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Ruthenium-Catalyzed Aromatic C−H Activation of Benzylic Alcohols via Remote Electronic Activation

Andrew J. A. Watson,*,† Aoife C. Maxwell,‡ and Jonathan M. J. Williams†

Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K., and GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.

ajaw20@bath.ac.uk

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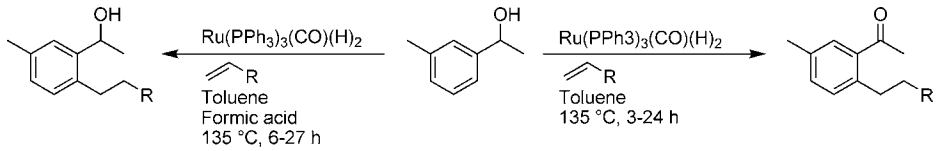
ABSTRACT



Remote electronic activation of benzylic alcohols via temporary oxidation facilitates ruthenium-catalyzed arene C−H activation for a range of aromatic alcohols.

Hydrogen transfer is a powerful tool for the oxidation of alcohols and reduction of ketones. Several groups including our own have used catalytic hydrogen transfer to activate alcohols toward C−C[1] and C−N[2] bond formation, as well as a range of oxidative transfomations.[3] Typically, this involves alcohol oxidation followed by interception of the newly formed carbonyl with nucleophiles before further transformation. However, it can be used to activate functional groups electronically;[4] for example, an allylic alcohol can be oxidized to an α,β-unsaturated ketone making the double bond far more susceptible to Michael additions. This allows the manipulation of less reactive functional groups by altering the electronics of the substrate indirectly, also known as "remote electronic activation". In contrast, applications of catalytic arene C−H activation with ruthenium by Murai[5] and others[6] have been mainly limited to electronically activated rings via the use of carbonyls and nitriles.[7] This provides an opportunity to combine both methodologies, allowing electronic activation of the aromatic ring toward C−H activation via the oxidation of an alcohol by hydrogen transfer (Scheme 1). The ruthenium complex needs to perform three separate functions to achieve this process, catalyzing: (i) alcohol oxidation by hydrogen transfer to

† University of Bath.
‡ GlaxoSmithKline Research and Development.

(1) (a) Hall, M. I.; Pridmore, S. J.; Williams, J. M. J. *Adv. Synth. Catal.* **2008**, *350*, 1975–1978. (b) Williams, V. M.; Leung, J. C.; Patman, R. L.; Krische, M. J. *Tetrahedron* **2009**, *65*, 5024–5029. (c) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394–1401.

(2) (a) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039–2042. (b) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667–2670.

(3) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Chem. Commun.* **2008**, 624–625.

(4) (a) Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Tetrahedron* **2005**, *61*, 1363–1374. (b) Edwards, M. G.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4740–4743. (c) Cami-Kobeci, G.; Williams, J. M. J. *Synlett* **2003**, *1*, 124–126.

(5) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatami, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531. (b) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681–682. (c) Kakiuchi, F.; Sato, T.; Igi, K.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 386–387. (d) Sonoda, M.; Kakiuchi, F.; Kamatani, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 109–110. (e) Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 679–680. Sato, T.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, 893–894.

(6) (a) Grigg, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 5737–5740. (b) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887–7895. (c) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. *Adv. Synth. Catal.* **2009**, *351*, 153–157. (d) Bartoszewicz, A.; Martín-Matute, B. *Org. Lett.* **2009**, *11*, 1749–1752.

(7) Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 1083–1084.

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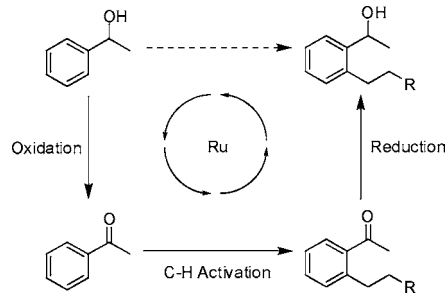
Scheme 1. Proposed Transformation Using Alcohols to Access Alkylated Ketones or Alcohols



an alkene, (ii) C−H activation/alkene insertion step, and (iii) reduction of the carbonyl group by hydrogen transfer to restore the alcohol.

Kim and co-workers[8] have reported the use of Wilkinson's catalyst to conduct tandem oxidation/alkyl C−H activation, whereas our work focuses on arene C−H activation and is the first example with a ruthenium-based catalyst. Initial experiments involved the tandem alcohol oxidation/C−H activation of a range of benzylic alcohols.

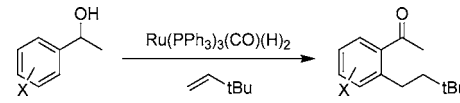
Initial screening of reported ruthenium-based C−H activation catalysts showed that commercially available $Ru(PPh_3)_3(CO)(H)_2$ was active for the tandem oxidation/C−H activation. Previously, we have found that this catalyst is more active in the presence of bidentate phosphine ligands such as xantphos.[1a] However, when applied to this system only oxidation was observed and no tandem C−H activation. This suggests that the use of diphosphine ligands shuts down the C−H activation pathway. One equivalent of alkene is incorporated into the product with an additional equivalent required as a hydrogen acceptor; optimization experiments revealed that 2.3 equiv of alkene was suitable.

