ORGANIC LETTERS

2013
Vol. 15, No. 3
718–720

Ruthenium-Catalyzed C–H Oxygenation on Aryl Weinreb Amides

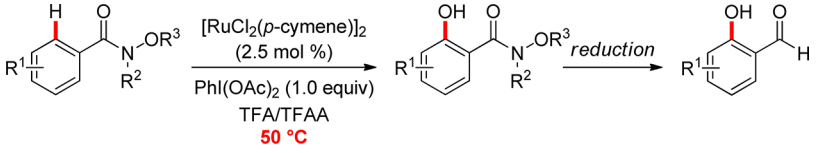
Fanzhi Yang and Lutz Ackermann*

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstrasse 2, 37077 Göttingen, Germany

Lutz.Ackermann@chemie.uni-goettingen.de

Received December 22, 2012

ABSTRACT



Versatile ruthenium catalysts enabled unprecedented C–H bond oxygenations of aryl Weinreb amides with ample scope under exceedingly mild reaction conditions, thereby also giving access to valuable *ortho*-hydroxylated aldehydes. Mechanistic studies provided strong support for a kinetically relevant C–H bond activation.

N-Methoxy-*N*-methylamides—Weinreb amides—represent functional groups of key importance in synthetic organic chemistry, because they are easily accessible, and because they can be chemoselectively transformed into the corresponding ketones and aldehydes.[1] Thus, these amides have found numerous applications in organic synthesis,[1] as, for instance, illustrated by the preparation of naturally occurring bioactive compounds.[2] In contrast, Weinreb amides have unfortunately been less explored for metal-catalyzed C–H bond functionalizations,[3] and direct oxygenations[4,5] of aryl Weinreb amides have, to the best of our knowledge, thus far proven elusive. Within our research program on sustainable ruthenium-catalyzed C–H bond functionalization,[6] we developed site selective C(sp^2)–H bond oxygenations on aryl Weinreb amides under remarkably mild reaction conditions, on which we report herein.

At the outset of our studies, we tested different terminal oxidants for the envisioned C–H bond oxygenation of Weinreb amide **1a** (Table 1). The transformation failed to proceed in the absence of a stoichiometric oxidant or of a ruthenium complex (entries 1 and 2). Likewise, copper(II) or silver(I) oxidants were found to be ineffective (entries 3 and 4). In contrast, *m*-CPBA, $K_2S_2O_8$, or $PhI(OAc)_2$ proved to be viable alternatives (entries 5–7), with optimal results being accomplished with the hypervalent iodine(III) reagent $PhI(OAc)_2$ at a reaction temperature of 50 °C

(1) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. Reviews: (b) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707–3738. (c) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517–524.

(2) Sected representative examples: (a) Paek, S.-M.; Seo, S.-Y.; Kim, S.-H.; Jung, J.-W.; Lee, Y.-S.; Jung, J.-K.; Suh, Y.-G. *Org. Lett.* **2005**, *7*, 3159–3162. (b) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2008**, *10*, 4489–4492. (c) Shimizu, T.; Satoh, T.; Murakoshi, K.; Sodeoka, M. *Org. Lett.* **2005**, *7*, 5573–5576. See also refs 1b, 1c.

(3) Illustrative recent reviews: (a) Arockiam, A. P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879–5918. (b) Hirano, K.; Miura, M. *Chem. Commun.* **2012**, *48*, 10704–10714. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (e) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212–11222. (f) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (g) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883 and references cited therein. For a representative example, see: (h) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191.

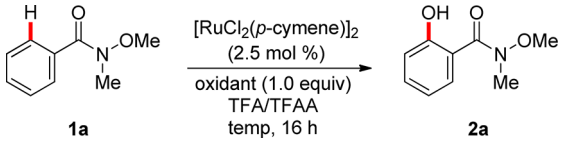
(4) Recent reviews on C(sp^2)–O bond forming reactions: (a) Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912–4924. (b) Alonso, D. A.; Najera, C.; Pastor, I. M.; Yus, M. *Chem.—Eur. J.* **2010**, *16*, 5274–5284. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169 and references cited therein.

