



# C-C Bond Formation

# Tandem C–C Bond Cleavage of Cyclopropanols and Oxidative Aromatization by Manganese(IV) Oxide in a Direct C–H to C–C Functionalization of Heteroaromatics

Desta Doro Bume,<sup>[a]</sup> Cody Ross Pitts,<sup>[a]</sup> and Thomas Lectka\*<sup>[a]</sup>

**Abstract:** We report a direct C–H to C–C bond functionalization of electron-deficient heteroaromatics enabled by mild C–C bond cleavage of cyclopropanols as a new route to  $\beta$ -aryl carbonyl-containing products. Additionally, as an alternative to using a "catalyst" that requires an excess amount of a sacrificial oxidant for regeneration and/or oxidative aromatization, this paper features manganese(IV) oxide as an inexpensive "dual role" reagent – effecting both C–C bond cleavage and ultimate rearomatization. Under the specified conditions, a variety of heterocycles proved competent for regioselective C–C bond formation, alongside a diverse array of cyclopropanols with broad functional-group tolerance. We highlight applications to complex-molecule synthesis and direct derivatization of biologically active alkaloids. Furthermore, kinetic isotope effect (KIE) experiments, radical scavengers, and some insight into the application of tri- and tetravalent manganese species are invoked to shape an initial mechanistic hypothesis.

# Introduction

The C-H to C-C bond functionalization of aromatic molecules is an essential part of organic synthesis. As the prototypical example, Friedel-Crafts chemistry has been instrumental in alkylation, arylation, and acylation of countless aromatic systems.<sup>[1]</sup> However, these reactions are less amenable to electrondeficient substrates, such as the nitrogen-based heterocycles that comprise a substantial portion of biologically relevant molecules.<sup>[2]</sup> Instead, such substrates provide a better electronic platform to construct C-C bonds by pairing, for instance, nucleophilic radicals with electron-deficient sites on the aromatic ring (thus guiding the opposite selectivity of Friedel-Crafts chemistry).<sup>[3]</sup> This concept has received a large amount of attention in recent decades, especially regarding the addition of sp<sup>3</sup>carbon-centered radicals to heteroaromatics by decarboxylation,<sup>[4]</sup> dehalogenation,<sup>[5]</sup> and the decomposition of alkylboron species<sup>[6]</sup> and metal sulfinate compounds,<sup>[7]</sup> among other methods.<sup>[8]</sup> From another vantage point, more efficient methods and increasingly complex structures may be accessible by applying direct C-C activation. Given our recent experience with cyclopropane ring-opening chemistry,<sup>[9]</sup> we envisioned that the generation of an alkyl radical by C-C bond cleavage of a cyclopropanol in the presence of an electron-deficient aromatic ring could yield an interesting variety of β-aryl carbonyl-containing products not previously reported in the literature.[10]

Notably, a common feature of modern heterocycle alkylation methods (e.g., in many decarboxylation reactions<sup>[4]</sup>) is the catalytic generation of alkyl radicals; yet, this is invariably counterbalanced by the necessity for an excess amount of a "sacrificial oxidant" to restore aromaticity and/or regenerate the catalyst.<sup>[11]</sup> Accordingly, it may be equally if not more advantageous to find one inexpensive reagent to play both roles efficiently by (1) generating alkyl radicals and (2) re-establishing aromaticity following radical addition, thus obviating the need for a sacrificial reagent. In this paper, the "dual role" reagent approach is applied to the search for conditions whereby heterocyclic C-C bond formation is achieved from cyclopropanol ring-opening chemistry. Upon screening a number of potential oxidants, we rapidly found that stoichiometric manganese(IV) oxide successfully balances this dual role (Scheme 1). Manganese(IV) oxide is inexpensive, mild, abundant, and relatively nontoxic, making it an ideal candidate.

proposed dual role of manganese(IV) oxide



Scheme 1. "Dual role" reagent.

