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Benzylic Oxidation Catalyzed by Dirhodium(II,III) Caprolactamate

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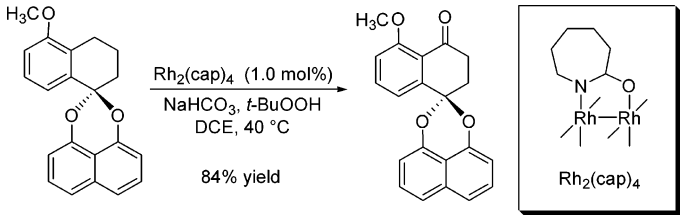
ABSTRACT



Dirhodium caprolactamate [$Rh_2(cap)_4$] is an effective catalyst for benzylic oxidation with *tert*-butyl hydroperoxide (TBHP) under mild conditions. Sodium bicarbonate is the optimal base additive for substrate conversion. Benzylic carbonyl compounds are readily obtained, and a formal synthesis of palmarumycin CP_2 using this methodology is described.

Selective oxidative functionalization of hydrocarbons using transition metal catalysis is a long-standing goal in organic process development.[1] Because of the stabilization offered to reaction intermediates, allylic and benzylic oxidations have been preferred targets,[2] and peroxide-based oxidants have been the reagents of choice.[3] Several transition-metal-catalyzed processes in conjunction with TBHP have been reported for benzylic oxidation,[4−7] which are generally less facile than allylic oxidations. However, reported benzylic oxidations have utilized only a limited number of substrates, and a general catalytic protocol capable of oxidizing a wide range of substrates has not been achieved.[8] Herein, we describe a mild, efficient, regio- and chemoselective benzylic oxidation using TBHP made possible through the catalytic intervention of mixed-valent dirhodium(II,III) tetrakis-(caprolactamate).[9]

We have recently reported that $Rh_2(cap)_4$ catalyzes the allylic oxidation of olefins in conjunction with TBHP.[10] In

(1) For transition-metal-catalyzed oxidations, see: (a) *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley: Weinheim, 2004. (b) Mimoun, H. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1987; Vol. 6, p 317. (c) Sheldon, R. A.; Kochi, J. K., *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

(2) (a) Bulman Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 7, p 83. (b) Olah, G. A.; Molnár, Á. Oxidation-Oxygenation. In *Hydrocarbon Chemistry*, 2nd ed; Wiley: Hoboken; 2003; p 427.

(3) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

(4) For Cr-catalyzed procedures, see: (a) Pearson, A. J.; Han, G. R. *J. Org. Chem.* **1985**, *50*, 2791. (b) Muzart, J. *Tetrahedron Lett.* **1986**, *27*, 3139. (e) Rathore, R.; Saxena, N.; Chandrasekaran, S. *Synth. Commun.* **1986**, *16*, 1493. (c) Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 2131. (d) Muzart, J.; Ajjou, A. N. A. *J. Mol. Catal.* **1991**, *66*, 155. (e) Choudary, B. M.; Prasad, A. D.; Bhuma, V.; Swapna, V. *J. Org. Chem.* **1992**, *57*, 5841. (f) Das, T. K.; Chaudhari, K.; Nandanan, E.; Chandwadkar, A. J.; Sudalai, A.; Ravindranathan, T.; Sivasanker, S. *Tetrahedron Lett.* **1997**, *38*, 3631. (g) Rothenberg, G.; Wiener, H.; Sasson, Y. *J. Mol. Catal. A*: *Chem.* **1998**, *136*, 253.

(5) For Co-catalyzed procedures, see: (a) Modica, E.; Bombieri, G.; Colombo, D.; Marchini, N.; Ronchetti, F.; Scala, A.; Toma, L. *Eur. J. Org. Chem.* **2003**, 2964. (b) Jurado-Gonzalez, M.; Sullivan, A. C.; Wilson, J. R. H. *Tetrahedron Lett.* **2003**, *44*, 4283.

