Organic LETTERS

Letter

pubs.acs.org/OrgLett

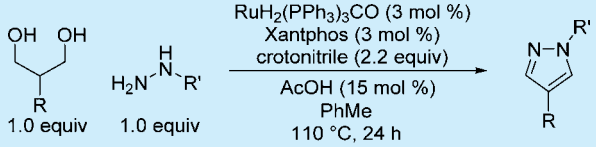
Synthesis of Pyrazoles from 1,3-Diols via Hydrogen Transfer Catalysis

Daniel C. Schmitt,* Alexandria P. Taylor, Andrew C. Flick, and Robert E. Kyne, Jr.†

Pfizer Global Research and Development, Eastern Point Road, Groton, Connecticut 06340, United States

Supporting Information

ABSTRACT: 1,3-Diols engage in ruthenium-catalyzed hydrogen transfer in the presence of alkyl hydrazines to provide 1,4-disubstituted pyrazoles. Regioselective synthesis of unsymmetrical pyrazoles from β-hydroxy ketones is also described.



Pyrazoles are an important structural subunit found in a variety of biologically active agents, including major drugs such as Viagra, Xalkori, Lexiscan, and Celebrex.[1] The prevalence of the pyrazole motif in medicinally relevant compounds,[2] dyes,[3] and ligands for metal catalysts[4] has inspired the development of many novel methods for their preparation.[5] Over the course of recent drug discovery efforts, the unmet need for an efficient route to 4-alkyl pyrazoles was identified. Despite an abundance of methodology for their synthesis, pyrazoles are most commonly constructed by the condensation of an alkyl hydrazine with a 1,3-dicarbonyl.[6] However, the inherent instability of many 1,3-dicarbonyls, particularly dialdehydes,[7] limits access to substituted pyrazoles. As a workaround, the use of vinylogous formamides or 1,3-diacetals has made a select number of these structural motifs accessible (Figure 1). These masked dialdehydes possess

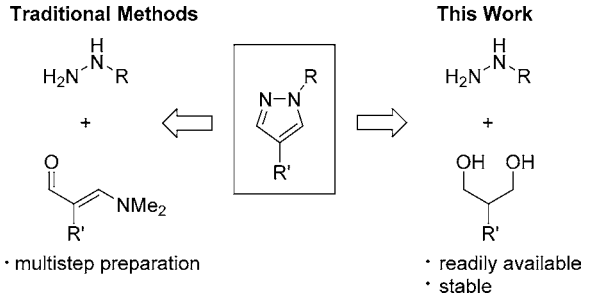


Figure 1. Pyrazoles from masked dialdehydes vs diols.

sensitive functional groups and typically require multistep preparation.[8] An additional challenge of traditional pyrazole syntheses lies in the preparation of unsymmetrical pyrazoles: conventional condensation often provides inseparable mixtures of pyrazole regioisomers.[9]

Metal-catalyzed alcohol dehydrogenation has recently emerged as a powerful tool for C–N bond formation in synthetic chemistry. These transformations permit the direct coupling of alcohols with amines, usually in the presence of an iridium or ruthenium catalyst, to provide imines, amides, or heterocycles.[10] Such dehydrogenative condensations circumvent the need for potentially unstable carbonyl intermediates and bypass alcohol oxidation steps, thus increasing synthetic efficiency. This approach has been utilized for the synthesis of benzazoles, pyridines, pyrazines, pyrroles, and indoles from readily available alcohol and amine building blocks.[11] To date, hydrogen transfer catalysis has not been applied to pyrazole synthesis.[12] Given the aforementioned limitations of condensative pyrazole synthesis, a method that addresses these issues would represent a valuable advance.

