Organic LETTERS

Letter

pubs.acs.org/OrgLett

Comparative Study of the Limitations and Challenges in Atom-Transfer C−H Oxidations

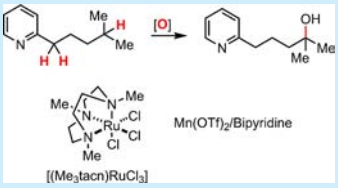
Ashley M. Adams,[†] J. Du Bois,[†] and Hasnain A. Malik*[,‡]

[†]Department of Chemistry, Stanford University, Stanford, California 94305, United States

[‡]Department of Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Inc., 100 Technology Square, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: A comparative study is disclosed that seeks to highlight the current limitations and challenges that exist in the field of atom-transfer C−H oxidations. State-of-the-art methods are benchmarked in order to showcase clear differences and similarities. A novel Mn-mediated method for C−H oxidation is disclosed that serves as a rapid and simple method for aliphatic C−H hydroxylation. Finally, two methods that allow for C−H oxidation in the presence of pyridine-containing substrates are studied, something that is rare in the field but of great interest to the chemical community.



Selective and predictable hydroxylation of C−H bonds in organic substrates remains a grand challenge in modern synthetic methods research.[1] Not only does this seemingly simple, one atom transformation stand as a testament to the chemist's ability to harness highly active catalysts, selective methods for the oxidation of C−H bonds have the potential to reorient the field of chemical synthesis.[2] Baran has elegantly described the potential of oxidation methodologies to transform the chemical landscape in "the oxidase phase" of biomimetic natural product synthesis.[3] Given that the presence of polar hydroxyl groups can substantially modulate a molecule's physiochemical properties in the context of lead optimization in drug discovery, a recent study leveraged the utility of oxidative methods for the efficient installation of hydroxyl groups for this very purpose.[4] Due to the potential metamorphic power of such methods, contemporaneous explorations in the complementary fields of metal and organic catalysts have been pursued.

While significant progress has been made in the area of C−H hydroxylation catalysis, formidable hurdles to the widespread application of these methods still persist. Such challenges include obtaining high levels of positional selectivity and expanding the substrate scope to include complex structures that contain more than a single polar functional group and/or heteroaromatic ring(s). This latter class is of particular importance to the pharmaceutical and agrochemical industries where heteroatom-containing compounds are ubiquitous.[5]

The purpose of the present work is to provide a comparative study of the current synthetic methods for C−H hydroxylation using a common set of substrates. These efforts attempt to define the current scope and limitations of existing technologies for C−H hydroxylation and provide a reference for practitioners of chemical synthesis. The focus of this analysis is on methods that proceed through a discrete atom-transfer event to oxidize sp^3 C−H bonds, an oxygenase type transfer mechanism akin to reactions catalyzed by cytochrome p450s.[6] These methods contrast organometallic methods for C−H oxidation, which have found principal use for sp^2 C−H bond hydroxylation.[7] While C−H hydroxylation methods have been used to great effect in total synthesis, it should be noted that many examples use *stoichiometric* quantities of dioxirane oxidants (see Figure S1, Supporting Information).[8−11]

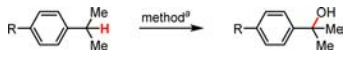
Methods that were selected for comparative study are derived from the recent literature and present a survey of different metals and stoichiometric oxidants and are, in our view, representative of the state-of-the-art in the field. One such system is the Fe-(*S*,*S*-PDP) system developed by White.[12,13] Ribas and Costas have developed another Fe-based system which shows significant promise that operates at lower catalyst loadings and with higher oxidant efficiency.[14] Another method using this ligand is the Mn-(*S*,*S*-PDP) system developed by Bryliakov.[15] Recently a $RuCl_3$ method was disclosed,[16] building upon work by Bakke and Waegell.[17] Inspired by Che's work,[18] another Ru-based method was developed using [(Me_3tacn)-$RuCl_3$] as a catalyst and was found to engage with a wide range of substrates.[19,20] The final method selected for comparative studies is a benzoxathiazine-based method, which stands as the first organocatalytic method for aliphatic C−H hydroxylation.[21]

