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Catalytic Allylic Oxidation of Cyclic Enamides and 3,4-Dihydro-2H-Pyrans by TBHP

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Abstract

Allylic oxidation of heteroatom substituted cyclic alkenes by *tert*-butyl hydroperoxide (70% TBHP in water) using catalytic dirhodium caprolactamate [Rh₂(cap)₄] forms enone products with a variety of 2-substituted cyclic enamides and 3,4-dihydro-2H-pyrans. These reactions occur under mild reaction conditions, are operationally convenient to execute, and are effective for product formation with as low as 0.25 mol% catalyst loading. With heteroatom stabilization of the intermediate allylic free radical two sites for oxidative product formation are possible, and the selectivity of the oxidative process varies with the heteroatom when R = H. Cyclic enamides produce 4-piperidones in good yields when R = alkyl or aryl, but oxidation of 2H-pyrans also gives alkyl cleavage products. Alternative catalysts for TBHP oxidations show comparable selectivities but give lower product yields.

Graphical Abstract

INTRODUCTION

Allylic oxidation is a popular methodology for the selective preparation of enones.¹ Initially investigated with selenium dioxide,² and reported with a wide variety of oxidants,^{1d,e,3} this methodology is currently focused on oxidations by *tert*-butyl hydroperoxide (TBHP), either in an anhydrous hydrocarbon medium or as the less expensive 70% solution in water (T-HYDRO).⁴ However, activation of TBHP as an oxidant requires a catalyst, most often a

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Notes

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Supporting Information

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Experimental tables, details of reaction time courses with additives, and ¹H and ¹³C NMR spectra of new compounds (PDF)

transition metal compound. A common role of the catalyst is to oxidatively convert TBHP into the *tert*-butylperoxy radical, which is selective for hydrogen atom abstraction from the allylic position, and to then be reduced to its original state through reaction with TBHP (Scheme 1).⁵ Subsequent reactions of the allyl radical with dioxygen produce the enone. Noteworthy is the observation that although cyclic alkenes produce conjugated cycloalkenones in high yield and are widely reported, reactions with cyclic enamide have not been described and with vinyl ethers with low (<10%) yields.⁶

Dirhodium(II) caprolactamate [Rh₂(cap)₄] is reported to be the most advantageous catalyst for allylic oxidations by TBHP.⁷ One of the reasons for this is its low oxidation potential,⁸ but another is the facility of this catalytic system to generate a continual flow of the *tert*-butylperoxy radical.^{4c} Although trapping of the intermediate allyl radical by dioxygen is dominant, minor processes have been reported to involve trapping by the *tert*-butylperoxy radical to form mixed peroxides,⁵ which are relatively stable under the reaction conditions. With only one known exception, attributable to steric factors,⁵ the more stable allyl radical is the primary product from allylic oxidation by the *tert*-butylperoxy radical.

Although not included in previous voluminous investigations of allylic oxidation reactions,^{1,4,9} heteroatom substituted cyclic olefins were considered to be potential substrates. In contrast to oxidations of cycloalkenes, heteroatom stabilization of the allyl radical was expected to be a factor in hydrogen atom abstraction and subsequent reactions.¹⁰ The intermediate allyl radical can be trapped by dioxygen at either the position proximal or distal to the heteroatom, thereby establishing direct routes to either β -heteroatom substituted enone **I** or unsaturated lactone **II** (Scheme 2) through oxidative processes previously reported to occur with cyclic alkenes.⁵

RESULTS AND DISCUSSION

Oxidation of Cyclic Enamides

N-Substituted 2,3-dihydro-4-piperidones represent key intermediates in the synthesis of biologically active piperidines, and their synthetic utility is well documented.¹¹ Recent efforts have demonstrated that these compounds are useful substrates for asymmetric conjugate addition¹² and intramolecular [2+2] cycloaddition.¹³ Notably, however, only a few methods exist for the construction of 2,3-dihydro-4(1*H*)-pyridinones (Scheme 3). Published approaches involve oxidative and reductive methods using reactants having the oxygen functional group already at the 4-position (with 4-oxypyridinium salts,¹⁴ 4-piperidone,¹⁵ and pyridin-4(1*H*)-one¹²) as well as cyclization methods (hetero Diels–Alder reactions with imines¹⁶ and intra-molecular 1,4-addition of amino-ynones¹⁷), and some of these methods have very limited scope. Cyclic enamides, which can be readily prepared from commercial δ -valerolactam^{18,19} or ϵ -caprolactam,¹⁸ would provide an expedient route to *N*-substituted 2,3-dihydro-4-piperidones via allylic oxidation. We report here the direct allylic oxidation of representative cyclic enamides that suggests the generality of the method and the comparative advantage of catalysis by dirhodium caprolactamate.

