

Communication

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SeO₂-Mediated Oxidative Transposition of Pauson–Khand Products

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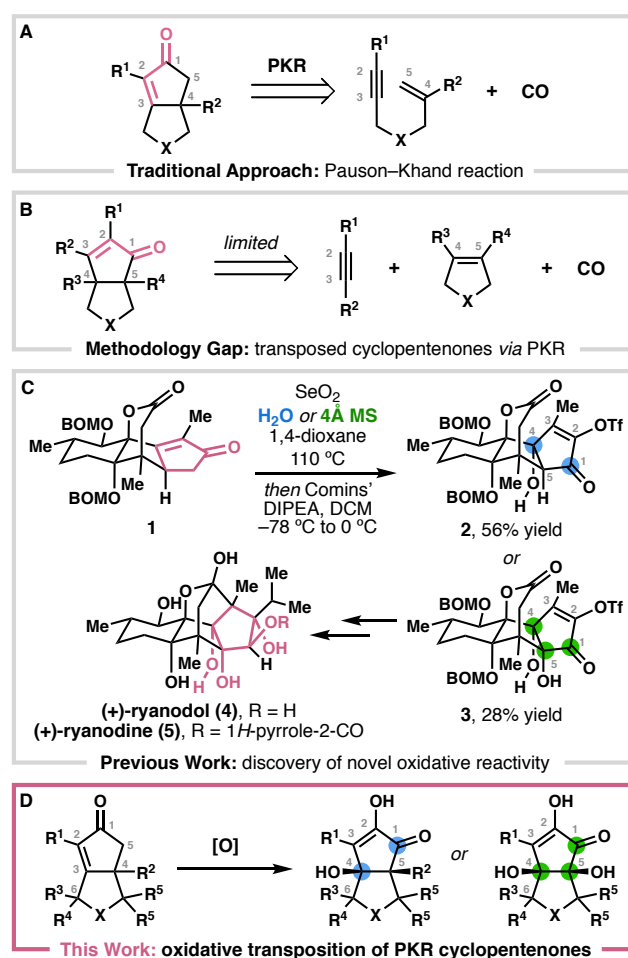
Supporting Information Placeholder

ABSTRACT: Oxidative transpositions of bicyclic cyclopentenones mediated by selenium dioxide (SeO₂) are disclosed. Treatment of Pauson–Khand reaction (PKR) products with SeO₂ in the presence or absence of water furnishes di- and trioxidized cyclopentenones, respectively. Mechanistic investigations reveal multiple competing oxidation pathways that depend on substrate identity and water concentration. Functionalization of the oxidized products via cross-coupling methods demonstrates their synthetic utility. These transformations allow rapid access to oxidatively transposed cyclopentenones from simple PKR products.

The Pauson–Khand reaction is a powerful method to prepare bicyclic cyclopentenones,¹ structural features found in many natural products. The intramolecular PKR is well-developed and affords 3,4-fused bicycles from the corresponding tethered enynes (Figure 1A).^{2a} In contrast, the intermolecular PKR, which is required to access the isomeric 4,5-fused bicycles, is less developed and has severe limitations in scope (Figure 1B).^{2b,c} A method to rapidly access 4,5-fused bicyclic enones, which are inaccessible directly by the PKR, would provide valuable synthetic building blocks.

As part of our recent syntheses of the complex diterpenes (+)-ryanodol (**4**) and (+)-ryanodine (**5**), we discovered an unusual oxidative transformation mediated by selenium dioxide (SeO₂).³ Treatment of PKR product **1** with SeO₂ under either aqueous or anhydrous conditions provided highly oxidized compounds **2** and **3**, respectively (Figure 1C). This serendipitous discovery streamlined access to 4,5-fused cyclopentenone **3**, a key intermediate in the synthesis of **4** and **5**. Although these di- and trioxidations were modest yielding, the ability to construct functional group relationships elusive via canonical PKRs led us to consider their wider application in synthesis (Figure 1D). In this communication, we investigate the SeO₂-mediated oxidative transposition of 3,4-fused PKR products and demonstrate the ability of this method to prepare highly substituted bicyclopentenones.

