

Ruthenium-Catalyzed C–H Oxygenation
on Aryl Weinreb Amides

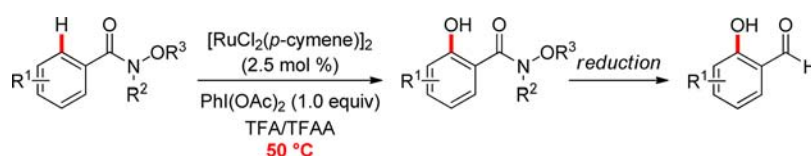
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ABSTRACT



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(sp²)–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, K₂S₂O₈, 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

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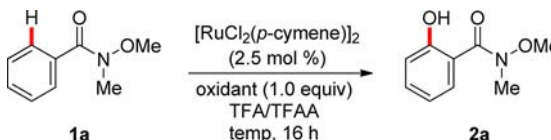
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(entries 7–10). It is important to note that this constitutes the lowest reaction temperature reported thus far for ruthenium-catalyzed C(sp²)–H bond oxygenations. [RuCl₂(PPh₃)₃] could be employed as the catalyst as well but furnished the desired product **2a** in a diminished yield (entry 11). However, the well-defined ruthenium(II) bis-carboxylate complex [Ru(O₂CMe)₂(*p*-cymene)]^{7,8} compared favorably with [RuCl₂(*p*-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 N₂ atmosphere (entry 14).

Table 1. Optimization of C–H Bond Oxygenation^a

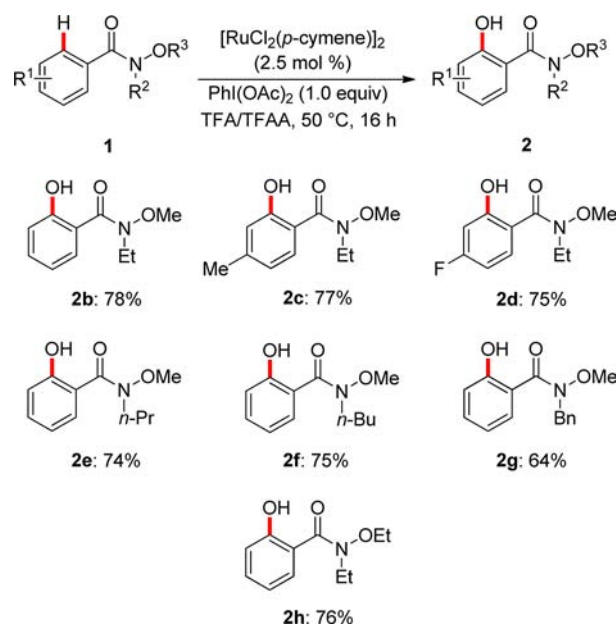
			
entry	oxidant	temp (°C)	yield
1	–	50	–
2	K ₂ S ₂ O ₈	50	– ^b
3	Cu(OAc) ₂ ·H ₂ O	50	–
4	AgOAc	50	<5% ^c
5	<i>m</i> -CPBA	50	39%
6	K ₂ S ₂ O ₈	50	57%
7	PhI(OAc) ₂	30	30%
8	PhI(OAc)₂	50	84%
9	PhI(OAc) ₂	80	60%
10	PhI(OAc) ₂	100	54%
11	PhI(OAc) ₂	50	57% ^d
12	PhI(OAc)₂	50	80% ^e
13	PhI(OAc) ₂	50	76% ^f
14	PhI(OAc) ₂	50	79% ^g

^a Reaction conditions: **1a** (0.5 mmol), [RuCl₂(*p*-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 [RuCl₂(PPh₃)₃] (5.0 mol %). ^e [Ru(O₂CMe)₂(*p*-cymene)] (2.5 mol %). ^f [RuCl₂(*p*-cymene)]₂ (1.3 mol %). ^g Under N₂.

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.