Our evaluation of enamide oxidations was initiated using *N*-Boc-1,2,3,4-tetrahydropyridine with 0.25 mol% dirhodium caprolactamate and T-HYDRO as the oxidant in

dichloromethane, conditions that have previously been reported as optimum for allylic oxidations of cycloalkenes.⁷ However, only a 25% yield of allylic oxidation products **2a** and **3a** was obtained with TBHP in water, or a 24% yield of **2a** + **3a** with anhydrous TBHP in decane after 2 days (entries 1–2, Table 1). 2,3-Dihydro-4(1*H*)-pyridinone (**2a**) was formed in preference to 5,6-dihydro-2(1*H*)-pyridinone (**3a**) in a ratio of nearly 5:1, so our challenges were to increase product yield and, possibly, regioselectivity. In our initial discovery of TBHP allylic oxidation, we reported that using 50 mol% of K₂CO₃ had a dramatic improvement on the reaction yield and rate,^{19,20} so we investigated the use of base additives on product yields. The oxidation of enamide compounds with potassium carbonate as an additive increased the yield of allylic oxidation products to 46% and slightly improved regioselectivity to 85:15 (entry 3, Table 1). By screening other additives, we found that the addition of 50 mol% of NaOAc significantly increased the yield to 76% with a further modest increase in regioselectivity (entry 5, Table 1). Other acetate salts and sodium formate gave no further improvement (see SI). With TBHP in decane a lower yield but similar regioselectivity was obtained. Higher catalyst loading to 1.0 mol% has no noticeable influence on yield or regioselectivity.

The influence of sodium acetate in increasing the yield of products and moderately increasing regioselectivity is surprising. Moreover, the presence of 0.5 equiv of sodium acetate significantly increased the reaction rate compared to the reaction with no additive, but with only 0.1 equiv of NaOAc the reaction becomes sluggish after 60% conversion (Figure 1). The role of this reagent appears to be as a mild base to increasing the rate of production of the *tert*-butylperoxy radical by increasing the concentration of the *tert*-butyl peroxy anion. Acetate does not become an axial ligand for Rh₂(cap)₄ since its presence does not inhibit reaction with TBHP.

Applying these conditions to other enamide compounds, including *N*-tosyl and *N*-Cbz amides, gave comparable outcomes with slightly different regioisomer ratios (**1b** and **1c**, Table 2), suggesting a modest influence of the amide on regiocontrol. The reaction conditions do not compromise the Cbz-protecting group, despite the potential for dirhodium catalyzed benzylic oxidation by TBHP. For the homologous ϵ -caprolactamate-derived *N*-Boc enamide (**1d**, Table 2) the desired enone **2d** was also obtained (0.25 mol% catalyst loading). In all cases, preference for oxidation is at the distal carbon position.

To further explore the scope of this reaction, alkyl and aryl substituted enamides **1e–g** were evaluated. Only 4-piperidone compounds **2e–g** were obtained with these substrates. In particular, the oxidation of 2-methyl substituted enamide (**1f**, Table 2) proceeded without oxidation of the methyl group, clearly demonstrating the efficiency and selectivity of this process.

Allylic oxidation of 4-BPin substituted *N*-Boc-1,2,3,4-tetrahydropyridine **1h** gave the single oxidation product from cleavage of the carbon–boron bond (**2a**) in 48% yield without any detectable other regioisomers (eq 1). 5-Membered enamide **1i** was also investigated. Instead of direct allylic oxidation, only dehydrogenation product **2i** was obtained (eq 2), suggesting that the allyl radical undergoes more rapid hydrogen atom donation than trapping by dioxygen.

(eq 1)

(eq 2)

To ascertain if the site of allylic hydrogen atom abstraction was a factor in determining regioselectivity, the regioisomer of **1c**, *N*-Cbz-1,2,3,6-tetrahydropyridine **7** was subjected to oxidation under the same conditions. The same products as from **1c** were formed in comparable yields (Table 3). The product ratio is, within experimental error, also the same, and potential products from hydrogen atom abstraction from the 5-position were not observed. This outcome is consistent with selective hydrogen atom abstraction from the 2-position of **7** and formation of the allyl radical corresponding to that formed from enamide **1c** whose subsequent oxidative reactions are the same.

This system provided an excellent opportunity to assess whether other catalysts promote allylic oxidation by TBHP in the same way. In addition to the use of dirhodium catalysis for allylic oxidation by TBHP, copper(I),²¹ palladium(II) hydroxide,²² cobalt acetate,²³ and ruthenium(III)²⁴ have also been employed. Also, the stoichiometric reactions with hypervalent (*tert*-butylperoxy)iodyne, which is a direct precursor of the *tert*-butylperoxy radical,²⁵ was also used. Although the *tert*-butylperoxy radical is the most likely hydrogen abstraction agent, the possibility of oxo-metal involvement, especially with ruthenium catalysts,¹ persists. If these reactions form the same allyl radical, and there is no further involvement by the catalyst, the same regioselectivity found with Rh₂(cap)₄ is expected. If, however, there is a difference in oxygen delivery, a change in regioselectivity would indicate this. Although product yields using different catalysts were significantly lower, the same regioselectivities were obtained (Table 3). Even Rh₂(OAc)₄ and Rh₂(oct)₄ catalyze the allylic oxidation of compounds **1c** and **7** by TBHP, but they occur with lower yields (entries 8–9, Table 3). Longer reaction times and higher catalyst loadings are required to obtain the reported yields with the dirhodium carboxylate catalysts, and the induction period for observation of the pink colored Rh₂(5⁺) oxidative intermediate several hours after TBHP was added (both Rh₂(OAc)₄ and Rh₂(oct)₄), while only several seconds for reactions catalyzed by Rh₂(cap)₄. The nearly identical regioselectivities from reactions with **1c** and **7** implies that they share the same allyl radical intermediate.