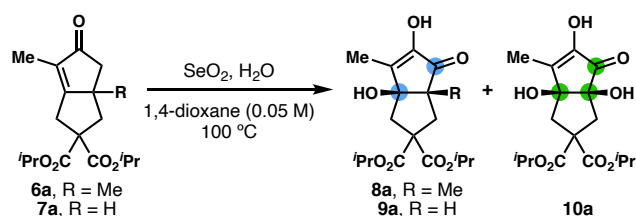
Figure 1. Motivation for Reaction Development



Our studies began with 3,4-fused bicycle **6a**, which is readily accessible from commercially available diisopropyl malonate (see SI). Substrate **6a** was selected for these initial studies because the C4- γ -quaternary substitution prevents trioxidation, simplifying reaction analysis for the dioxidation process. Although **6a** successfully underwent the desired dioxidation under our previously reported conditions,³ the yield was significantly lower than that observed in the ryanodane system (Table 1, entry 1). Fortunately, increasing the amount of

water led to a significant boost in conversion, providing **8a** in 71% yield (entry 3). Under these optimized conditions, the primary mass balance was unreacted starting material (**6a**) and minor amounts of over-oxidation to the C3-tertiary alcohol (see SI).

Table 1. Optimization of Conditions



| Entry | R | SeO ₂ (equiv) | H ₂ O (equiv) | Time (h) | 8a or 9a (%) ^a | 10a (%) ^a |
|-------|----|--------------------------|--------------------------|----------|---------------------------|----------------------|
| 1 | Me | 10 | 10 | 24 | 13 | — |
| 2 | Me | 10 | 0 | 3 | 11 | — |
| 3 | Me | 10 | 100 | 38 | 71 ^b | — |
| 4 | Me | 3 | 30 | 24 | 32 | — |
| 5 | Me | 1.5 | 15 | 24 | 29 | — |
| 6 | Me | 3 | 100 | 48 | 62 | — |
| 7 | Me | 1.5 | 100 | 120 | 42 | — |
| 8 | H | 10 | 100 | 4 | 64 ^b | 0 |
| 9 | H | 10 | 100 | 46 | 0 | 14 |
| 10 | H | 10 | 10 | 1 | 0 | 15 |
| 11 | H | 10 | 0 | 2 | 0 | 21 ^b |
| 12 | H | 3 | 0 | 3 | 0 | 10 |

^aYield determined by ¹H NMR versus an internal standard. See SI for additional information. ^bIsolated yield.

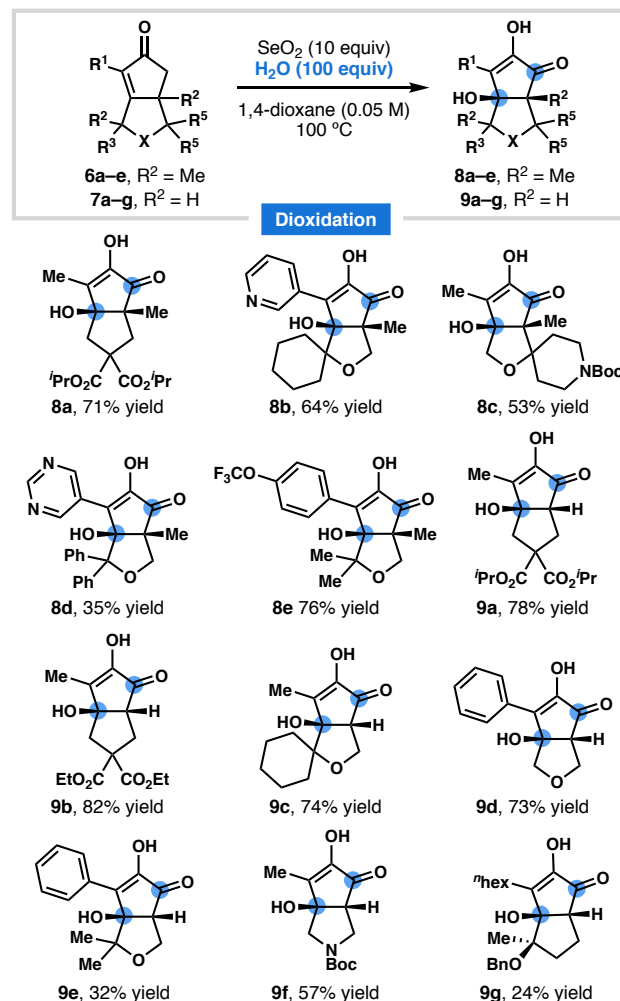
In addition to improving the yield of **8a**, increasing the [H₂O] also drastically improved the reaction profile. When the equivalents of SeO₂ were reduced but a 10:1 ratio of water to SeO₂ maintained, the yield of **8a** dropped (entries 4 and 5). However, increasing the equivalents of water with reduced amounts of SeO₂ improved the yield, affording **8a** in 42% yield with just 1.5 equiv SeO₂ (entry 7).⁴ When substrate **7a**, which lacks the C4- γ -quaternary center, was subjected to the optimized conditions, dioxidation product **9a** was formed in comparable yield to that of **8a** (entry 8). Interestingly, subjecting of **7a** to these same conditions for extended reaction times led to the formation of trioxidation product **10a**, which had previously only been observed under rigorously anhydrous conditions (entry 9).^{3a} Motivated by this observation, we turned our attention to investigating the formation of **10a**.

