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Synthesis of Benzopyrans by Pd(II)- or Ru(II)-Catalyzed C−H Alkenylation of 2-Aryl-3-hydroxy-2-cyclohexenones

Suresh Reddy Chidipudi, Martin D. Wieczysty, Imtiaz Khan, and Hon Wai Lam*

EaStCHEM, School of Chemistry, University of Edinburgh, Joseph Black Building, The King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, United Kingdom

h.lam@ed.ac.uk

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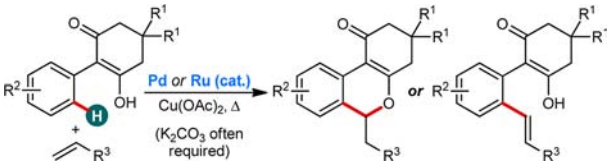
ABSTRACT



2-Aryl-3-hydroxy-2-cyclohexenones are shown to be competent substrates for palladium- and ruthenium-catalyzed C−H alkenylation reactions with terminal alkenes, providing, in most cases, benzopyrans.

The metal-catalyzed alkenylation of aromatic C(sp^2)−H bonds, directed by a coordinating functional group, has proven to be a versatile strategy in organic synthesis,[1−3] successfully complementing alternatives such as the Mizoroki−Heck reaction[4,5] and the Fujiwara−Moritani reaction.[6,7] Directing groups not only offer enhanced reactivity but also high site selectivity, which minimizes the formation of unwieldy mixtures of positional isomers.[1−3] Strategically, however, the use of directing groups can be a limitation, especially if several steps are required to convert the directing group into the final desired functional group.[8] Nevertheless, this drawback is mitigated by the continued development of new procedures that employ an expanded range of directing groups, thus increasing the toolbox of methods available for catalytic C−H alkenylation and allowing access to a greater diversity of products.

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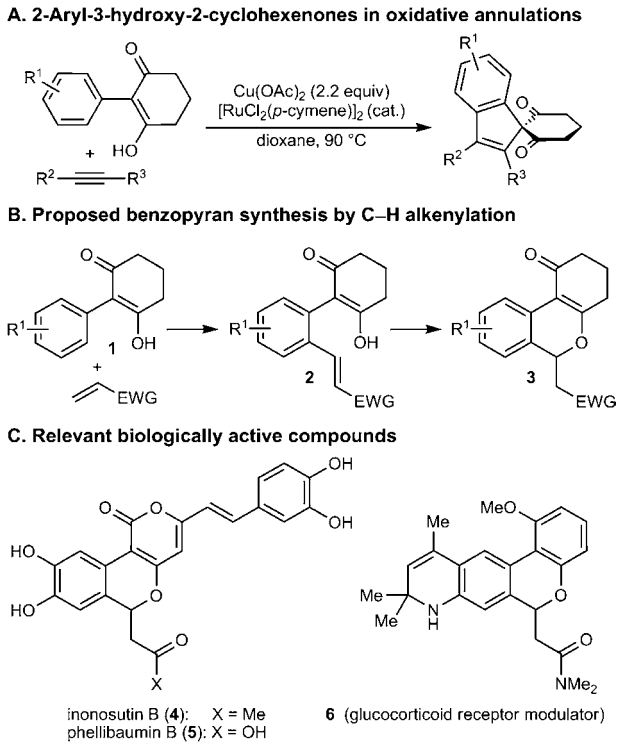
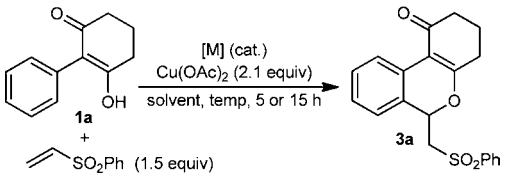


Figure 1. C−H functionalization of 2-aryl-3-hydroxy-2-cyclohexenones (A and B) and bioactive benzopyrans (C).

