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A Cyclization/Oxygenation Scheme for the Conversion of Polyenes into C3-Oxygenated Polycycles

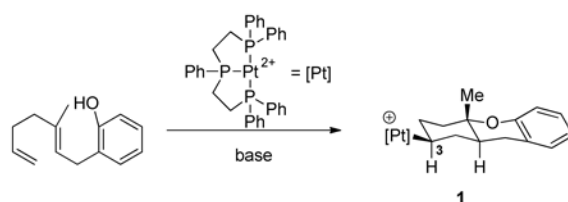
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Oxidatively induced halogenation and oxygenation reactions of complex Pt(II) organometallic complexes provides a route to a catalytic cation-olefin cyclization/oxygenation sequence. The evidence suggests the involvement of a Pt(III) intermediate, which reacts homolytically to generate an organic free radical that can be intercepted by O₂ followed by the Russell breakdown of the resulting alkyl peroxy radicals, or by CuX₂ (X = Br or Cl) to yield the X-R product.

Sterol biosynthesis, the conversion of polyenes into polycyclic structures by cyclase enzymes, occurs in two flavors; one practiced by higher organisms on (3*S*)-oxido-squalene (Scheme 1) and a more primitive version practiced by bacteria on squalene itself.¹ Approaches to mimicking such cascade reactions have been developed, including those that lead to products devoid of oxygenation at the C3 position (e.g. H⁺ and M⁺ initiated) and others that utilize an epoxide or oxocarbenium ion to both initiate the cascade and provide C3-oxygenation. A small subset of electrophilic methods can initiate the cascade under catalyst enantiocontrol (H⁺, I⁺, or M⁺),² but none of these provide C3-oxygenated sterols (e.g. Scheme 1).³ Given this lack of methodology, we initiated an effort to develop an electrophilic metal mediated direct cyclization/C3-oxygenation of achiral polyenes.⁴

We have previously reported electrophilic Pt catalysts that efficiently initiate the cation-olefin cyclization cascade, and proceed through Pt-C intermediates (e.g. eq 1). Depending on the coordination environment of the complex, these organometallic complexes may either be stable⁵ (PPP or PNP pincer ligands) or susceptible (diphosphines) to β-H elimination.⁶ We report herein, experiments demonstrating that this intermediate may be alternately trapped and oxygenated under O₂ to generate polycyclic C3-oxygenation products while returning the Pt product to a state capable of reinitiating polyene cyclization.



(1)

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Experimental procedures as well as spectroscopic data are available in the supporting information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The insertion of molecular oxygen into Pt-⁷ and Pd-Me⁸ bonds to yield methyl peroxy metal complexes occurs by a variety of mechanisms.⁹ (bpy)PdMe₂ inserts O₂ by a radical chain that is propagated by CH₃O-O• addition/oxidation to (bpy)PdMe₂. The resulting Pd(III)¹⁰ complex homolyzes a Pd-Me bond which traps with O₂ to reform CH₃O-O• and (bpy)PdMe(OOMe). In contrast, a direct insertion of ¹O₂ was proposed for the photo insertion of O₂ into (NNN)Pt-CH₃⁺ (NNN= 6,6'-diamino terpyridine).^{7a} In this case the alkyl peroxy-Pt product thermally rearranges to (NNN)Pt-OH⁺ and formaldehyde. These reports stimulated efforts to utilize O₂ to oxy-functionalize [(triphos)Pt-R][BF₄] (**1**), a Pt-C product of cyclization that is stable and isolable.

Since O₂ insertions in the above cases were sensitive to photolysis,⁷ we began by irradiating **1** with a 20W CFL under an atmosphere of oxygen. This approach provided ketone **2** in 60% yield over 18 hours (entry 1, Table 1), though the putative O₂ insertion product was not detected; the mass balance consisted of the β-hydride elimination product **4**. Confirming an important role for oxygen, its exclusion prevented formation of **2** and led to a mixture of **4**^{6a} and proto-demetalation product.^{5c} Unfortunately, the photo oxygenation conditions caused extensive decomposition of the Pt, precluding its further development for catalytic applications.

