

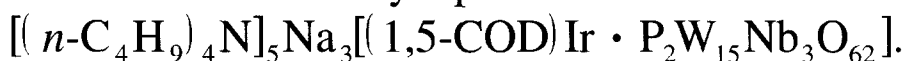


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Co-oxidative epoxidation of cyclohexene with molecular oxygen, isobutyraldehyde reductant, and the polyoxoanion-supported catalyst precursor



The importance of key control experiments including omitting the catalyst and adding radical-chain initiators.

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Abstract

To reveal the underlying problems and misleading results that can be obtained from *uninitiated* O₂/aldehyde/olefin co-oxidative epoxidations that proceed by a radical-chain mechanism, a series of nearly identical experiments were set up at the University of Tokyo and Colorado State University. The main catalyst precursor studied is the oxidatively resistant, polyoxoanion-supported organometallic complex [(*n*-C₄H₉)₄N]₅Na₃[(1,5-COD)Ir · P₂W₁₅Nb₃O₆₂], **1**. Three other L_{*n*}M · P₂W₁₅Nb₃O₆₂^{*n*-} complexes were also examined [L_{*n*}M = Re(CO)₃⁺, Ru(C₆H₆)₂²⁺, and Rh(1,5-COD)⁺], as well as the framework-incorporated cobalt(II) complex, [(*n*-C₄H₉)₄N]₄H[PW₁₁Co^{II}O₃₉]⁻. Several types of important but often omitted control reactions were also performed, again to expose the pitfalls in studies of O₂/aldehyde/olefin co-oxidative epoxidations, specifically: (i) the control of leaving out the catalyst completely, (ii) controls for O₂-mass-transfer limitations, (iii) controls examining a range of different solvents (CH₃CN, CH₂Cl₂, ClCH₂CH₂Cl, and Cl₂CHCHCl₂), and (iv) controls comparing uninitiated versus deliberately peroxide-initiated reactions. The resultant reproducibilities, product conversions, selectivities, and yields are presented and discussed, as are stereochemical results using *cis*- and *trans*-stilbene. Several important insights are generated for the area of co-oxidative epoxidations proceeding by a radical-chain mechanism, most notably that the catalyzed results are *inferior to ROOH-initiated, uncatalyzed* co-oxidative epoxidations examined under otherwise identical conditions.

Keywords: Olefin co-oxidations; Aldehyde autoxidation; Radical-chain reactions; Acylperoxy radicals; Olefin epoxidation; Catalysis; Polyoxoanion-supported catalysis; No-catalyst control reactions; Added radical-chain initiator control reactions; Stereochemical studies; Mechanistic studies

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1. Introduction

An attractive and technologically significant aspect of polyoxometalates in catalysis [1] is their inherent stability towards important oxygen donors such as H_2O_2 or, better, molecular oxygen itself [2–5]. For example, heteropolyoxometalate catalysts are useful for liquid-phase oxidations using hydrogen peroxide of alcohols [6], allyl alcohols [7], olefins [8,9], alkynes [10], β -unsaturated acids [11], *vic*-diols [12], phenol [13], and amines [14]. Polyoxometalate-based catalysts are also useful olefin epoxidation and paraffin oxygenation catalysts using iodobenzene or *t*-butyl hydroperoxide [2–5,15] as oxidants. Polyoxometalate-based catalysts are especially significant as prototype catalysts for *mechanistic* investigations of oxidative catalysis, since their oxidative stability minimizes the otherwise complicating issue of catalyst degradation effects upon selectivity, kinetic and mechanistic studies.

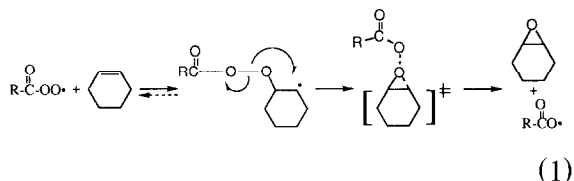
Olefin epoxidation is an especially important oxygenation reaction, both industrially and in organic synthesis, due to the usefulness of epoxides as synthetic intermediates. Consistent with the high interest in olefin epoxidations, many ruthenium, molybdenum, and titanium complexes have been reported to be active catalysts for epoxidations with peracids or peroxides [16]. However, much less is known about the oxygenation of olefins using *molecular oxygen* in combination with polyoxoanion catalysts [17–20]. Previously, we reported that the prototype $P_2W_{15}Nb_3O_{62}^{9-}$ -supported $Ir^I(1,5-COD)^+$ organometallic complex, $[(n-C_4H_9)_4N]_5Na_3[(1,5-COD)Ir \cdot P_2W_{15}Nb_3O_{62}]$, **1**, serves as an effective precatalyst for the allylic oxygenation (autoxidation) of cyclohexene by molecular oxygen [17]. Ishii and co-workers have reported that V^{5+} -substitution for Mo^{6+} in $P_2Mo_{12}O_{40}^{3-}$ leads to an effective epoxidation catalyst using molecular oxygen [20]. Less is known, however, about the underlying *mechanisms* of these processes. One exception is the $[(n-C_4H_9)_4N]_5Na_3[(1,5-COD)Ir \cdot$

$P_2W_{15}Nb_3O_{62}]$ based system, where detailed product, kinetic and mechanistic studies have been completed and are being readied for publication [17]d.

In the area of co-oxidative epoxidation of olefins using molecular oxygen, one of us has previously reported that $PW_{11}Co^{II}O_{39}^{5-}$ is an active catalyst for cyclohexene, 1-decene, and styrene epoxidation with molecular oxygen in the presence of isobutyraldehyde as the reductant [19]. However, the highest yields reported to date for such *metal-catalyzed* co-oxidative epoxidations are typically \leq ca. 90%, a value still lower than desired [19–22]. A significant but little appreciated point is that the yield of cyclohexene oxide is *within experimental error* of the *uncatalyzed* yield of 87% for cyclohexene co-oxidation with aldehydes reported by Kaneda and co-workers — a key, but often neglected, paper [21]. As this result implies, there is a need for additional definitive mechanistic work in the O_2 /aldehyde/olefin co-oxidation area, although unequivocal evidence for a radical-chain mechanism for RCHO autoxidation — involving acyl radical, $RC(O)^\cdot$ and, following capture by O_2 , acylperoxy radical, $RC(O)OO^\cdot$, intermediates — has been available for more than 30 years now [21,23,24]. Unfortunately, this classic work is little cited in most current studies of O_2 /RCHO/olefin co-oxidative epoxidations. Of special note is that irreproducibility was the hallmark of early RCHO plus O_2 oxidation studies done around 1950, irreproducibility due to the failure to control the initiation and termination steps of this radical-chain process [23]c.

