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Ruthenium-Catalyzed C−H Bond Oxygenations with Weakly Coordinating Ketones

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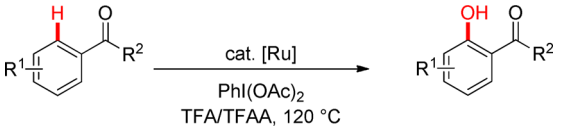
ABSTRACT



Ruthenium complexes enabled first C(sp^2)−H bond oxygenations of aromatic ketones with excellent functional group tolerance, and broad scope as well as high chemoselectivity and site selectivity.

Catalyzed functionalizations of unreactive C−H bonds have been recognized as valuable tools for step-economical syntheses of organic compounds.[1] Direct oxygenation reactions are particularly attractive, and palladium(II) complexes have emerged as arguably the most versatile catalysts,[2] with recent progress being accomplished by inter alia Sanford and Yu.[3] Despite these advances, C−H bond oxygenations of substrates bearing only weakly coordinating directing groups continue to be challenging.[1−3] Hence, direct C(sp^2)−H bond oxygenations of aryl ketones have thus far proven elusive, because ketones are poor ligands for palladium(II), and, therefore, are generally ineffective directing groups for palladium(II/IV)-catalyzed C−H bond oxygenations.[3m,4] In order to address these limitations *O*-acetyl oximes were utilized in lieu of ketones, serving as transformable directing groups for palladium-catalyzed C−H bond functionalizations.[4]

As of yet, rather inexpensive ruthenium[5] complexes have been underappreciated for C(sp^2)−H[6] oxygenation reactions. However, we[7] and Rao[8] very recently developed site-selective hydroxylations of unactivated C(sp^2)−H bonds in aromatic amides and esters. Within our research program on sustainable C−H bond functionalizations,[9] we now developed the first C−H bond oxygenation of arenes with weakly coordinating ketones, on which we report herein. Notably, the thus obtained hydroxylated aryl ketones are

(1) Illustrative recent reviews: (a) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936–946. (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (d) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (e) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. (g) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212–11222. (h) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (i) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (j) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (k) Livendahl, M.; Echavarren, A. M. *Isr. J. Chem.* **2010**, *50*, 630–651. (l) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (m) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883 and references cited therein.

(2) 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.

(3) Selected examples: (a) Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504–9509. (b) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094–4097. (c) Li, W.; Sun, P. *J. Org. Chem.* **2012**, *77*, 8362–8366. (d) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724–3727. (e) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134–137. (f) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Chem.—Eur. J.* **2012**, *18*, 5541–5545. (g) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511–2513. (h) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726–5729. (i) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655. (j) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791. (k) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790–12791. (l) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420–7424. (m) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543. (n) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (o) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35–40 and references cited therein.

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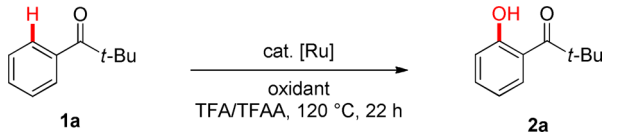
key structural motifs in bioactive compounds and represent versatile intermediates in organic synthesis.[10]

We initiated our studies by probing various sacrificial oxidants and ruthenium complexes for the envisioned oxygenation of ketone **1a** (Table 1). Not surprisingly, in the absence of a ruthenium complex or an oxidant the desired C−H bond oxygenation was not observed (entries 1 and 2). Among a variety of terminal oxidants, oxone, $K_2S_2O_8$, and hypervalent iodine(III) reagents furnished product **2a**, with $PhI(OAc)_2$ being most effective (entries 3−10). Ruthenium complexes in various oxidation states served as efficient catalysts (entries 11−15), and particularly promising results were accomplished with inexpensive $[RuCl_3(H_2O)_n]$[11] as well as $[Ru(O_2CMes)_2(p\text{-cymene})]$.[12]

Table 1. Optimization of C−H Bond Oxygenation with Ketone **1a**[a]