To facilitate the screening process for C−H hydroxylation reactivity, we aimed to identify a novel and rapid method for C−H hydroxylation. Thus, we outline the first disclosure of a new hydroxylation method. Inspired by the Mn oxidation literature,[22] we examined a combination of ligands, metal salts, and oxidants. Employing $Mn(OTf)_2$, bipyridine, and AcOOH, 3° alcohol products could be obtained within seconds. Notably, the highly active Mn-based oxidant generated under these conditions rapidly oxidizes C−H bonds that are known to be recalcitrant toward C−H functionalization by other methods (Table 2, entry 5). Due to the low metal loadings, the rapidity

Received: October 26, 2015
Published: December 9, 2015

DOI: 10.1021/acs.orglett.5b03047
Org. Lett. 2015, 17, 6066−6069

Table 1. Oxidation of Substituted Cumene Derivatives with Different Catalyst Systems



	substituent, R[b], σ_p				
method[a]	−OPiv, 0.31	−OMs, 0.36	−OTf, 0.53	−CN, 0.66	−NO_2, 0.78
$Mn(OTf)_2$/bipyridine[c]	38 [12] (84)	46 [18] (80)	34 [22] (99)	48 [25] (88)	44 [30] (87)
$RuCl_3$[d]	28 [0] (99)	35 [2] (99)	37 [3] (99)	27 [3] (85)	34 [4] (75)
[(Me_3tacn)$RuCl_3$][e]	75 [13] (99)	78 [15] (96)	60 [6] (99)	68 [10] (80)	73 [15] (95)
Fe-(*S*,*S*-PDP)[f]	4 [0] (95)	6 [0] (90)	36 [10] (90)	40 [9] (80)	45 [14] (76)
Mn-(*S*,*S*-PDP)[g]	43 [1] (66)	57 [2] (69)	52 [6] (79)	40 [13] (80)	45 [15] (72)
Benzoxathiazine[h]	20 [0] (60)	60 [0] (62)	50 [7] (65)	43 [0] (82)	43 [7] (75)

[a]Reactions conducted on 0.25 mmol scale and analyzed by quantitative NMR with pyrazine as internal standard. [b]Values shown are alcohol product, [acetophenone], and (conversion). [c]Reaction conducted with $Mn(OTf)_2$ (0.1%), bipyridine (1%), AcOOH (3.0 equiv), AcOH, 90 s. [d]Reaction conducted with $RuCl_3$ (5%), C_5H_5N (10%), $KBrO_3$ (3.0 equiv), CH_3CN/H_2O, 60 °C, 24 h. [e][(Me_3tacn)$RuCl_3$] (2%), $AgClO_4$ (8%), CAN (6.0 equiv), *t*-BuOH/H_2O, 4 h. [f][Fe-(*S*,*S*-PDP) (5%), AcOH (50%), H_2O_2 (1.2 equiv)] 3×, CH_3CN. [g]Mn-(*S*,*S*-PDP) (0.1%), H_2O_2 (1.3 equiv), 0 °C, 2 h. [h]Benzoxathiazine (20%), Oxone (2.5 equiv), HFIP/H_2O, 70 °C, 12 h.

of the oxidation, and the ease of *in situ* catalyst formation, we envision that this oxidative method will find use as a rapid screening tool (see Supporting Information for more details).

As an initial test for general applicability, we examined the ability of these six catalytic systems to engage with the benzylic C−H bonds of a variety of cumene derivatives (Table 1). Substituted aromatic rings frequently appear in both simple and complex substrates, and yet previous studies with metal-based and dioxirane oxidants have noted problems with deleterious arene oxidation. Substrates were initially oxidized with the Mn/bipy system due to the rapidity and ease of the reaction. These reactions proceeded with high conversions (>80%), where the major product was the desired 3° alcohol.

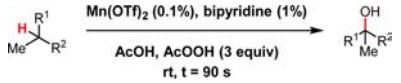
When cumene substrates were subjected to oxidation using $RuCl_3$, alcohol formation mirrored those recorded with the Mn/bipy catalyst; however, the amount of starting material unproductively consumed was elevated.[23] By contrast, reactions with [(Me_3tacn)$RuCl_3$] afforded uniformly high conversions and significant amounts of 3° alcohol product for all substrates.