Oxidation of Dihydropyrans

Polyfunctional pyran derivatives commonly appear in numerous natural products and biologically active compounds.²⁶ Although many synthetic methods have been developed for their synthesis, limited substrate scope and expensive or difficult synthetic precursors restrict their applications.²⁷ Oxidative methods have had very limited applications and success.^{6,28} As a comparison with the corresponding enamide analogues we examined the use of dirhodium caprolactamate for the TBHP oxidation of 3,4-dihydro-2*H*-pyrans. Would the same oxidative efficiencies and selectivities prevail? In an earlier investigation of oxidations by hypervalent (*tert*-butylperoxy)iodanes involving oxoradical hydrogen atom abstraction, noncyclic allyl ethers were converted to acrylate esters in moderate to good yields,^{25a} and we found the same outcome from Rh₂(cap)₄ catalyzed oxidation reactions (Scheme 4).

Oxidation of 3,4-dihydropyran **4a** was conducted under the same conditions as were employed for oxidations of enamide compounds. Surprisingly, 2*H*-pyran-4-one **5a** was obtained together with its regioisomeric α,β -unsaturated lactone **6** as a 1:1 mixture in 77% total yield (entry 1, Table 4), and in the reaction without sodium acetate the **5a**:**6** ratio was 24:76 (35% yield). Consistent with the matching outcome for oxidations of **1c** and **7** (Table 3), the oxidation of 3,6-dihydropyran gave the same **5a**:**6** product ratio (53:47, 67% yield) as did 3,4-dihydropyran **4a** under the same reaction conditions. Not surprisingly, 2-alkyl-substituted 2*H*-pyran compounds **4b–d** underwent oxidation only at the 4-position to form **5b–d**, respectively (entries 2–3, Table 4). Moreover, only the endocyclic allylic oxidation products were obtained when these dihydropyrans were employed, and the potentially oxidizable benzylic methylene group underwent benzylic oxidation only after extended reaction times. The 1:1 regioselectivity in the oxidation of **4a** contrasts with the significant regiocontrol that was obtained for the oxidation of enamides **1a–d**, and this evidence suggests that the ether oxygen does not exert directive influence on product formation. In contrast with results with enamide **1c**, reactions with dihydropyran **4a** using the same set of alternative oxidation catalysts for TBHP oxidation gave variable selectivities with RuCl₃ and Co(OAc)₂, but not with (*tert*-butylperoxy)iodane or CuI (Table 5). The indication from regioselectivities with RuCl₃ and Co(OAc)₂ catalysts is that oxygen delivery is different,²⁹ at least in part, but the common regioselectivities obtained with Rh₂(cap)₄, CuI, and (*tert*-butylperoxy)iodane describe the same allyl radical pathway. The influence of sodium acetate in increasing the yield of products and increasing regioselectivity is uncertain.

During our investigation of the oxidation of 2*H*-pyran compounds **4b**, we isolated minor, but reproducible, amounts of alkyl cleavage product **6** (14% isolated yield) in addition to the anticipated allylic oxidation products **5b** (eq 3, Scheme 5). Similar cleavage reactions were also found with substituted 2*H*-pyrans **4c** and **4d** (eq 4, Scheme 5). Cleavage products were not observed in reactions of enamides. Increasing the oxygen content of the solvent led to a higher yield of cleavage product, albeit with lower overall yield.

The formation of **6** in the oxidation of **4b** represents the cleavage of the C–C single bond between the *n*-butyl substituent and 2*H*-pyran. Although not previously reported in allylic oxidation reactions, this C–C single bond cleavage reaction can be considered to be the

outcome of the trapping of the initially formed allyl radical at the 2-position, subsequent hydrogen atom transfer to the peroxy radical, and oxidative cleavage of the hydroperoxide to form an oxoradical (Scheme 6).³⁰

Results obtained for allylic oxidation of cyclic enamides and dihydropyrans show limitations relative to allylic oxidations of their carbocyclic counterparts. Although product yields are comparable in many cases, regioselectivity and cleavage issues have been identified as potential concerns. A possible explanation for the absence of cleavage products in reactions with cyclic eneamides may be the relative stability of the dioxygen captured allyl radical. If that step is reversible, and the C–C bond cleavage reaction is dependent on hydrogen atom transfer, then C–C bond cleavage will be dependent on the lifetime of the intermediate peroxy radical (Scheme 7). Similarly, the relative stability of peroxy radical intermediates may be the cause of the observed regioselectivities found with the tetrahydropyridines and dihydropyran. However, an alternative explanation is that there is a stabilizing stereo-electronic effect originating from strong anomeric $n_O \rightarrow \sigma^*_{CO}$ interactions with dioxygen capture at the 2-position that is absent in the peroxy radical intermediate from oxygen capture at the 4-position.³¹ With enamides, this anomeric stabilization by nitrogen is much less, and the regioselectivity differences observed in this investigation are consistent with this explanation.

In summary, dirhodium caprolactamate has been shown to be a viable catalyst for the allylic oxidation of cyclic enamides and enol ethers. The reaction conditions are mild, occur with 70% TBHP in water, and require low catalyst loading. The oxidation of enamides offers a facile route to substituted 2,3-dihydro-4-piperidones, and applications to enol ethers provide substituted 4-pyranone compounds but with competitive C–C cleavage.