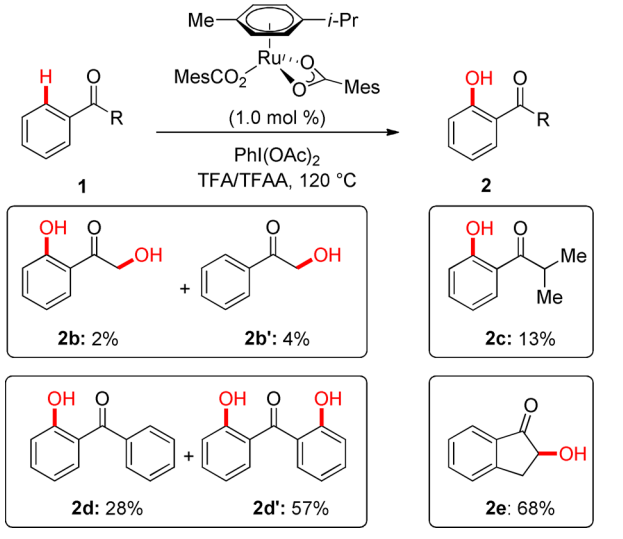


entry	[Ru]	oxidant	yield (%)
1	–	$PhI(OAc)_2$	–
2	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	–	–
3	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	O_2	–
4	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	$Cu(OAc)_2 \cdot H_2O$	–
5	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	*t*-BuOOH	–
6	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	oxone	46
7	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	$K_2S_2O_8$	47
8	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	$PhI(OAc)_2$	86
9	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	$PhI(TFA)_2$	85
10	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	$PhI(OPiv)_2$	87
11	$[RuCl_2(p\text{-cymene})]_2$ (2.5)	$PhI(OAc)_2$	84
12	$[RuCl_3(H_2O)_n]$ (5.0)	$PhI(OAc)_2$	83
13	$[Ru_2(hp)_4Cl]$ (5.0)	$PhI(OAc)_2$	54
14	$[Ru_2(OAc)_4Cl]$ (5.0)	$PhI(OAc)_2$	84
15	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (2.5)	$PhI(OAc)_2$	85

[a] Reaction conditions: **1a** (1.0 mmol), oxidant (1.2 equiv), cat. [Ru], TFA/TFAA (2.5 mL; 3/2), 22 h, isolated yields.

With an effective catalytic system in hand, we tested the influence of the ketone substitution pattern on the C−H bond oxygenation (Scheme 1). While acetophenone (**1b**) and isobutyrophenone (**1c**) gave unsatisfactory results, benzophenone (**1d**) led to the mono- and dihydroxylated products **2d** (28%) and **2d′** (57%) in high isolated yields. In contrast, annulated ketone **1e** was chemoselectively oxygenated at the C(sp^3)−H bond to deliver mono-α-hydroxylated ketone **2e** as the sole product—a reaction that also occurred in the absence of the metal catalyst (64% yield).

Scheme 1. Variation of the Ketone Substitution Pattern



(4) Neufeldt, S. R.; Sanford, M. S. *Org. Lett.* **2010**, *12*, 532–535.

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

(6) Selected examples of ruthenium-catalyzed oxygenations of C(sp^3)−H bonds with lower dissociation energies: (a) McNeill, E.; Du Bois, J. *Chem. Sci.* **2012**, *3*, 1810–1813. (b) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465–3468 and references cited therein.

(7) Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4210–4213.

(8) Yang, Y.; Lin, Y.; Rao, Y. *Org. Lett.* **2012**, *14*, 2874–2877.

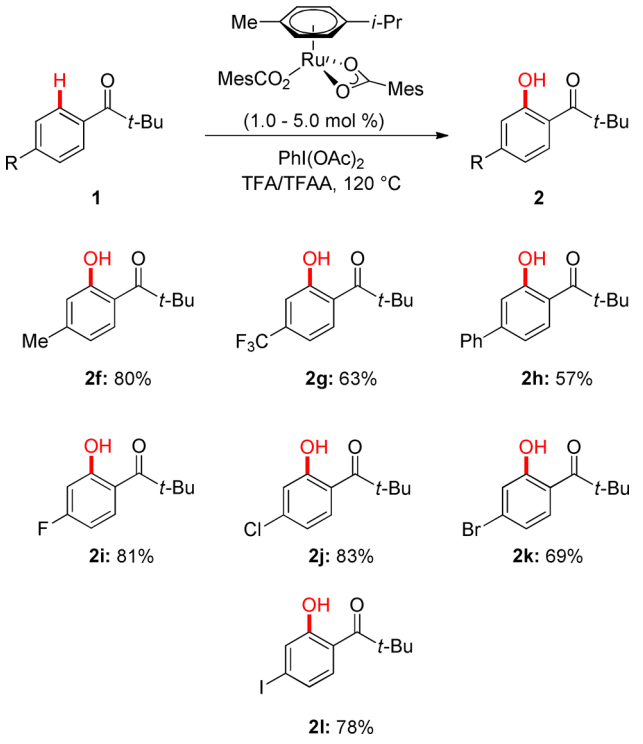
(9) For recent reviews, see: (a) Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2012**, DOI:10.1039/C2CY20505J. (b) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652–663. (c) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413.