Consistent with our prior studies,^{3a} reducing the equivalents of water in the SeO₂-mediated reaction provided trioxidation product **10a** in faster rates with cleaner reaction profiles (entry 10 vs. entry 9). The complete exclusion of water provided **10a** in 21% yield with no trace of undesired **9a** (entry 11). Reducing the amount of SeO₂ decreased the yield of **10a** (entry 12), and thus the conditions of entry 11 were selected as optimal for the trioxidation reaction. Under these optimized conditions, the mass balance consisted of unreacted starting material (**7a**) and a complex mixture of minor

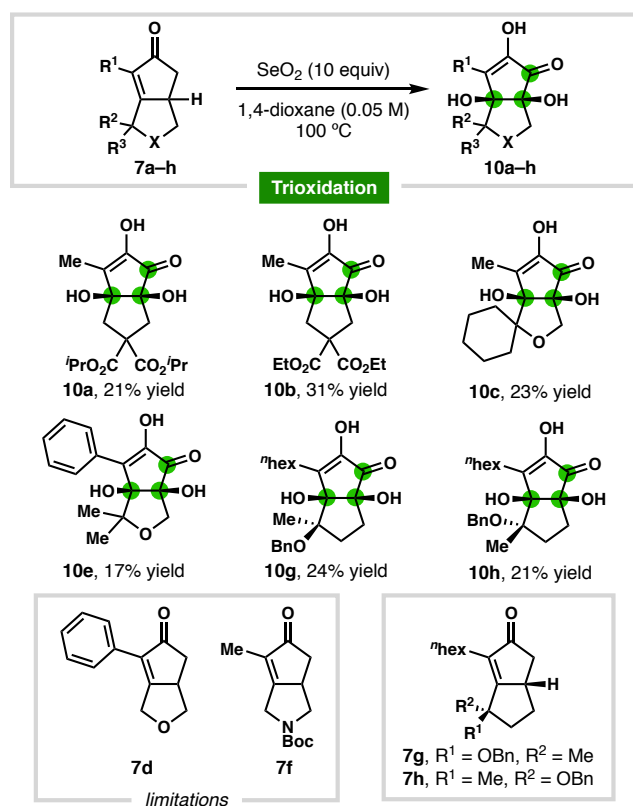
reaction byproducts.

With optimized conditions in hand, we investigated the scope of both oxidative transformations. A variety of carbo- and heterocyclic 3,4-fused cyclopentenones were prepared via the PKR and subjected to the dioxidation conditions (Table 2). Most substrates underwent the oxidative transposition in good yields, providing the oxidized 4,5-fused bicycles as single diastereomers.⁵ The reaction is tolerant of heterocycles (**8b–e** and **9c–f**), C6- γ -quaternary centers (**8b**, **8d–e**, **9c**, **9e**, and **9g**), and protected amines (**8c** and **9f**). Triflation of **8e** afforded the enol triflate as a crystalline solid, and single crystal X-ray diffraction confirmed the *syn* ring fusion (see SI).⁶