EXPERIMENTAL SECTION

General Information

Anhydrous reactions, unless noted, were performed in oven-dried (120 °C) glassware with magnetic stirring under an inert atmosphere of dry nitrogen. Allylic oxidation reactions were performed in vials under air atmosphere. Analytical thin layer chromatography (TLC) was carried out using silica gel plates; visualization was accomplished with UV light (254 nm). Liquid chromatography was performed by flash chromatography of the indicated system on silica gel (230–400 mesh). ¹H NMR spectra were recorded on a 500 MHz spectrometer, and chemical shifts were reported in ppm. The peak information was described as br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite; coupling constant(s) in Hz. The number of protons (*n*) for a given resonance was indicated by *n*H. Coupling constants were reported as *J*-values in Hz. ¹³C NMR spectra were recorded on a 125 MHz spectrometer with complete proton decoupling. High-resolution mass spectra (HRMS) were performed on a TOF-CS mass spectrometer using CsI as the standard. Accurate masses were reported for the molecular ion [M+Cs]⁺, [M+Na]⁺, or [M+H]⁺.

Materials

$\text{Rh}_2(\text{cap})_4$ was prepared according to the literature procedure.⁷ Substrates **1a–d**,¹⁹ **1e**,³² **1f**,³³ and **4a–c**,³⁴ and 3,6-dihydro-2*H*-pyran³⁵ were synthesized and characterized according to literature procedures. The iodinate reagent was generated in situ following Yeung's procedure.^{25b} Other metal catalysts, solvents, and the other reagents were obtained from commercial sources and used without further purification.

Synthetic Procedure for *tert*-Butyl 7-Phenyl-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (**1g**)

Sodium bis(trimethylsilyl)-amide (2.0 M in THF, 2.40 mL, 4.8 mmol) was added into a precooled solution of *tert*-butyl 2-oxoazepane-1-carboxylate (0.8531 g, 4.0 mmol) in 10 mL dried THF at -78°C . The reaction mixture was stirred at that temperature for 1 h. Diphenylphosphinic chloride (1.14 g, 4.8 mmol) was added dropwise via syringe at -78°C and stirred for additional 2 h, and the reaction solution was then warmed to room temperature. The reaction was quenched by H_2O . The two layers were separated, and the aqueous phase was extracted with ethyl acetate (10 mL $\times$ 3). The combined organic phase was dried over anhydrous MgSO_4 and concentrated under vacuum. The residue was directly used without further purification. To a 50 mL flame-dried Schlenk flask containing a magnetic stirring bar, $\text{Pd}(\text{OAc})_2$ (26.9 mg, 0.12 mmol, 0.10 equiv) and PPh_3 (94.2 mg, 0.359 mmol, 0.3 equiv) were added, and the atmosphere above these reactants was vacuum and nitrogen purge three times. 1,2-Dimethoxyethane (12 mL) was added into the reaction flask, and the resulting mixture was stirred for 15 min. Then the crude enol phosphinate (495.6 mg, 1.199 mmol), $\text{PhB}(\text{OH})_2$ (336.3 mg, 2.758 mmol, 2.30 equiv), and 2 M Na_2CO_3 aqueous solution (1.8 mL, 3.6 mmol, 3.0 equiv) were added sequentially under a nitrogen atmosphere. The reaction mixture was then heated to 80°C and maintained at that temperature for 4 h. The reaction was quenched by the addition of H_2O , and the two layers were separated, the aqueous phase was extracted with ethyl acetate (10 mL $\times$ 3), and the combined organic phase was dried over anhydrous MgSO_4 and concentrated in vacuum. The residue was purified by flash chromatography on silica gel using hexanes/ethyl acetate (5:1) as the eluent to afford the corresponding product **1g** as a colorless liquid (204.2 mg, 62% for 2 steps). The spectral characteristics of this compound are identical to those reported in the literature.³⁶

Synthetic Procedure for 6-(3-Phenylpropyl)-3,4-dihydro-2*H*-pyran (**4d**)

t-BuLi (1.2 M in pentane, 8.0 mL, 9.6 mmol, 1.2 equiv) was added to a precooled solution of 3,4-dihydro-2*H*-pyran (672.1 mg, 7.990 mmol) in 20 mL dried THF at -78°C . The reaction mixture was warmed to 0°C and stirred for 1 h. Then the reaction was cooled to -78°C , and 3-phenylpropyl bromide (1.9113 g, 9.588 mmol, 1.20 equiv) was added dropwise. The reaction solution was stirred for additional 2 h, then slowly warmed to room temperature. Saturated aqueous NH_4Cl (ca. 10 mL) was added to quench the reaction. The two layers were separated, and the aqueous phase was extracted with diethyl ether (10 mL $\times$ 3). The combined organic phase was dried over anhydrous MgSO_4 and concentrated in vacuum. The residue was purified by flash chromatography on silica gel using hexanes:ethyl acetate (5:1) as the eluent to afford the corresponding product **4d** as a colorless liquid (727.2 mg,

45%). ^1H NMR (500 MHz, acetonitrile- d_3) δ 7.28–7.25 (m, 2H), 7.20–7.15 (m, 3H), 4.47 (t, J = 3.7 Hz, 1H), 3.92 (t, J = 5.3 Hz, 2H), 2.59 (t, J = 7.9 Hz, 2H), 1.98–1.94 (m, 4H), 1.76–1.69 (m, 4H); ^{13}C NMR (126 MHz, acetonitrile- d_3) δ 155.0, 143.7, 129.4, 129.2, 126.6, 96.4, 66.8, 35.8, 34.5, 29.8, 23.3, 21.0. HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$: 203.1430; found: 203.1433.

