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Diastereoselective Pt Catalyzed Cycloisomerization of Polyenes to Polycycles

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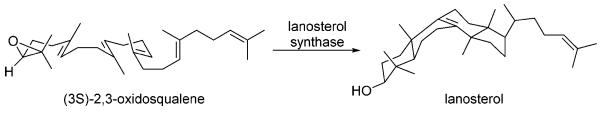
Supporting Information

ABSTRACT: Application of a tridentate NHC containing pincer ligand to Pt catalyzed cascade cyclization reactions has allowed for the catalytic, diastereoselective cycloisomerization of biogenic alkene terminated substrates to the their polycyclic counterparts.

The construction of complex polycyclic hydrocarbon frameworks from simple polyene substrates by cyclaze enzymes (e.g., eq 1) has long been the envy of synthetic chemists.[1] The remarkably selective fashion in which products are formed has attracted a variety of biomimetic approaches.[2] Of note are recent reports in which cyclization is initiated by organocatalysts,[3] M^+,[4] H^+,[5] and X^+ reagents.[6]

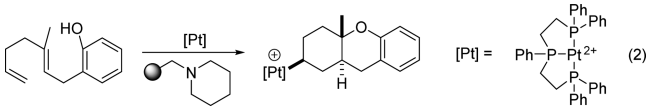
The formation of polycycles via cascade cyclization reactions has long benefitted from the installation of nucleophilic terminating groups, which enhance the efficiency of the cyclization.[1,2] By contrast, the cyclization of strictly hydrocarbon containing substrates must overcome the lack of H-bond assistance in the terminating alkene, often leading to slow reactions and incomplete cyclization. While aryl terminating groups have been well tolerated as a result of cation–π stability,[4a,e,5a,b,6a,b] few examples of strictly polyene containing substrates are known.[4d,7]



(1)

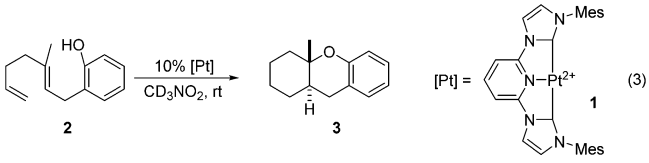
We have previously reported the synthesis of polycyclic Pt-alkyl compounds from simple and complex polyenes using Pt(triphos)$^{2+}$ as the cyclization initiator (eq 2).[8,9] The triphosphino pincer ligand renders the resulting Pt-alkyl compounds remarkably stable, but susceptible to Pt–C bond functionalization with strongly oxidizing agents (e.g., F^+ or Cu^{2+}).[10] We also considered the feasibility of an alternative oxidant, H^+, which oxidatively protonates the metal as the first elementary step in the protodemetalation of a Pt^{II}–C bond.[11] By following a Pt(II) initiated electrophilic cascade cyclization with an oxidative protonolysis scheme, we sought a cyclization/protonation approach to sterol-like polycyclic compounds. Despite the desirability of such an atom economical cycloisomerization procedure, this goal required a solution to the high stability of Pt-alkyl cations to acid.[12]

To facilitate such a scheme, we required a catalyst that was not only sufficiently electrophilic to initiate the cation olefin cyclization but also electron rich enough to undergo rapid protodemetalation. Our catalyst design features centered on the hypothesis that the electrophilic activation of a coordinated alkene would be principally controlled by its *trans* ligand, while its two *cis* ligands would primarily impact the facility with which it could be oxidized at the Pt-alkyl stage. This led us to seek a pincer ligand with a poorly donating *trans* ligand and strongly donating *cis* ligands. Limbach et al. have recently reported the hydrovinylation[13] and hydroamination[14] of ethylene mediated by a series of Pt catalysts engendering these target features, two cis NHC ligands and a trans pyridine.



(2)

We initiated our studies by examining the ability of complex **1** to induce cyclization of **2**. Remarkably, after only 3 h at room temperature, complete conversion to the cyclization/protonolysis product **3** was observed. Surprisingly, the cyclization proceeded in the absence of added base and provided none of the previously observed Brønsted acid catalyzed monocyclization product **4**,[15] which reports on the buildup of acid; i.e., H^+ is rapidly consumed *in situ*.



(3)

Our working mechanism has the reaction being initiated by selective coordination of the Pt electrophile to the least substituted alkene,[16] and subsequent ionic cyclization to **B** with liberation of H^+ from the phenol terminating group (Scheme 1). Protodemetalation of **B** generates **3** and regenerates the Pt catalyst. The lack of **4** indicates that H^+ never builds up and it reacts more quickly with **B** than it does with **2**.