(6) For Ru-catalyzed procedures, see: (a) Murahashi, S.; Oda, Y.; Naota, T.; Kuwabara, T. *Tetrahedron Lett.* **1993**, *34*, 1299. (b) Nikalje, M. D.; Sudalai, A. *Tetrahedron* **1999**, *55*, 5903.

(7) For Mn-catalyzed procedures, see: (a) Blay, G.; Fernández, I.; Giménez, T.; Pedro, J. R.; Ruiz, R.; Pardo, E.; Lloret, F.; Muñoz, M. C. *Chem. Commun.* **2001**, 2102. (b) Pan, J. F.; Chen, K. M. *J. Mol. Catal. A*: *Chem.* **2001**, *176*, 19.

(8) For recent work, see: (a) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. *J. Org. Chem.* **1995**, *60*, 3934. (b) Yamazaki, S. *Org. Lett.* **1999**, *1*, 2129. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2001**, *123*, 3183. (d) Lee, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 13978 (e) Yang, G.; Zhang, Q.; Miao, H.; Tong, X.; Xu, J. *Org. Lett.* **2005**, *7*, 263.

(9) For mixed-valent dirhodium(II,III) tetrakis(caprolactamate), see: Catino, A. J.; Nichols, J. M.; Forslund, R. E.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 2787.

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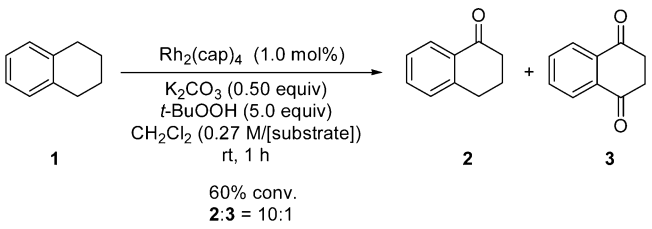
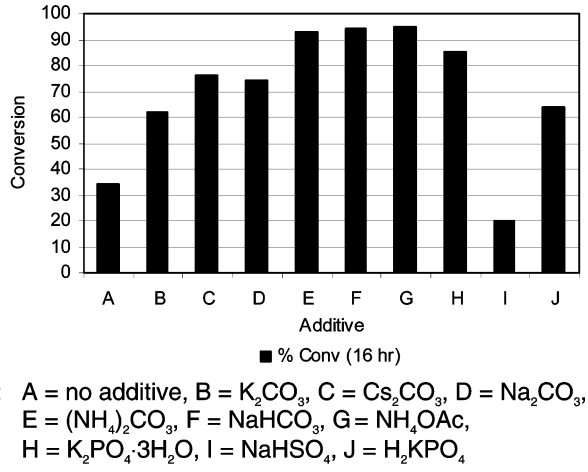
an effort to extend the utility of dirhodium catalysis beyond allylic substrates, we considered the feasibility of benzylic oxidation. Promising initial results were obtained with 1,2,3,4-tetrahydronaphthalene **1** (Scheme 1). After 1 h, 60%

Scheme 1



conversion of **1** was observed using the same conditions as were employed for allylic oxidation [$Rh_2(cap)_4$ (1.0 mol %), K_2CO_3, and TBHP].[11,12] However, no further conversion occurred after 1 h.[13] Analysis of the crude reaction mixture by ^1H NMR revealed a 10:1 mixture of α-tetralone **2** and dione **3** remarkably free of products from intermediate oxidation stages.

Seeking to overcome low substrate conversion, we took a parallel screening approach to identify critical reaction variables. During screening we discovered the pivotal role of base in this reaction (Figure 1). Notably, K_2CO_3 was



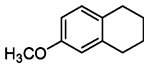
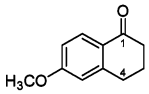
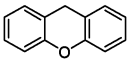
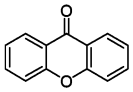
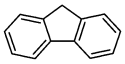
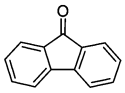
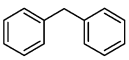
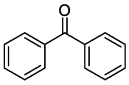
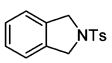
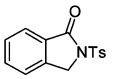
Key: A = no additive, B = K_2CO_3, C = Cs_2CO_3, D = Na_2CO_3, E = $(NH_4)_2CO_3$, F = $NaHCO_3$, G = NH_4OAc, H = $K_2PO_4 \cdot 3H_2O$, I = $NaHSO_4$, J = H_2KPO_4