General Procedure for the Oxidation of Enamides **1** and 2*H*-Pyrans **4**

TBHP (70 wt% in water, 0.17 mL, 1.0 mmol) was added in one portion into a mixture of **1** or **4** (0.2 mmol, 1 equiv), NaOAc (8.2 mg, 0.1 mmol, 0.5 equiv) and $\text{Rh}_2(\text{cap})_4$ (0.32 mg, 0.00049 mmol, 0.25 mol%) in 0.75 mL of DCM at room temperature under air atmosphere. Characteristic of the oxidative conversion of dirhodium(4^+) to dirhodium(5^+), the color of the reaction mixture turned a red color. The reaction was complete in 1–2 h. After concentration, the residue was purified by flash chromatography on silica gel using hexanes:ethyl acetate (5:1 $\rightarrow$ 3:1) as the eluent to afford the corresponding product **2** or **5**. Product yields are the isolated yields of both regioisomers if R_2 is H. Product ratios were determined by ^1H NMR.

Characterization Data for **2** and **5**

Characterization data of compounds **2a**,^{15a} **2b**,^{12c} **2c**,¹³ **2e**,³⁷ **2i**,³⁸ **3a**,³⁹ **3b**,⁴⁰ **3c**,⁴¹ **3d**,⁴² **5a**,⁴³ and **6**⁴⁴ were previously reported and their spectral or HPLC confirmation are provided in the Supporting Information.

tert-Butyl 5-Oxo-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (2d**)**—62% yield of **2d** and **3d** (**2d**:**3d** = 90:10). Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.44 (d, J = 10.6 Hz, 1H), 5.21 (d, J = 10.6 Hz, 1H), 3.97–3.86 (m, 2H), 2.66 (t, J = 6.5 Hz, 2H), 2.10–1.98 (m, 2H), 1.54 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 201.0, 152.0, 137.7, 108.7, 83.4, 42.7, 28.0, 27.9, 22.7. HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 212.1281; found: 212.1285.

tert-Butyl 6-Methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (2f**)**—52% yield. Light yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 5.31 (s, 1H), 4.01 (t, J = 6.9 Hz, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.31 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 194.3, 157.6, 152.1, 111.8, 83.1, 46.0, 36.7, 28.1, 23.8. HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 212.1281; found: 212.1285.

tert-Butyl 5-Oxo-7-phenyl-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (2g**)**—60% yield. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.51–7.31 (m, 5H), 5.85 (s, 1H), 3.96 (t, J = 7.0 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H), 2.30–2.15 (m, 2H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 200.5, 158.4, 152.8, 130.0, 128.4, 126.6, 120.5, 81.8, 51.0, 40.9, 27.6, 26.4. HRMS (ESI) calculated for $\text{C}_{17}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 288.1594; found: 288.1594.

6-Butyl-2*H*-pyran-4(3*H*)-one (5b**)**—62% yield. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 5.34 (s, 1H), 4.45 (t, J = 6.8 Hz, 2H), 2.51 (t, J = 6.8 Hz, 2H), 2.24 (t, J = 7.6 Hz, 2H), 1.54 (p, J = 7.5 Hz, 2H), 1.35 (h, J = 7.4 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR

(126 MHz, CDCl₃) δ 192.3, 178.1, 104.5, 67.9, 35.6, 34.5, 28.4, 22.1, 13.7. HRMS (ESI) calculated for C₉H₁₅O₂ [M+H]⁺: 155.1067; found: 155.1069.

6-Isobutyl-2H-pyran-4(3H)-one (5c)—65% yield. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.32 (s, 1H), 4.45 (t, *J* = 6.8 Hz, 2H), 2.51 (t, *J* = 6.8 Hz, 2H), 2.11 (d, *J* = 7.2 Hz, 2H), 2.00–1.93 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 192.2, 177.1, 105.6, 67.9, 44.0, 35.7, 26.5, 22.3. HRMS (ESI) calculated for C₉H₁₅O₂ [M+H]⁺: 155.1067; found: 155.1070.