(5) Representative examples of metal-catalyzed direct oxygenations: (a) Mo, F.; Trzepkowski, L. J.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 13075–13079. (b) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070–13074. (c) Thirunavukkarasu, V. S.; Ackermann, L. *Org. Lett.* **2012**, *14*, 6206–6209. (d) Yang, Y.; Lin, Y.; Rao, Y. *Org. Lett.* **2012**, *14*, 2874–2877. (e) Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4210–4213. (f) Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504–9509. (g) McNeill, E.; Du Bois, J. *Chem. Sci.* **2012**, *3*, 1810–1813. (h) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094–4097. (i) Li, W.; Sun, P. *J. Org. Chem.* **2012**, *77*, 8362–8366. (j) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134–137. (k) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Chem.—Eur. J.* **2012**, *18*, 5541–5545. (l) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655. (m) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (n) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465–3468. (o) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35–40 and references cited therein.

10.1021/ol303520h
Published on Web 01/22/2013

(entries 7–10). It is important to note that this constitutes the lowest reaction temperature reported thus far for ruthenium-catalyzed C(sp^2)–H bond oxygenations. $[RuCl_2(PPh_3)_3]$ could be employed as the catalyst as well but furnished the desired product **2a** in a diminished yield (entry 11). However, the well-defined ruthenium(II) biscarboxylate complex $[Ru(O_2CMes)_2(p\text{-cymene})]$[7,8] compared favorably with $[RuCl_2(p\text{-cymene})]_2$ (entries 12 and 13). Generally, the ruthenium catalysts were found to be highly robust, as showcased by all catalytic reactions being performed without strict exclusion of moisture under an atmosphere of air. Yet, the C–H bond oxygenation also occurred readily under an inert N_2 atmosphere (entry 14).

Table 1. Optimization of C–H Bond Oxygenation[a]



1a 2a

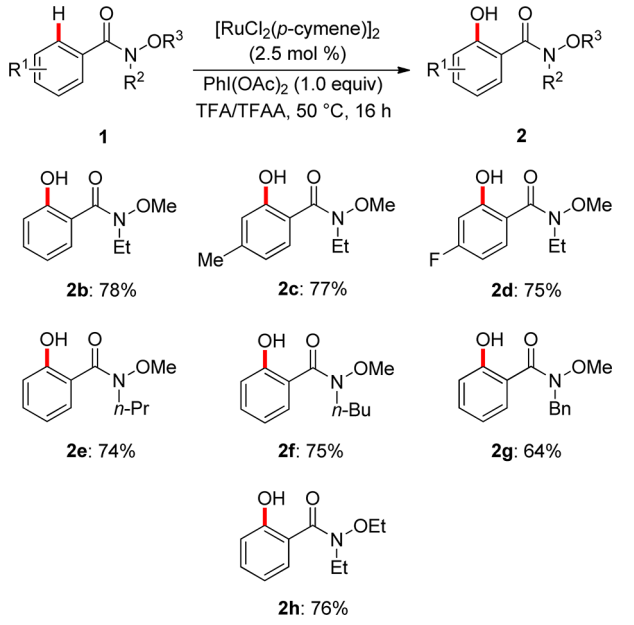
entry	oxidant	temp (°C)	yield
1	–	50	–
2	$K_2S_2O_8$	50	–[b]
3	$Cu(OAc)_2 \cdot H_2O$	50	–
4	AgOAc	50	<5%[c]
5	*m*-CPBA	50	39%
6	$K_2S_2O_8$	50	57%
7	$PhI(OAc)_2$	30	30%
8	**$PhI(OAc)_2$**	**50**	**84%**
9	$PhI(OAc)_2$	80	60%
10	$PhI(OAc)_2$	100	54%
11	$PhI(OAc)_2$	50	57%[d]
12	**$PhI(OAc)_2$**	**50**	**80%**[e]
13	$PhI(OAc)_2$	50	76%[f]
14	$PhI(OAc)_2$	50	79%[g]

[a] Reaction conditions: **1a** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), oxidant (0.5 mmol), TFA/TFAA (2.0 mL; 3/1); isolated yields. [b] No catalyst. [c] GC conversion. [d] $[RuCl_2(PPh_3)_3]$ (5.0 mol %). [e] $[Ru(O_2CMes)_2(p\text{-cymene})]$ (2.5 mol %). [f] $[RuCl_2(p\text{-cymene})]_2$ (1.3 mol %). [g] Under N_2.

With an effective catalytic system in hand, we studied the influence of the amide *N*-substitution pattern on the efficacy of the C–H bond oxygenation (Scheme 1). Notably, a variety of groups on the amides was well tolerated by the catalytic system to furnish the corresponding products **2b**–**2h**, even when being sterically hindered.