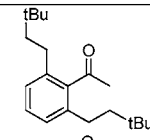
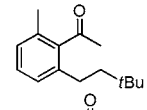
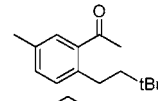
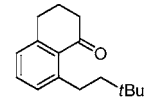
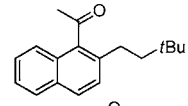
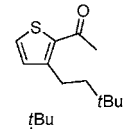
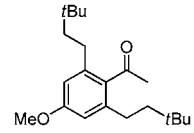
Having optimized the tandem oxidation/C−H activation, the conditions were then applied to a range of benzylic alcohols (Table 1). Using a large excess of alkene (Table 1, entry 1) with acetophenone gave the expected dialkylated product, while the introduction of a methoxy group in the para position (Table 1, entry 7) significantly increased the reactivity of the monoalkylated intermediate such that it was never observed in significant quantities and hence was also isolated as the dialkylated product. Sterically hindered alcohols (Table 1, entries 2, 4, and 5) were also isolated in high yields as well as a heterocyclic example (Table 1, entry 6).

Having optimized the initial two steps, we turned our attention to a hydrogen source for the final reduction back to the alkylated alcohol. While ruthenium catalysts have been shown to perform direct hydrogenations of ketones with H_2 gas, we wished to avoid this to maintain a relatively simple reaction setup. The use of isopropanol was favorable (Scheme 2), although it was unable to drive the reaction to completion. An alternative to

(8) Jun, C.-H.; Lee, D.-Y.; Kim, Y.-H.; Lee, H. *Organometallics* **2001**, *20*, 2928–2931.

Table 1. Tandem Oxidation/C−H Activation of Benzylic Alcohols[a]

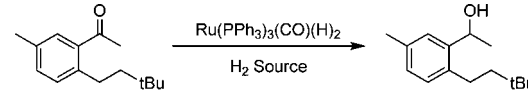


entry	product	time (h)	equiv. of alkene	yield (%)[b]
1		5	5	98
2		3	2.3	97
3		3	2.3	96
4		6	2.3	81
5		8	2.3	99
6		24	3	76
7		4	4	85

[a] Reaction conditions: alcohol (1 mmol), alkene (amount shown in the table), $Ru(PPh_3)_3(CO)(H)_2$ (5 mol %), toluene (1 mL), 135 °C for time indicated. [b] Isolated yield of product after column chromatography is based on alcohol.

isopropanol is butane-1,4-diol,[9] and while showing conversion to the desired product, the reaction was sluggish.

Scheme 2. Catalytic Hydrogen Transfer of Ketone to Alcohol



H_2 Source:	Conversion:
Isopropanol (13 equiv.) 4 h	94%
Formic acid (5 equiv.) 3 h	98%

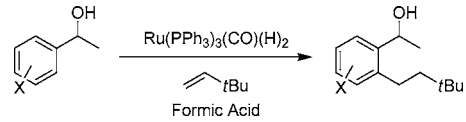
However, we were pleased to find that the catalyst was able to hydrogenate the ketone using formic acid (Scheme 2). The use of HCO_2H/Et_3N (5:2) was also screened and was found to be equally as effective, although we chose to use formic acid due to relative ease.

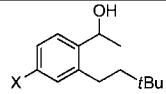
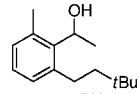
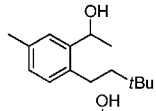
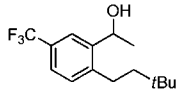
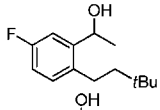
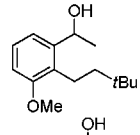
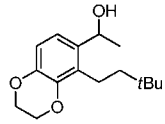
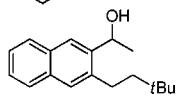
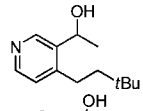
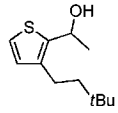
After optimizing the conditions, they were applied to a range of benzylic alcohols (Table 2). Entries 1−3 posed a potential challenge as the mixture of product from the initial oxidation/C−H activation step gave a mixture of mono- and disubstituted aryl ketones, as seen previously. However, the monosubstituted aryl ketone was selectively reduced, presumably due to steric effects for the disubstituted aryl ketone, allowing easy separation of the products. The product formed in entry 4 required the reduction of the ketone between two bulky groups and part of three consecutive sp^2 centers.

The reduction did not occur with isopropanol, but with HCO_2H we were pleased to see at least some conversion into the alcohol. Meta-substituted products (Table 2, entries 5−7) were formed in good yields after 3 h, while the introduction of electron-donating groups (Table 2, entry 8) led to a mixture of regioisomers. Interestingly, the electronically similar dioxane substrate (Table 2, entry 9) was isolated as a single regioisomer despite two regioisomers[10] being present after the oxidation/C−H activation, again demonstrating the selectivity of the reduction favoring unhindered ketones. Finally, the use of heterocycles (Table 2, entries 10 and 11) was tolerated and gave the products in reasonable yields.