6-(3-Phenylpropyl)-2H-pyran-4(3H)-one (5d)—55% yield. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.33–7.27 (m, 2H), 7.23–7.13 (m, 3H), 5.34 (s, 1H), 4.44 (t, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.51 (t, *J* = 6.8 Hz, 2H), 2.27 (t, *J* = 7.6 Hz, 2H), 1.90 (p, *J* = 7.6 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 192.2, 177.4, 141.2, 128.4, 126.1, 104.8, 104.7, 68.0, 35.7, 35.1, 34.2, 27.8. HRMS (ESI) calculated for C₁₄H₁₇O₂ [M+H]⁺: 217.1223; found: 217.1225.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. General reviews of allylic oxidation: Eames J, Watkinson M. *Angew Chem, Int Ed.* 2001; 40:3567. Andrus MB, Lashley JC. *Tetrahedron.* 2002; 58:845. Moiseev II, Vargaftik MN. *Coord Chem Rev.* 2004; 248:2381. Nakamura A, Nakada M. *Synthesis.* 2013; 45:1421. Weidmann V, Maison W. *Synthesis.* 2013; 45:2201. Chen K, Zhang P, Wang Y, Li H. *Green Chem.* 2014; 16:2344.
2. Recent review of selenium dioxide oxidations: Młochowski J, Wójtcowicz-Młochowska H. *Molecules.* 2015; 20:10205. [PubMed: 26046320]
3. Wendell SG, Edward JP. *J Steroids Horm Sci.* 2016; 7:171.
4. Recent reviews of tert-butyl hydroperoxide: Gao L, Xiong S, Wan C, Wang Z. *Synlett.* 2013; 24:1322. Ratnikov MO, Doyle MP. *Mendeleev Commun.* 2014; 24:187. Wu XF, Gong JL, Qi X. *Org Biomol Chem.* 2014; 12:5807. [PubMed: 24846326]
5. McLaughlin EC, Choi H, Wang K, Chiou G, Doyle MP. *J Org Chem.* 2009; 74:730. [PubMed: 19072696]
6. Novaes LFT, Sarotti AM, Pilli RA. *J Org Chem.* 2015; 80:12027. [PubMed: 26513545]
7. Ratnikov MO, Goldman PL, McLaughlin EC, Doyle MP. *Org Synth.* 2012; 89:19.
8. Doyle MP, Ren T. *Prog Inorg Chem.* 2001; 49:113.
9. Representative reports: Salvador JAR, Silvestre SM, Moreira VM. *Curr Org Chem.* 2006; 10:2227. Muzart J. *Mini-Rev Org Chem.* 2009; 6:9.
10. Wright JS, Shadnia H, Chepelev LL. *J Comput Chem.* 2009; 30:1016. [PubMed: 18825692]
11. Weintraub PM, Sabol JS, Kane JM, Borcharding DR. *Tetrahedron.* 2003; 59:2953.
12. For asymmetric conjugate addition to 2,3-dehydro-4-piperidones see: Shintani R, Tokunaga N, Doi H, Hayashi T. *J Am Chem Soc.* 2004; 126:6240. [PubMed: 15149215] Jagt RBC, de Vries JG, Feringa BL, Minnaard AJ. *Org Lett.* 2005; 7:2433. [PubMed: 15932216] Šebesta R, Pizzuti MG, Boersma AJ, Minnaard AJ, Feringa BL. *Chem Commun.* 2005; 1711 Xu Q, Zhang R, Zhang T, Shi