Noteworthy recent catalyst survey, product and stereochemical work by Nam and co-workers [25] provide stereochemical evidence that *cis*-stilbene co-oxidative epoxidation with isobutyraldehyde and O_2 proceeds with a loss of stereochemistry to yield *both* the *cis*- and *trans*-epoxide. The authors interpret their results primarily in terms of a precedent $RC(O)OO^\cdot$ radical epoxidizing agent, Eq. (1) [24], an interpretation that is, however and unfortunately,

equivocal based on the data provided.¹ Nam and co-workers also point out that their evidence suggests the presence of a less important, *metal-dependent* epoxidation pathway, possibly via a $M\text{-OOC(O)R}$, $M\text{-O(H)OC(O)R}$, or $M=O$ species [25].



Herein we examine polyoxoanion-supported organometallic precatalysts such as $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **1**, in the co-oxidative epoxidation of cyclohexene with molecular oxygen and using isobutyraldehyde as the reductant. This system provides cyclohexene oxide in as high yield as has been previously seen for a *metal-catalyzed process*, 88–94% yield at $97 \pm 3\%$ conversion, depending upon the exact conditions. The selectivity ratio (SR, the ratio of the desired cyclohexene epoxide to the two minor side products, cyclohexene-1-ol and -1-one) is typical for such reactions, SR = 10–15. A significant finding, however, is that a 2–4 fold *higher* selectivity ratio, SR = 28–37, at nearly as good a cyclohexene conversion, 76–88%, is seen in the control reaction consisting of the *uncatalyzed process*. Furthermore, key experiments have been repeated independently at both the University of Tokyo (UT) and at Colorado State University (CSU). The expectation in designing these experiments was that they would reveal the readily

predictable² variable induction periods, resultant variable reaction times, and thus variable yields that one *expects* for a radical-chain process that is not initiated (i.e., one run without added radical-chain initiators such as ROOH). Such expected effects have not been clearly revealed in the previous O_2 /aldehyde/olefin co-oxidation literature. Indeed, a non-optimum feature in all of the 20 previous O_2 /aldehyde/olefin co-oxidative epoxidations in the literature [19–22] is the failure to *deliberately initiate them with ROOH or other, radical-chain initiators*. (While arguably a fatal flaw only in kinetic or other, more quantitative studies, the results herein will demonstrate that an added initiator is a necessary feature in *reproducible* synthetic studies as well.) Finally, and perhaps most significantly, the results led us to compare the best *catalyzed process* herein or in the literature to an *initiated, uncatalyzed process*. The results are interesting, and have significant implications for this subarea of oxidation catalysis, *vide infra*.

2. Experimental

2.1. General

$[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **1**, $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Rh} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **2**, $[(n\text{-C}_4\text{H}_9)_4\text{N}]_{4.5}\text{Na}_{2.5}[(\text{C}_6\text{H}_6)\text{Ru} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **3**, and $[(n\text{-C}_4\text{H}_9)_4\text{N}]_8[(\text{CO})_3\text{Re} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **4**, were prepared from $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$.

¹ The data provided are not definitive in establishing the desired evidence for a RC(O)OO^\cdot or other, radical-mediated epoxidation process, since the often competing rate of radical catalyzed *cis*- to *trans*-stilbene isomerization is not established (i.e., by an examination of the ratio of *cis*- to *trans*-stilbene in recovered starting material). In other words, the authors did not consider and thus did not rule out a mechanism where a radical-catalyzed *cis*- to *trans*-stilbene isomerization occurs *prior* to the epoxidation step (and thus that the observed loss of stereochemistry reflects that step, and not the desired epoxidation step).

² Restated, the results presented herein reveal a principle well-known to kineticists, but neglected in this subarea of oxidation catalysis: no study of any radical-chain reaction should be conducted without a prior derivation of at least an expected rate law (i.e., one based on a literature-based, ‘best-guess’ mechanism). Doing just this *before* the present studies revealed a typical rate law for such a radical-chain mechanism, rate α [radical-chain – initiator]^{1/2}. In other words, if zero (or variable) adventitious initiator is present and the reaction is not deliberately initiated, then the expected rate is *zero* (or variable). These predicted results are just those seen in several of the oxidation runs in the present paper (e.g., those in CH_2Cl_2 , Table 1).

$C_4H_9)_4N]_9P_2W_{15}Nb_3O_{62}$ and $[(1,5-COD)MCl]_2$ ($M = Ir, Rh$), $[(C_6H_6)RuCl_2]_2$ or $[(CO)_3Re(NCCH_3)_3]BF_4$ in a ≤ 1 ppm O_2 concentration, Vac Atmospheres drybox following our literature procedures [17]. Solvents were distilled under dry N_2 and from the indicated drying agents prior to use: 1,2-dichloroethane [Wako Pure Chemicals, from CaH_2 (at UT); Aldrich, from CaH_2 (at CSU)], dichloromethane [Wako Pure Chemicals, from CaH_2 (at UT); Aldrich, from CaH_2 (at CSU)], acetonitrile [Wako Pure Chemicals, from CaH_2 (at UT); Aldrich, from 5 Å mol sieves (at CSU)], 1,1,2,2-tetrachloroethane [activated 5 Å molecular sieve (at CSU)] and cyclohexene [Tokyo Kasei, from Na under N_2 (at UT); Aldrich, from Na under N_2 , and passed through alumina in the drybox prior to use to remove residual, trace peroxides (at CSU)]. Isobutyraldehyde was used as commercially obtained [Tokyo Kasei (UT) or Aldrich (CSU)]. Oxygen gas was commercially obtained from Tomoe Shokai (UT) or General Air (CSU) and used without further purification. *Cis*- and *trans*-stilbenes for stereochemical experiments done at CSU, as well as the *cis*- and *trans*-stilbene oxide products, were obtained from Aldrich, stored in a 4°C refrigerator, and used as received.