# **Results and Discussion**

We began screening with 2-n-hexyl-1-methylcyclopropan-1-ol (1) and an excess of pyridinium tosylate (2) in MeCN in the

 <sup>[</sup>a] Department of Chemistry, Johns Hopkins University 3400 North Charles Street, Baltimore, MD, 21218, USA E-mail: Lectka@jhu.edu lectka.chemistry.jhu.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201501405.





presence of the oxidants in Table 1 under N<sub>2</sub>. Although most of these oxidants consumed the starting material (primarily generating the corresponding enone<sup>[12]</sup>), we quickly found that manganese(IV) oxide was competent in eliciting the desired heterocycle alkylation reaction. Manganese(IV) oxide is a very logical "dual role" candidate, as there is precedent for this reagent playing both necessary roles. For instance, manganese(IV) oxide has been widely utilized as a mild oxidant for allylic, benzylic, and propargylic alcohols, and under certain circumstances saturated alcohols.<sup>[13]</sup> It has also been used as an oxidant in the rearomatization of 1,4-dihydropyridines.<sup>[14]</sup>

Table 1. Screening for "dual role" oxidants.

H <sub>3</sub> C(H <sub>2</sub> C) <sub>5</sub>	Me + N 1 OH + Tos 0 equiv.) (5.0 equiv.)	⊖ MnO <sub>2</sub> (1.1 € → MeCN, r.t.,	equiv.) Het O $12 h R - (CH_2)_5 CH_3$
Entry	Oxidant	Equiv.	Isolated yield (%) <sup>[a]</sup>
1	MnO <sub>2</sub>	1.1	66 <sup>[b]</sup>
2	MnO <sub>2</sub>	0.5	40 <sup>[b]</sup>
3	MnO <sub>2</sub> (no acid)	1.1	trace
4	Mn(OAc) <sub>3</sub> •2H <sub>2</sub> O	1.0	35
5	Mn(OAc) <sub>2</sub> •4H <sub>2</sub> O	1.0	8
6	none	-	0
7	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	1.0	trace
8	(NH <sub>4</sub> ) <sub>2</sub> Ce(NO <sub>3</sub> ) <sub>6</sub>	1.0	0
9	DDQ	1.0	0
10	FeCl <sub>3</sub>	1.0	0

[a] Combined 2- and 4-isomers of alkylated pyridine. [b] Using pyridinium tosylate or pyridine/trifluoroacetic acid.

Regarding additional reaction optimization, we found that: (1) Pyridine (as opposed to pyridinium) is significantly less competent in the reaction. This is likely due to more favorable orbital overlap of the pyridinium LUMO with the HOMO of the nucleophilic carbon-centered radical.<sup>[15]</sup> (2) For ease of preparation, the pyridinium salt can be generated in situ with equimolar trifluoroacetic acid and with no sacrifice in yield. (3) Heating of the reaction mixture to 80 °C provides no further increase in yield. (4) Decreasing the amount of pyridinium (and also the  $MnO_2$ ) is accompanied by a decrease in yield.<sup>[16]</sup> (5) Lowervalent manganese species (Entries 4 and 5, Table 1) are less competent. Thus, the optimal conditions require stirring of 1.0 equiv. of the cyclopropanol, 1.1 equiv. of  $MnO_2$ , 5.0 equiv. of trifluoroacetic acid, and 5.0 equiv. of pyridine at room temperature in MeCN overnight.

Using these conditions, we surveyed the scope of the reaction for various commercially available heterocycles using 2benzyl-1-methylcyclopropan-1-ol and 2-*n*-hexyl-1-methylcyclopropan-1-ol (Figure 1). In the prototypical example, 2- and 4alkylated adducts of pyridine were isolated in 80 % yield in a 2.4:1 (**3a/3b**) ratio using 2-benzyl-1-methylcyclopropan-1-ol [similar ratio of 2:1 (**4a/4b**) using **1**]. When obstructing the 4position of pyridine with electron-withdrawing substituents (e.g. **5**, **6**, and **7**), the only major product was alkylated in the 2-position.<sup>[17]</sup> No 3-alkylated products were isolated in any instance, and the presence of electron-donating substituents on the ring produced a substantial decrease in yield (i.e. 4-meth-oxypyridine derivative **8** was isolated in only 22 % yield). This is consistent with the concept of pairing a nucleophilic carbon radical with the most electron-deficient site(s) on the heterocycle.



Figure 1. Reaction scope: varying heterocycles. Isolated yields reported. [a] Unless otherwise specified.

