5-*exo* cyclization to yield a single product or a mixture of 5- and 6-ring isomers.[4a,d−g,i] When $PhI(OAc)_2$ was employed as the oxidant, importantly, the aminoacetoxylation reaction of alkenes also occurred in the absence of palladium catalyst but with a slow reaction rate,[3a] which should impede the enantioselective reaction. Furthermore, employment of these strong oxidants often produces a large amount of byproducts.

Recently, the oxidative transformation with green oxidant, such as dioxygen or hydrogen peroxide, is in high demand and has become an important new trend in organic chemistry.[5] Meanwhile, our recent study revealed that H_2O_2 can be used as the sole oxidant to achieve intramolecular aminochlorination of alkenes with palladium catalyst (Scheme 1),[6a] in which a high-valent palladium was involved as the key intermediate to generate the C−Cl bond and the oxidation of Pd^{II} to Pd^{IV} by H_2O_2 contributed to the turnover-determining step.[6a,c] For our long-term goal on the enantioselective transformation, however, the strong coordination ability of chloride toward the palladium center should compete with chiral ligand, which also impedes the potential asymmetric reaction.[7] We thought that exploration of the cyclization reaction in the absence of halides could be a precondition for future asymmetric study. Inspired by our previous aminochlorination[6a] and amino-oxygenation reactions,[4h] we speculated that when substrate **1a** was treated under standard aminochlorination conditions but without $CaCl_2$ the alkyl-Pd^{IV} intermediate might react with acetate to deliver 3-acetoxylated piperidine products. Herein, we report a highly selective palladium-catalyzed intramolecular aminoacetoxylation of unactivated alkenes under very mild reaction condition, in which hydrogen peroxide was used as a green oxidant (Scheme 1). Various 3-acetoxylated piperidines were obtained in high yields with excellent regio- and diastereoselectivity.

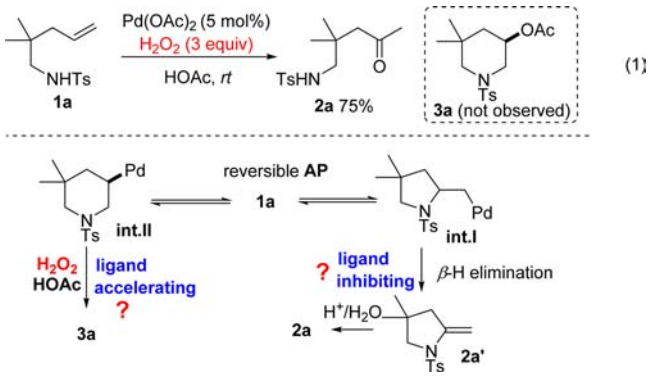
Scheme 1. Pd-Catalyzed Oxidative Amination of Alkenes



To test the above hypothesis, substrate **1a** was treated by palladium catalyst in the presence of H_2O_2. Unfortunately, the reaction failed to give cyclization product **3a** but instead Wacker oxidation product **2a** in 75% yield (eq 1). Our recent results revealed that product **2a** was derived from a sequential intramolecular Wacker oxidation and hydrolysis of enamide **2a′**

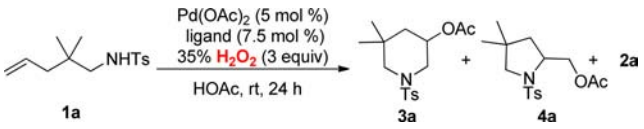
Received: February 5, 2015
Published: March 5, 2015