Reports of homolytic cleavage of M-C bonds through one electron oxidation of the metal centre led us to examine several chemical oxidants for C3 radical generation.¹¹ Though ferrocenium salts used to induce Pd oxidation¹² and Pd-Me bond homolysis^{11a, b} were unreactive (Cp₂Fe⁺/Cp₂Fe = 0.4 V vs SCE),¹³ several Cu(II) salts proved effective. Particularly intriguing was Cu(OTf)₂ (Cu(OTf)₂/Cu(OTf) = 0.8 V vs SCE),¹⁴ one equivalent of which provided **2** and **3** in a combined yield of up to 80% (entries 2–4, Table 1). Of note, **2** and **3** were formed in a 1:1 ratio and **3** was a 1:1 mixture of diastereomers. Importantly, these reactions generated (triphos)Pt-(NCCH₃)²⁺, a Pt(II) species that could potentially reinitiate polyene cyclization.¹⁵

The 1:1 ratio of C3-ketone and C3-alcohol is consistent with an oxidation induced process that first generates a transient Pt(III) species **A** (Scheme 2), which after Pt-C homolysis¹⁶ and trapping by O₂ yields a secondary alkylperoxy radical (**C**)¹⁷ that undergoes Russell disproportionation to a 1:1:1 mixture of alcohol, ketone and ¹O₂ (Scheme 2).¹⁸ While the divergence in reactivity from the Goldberg and Britovsek reactivity^{7–8} may be the result of increased steric congestion¹⁹ combined with 2° peroxy radicals being more prone to Russell breakdown,¹⁷ trapping with O₂ and subsequent Russell breakdown mirrors Kochi's oxidation of Pt dialkyl complexes with IrCl₆²⁻.^{11c} In the absence of O₂ **4** was the dominant product (entry 5, Table 1).²⁰

When **1** was reacted with 2 equiv. of CuX₂ (X= Cl, Br), the halogenated X-R products were formed as a mixture of diastereomers (entries 1–2, Table 2), consistent with the non-selective interception of **B** with a second equivalent of CuX₂ (Scheme 2). Reactions with less than 2 equiv. of CuX₂ only partially consumed **1**. The relative rates of radical trapping by O₂ versus CuBr₂ were informed by the reaction of **1** with 2 equiv of CuBr₂ under O₂ (2 atm), which provided 37% **2**, 49% **3** (1:1 dr), and 14% Br-R (1:1 dr) by GC-MS (entry 6, Table 1).²¹ Under these conditions the Pt product was (PPP)Pt-X⁺ (X= Cl, Br), an inactive alkene initiator. These experiments demonstrated that other Cu(II) species provided products consistent with initial 1-electron oxidation and Pt(II) formation.

In contrast to one electron oxidants, reactions with halonium sources produced the halo product with high selectivity for the equatorial (i.e. retentive) isomer (>10:1 dr)(entries 3–5, Table 2). These observations are consistent with stereoretentive reductive elimination from a putative Pt(IV) centre, and thus parallel previous work with “F⁺” sources and **1**.^{19,22} C-X

reductive elimination has been well studied²³ and generally proceeds in an invertive fashion in Pt(IV) complexes.²⁴ To the best of our knowledge, concerted mechanisms have only been reported in a few C-F,¹⁹ C-Cl²⁵ and C-O²⁶ bond forming reductive eliminations. The current reactions suggest rare examples of retentive C-X reductive eliminations from a Pt(IV) centre, and a mechanistic divergence from 1-electron oxidation behavior.