Subsequently, we evaluated the versatility of the C–H bond oxygenation with Weinreb amides **1** bearing substituents on the aromatic moiety (Scheme 2). The catalytic system showed high chemoselectivity, in that it fully tolerated

Scheme 1. Variation of the Amide Substitution Pattern



important electrophilic functional groups, including chloro, bromo, or iodo substituents as well as a benzyl chloride.

Intramolecular competition experiments with *meta*-substituted arenes **1** highlighted steric effects to primarily influence the site selectivity of the C–H bond functionalization with methyl-substituted substrate **1p** (Scheme 3). Contrarily, *meta*-fluoro-substituted arene **1q** led to significant amounts of product **2q″**.

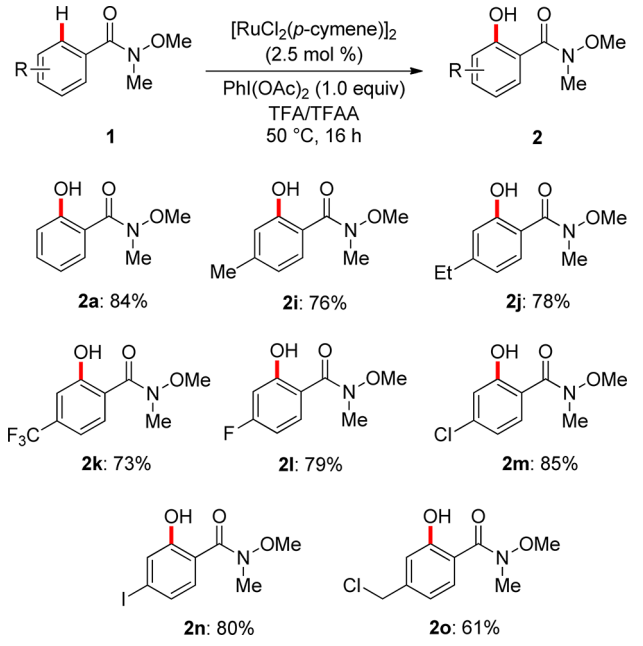
Given the high catalytic activity of our ruthenium complex, we became interested in performing mechanistic studies to rationalize its working mode. To this end, intermolecular competition experiments with arenes **1** showed electron-rich substrates to be preferentially functionalized (Scheme 4).

(6) Recent reviews: (a) Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2013**, *3*, DOI:10.1039/C2CY20505J. (b) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652–663. (c) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (d) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413.

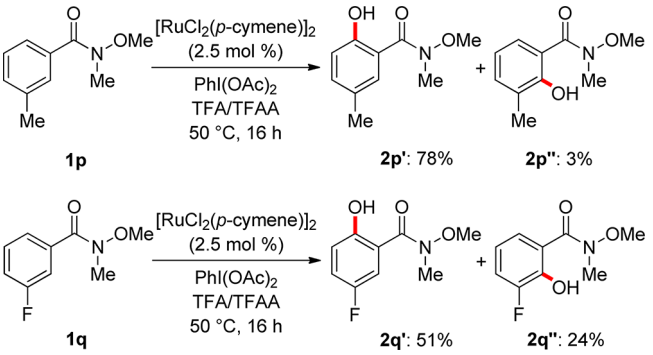
(7) For the use of $[Ru(O_2CMes)_2(p\text{-cymene})]$ in direct alkylations or arylations, see: (a) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146–2149. (b) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035. (c) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048.

(8) Selected recent examples of carboxylate assistance in oxidative ruthenium-catalyzed C–H bond functionalizations: (a) Ma, W.; Graczyk, K.; Ackermann, L. *Org. Lett.* **2012**, *14*, 6318–6321. (b) Singh, K. S.; Dixneuf, P. H. *Organometallics* **2012**, *31*, 7320–7323. (c) Zhao, P.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 5506–5509. (d) Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 3478–3481. (e) Li, J.; Kornhaass, C.; Ackermann, L. *Chem. Commun.* **2012**, *48*, 11343–11345. (f) Kornhaass, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190–9198. (g) Li, B.; Devaraj, K.; Darcel, C.; Dixneuf, P. H. *Green Chem.* **2012**, *14*, 2706–2709. (h) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416–3419. (i) Kishor, P.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 1134–1137. (j) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736–739. (k) Hashimoto, Y.; Ortloff, T.; Hirano, K.; Satoh, T.; Bolm, C.; Miura, M. *Chem. Lett.* **2012**, *41*, 151–153. (l) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 2030–2032. (m) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930–933. (n) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767. (o) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177–180. (p) Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 1165–1166. (q) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551. (r) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153–4155. (s) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278–3281. (t) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706–708. (u) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379–6382. (v) Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. *Synthesis* **2010**, 2245–2253. (w) A review: Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, DOI:10.1039/C2SC21524A.