(10) Selected examples: (a) Schmidt, S.; Jürgenliemk, G.; Schmidt, T. J.; Skaltsa, H.; Heilmann, J. *J. Nat. Prod.* **2012**, *75*, 1697–1705. (b) Liau, B. B.; Milgram, B. C.; Shair, M. D. *J. Am. Chem. Soc.* **2012**, *134*, 16765–16772. (c) Woo, C. M.; Beizer, N. E.; Janso, J. E.; Herzon, S. B. *J. Am. Chem. Soc.* **2012**, *134*, 15285–15288. (d) Wein, A. N.; Williams, B. N.; Liu, S.; Ermolinsky, B.; Provenzano, D.; Abagyan, R.; Orry, A.; Leppla, S. H.; Peredelchuk, M. *J. Med. Chem.* **2012**, *55*, 7998–8006. (e) Trail, P. A.; Willner, D.; Lasch, S. J.; Henderson, A. J.; Hofstead, S.; Casazza, A. M.; Firestone, R. A.; Hellstrom, I.; Hellstrom, K. E. *Scinece* **1993**, *261*, 212–215. (f) Kollár, L., Ed. *Modern Carbonylation Methods*; Wiley-VCH: Weinheim, 2008. Reviews on Bayer−Villiger oxidations: (g) Bäckvall, J.-E., Ed. *Modern Oxidation Methods*, 2nd ed.; Wiley-VCH: Weinheim, 2010. (h) Reetz, M. T. *J. Org. Chem.* **2009**, *74*, 5767–5778.

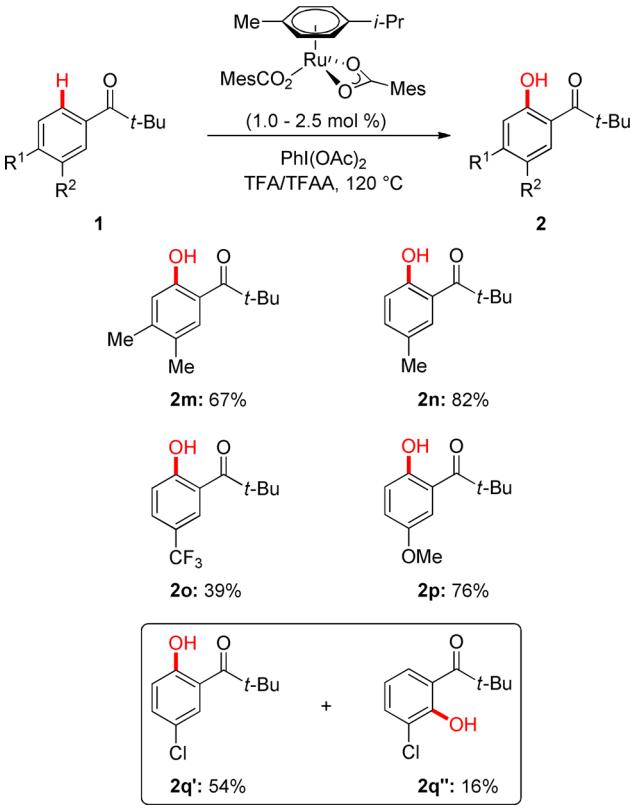
(11) Examples of $[RuCl_3(H_2O)_n]$ as the catalyst in C−H bond functionalizations: (a) Simon, M.-O.; Genet, J.-P.; Darses, S. *Org. Lett.* **2010**, *12*, 3038–3041. (b) McNeill, E.; Du Bois, J. *J. Am. Chem. Soc.* **2010**, *132*, 10202–10204. (c) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115–6124. (d) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836.

(12) For the recent 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.