DOI: 10.1021/acs.orglett.5b00373
Org. Lett. 2015, 17, 1485−1488



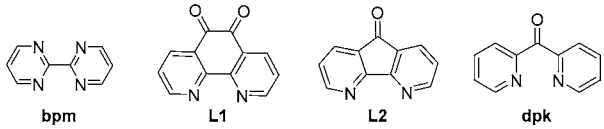
in the acidic solution.[8] In this way, the reaction of **1a** could undergo 5-*exo* aminopalladation to deliver palladium complex **int-I**, which proceeded via β-H elimination in the absence of Cl^-.[7a−c] During our previous study, oxidation of alkyl-Pd(II) by H_2O_2 contributes the turnover-limiting step. Thus, how to accelerate oxidation or inhibit β-H elimination of the alkyl-Pd(II) complex is crucial for the desired aminoacetoxylation reaction. Beside halides, Lu and co-workers demonstrated that bis-nitrogen ligand could also suppress β-H elimination of palladium complex.[9] Thus, a series of bidentate nitrogen ligands were screened. As shown in Table 1, to our delight, when bipyridine (bpy) was employed, the reaction did give **3a** as a major product in 30% yield, along with a trace amount of 5-*exo* cyclization product **3a** with 13:1 ratio of regioselectivity. However, a significant amount of Wacker oxidation product **2a** still existed (entry 1). Other bpy-type ligands were also proven to be less effective (entries 2−4). Furthermore, 1,10-phenanthroline and related ligands were also surveyed to give similar reactivity and selectivity (entries 5−9). Excitingly, we found that 2,2′-bipyrimidine (bpm) exhibited good reactivity to provide **3a** in 73% yield with 5:1 regioselectivity, and only a trace **2a** was observed (entry 10). Furthermore, when electron-deficient bidentate nitrogen ligands **L1**−**L2** were employed, product **3a** was given in good yields and selectivities (entries 11−12). Finally, dipyridinyl ketone (dpk) showed excellent selectivity to give single product **3a** in 93% yield (entry 13). Notably, the reaction with dpk ligand exhibited a faster rate than other ligands.

Table 1. Screening of Ligands[a]



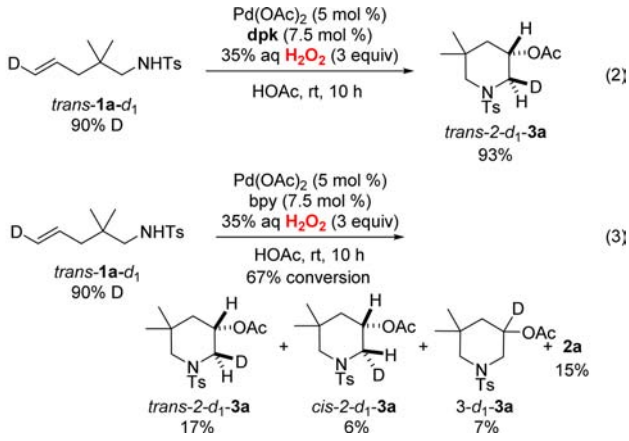
entry	ligand	conv (%)	yield[b] (%) 3a(3a:4a)[c]	2a
1	bpy	70	30 (13:1)[b]	15
2	4,4′-Me-bpy	64	32 (10:1)	24
3	4,4′-^{t}Bu-bpy	65	22 (11:1)	35
4	6,6′-Me-bpy	5	<5	<5
5	phen	50	15 (4:1)	20
6	4,7-Me-phen	40	18 (5:1)	13
7	4,7-Ph-phen	15	<5	<5
8	2,9-Me-phen	38	10	14
9	4,7-Ph-2,9-Me-phen	5	<5	<5
10	bpm	100	73 (5:1)	<5
11	**L1**	100	67 (20:1)	<5
12	**L2**	100	74 (11:1)	<5
13[d]	dpk	100	93 (>20:1)	0

[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand (7.5 mol %), and 35% aq H_2O_2 (3 equiv) in HOAc (2 mL) at rt for 24 h. [b]^{1}H NMR yield with trimethoxylbenzene as internal standard. [c]Ratio of **3a**:**4a** in parentheses; [d]12 h. bpy = 2,2′-bipyridine, phen = 1,10-phenanthroline.



With the optimized reaction conditions in hand, the substrate scope was examined (Table 2). First, substrates with various protecting groups on nitrogen were surveyed. Substrates **1a**−**d** with sulfonyl groups were good for the transformation to give *6-endo* products **3a**−**d** in excellent yields and excellent regioselectivities. However, the substrates with a carbonyl group, such as Cbz (**1e**), Boc (**1f**), or urea (**1g**), were ineffective. Then, substrates **1h**−**l** bearing different *gem*-disubstitutions were tested, and the reactions also proceeded smoothly to provide products **3h**−**l** in good to excellent yields and regioselectivities. Compared to monosubstituted alkenes, 1,1-disubstituted alkenes **1m** and **1n** were proven to be excellent substrates to produce **3m** and **3n** with high efficiency. Interestingly, substrate **1o** with one more carbon on the chain was also compatible with the reaction conditions to deliver 7-*endo* and 6-*exo* products **3o** and **3o**′ in good yield, albeit with low regioselectivity (3:1). Furthermore, when a substituent was introduced to the carbon adjacent to nitrogen, the reaction also proceeded very well to produce the desired products **3p**−**v** in good yields and regioselectivities. More importantly, excellent diastereoselectivity was observed in all these reactions. The configuration of *cis*-product **3q** was determined by X-ray analysis (Figure 1).

