Cyclase Enzyme Mimics

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Terminating Platinum-Initiated Cation-Olefin Reactions with Simple Alkenes**

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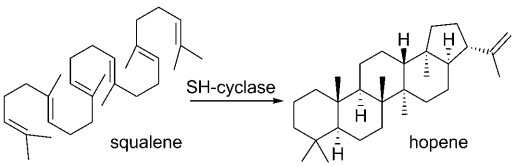
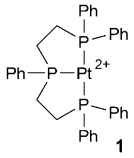
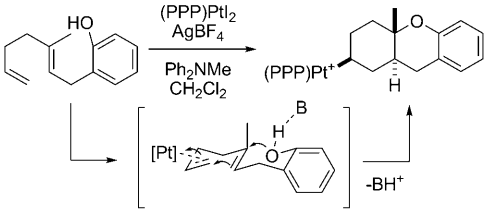
The en masse cyclization of polyolefins into polycyclic terpenoids by cyclase enzymes (e.g. squalene to hopene), is a biosynthetic reaction of particular fascination to chemists.[1] Noteworthy recent additions to synthetic mimics[2] of the cyclase enzymes are asymmetric methods that include Brønsted–Lewis acids (BLA),[3] masked equivalents of Br^+ and I^+,[4] organocatalysts,[5] and electrophilic metal catalysts.[6] With the exception of Hg^{II} reagents,[7] few electrophilic metal catalysts cyclize polyenes with bio-like alkene terminators.[8] The development of methods whose catalysts can initiate, cyclize, and terminate polyenes under ligand control would significantly advance the state of the art.



Herein, we describe the development of an alkene-terminated cation-olefin cascade reaction that is initiated by the dicationic platinum complex $[(PPP)Pt][BF_4]_2$ (PPP = bis-(2-diphenylphosphanylethyl)phenylphosphane), **1**.[9] Compound **1** is especially efficient at initiating cyclizations wherein the polyene carries a monosubstituted alkene terminus.[10] In addition to diastereoselectively forming polycyclic products with a broad variety of terminating alkenes, the reactions described herein contrast Hg^{II} reagents by the lack of premature termination processes.[11]



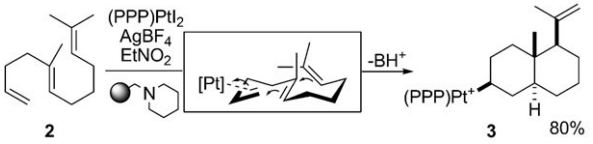
Our research group previously reported that L_nPt^{2+} sources will initiate the cation-olefin cascade with subsequent termination by the intramolecular addition of a protic trap [alcohol, phenol, or sulfonamide, for example; Eq. (1)].[12] Computational analysis showed that when a base was hydrogen bonded to the protic terminus and the alkene was in a suitable geometry, the cyclization was highly favorable and virtually barrierless.[13] In contrast, calculations under base-free conditions were characterized by high-energy intermediates and significantly less favorable thermodynamics.



(1)

This latter scenario most likely describes the early stages of a polyene cascade that terminates with a nonprotic group, and in the case of an alkene is not even acidic until the cation is fully formed. The difficulty of productively engaging a Brønsted base at an alkene terminus thus likely explains the paucity of synthetic examples.[14,15]

The combination of a polar solvent ($EtNO_2$) and either Ph_2NMe or, more conveniently, a resin N-bound piperidine base led to an efficient and highly diastereoselective cyclization of triene **2** into **3** [Eq. (2)]. In contrast to protic terminators, however, the reaction proceeds much more slowly [minutes for Eq. (1) vs. 36 hours for Eq. (2)], a difference which we interpret as reflecting the kinetic cost of generating a discrete tertiary cation.



(2)

X-ray crystallographic characterization of **3**[16] pointed to a predictable initiation at the least-substituted alkene, a chair/chair cyclization conformer, and the intermediacy of an exocyclic tertiary cation that eliminates to the isopropenyl group (Figure 1). Several features are notable in the solid-state structure of **3**. The first is the Pt–CH orientation, which positions the C–H vector in the square plane to minimize

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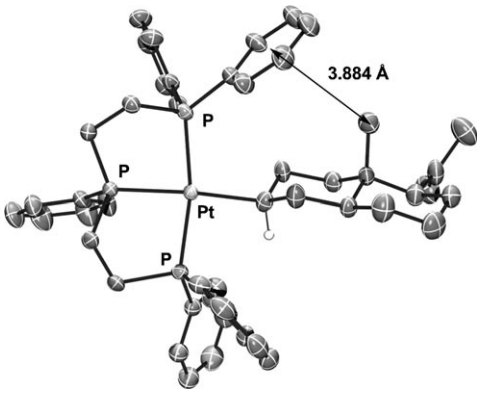