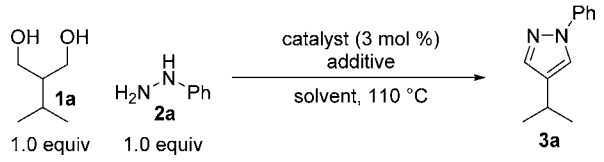
We proposed that hydrogen transfer could enable the use of 1,3-diols rather than the typical masked dialdehydes for pyrazole synthesis. Recent reports of 1,3-diols undergoing Ir-catalyzed double allylation and crotylation indicate their potential as synthetic equivalents to 1,3-dialdehydes.[13] The compatibility of alkyl hydrazines with the reaction conditions remained a concern, as few examples exist of alcohol dehydrogenation in the presence of hydrazines. However, recent research by Li and Porcheddu demonstrates the stability of hydrazines to both Ir- and Ru-catalyzed hydrogen transfer.[11g,14] As a starting point, we selected commercially available *i*-Pr diol **1a** and phenylhydrazine to investigate the proposed reaction (Table 1).

Initial experiments surveyed common hydrogen transfer catalysts, in both the presence and absence of a hydrogen acceptor (crotonitrile). No pyrazole formation was observed in the presence of $[Cp^*IrCl_2]_2$, Milstein's catalyst, or $RuCl_2(PPh_3)_3$ (Table 1, entries 1–3). $[Ru_3(CO)_{12}]$ and Xantphos in *tert*-amyl alcohol, which was utilized by Beller and co-workers for vicinal diol dehydrogenation,[11e] provided 9% of the desired pyrazole. $RuH_2(PPh_3)_3CO$ and Xantphos in the presence of piperidinium acetate, a system developed by Williams for transfer of hydrogen from alcohols to crotonitrile,[11b,15] successfully yielded 68% of pyrazole **3a** (entry 5). Notably, omission of piperidinium acetate results in no desired product formation. Substitution of piperidinium acetate with AcOH boosted the yield to 75% (entry 7). The importance of acidic additives may be due to acceleration of both aldehyde condensation steps. Under otherwise identical conditions, but with a decreased catalyst loading, a 40% yield of pyrazole **3a** was isolated (entry 8). Omission of Xantphos led to unreacted diol **1a**, without any formation of the desired pyrazole (entry

Received: January 27, 2015
Published: February 26, 2015

DOI: 10.1021/acs.orglett.5b00266
Org. Lett. 2015, 17, 1405–1408

Table 1. Reaction Optimization



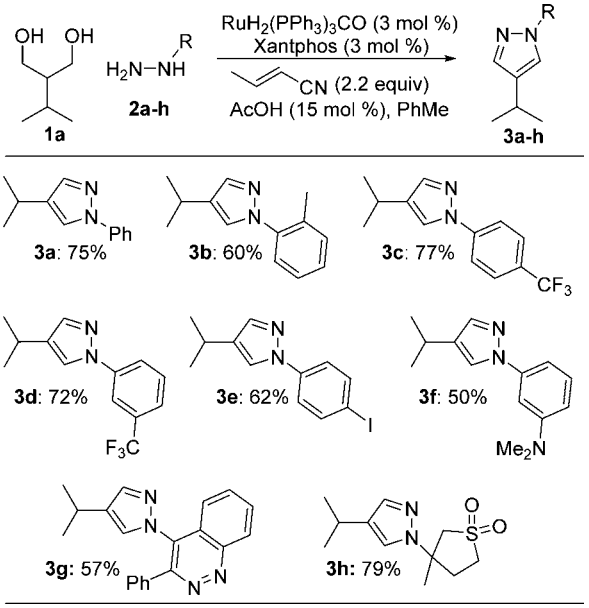
entry	catalyst	solvent	additive[a]	yield
1	Milstein's catalyst	PhMe	–	0%
2	$RuCl_2(PPh_3)_3$	PhMe	crotonitrile	0%
3	$[Cp^*IrCl_2]_2$	PhMe	–	0%
4	$Ru_3(CO)_{12}$/**L1**[b]	*t*-amylOH	–	9%
5	$RuH_2(PPh_3)_3CO$/**L1**	PhMe	crotonitrile/**A**[c]	68%
6	$RuH_2(PPh_3)_3CO$/**L1**	PhMe	crotonitrile	0%
7	$RuH_2(PPh_3)_3CO$/**L1**	PhMe	crotonitrile/AcOH	75%
8	1 mol % [Ru]/**L1**	PhMe	crotonitrile/AcOH	40%
9	$RuH_2(PPh_3)_3CO$	PhMe	crotonitrile/AcOH	0%
10	$RuH_2(PPh_3)_3CO$/**L1**	*t*-amylOH	crotonitrile/AcOH	40%

[a]15 mol % of each additive was used, except crotonitrile (2.2 equiv used). [b]Ligand **L1** is Xantphos (3 mol %). [c]Additive **A** is piperidinium acetate (15 mol %).