The above exploratory studies suggested the feasibility of a catalytic protocol utilizing (triphos)Pt²⁺, and 1.1 equiv of Cu(OTf)₂ under 2 atm of O₂. Switching to CD₃NO₂ to avoid the Lewis basic CH₃CN and adding a resin-bound tertiary amine base to neutralize HOTf led to reactions that completely consumed the starting material (entry 2, Table 3) and indeed generated C3-oxygenated products.²⁷ Increasing the catalyst load from 10 to 20% increased the yield of **2/3** and lessened the competing Brønsted acid pathway. Notably, the addition of a ligand to Cu(OTf)₂ or the use of a soluble amine base prevented oxidation of the Pt organometallic. Worth noting is an apparent lack of peroxy radical or alkyl radical quenching by the PhOH substrate.²⁸ Catalytic cyclization/oxygenation employing several polyene substrates was briefly explored (entries 3–4, Table 3). Compound **12** generated the desired products, albeit in low yield, while no turnover was observed with compound **13**. These results and control experiments with Cu(OTf)₂ and polyenes point to the undesired reduction of Cu(OTf)₂ by the substrate, which simultaneously prevents turnover of the Pt-alkyl and decomposes the substrate.²⁹

In summary, we report a proof of principle study demonstrating that Pt catalysts can initiate the cation-olefin cyclization cascade, and subsequently oxygenate the resulting Pt-C bond with O₂ in a fashion compatible with catalyst control. The successful implementation of the oxy-functionalization approach hinges on the facile reactivity of one electron oxidants towards (triphos)Pt-R⁺ intermediates, but not (triphos)Pt²⁺. This selectivity ensures that activation of the catalyst only occurs after the cation-olefin cyclization step. The homolytic cleavage of putative Pt(III)-C bonds under O₂ provides a synthetically valuable stoichiometric cation-olefin cyclization/oxygenation protocol and access to a C3-oxygenated polycycle. Efforts to improve and expand the scope of the catalytic variant are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

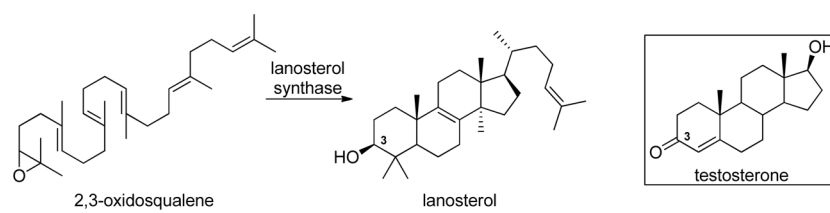
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References

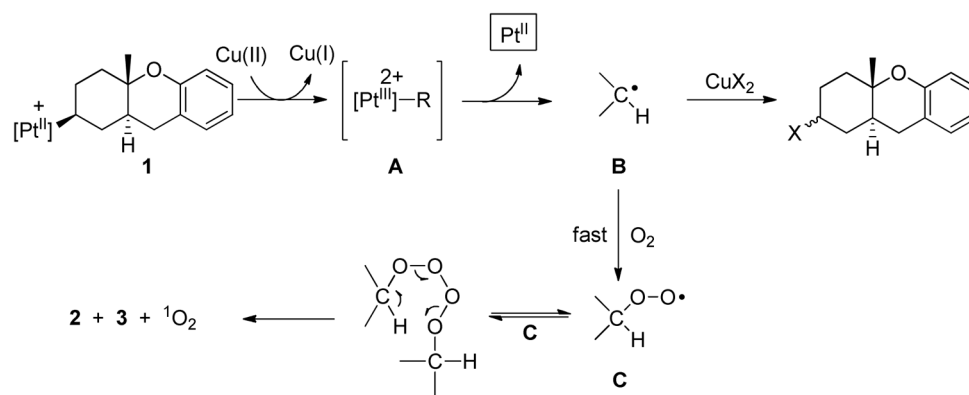
- (a) Kotora M, Hessler F, Eigenerová B. *Eur J Org Chem.* 2012;29.(b) Johnson WS. *Acc Chem Res.* 1968; 1:1.(c) Yoder RA, Johnston JN. *Chem Rev.* 2005; 105:4730. [PubMed: 16351060] (d) Wendt KU, Schulz GE, Corey EJ, Liu DR. *Angew Chem Int Ed.* 2000; 39:2812.
- (a) Uyanik M, Ishibashi H, Ishihara K, Yamamoto H. *Org Lett.* 2005; 7:1601. [PubMed: 15816762] (b) Sakakura A, Ukai A, Ishihara K. *Nature.* 2007; 445:900. [PubMed: 17314976] (c) Nakamura S, Ishihara K, Yamamoto H. *J Am Chem Soc.* 2000; 122:8131.(d) Kang SH, Lee SB, Park CM. *J Am Chem Soc.* 2003; 125:15748. [PubMed: 14677957] (e) Sethofer SG, Mayer T, Toste FD. *J Am Chem Soc.* 2010; 132:8276. [PubMed: 20518531] (f) Schafroth MA, Sarlah D, Krautwald S, Carreira EM. *J Am Chem Soc.* 2012; 134:20276. [PubMed: 23193947]