The present study was initiated by our recent finding that 2-aryl-3-hydroxy-2-cyclohexenones are effective substrates for ruthenium-catalyzed oxidative annulations with alkynes (Figure 1A).[9] Proceeding via sequential C(sp^2)−H and C(sp^3)−H functionalization, this process affords a range of spiroindenes in generally good yields.[9] In light of these results, we wondered whether replacement of the alkyne with a terminal alkene would enable the corresponding C(sp^2)−H alkenylation of these substrates to proceed (Figure 1B). If successful, the initially formed product **2** would likely undergo cyclization of an enolate oxygen atom onto the electron-deficient alkene. This process would be attractive as the resulting benzopyrans **3** resemble the core structures of biologically active natural products and drug candidates **4**–**6** (Figure 1C).[10−12] A related precedent for this approach comes in the form of a study by Miura and co-workers, who described the palladium-catalyzed C−H alkenylation of 2-phenylphenols.[1a] Yu and co-workers also reported the palladium-catalyzed hydroxyl-directed C−H alkenylation of homobenzylic alcohols.[13] However, to our knowledge, the use of 2-aryl-3-hydroxy-2-cyclohexenones as substrates for metal-catalyzed directed C−H alkenylation has not been reported previously. In this paper, we describe the successful use of these substrates in the strategy presented in Figure 1B. Furthermore, these reactions proceed using not only well-established palladium catalysis[1a−c,2a,b,e] but also more recently developed ruthenium catalysis.[3a−c,14,15]

Table 1. Evaluation of Reaction Conditions[a]



entry	[M]	mol %	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Pd(OAc)_2$	5	DMF	120	5	78
2	$[RuCl_2(p\text{-cymene})]_2$	2.5	DMF	120	15	30
3[c]	$[RuCl_2(p\text{-cymene})]_2$	2.5	DMF	120	15	7
4	$[RuCl_2(p\text{-cymene})]_2$	2.5	*t*-AmOH	90	15	8
5[c]	$[RuCl_2(p\text{-cymene})]_2$	2.5	*t*-AmOH	90	15	61
6	$[RhCp^*Cl_2]_2$	2.5	DMF	120	15	69
7[c]	$[RhCp^*Cl_2]_2$	2.5	*t*-AmOH	90	15	51

[a] Reactions were conducted using 0.50 mmol of **1a**. [b] Isolated yield. [c] Reaction conducted in the presence of K_2CO_3 (2.0 equiv).

This study began with an investigation of metal precatalysts and reaction conditions for the reaction of 3-hydroxy-2-phenyl-2-cyclohexenone (**1a**) with phenyl vinyl sulfone, using $Cu(OAc)_2$ (2.1 equiv) as the oxidant (Table 1).[16] Pleasingly, $Pd(OAc)_2$ (5 mol %) provided benzopyran **3a** in 78% yield in DMF at 120 °C (entry 1). $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), which had proven successful in our previous study of spiroindene synthesis,[9] was less effective and gave a 30% yield of **3a** in DMF (entry 2). Although the use of *t*-AmOH as the solvent offered no improvement (entry 4), the addition of K_2CO_3 (2.0 equiv) to the reaction enabled **3a** to be isolated in 61% yield (entry 5).[17] The beneficial effect of K_2CO_3 was not replicated using DMF as the solvent (entry 3, compare with entry 2).

(8) For a review of directing-group-free C−H functionalizations, see: Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236–10254.

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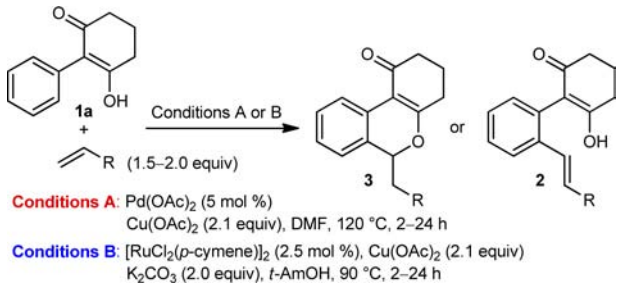
(14) For Ru-catalyzed oxidative coupling of simple arenes with alkenes using molecular oxygen as the oxidant, see: Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2000**, *123*, 337–338.

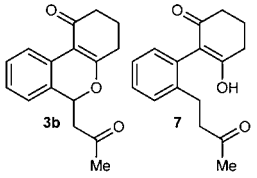
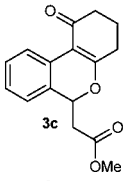
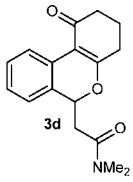
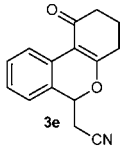
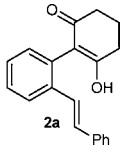
(15) For reviews of Ru-catalyzed C−H functionalization, see refs 2h, 2i and: Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229.

(16) Substrate **1a** is sensitive to acid-catalyzed decomposition under the reaction conditions (this process generates AcOH). In reactions where low yields of benzopyran **3a** were obtained, the remaining mass balance was composed of a complex mixture of byproducts.

