Organic LETTERS

Letter

pubs.acs.org/OrgLett

Palladium-Catalyzed Benzylic Arylation of Pyridylmethyl Silyl Ethers: One-Pot Synthesis of Aryl(pyridyl)methanols

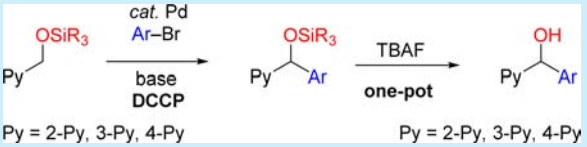
Alexandra R. Rivero,[†,‡] Byeong-Seon Kim,[†] and Patrick J. Walsh*[,†]

[†]Roy and Diana Vagelos Laboratories, Penn/Merck Laboratory for High-Throughput Experimentation, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

[‡]Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain

Supporting Information

ABSTRACT: An efficient palladium-catalyzed direct arylation of pyridylmethyl silyl ethers with aryl bromides is described. A $Pd(OAc)_2$/NIXANTPHOS-based catalyst provides aryl(pyridyl)-methyl alcohol derivatives in good to excellent yields (33 examples, 57−100% yield). This protocol is compatible with different silyl ether protecting groups, affording either the protected or the free alcohols in an effective one-pot process. The scalability of the reaction is demonstrated.



Nitrogen heterocycles are among the most widespread structural components of pharmaceuticals.[1] Among these, pyridines are frequent subunits of medicinally relevant molecules and materials.[1g−n] Specifically, the aryl(pyridyl)-methanol core is commonly found in drug candidates, either as the free alcohol or ether (Figure 1).[2]

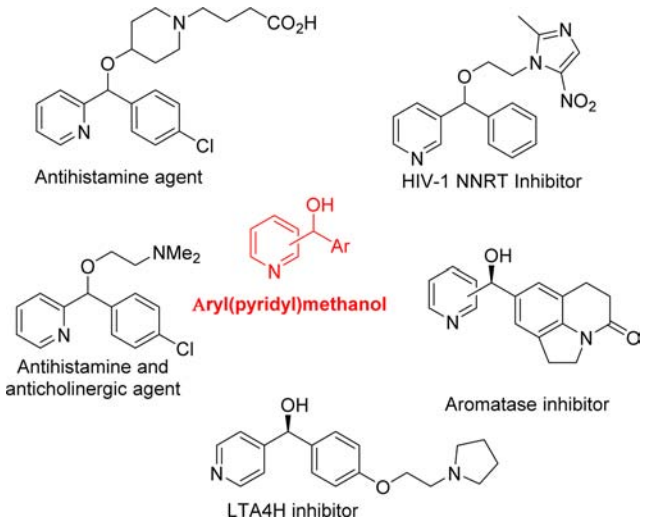


Figure 1. Biologically active compounds containing aryl(pyridyl)-methanol subunits.

Palladium-catalyzed benzylic arylation of picolinyl derivatives has been employed to access heterocyclic building blocks.[3] Traditionally, such reactions require the presence of directing groups, such as 2-(2-pyridyl)ethanols,[3b] pyridine *N*-oxides,[3d,4] *N*-iminopyridines,[3e] or 2-(2-pyridyl)acetic acids.[3h] Other methods for the benzylic functionalization of substituted pyridines rely on the addition of activating agents. For instance, a Lewis acid can be added to the reaction mixture to bind the pyridyl nitrogen, preventing its coordination while also increasing the acidity of the benzylic hydrogens and facilitating the catalytic process.[3j,5] Although effective, these methods have limited substrate scope and reduced synthetic efficiency. The coordination of the pyridyl group to palladium and inhibition or deactivation of the catalyst is also problematic.[6]

Given the success of deprotonative cross-coupling processes (DCCP) in the functionalization of a variety of weakly acidic sp^3 C−H bonds,[7] we envisioned application of this approach to the functionalization of substituted pyridines.[7q,u] We recently reported the $Pd(OAc)_2$/NIXANTPHOS-catalyzed DCCP of pyridylmethyl ethers to generate either arylated secondary ethers (Scheme 1A) or tertiary alcohols via tandem arylation/[1,2]-Wittig rearrangement (Scheme 1B).[7u] Secondary aryl-(pyridyl)methanols (Figure 1) are also highly desirable but not accessible via the chemistry in Scheme 1A or B.