3. For recent organocatalytic approaches, see: Sakakura A, Sakuma M, Ishihara K. *Org Lett*. 2011; 13:3130. [PubMed: 21591803] Rendler S, MacMillan DWC. *J Am Chem Soc*. 2010; 132:5027. [PubMed: 20334384] Knowles RR, Lin S, Jacobsen EN. *J Am Chem Soc*. 2010; 132:5030. [PubMed: 20369901] Moyano A, Rios R. *Chem Rev*. 2011; 111:4703. [PubMed: 21615119]
4. For a review on the Pd-catalyzed oxidation of unsaturated hydrocarbons using molecular oxygen, see: Wu W, Jiang H. *Acc Chem Res*. 2012; 45:1736. [PubMed: 22839752]
5. (a) Hahn C, Cucciolito ME, Vitagliano A. *J Am Chem Soc*. 2002; 124:9038. [PubMed: 12148993] (b) Sokol JG, Korapala CS, White PS, Becker JJ, Gagné MR. *Angew Chem Int Ed*. 2011; 50:5658. (c) Koh JH, Gagné MR. *Angew Chem Int Ed*. 2004; 43:3459. (d) Feducia JA, Gagné MR. *J Am Chem Soc*. 2008; 130:592. [PubMed: 18095679]
6. (a) Mullen CA, Gagné MR. *J Am Chem Soc*. 2007; 129:11880. [PubMed: 17850150] (b) Mullen CA, Campbell AN, Gagné MR. *Angew Chem Int Ed*. 2008; 47:6011. (c) Cochrane NA, Brookhart MS, Gagné MR. *Organometallics*. 2011; 30:2457. [PubMed: 21572581]
7. (a) Taylor RA, Law DJ, Sunley GJ, White AJP, Britovsek GJP. *Angew Chem Int Ed*. 2009; 48:5900. (b) Grice KA, Goldberg KI. *Organometallics*. 2009; 28:953.
8. Boisvert L, Denney MC, Hanson SK, Goldberg KI. *J Am Chem Soc*. 2009; 131:15802. [PubMed: 19827779]
9. For a review on the reaction of late transition metal complexes with O₂, see: Boisvert L, Goldberg KI. *Acc Chem Res*. 2012; 45:899. [PubMed: 22578038]
10. recent developments in Pd(III) chemistry see: Powers DC, Ritter T. *Top Organomet Chem*. 2011; 35:129. [PubMed: 21461129] Khusnutdinova JR, Rath NP, Mirica LM. *J Am Chem Soc*. 2011; 134:2414. [PubMed: 22239690] Khusnutdinova JR, Rath NP, Mirica LM. *Angew Chem Int Ed*. 2011; 50:5532. Mirica LM, Khusnutdinova JR. *Coord Chem Rev*.