Beyond substituted pyridines, other nitrogen-based heterocycles proved equally competent in the reaction, particularly quinoline derivatives 9-14. Quinoline behaved similarly to pyridine, providing only the 2- and 4-alkylated adducts in up to 81 % yield (11 and 12). Blocking the 2- or 4-position also resulted in only one product (9, 10, and 13). Additionally, 4bromoisoquinoline and polycyclic heterocycles, such as acridine and phenanthridine, were regioselectively converted into one alkylated product (14-16). Aromatic molecules that contain multiple heteroatoms (i.e. guinoxaline and benzothiazole) also exhibit efficient regioselective alkylation (17 and 18). Lastly, we demonstrate the value of these products as potential building blocks in complex-molecule synthesis, e.g., the dehydration of alkylated isoquinoline (obtained from the reaction of 19 and 20) to obtain the extended benzopyrrocoline skeleton 21, present in the lamellarin natural products (Scheme 2).<sup>[18]</sup>

27



#### easy access to benzopyrrocoline derivatives



Scheme 2. Potential application to natural-product synthesis.

Next, we examined the substrate scope with respect to varying the cyclopropanols (Figure 2). The majority of cyclopropanols in Figure 2 were easily prepared by Kulinkovich chemistry,<sup>[19]</sup> and acridine was chosen for screening purposes due to high regioselectivity and ease of isolation. The reaction consistently afforded very good yields for cyclopropanols that putatively involve both primary and secondary carbon-centered radical intermediates (22-33). To highlight a few entries: (1) The cyclopropanol derived from safrole produced compound 22 in 86 % yield; this reasonably translated into a gram-scale application of the reaction. (2) The tricyclic cyclopropanol derived from norbornene produced the bicyclo[2.2.1]heptane derivative 25 in 73 % yield. (3) The presence of an amine or ether substituent does not greatly affect the product yields (28 and 30). (4) Bicyclo[3.1.0]hexan-1-ol selectively ungergoes a ring expansion to afford  $\beta$ -substituted cyclohexanone **31** in good yield. (5) If the cyclopropanol employed is a hemiacetal, the β-substituted ester is equally accessible (32). (6) Finally, the reaction can also be applied to larger molecular skeletons, such as 33 (whose starting cyclopropanol was derived from methyl lithocholate<sup>[20]</sup>). Remarkably, the secondary alcohol (in the 3-position) is not oxidized over the course of the reaction.





Figure 2. Reaction scope: varying cyclopropanols. Isolated yields reported. [a] Alkylated solely in the 9-position.



In addition to the synthesis of non-natural steroid **33**, we also briefly explored the application of this reaction to other particularly complex substrates that represent drug derivatives and/or natural products (Figure 3). Bisacodyl, a known laxative containing a substituted pyridine,<sup>[21]</sup> was alkylated in the 2- and 4-positions in a 1:1 ratio in 44 % yield (**34**). Benzoylquinine, an antimalarial derivative<sup>[22]</sup> also employed as an asymmetric catalyst,<sup>[23]</sup> was selectively alkylated in the 2-position of its quinoline ring in 39 % yield (**35**).



Figure 3. Direct application to complex molecules.

As a final point of interest, we offer initial insight into the reaction mechanism. The first step of our working hypothesis involves putative coordination of manganese(IV) oxide and one-electron oxidation of the cyclopropanol, activating the more substituted C–C bond to produce a  $\beta$ -oxo carbon-centered radical intermediate (possibly in equilibrium with the corresponding metalloradical<sup>[24]</sup>).<sup>[25]</sup> In the presence of TEMPO (**36**), a notorious radical scavenger,<sup>[26]</sup> no alkylation of the heterocycle was observed in the <sup>1</sup>H NMR spectrum of the crude reaction mixture (Scheme 3). Additionally, we took the opportunity to apply Selectfluor (**37**) as a radical trap, as it is an established source of atomic fluorine in the presence of alkyl radicals (Scheme 3).<sup>[27]</sup> The  $\beta$ -fluorinated product **38** is, in fact, observed by <sup>19</sup>F NMR spectroscopy, strongly supporting initial cyclopropanol ring-opening to produce a radical intermediate.<sup>[28]</sup>



Scheme 3. Radical scavengers.

