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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 IrCl₆^{2-,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.

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20. Complete consumption of **1** in the absence of O₂ required 2 equivalents of Cu(OTf)₂.
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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.
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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) ^b	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	
	11	2	3	
3				46%
		12	9	
4				0%
		13		

^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⁺