Scheme 2. Scope of C−H Oxygenation of Weinreb Amides **1**



Scheme 3. Reactions of *meta*-Substituted Weinreb Amides **1**



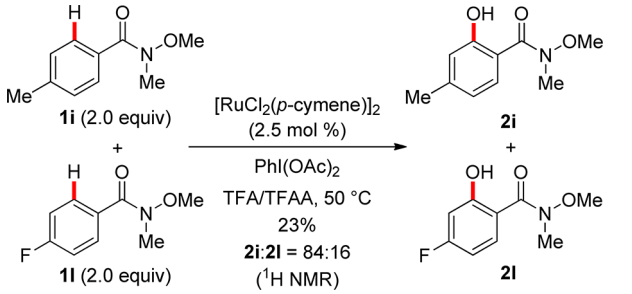
Catalytic oxygenations of labeled Weinreb amide [D_5]-**1a** were suggestive of an irreversible C−H bond metalation event (Scheme 5).

Additionally, more detailed studies with substrate [D_5]-**1a** provided strong support for a kinetically relevant C−H bond metalation with a kinetic isotope effect (KIE) of $k_H/k_D \approx 3.0$ (Scheme 6).

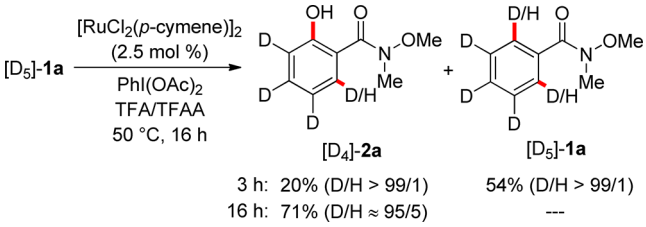
Finally, the practical importance of C−H bond oxygenations on aryl Weinreb amides **1** was illustrated by the high yielding preparation of the corresponding *ortho*-hydroxybenzaldehydes (Scheme 7), which are as of yet not accessible *via* direct C−H bond oxygenation methods.[4,5]

In summary, we have reported on the first C−H bond oxygenation of aryl Weinreb amides. Thus, a versatile ruthenium catalyst allowed for the step- and atom-economical synthesis of *ortho*-hydroxylated Weinreb amides with a broad scope, occurring under exceedingly mild reaction conditions. Mechanistic studies were suggestive of an irreversible kinetically relevant C−H bond activation.

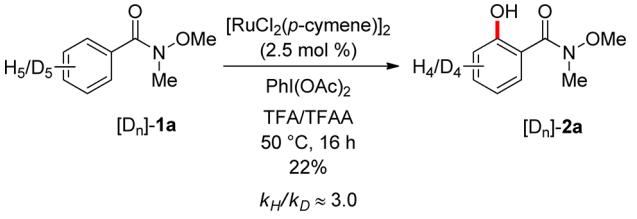
Scheme 4. Intermolecular Competition Experiment



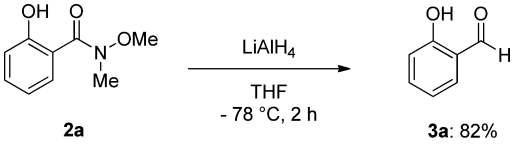
Scheme 5. C−H Oxygenation with Labled Substrate [D_5]-**1a**



Scheme 6. C−H Fuctionalization with Substrates **1a** and [D_5]-**1a**



Scheme 7. Synthesis of *ortho*-Hydroxybenzaldehyde **3a**



Acknowledgment. Support by the Chinese Scholarship Council (fellowship to F.Y.), the CaSuS PhD program, AstraZeneca, and the European Research Council under the European Community's Seventh Framework Program (FP7 2007−2013)/ERC Grant Agreement No. 307535 is gratefully acknowledged.

Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.