(17) A possible reason for the higher yield of **3a** in Table 1, entry 5 compared with entry 4 is a reduction in the rate of acid-catalyzed decomposition of the substrate in the presence of K_2CO_3 (see ref 16).

Table 2. Catalytic Alkenylation of **1a**[a]



entry	product(s)	conditions	yield (%)[b]
1		A	72[c]
2		B	19[c] (54)[d]
3		A	65
4		B	76
5		A	47
6		B	64
7		A	45
8		B	61
9[e]		A	59
10		B	52

[a] Reactions were conducted using 0.50 mmol of **1a**. [b] Isolated yield. [c] Yield of **3b**. [d] Yield of **7**. [e] Reaction conducted at 90 °C, as the reaction conducted at 120 °C led to a complex mixture.

The use of $[RhCp^*Cl_2]_2$[18] (2.5 mol %) was almost as effective as $Pd(OAc)_2$ (entries 6 and 7), and **3a** was formed in 69% yield in DMF at 120 °C (entry 6). Although $Pd(OAc)_2$ was optimal for the formation of **3a**, these results show that $[RuCl_2(p\text{-cymene})]_2$ and $[RhCp^*Cl_2]_2$ are also viable candidates for further evaluation of the scope of the process. Due to the high cost of $[RhCp^*Cl_2]_2$, further exploration was carried out with palladium and ruthenium catalysis.

Table 2 presents a comparison of palladium and ruthenium catalysis in the reaction of **1a** with a range of other terminal alkenes. Electron-deficient alkenes including methyl vinyl ketone (entry 1), methyl acrylate (entry 3), *N*,*N*-dimethylacrylamide (entry 5), and acrylonitrile (entry 7) were effective in the C−H alkenylation of **1a** using palladium catalysis and provided benzopyrans in 45−72% yield. In the case of methyl acrylate, *N*,*N*-dimethylacrylamide, and acrylonitrile, the yields of the products obtained using $[RuCl_2(p\text{-cymene})]_2$ as the precatalyst (entries 4, 6, and 8, respectively) were slightly higher than those obtained using $Pd(OAc)_2$. Interestingly, when methyl vinyl ketone was the reaction partner, benzopyran **3b** was obtained in only 19% yield using $[RuCl_2(p\text{-cymene})]_2$; the major product isolated was the addition product **7** (54% yield, entry 2).[19] With styrene as the terminal alkene, palladium and ruthenium catalysis were comparable in performance, giving alkene **2a** in 59% and 52% yield, respectively (entries 9 and 10).

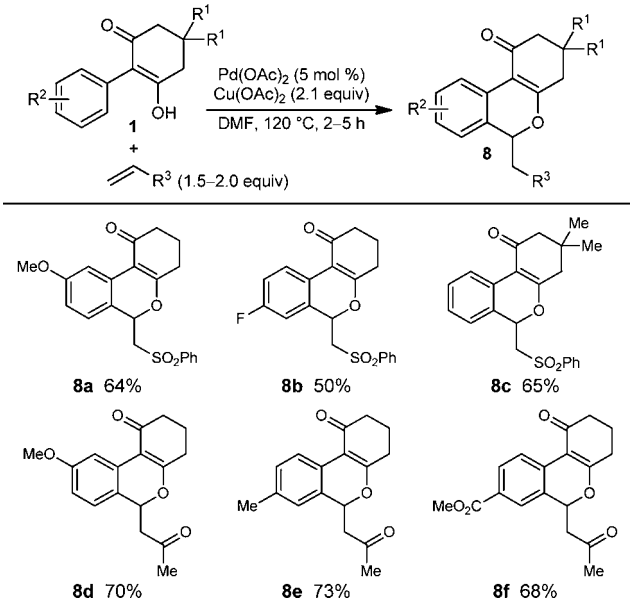


Figure 2. Pd(II)-catalyzed alkenylation of various 2-aryl-3-hydroxy-2-cyclohexenones with phenyl vinyl sulfone or methyl vinyl ketone. Reactions were conducted with 0.50 mmol of **1b**−**1f**. Yields are of isolated material.

Based on the results shown in Tables 1 and 2, investigation of the reactions of various 2-aryl-3-hydroxy-2-cyclohexenones with phenyl vinyl sulfone and methyl vinyl ketone was undertaken using palladium catalysis (Figure 2). Pleasingly, a range of substituents (methoxy, fluoro, methyl, or carbomethoxy) at the *meta* or *para* positions of the 2-aryl group of substrates **1b**−**1f**[20] were tolerated to provide various benzopyrans **8a**−**8f** in 50−73% yield. A dimedone-derived substrate was also effective, providing benzopyran **8c** in 65% yield. In the case of a substrate

(18) For reviews of Rh-catalyzed C−H functionalization, see refs 2c, 2f, 2g.