2.2. Co-oxidation reactions performed at the University of Tokyo

In a Vac Atmospheres drybox, 23–25 mg (4.06–4.14 μmol) of the precatalyst $[(n-C_4H_9)_4N]_5Na_3[(1,5-COD)Ir \cdot P_2W_{15}Nb_3O_{62}]$, **1**, was placed in a sealable glass vial (40 ml) containing a magnetic stir bar (10 mm) and 3 ml of the prechosen solvent (see Table 1). Next, 250 μmol of cyclohexene and aldehyde (1000 μmol) were added to the solution, the vial was sealed with a teflon seal and cap, and the vial was brought out of the drybox. The reaction was initiated by introducing 1 atm O_2 into the system by simply removing the cap and flowing O_2 over the solution. The reaction vessel was then placed in a 38°C constant-temperature wa-

ter bath, and vigorously stirred without protection from room light (since controls, *vide infra*, showed that light had no detectable effect on the yields or selectivities). The reaction vessel was removed from the bath every 10 min to refill the vial with 1 atm of O_2 , and the reaction solution was periodically sampled by syringe (and the time noted) for analysis by gas chromatography (Unisole F-200 glass column, 2 m, FID detector) using *n*-hexane as an internal standard in comparison to response factors obtained from authentic product samples. All runs with **1** were repeated twice and the error bars quoted are the rough estimates based on these two runs. (More data for better statistics was judged a poor use of manpower given the much more meaningful error bars available by comparing the UT and the CSU experiments, *vide infra*.)

2.3. Co-oxidation reactions performed at Colorado State University

At CSU, the co-oxidation of cyclohexene and the control reactions cited below were also carried out at 1 atm dioxygen pressure and in a $38 \pm 0.1^\circ\text{C}$ constant temperature bath (Fischer Scientific). In a Vac Atmospheres (≤ 1 ppm O_2 concentration) drybox, a 25 mL side-arm round bottom flask was fitted with a septum and a magnetic stir bar (20 mm). The precatalyst $[(n-C_4H_9)_4N]_5Na_3[(1,5-COD)Ir \cdot P_2W_{15}Nb_3O_{62}]$, **1**, (50 mg; 8.82 μmol) was dissolved in the 25 mL side-arm round bottomed flask using 6 mL of the prechosen solvent. Next, 50 μL (494 μmol) freshly distilled cyclohexene and isobutyraldehyde (200 μL , 2202 μmol , ca. 4 equivalents) were added to the solution via a gas-tight syringe. The side-arm flask was sealed, and then brought out of the drybox. Next, the flask was attached to an oxidation apparatus consisting of a condenser, fitted with a Claisen adapter, and then capped at its top with an upside-down, 250 mL round-bottomed flask with a male 24/40 joint (this 250 mL flask served as a oxygen reservoir). The oxidation apparatus was connected to a vacuum line using a hose attached to

a glass-tube-fitted stopper, where the stopper was placed into the side-arm ('U-tube') 24/40 opening of the Claisen adapter (a detailed drawing of this apparatus will be available elsewhere [27]). The bottom-most, 25 mL side-arm round-bottomed flask portion of the oxidation apparatus was then cooled to 77 K with liquid nitrogen (in a bath supported on a jack-stand), and the whole system was placed under vacuum, before being refilled with 1 atm of oxygen. A pressure of 1 atm oxygen was maintained at all times.

Next, the 77 K bath was removed, the jack-stand was lowered, and the 25 mL side-arm reaction vessel was carefully placed into a $38 \pm 0.1^\circ\text{C}$ constant temperature bath, where it came up to the bath temperature within 2–3 min, and was vigorously vortex stirred (at ≥ 1400 rpm) via its 20 mm long stir bar. (The stir bar size, and the vortex stirring at ≥ 1400 rpm, are crucial as they are required to avoid O_2 -mass-transfer limitations, *vide infra*.) The reaction's progress was then followed periodically by sampling via a gas-tight syringe and analyzing the mixture by gas chromatography (DB-1 capillary column, temp. (initial) 50°C for 3 min, 10°C per minute temperature ramp, temp. (final) 160°C for 6 min, He carrier gas flow 1–2 mL per min and 12 psig head pressure). Cyclohexyl chloride was used as an internal standard (20 μL , which was added at the *start* of the reaction³), and

response factors were obtained using authentic compounds. Time $t = 0$ was defined as after the oxygen had been added and when the solution warmed to 38°C . The identities of the three observed products (cyclohexene oxide, 1-ol and 1-one) were established by co-injection as well as by gc-ms in the case of **1** in CH_2Cl_2 .

2.4. Mass-transfer controls (done at CSU)

A previous report [28]a suggests that air oxidation of aliphatic aldehydes is mass-transfer limited at room temperature and at aldehyde concentrations of more than 2–5 mol%. This prompted us to use low aldehyde concentrations in all experiments. In addition, to confirm that solution chemistry (and not oxygen uptake by the liquid phase) is the rate-determining step as desired, the reaction rate was measured as a function of stirring speed. A standard reaction of **1** under the CSU conditions described above is indeed stirring rate *dependent* at stirring rates ≤ 800 rpm. However, above ≥ 1400 rpm the initial rate of olefin disappearance became *independent* from the stirring speed (i.e., in the CSU apparatus and with a 20 mm stir bar), demonstrating that, under the specific conditions used herein, these oxidation reactions are *not* O_2 -mass-transfer limited.

2.5. Controls showing the lack of influence of light (done at CSU)

Autoxidations of aldehydes to peroxyacids can be light-initiated [23]c,d. Hence, early control experiments were performed in the presence of diffuse laboratory light and then in its absence. The results, Table 2, show that light does not alter the reaction conversion, within experimental error, when compared to identical experiments in which the reaction vessel and mixture were protected from light by wrapping with 2 layers of black electrical tape. Subsequently, all reactions were performed *without* protection from light.

³ A referee has inquired whether or not the RCl internal standard is consumed under the radical-generating reaction conditions, presumably since a R–Cl and RCHO C–H bond dissociation energies (BDEs) are roughly the same values, ca. 85 ± 2 kcal/mol. The answer, experimentally, is "no", since control experiments: (i) show no ($< 10\%$) consumption of the RCl over the 4–6 h reaction times, and (ii) there are no detected Cl^- -containing products (and the reaction is very clean and the mass balance high). Note that this is the expected result: the RCO^\cdot radical is captured at diffusion controlled rates by the (diradical) O_2 , so that the species that would have had to do the Cl^\cdot abstraction is RC(O)OO^\cdot . But, the O–Cl BDE in ' RC(O)OO–Cl ' is low, so that the hypothetical reaction ' $\text{RC(O)OO}^\cdot + \text{RCl} \rightarrow \text{RC(O)OO–Cl} + \text{R}^\cdot$ ' is thermodynamically uphill leading, ultimately, to a high kinetic-based selectivity in this radical reaction.