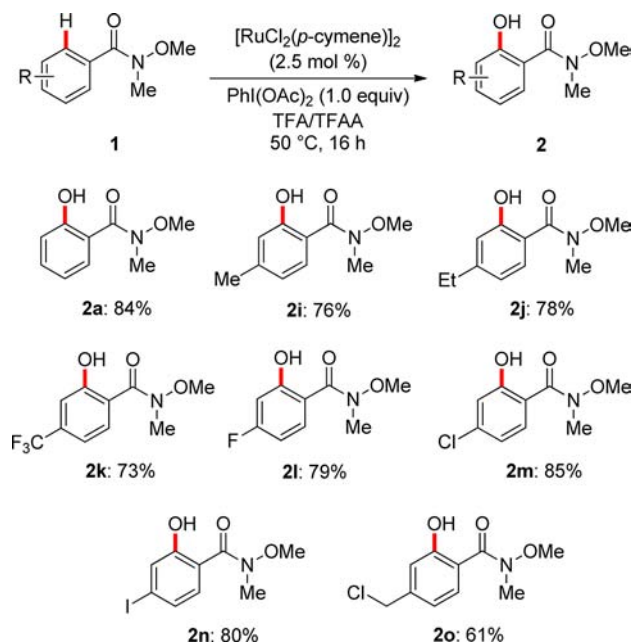
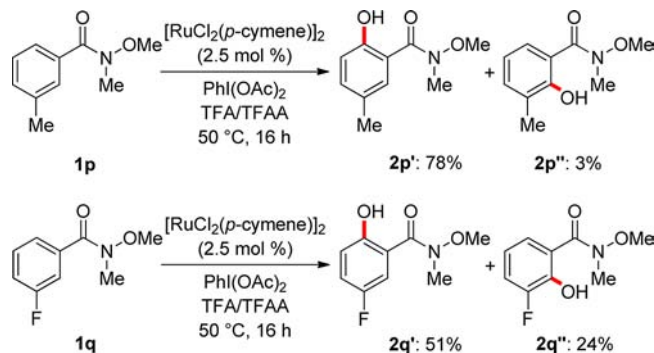
Intramolecular competition experiments with *meta*-substituted arenes **1** highlighted steric effects to primarily influence the site selectivity of the C–H bond functionalization with methyl-substituted substrate **1p** (Scheme 3). Contrarily, *meta*-fluoro-substituted arene **1q** led to significant amounts of product **2q**¹¹.

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).

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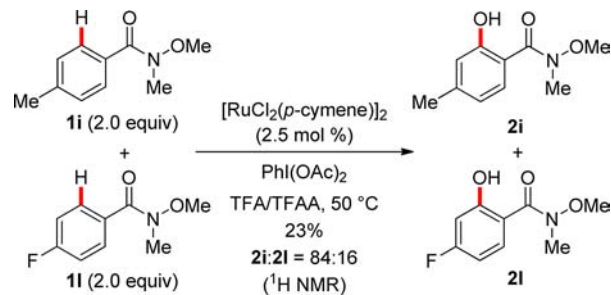
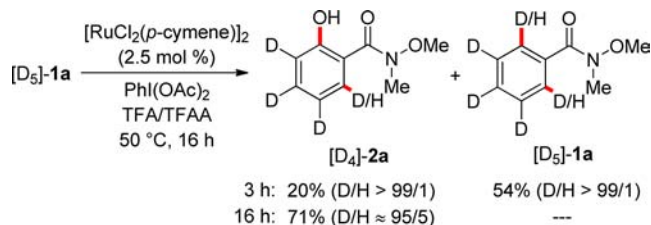
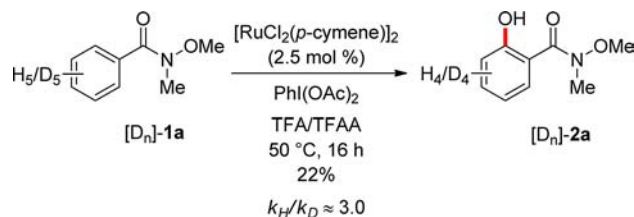
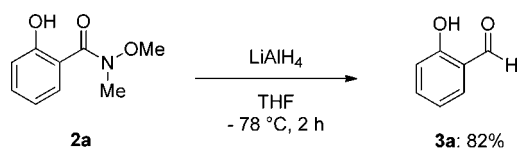
Scheme 2. Scope of C–H Oxygenation of Weinreb Amides **1****Scheme 3.** Reactions of *meta*-Substituted Weinreb Amides **1**

Catalytic oxygenations of labeled Weinreb amide **[D₅]-1a** were suggestive of an irreversible C–H bond metalation event (Scheme 5).

Additionally, more detailed studies with substrate **[D₅]-1a** provided strong support for a kinetically relevant C–H bond metalation with a kinetic isotope effect (KIE) of $k_{\text{H}}/k_{\text{D}} \approx 3.0$ (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 Labeled Substrate **[D₅]-1a****Scheme 6.** C–H Functionalization with Substrates **1a** and **[D₅]-1a****Scheme 7.** Synthesis of *ortho*-Hydroxybenzaldehyde **3a**

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Supporting Information Available. Experimental procedures, characterization data, and ¹H and ¹³C 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.