9). Neat conditions, employed successfully by Porcheddu with this catalytic system,[16] resulted in decomposition in this case.

With suitable conditions in hand, the scope of the reaction was examined. Diol **1a** was evaluated with various monosubstituted hydrazines. Phenyl hydrazines bearing functional groups such as iodide and trifluoromethyl were tolerated (Scheme 1). 2-Toluyl hydrazine provided a slightly lower yield than phenylhydrazine, likely due to steric hindrance of the condensation step. Since tertiary amines and *N*-heterocycles are common subunits of pharmaceutical agents, dimethylaminophenyl hydrazine and 4-hydrazinyl-3-phenylcinnoline were

Scheme 1. Hydrazine Scope[a,b]

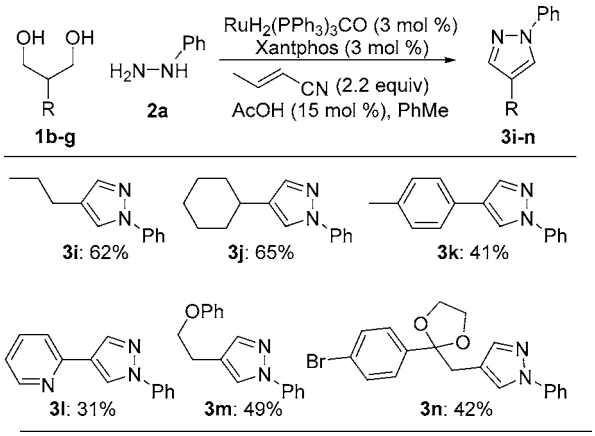


[a]All reactions were conducted in round-bottom flasks fitted with reflux condensers at 0.50 M concentration with **1a–f** (1.00 equiv), **2a–h** (1.00 equiv), crotonitrile (2.20 equiv), $RuH_2(PPh_3)_3CO$ (3 mol %), Xantphos (3 mol %), and AcOH (15 mol %) at 110 °C. [b]Yield of isolated product.

evaluated, affording 42% and 57% yields, respectively (**3f** and **3g**). Interestingly, aliphatic hydrazines which possessed a C–H adjacent to nitrogen were not competent nucleophiles; methyl and isopropylhydrazine both failed to provide the desired pyrazoles, whereas α-quaternary aliphatic hydrazine **2h** provided the desired pyrazole (**3h**). In all cases, flash chromatography easily separated the pyrazole product from any unreacted starting materials due to the significant difference in polarity.

The scope of the diol component was evaluated with phenylhydrazine. In addition to *i*-Pr diol (**3a**), *n*-propyl (**3i**), and cyclohexyl (**3j**) diols were well-tolerated (Scheme 2).

Scheme 2. Diol Scope[a,b]

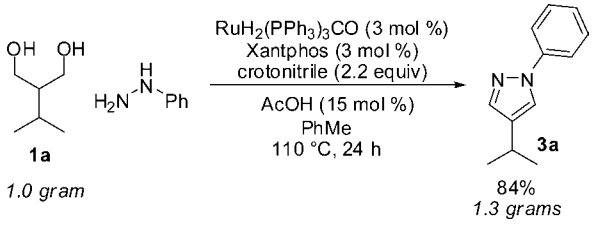


[a]All reactions were conducted in round-bottom flasks fitted with reflux condensers at 0.50 M concentration with **1b–g** (1.00 equiv), **2a** (1.00 equiv), crotonitrile (2.20 equiv), $RuH_2(PPh_3)_3CO$ (3 mol %), Xantphos (3 mol %), and AcOH (15 mol %) at 110 °C. [b]Yield of isolated product.