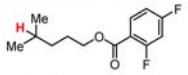
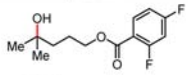
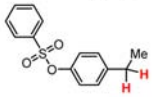
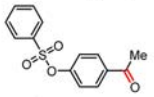
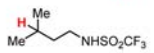
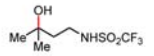
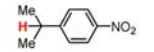
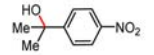
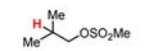
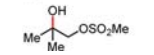
Striking differences in product conversions appear between the Mn- and Fe-(*S*,*S*-PDP) methods, particularly with arene substrates bearing *para*-substituent groups such as −OPiv and −OMs. While the reagents are remarkably similar, there are differences in reaction protocols. Reactions with catalytic Fe-(*S*,*S*-PDP) are conducted using an iterative addition (3×) of both the catalyst and oxidant at room temperature, while Mn-(*S*,*S*-PDP) reactions are conducted at 0 °C with an hour long addition of oxidant. The Mn system uses less catalyst than the Fe-based system (1% vs 15%). Following the latter protocol with Fe-(*S*,*S*-PDP) as the catalyst gave <5% conversion in reactions with pivaloylated and mesylated cumenes. Clearly, there are intrinsic differences between the active oxidants formed at the Fe- and Mn-metal centers. The Mn-(*S*,*S*-PDP) system is able to perform benzylic oxidation on a wider range of aromatic substrates at much lower catalyst loadings, with a performance that mirrors the results obtained with the Mn/bipy complex (Table 2).

In contrast to metal-mediated oxidation reactions, the organocatalytic benzoxathiazine system performs well with hydrolytically stable protecting groups (e.g., −OMs, −OTf). However, with systems amenable to possible hydrolysis, the oxidation reaction suffers due to the elevated temperatures and mildly acidic nature of the aqueous media.

This study identifies distinct catalyst-based trends in the oxidation of the benzylic C−H bonds of aryl alkanes, and the success or failure of a reaction to proceed to give the desired products can be predicted by the Hammett values for the substitution on the arenes.

Table 2. Substrate Scope of the Mn/bipy Catalyzed Reaction



entry	substrate	product	% yield[a]
1			32
2			80
3			37
4			44
5			34

[a]Reaction conducted on a 1 mmol scale with $Mn(OTf)_2$ (0.1%), bipyridine (1%), AcOOH (3.0 equiv), AcOH, 90 s. Isolated yields are shown.

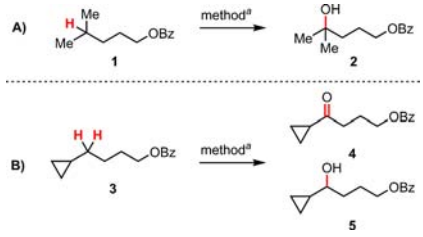
Of the six oxidation protocols, the four top performers ($Mn(OTf)_2$/bipyridine, [(Me_3tacn)$RuCl_3$], Mn-(*S*,*S*-PDP), and the benzoxathiazine) were selected for comparative analysis in the oxidation of nonbenzylic C−H bonds (Table 3).

Two substrates, **1** and **3**, were used for the purpose of these experiments. Since these substrates bear benzoyl groups, the use of both the $RuCl_3$ and Fe-(*S*,*S*-PDP) methods is precluded. Neither of these aforementioned protocols were found to be chemically tolerant of substrates with pendant benzoyl groups, consistent with the results outlined in Table 1. All reaction protocols tested oxidize benzoate **1** in yields exceeding 40%. [(Me_3tacn)$RuCl_3$] performed best with **1** and cyclopropane **3**. Mn-(*S*,*S*-PDP) and the benzoxathiazine also performed admirably with the tertiary substrate **1**. Reactions with cyclopropane **3** were uniformly low yielding irrespective catalyst choice, and in two cases both ketone and 2° alcohol products were obtained.