Scheme 2. Scope of C−H Oxygenation of Aromatic Ketones **1**



Scheme 3. Oxygenations with *meta*-Substituted Ketones **1**

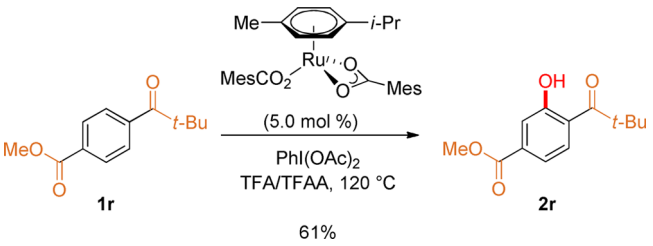


Subsequently, we explored the versatility of the C−H bond oxygenation with various *para*-substituted *tert*-butyl ketones **1** (Scheme 2). We were delighted to find that the ruthenium(II) catalyst proved tolerant of valuable electrophilic functional groups, including fluoro, chloro, bromo, or iodo substituents.

Intramolecular competition experiments with *meta*-substituted arenes **1m**−**1p** revealed steric interactions to primarily influence the site selectivity of the C−H bond functionalization process (Scheme 3). In contrast, only *meta*-chloro-substituted arene **1q** furnished significant amounts of product **2q**″ through oxygenation of the more sterically hindered C−H bond.

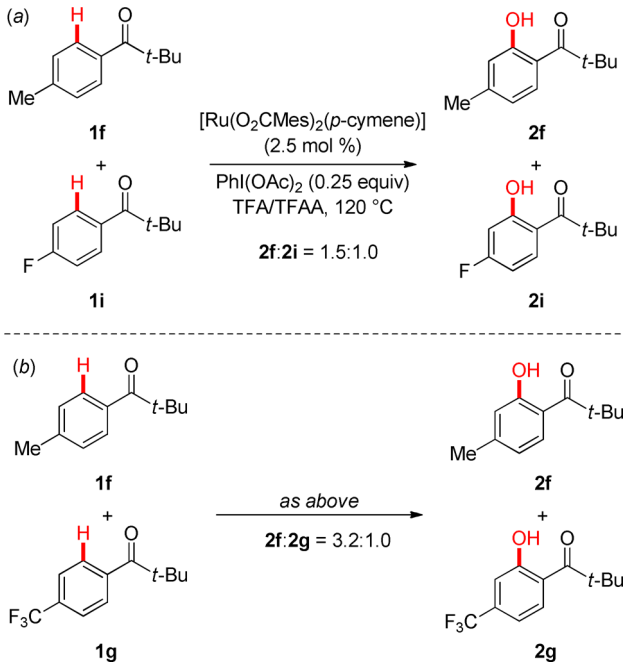
The oxygenation of substrate **1r** clearly highlighted the superior directing group ability of the *tert*-butyl ketone as compared to an ester moiety (Scheme 4).[13]

Scheme 4. Competitive Directing Group Abilities

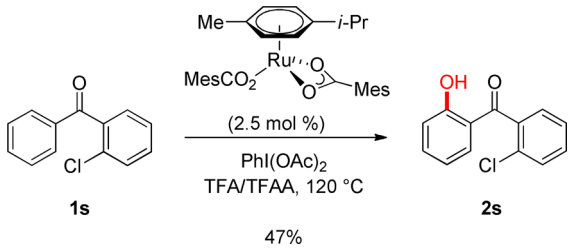


In consideration of the remarkable catalytic activity and chemoselectivity exerted by the ruthenium complex, we performed initial mechanistic studies to unravel its mode of action. To this end, intermolecular competition experiments

Scheme 5. Intermolecular Competition Experiments



Scheme 6. Intramolecular Competition Experiment



showed electron-rich ketones **1** to be preferentially functionalized (Scheme 5 and Supporting Information).

Furthermore, an intramolecular competition experiment with diaryl ketone **1s** highlighted the electron-rich arene to more readily undergo the direct oxygenation reaction (Scheme 6).

(13) Formation of another isomer was not observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

In summary, we have disclosed the first catalyzed C(sp^2)–H bond oxygenations of arenes bearing weakly coordinating ketones. The intermolecular oxidative C–O bond forming reactions were achieved with oxone, $K_2S_2O_8$, or $PhI(OAc)_2$ as the terminal oxidant and inexpensive $[RuCl_3(H_2O)_n]$ or well-defined $[Ru(O_2CMes)_2(p\text{-cymene})]$ as the catalyst. Thereby, highly efficient C(sp^2)–H bond hydroxylations proved viable with excellent functional group tolerance and ample scope.

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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.