Figure 1. Conversion of **1** as a function of additive. Conditions: $Rh_2(cap)_4$ (1 mol %), additive (50 mol %), TBHP (5.0 equiv), CH_2Cl_2 (0.27 M/[substrate]), rt, 16 h.

inferior to other bases examined. Both $(NH_4)_2CO_3$ and NH_4OAc showed promising results for the conversion of **1** but caused substrate decomposition when applied to compounds containing acid-labile groups (e.g., entries 1−3, Table 2). $NaHCO_3$ exhibited the widest versatility toward a range of substrates. During the course of this investigation, oxygen evolution was also evaluated as a function of additive. Dramatically less oxygen evolution, indicative of background TBHP decomposition,[14] was observed in reactions using $NaHCO_3$ as opposed to K_2CO_3. The amount of $NaHCO_3$ was found to be optimal at 50 mol % loading. Finally, 1,2-dichloroethane (DCE) provided access to higher temperatures without detracting from the reaction efficiencies observed in dichloromethane.

With optimized conditions, we examined a series of hydrocarbons containing benzylic methylene groups (Table 1). Excellent conversion (>95%) was obtained for most

Table 1. Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$[a]

entry	substrate	product	yield (%)[b]
1			60[c]
2			84[d]
3			60[e,f]
4			79
5			99
6			55
7			69[g]

[a] Reactions were performed at room temperature for 16 h unless otherwise noted using $Rh_2(cap)_4$ (1 mol %), substrate (1 equiv), $NaHCO_3$ (0.50 equiv), and TBHP (5.0 equiv) in DCE (0.27 M/[substrate]). [b] Isolated yield after column chromatography. [c] Dione **3** was isolated in 27% from the reaction. [d] $(NH_4)_2CO_3$ (50 mol %) was used. [e] Isolated as a mixture of C1/C4 isomers (1:1). [f] Dione **5** was isolated in 29% from the reaction. [g] Reaction was complete in 4 h.

substrates examined.[15] Moderate isolated yields for entries 1 and 3 (Table 1) are reflective of product oxidation resulting

(10) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622.

(11) For the preparation of $Rh_2(cap)_4$, see: Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

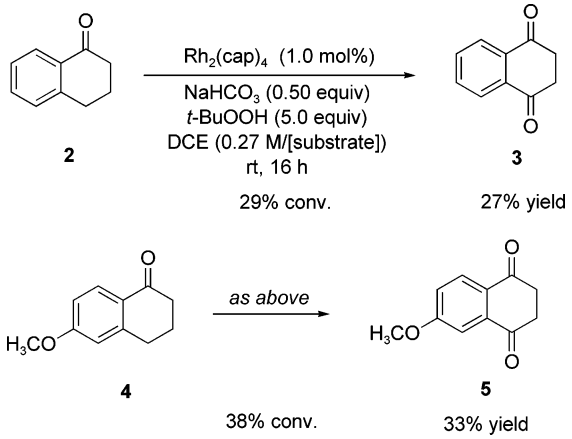
(12) Anhydrous TBHP in decane was used.

(13) In addition, catalyst decomposition was apparent after 1 h by a color change from dark red (indicative of a dirhodium(II,III) complex) to yellow/orange.