Table 2. Scope of Dioxidation



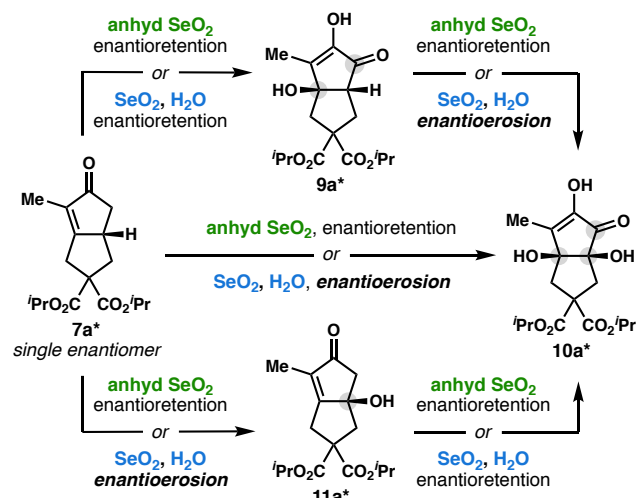
We next explored the scope of the trioxidation reaction (Table 3). While competitive decomposition of the trioxidation products (**10a–h**) generally resulted in diminished yields relative to those of the dioxidations, the desired products could be isolated in approximately 20–30% yield, similar to that observed in the trioxidation of **1**. Substrates containing unsubstituted saturated heterocyclic rings, such as **7d** and **7f**, marked a limitation of this method. Trioxidation products **10g** and **10h** were formed as single diastereomers from cyclopentenones **7g** and **7h**, respectively.

Table 3. Scope of Trioxidation

These results led us to investigate potentially operative reaction pathways. To this end, we separated enantiomers of model substrate **7a** via chiral HPLC (**7a***, Table 4).⁷ Treatment of **7a*** with SeO_2 in the presence of water furnished dioxidation product **9a*** with retention of enantiomeric excess (ee, entry 1). Under the same conditions, trace yield of trioxidation product **10a*** was formed after extended reaction times; however, formation of **10a*** under these conditions proceeded with significant enantioerosion (entry 3). In contrast, treatment of **7a*** with anhydrous SeO_2 provided **10a*** with enantioretention (entry 4). Treatment of dioxidation product **9a*** with H_2O/SeO_2 resulted in the slow formation of **10a*** with substantial loss of ee (entry 5), whereas subjection of **9a*** to anhydrous SeO_2 resulted in the fast conversion to **10a*** with complete retention of ee (entry 6).

Close monitoring of the above reactions revealed the presence of a fleeting species with a mass consistent with mono-oxidation. This species was isolated and characterized as tertiary alcohol **11a***, which presumably arises via an allylic C–H oxidation pathway (Table 4, entries 7 and 8).⁸ Subjection of **11a*** to both standard anhydrous and aqueous conditions resulted in conversion to trioxidation product **10a*** with retention of enantiopurity (entries 9 and 10). Taken together, these results demonstrate that under optimal conditions both **9a*** and **10a*** can be formed with enantioretention and that both **9a*** and **11a*** are viable intermediates to **10a***. While the exact mechanism for enantioerosion is currently unclear, control

experiments have confirmed that **7a*** and **10a*** are configurationally stable under both the dioxidation and trioxidation reaction conditions. On the other hand, **9a*** undergoes slow enantioerosion in the presence of both SeO_2 and H_2O (see SI). Whereas the racemization of **9a*** could lead to **10a*** with enantioerosion, a second possibility is that in the presence of SeO_2 and H_2O , there is a competing oxidation pathway for **7a*** or **9a*** that involves an achiral cyclopentadienone intermediate.

Table 4. Stereochemical Analysis of Oxidations^a

| Entry | Reaction | Conditions | ee (%) | Yield (%) | Time (h) |
|-------|---------------------------|---------------|-----------|-----------|----------|
| 1 | 7a* → 9a* | SeO_2, H_2O | >99 → >99 | 59 | 24 |
| 2 | 7a* → 9a* | anhyd SeO_2 | >99 → >99 | 4 | 1 |
| 3 | 7a* → 10a* | SeO_2, H_2O | >99 → 60 | 3 | 24 |
| 4 | 7a* → 10a* | anhyd SeO_2 | >99 → >99 | 15 | 1 |
| 5 | 9a* → 10a* | SeO_2, H_2O | >99 → 46 | 12 | 46 |
| 6 | 9a* → 10a* | anhyd SeO_2 | >99 → >99 | 24 | 2 |
| 7 | 7a* → 11a* | SeO_2, H_2O | >99 → 36 | 2 | 1 |
| 8 | 7a* → 11a* | anhyd SeO_2 | >99 → 92 | 10 | 1 |
| 9 | 11a* → 10a* | SeO_2, H_2O | 92 → 92 | 5 | 60 |
| 10 | 11a* → 10a* | anhyd SeO_2 | 92 → 92 | 1 | 3 |

^aReactions performed under anhydrous [SeO_2 (10 equiv), 1,4-dioxane (0.05 M), 100 °C] or aqueous [with H_2O (100 equiv)] conditions.