- M. *J Org Chem.* 2010; 75:3935. [PubMed: 20446712] Muller D, Alexakis A. *Org Lett.* 2012; 14:1842. [PubMed: 22420463]
13. Brimiouille R, Bach T. *Science.* 2013; 342:840. [PubMed: 24233720]
14. (a) Connns DL, Brown JD. *Tetrahedron Lett.* 1986; 27:4549.(b) Comins DL, Chung G, Foley MA. *Heterocycles.* 1994; 37:1121.
15. (a) Diao T, Stahl SS. *J Am Chem Soc.* 2011; 133:14566. [PubMed: 21851123] (b) Unterhalt B, Hanewacker GA. *Arch Pharm.* 1988; 321:749.(c) Nicolaou KC, Montagnon T, Baran PS. *Angew Chem, Int Ed.* 2002; 41:993.(d) Grierson D. *Org React.* 1990; 39:85.
16. Málek J. *Org React.* 1988; 36:249.
17. (a) Badorrey R, Cativiela C, Diaz-de-Villegas MD, Galvez JA. *Tetrahedron.* 2002; 58:341.(b) Alcaide B, Almendros P, Alonso JM, Aly MF. *Chem - Eur J.* 2003; 9:3415. [PubMed: 12866084] (c) Josephsohn NS, Snapper ML, Hoveyda AH. *J Am Chem Soc.* 2003; 125:4018. [PubMed: 12670201] (d) Andreassen T, Haland T, Hansen LK, Gautun OR. *Tetrahedron Lett.* 2007; 48:8413. (e) Newman CA, Antilla JC, Chen P, Predeus AV, Fielding L, Wulff WD. *J Am Chem Soc.* 2007; 129:7216. [PubMed: 17503816]
18. (a) Turunen BJ, Georg GI. *J Am Chem Soc.* 2006; 128:8702. [PubMed: 16819843] (b) Niphakis MJ, Turunen BI, Georg GI. *J Org Chem.* 2010; 75:6793. [PubMed: 20929269]
19. Yu J, Truc V, Riebel P, Hierl E, Mudryk B. *Org Synth.* 2008; 85:064.
20. Catino AJ, Forslund RE, Doyle MP. *J Am Chem Soc.* 2004; 126:13622. [PubMed: 15493912]
21. (a) Rothenberg G, Feldberg L, Wiener H, Sasson YJ. *Chem Soc, Perkin Trans 2.* 1998:2429.(b) Arsenou ES, Koutsourea AI, Foustieris MA, Nikolaropoulos SS. *Steroids.* 2003; 68:407. [PubMed: 12798491]
22. Yu JQ, Corey EJ. *J Am Chem Soc.* 2003; 125:3232. [PubMed: 12630876]
23. Salvador JAR, Clark JH. *Chem Commun.* 2001:33.
24. Miller RA, Li W, Humphrey GR. *Tetrahedron Lett.* 1996; 37:3429.
25. (a) Ochiai M, Ito T, Takahashi H, Nakanishi A, Toyonari M, Sueda T, Goto S, Shiro M. *J Am Chem Soc.* 1996; 118:7716.(b) Zhao Y, Yeung YY. *Org Lett.* 2010; 12:2128. [PubMed: 20387842]
26. For reviews, see: Boivin TLB. *Tetrahedron.* 1987; 43:3309.Faul MM, Huff BE. *Chem Rev.* 2000; 100:2407. [PubMed: 11749289]
27. Astashko DA, Tyvorskii VI. *Tetrahedron Lett.* 2011; 52:4792.
28. Campos JL, De Giovani WF, Romero JR. *Synthesis.* 1990; 1990:597.
29. Murahashi SI, Komiya N, Oda Y, Kuwabara T, Naota T. *J Org Chem.* 2000; 65:9186. [PubMed: 11149868]
30. Cleavage of C–C bond adjacent to alkoxy radical: Kurouchi H, Andujar-De Sanctis IL, Singleton DA. *J Am Chem Soc.* 2016; 138:14534. [PubMed: 27764943] Yayla HG, Wang H, Tarantino HSO, Knowles RR, Orbe HS. *J Am Chem Soc.* 2016; 138:10794. [PubMed: 27515494] Bietti M, Gente G, Salamone M. *J Org Chem.* 2005; 70:6820. [PubMed: 16095301] Bietti M, Lanzalunga O, Salamone M. *J Org Chem.* 2005; 70:1417. [PubMed: 15704978] Wilsey S, Dowd P, Houk KN. *J Org Chem.* 1999; 64:8801. [PubMed: 11674782]
31. Gomes GP, Vil' V, Terent'ev A, Alabugin IV. *Chem Sci.* 2015; 6:6783. [PubMed: 28757970]
32. Occhiato EG, Lo Galbo FL, Guarna A. *J Org Chem.* 2005; 70:7324. [PubMed: 16122254]
33. Poittevin C, Liautard V, Beniazza R, Robert F, Landais Y. *Org Lett.* 2013; 15:2814. [PubMed: 23697880]
34. Li G, Kaplan MJ, Wojtas L, Antilla JC. *Org Lett.* 2010; 12:1960. [PubMed: 20361794]
35. Suto MJ, Stier MA, Werbel LM, Arundel-Suto CM, Leopold WR, Elliott WE, Sebolt-Leopold JS. *J Med Chem.* 1991; 34:2484. [PubMed: 1875345]
36. Lepifre F, Clavier S, Bouyssou P, Coudert G. *Tetrahedron.* 2001; 57:6969.
37. Gouault N, Le Roch M, Cheignon A, Uriac P, David M. *Org Lett.* 2011; 13:4371. [PubMed: 21790147]
38. Carafa M, Distaso M, Mele V, Trani F, Quaranta E. *Tetrahedron Lett.* 2008; 49:3691.
39. Winter DK, Drouin A, Lessard J, Spino C. *J Org Chem.* 2010; 75:2610. [PubMed: 20230016]

40. Dake GR, Fenster MDB, Hurley PB, Patrick BO. *J Org Chem.* 2004; 69:5668. [PubMed: 15307738]
41. Pineschi M, Del Moro F, Gini F, Minnaard AJ, Feringa BL. *Chem Commun.* 2004:1244.
42. Álvarez S, Domínguez G, Gradillas A, Pérez-Castells J. *Eur J Org Chem.* 2013; 2013:3094.
43. Nishino, S., Hirotsu, K., Shima, H., Suzuki, S. Processes for producing tetrahydropyran-4-one and pyran-4-one. Patent. WO2005061479A1. Jul 7. 2005
44. D'Annibale A, Ciaralli L, Bassetti M, Pasquini C. *J Org Chem.* 2007; 72:6067. [PubMed: 17629335]

Figure 1.

Time course for the reactions of NaOAc at 20 °C. Catalyst loading was 0.25 mol% and the reaction concentration was 0.27 M.

Scheme 1. Catalytic Formation of the *tert*-Butylperoxy Radical by One-Electron Transfer Catalysts

Scheme 2.

Allylic Oxidation of Heteroatom-Substituted Cyclic Alkenes

Scheme 3.
General Approaches Towards the Synthesis of 4-Piperidones

Scheme 4.
Allylic Oxidation of Acrylate Esters

Scheme 5.
C–C Single Bond Cleavage

Scheme 6.
Plausible Pathway for C–C Bond Cleavage

Scheme 7.
Possible Explanation for Different Outcomes in Reactions between Eneamides and Dihydropyrans

Table 1Screening Reaction Conditions for the Oxidation of **1a**^a

entry	additives	yield (%) ^b	regioselectivity ^c
1	none	25	82:18
2 ^d	none	24	81:19
3	K_2CO_3	46	85:15
4	Cs_2CO_3	58	84:16
5	NaOAc	76	88:12
6 ^e	NaOAc	62	87:13

^aStandard reaction conditions: T-HYDRO (1.0 mmol, 5.0 equiv) was added into a solution of **1a** (0.20 mmol), additives (0.1 mmol, 0.5 equiv), $\text{Rh}_2(\text{cap})_4$ (0.0005 mmol) in DCM (0.75 mL, 0.27 M) at room temperature. The oxidations are complete within 2 h.