2.6. Controls showing the reproducibility of ROOH-initiated, catalyzed reactions (done at CSU)

To confirm our prediction of better reproducibility in deliberately initiated co-oxidation reactions, a series of 4 runs were done that were under the standard CSU conditions with added cyclohexene hydroperoxide as initiator: The precatalyst $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **1** (50 mg; 8.82 μmol) was dissolved in the 25 mL round bottom flask using 6 mL of 1,2-dichloroethane as solvent. Next, 50 μL (494 μmol) freshly distilled cyclohexene, isobutyraldehyde 200 μL (2202 μmol), and 5 μL (35.04 μmol , 80% active ROOH by I^- /starch titration) cyclohexene hydroperoxide were added to the solution via a gas-tight syringe. A temperature of 38°C, and 1 atm O_2 , were maintained during the ca. 6 h reaction time. The results show reproducible cyclohexene conversions of $87 \pm 6\%$, and $80 \pm 6\%$ cyclohexene oxide was obtained with a selectivity ratio of $11 \pm 1\%$.

2.7. No catalyst and solvent variation control reactions (done at UT and at CSU)

In these control reactions, done under the otherwise identical reaction conditions detailed previously for experiments at each institution, the O_2 /cyclohexene/RCHO reaction was examined with and without added metal catalysts. In addition, conversions and selectivities were examined in the solvents CH_3CN , CH_2Cl_2 , 1,2- $\text{C}_2\text{H}_4\text{Cl}_2$, and (at CSU) 1,1,2,2- $\text{C}_2\text{H}_2\text{Cl}_4$. The results are summarized in Table 1 and in the Results and discussion section.

2.8. Stereochemical studies using *cis*- and *trans*-stilbene (done at CSU)

The co-oxidation of *cis*- and *trans*-stilbene with isobutyraldehyde was carried out at $38 \pm 0.1^\circ\text{C}$ and 1 atm oxygen in the CSU oxidation

apparatus described earlier. All conditions were identical to those in a typical CSU oxidation run, except where noted below. Eight total experiments were done, four using *cis*- and four using *trans*-stilbene as starting material, each pair in the four different solvents CH_2Cl_2 , 1,2- $\text{C}_2\text{H}_4\text{Cl}_2$, $\text{C}_2\text{H}_5\text{OH}$, and CH_3CN . These experiments, all done *without* added peroxide initiator, under light, and *without added metal catalyst*, employed 6 mL of the indicated solvent, 50 mg (594 μmol) olefin and 200 μL (2202 μmol) isobutyraldehyde. The *cis*- and *trans*-stilbene reactants and epoxide products were analyzed by gc using a DB-1 capillary column (temperature program: temp. (initial) 80°C initially (i.e., for 0 min), 10°C per minute temperature ramp, temp. (final) 200°C for 28 min, injector and detector temperatures, 200°C; He carrier gas flow 1–2 mL per min and 12 psig head pressure). The results obtained as a function of solvent are summarized in Table 3. A control reaction showed that *cis*-stilbene in CH_2Cl_2 did *not* isomerize to *trans*-stilbene, in the absence of O_2 and isobutyraldehyde, but under otherwise unchanged reaction and analysis conditions.

3. Results and discussion

3.1. Product and selectivity studies

The time course of cyclohexene oxidation by molecular oxygen in CH_3CN , using isobutyraldehyde as reductant and with $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **1**, as precatalyst, is shown in Fig. 1a and b, data obtained at the University of Tokyo. The observed induction period seen in Fig. 1a and b is the first piece of evidence, among many to be described, consistent with the expected radical-chain autoxidation of isobutyraldehyde to produce $\text{RC}(\text{O})\text{OO}^\cdot$ (R = isobutyl) and other radical intermediates [23]. Cyclohexene oxide and small amounts (1–4%) of 2-cyclohexen-1-ol and

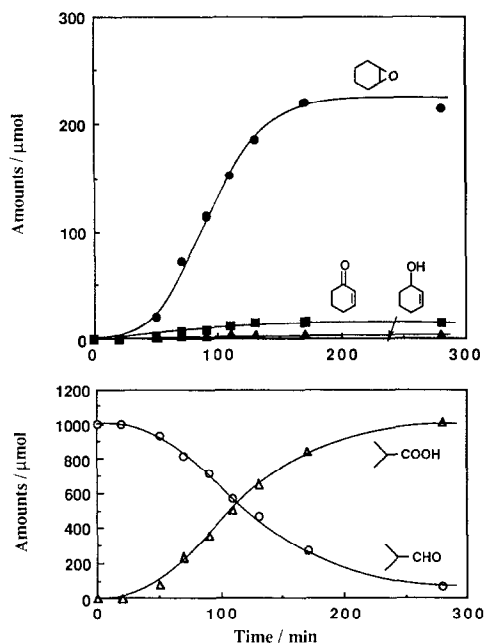


Fig. 1. Top: time course of cyclohexene epoxidation by molecular oxygen in the presence of isobutyraldehyde and $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **1**, as precatalyst (University of Tokyo conditions and results). $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, 24.8 mg (4.37 μmol); cyclohexene, 21 μL (250 μmol); isobutyraldehyde, 90.8 μL (1000 μmol); P_{O_2} , 1 atm; 3 mL dichloromethane solvent, 38°C. Bottom: time course of formation of isobutyric acid (ca. 400% yield under this particular set of conditions). Note the induction periods in each figure, signaling the production of an intermediate (e.g., RC(O)OO^\cdot or RC(O)OOH) that causes auto-catalysis of the reaction.

2-cyclohexen-1-one are observed along with ca. 4 equivalents (i.e., 400%) of isobutyric acid⁴, products typical of such $\text{O}_2/\text{RCHO}/\text{cyclohexene}$ co-oxidative epoxidations. In CH_3CN , an often used solvent system (but one shown herein to be non-optimum, *vide infra*), the cyclohexene conversion after 3 h is $37 \pm 3\%$, and product selectivity is $32 \pm 2\%$ cyclohexene oxide, $1 \pm 0.1\%$ 2-cyclohexen-1-ol, and $4 \pm 0.1\%$ 2-cyclohexen-1-one. These products correspond to a relatively low selectivity ratio of 6.4 ± 0.4 (i.e., $32 \pm 2/[4.0 \pm 0.1 + 1.0 \pm 0.1]$).