In order to better understand the dioxidation reaction, we searched for potential intermediates in the oxidation of C4- γ -quaternary substituted substrate **6a**. Under the standard dioxidation conditions (H_2O/SeO_2), no species *en route* to **8a** could be observed. However, with the exclusion of water, **6a** was observed by 1H and ^{13}C NMR to convert to the product of a Riley oxidation (**12a**, Figure 2A).⁹ Following *in situ* formation of ene-diketone **12a**, D_2O was added to determine if **12a** was a viable intermediate to **8a**. Indeed, deuterated dioxidation product **8a-d₂** was formed. Addition of deuterated methanol instead of D_2O provided the analogous compound **13-d₄** in excellent yield.¹⁰ Preliminary efforts to expand the scope of these SeO_2 -mediated oxidations to other, non-cyclopentane-fused cyclopentenones have not been successful;

while the initial Riley oxidation to the ene-diketone is observed, these systems do not undergo spontaneous addition of water (see SI).

To further support the hypothesis that conjugate addition to an ene-diketone intermediate leads to the dioxidation products, we studied each step individually (see SI). Correlation of the measured reaction rates with Hammett parameters¹¹ (Figure 2B) indicated that the rate of the conjugate addition (k_2 , blue) is more dependent on the substrate electronics than the rate of the Riley oxidation (k_1 , green). These studies revealed that the oxidation step proceeded faster for electron-rich substrates, whereas conjugate addition proceeded faster for electron-deficient systems. Given that excess water depressed the rate of the Riley oxidation, we postulated that a protocol separating the two steps could allow faster access to dioxidation products while maintaining clean reaction profiles. Indeed, this alternative protocol proceeds with only 1.5 equiv SeO_2 and can afford dioxidation products in yields comparable to those resulting from the standard aqueous conditions (Figure 2C).¹²

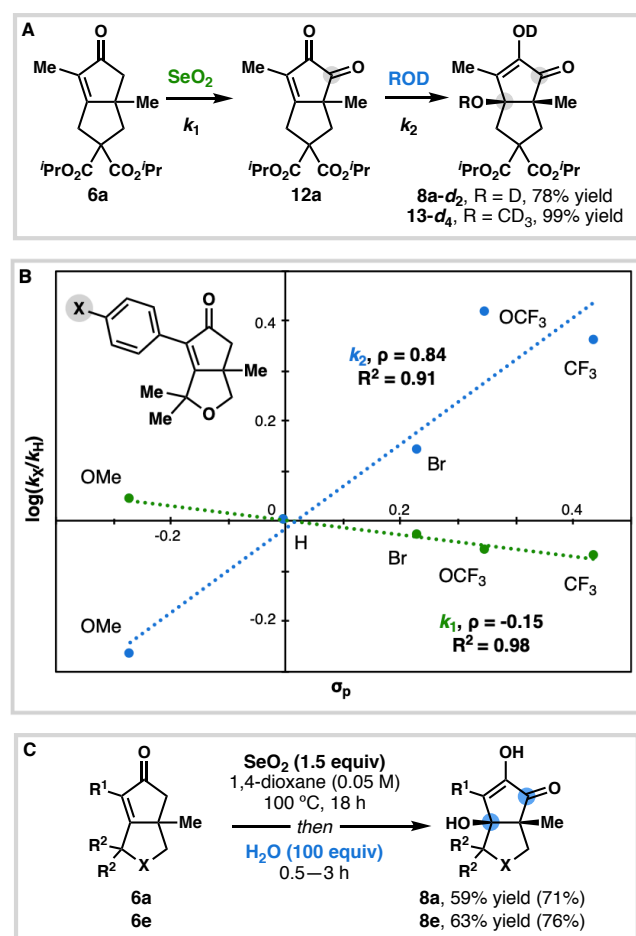
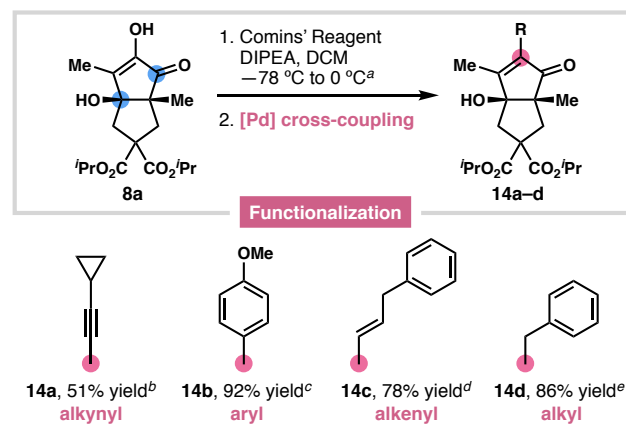