We hypothesized that pyridylmethyl silyl ethers might undergo reversible deprotonation in the presence of a palladium catalyst and aryl bromides to generate arylated silyl ethers or the corresponding free alcohols (Scheme 1C). Herein, we report the catalytic arylation of pyridylmethyl silyl ethers to afford either the silyl protected or free alcohols, using a Pd(NIXANTPHOS)-based catalyst.

Based on the general utility of the $Pd(OAc)_2$/NIXANT-PHOS-based catalyst in a range of reactions,[7j−u] we began by investigating the benzylic C−H arylation of 2-pyridylmethyl silyl ether **1a** with bromobenzene **2a** using $Pd(OAc)_2$ (1 mol %) and NIXANTPHOS (1.5 mol %, see Table 1 for structure). Several combinations of silyl amide bases $MN(SiMe_3)_2$ (M = Li, Na, K) and solvents [toluene, 1,4-dioxane, THF, 2-methyltetrahydrofuran (2-MeTHF), cyclopentyl methyl ether (CPME), and 1,2-dimethoxyethane (DME)] were evaluated to identify suitable reaction conditions (Table 1, entries 1−10).

Received: February 16, 2016
Published: March 23, 2016

DOI: 10.1021/acs.orglett.6b00450
Org. Lett. 2016, 18, 1590−1593

Scheme 1. Pd-Catalyzed Benzylic C−H Arylation of Pyridylmethyl Ethers

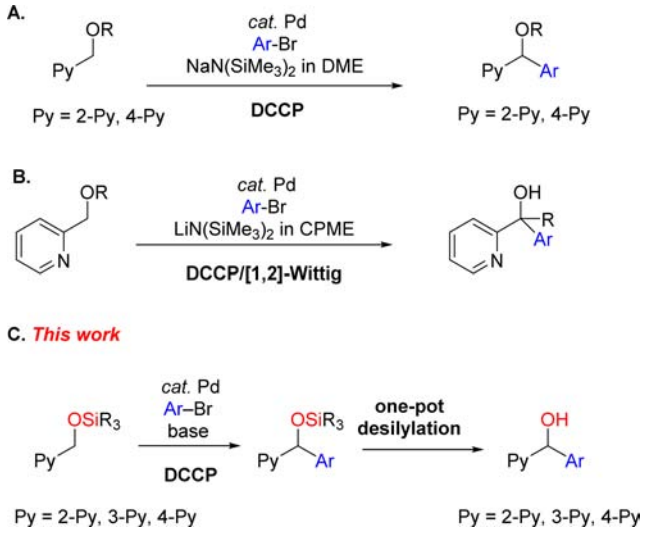
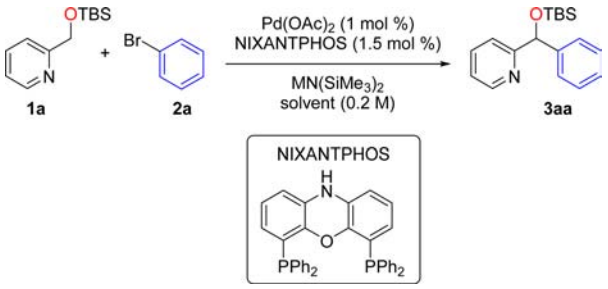


Table 1. Optimization of Benzylic C−H Arylation of 2-Pyridylmethyl Silyl Ether 1a[a]