Intrigued by the efficiency with which **1** induces cyclization in phenol terminating substrate **2**, we explored its applicability with the significantly more challenging alkene terminating groups.[8b] Remarkably, **1** proved effective at initiating the diastereoselective cyclization of a variety of polyene substrates. Bi-, tri-, and tetracyclization reactions all proceeded in the presence of 10% **1**. Additionally tolerated were terminating

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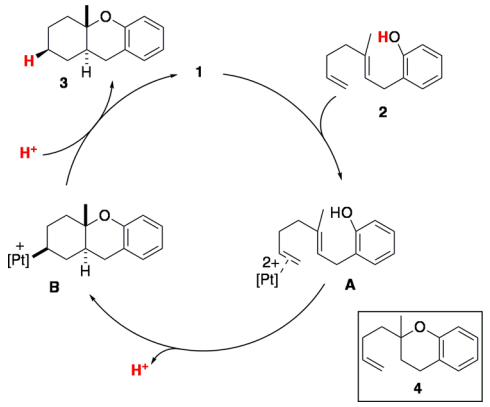
Scheme 1. Polyene Cycloisomerization Mechanism

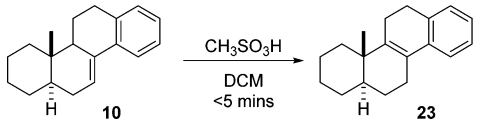


reactions to generate tertiary carbenium ions via 5-exo, 6-endo, and 6-exo cyclization geometries.

Reaction times varied, from 5 h for **9** to up to 2 days for the slower bicyclization reactions (e.g., **5**). While the bicyclizations of **5** and **7** do not proceed to completion after 48 h, addition of 20 mol % Ph_2NH as a proton shuttle allows for full consumption of starting material (e.g., **5**) and shorter reaction times (e.g., **7**, <24 h). Thus a positive role for a proton shuttle is noted, at least for some problematic cascade reactions.

In addition to the **2**→**3** transformation and the faster protonolysis of **B** than **2**, the cyclization of **9**→**10** also reports on a low steady-state concentration of H^+, as **10** is prone to conversion to **23** under acidic conditions (Scheme 2).[17] In this

Scheme 2. Conversion of Kinetic Product 10 to Thermodynamic Product 23



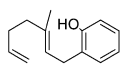
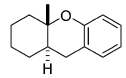
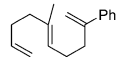
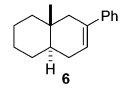
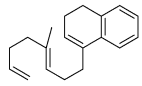
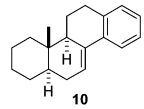
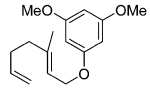
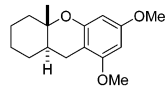
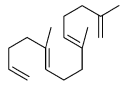
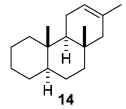
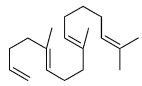
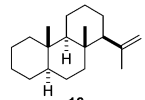
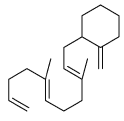
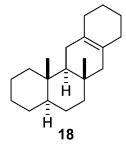
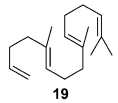
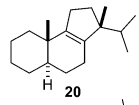
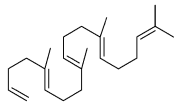
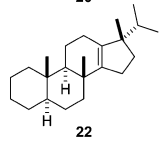
case, formation of **10** uncontaminated with **23** again suggests that Pt-alkyl protodemetalation occurs quickly, in this situation faster than alkene isomerization. As Yamamoto has previously observed using a Brønsted–Lewis acid (BLA) catalyst, the aryl ether substrate **11** cyclizes to rearranged **12**.[18]

Cyclization of **15** also proceeded rapidly to a mixture of two products, the desired tricyclization product with 5-contiguous stereocenters and an unknown bicyclic product. Compound **16** terminates the C-ring with a 3° cation-generating 6-exo cyclization followed by elimination (23% yield, Table 1). In a rare example of premature termination in Pt-initiated cascade cyclizations, an unidentified bicyclic product is competitively generated (46% yield, see Supporting Information (SI)).

For **19** to terminate in a 3° carbocation requires a C-ring 5-exo cyclization, the carbenium ion from which is particularly prone to Wagner–Meerwein rearrangements.[7a,8b] In this way the thermodynamically more stable tetrasubstituted alkene product **20** forms from a combination of hydride/methyl shift and subsequent elimination (39%). A compound consistent with **24** is formed as a minor product (10%; see SI), likely the result of a single hydride shift that instead eliminates to give the trisubstituted alkene (Scheme 3).