In the subsequent step of the mechanism, the heterocycle acts as the "radical trap", and the C–C bond is formed. Then, a manganese species is likely responsible for oxidative aromatization. To investigate the C–C bond formation and C–H cleavage steps, we designed both inter- and intramolecular kinetic isotope effect (KIE) experiments with deuterated pyridine derivatives (Scheme 4). Both instances reflect a small, secondary iso-



tope effect (average intermolecular KIE = 1.03 for the 2- and 4positions, average intramolecular KIE = 1.18 for the 2-position), allowing us to state with certainty that C-H cleavage is not rate-determining.<sup>[29]</sup> This step is expectedly facile due to a gain in aromaticity.<sup>[30]</sup>

#### intermolecular KIE



Scheme 4. Competitive kinetic isotope effects (averages of at least two runs).  $[P_H] = product of C-H bond cleavage; [P_D] = product of C-D bond cleavage.$ 

Perhaps the most complicated aspect of the mechanism involves the precise nature of the reactive manganese species. Although an in-depth mechanistic study is beyond the scope of this article, we offer a few notes on the involvement of manganese in cyclopropanol ring-opening and oxidative aromatization. In the literature, manganese(III) reagents have been successfully employed in cyclopropanol ring-opening chemistry.<sup>[31]</sup> In our hands, both manganese(IV) and manganese(III) reagents produced the desired product; however, the product yield when using manganese(III) is virtually one-half that of the optimized conditions (Table 1). The fact that a manganese(III) reagent produces the desirable product at all may hint at the idea that manganese(III) could be a key player in oxidative aromatization. In fact, there is literature precedent for the rearomatization of 1,4-dihydropyridines (i.e., Hantzsch esters 39 to 40) using both manganese(III) and manganese(IV) reagents (Scheme 5).<sup>[14,32]</sup> Depending on the nature of the substrate, it is conceivable that rearomatization could occur by an electron transfer/loss of proton or a hydrogen atom abstraction mechanism.<sup>[8b,32,33]</sup> In any case, current findings suggest that both oxidation states of manganese could play a role in the cyclopropanol C-C bond cleavage and rearomatization steps. One feasible mechanistic pathway is proposed in Scheme 6.



Scheme 5. Precedent for the role of tri- and tetravalent manganese in the oxidative aromatization of Hantzsch esters.





Scheme 6. Working mechanistic hypothesis.

### Conclusions

The "dual role" nature of manganese(IV) dioxide allows for efficient (1) C–C bond cleavage of cyclopropanols and (2) rearomatization following C–C bond formation in the alkylation of heterocycles. This method is tolerant of multiple combinations of heterocycles and cyclopropanols, containing a variety of substituents. We demonstrate that products of this reaction can be used as building blocks for natural-product synthesis; we also explore the direct derivatization of complex biologically relevant molecules. Initial mechanistic insights suggest a radicalbased mechanism from radical scavenger experiments, that C– H cleavage is not rate-limiting from competitive KIE experiments, and that at least two different oxidation states of manganese (III and IV) might play a role in both C–C bond cleavage and rearomatization.

## **Experimental Section**

**Supporting Information** (see footnote on the first page of this article): General experimental procedures and characterization data.

## Acknowledgments

T. L. would like to thank the National Science Foundation (NSF) (CHE 1152996, CHE 1465131) for support. The authors also would like to thank James Levi Knippel for his assistance.