(14) (a) Bartlett, P. D.; Gunther, P. *J. Am. Chem. Soc.* **1966**, *88*, 3288. (b) Bartlett, P. D.; Guaraldi, G. *J. Am. Chem. Soc.* **1967**, *89*, 4799.

in dione formation. The origin of these products was confirmed by submitting **2** and 6-methoxy tetralone **4** to the reaction conditions to give diones **3** and **5**, respectively (Scheme 2).[16] The observed yields of dione correspond

Scheme 2

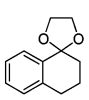
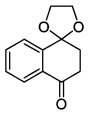
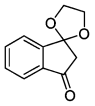
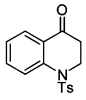
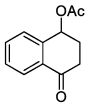
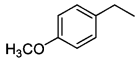
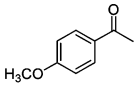
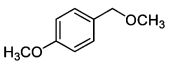
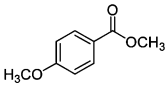


directly to the amount of dione observed in the reactions of the parent hydrocarbons. Furthermore, analysis of the product mixture at partial conversion for entries 1 and 3 (Table 1) shows the expected lower ratio of dione to tetralone.

$Rh_2(cap)_4$ in combination with $NaHCO_3$ and additional TBHP at 40 °C facilitated the clean oxidation of a diverse selection of substrates (Table 2). Acid-labile compounds containing acetals (Table 2, entries 1 and 2,) as well as *N*-protected tetrahydroquinolines (Table 2, entries 3 and 4) underwent oxidation to the corresponding keto-derivatives. The chroman class of substrates has proven to be a challenge for benzylic oxidation due to poor regioselectivity as a result of their antioxidant nature,[17] but with our methodology chroman (Table 2, entry 5,) underwent smooth oxidation to give chromanone exclusively in 92% isolated yield. Regioselectivity was also observed with 1-acetoxy-tetrahydronaphthalene (Table 2, entry 6) to give the C-4 tetralone in high isolated yield. In addition, acyclic substrates (Table 2, entries 7−9) were also viable participants for benzylic oxidation.[18]

During our investigation of the oxidation of isochroman under conditions reported in Table 1, we obtained 70% of expected isochromanone **6** and 7% of *tert*-butyl mixed-peroxide **7**, a suspected reaction intermediate (Scheme 3). By reducing the amount of TBHP to 2 equiv, inspection of the crude reaction mixture at 16 h revealed a 1.5:1 mixture of **6**:**7**. We initially considered the base additive as mediating the transformation of **7** to **6** through a Kornblum-type decomposition pathway.[19] Treatment of **7** with 50 mol % $NaHCO_3$ over 16 h did *not* yield **6** in any detectable quantity.[20] Treatment of the final crude reaction mixture with additional TBHP (2 equiv), however, increased the ratio of **6** to **7** from 1.5:1 to 6:1 (without material loss), indicating

Table 2. Benzylic Oxidation Catalyzed by $Rh_2(cap)_4$[a]

entry	substrate	product	conv. (%)[b]	yield (%)[c]
1			>95	84
2			48	32
3			>95	82
4			>95	84
5			>95	92
6			>95	88
7			42[d]	20
8			90	75
9			>95	84

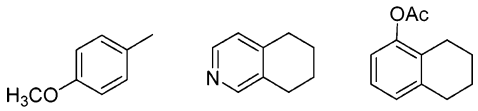
[a] Reactions were performed at 40 °C for 16 h using $Rh_2(cap)_4$ (1 mol %) added in two portions (0.5 mol % catalyst and 5 equiv of TBHP at the start and another 0.5 mol % catalyst and 5 equiv of TBHP after 3 h), substrate (1 equiv), and $NaHCO_3$ (0.50 equiv) in DCE (0.27 M/[substrate]). [b] Conversion determined by ^1H NMR analysis of the crude reaction mixture prior to purification. [c] Isolated yield after column chromatography. [d] Conversion determined by GC analysis of the crude reaction mixture.

(15) Conversion was determined by ^1H NMR analysis of the crude reaction mixture prior to purification. Diphenylmethane (entry 6, Table 1) gave 57% conversion.

(16) Diones **3** and **5** are chromatographically stable but must be stored in a freezer to avoid decomposition.

(17) Hodgetts, K. J. *Tetrahedron Lett.* **2001**, *42*, 3763 and references therein.