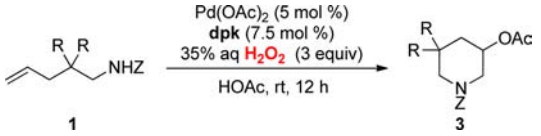
To gain more insight into the mechanism, deuterium-labeled substrate *trans*-**1a**-d_1 was subjected to the standard reaction conditions. A single isomer *trans*-2-d_1-**3a** was obtained, which is similar to the previous aminochlorination reaction (eq 2).



Thus, we thought that the reaction also involves a reversible aminopalladation in the catalytic reaction to generate alkyl-Pd intermediates **C** (*6-endo*) and **E** (*5-exo*), and the reaction underwent a *trans*-aminopalladation pathway under the acidic reaction conditions. For the predominant formation of *6-endo* cyclization product **3a**, a possible reason is that the oxidation of alkyl-Pd(II) by H_2O_2 is the turnover-determining oxidation step, and the more electron-rich complex **C** presented a faster

DOI: 10.1021/acs.orglett.5b00373
Org. Lett. 2015, 17, 1485−1488

Table 2. Pd-Catalyzed Aminoacetoxylation of Alkenes[a]



entry	alkene	product	yield (%)[b]
1	**1a** Z = Ts	**3a**	93% (>20:1)
2[c]	**1b** Z = *p*-Ns	**3b**	95% (>20:1)
3[c]	**1c** Z = *o*-Ns	**3c**	90% (>20:1)
4	**1d** Z = SO_2Ph	**3d**	91% (>20:1)
5	**1e** Z = Cbz	**3e**	0
6	**1f** Z = Boc	**3f**	0
7	**1g** Z = $CONMe_2$	**3g**	0
8	**1h** Z = Ts	**3h**	83% (12:1)
9[c]	**1i** Z = *p*-Ns	**3i**	88% (15:1)
10	**1j** R = Bn	**3j**	94% (>20:1)
11[c]	**1k** R = CO_2Me	**3k**	87% (7:1)
12	**1l** R = H	**3l**	92% (>20:1)
13	**1m** R = Me	**3m**	88% (>20:1)
14	**1n**	**3n**	92% (>20:1)
15[c]	**1o**	**3o** + **3o'**	87% (3:1)
16[d]	**1p** R = Ph	**3p**	60%[e] (>20:1)
17[d]	**1q** R = Me	**3q**	62%[e] (>20:1)
18[d]	**1r** R = Ph	**3r**	82%[e] (11:1)
19[d]	**1s** R = Me	**3s**	85%[e] (12:1)
20[d]	**1t** R = Me	**3t**	86%[e] (10:1)
21	**1u** R = Bu^n	**3u**	85%[e] (7:1)
22	*cis*-**1v**	**3v**	92%[e] (20:1)

[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), dpk (7.5 mol %), and 35% aq H_2O_2 (3 equiv) in HOAc (2 mL) at rt for 12 h. [b]Isolated yield, the ratios of **3**/**4** in parentheses. [c]24 h. [d]48 h. [e]dr > 20:1.