⁴ Less aldehyde oxidation to isobutyric acid, ca. 130%, is seen in CH_2Cl_2 , for example, *vide infra*.

3.2. Survey of other solvent systems




The solvent dependence of the co-oxidation of cyclohexene and isobutyraldehyde with molecular oxygen, and using $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1,5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **1**, as a prototype precatalyst, was examined in some detail. First, both the Tokyo and the Colorado State conditions were used to examine the yields and selectivity to cyclohexene oxide in CH_2Cl_2 and in $\text{ClCH}_2\text{CH}_2\text{Cl}$, Table 1. The Tokyo experiments revealed a decreased epoxide yield after ca. 3 h in the following order: 1,2-dichloroethane $94 \pm 5\% \geq$ dichloromethane $88 \pm 4\% >$ acetonitrile $37 \pm 3\%$, Table 1, first 3 entries. The CSU conversion (95%) and epoxide yield (88%) in the preferred solvent, 1,2-dichloroethane, agreed nicely with the Tokyo results ($100 \pm 5\%$ conversion and $94 \pm 5\%$ epoxide) within experimental error, Table 1, entry 3. There is, however, a noticeable lack of detectable cyclohexene-1-ol in the CSU results in 1,2-dichloroethane, although the data suggest that the cyclohexene-1-ol seen in the Tokyo experiments has been overoxidized to cyclohexene-1-one under the CSU conditions [i.e., since the total CSU percentage (7%) of cyclohexene-1-one agrees nicely within experimental error of the Tokyo *total* yield (6%) of cyclohexene-1-ol (2%) and cyclohexene-1-one (4%)].

Of even greater interest, because of what it reveals about how to properly conduct such radical-chain co-oxidative reactions, is the *quite variable conversions and selectivities in CH_2Cl_2* in the two labs. At CSU, one run in CH_2Cl_2 failed to give any product whatsoever (no conversion of cyclohexene nor isobutyraldehyde was observed after more than 6 h), not even after the subsequent addition of authentic, independently prepared ROOH initiator (R = cyclohex-2-enyl). A second, ostensibly identical CSU reaction in CH_2Cl_2 did start, but provided only 46% conversion in comparison to 96% for the analogous Tokyo run, even though the CSU reaction time (5–8 h) was more than twice as long as that in the Tokyo experiment (3 h),

Table 1, entry 2. These are just the predicted results in such *deliberately* (at least in these studies!) *uninitiated, and hence uncontrolled and variable, RCHO radical-chain autoxidations*.

The superiority of the chlorinated hydrocarbon solvents in terms of percent conversions and yields suggests either (or both) (a) the initiation of the reaction by trace ROOH or other impurities, or (b) the involvement of sol-

Table 1
Co-oxidative epoxidations using **1** as precatalyst in different solvents plus key, no-catalyst and other control reactions ^{a,b}

Solvent (Tokyo and/or CSU results)	Conv. (%)	Yield (%)		
				
CH ₃ CN				
Tokyo results	37 ± 3	32 ± 2	1 ± 0.1	4 ± 0.1
CH ₂ Cl ₂				
Tokyo results	96 ± 5	88 ± 4	2 ± 0.1	6 ± 0.1
CSU results #1	0	0	0	0
CSU results #2	46	34	4	8
1,2-C ₂ H ₄ Cl ₂				
Tokyo results	100 ± 5	94 ± 5	2 ± 0.1	4 ± 0.1
CSU results	95	88	nd ^c	7
1,1,2,2-C ₂ H ₂ Cl ₄				
CSU results	90	82	nd ^c	8
No catalyst, in CH ₂ Cl ₂ ^d				
CSU results	25	22	nd ^c	3
No catalyst, in 1,2-C ₂ H ₄ Cl ₂				
Tokyo results ^e	88 ± 4	85 ± 4	1 ± 0.1	2 ± 0.1
CSU results ^f	76	74	nd ^c	2
TBA ₉ P ₂ W ₁₅ Nb ₃ O ₆₂ in 1,2-C ₂ H ₄ Cl ₂				
CSU results	85	80	nd ^c	5
With catalyst, 1 , ROOH initiated, in 1,2-C ₂ H ₄ Cl ₂				
CSU results	87 ± 6	80 ± 6	1 ± 0.2	6 ± 1
[(n-C ₄ H ₉) ₄ N] ₄ HPW ₁₁ Co ^{II} O ₃₉ ³⁻ in 1,2-C ₂ H ₄ Cl ₂ ^g				
Tokyo results	78 ± 4	70 ± 4	3 ± 0.1	5 ± 0.1

^a Tokyo reaction conditions: 23–25 mg (4.06–4.41 μmol) precatalyst; 3 mL solvent; 21 μL (250 μmol) cyclohexene; 90.8 μL (1000 μmol) isobutyraldehyde; 1 atm O₂; 38°C; reaction time ca. 3 h.

^b CSU reaction conditions: 50 mg (8.82 μmol) precatalyst; 6 mL solvent; 50 μL (594 μmol) cyclohexene; 200 μL (2202 μmol) isobutyraldehyde; 1 atm O₂; 38°C; reaction time 5–8 h.

^c Not detectable (< 1%).

^d A small but detectable, ≤ 20 min induction period was seen in this no-catalyst control reaction.

^e The induction period in this no-catalyst control reaction was ca. 1.5 h, and the 88% conversion was obtained after 4 h.

^f A small but detectable, ≤ 20 min induction period was observed. The 76% conversion was obtained after 6 h.

^g Results reported for the reaction conditions: 4 mg (1.2 μmol) precatalyst; 3 mL 1,2-C₂H₄Cl₂ solvent; 21 μL (250 μmol) cyclohexene; 90.8 μL (1000 μmol) isobutyraldehyde; 1 atm O₂; 30°C; GC analysis: Unisole F-200 (glass column, 2 m), FID detector. Further increases in precatalyst weight *decreased* the yield of cyclohexene oxide, presumably due to capture of the RC(O)OO·, epoxide-forming (or other radical) intermediate(s) by the HPW₁₁Co^{II}O₃₉⁴⁻ precatalyst.

vent radicals such as $\text{Cl}_2\text{CH}\cdot$, $\text{ClCH}_2\text{CH}\cdot(\text{Cl})$, or $\text{Cl}_2\text{CHC}\cdot(\text{Cl}_2)$ [25] in, most probably, the RCHO autoxidation process⁵. Multiple, chlorinated trace-products have been identified in our detailed product, kinetic and mechanistic studies of the autoxidation of cyclohexene by O_2 and **1** in CH_2Cl_2 (i.e., cyclohexene alone, without added RCHO), thereby providing direct evidence for the participation of CH_2Cl_2 in at least that radical-chain reaction [17]d.

