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

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Cyclase Enzyme Mimics

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 poly-enes with bio-like alkene terminators.^[8] The development of methods whose catalysts can initiate, cyclise, and terminate poly-enes under ligand control would significantly advance the state of the art.

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Herein we describe the development of an *alkene terminated* cation-olefin cascade reaction that is initiated by the dicationic platinum complex [(PPP)Pt][BF₄]₂ (PPP = bis(2-diphenylphosphanylethyl) phenylphosphane), **1**.^[9] Compound **1** is especially efficient at initiating cyclizations wherein the polyene carries a mono-substituted 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]

We previously reported that L_nPt²⁺ sources will initiate the cation-olefin cascade with subsequent termination by the intramolecular addition of a protic trap (alcohol, phenol, or sulfonamide, e.g. eq 1).^[12] Computational analysis showed that when a base was H-bonded to the protic terminus and the alkene was in a suitable geometry, the cyclization was highly favourable and virtually barrierless.^[13] In contrast, base-free calculations were characterized by high energy intermediates and significantly less favourable thermodynamics.

(1)

This latter scenario most likely describes the early stages of a poly-ene cascade that terminates with a non-protic group, which 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 (EtNO₂) and either Ph₂NMe or, more conveniently, a resin *N*-bound piperidine base led to an efficient and highly diastereoselective cyclization of triene **2** to **3** (eq 2). In contrast to protic terminators however, the reaction proceeds much more slowly (minutes for eq. 1 vs. 36 h for eq. 2), a difference which we interpret as reflecting the kinetic cost of generating a discrete tertiary cation.

(2)

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. 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 steric congestion. This rotamer positions the angular CH₃ group near the face of one P-Ph group, which causes an upfield shifting of this CH₃ group in the ¹H NMR (to ~0.1 ppm). This resonance proved to be diagnostic and was observed in each of the described structures (*vide infra*).

A number of poly-enes with terminating tertiary carbocations were examined that varied in the number of rings formed (two-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* analog **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 cation at C5 or C9 were not observed (<5%). In most cases, the structure of the resulting Pt-complex was confirmed by X-ray methods (see SI).

Even more reactive were conformationally constrained dihydro-naphthalene terminating groups (**6**, **8**, and **10**), which efficiently converted to the tetra- and pentacyclic products (entries 3–5).^[8] The conversion of **8** to **9** was ~4 fold faster than the non-methoxy substituted example (entry 3), 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 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 to the tetra substituted isomer at the B/C ring junction.^[19] As reported by Corey,^[8] 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]

An entirely different path was followed when terminating the cascade to a 3° carbenium ion required a 5-*exo* geometry. In these cases a clean Wagner-Meerwein rearrangement converted the tertiary cation to the rearranged carbon skeleton of **15**,^[22] which was confirmed by X-ray analysis.^[16]

To gain insight into the diverging behaviour of 6-*exo* and 5-*exo* terminated reactions, a computational analysis (DFT B3LYP/6-31G*)^[23] of the key 1,2-shifts were carried out on simplified model systems (Scheme 3). Revealing was the differential activation energy for the initiating 1,2-hydride shift, which was 7.3 kcal/mol more favourable for the 5-*exo* terminated ring systems than for the 6-*exo*. The subsequent steps were lower in energy suggesting that it is a slower initiating 6-6 1,2-H-transfer that diverts the reaction towards a competitive base induced elimination.

Compound **1** was additionally investigated for its ability to cyclise a squalene analog that lacks the terminal methyl groups (eq. 3). Although the spectral complexity was significant and more than one isomer was formed, similarities to **15** suggested that the cyclization followed a 6-6-5-*exo* pathway to a C14 cation, which non-selectively 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-mediated reactions on squalene oxide.^[26]

(3)

The viability of performing an asymmetric cascade cyclization was investigated using the chiral P_2Pt^{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 cycloarrangement reactions with high ee's.^[27] When **19** was reacted 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 Pt(II) mediated cyclization methodology that explores the boundaries of poly-alkene 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 poly-ene reactants. The results pave the way to as of yet unknown catalytic asymmetric cation-olefin cyclizations of poly-alkenes.

Experimental Section

Standard Cyclization Reaction. To 30 mg of $(PPP)PtI_2$ was added 15 mg of $AgBF_4$ followed by 0.75 mL $EtNO_2$. 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). 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 $tBuOMe$. The mixture was centrifuged and the solvent was decanted off. The crude was purified by flash column chromatography.

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Figure 1. X-ray structure of **3** showing the diagnostic interaction between the axial-methyl group and the P-Ph ring.

Scheme 1.

Chair-chair-chair cyclization with 6-endo termination

Scheme 2.
Reaction termination by selective deprotonation

Scheme 3.

A comparison of the 6,5 (**a**) and 6,6 (**b**) energies (kcal/mol) along the Wagner-Meerwein reaction coordinate

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

Entry	Substrate ^[a]	Product ^[b]	Isolated Yield (%)
1			80
	2	3 X-ray	
2			74
	4	5

3	6	7	89
4	8	9 X-ray	97
5			95
	10	11 X-ray	
6			76
	12	13 X-ray	
7			80
	14	15 X-ray	

^[a] Conditions: (PPP)PtI₂, 2 eq substrate, 2.5 eq AgBF₄, 3 eq piperidine resin base, and EtNO₂.^[b] [Pt]⁺ = [(PPP)Pt]⁺