Notably, lower yields were obtained from 2-aryl-1,3-diols (**3k** and **3l**). This result could be due to impeded dehydrogenation or accelerated enolization of the α-aryl aldehyde intermediates, which could subsequently dimerize or undergo Michael addition to crotonitrile. Useful functional groups such as aryl bromides and ketals were also tolerated on the diol component, albeit in modest yield (**3n**). Whereas various primary 1,3-diols were effective reactants, attempts to generate pyrazoles from secondary alcohols were unsuccessful, likely due to the significantly diminished rate of secondary alcohol dehydrogenation relative to primary alcohol dehydrogenation.[17]

To test the scalability of the reaction, 1 g of diol **1a** (8.5 mmol) was subjected to the standard conditions in the presence of phenylhydrazine (Scheme 3). After 24 h in toluene at reflux, pyrazole **3a** was isolated in 84% yield.

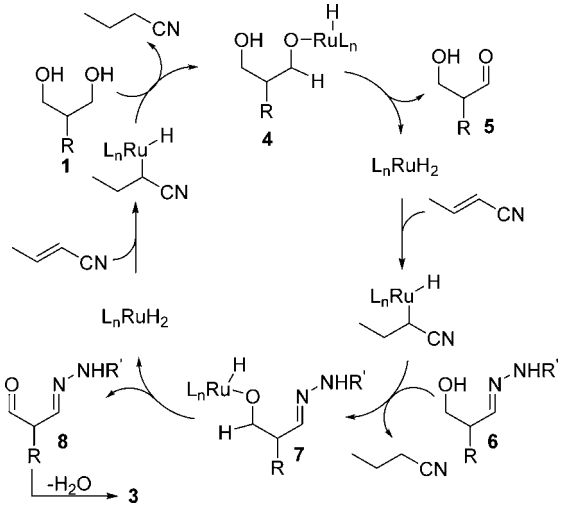
Scheme 3. Gram-Scale Reaction



DOI: 10.1021/acs.orglett.5b00266
Org. Lett. 2015, 17, 1405–1408

The postulated mechanism may involve an initial migratory insertion of the Ru dihydride catalyst with crotonitrile (Scheme 4). The resulting C−Ru bond could undergo protodemetalation with diol **1** to generate Ru alkoxide **4**. Dehydrogenation would provide aldehyde **5**, which is believed to dissociate from Ru prior to condensation with the hydrazine, resulting in *β*-hydroxy hydrazone **6**.[18] Hydrogen transfer to crotonitrile followed by protodemetalation would produce butyronitrile and ruthenium alkoxide **7**.[16] Subsequent dehydrogenation would regenerate the Ru dihydride species as well as *β*-hydrazino aldehyde **8**, which could cyclodehydrate to provide the observed pyrazole product **3**.

Scheme 4. Proposed Mechanism

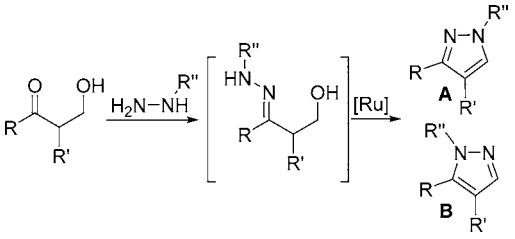


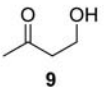
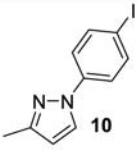
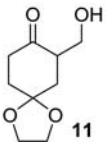
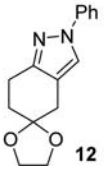
An alternative mechanism could involve full oxidation of diol **1** to a dialdehyde prior to condensation with the hydrazine. However, the dehydrogenation of electron-poor alcohols, such as *β*-hydroxy aldehyde **5**, is usually slow and probably does not proceed until after formation of hydrazone **6**. Furthermore, monitoring of the reaction by LC-MS revealed a mass indicative of *β*-hydroxy hydrazone **6**, which is consistent with the depicted catalytic cycle.