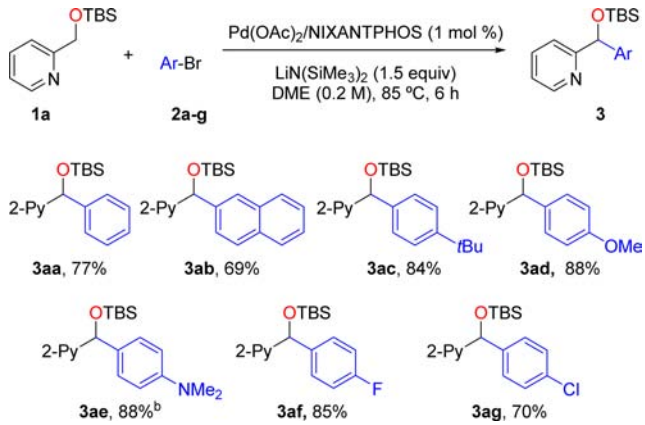
entry	M (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	Li (3)	toluene	45	12	0
2	Li (3)	dioxane	45	12	22
3	Li (3)	THF	45	12	71
4	Li (3)	2-MeTHF	45	12	42
5	Li (3)	CPME	45	12	66
6	Li (3)	DME	45	12	100
7	Na (3)	THF	45	12	45
8	Na (3)	CPME	45	12	48
9	Na (3)	DME	45	12	15
10	K (3)	CPME	45	12	82
11	Li (1.5)	DME	45	18	70
12	Li (1.5)	DME	85	3	98
13[c]	Li (1.5)	DME	85	3	98
14[c]	**Li (1.5)**	**DME**	**85**	**3**	**89[d]**

[a]Reactions were conducted on a 0.2 mmol scale using **1a** (1 equiv), **2a** (1.2 equiv), $Pd(OAc)_2$ (1 mol %), and NIXANTPHOS (1.5 mol %). [b]Yield determined by ^1H NMR spectroscopy of the crude reaction mixture. [c]1 equiv of **2a** was used. [d]1 mol % of $Pd(OAc)_2$ and 1 mol % of NIXANTPHOS.

It was found that $LiN(SiMe_3)_2$ in DME provided a quantitative yield of the desired coupling (Table 1, entry 6). Unfortunately, attempts to decrease the amount of $LiN(SiMe_3)_2$ from 3 equiv to 1.5 equiv resulted in incomplete reaction after 18 h at 45 °C (entries 6 and 11). Increasing the temperature from 45 to 85 °C and using 1.5 equiv of $LiN(SiMe_3)_2$ led to 98% yield after 3 h (entry 12). We were surprised to find that reducing the amount of bromobenzene (**2a**) to 1.0 equiv still gave 98% yield (entry 13). Furthermore, only a small drop in the reaction yield (from 98% to 89%) was found when the NIXANTPHOS loading was dropped from 1.5 to 1.0 mol % (entries 13 and 14).

With the optimized reaction conditions in hand [pyridylmethyl silyl ether (**1**, 1 equiv), aryl bromide (**2**, 1 equiv), $LiN(SiMe_3)_2$ (1.5 equiv), $Pd(OAc)_2$/NIXANTPHOS (1 mol % each), DME (0.2 M) at 85 °C], we explored the scope of aryl bromides in the DCCP (Scheme 2). In general, a variety of aryl

Scheme 2. Scope of Aryl Bromides 2 in Benzylic C−H Arylation of 2-Pyridylmethyl Silyl Ether 1a[a]



[a]Isolated yields with reactions conducted on a 0.2 mmol scale using **1a** (1 equiv), Ar−Br (1 equiv), and $LiN(SiMe_3)_2$ (1.5 equiv) in DME (0.2 M) at 85 °C for 6 h. [b]24 h.