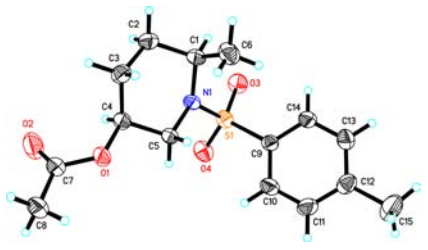
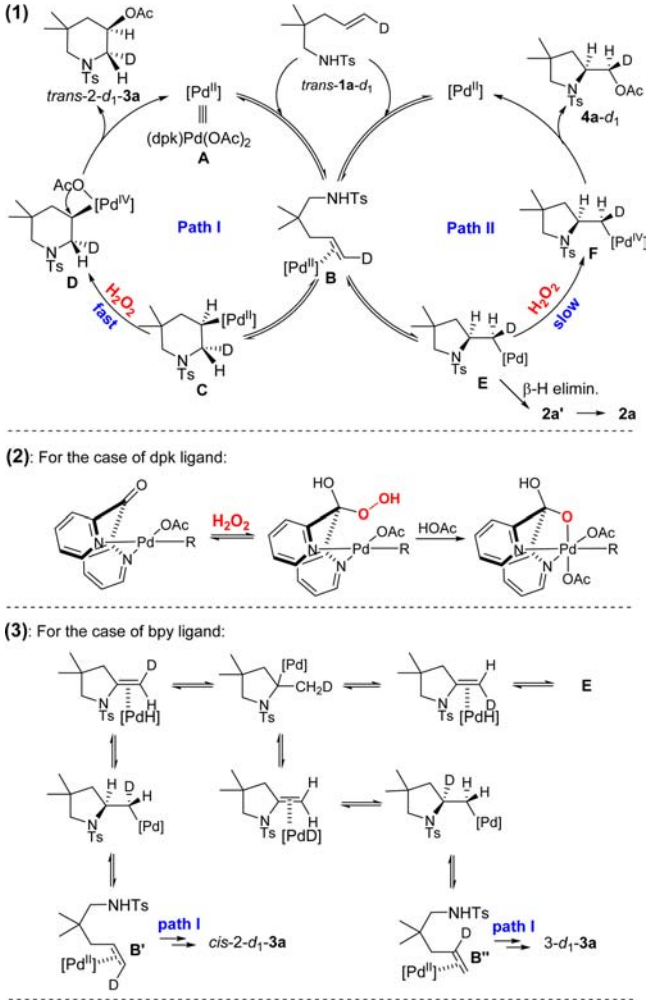


Figure 1. X-ray structure of product **3q**.

rate than that of complex **E**. The following direct reductive elimination on the Pd(IV) center provides the single isomer *trans*-2-d_1-**3a** (Scheme 2 (1)). Notably, ligand dpk plays an important role for the oxidation of alkyl-Pd(II) complex, in which the semiketal derived from the reversible nucleophilic addition of H_2O_2 to carbonyl group of **dpk** could facilitate the Pd(II) oxidation reaction (Scheme 2 (2)).[10]

Scheme 2. Proposed Mechanism



In contrast, when 2,2′-bypyridine was employed as the ligand, the reaction provided a mixture of aminoacetoxylation products in total 30% yield, in which the migration of deuterium atom occurred (eq 3). We reasoned that complex **C** with the bpy ligand exhibited a slower oxidation rate than that of dpk, and then sequential revisible aminopalladation and *β*-H elimination resulted in alkene isomerization to give complexes **B**′ and **B**″, which generated the *cis*-2-d_1-**3a** and 3-d_1-**3a** (Scheme 2 (3)).

In summary, we have developed an efficient palladium-catalyzed intramolecular aminoacetoxylation of unactivated alkenes in which 35% aq H_2O_2 was used as a green and inexpensive oxidant. The use of dpk as the ligand was critical for the success of this transformation, and the competing Wacker oxidation reaction was completely inhibited. A variety of *β*-acetoxylated piperidines were efficiently synthesized with good regio- and diastereoselectivities. Further investigation of asymmetric aminoacetoxylation is in progress.

DOI: 10.1021/acs.orglett.5b00373
Org. Lett. 2015, 17, 1485−1488

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, mechanistic study data, and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gliu@mail.sioc.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Basic Research Program of China (973-2015CB856600), the National Nature Science Foundation of China (Nos. 21225210, 21421091, and 21472217), and Science Technology Commission of the Shanghai Municipality (12ZR1453400). P.H.C. also thanks the Key Laboratory of Functional Small Organic Molecules, Ministry of Education, Jiangxi Normal University (No. KLFS-KF-201402), for the financial support.