Additional utility of this method lies in the regioselective preparation of unsymmetrical pyrazoles. A well-documented problem with conventional pyrazole synthesis is unreliable regioselectivity in the cyclocondensation of hydrazines with vinylogous amides or esters.[19] In contrast, dehydrogenative coupling of commercially available *β*-hydroxy ketone **9** provides 3-alkyl pyrazole **10** exclusively (Table 2). Complete regioselectivity was also observed in the preparation of fused pyrazole **12**. The observed regioselectivity may be attributed to condensation of the unsubstituted hydrazine nitrogen with the ketone prior to alcohol dehydrogenation. Although complex *β*-hydroxy ketones are not commercially available, they may be prepared reliably via aldol reaction with aqueous formaldehyde.[20]

In summary, 4-alkyl-pyrazoles may be prepared directly from 2-alkyl-1,3-diols and hydrazines by means of Ru-catalyzed hydrogen transfer to crotonitrile. This method enhances the synthetic accessibility of 4-alkyl pyrazoles, which are difficult to produce by other means. The reaction tolerates both aromatic and aliphatic substituents on both the hydrazine and diol component. Beyond entry into elusive 4-alkyl-pyrazole chemical space, this method enables the synthesis of unsymmetrical pyrazoles with excellent regioselectivity. The ability to use diols as dicarbonyl equivalents will likely find further utility in the synthesis of other heterocycles, which will be the subject of future studies.

Table 2. Regioselective Pyrazole Synthesis



β-hydroxy ketone	product	yield (A:B)
 9	 10	61% (>20:1)
 11	 12	56% (>20:1)

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: daniel.schmitt@pfizer.com.

Present Address

†Celgene Avilomics Research, 45 Wiggins Ave., Bedford, MA 01730.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank David Lin and James Mousseau for reviewing this manuscript. Kathleen Farley and Martin Berliner are thanked for helpful discussions. All colleagues acknowledged are affiliated with Pfizer, Inc., Groton, CT, USA.

■ REFERENCES

(1) (a) Zablocki, J.; Palle, V.; Blackburn, B.; Elzein, E.; Nudelman, G.; Gothe, S.; Gao, Z.; Li, Z.; Meyer, S.; Belardinelli, L. *Nucleosides, Nucleotides, Nucleic Acids* **2001**, *20*, 343−360. (b) Cui, J. J.; Tran-Dubé, M.; Shen, H.; Nambu, M.; Kung, P.-P.; Pairish, M.; Jia, L.; Meng, J.; Funk, L.; Botrous, I.; McTigue, M.; Grodsky, N.; Ryan, K.; Padrique, E.; Alton, G.; Timofeevski, S.; Yamazaki, S.; Li, Q.; Zou, H.; Christensen, J.; Mroczkowski, B.; Bender, S.; Kania, R. S.; Edwards, M. P. *J. Med. Chem.* **2011**, *54*, 6342−6363. (c) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.;