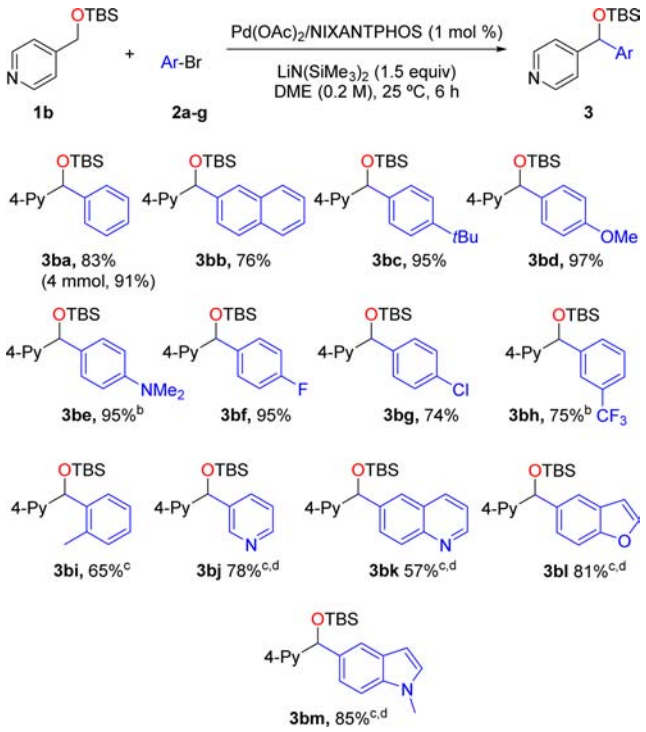
bromides (**2a−g**) led to the formation of aryl(2-pyridyl)methyl silyl ethers **3** with good to high yields (69−88%). The arylation was compatible with aryl bromides bearing electron-donating substituents 4-*t*-Bu, 4-OMe, 4-NMe_2 (**3ac−ae**, 84−88% yield) or electron-withdrawing 4-F and 4-Cl (**3af** and **3ag** in 85% and 70% yield, respectively).

The presence of the 2-pyridyl groups in Scheme 2 might lead to the conclusion that chelation is a prerequisite for arylation. Thus, we examined the 4-pyridyl analogues to probe this question and expand the method (Scheme 3). The arylation of 4-pyridylmethyl silyl ether **1b** took place at room temperature, suggesting these substrates are more reactive than the 2-pyridyl derivatives. This result is consistent with the greater acidity of 4-methylpyridine over 2-methylpyridine.[8] The reactions of 4-pyridylmethyl silyl ethers provided the desired products with a broad range of aryl bromides. These include electronically neutral (Ph, 2-naphthyl, 4-*t*-Bu,) and electron-rich (4-OMe, 4-NMe_2) aryl bromides, which provided products **3ba−be** in 83−97% yield. Aryl bromides with electron-withdrawing groups, such as 4-F and 4-Cl, 3-CF_3, formed products **3bf−bh** in 74−95% yield. In addition, more challenging substrates, such as sterically hindered 2-bromotoluene and heterocycles (3-bromopyridine, 6-bromoquinoline, 5-bromobenzofuran, and *N*-methyl-5-bromoindole) successfully underwent DCCP at room temperature (**3bi−bm**, 57−85%), albeit at 5 mol % catalyst loading (Scheme 3). Moreover, the scalability of the method was evaluated by performing the arylation of 4-pyridylmethyl silyl ether **1b** with bromobenzene (**2a**) on a 4 mmol scale. The desired product (**3ba**) was obtained in 91% yield (1.09 g, Scheme 3).

Next, we assessed different silyl groups. In order to evaluate the impact of silyl group size on the arylation reaction outcome,

DOI: 10.1021/acs.orglett.6b00450
Org. Lett. 2016, 18, 1590−1593

Scheme 3. Scope of Aryl Bromides 2 in Benzylic C−H Arylation of 4-Pyridylmethyl Silyl Ether 1b[a]



[a]Isolated yields with reactions conducted on a 0.2 mmol scale using **1b** (1 equiv), Ar−Br (1 equiv), and $LiN(SiMe_3)_2$ (1.5 equiv) in DME (0.2 M) at 25 °C for 6 h. [b]24 h. [c]$LiN(SiMe_3)_2$ (3 equiv). [d]5 mol % $Pd(OAc)_2$ and 5 mol % of NIXANTPHOS.