The scope of the catalyst toward C−H activation has been studied extensively by Murai.[11] This allowed a selection of alkenes to be chosen, demonstrating that previously successful (Table 3, entries 1, 3, 5, and 6) and unsuccessful (Table 3, entry 2) alkenes were in agreement with expected results. However, some of these products (Table 3, entires 2−4) proved difficult

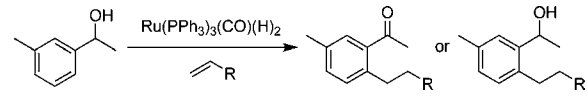
Table 2. Consecutive Oxidation/C−H Activation/Reduction of Benzylic Alcohols[a]

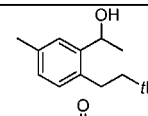
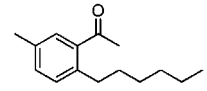
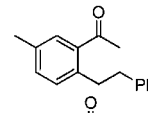
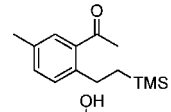
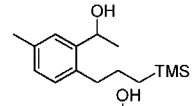
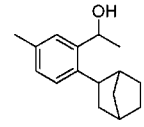


entry	product	time (h)[b]	equiv. of alkene	yield (%)[c]
1	 X = H	3	2.7	76
2	Me	3	2.1	56
3	F	3.5	2.7	62
4		3	2.3	41
5		3	2.3	72
6		3	2.3	87
7		3	2.3	62
8		4	2.3	70 (79:21)[d]
9		4	2.3	53
10		3	2.3	89
11		4	3	55
12		24	3	55

[a] Reaction conditions: alcohol (1 mmol), alkene (2.1−3 mmol), $Ru(PPh_3)_3(CO)(H)_2$ (5 mol %), toluene (1 mL), 135 °C for time indicated, then HCO_2H (5 mmol), 135 °C, 3 h. [b] Time for the tandem oxidation/C−H activation only. A further 3 h was required for reduction. [c] Isolated yield of product after column chromatography is based on alcohol. [d] Mixture of regioisomers with the major isomer shown.

Table 3. Alkene Scope[a,b]



entry	product	time (h)[c]	equiv. of alkene	yield (%)[d]
1		3	2.3	72
2		24	2.5	12[e]
3		24	4.5	67
4		5	3	59 (21:79)[f]
5		24	4.5	68
6		3	2.3	84

[a] Reaction conditions: alcohol (1 mmol), alkene (amount shown in the table), $Ru(PPh_3)_3(CO)(H)_2$ (5 mol %), toluene (1 mL), 135 °C, (*x* h). [b] Reaction conditions: alcohol (1 mmol), alkene (*x* mmol), $Ru(PPh_3)_3(CO)(H)_2$ (5 mol %), toluene (1 mL), 135 °C (*x* h), then HCO_2H (5 mmol), 135 °C, 3 h. [c] Time for the tandem oxidation/C−H activation only. A further 3 h was required for reduction. [d] Isolated yield of product after column chromatography is based on alcohol. [e] Conversion based on the alcohol and determined by ^1H NMR. [f] Mixture of mono- and dialkylated material with the major product shown.

(9) (a) Maytum, H. C.; Tavassoli, B.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 4387–4389. (b) Maytum, H. C.; Francos, J.; Whatrup, D. J.; Williams, J. M. J. *Chem. Asian J.* **2010**, *5*, 538–542.

to reduce and so were isolated as ketones. We were surprised to find that the use of trimethylvinylsilane (Table 3, entry 4) gave a mixture (21:79) of mono- and disubstituted ketone, respectively, in contrast to the selectivity of the carbon equivalent (Table 3, entry 1). We attributed this to the increased C−Si bond length, allowing easier insertion into the more crowded position between the ketone and methyl group.

Having screened a series of alcohols and alkenes, we were confident that the reaction was indeed proceeding via our proposed scheme, having observed no trace of alkylated alcohol in any of the reactions. However, to rule out any possibility of C−H activation at the alcohol oxidation level occurring, we devised three test substrates (Figure 1). The ether (**1**) and tertiary alcohol (**2**) would both be inert to oxidation and maintain the same oxidation level as the model alcohol, while the α-trifluoromethyl group in substrate (**3**) makes the oxidation thermodynamically unfavorable. In all cases, relatively forcing conditions (5 equiv of alkene, reflux, 24 h) were applied, and no oxidation or C−H activation was observed. Thus, we can conclude that the initial oxidation occurs before any C−H activation can occur.

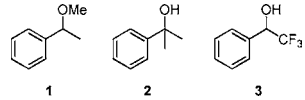


Figure 1. Inert substrates.

From the results obtained, we have demonstrated that $Ru(PPh_3)_3(CO)(H)_2$ is active for the catalysis of up to three consecutive reaction steps. Further research into the temporary electronic activation of arenes toward other reactions is now underway.

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Supporting Information Available: Details of experimental procedures and characterization data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **1995**, *504*, 151–152.
(11) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatami, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62–83.