Figure 2. (a) Formation of **12a** under anhydrous conditions [SeO_2 (10 equiv), 1,4-dioxane- d_8 (0.1 M), 100 °C] followed by trapping with deuterated water or methanol (100 equiv). Yield of **8a-d₂** and **13-d₄** from **12a** determined by ^1H NMR versus an internal standard. (b, green) Hammett plot for the oxidation of enones [X = OMe (**6f**), H (**6g**), Br (**6h**), OCF₃ (**6e**), CF₃ (**6i**)]

under anhydrous conditions [SeO_2 (10 equiv), 1,4-dioxane- d_8 (0.1 M), 100 °C]. (b, blue) Hammett plot for the addition of deuterated water to ene-diketones (**12e-i-d₂**) [D_2O (100 equiv), 1,4-dioxane- d_8 (0.1 M), 100 °C]. (c) Yields determined by ^1H NMR versus an internal standard. In parentheses are isolated yields obtained under standard dioxidation conditions.

Having improved the accessibility of dioxidation products through mechanistic insight, we turned our attention to investigating their synthetic utility. Modern cross-coupling methods offer many opportunities for further elaboration of the α -hydroxyenone functionality. To this end, the enol triflate of **8a** was prepared (90% yield) and treated with a variety of palladium catalysts and coupling partners (Table 5). Although **8a** is a challenging cross-coupling substrate, Sonogashira and Suzuki reactions produced highly functionalized products **14a-d** in good to excellent yields.¹³ Reaction with alkynyl, aryl, alkenyl and alkyl partners demonstrates the ability to access diverse, fully substituted cyclopentenones from simple PKR products.

Table 5. Functionalization of Dioxidation Product



^a90% isolated yield. ^bethynylcyclopropane, Pd(PPh₃)₂Cl₂, CuI, Et₃N, 50 °C. ^c(4-methoxyphenyl)boronic acid, Pd(OAc)₂, PCy₃, KF, THF. ^d(*E*)-(3-phenylprop-1-en-1-yl)boronic acid, Pd(OAc)₂, PCy₃, KF, THF. ^epotassium benzyltrifluoroborate, Pd(dppf)Cl₂, Cs₂CO₃, THF/H₂O, 80 °C.

In conclusion, SeO_2 -mediated oxidative transpositions of PKR products have been developed to access highly oxidized 4,5-fused bicyclic enones. The reactions occur under aqueous or anhydrous conditions to afford di- or trioxidized products, respectively. Investigation of the mechanism identified potential intermediates and elucidated the reactivity dependence on water concentration. Notably, the di- and trioxidations enable the construction of transposed and highly functionalized PKR products pertinent to the synthesis of complex targets.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data (^1H and ^{13}C NMR, HRMS, FTIR) for all new compounds (pdf). The X-ray crystal structure data for compound **15e** has been submitted to the Cambridge Crystallographic Data Center, no. 1970101.

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- (4) The use of fewer equiv SeO_2 (1.5 or 3.0) proved to be less general (see SI), thus the conditions of entry 3 were selected as optimal for investigating the scope of the dioxidation reaction.
- (5) The *trans*-fused isomer of **8a** was calculated to be 18.5 kcal/mol less stable (calculated using Spartan'14, Hartree-Fock model using the 6-

311+G** basis set).

(6) Stereochemical assignments of oxidation products were made by analogy to **8e**.

(7) Both enantiomers of **7a***, obtained by chromatographic separation, were used for these studies (see SI). Efforts to prepare **7a*** by asymmetric PKR gave the product in 59% yield and 72% ee ($[\text{RhCl}(\text{CO})_2]_2$, (R)-BINAP, PhMe, CO, 90 °C). See: Furusawa, T.; Morimoto, T.; Ikeda, K.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K.; Jeong, N. Asymmetric Pauson-Khand-Type reactions of 1,6-enynes using formaldehyde as a carbonyl source by cooperative dual rhodium catalysis. *Tetrahedron* **2015**, *71*, 875.

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