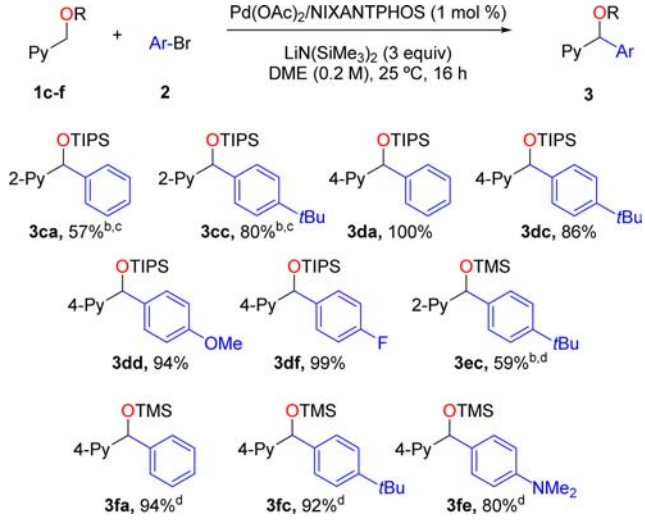
triisopropylsilyl (TIPS) ether and trimethylsilyl (TMS) ether protecting groups were examined.

Both 2- and 4-pyridine derivatives with TIPS and TMS groups coupled with aryl bromides to provide the desired products in good to excellent yields (57−100%, Scheme 4). 2-Pyridyl-containing substrates with bulky TIPS groups required 3 equiv of base and 2 mol % catalyst loading for complete conversion.

Finally, we explored the feasibility of a one-pot arylation/desilylation sequence to generate free secondary alcohols. Substrates with different silyl groups were arylated under the standard reaction conditions and then directly treated with 1.5 equiv of TBAF. As shown in Scheme 5, 4-pyridylmethyl silyl ether **1b** and 2-pyridylmethyl silyl ether **1e** provided the corresponding alcohols **4ba** and **4ea** respectively, with high yields (94% and 84%). The 3-pyridylmethyl silyl ether **1g** is more challenging because of the higher pK_a of the benzylic C−H's.[8] After some optimization, we found that 3 equiv of $LiN(SiMe_3)_2$, 2 equiv of 4-*tert*-butylbromobenzene (**2c**), and 5 mol % catalyst loading in DME at 85 °C generated arylation product. Workup with 1.5 equiv of TBAF provided the free alcohol **4gc** in 66% yield.

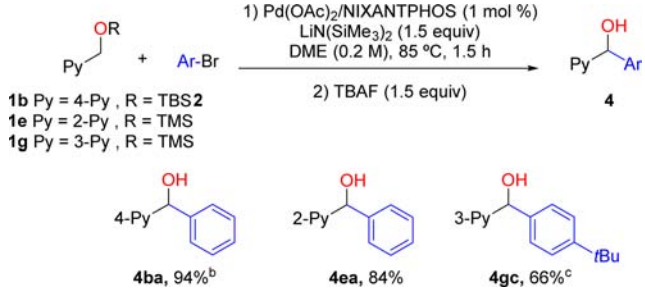
In summary, a deprotonative cross-coupling process for the direct arylation of pyridylmethyl silyl ethers has been developed. In most cases, this method requires 1 equiv of aryl bromide, 1.5 equiv of base, and many substrates react well at 1 mol % catalyst loading. Electron-donating and electron-withdrawing aryl bromides as well as heteroaryl bromides undergo the coupling in good to excellent yields. In addition, the reaction is compatible with different sized silyl-protecting

Scheme 4. Scope of Arylation of Pyridylmethyl Silyl Ethers[a]



[a]Isolated yields with reactions conducted on a 0.2 mmol scale using **1** (1 equiv), Ar−Br (1 equiv), and $LiN(SiMe_3)_2$ (3 equiv) in DME (0.2 M) at 25 °C for 16 h. [b]Conducted at 85 °C. [c]2 mol % of $Pd(OAc)_2$ and 2 mol % of NIXANTPHOS at 85 °C. [d]$LiN(SiMe_3)_2$ (1.5 equiv) for 1.5 h.