11. (a) Seligson AL, Trogler WC. *J Am Chem Soc*. 1992; 114:7085. (b) Johansson L, Ryan OB, Rømming C, Tilset M. *Organometallics*. 1998; 17:3957. (c) Chen JY, Kochi JK. *J Am Chem Soc*. 1977; 99:1450. (d) Wong CL, Kochi JK. *J Am Chem Soc*. 1979; 101:5593. (e) Rogers WN, Page JA, Baird MC. *Inorg Chem*. 1981; 20:3521. (f) Joseph MF, Page JA, Baird MC. *Organometallics*. 1984; 3:1749.
12. Lanci MP, Remy MS, Kaminsky W, Mayer JM, Sanford MS. *J Am Chem Soc*. 2009; 131:15618. [PubMed: 19824643]
13. Connelly NG, Geiger WE. *Chem Rev*. 1996; 96:877. [PubMed: 11848774]
14. Schmidt SP, Basolo F, Trogler WC. *Inorg Chim Acta*. 1987; 131:181.
15. Acetonitrile itself is not suitable as it coordinates too strongly, but electron deficient nitriles have been shown to be effective, see reference 5b and Becker JJ, Van Orden LJ, White PS, Gagné MR. *Org Lett*. 2002; 4:727. [PubMed: 11869112]
16. Attempts to trap the alkyl radical proved unsuccessful, likely due to its rapid consumption by Cu. See reference 21.
17. Ingold KU. *Acc Chem Res*. 1969; 2:1.
18. (a) Russell GA. *J Am Chem Soc*. 1957; 79:3871. (b) Howard JA, Ingold KU. *J Am Chem Soc*. 1968; 90:1056.
19. For an example of steric congestion enhancing reductive elimination in (triphos)Pt-R(F)²⁺ complexes, see: Zhao SB, Becker JJ, Gagné MR. *Organometallics*. 2011; 30:3926. [PubMed: 21869853]
20. Complete consumption of **1** in the absence of O₂ required 2 equivalents of Cu(OTf)₂.
21. The rate constant for the reaction of c-C₆H₁₁• with O₂ is 3–5×10⁹ M⁻¹s⁻¹. See Maillard B, Ingold KU, Scaiano JC. *J Am Chem Soc*. 1983; 105:5095. The rate constant for the bromination of c-C₄H₇• with CuBr₂ is ~4×10⁹ M⁻¹s⁻¹. See Jenkins CL, Kochi JK. *J Am Chem Soc*. 1972; 94:856. Kochi has also measured the rate of direct oxidation of secondary radicals with Cu(OTf)₂ and found the rates to be slower (~2×10⁷ M⁻¹s⁻¹) and provide alkenes and oxidative solvolysis products. See Jenkins CL, Kochi JK. *J Am Chem Soc*. 1972; 94:843.
22. Zhao SB, Wang RY, Nguyen H, Becker JJ, Gagne MR. *Chem Commun*. 2012; 48:443.
23. (a) Vigalok A, Kaspi A. *Top Organomet Chem*. 2010; 31:19. (b) Vigalok A. *Chem Eur J*. 2008; 14:5102. [PubMed: 18418836]