3.3. The contrastingly high reproducibility, high conversion of ROOH-initiated, catalyzed co-oxidative epoxidations

To confirm the prediction provided by the kinetic analysis given earlier, a series of runs were done using **1** as precatalyst and that were under the standard CSU conditions, except that 0.071 equivalents of ROOH (R = cyclohexen-2-yl) initiator versus the 494 μmol cyclohexene were added. The results of 4 identical runs showed a reproducible $87 \pm 6\%$ conversion, $80 \pm 6\%$ epoxide, and a selectivity ratio of 11 ± 1 , Table 1, next-to-last entry.

3.4. The influence of different polyoxoanion-supported transition-metal precatalysts

The effect of changing the polyoxoanion-supported organometallic precatalyst was investigated in dichloromethane in experiments done at CSU. The percent conversions (and selectivities to epoxide) observed after 6–10 h for these uninitiated reactions are: $[(n\text{-C}_4\text{H}_9)_4\text{N}]_8[(\text{CO})_3\text{Re} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **4**, 62% conversion (81% epoxide)⁶ after 6 h $> [(n\text{-C}_4\text{H}_9)_4\text{N}]_7[(\text{C}_6\text{H}_6)\text{Ru} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **3**, 55% conversion (and 79% epoxide) after 10 h [and 91% conversion (and 78% selectivity) after 20 h] $> [(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1.5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **1**, 46% (and 81% epoxide) after 6 h. Note that the selectivity does not change significantly for these precatalysts (it is somewhat solvent dependent, however⁷), as in each case where activity is observed, the percent epoxide is between 55–79%, and the side products are roughly constant, 2–8% cyclohexene-1-one, and $\leq 2\%$ cyclohexene-1-ol. These results are identical in their general finding to the recent report by Nam and co-workers [25]: the catalyst has a relatively small effect on the selectivity. As previously interpreted [25], this is strong evidence that the metal catalyst is *not* involved in the kinetically dominant epoxidation step.

3.5. Comparisons of the polyoxoanion-supported catalyzed and uncatalyzed systems to literature catalysts

Given the results presented here (i.e., the condition and solvent-dependent induction times, conversions and selectivities), a comparison of different co-oxidative epoxidation results from different laboratories is problematic if not dangerous, especially the results of *uninitiated* catalytic results. However, a comparison of the best catalyzed co-oxidation process reported to date to the best uncatalyzed process reported herein is highly desirable and (*vide infra*) provides important insights. This in turn means that it is necessary to push, as far as the literature

⁵ We note that the literature precedent available prior to the present studies implicates solvent-radical participation only for tetra-chloroethylene, $\text{Cl}_2\text{CHCHCl}_2$, and then only in long-chain processes for a reaction in which excellent $\text{H}\cdot$ donors such as RCHO were not present [26].

⁶ The $[(n\text{-C}_4\text{H}_9)_4\text{N}]_8[(\text{CO})_3\text{Re} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$, **4**, precatalyst yields a white precipitate after ca. 5–6 h reaction, and the oxidation reaction stopped after ca. 7–8 h, apparently due to the formation of an insoluble, catalyst-depleting by-product.

⁷ In the survey of different polyoxoanion-supported transition-metal precatalysts done in Tokyo in CH_3CN and again deliberately *uninitiated*, the cyclohexene oxide yields after 6.5 h decreased in the order $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1.5\text{-COD})\text{Ir} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$ ($83 \pm 4\%$ epoxide) $\approx [(n\text{-C}_4\text{H}_9)_4\text{N}]_{4.5}\text{Na}_{2.5}[(\text{C}_6\text{H}_6)\text{Ru} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$ ($79 \pm 4\%$ epoxide) $> > [(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[(1.5\text{-COD})\text{Rh} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}] = 0$. The fact that the relatively sluggish Rh precatalyst does yield some epoxide, but only after a 4 day induction period, is again as expected for a trace-ROOH or other impurity-initiated, RCHO radical-chain autoxidation pathway.

Table 2

Additional control reactions without catalyst, with and without added cyclohex-2-enyl hydroperoxide (CyHP), and with or without light ^a (done at CSU)

Experiment No.	Additional conditions	Conversion ^b (%)	Selectivity versus epoxide ^c (%)
I	no catalyst, no initiator, in diffuse room light ^d	25 ^e	88
II	no catalyst, no initiator, in the dark	45 ^e	94 ^f
III	no catalyst, CyHP initiator added, in diffuse room light	100	96 ^g
IV	no catalyst, CyHP initiator added, in the dark	95	93

^a Reaction conditions: 6 mL CH₂Cl₂ solvent; 50 μL (594 μmol) cyclohexene; 200 μL (2202 μmol) isobutyraldehyde; 1 atm O₂; 38.0 ± 0.1°C; reaction time ca. 6 h.

^b Conversion was defined as: $\{([\text{olefin}]_{t=0} - \Sigma[\text{all products}]) / [\text{olefin}]_{t=0}\} \times 100$.

^c Selectivity was defined as: $\{[\text{cyclohexene oxide}] / \Sigma[\text{all products}]\} \times 100$.

^d The results were obtained after 6 h; cyclohexen-1-one (trace) and cyclohexen-1-ol (ca. 4%) are also formed.

^e These 25% (experiment #I) and 45% (experiment #II) conversions are, for such *uninitiated reactions*, the same within experimental error — see for instance the Tokyo versus CSU entries for CH₂Cl₂ as solvent in Table 1, second set of entries.

^f For experiment II the side products are 6% cyclohexene-1-one, but no detectable (< 1%) cyclohexene-1-ol, for a selectivity ratio of 15.7.

^g For experiment III the side products are 4% cyclohexene-1-one, but no detectable (< 1%) cyclohexene-1-ol, for a selectivity ratio of 17.7.

data allow, a comparison of the efficacy of the prototype polyoxoanion-supported precatalyst such as [(n-C₄H₉)₄N]₅Na₃[(1,5-COD)Ir · P₂W₁₅Nb₃O₆₂], **1**, to the previous best literature catalyst for O₂/aldehyde/olefin co-oxidative epoxidations.