(19) Presumably, product **7** results from protodemetalation of intermediates **11** or **12** in the proposed catalytic cycle, before β-hydride elimination occurs (see Supporting Information).

(20) See the Supporting Information for the structures of **1b**−**1h**.

containing a *m*-methoxyphenyl group, C−H functionalization occurred exclusively at the more sterically accessible site (products **8a** and **8d**), which is consistent with our previous study.[9] X-ray crystallography allowed unambiguous confirmation of the site selectivity in the formation of **8a** (Figure 3). No C−H alkenylation occurred with a substrate containing an *o*-methylphenyl group.[21]

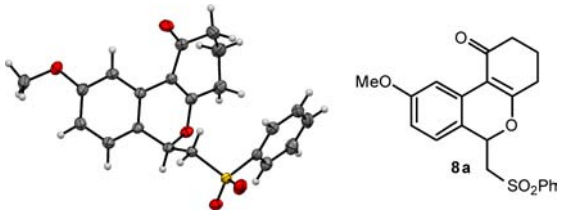


Figure 3. X-ray structure of benzopyran **8a**.

Further examination of the scope of the process using methyl acrylate, *N*,*N*-dimethylacrylamide, or acrylonitrile as the alkene reaction partner was performed using ruthenium catalysis (Figure 4). Again, a range of substituents at the *meta* or *para* positions of the 2-aryl group of substrates **1c**−**1e**, **1g**, or **1h**[20] were tolerated to provide various benzopyrans **8g**−**8l** in 45−74% yield. With a *m*-(trifluoromethyl)-phenyl-containing substrate, C−H alkenylation occurred exclusively at the more sterically accessible site (product **8i**).

In summary, we have demonstrated that 2-aryl-3-hydroxy-2-cyclohexenones, which have recently been reported to undergo metal-catalyzed oxidative annulations with alkynes,[9] are also highly effective substrates in catalytic C−H alkenylation reactions.[22] These reactions proceed not only under the action of well-established palladium catalysis but also with more recently developed ruthenium catalysis to provide benzopyrans in up to 78% yield. The application of 2-aryl-3-hydroxy-2-cyclohexenones and related substrates in further catalytic C−H functionalizations is the subject of ongoing efforts in our group.

(21) This substrate provided decomposition products along with returned starting material.

(22) For a possible catalytic cycle for these reactions, see the Supporting Information.

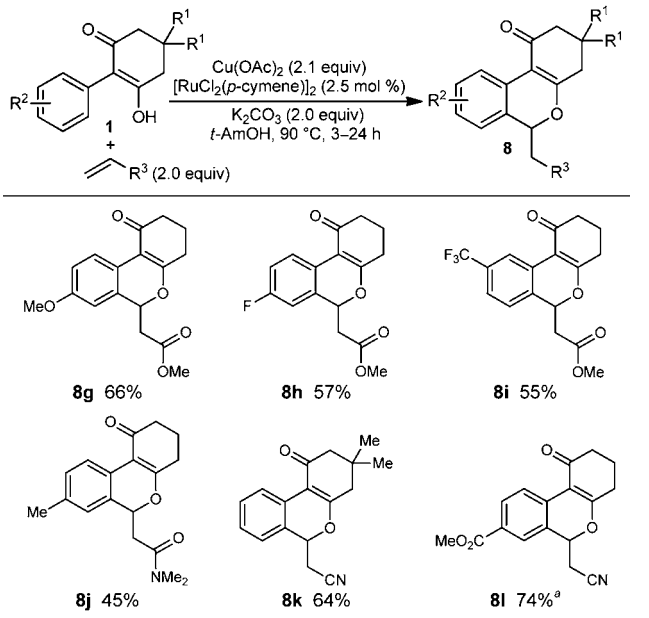


Figure 4. Ru(II)-catalyzed alkenylation of various 2-aryl-3-hydroxy-2-cyclohexenones with methyl acrylate, *N*,*N*-dimethylacrylamide, or acrylonitrile. Reactions were conducted with 0.50 mmol of **1c**−**1e**, **1g**, or **1h**. Yields are of isolated material. [a] Reaction conducted in the absence of K_2CO_3, as **8l** was formed in a low yield when K_2CO_3 was employed.

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Supporting Information Available. Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.