**Keywords:** Manganese · C-H functionalization · Heterocycles · Cyclopropanols · Dual role reagent

- For some reviews, see: a) N. O. Calloway, *Chem. Rev.* **1935**, *17*, 327–392;
   b) P. H. Gore, *Chem. Rev.* **1955**, *55*, 229–281; c) M. Rueping, B. J. Nachtscheim, *Beilstein J. Org. Chem.* **2010**, DOI: 10.3762/bjoc.6.6.
- [2] See: a) J. E. Robbers, M. K. Speedie, V. E. Tyler, *Pharmacognosy and Pharmacobiotechnology*, Lippincott, Williams & Wilkins, Philadelphia, **1996**, pp. 143–185; b) T. Naito, *Chem. Pharm. Bull.* **2008**, *56*, 1367–1383; c) P. Russo, A. Frustaci, A. Del Bufalo, M. Fini, A. Cesario, *Curr. Med. Chem.* **2013**, *20*, 1686–1693; d) P. Kittakoop, C. Mahidol, S. Ruchirawat, *Curr. Top. Med. Chem.* **2014**, *14*, 239–252; e) T. P. Cushnie, B. Cushnie, A. J. Lamb, *Int. J. Antimicrob. Agents* **2014**, *44*, 377–386; f) S. Qiu, H. Sun, A.-H. Zhang,





H.-Y. Xu, G.-L. Yan, Y. Han, X.-J. Wang, Chin. J. Nat. Med. 2014, 12, 401–406.

- [3] F. O'Hara, D. G. Blackmond, P. S. Baran, J. Am. Chem. Soc. 2013, 135, 12122–12134.
- [4] a) F. Minisci, R. Bernadi, F. Bertini, R. Galli, M. Perchinunno, *Tetrahedron* 1971, 27, 3575–3580; b) F. Minisci, E. Vismara, F. Fontana, *Heterocycles* 1989, 28, 489–519; c) F. Minisci, F. Fontana, E. Vismara, J. Heterocycl. Chem. 1990, 27, 79–96; d) C. J. Cowden, Org. Lett. 2003, 5, 4497–4499;
  e) P. B. Palde, B. R. McNaughton, N. T. Ross, P. C. Gareiss, C. R. Mace, R. C. Spitale, B. L. Miller, Synthesis 2007, 15, 2287–2290.
- [5] a) F. Minisci, E. Vismara, F. Fontana, J. Org. Chem. 1989, 54, 5224–5227;
  b) J. A. Murphy, M. S. Sherburn, *Tetrahedron Lett.* 1990, 31, 1625–1628;
  c) J. A. Murphy, M. S. Sherburn, *Tetrahedron Lett.* 1990, 31, 3495–3496;
  d) F. Minisci, F. Fontana, G. Pianese, Y. M. Yan, J. Org. Chem. 1993, 58, 4207–4211;
  e) M. A. J. Duncton, M. A. Estiarte, R. J. Johnson, M. Cox, D. J. R. O'Mahony, W. T. Edwards, M. G. Kelly, J. Org. Chem. 2009, 74, 6354–6357.
- [6] a) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianattassio, M. D. Bel, P. S. Baran, J. Am. Chem. Soc. 2011, 133, 3292–3295; b) G. A. Molander, V. Colombel, V. A. Braz, Org. Lett. 2011, 13, 1852–1855.
- [7] Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95–99.
- [8] a) D. A. DiRocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway, M. Tudge, *Angew. Chem.* 2014, *126*, 4902–4906; b) N. Nishida, H. Ida, Y. Kuninobu, M. Kanai, *Nat. Commun.* 2014, *5*, 3387; c) J. Jin, D. W. C. MacMillan, *Angew. Chem.* 2015, *127*, 1585–1589; d) R.-J. Tang, L. Kang, L. Yang, *Adv. Synth. Catal.* 2015, *357*, 2055–2060.