Oxidation of substrates bearing heterocyclic and basic amine groups remains an extremely important yet unsolved problem in C−H functionalization catalysis. Principal issues that arise with such substrates stem from the metal coordinating ability of

DOI: 10.1021/acs.orglett.5b03047
Org. Lett. 2015, 17, 6066−6069

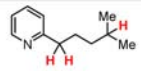
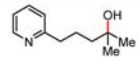
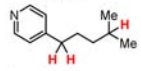
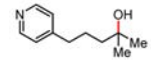
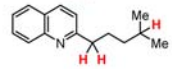
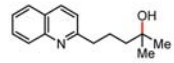
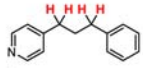
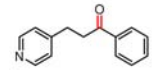
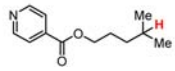
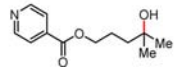
Table 3. Oxidation of Aliphatic C−H Bonds with Different Catalyst Systems



	% yield (conversion)	
method[a]	A	B[b]
[(Me$_3$tacn)RuCl$_3$]	75 (90)	30 (33)
Mn(OTf)$_2$/bipyridine	40 (78)	**4**: 17 (47)
		5: 17 (5)
Mn-(*S*,*S*-PDP)	55 (60)	0 (10)
Benzoxathiazine	71 (84)	**4**: 21 (50)
		5: 12 (5)

[a]Reactions conducted on 0.25 mmol scale and analyzed by quantitative NMR. [b]Values shown are for product **4**, unless otherwise indicated.

Table 4. Hydroxylation of C−H Bonds in the Presence of Basic Heterocycles

entry	substrate	product[a]	method A[b]	method B[c]
1			66%	40%
2			50%	38%
3			43%	35%
4			60%	38%
5			40%[d]	10%[e]

[a]Isolated yields (0.5 mmol scale). [b]Reactions conducted with [(Me$_3$tacn)RuCl$_3$] (2%), AgClO$_4$ (8%), CAN (6.0 equiv), *t*-BuOH/H$_2$O, 4 h. [c]Reactions conducted with Mn(OTf)$_2$ (0.1%), bipyridine (1%), AcOOH (3.0 equiv), AcOH, 90 s. [d]Reactions conducted with [(Me$_3$tacn)RuCl$_3$] (2%), AgClO$_4$ (8%), CAN (6.0 equiv), *t*-BuOH/H$_2$O, 2 h. [e]40% *N*-Oxide was isolated as well.

the nitrogen atoms, which can result in catalyst arrest, and the susceptibility of the N-center to oxidation.[24] *N*-Oxide formation with electrophilic oxidants is quite facile and often outcompetes C−H bond oxidation. We postulated that, under acidic reaction conditions, heterocycles should be protonated *in situ* and that protonation would mitigate problems arising from coordination and/or competing oxidation.[25] For example, upon addition of CAN to [(Me$_3$tacn)RuCl$_3$] the resulting solution reaches a pH of ∼2. At this pH, the pyridyl nitrogen (pK_a = 5.17)[26] should be predominately protonated, thus masking the N-heteroatom and enabling the desired C−H bond oxidation to occur. The acidic nature of the Mn/bipy catalyst system should function analogously.

Strikingly, the substrates that possess reactive nitrogen centers (2-picoline and 4-picoline derivatives) are smoothly hydroxylated at the 3° C−H center under both [(Me$_3$tacn)RuCl$_3$] and Mn/bipy reaction conditions. The ability to oxidize these sites in the presence of the basic heteroaromatic nitrogen groups highlights a perhaps heretofore underappreciated facet of these C−H oxidations: the acidity of the reaction media. Under suitably acidic conditions, the active oxidants can engage with a variety of substituted heteroaromatic groups including quinoline (pK_a of 2-methyl quinoline is 4.44).[27] The oxidation of 4-(3-phenylpropyl)pyridine yielded the product of selective benzylic oxidation with both Ru- and Mn-oxidation methods. The high degree of selectivity is indicative of the deactivating effect of the protonated pyridine ring on the pseudobenzylic position. Results with the isonicotinic acid ester (pK_a of 4-CO$_2$Et pyridine is 3.45)[26] in Table 4, entry 5 are consistent with the hypothesis that protonation of the ring nitrogen is needed for productive hydroxylation to occur. This substrate is smoothly oxidized under the [(Me$_3$tacn)RuCl$_3$] conditions, while a significant amount of *N*-oxide is formed under the Mn/bipy conditions.