^bIsolated yield.

^cRegioselectivity was determined by 500 MHz ^1H NMR.

^dTBHP (5.5 M in decane) was used.

^e0.1 equiv NaOAc was used.

Table 2

Allylic Oxidation of Enamides^a

^aStandard reaction conditions: T-HYDRO (1.0 mmol, 5.0 equiv) was added into a solution of **1a–g** (0.2 mmol), NaOAc (0.1 mmol, 0.5 equiv), Rh₂(cap)₄ (0.0005 mmol) in DCM (0.75 mL, 0.27 M) at room temperature. The oxidations are complete within 2 h.

^bTotal isolated yield for the two isomers.

^cRegioselectivity was determined by 500 MHz ¹H NMR.

Table 3

Comparison of Methods for Oxidation of **1c** and **7**

entry	conditions ^a	substrate 1c		substrate 7	
		total yield (%) ^b	2c:3c	total yield (%) ^b	2c:3c
1	Rh ₂ (cap) ₄ (0.25 mol%), NaOAc (0.5 equiv)	67	86:14	62	88:12
2	(<i>tert</i> -butyl-peroxy)iodane ^d	30	80:20	37	82:18
3	CuBr (10 mol%)	15	83:17	12	84:16
4	CuI (5 mol%) ^e	26	85:15		
5	RuCl ₃ (5 mol%)	7	87:13	9	86:14
6	Pd(OH) ₂ (5 mol%) and K ₂ CO ₃ (0.5 equiv) ^f	45	83:17	40	85:15
7	Co(OAc) ₂ ·4H ₂ O (2.5 mol%) ^g	35	87:13	33	87:13
8	Rh ₂ (OAc) ₄ (1 mol%)	52	90:10	42	91:9
9	Rh ₂ (oct) ₄ (1 mol%)	60	90:10	52	91:9

^aStandard reaction conditions: T-HYDRO (1.0 mmol, 5.0 equiv) was added into a solution of **1c** or **7** (0.2 mmol), metal catalyst in DCM (1 mL) at room temperature. No reaction occurred with ferric chloride in either acetonitrile or DCM.

^bIsolated yield.

^cRegioselectivity was determined by 500 MHz ¹H NMR.

^dTBHP (5.5 M in decane, 0.8 mmol) was added into a solution of **7** (0.2 mmol), PhI(OAc)₂ (0.6 mmol), and K₂CO₃ (0.1 mmol) in CH₃COO*n*-Bu (1.0 mL) at -20 °C.

^eReaction performed in acetonitrile.

^f10 equiv. TBHP (5.5 M in decane) was used.

^gCH₃CN was used as the solvent at 50 °C.

Table 4

Allylic Oxidation of 2*H*-Pyrans Compounds^a

entry	substrate	Product	yield (%) ^b
1		+ 52 : 48 ^c	77
2			52
3			65
4 ^d			61

^aStandard reaction conditions: T-HYDRO (1.0 mmol, 5.0 equiv) was added into a solution of **4a–d** (0.2 mmol), NaOAc (0.1 mmol, 0.5 equiv), Rh₂(cap)₄ (0.0005 mmol) in DCM (0.75 mL, 0.27 M) at room temperature. The oxidations are complete within 2 h.

^bIsolated yield.

^cRegioselectivity was determined by 500 MHz ¹H NMR analysis.

^dThe product derived from oxidizing benzylic and allylic methylenes is generated when the reaction time is over 24 h.

Table 5

Other Methods for Oxidation of Dihydropyran Involving the *tert*-Butylperoxy Radical

entry	conditions ^a	total yield of 5a and 6 (%) ^b	5a: 6 ^c
1	(<i>tert</i> -butylperoxy)iodane ^d	28	53:47
2	CuBr (10 mol%)	40	55:45
3	RuCl ₃ (5 mol%)	20	63:37
4	Pd(OH) ₂ (5 mol%) and K ₂ CO ₃ (0.5 equiv)	trace	n.d.
5	Co(OAc) ₂ ·4H ₂ O (2.5 mol%) ^e	52	34:66
6	Rh ₂ (cap) ₄ (0.25 mol%), NaOAc (0.5 equiv)	77	52:48

^aStandard reaction conditions: T-HYDRO (3.0 mmol, 5.0 equiv) was added into a solution of **4a** (0.6 mmol), metal catalyst in DCM (2 mL) at room temperature.

^bIsolated yield.

^cRegioselectivity was determined by 500 MHz ¹H NMR analysis.

^dTBHP (5.5 M in decane, 2.0 mmol) was added into a solution of **4a** (0.5 mmol), PhI(OAc)₂ (1.5 mmol), and K₂CO₃ (0.25 mmol) in CH₃COO*n*-Bu (1.0 mL) at -20 °C.

^eCH₃CN was used as the solvent at 50 °C.