- [9] S. Bloom, D. D. Bume, C. R. Pitts, T. Lectka, Chem. Eur. J. 2015, 21, 8060– 8063.
- [10] Note that non-heteroaromatic β-aryl carbonyl-containing products can be accessed using cyclopropanols and palladium chemistry; see: a) D. Rosa, A. Orellana, *Chem. Commun.* **2013**, *49*, 5420–5422; b) D. Rosa, A. Nikolaev, N. Nithiy, A. Orellana, *Synlett* **2015**, *26*, 441–448. Also, note that heteroaromatic β-aryl carbonyl-containing products can be accessed using conjugate addition chemistry; see: c) A. C. Spivey, L. Shukla, J. F. Hayler, *Org. Lett.* **2007**, *9*, 891–894; d) X.-Q. Yu, Y. Yamamoto, N. Miyaura, *Synlett* **2009**, *6*, 994–998; e) J.-L. Shih, T. S. Nguyen, J. A. May, *Angew. Chem. Int. Ed.* **2015**, *54*, 9931–9935.
- [11] Many catalytic methods for generating alkyl radicals for heterocycle alkylation in the literature require typically a three- to ten-fold excess of a sacrificial oxidant; see ref.<sup>[4-8]</sup>
- [12] a) J. Jiao, L. X. Nguyen, D. R. Patterson, R. A. Flowers II, Org. Lett. 2007, 9, 1323–1326; b) H. Tsuchida, M. Tamura, E. Hasegawa, J. Org. Chem. 2009, 74, 2467–2475.
- [13] a) A. J. Fatiadi, Synthesis **1976**, 2, 65–104; b) R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, Acc. Chem. Res. **2005**, 38, 851–869; c) G. Tojo, M. Fernández, Oxidation of Alcohols to Aldehydes and Ketones, Springer, New York, **2006**, pp. 290–309.
- [14] J. J. V. Eynde, F. Delfosse, A. Mayence, Y. Van Haverbeke, *Tetrahedron* 1995, 51, 6511–6516.
- [15] J. Tauber, D. Imbri, T. Opatz, Molecules 2014, 19, 16190-16222.
- [16] With some exceptions, most direct heterocycle alkylation reactions to date require a threefold or higher excess of either the radical source or the heterocycle.
- [17] Note that obstructing the 3-position of pyridine may result in three regioisomers. As the result is a decrease in yield of each individual isomer (detrimental to synthetic utility), starting materials with this substitution were not explored further in this work.
- [18] a) A. R. Quesada, M. D. García Grávalos, J. L. Fernández Puentes, Br. J. Cancer 1996, 74, 677–682; b) C. Bailly, Curr. Med. Chem. Anti-Cancer Agents 2004, 4, 363–378; c) D. Pla, F. Albericio, M. Alvarez, Anti-Cancer Agents Med. Chem. 2008, 8, 746–760.
- [19] a) O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski, *Synthesis* 1991, *3*, 234;
   b) O. G. Kulinkovich, *Chem. Rev.* 2003, *103*, 2597–2632.