Scheme 5. One-Pot Arylation/Deprotection of Pyridylmethyl Silyl Ethers[a]



[a]Isolateds yields with reactions conducted on a 0.2 mmol scale using **1** (1 equiv), Ar−Br (1 equiv), and $LiN(SiMe_3)_2$ (1.5 equiv) in DME (0.2 M) at 85 °C for 1.5 h. [b]Conducted at 25 °C. [c]Ar−Br (2 equiv), $LiN(SiMe_3)_2$ (3 equiv), 5 mol % of $Pd(OAc)_2$, and 5 mol % of NIXANTPHOS for 24 h.

groups. A convenient one-pot cross-coupling/desilylation sequence was demonstrated to directly obtain arylated secondary alcohols. Our method has advantages over the addition of organometallic reagents, such as organolithiums and Grignard reagents, to aldehydes. Many more aryl bromides are commercially available than aryl Grignard reagents. Furthermore, our method circumvents the use of aldehydes, which are often contaminated with oxidation products. We anticipate that this method will be useful in the synthesis of aryl pyridylmethyl alcohols for exploration of their structure−activity relationship.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00450.

Experimental details and characterization data for all new compounds (PDF)

DOI: 10.1021/acs.orglett.6b00450
Org. Lett. 2016, 18, 1590−1593

AUTHOR INFORMATION

Corresponding Author

*E-mail: pwalsh@sas.upenn.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support for this work was provided by NIH/NIGMS (GM 104349) and the National Science Foundation (CHE-1464744). A.R.R. acknowledges the Spanish MEC for an FPU grant and a Visiting Scientist Fellowship to University of Pennsylvania.

REFERENCES

(1) (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (c) Laird, T. *Org. Process Res. Dev.* **2006**, *10*, 851. (d) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265. (e) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845. (f) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (g) Jiang, Q.; Van Plew, D.; Murtuza, S.; Zhang, X. *Tetrahedron Lett.* **1996**, *37*, 797. (h) Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879. (i) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734. (j) Rennison, D.; Bova, S.; Cavalli, M.; Ricchelli, F.; Zulian, A.; Hopkins, B.; Brimble, M. A. *Bioorg. Med. Chem.* **2007**, *15*, 2963. (k) Maywald, M.; Pfaltz, A. *Synthesis* **2009**, *2009*, 3654. (l) *Catalysis in Asymmetric Synthesis*; Wiley−VCH: Chichester, U.K., 2009. (m) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; John Wiley & Sons: Chichester, U.K., 2010. (n) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, 2nd ed.; John Wiley & Sons: Chichester, U.K., 2011.

(2) (a) Hite, G.; Barouh, V.; Dall, H.; Patel, D. *J. Med. Chem.* **1971**, *14*, 834. (b) De Martino, G.; La Regina, G.; Di Pasquali, A.; Ragno, R.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; Maga, G.; Crespan, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2005**, *48*, 4378. (c) Davies, D. R.; Mamat, B.; Magnusson, O. T.; Christensen, J.; Haraldsson, M. H.; Mishra, R.; Pease, B.; Hansen, E.; Singh, J.; Zembower, D.; Kim, H.; Kiselyov, A. S.; Burgin, A. B.; Gurney, M. E.; Stewart, L. J. *J. Med. Chem.* **2009**, *52*, 4694. (d) Lyseng-Williamson, K. A. *Drugs* **2010**, *70*, 1579. (e) Yin, L.; Hu, Q.; Hartmann, R. W. *J. Med. Chem.* **2013**, *56*, 460.