■ REFERENCES

(1) (a) Brown, E. G. In *Ring Nitrogen and Key Biomolecules*; Springer: Boston, MA, 1998. (b) Brunhofer, G.; Fallarero, A.; Karlsson, D.; Batista-Gonzalez, A.; Shinde, P.; Gopi, M.; Vuorela, P. *Bioorg. Med. Chem.* **2012**, *20*, 6669. (c) Zhu, S.; Chandrashekar, G.; Meng, L.; Robinson, K.; Chatterji, D. *Bioorg. Med. Chem.* **2012**, *20*, 927. (d) Sriphong, L.; Sotanaphun, U.; Limsirichaikul, S.; Wetwitayaklung, P.; Chaichantipyuth, C.; Pummangura, S. *Planta Med.* **2003**, *69*, 1054.

(2) (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) *Catalytic Heterofunctionalization*; Brunet, J. J., Neibecker, D., Eds.; Wiley-VCH: Weinheim, 2001; pp 91. (c) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (d) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

(3) For some reviews, see: (a) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *111*, 2981. (c) Romero, R. M.; Wöste, T. H.; Muñiz, K. *Chem. Asian. J.* **2014**, *9*, 972. (d) Shimizu, Y.; Kanai, M. *Tetrahedron Lett.* **2014**, *55*, 3727. (e) Chen, P.; Liu, G.; Engle, K. M.; Yu, J.-Q. In *Science of Synthesis: Organometallic Complexes of Palladium*; Stoltz, B. M., Ed.; Thieme: Stuttgart, 2013; Vol. *1*, p 63. (f) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (g) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (h) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (i) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

(4) For selected references on palladium-catalyzed aminooxygenation of alkenes, see: (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. (b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (c) Desai, L.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. (d) Muniz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (e) Hovelmann, C. H.; Streuff, J.; Brelot, L.; Muniz, K. *Chem. Commun.* **2008**, 2334. (f) Muñiz, K.; Iglesias, A.; Fang, Y. *Chem. Commun.* **2009**, 5591. (g) Liskin, D. V.; Sibbald, P. A.; Rosewall, C. F.; Michael, F. E. *J. Org. Chem.* **2010**, *75*, 6294. (h) Chen, S.; Wu, T.; Liu, G.; Zhen, X. *Synlett* **2011**, *7*, 891. (i) Tang, S.; Peng, P.; Wang, Z.-Q.; Tang, B.; Li, J.-H.; Wang, N.-X. *Org. Lett.* **2008**, *9*, 1875.

(5) For some reviews, see: (a) Vedernikov, A. N. *Acc. Chem. Res.* **2012**, *45*, 803. (b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (c) Piera, J.; Backvall, J.-E. *Angew.Chem. Int. Ed.* **2008**, *47*, 3506. (d) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977.

(6) (a) Yin, G.; Wu, T.; Liu, G. *Chem.—Eur. J.* **2012**, *18*, 451. (b) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442. (c) Zhu, H.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 1766.

(7) Excess amounts of halides can suppress β-H elimination of the alkyl-Pd complex. For details, see: (a) Wang, Z.; Zhang, Z.; Lu, X. *Organometallic* **2000**, *19*, 775. (b) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120. (c) Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, 115. (d) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26. For the symmetric chlorination with moderate enantioselectivity, see: (e) Takenaka, K.; Hashimoto, S.; Takizawa, S.; Sasai, H. *Adv. Synth. Catal.* **2011**, *353*, 1067.

(8) Cheng, J.; Chen, P.; Liu, G. *Org. Chem. Front.* **2014**, *1*, 289.

(9) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604. (b) Zhang, Q.; Lu, X. *J. Org. Chem.* **2001**, *66*, 7676.

(10) (a) Oloo, W.; Zavalij, P. Y.; Zhang, J.; Khaskin, E.; Vedernikov, A. N. *J. Am. Chem. Soc.* **2010**, *132*, 14400. (b) Khusnutdinova, J. R.; Newman, L. L.; Vedernikov, A. N. *J. Organomet. Chem.* **2011**, *696*, 3998. (c) Oloo, W. N.; Zavalij, P. Y.; Vedervnikov, A. N. *Organometallics* **2013**, *32*, 5601.

DOI: 10.1021/acs.orglett.5b00373
Org. Lett. 2015, 17, 1485−1488