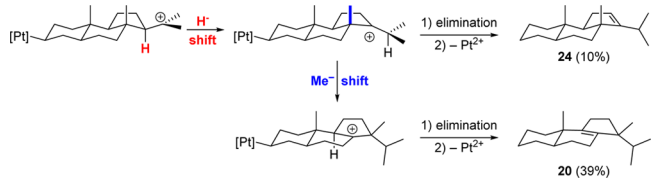
Finally, cyclization of **21** provided the tetracycle **22** in 44% yield, forming five stereocenters and providing the 6–6–6–5 sterol framework in a single step. Initial cyclization again

Table 1. Polyene Cycloisomerization

Entry[a,b]	Substrate	Product	Solvent	Isolated Yield
1	 **2**	 **3**	CD_3NO_2	93%
2			CD_3NO_2	88%(5 mol%)
3	 **5**	 **6**	CD_3NO_2	68%[c]
4			CH_2Cl_2	77%[c]
5	 **7**	 **8**	CD_3NO_2	80%[c]
6	 **9**	 **10**	CD_3NO_2	70%
7	 **11**	 **12**	CD_3NO_2	52%
8			CH_2Cl_2	59%
9	 **13**	 **14**	CD_3NO_2	61%
10	 **15**	 **16**	CD_3NO_2	23%
11	 **17**	 **18**	CH_2Cl_2	59%
12	 **19**	 **20**	CH_2Cl_2	39%
13	 **21**	 **22**	CH_2Cl_2	44%

[a]Products formed as a single diastereomer. [b]Conditions: **1** (0.015 mmol), substrate (0.15 mmol), solvent (1 mL). [c]Ph_2NH (0.030 mmol).

Scheme 3. Competing Wagner–Meerwein Rearrangement of a Polycyclic Cation Intermediate Derived From 19



terminates the D-ring in a 5-exo manner to generate an exocyclic tertiary cation akin to the protosterol cation observed in the conversion of 2,3-oxidosqualene to lanosterol (Scheme 4). From this exocyclic cation, a methyl and a hydride shift generates a tertiary cation at C13, with elimination to C14 creating the unsaturation at the C/D ring junction.[19] In contrast, from the protosterol cation, a series of two hydride

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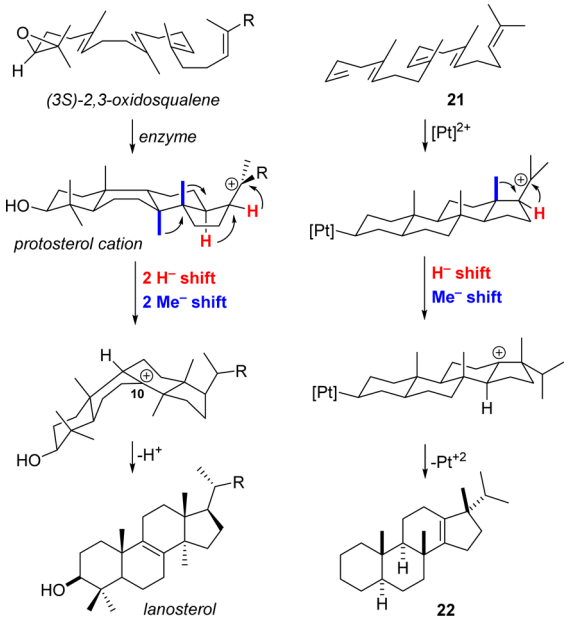
Scheme 4. Terminating Events in Cyclization of 2,3-Oxidosqualene and 21



and two methyl shifts generates a tertiary cation at C10 with elimination to C9 forming the unsaturation at the B/C ring junction of lanosterol.[20]

Nitromethane proved a suitable solvent in most cases; however, several slow reacting or incomplete cyclizing cases benefitted from a change to dichloromethane. Although **1** has a tendency to abstract chloride from dichloromethane,[13] it provided shorter reaction times in the case of substrates **17**, **19**, and **21**. It additionally enabled complete consumption of **19** while leaving the product distribution unchanged. Previous studies have shown that the equilibrium position of bicyclizations can be significantly shifted to the product state in the more poorly solvating solvent.[21] These data additionally suggest that a lower dielectric solvent may also increase the rate of cyclization.

In summary, we have reported an efficient, atom economical process for the conversion of a variety of polyene substrates to polycycles. This method hinges upon the paradoxical combination of high electrophilicity at the $(CNC)Pt^{2+}$ stage and ease of protonative oxidation at the $(CNC)Pt-R^{+}$ stage.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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.

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Notes

The authors declare no competing financial interest.

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