(3) (a) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373. (b) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2643. (c) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105. (d) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (e) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641. (f) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155. (g) Burton, P. M.; Morris, J. A. *Org. Lett.* **2010**, *12*, 5359. (h) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391. (i) Song, G.; Su, Y.; Gong, X.; Han, K.; Li, X. *Org. Lett.* **2011**, *13*, 1968. (j) Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7686. (k) Zhao, D.; Zhu, M.-X.; Wang, Y.; Shen, Q.; Li, J.-X. *Org. Biomol. Chem.* **2013**, *11*, 6246.

(4) (a) Mai, W.; Yuan, J.; Li, Z.; Yang, L.; Xiao, Y.; Mao, P.; Qu, L. *Synlett* **2012**, *23*, 938. (b) Kianmehr, E.; Faghih, N.; Khan, K. M. *Org. Lett.* **2015**, *17*, 414.

(5) (a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (b) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056.

(6) (a) Onishi, M.; Hiraki, K.; Maeda, K.; Itoh, T. *J. Organomet. Chem.* **1980**, *188*, 245. (b) Isobe, K.; Nakamura, Y.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1802. (c) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650.

(7) (a) McGrew, G. I.; Temaismithi, J.; Carroll, P. J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5541. (b) McGrew, G. I.; Stanciu, C.; Zhang, J.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J. *Angew. Chem.* **2012**, *124*, 11678. (c) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 1690. (d) Jia, T.; Bellomo, A.; El Baina, K.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 3740. (e) Montel, S.; Jia, T.; Walsh, P. J. *Org. Lett.* **2014**, *16*, 130. (f) Zheng, B.; Jia, T. Z.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 4190. (g) Montel, S.; Raffier, L.; He, Y.; Walsh, P. J. *Org. Lett.* **2014**, *16*, 1446. (h) Hussain, N.; Frensch, G.; Zhang, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3693. (i) Zheng, B.; Jia, T.; Walsh, P. J. *Adv. Synth. Catal.* **2014**, *356*, 165. (j) Zhang, J.; Bellomo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 13765. (k) Frensch, G.; Hussain, N.; Marques, F. A.; Walsh, P. J. *Adv. Synth. Catal.* **2014**, *356*, 2517. (l) Gao, F.; Kim, B.-S.; Walsh, P. J. *Chem. Commun.* **2014**, *50*, 10661. (m) Li, M.; Berritt, S.; Walsh, P. J. *Org. Lett.* **2014**, *16*, 4312. (n) Li, M.; Yücel, B.; Adrio, J.; Bellomo, A.; Walsh, P. J. *Chem. Sci.* **2014**, *5*, 2383. (o) Zhang, J.; Bellomo, A.; Trongsiriwat, N.; Jia, T.; Carroll, P. J.; Dreher, S. D.; Tudge, M. T.; Yin, H.; Robinson, J. R.; Schelter, E. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 6276. (p) Yücel, B.; Walsh, P. J. *Adv. Synth. Catal.* **2014**, *356*, 3659. (q) Kim, B.-S.; Jiménez, J.; Gao, F.; Walsh, P. J. *Org. Lett.* **2015**, *17*, 5788. (r) Mao, J.; Eberle, K.; Zhang, J.; Rodríguez-Escrich, C.; Xi, Z.; Pericàs, M. A.; Walsh, P. J. *Tetrahedron Lett.* **2015**, *56*, 3604. (s) Sha, S.-C.; Zhang, J.; Walsh, P. J. *Org. Lett.* **2015**, *17*, 410. (t) Cao, X.; Sha, S.-C.; Li, M.; Kim, B.-S.; Morgan, C.; Huang, R.; Yang, X.; Walsh, P. J. *Chem. Sci.* **2016**, *7*, 611. (u) Gao, F.; Kim, B.-S.; Walsh, P. J. *Chem. Sci.* **2016**, *7*, 976. (v) Hussain, N.; Kim, B.-S.; Walsh, P. J. *Chem. - Eur. J.* **2015**, *21*, 11010.

(8) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232.

DOI: 10.1021/acs.orglett.6b00450
Org. Lett. 2016, 18, 1590−1593