One of the aforementioned issues with C−H oxidation in the presence of basic heterocycles is competitive *N*-oxide formation. While it may be expected that the protection of pyridyl groups as *N*-oxides would allow for the formation of the desired tertiary alcohol product, that does not occur under these conditions. Oxidations attempted on the *N*-oxide of Table 4, entry 1 resulted in quantitative decomposition under the [(Me$_3$tacn)RuCl$_3$] conditions, and in a complex mixture of products with the Mn/bipy conditions. Therefore, the oxidation of the heterocyclic nitrogen is not a viable solution to the oxidation of C−H bonds in the presence of basic heterocycles.

These studies have identified several key shortcomings in atom-transfer C−H oxidations that must be addressed in future efforts. One of the key issues that can plague these transformations is the incompatibility of certain methods with a subset of arene rings. The differences between the oxidative preferences of catalysts despite similarities in ligand and reaction conditions indicate a fundamental difference between metal-based species. The impediments surrounding the oxidation of heterocycles have been explored and we have proposed a solution for C−H hydroxylation even in the presence of such moieties that relies on the protective acidity of the reaction media. This report stands as one of very few where oxidation in the presence of pyridyl substrates can proceed through an oxygenase-type reaction.[25b] Furthermore, we believe that the juxtaposition of various methods outlined herein will facilitate a greater understanding of the underlying principles governing catalytic methods. In the future, the performance of new catalyst complexes would derive beneficial context by being benchmarked against the six catalyst systems discussed in this report. The great potential of C−H oxidation as a selective method for chemical synthesis justifies continued efforts to advance such technologies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03047.

Experimental details (PDF)

DOI: 10.1021/acs.orglett.5b03047
Org. Lett. 2015, 17, 6066−6069

AUTHOR INFORMATION

Corresponding Author

*E-mail: hasnain.malik@novartis.com.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to Professor Dan Stack and Dr. Brian Smith (Stanford University) for sharing with us details of $Mn(OTf)_2$-catalyzed oxidation reactions performed in their lab. The authors thank Dr. Lawrence G. Hamann, Dr. Andrew W. Patterson, and Jonathan E. Grob (Novartis Institutes for BioMedical Research, Inc.) for helpful discussions. Rhiannon Thomas-Tran (Stanford University) is thanked for her assistance in obtaining HRMS data. A.M.A. and J.D.B. gratefully acknowledge the National Science Foundation under the CCI Center for Selective C−H Functionalization (Grant CHE-1205646).

REFERENCES

(1) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. - Eur. J.* **2010**, *16*, 2654−2672.

(2) (a) White, M. C. *Science* **2012**, *335*, 807−809. (b) Godula, K.; Sames, D. *Science* **2006**, *312* (67), 7210−7220.

(3) (a) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976−1991. (b) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657−4673.

(4) Michaudel, Q.; Journot, G.; Reguerio-Ren, A.; Goswami, A.; Guo, Z.; Tully, T. P.; Zou, L.; Rmabhadran, R. O.; Houk, K. N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 12091−12096.

(5) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274. (b) Dua, R.; Shrivastava, S. H.; Sonwane, S. K.; Srivastava, S. K. *Adv. Biol. Res.* **2011**, *5*, 120−144.

(6) Que, L.; Tolman, W. B. *Nature* **2008**, *455*, 333−340. (b) Denisov, I. G.; Makris, T. M.; Sligar, S. G.; Schlichting, I. *Chem. Rev.* **2005**, *105*, 2253−2278.

(7) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169.

(8) (a) Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 2182−2184. (b) Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 5052−5054. (c) Iida, T.; Yamaguchi, T.; Nakamori, R.; Hikosaka, M.; Mano, N.; Goto, J.; Nambara, T. *J. Chem. Soc. Perkin Trans. 1* **2001**, 2229−2236. (d) Lee, J. S.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2247−2250.

(9) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824−828.

(10) (a) Wender, P. A.; Hilinski, M. K.; Mayweg, A. V. W. *Org. Lett.* **2005**, *7*, 79−82. (b) Hilinski, M. K.; Pierce, C. J. *Org. Lett.* **2014**, *16*, 6504−6507.