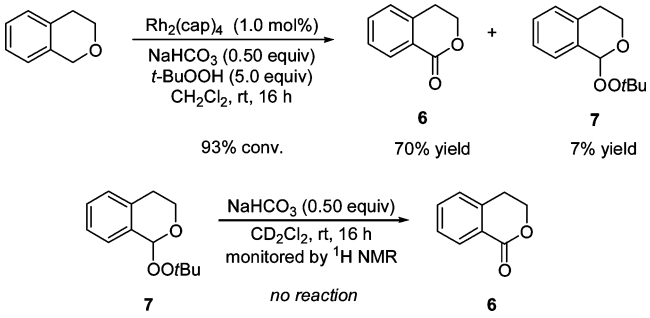
(18) Substrates containing a primary benzylic position, strong coordinating groups (e.g., pyridines or nitriles), or strong electron-withdrawing groups were unreactive under our protocol. The following substrates were examined and exemplify recalcitrant substrate classes:



(19) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880.

(20) Similar treatment with K_2CO_3 did not convert **7** to **6**.

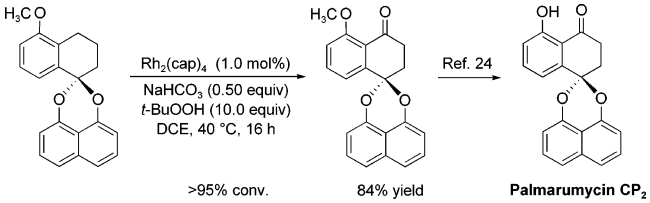
Scheme 3. Oxidation of Isochroman



that the mixed-peroxide can be converted to carbonyl product under the reaction conditions.[21,22]

The utility of $Rh_2(cap)_4$ as a catalyst for benzylic oxidation was demonstrated with spirocyclic acetal **8** for a formal synthesis of palmarumycin CP_2 (Scheme 4). Isolated in 1994

Scheme 4. Benzylic Oxidation for the Formal Synthesis of Palmarumycin CP_2



by Singh and co-workers, palmarumycin CP_2 is a biosynthetic precursor to the preussomerin class of natural products and exhibits a wide range of biological activity.[23] Chromium-catalyzed procedures (catalyst loadings from 10 to 250 mol % chromium) in combination with TBHP (16−30 equiv) have offered the only reported means of accessing ketone **9** in moderate yields.[24] It has also been noted that IBX-mediated oxidations were not as effective for this particular substrate.[20d] Using dirhodium catalysis, this acetal was readily converted to **9** in 84% isolated yield.

In summary, we have developed a catalytic benzylic oxidation protocol using $Rh_2(cap)_4$ and stoichiometric TBHP. The reaction proceeds under mild conditions with the aid of $NaHCO_3$. A diverse selection of substrates have been converted to carbonyl compounds, and a formal synthesis of palmarumycin CP_2 has been achieved. Mechanistic experiments have suggested an advanced role for base in the reaction. Efforts are underway to shed light on the mechanism of dirhodium(II,III) catalyzed oxidations while continuing to develop new transformations.

Acknowledgment. This work was supported by the National Science Foundation and the National Institutes of Health (GM 46503).

Supporting Information Available: Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This experiment also demonstrates that catalytic activity can be restarted by simply applying additional oxidant.

(22) The formation of ketones from mixed-peroxides with *t*-BuOOH under metal-catalyzed conditions has been reported: Muzart, J.; Ajjou, A. N. *J. Mol. Catal.* **1994**, *92*, 141. We thank the reviewer for bringing this to our attention.

(23) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296.

(24) For the oxidation of **8** to **9**, see: (a) Barrett, A. G. M.; Hamprecht, D.; Meyer, T. *Chem. Commun.* **1998**, 809. (b) Ragot, J. P.; Alcaraz, M. L.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 4921. (c) Ragot, J. P.; Steeneck, C.; Alcaraz, M. L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1073. (d) Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D.; Williams, D. J. *J. Org. Chem.* **2002**, *67*, 2735.