The available data [19–22] reveal that **1**, in the preferred chlorinated solvents (Table 1), gives as high a reported yield of cyclohexene oxide (88–94%) as any previously reported catalysts, notably the better catalysts PW₁₁Co^{II}O₃₉⁵⁻ (70 ± 4%, Table 1, last entry), PV₂Mo₁₀O₄₀⁵⁻, Ni^{II}(dmp)₂, Ni^{II}(mac)₂ or Fe^{II}(dmp)₃ [19–22] (where dmp = the bis[1,3-di(*p*-methoxyphenyl)-1,3-propanedionato] ligand, and mac = the bis[3-methyl-2,4-pentanedionato] ligand). Also noteworthy here is that the present O₂ plus isobutyraldehyde epoxidation system is more effective in terms of its epoxide yield than the use of either iodosylbenzene [3,19] or hydrogen peroxide [9].

3.6. Comparison of the best, polyoxoanion-based catalyst to the 'no catalyst' control reaction

The above results allowed us to do an important, previously unavailable experiment: to quantitatively compare *both* the selectivity and the relative conversions (i.e., the relative rates) of the best, catalyst- and solvent-optimized, *cat-*

alyzed O₂/RCHO/olefin co-oxidation process to the results from an *uncatalyzed* (and, presently, *uninitiated* and otherwise *unoptimized*) control reaction done under identical conditions. The Tokyo results, Table 1, entries 5 (in CH₂Cl₂) and 6 (in Cl₂CHCHCl₂) versus their catalyzed reference points, entries 2 (in CH₂Cl₂) and 3 (in Cl₂CHCHCl₂) show that the unoptimized, *uncatalyzed* process in the preferred solvent Cl₂CHCHCl₂ proceeds with a *nearly 2-fold superior* selectivity ratio of 28.3 ± 1.3 ⁸ (versus that of 15.6 ± 1.2 for the *cat-*

⁸ Significantly, Kaneda and co-workers see the same *uncatalyzed* cyclohexene oxide yield (87%) [21] as we do (88%), within ± 1% [21]. This suggests, as Nam and co-workers also saw [25], that such O₂/RCHO/olefin co-oxidation processes show selectivities that are largely (albeit not completely [25]) catalyst independent. Consistent with this statement, Nam and co-workers find a product selectivity ratio for cyclohexene co-oxidation of 15 in CH₃CN, using isobutyraldehyde and with Fe(cyclam)(CF₃SO₃)₂ as precatalyst. As further evidence that this selectivity ratio is a useful mechanistic indicator, others report that cyclohexene co-oxidation with RCHO and Fe powder (or Fe(OAc)₃ or FeCl₃ · 6 H₂O) in CH₂Cl₂ gives 71% cyclohexene oxide, 1% 2-cyclohexene-1-ol, and 3% 2-cyclohexene-1-one, for a selectivity ratio of 17.8, that is, again in the same general range as seen previously and seen herein [18]h.

Note, however, that these latter authors conclude erroneously (on p. 7913 of their paper [18]h) that the selective formation of epoxides indicates "the presence of an *oxometal* species" (italics have been added). The literature [24,25] and the results herein all point, instead, to RC(O)OO· as the kinetically dominant epoxidizing agent.

alyzed process). The conversion is nearly as good as well, $88 \pm 4\%$ (versus 96 ± 5 in 3 h for the catalyzed process). Not surprisingly, a longer period of ca. 1 h is required for the 88% conversion in the uncatalyzed process, a finding again consistent with the metal being involved in primarily the RCHO autoxidation process. The CSU results in $\text{Cl}_2\text{CHCHCl}_2$ show an identical trend, but now with a nearly 4-fold superior selectivity ratio of 37 (versus that of 10 for the catalyzed process), and again nearly as good a conversion, 76% (versus 90% in 3 h for the catalyzed process).

The implication here is obvious: an *uncatalyzed*, but *initiated and optimized*, process needs to be carefully examined to see if it cannot in fact be made to be superior to the best reported catalyzed process. Two preliminary experiments testing just this hypothesis are presented in Table 2. They reveal a 95–100% conversion and a 93–96% selectivity to epoxide, along with a selectivity ratio of 12.6 to 15.7! The preliminary conclusion here is apparent: an as yet unoptimized, *initiated, but uncatalyzed* $\text{O}_2/\text{RCHO}/\text{olefin}$ co-oxidative epoxidation process is as good as the best reported, fairly optimized, *catalyzed* (but uninitiated) process! The needed additional quantitative optimization, kinetic and mechanistic studies of primarily the uncatalyzed process are in progress,

and will be reported in detail elsewhere shortly [27].

3.7. Stereochemical and prior isomerization control experiments with *cis*- and *trans*-stilbene: Stereochemical evidence consistent with and fully supportive of $\text{RC(O)OO}\cdot$ as the predominant epoxidizing agent

To provide evidence for or against a radical-based epoxidizing agent, stereochemical studies were performed using *cis*- and *trans*-stilbene. Note that these were deliberately done *without* added metal catalyst, and are deliberately uninitiated, given the results of the control experiments described immediately above [and given the desire to examine the stereochemistry under the (uninitiated) conditions that most closely tie into the rest of the studies presented herein]. Stereochemical studies under *initiated*, uncatalyzed conditions are being done as well and will be reported elsewhere [27]. Note also that the stereochemical studies without catalyst provided below avoid the possibility of any *metal catalyzed* contribution to the observed (*vide infra*) *cis*- to *trans*-stilbene isomerization.

The observed stereochemistry as a function of solvent, Table 3, reveals a highly consistent, nearly invariant, picture: *trans*-stilbene oxide is the predominant product, regardless of whether

Table 3
Stereochemical studies of *cis*- and *trans*-stilbene co-oxidative epoxidation^a

Solvent	Olefin	Conv. ^b (%)	Products (%)			
			<i>trans</i> -stilbene	<i>cis</i> -stilbene	<i>trans</i> -stilbene oxide	<i>cis</i> -stilbene oxide
CH_2Cl_2 ^c	<i>cis</i> -stilbene	42	18	58	19	5
	<i>trans</i> -stilbene	63	37	1	62	nd ^d
$\text{C}_2\text{H}_2\text{Cl}_4$	<i>cis</i> -stilbene	16	5	84	11	nd ^d
	<i>trans</i> -stilbene	35	65	-nd-	35	nd
$\text{C}_2\text{H}_5\text{OH}$	<i>cis</i> -stilbene	47	24	53	17	6
	<i>trans</i> -stilbene	57	43	2	55	nd ^d
CH_3CN	<i>cis</i> -stilbene	34	22	66	11	1
	<i>trans</i> -stilbene	62	38	2	60	nd ^d

^a Reaction conditions: 6 mL solvent; 594 μmol olefin; 2202 μmol isobutyraldehyde; 1 atm O_2 ; $38 \pm 0.1^\circ\text{C}$, reaction time, 16 h.