(11) Curci, R.; Dinoi, A. *Pure Appl. Chem.* **1995**, *67*, 811−822.

(12) (a) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783−787. (b) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566−571. (c) Vermeulen, N.; Chen, M. S.; White, M. C. *Tetrahedron* **2009**, *65*, 3078−3084. (d) Bigi, M. A.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721−9726. (e) Bigi, M. A.; Reed, S. A.; White, M. C. *Nat. Chem.* **2011**, *3*, 216−222.

(13) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052−14055.

(14) (a) Gómez, L.; Garcia-Bosch, I.; Company, A.; Benet-Buchholz, J.; Polo, A.; Sala, X.; Ribas, X.; Costas, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5720−5723. (b) Prat, I.; Gómez, L.; Canta, M.; Ribas, X.; Costas, M. *Chem. - Eur. J.* **2013**, *19*, 1908−1913. (c) Gómez, L.; Canta, M.; Font, D.; Prat, I.; Ribas, X.; Costas, M. *J. Org. Chem.* **2013**, *78*, 1421−1433.

(15) Ottenbacher, R. V.; Samsonenko, D. G.; Talsi, E. P.; Bryliakov, K. P. *Org. Lett.* **2012**, *14*, 4310−4313.

(16) McNeill, E.; Du Bois, J. *J. Am. Chem. Soc.* **2010**, *132*, 10202−10204.

(17) (a) Bakke, J. M.; FrØhaug, A. E. *J. Phys. Org. Chem.* **1996**, *9*, 310−318. (b) Bakke, J. M.; Lundquist, M. *Acta Chem. Scand.* **1986**, *40*, 430−433. (c) Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838−3840.

(18) Cheng, W. C.; Yu, W. Y.; Cheung, K. K.; Che, C. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1063−1064.

(19) McNeill, E.; Du Bois, J. *Chem. Sci.* **2012**, *3*, 1810−1813.

(20) Flender, C.; Adams, A. M.; Roizen, J. L.; McNeill, E.; Du Bois, J.; Zare, R. N. *Chem. Sci.* **2014**, *5*, 3309−3314.

(21) (a) Brodsky, B. H.; Du Bois, J. *J. Am. Chem. Soc.* **2005**, *127*, 15391−15393. (b) Litvinas, N. D.; Brodsky, B. H.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4513−4516. (c) Adams, A. M.; Du Bois, J. *Chem. Sci.* **2014**, *5*, 656−659.

(22) (a) Murphy, A.; Dubois, G.; Stack, T. D. P. *J. Am. Chem. Soc.* **2003**, *125*, 5250−5251. (b) Shen, D.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *Org. Lett.* **2014**, *16*, 1108−1111. (c) Smith, B. J. Dissertation, Stanford University, 2012.

(23) Plietker, B. *Synthesis* **2005**, 2453−2472.

(24) (a) Malik, H. A.; Taylor, B. L.; Kerrigan, J. R.; Grob, J. E.; Houk, K. N.; Hamann, L. G.; Patterson, A. W. *Chem. Sci.* **2014**, *5*, 2352−2361. (b) He, J.; Hamann, L. G.; Davies, H. M. L.; Beckwith, R. E. J. *Nat. Commun.* **2015**, *6*, 5943−5946. (c) Salamone, M.; Giammarioli, I.; Bietti, M. *Chem. Sci.* **2013**, *4*, 3255−3262. (d) Asensio, G.; Gonzalez-Nunez, M. E.; Bernardini, C. B.; Mello, R.; Adam, W. *J. Am. Chem. Soc.* **1993**, *115*, 7250−7253.

(25) (a) Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 12796−12799. (b) During the course of publication of this manuscript, we became aware of a related study: Howell, J. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 14590−14593.

(26) Clarke, K.; Rothwell, K. *J. Chem. Soc.* **1960**, 1885−1895.

(27) Brown, H. C.; McDaniel, D. H.; Häfliger, O. Dissociation Constants. In *Determination of Organic Structures by Physical Methods*, Braude, E. A.; Nachod, F. C., Eds.; Academic Press: New York, 1955; pp 657−662.

DOI: 10.1021/acs.orglett.5b03047
Org. Lett. 2015, 17, 6066−6069