Figure 1. ORTEP plot of **3** showing the diagnostic interaction between the axial methyl group and the Ph ring at phosphorus. Thermal ellipsoids at 50% probability and hydrogen atoms are omitted for clarity.

steric congestion. This rotamer positions the angular CH_3 group near the face of one P–Ph group, which causes an upfield shifting of this CH_3 group in the ^1H NMR spectrum (to ≈0.1 ppm). This resonance proved to be diagnostic and was observed in each of the described structures (see below).

A number of polyenes with terminating tertiary carbocations were examined that varied in the number of rings formed (two or three), the arrangement of the terminating alkene (*endo*- versus *exo*-cyclic), and the ring size (Table 1). Even more facile than the 6-*exo* termini were reactions wherein the terminating alkene was arranged to react with the 6-*endo* geometry.[17] These reactions were 2–4 times faster than the 6-*exo* analogue **2**, and provided a number of carbon skeletons. In the case of **5**, the putative tertiary cation, formed from a chair/chair/chair transition state, eliminates to give the more stable C12/13 alkene isomer (Scheme 1). Products that would have arisen from premature quenching of a putative

Scheme 1. Chair/chair/chair cyclization with 6-*endo* termination.

cation at C5 or C9 were not observed (< 5%). In most cases, the structure of the resulting platinum complex was confirmed by single-crystal X-ray analysis (see the Supporting Information).[16]

Even more reactive were compounds with conformationally constrained dihydronaphthalene terminating groups (**6**, **8**, and **10**), which efficiently converted to the tetra- and pentacyclic products (Table 1, entries 3–5).[8] The conversion of **8** to **9** was ≈4 fold faster than the non-methoxy-substituted example (Table 1, entry 3), thus suggesting that the nucleophilicity[18] and/or cation stability of the terminus plays a significant role in the reaction kinetics. As judged by comparing the cyclization rates of **8** and **10**, an additional

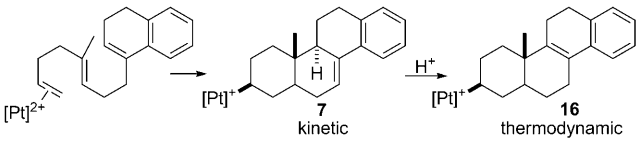
Table 1: Yields and scope of polyene cyclizations initiated by dicationic platinum complex **1**.

Entry	Substrate[a]	Product[b]	Yield [%][c]
1	**2**	**3** (X-ray)[16]	80
2	**4**	**5**	74
3	**6**: R = H	**7**	89
4	**8**: R = OMe	**9** (X-ray)[16]	97
5	**10**	**11** (X-ray)[16]	95
6	**12**	**13** (X-ray)[16]	76
7	**14**	**15** (X-ray)[16]	80

[a] Reaction conditions: $(PPP)PtI_2$, 2 equivalents of substrate, 2.5 equivalents of $AgBF_4$, 3 equivalents of piperidine resin base, and $EtNO_2$. [b] $[Pt]^+ = [(PPP)Pt]^+$. [c] Yield of isolated product.

isoprene unit in the main chain does not significantly affect the reaction barrier.

In the case of **6**, extended reaction times led to a partial conversion into the tetrasubstituted isomer at the B/C ring junction (Scheme 2).[19] As reported by Surendra and Corey,[8]



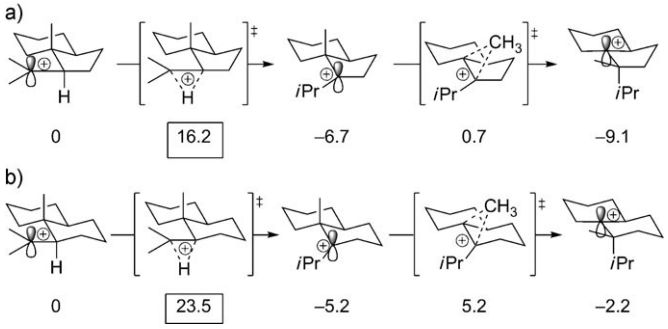
Scheme 2. Reaction termination by selective deprotonation.

this isomerization could be accelerated by acids, though the sulfonic acids also caused partial protodemetalation of the Pt.[20] By contrast, the tertiary cation formed on cyclizing **12** preferentially eliminates to the more stable tetrasubstituted alkene product **13**.[21]