^b Conversion was defined as: $\{([\text{olefin}]_{t=0} - \Sigma[\text{all products}]_{t=0})/[\text{olefin}]_{t=0}\} \times 100$.

^c Reaction time 20 h.

^d Not detected (i.e., < 1%).

or not one starts with *cis*- or *trans*-stilbene; there is also accompanying *cis*- to *trans*-isomerization of stilbene. These stereochemical results agree completely with those of Nam and co-workers [25] in that the loss of stereochemistry is seen in all cases examined. The present results can be taken a step further, in that they report the ratio of recovered *trans*-stilbene/*cis*-stilbene for each experiment, Table 3. Since in every case in Table 3 beginning with *cis*-stilbene the ratio of recovered *trans*-stilbene/*cis*-stilbene is $\ll 1$, but the ratio of *trans*-epoxide/*cis*-epoxide product is $\gg 1$, the results rule out a mechanism for the observed scrambling involving a *cis*- to *trans*-stilbene *prior* equilibrium, followed by preferential epoxidation of the thermodynamically more stable *trans*-isomer. The stereochemical evidence provides, then, compelling evidence for a radical-based species as the kinetically dominant epoxidizing agent. The literature [24] provides a compelling case that this radical is the acylperoxy radical, RC(O)OO^\cdot . Hence, the RC(O)OO^\cdot epoxidation process shown back in Eq. (1) derives full support from the present studies.

4. Summary and conclusions

The key findings of the this study are as follows:

(1) As far as uninitiated but catalyzed processes go, the polyoxoanion-supported precatalysts $[(n\text{-C}_4\text{H}_9)_4\text{N}]_5\text{Na}_3[\text{L}_n\text{M} \cdot \text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{62}]$ ($\text{L}_n\text{M} = (1,5\text{-COD})\text{Ir}^+$, $\text{Re}(\text{CO})_3^+$, $\text{Ru}(\text{C}_6\text{H}_6)^{2+}$) are as efficacious, and as oxidatively robust, a precatalyst for $\text{O}_2/\text{RCHO}/\text{olefin}$ co-oxidations as any reported.

(2) However, the conversions and yields of such non-initiated $\text{O}_2/\text{RCHO}/\text{olefin}$ co-oxidative epoxidations are almost surely much more variable, and more solvent and other condition-dependent, than has been generally reported in the literature.

(3) Such a variability is exactly what one expects from an analysis of the rate law antici-

pated for such a radical-chain reaction, a rate α $[\text{initiator}]^{1/2}$, for example [27,30].

(4) Hence, one should not study this, or any other, radical-chain reaction without (a) first predicting the probably rate law if at all possible (i.e., for the literature-based, best-guess mechanism), and (b) without controlling the chain-initiation step by deliberately adding ROOH or other initiators. These principles apply to arguably all radical-chain reactions⁹ [29,30].

(5) An important experiment in this area — indeed, for any ‘catalyzed process’ — is to do the control to see what the yield is in the *uncatalyzed* reaction.

(6) The observed selectivities are, fortunately, fairly constant for the $\text{O}_2/\text{RCHO}/\text{olefin}$ co-oxidative epoxidations reported to date, ranging from a selectivity ratio of 10–40. This previously unreported finding argues strongly for a common mechanism among all the studies reported to date.

(7) A quantitative comparison of the catalyzed and uncatalyzed co-oxidative epoxidation reactions reveals that even the *unoptimized, uncatalyzed* process has a 2–4 fold higher, 28–40 selectivity ratio and nearly as high a conversion (76–88%) and epoxide yield (74–85%).

(8) Preliminary data for a *ROOH-initiated, uncatalyzed* process as suggested in (7) reveals as high a conversion ($95 \pm 5\%$), as good if not better epoxide yields (93–96%), and equivalent selectivity ratios (15.7 to 17.7) in comparison to even the best reported, *largely optimized, catalyzed* process (95–100% conversions, 88–94% epoxide, and 15.6 selectivity ratio). Additional optimization, stereochemical and kinetic and mechanistic experiments of primarily the uncatalyzed process are in progress [27].

⁹ A case demonstrating this point, and expanding it to demonstrate the importance of controlling the *chain-termination steps* too when possible, is a classic study of radical-based oxidative additions by Hill and Puddephatt, discussed in detail elsewhere [29]. An examination of the kinetics of any radical-chain reaction reveals the well-established point [30] that the initiation and termination often dominate the observed kinetics and thus rates (the propagation steps are, of course, also important [30]).

(9) Stereochemical studies of *cis*- and *trans*-stilbene epoxidation, in conjunction with the necessary control of analyzing the ratio of *trans*-stilbene/*cis*-stilbene in the recovered starting material, confirm that a well-precedented RCHO radical-chain autoxidation yields a acylperoxy radical, $RC(O)OO\cdot$, as the kinetically dominant epoxidizing agent. Such a mechanism is consistent with, and fully supported by, both the present work and key prior mechanistic work [24,25].

Lastly, we believe the intrinsically environmentally friendly nature¹⁰ of the in-situ, low-level, on-site generation of active epoxidation reagents such as $RC(O)OO\cdot$ (i.e., in comparison to the inefficient and inherently less safe transport of even dilute oxidants such as $RC(O)OOH$ or H_2O_2) is noteworthy. For this latter reason alone, such co-oxidative epoxidation processes deserve additional close scrutiny [27].

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¹⁰ This statement of course assumes that the co-oxidation product, isobutyric acid in the present example, is either also of value (e.g., its commercial dehydrogenation to methacrylic acid), or can be recycled by reduction back to the corresponding aldehyde (+ H_2O). In this latter case, such co-oxidation processes are, of course, equivalent to the use of either $H_2 + O_2$ or H_2O_2 .

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