DOI: 10.1021/acs.orglett.5b00266
Org. Lett. 2015, 17, 1405−1408

Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347−1365. (d) Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819−1824.
(2) (a) Lee, F.-Y.; Lien, J.-C.; Huang, L.-J.; Huang, T.-M.; Tsai, S.-C.; Teng, C.-M.; Wu, C.-C.; Cheng, F.-C.; Kuo, S.-C. *J. Med. Chem.* **2001**, *44*, 3746−3749. (b) Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Suzuki, K.; Ueda, T.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J.-I. *Bioorg. Med. Chem.* **2004**, *12*, 5515−5524.
(3) Lee, H.; Berezin, M. Y.; Tang, R.; Zhegalova, N.; Achilefu, S. *Photochem. Photobiol.* **2013**, *89*, 326−331.
(4) C. Constable, E.; J. Steel, P. *Coord. Chem. Rev.* **1989**, *93*, 205−223.
(5) Reviews on pyrazole synthesis: (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984−7034. (b) Li, M.; Zhao, B.-X. *Eur. J. Med. Chem.* **2014**, *85*, 311−340. (c) Chakroborty, S.; Bhanja, C.; Jena, S. *Heterocycl. Commun.* **2013**, *19*, 79−87. (d) Yet, L. Chapter 5.4 - Five-Membered Ring Systems: With More than One N Atom. In *Progress in Heterocyclic Chemistry*; Gordon, W. G., John, A. J., Eds.; Elsevier: 2012; Vol. *24*, pp 243−279. (e) Kumari, S.; Paliwal, S.; Chauhan, R. *Synth. Commun.* **2014**, *44*, 1521−1578.
(6) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2597−2599.
(7) Wu, L.; Feng, L.; Zhang, H.; Liu, Q.; He, X.; Yang, F.; Xia, H. *J. Org. Chem.* **2008**, *73*, 2883−2885.
(8) Reger, D. L.; Gardinier, J. R.; Christian Grattan, T.; Smith, M. R.; Smith, M. D. *New J. Chem.* **2003**, *27*, 1670−1677.
(9) (a) Comes Franchini, M.; Bonini, B. F.; Camaggi, C. M.; Gentili, D.; Pession, A.; Rani, M.; Strocchi, E. *Eur. J. Med. Chem.* **2010**, *45*, 2024−2033. (b) Balbi, A.; Anzaldi, M.; Macciò, C.; Aiello, C.; Mazzei, M.; Gangemi, R.; Castagnola, P.; Miele, M.; Rosano, C.; Viale, M. *Eur. J. Med. Chem.* **2011**, *46*, 5293−5309.
(10) Reviews on alcohol dehydrogenation: (a) Watson, A. J. A.; Williams, J. M. J. *Science* **2010**, *329*, 635−636. (b) Guillena, G.; J. Ramón, D.; Yus, M. *Chem. Rev.* **2009**, *110*, 1611−1641. (c) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (d) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575. (e) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2009**, *110*, 681−703. (f) Marr, A. C. *Catal. Sci. Technol.* **2012**, *2*, 279−287. (g) Pera-Titus, M.; Shi, F. *ChemSusChem* **2014**, *7*, 720−722. (h) Obora, Y. *ACS Catal.* **2014**, *4*, 3972−3981.
(11) (a) Peña-López, M.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2014**, *20*, 1818−1824. (b) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039−2042. (c) Michlik, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 6326−6329. (d) Gnanaprakasam, B.; Balaraman, E.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12240−12244. (e) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597−601. (f) Srimani, D.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012−4015. (g) Porcheddu, A.; Mura, M. G.; De Luca, L.; Pizzetti, M.; Taddei, M. *Org. Lett.* **2012**, *14*, 6112−6115. (h) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384−11388.
(12) For an example of oxidative pyrazole synthesis from 1,2-diols, see: Panda, N.; Jena, A. K. *J. Org. Chem.* **2012**, *77*, 9401−9406.
(13) (a) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018−5021. (b) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795−12800.
(14) Li, F.; Sun, C.; Wang, N. *J. Org. Chem.* **2014**, *79*, 8031−8039.
(15) Hall, M. I.; Pridmore, S. J.; Williams, J. M. J. *Adv. Synth. Catal.* **2008**, *350*, 1975−1978.
(16) Mura, M. G.; De Luca, L.; Taddei, M.; Williams, J. M. J.; Porcheddu, A. *Org. Lett.* **2014**, *16*, 2586−2589.
(17) (a) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3195−3198. (b) Shin, I.; Wang, G.; Krische, M. J. *Chem.—Eur. J.* **2014**, *20*, 13382−13389.
(18) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766−1774.
(19) (a) Flores, A. F. C.; Brondani, S.; Pizzuti, L.; Martins, M. A. P.; Zanatta, N.; Bonacorso, H. G.; Flores, D. C. *Synthesis* **2005**, *2005*, 2744−2750. (b) Martins, M. A. P.; Emmerich, D.; Beck, P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Brondani, S.; Peres, R.; Teixeira, M. V. M.; Bonacorso, H. G.; Zanatta, N. *Synth. Commun.* **2004**, *34*, 1915−1923. (c) Černuchová, P.; Vo-Thanh, G.; Milata, V.; Loupy, A.; Jantová, S.; Theiszová, M. *Tetrahedron* **2005**, *61*, 5379−5387. (d) Calle, M.; Calvo, L. A.; González-Ortega, A.; González-Nogal, A. M. *Tetrahedron* **2006**, *62*, 611−618.
(20) Wipf, P.; Aslan, D. C. *J. Org. Chem.* **2000**, *66*, 337−343.

DOI: 10.1021/acs.orglett.5b00266
Org. Lett. 2015, 17, 1405−1408