- [20] A. Enhsen, W. Kramer, G. Wess, Drug Discovery Today 1998, 9, 409-418.
- [21] S. D. Wexner, D. E. Beck, T. H. Baron, R. D. Fanelli, N. Hyman, B. Shen, K. E. Wasco, *Gastrointest. Endosc.* **2006**, *63*, 894–909.
- [22] World Health Organization, WHO Model List of Essential Medicines, 19th ed., WHO, 2015, http://www.who.int/medicines/publications/essentialmedicines/en/.
- [23] For instance: a) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* 2003, *103*, 2985–3012; b) S. France, A. Weatherwax, A. E. Taggi, T. Lectka, *Acc. Chem. Res.* 2004, *37*, 592–600; c) D. H. Paull, C. J. Abraham, M. T. Scerba, T. Lectka, *Acc. Chem. Res.* 2008, *41*, 655–663; d) D. H. Paull, A. Weatherwax, T. Lectka, *Tetrahedron* 2009, *65*, 6771–6803.
- [24] For a review on manganese(III) chemistry, see: B. B. Snider, Chem. Rev. 1996, 96, 339–363.
- [25] We draw an analogy of the proposed ring-opening step to the proposed manganese(IV) oxide oxidation of alcohols mechanism; however, in this system, C-C cleavage occurs to relieve ring strain and produce an alkyl radical, as opposed to H-atom abstraction. For reports on the mechanism of alcohol oxidation, see: R. J. Gritter, G. D. Dupre, T. J. Wallace, *Nature* **1964**, *202*, 179–181, and references therein.
- [26] V. W. Bowry, K. U. Ingold, J. Am. Chem. Soc. 1992, 114, 4992-4996.
- [27] For an in-depth mechanistic study on this topic, see: C. R. Pitts, S. Bloom, R. Woltornist, D. J. Auvenshine, L. R. Ryzhkov, M. A. Siegler, T. Lectka, J. Am. Chem. Soc. 2014, 136, 9780-9791. For applications, see: a) M. Rueda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin, G. M. Sammis, J. Am. Chem. Soc. 2012, 134, 4026-4029; b) S. Bloom, C. R. Pitts, D. Miller, N. Haselton, M. G. Holl, E. Urheim, T. Lectka, Anaew. Chem. Int. Ed. 2012, 51, 10580-10583; Anaew. Chem. 2012, 124, 10732; c) S. Bloom, C. R. Pitts, R. Woltornist, A. Griswold, M. G. Holl, T. Lectka, Org. Lett. 2013, 15, 1722-1724; d) S. Bloom, S. A. Sharber, M. G. Holl, J. L. Knippel, T. Lectka, J. Org. Chem. 2013, 78, 11082–11086; e) Y. Amaoka, M. Nagamoto, M. Inoue, Org. Lett. 2013, 15, 2160-2163; f) J.-B. Xia, C. Zhu, C. Chen, J. Am. Chem. Soc. 2013, 135, 17494-17500; g) S. Bloom, J. L. Knippel, T. Lectka, Chem. Sci. 2014, 5, 1175-1178; h) C. R. Pitts, B. Ling, R. Woltornist, R. Liu, T. Lectka, J. Org. Chem. 2014, 79, 8895-8899; i) S. Bloom, M. McCann, T. Lectka, Org. Lett. 2014, 16, 6338-6341; j) J.-B. Xia, C. Zhu, C. Chen, Chem. Commun. 2014, 50, 11701-11704; k) J.-B. Xia, Y. Ma, C. Chen, Ora. Chem. Front. 2014, 1, 468-472; I) C. W. Kee, K. F. Chin, M. W. Wong, C.-H. Tan, Chem. Commun. 2014, 50, 8211-8214; m) M. Rueda-Becerril, O. Mahe, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis, J.-F. Paquin, J. Am. Chem. Soc. 2014, 136, 2637-2641; n) D. Cantillo, O. de Frutos, J. A. Rincon, C. Mateos, O. C. Kappe, J. Org. Chem. 2014, 79, 8486-8490; o) S. D. Halperin, H. Fan, S. Chang, R. E. Martin, R. Britton, Angew. Chem. Int. Ed. 2014, 53, 4690-4693; Angew. Chem. 2014, 126, 4778.
- [28] Note that the  $\beta\mbox{-fluorinated}$  product is prone to dehydrofluorination upon isolation; see ref.  $\space{[9]}$
- [29] a) E. V. Anslyn, D. A. Dougherty, Modern Physical Organic Chemistry, University Science Books, Sausalito, CA, 2006; b) E. M. Simmons, J. F. Hartwig, Angew. Chem. Int. Ed. 2012, 51, 3066–3072; Angew. Chem. 2012, 124, 3120.
- [30] For some examples of similar kinetic isotope effects in other Miniscitype reactions, see: a) Z. Shi, F. Glorius, *Chem. Sci.* 2013, *4*, 829–833; b)
   R. Xia, M.-S. Xie, H.-Y. Niu, G.-R. Qu, H.-M. Guo, *Org. Lett.* 2014, *16*, 444–447; c) J. Kan, S. Huang, J. Lin, M. Zhang, W. Su, *Angew. Chem. Int. Ed.* 2015, *54*, 2199–2203; *Angew. Chem.* 2015, *127*, 2227.
- [31] a) N. Iwasawa, S. Hayakawa, M. Funahashi, K. Isobe, K. Narasaka, Bull. Chem. Soc. Jpn. **1993**, 66, 819–827; b) Y.-F. Wang, S. Chiba, J. Am. Chem. Soc. **2009**, 131, 12570–12572; c) Y.-F. Wang, K. K. Toh, E. P. Ng, S. Chiba, J. Am. Chem. Soc. **2011**, 133, 6411–6421.
- [32] R. S. Varma, D. Kumar, Tetrahedron Lett. 1999, 40, 21–24.
- [33] a) M. Moghadam, M. Naser-Esfahani, S. Tangestaninejad, V. Mirkhani, *Bioorg. Med. Chem. Lett.* 2006, *16*, 2026–2030; b) A. Saini, S. Kumar, J. S. Sandhu, *J. Sci. Ind. Res.* 2008, *67*, 95–111, and references cited therein.

Received: November 6, 2015 Published Online: November 24, 2015