24. (a) Luinstra GA, Wang L, Stahl SS, Labinger JA, Bercaw JE. *J Organomet Chem.* 1995; 504:75.(b) Williams BS, Goldberg KI. *J Am Chem Soc.* 2001; 123:2576. [PubMed: 11456927] (c) Goldberg KI, Yan J, Breitung EM. *J Am Chem Soc.* 1995; 117:6889.(d) Williams BS, Holland AW, Goldberg KI. *J Am Chem Soc.* 1999; 121:252.
25. Crosby SH, Thomas HR, Clarkson GJ, Rourke JP. *Chem Commun.* 2012; 48:5775.
26. Khusnutdinova JR, Newman LL, Zavalij PY, Lam YF, Vedernikov AN. *J Am Chem Soc.* 2008; 130:2174. [PubMed: 18220400]
27. Stoichiometric reactions of **1** with Cu(OTf)₂ and O₂ in CD₃NO₂ were slower than in CH₃CN.
28. The forward rate constant for ROO· + PhOH is $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$, while its reverse is $> 2 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, suggesting that if H· abstraction occurs it is likely reversible, see reference 17.
29. Tschan MJL, Thomas CM, Strub H, Carpentier JF. *Adv Synth Catal.* 2009; 351:2496.

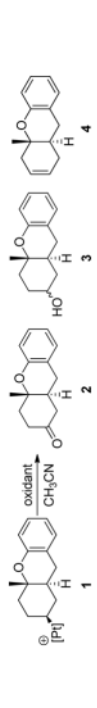


Scheme 1.
Conversion of 2,3-oxidosqualene to lanosterol and an example of a C3-oxygenated natural product



Scheme 2.
1-electron oxidation induced functionalization of Pt-C bond

Table 1

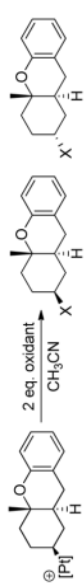
Oxygenation reactions of **1**


| Entry ^a | Oxidant | Time | Atmosphere | Yield (2+3 / 4) | Ratio 2:3 |
|--------------------|----------------------------|----------|----------------------|---------------------------------|------------------|
| 1 | 20W CFL | 18 hours | O ₂ | 60% | 1:0 |
| 2 | 1 eq. Cu(OTf) ₂ | <5 min | air | 53% | 1:1 |
| 3 | 2 eq. Cu(OTf) ₂ | <5 min | air | 33% | 1:1 |
| 4 | 1 eq. Cu(OTf) ₂ | <5 min | 2 atm O ₂ | 80% | 1:1 |
| 5 ^c | 2 eq. Cu(OTf) ₂ | <5 min | N ₂ | 0% | - |
| 6 | 2 eq. CuBr ₂ | <5min | 2 atm O ₂ | 63% | 1:1 |

^a Conditions: **1** (0.04 mmol), dry CH₃CN (3 mL).^b Isolated yield of **2 + 3**.^c mass balance **4**

Table 2

Halogenation of 1



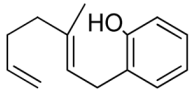
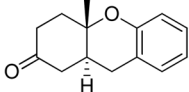
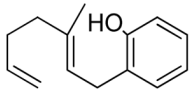
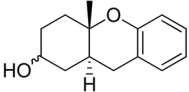
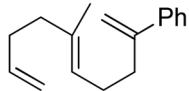
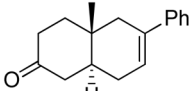
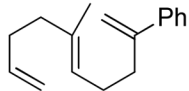
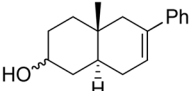
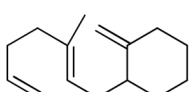
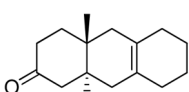
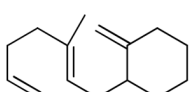
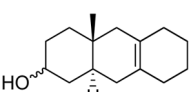
| Entry ^a | Halide Source | X = | Time | Yield ^b | dr. |
|--------------------|-------------------|-----|----------|--------------------|-------|
| 1 | CuCl ₂ | Cl | <5 mins | 54% | 1:1 |
| 2 | CuBr ₂ | Br | <5 mins | 66% | 1:1.8 |
| 3 | I ₂ | I | <5 mins | 89% | >10:1 |
| 4 | NBS | Br | 3 hours | 58% | >10:1 |
| 5 | NCS | Cl | 18 hours | 43% | >10:1 |

^a Conditions: 1 (0.04 mmol), dry CH₃CN (3 mL).

^b Isolated yield

Table 3

Catalytic cyclization/oxygenation

| Entry ^a | Substrate | Products | Isolated Yield ^b |
|--------------------|---|---|-----------------------------|
| 1 |  |  | 64% |
| 2 |  |  | 54% ^c |
| 3 |  |  | 46% |
| |  |  | |
| 4 |  |  | 0% |
| |  |  | |

^aConditions: 20 mol% (PPP)Pt²⁺, 2 eq. resin base, 2 atm. O₂, 1.1 eq. Cu(OTf)₂, 0.2 mmol substrate, dry CD₃NO₂ (1 mL).

^bProducts isolated as 1:1 mixture of ketone:alcohol

^c10 mol% (PPP)Pt²⁺