When a 5-*exo* geometry was required for the formation of a tertiary carbenium ion to terminate the cascade, an entirely different path was followed. In these cases a clean Wagner–

Meerwein rearrangement converted the tertiary cation into the rearranged carbon skeleton of **15**,[22] which was confirmed by single-crystal X-ray analysis.[16]

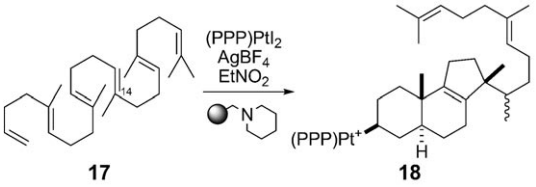
To gain insight into the diverging behavior of 6-*exo* and 5-*exo* terminated reactions, a computational analysis (DFT B3LYP/6-31G*)[23] of the key 1,2-shifts was carried out on simplified model systems (Scheme 3). Revealing was the



Scheme 3. A comparison of the 6,5 (a) and 6,6 (b) energies (kcal mol^{-1}) along the Wagner–Meerwein reaction coordinate.

differential activation energy for the initiating 1,2-hydride shift, which was 7.3 kcal mol^{-1} more favorable for the 5-*exo* terminated ring systems than for the 6-*exo*. The subsequent steps were lower in energy, thus suggesting that it is the slower initiating 1,2-hydrogen transfer in the 6,6 case which diverts the reaction towards a competitive base-induced elimination.

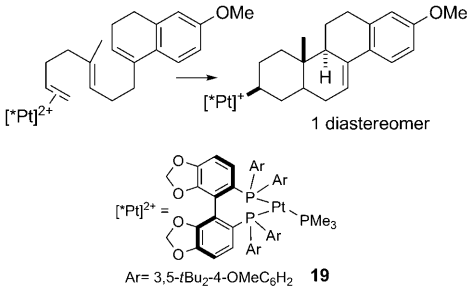
Compound **1** was additionally investigated for its ability to cyclize a squalene analogue that lacks the terminal methyl groups [Eq. (3)]. Although the complexity of the spectra was



(3)

significant and more than one isomer was formed, similarities to **15** suggested that the cyclization followed a 6,6,5-*exo* pathway to give a cation at C14, which nonselectively rearranged akin to **4**. Unlike cyclase enzymes, the environment of the terminating cation is not conducive to ring expansion/D-ring annulation.[24,25] van Tamelen made similar observations in Brønsted acid mediated reactions on squalene oxide.[26]

The viability of performing an asymmetric cascade cyclization was investigated using the chiral $[P_2PPt]^{2+}$ complex (P_2 = DTBM-SEGPHOS, P = PMe_3) **19**. The combination of a chiral P_2 ligand and an achiral monodentate phosphine has been previously shown to catalyze cyclorearrangment reactions with high enantiomeric excess.[27] When **19** was treated with **8** under the standard conditions (Table 1), NMR spectroscopy indicated that a single stereoisomer was obtained (^1H, ^{31}P), i.e. the chiral initiator



efficiently and diastereoselectively activates a single olefin face.

In summary, we report the results of a platinum(II)-mediated cyclization method that explores the boundaries of polyalkene cation-olefin reactions. These data reinforce the notion that the nucleophilicity/cation stability of the terminating alkene is of paramount importance and the termination outcomes depend on structure. Electrophilic Pt dications are also shown to be unique in their ability to activate and mediate the cascade reactivity of polyene reactants. The results pave the way to as of yet unknown catalytic asymmetric cation-olefin cyclizations of polyalkenes.

Experimental Section

Standard cyclization reaction: To 30 mg of $[(PPP)PtI_2]$ was added 15 mg of $AgBF_4$ followed by 0.75 mL of $EtNO_2$. The mixture was then stirred for 1 h in the dark. The contents were filtered through a 0.2 μm PTFE syringe filter, washing out the flask and syringe with 0.25 mL $EtNO_2$, into a flask containing 2 equiv of substrate and 3 equiv of piperidine resin. The reaction mixture was stirred in the dark until the reaction was complete (3–48 h, verified by ^{31}P NMR spectroscopy). The reaction mixture was passed through a 0.2 μm PTFE syringe filter, washing out the flask and syringe filter with 0.25 mL $EtNO_2$. Solvent was then removed under a stream of N_2. The complex was twice reconstituted in a minimum amount of CH_2Cl_2 and force precipitated with cold *t*BuOMe. The mixture was centrifuged and the solvent was decanted off. The crude residue was purified by flash column chromatography on silica gel.

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