

Electrophilic Pt(II) Complexes: Precision Instruments for the Initiation of Transformations Mediated by the Cation–Olefin Reaction

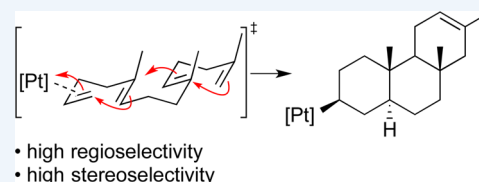
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CONSPECTUS: A discontinuity exists between the importance of the cation–olefin reaction as the principal C–C bond forming reaction in terpene biosynthesis and the synthetic tools for mimicking this reaction under catalyst control; that is, having the product identity, stereochemistry, and functionality under the control of a catalyst. The main reason for this deficiency is that the cation–olefin reaction starts with a reactive intermediate (a carbocation) that reacts exothermically with an alkene to reform the reactive intermediate; not to mention that reactive intermediates can also react in nonproductive fashions. In this Account, we detail our efforts to realize catalyst control over this most fundamental of reactions and thereby access steroid like compounds. Our story is organized around our progress in each component of the cascade reaction: the metal controlled electrophilic initiation, the propagation and termination of the cyclization (the cyclase phase), and the turnover deplatinating events. Electrophilic Pt(II) complexes efficiently initiate the cation–olefin reaction by first coordinating to the alkene with selection rules that favor less substituted alkenes over more substituted alkenes. In complex substrates with multiple alkenes, this preference ensures that the least substituted alkene is always the better ligand for the Pt(II) initiator, and consequently the site at which all electrophilic chemistry is initiated. This control element is invariant. With a suitably electron deficient ligand set, the catalyst then activates the coordinated alkene to intramolecular addition by a second alkene, which initiates the cation–olefin reaction cascade and generates an organometallic Pt(II)-alkyl. Deplatination by a range of mechanisms (β -H elimination, single electron oxidation, two-electron oxidation, etc.) provides an additional level of control that ultimately enables A-ring functionalizations that are orthogonal to the cyclase cascade. We particularly focus on reactions that combine an initiated cyclization reaction with a turnover defining β -hydride elimination, fluorination, and oxygenation. These latter demetalation schemes lead to new compounds functionalized at the C3 carbon of the A-ring (steroid numbering convention) and thus provide access to interesting potentially bioactive targets. Progress toward efficient and diverse polycyclization reactions has been achieved by investing in both synthetic challenges and fundamental organometallic reactivity. In addition to an interest in the entrance and exit of the metal catalyst from this reaction scheme, we have been intrigued by the role of neighboring group participation in the cyclase phase. Computational studies have served to provide nuance and clarity on several key aspects, including the role (and consequences) of neighboring group participation in cation generation and stabilization. For example, these calculations have demonstrated that traversing carbonium ion transition states significantly impacts the kinetics of competitive 6-endo and 5-exo A-ring forming reactions. The resulting nonclassical transition states then become subject to a portion of the strain energy inherent to bicyclic structures, with the net result being that the 6-endo pathway becomes kinetically favored for alkene nucleophiles, in contrast to heteroatom nucleophiles which progress through classical transition states and preferentially follow 5-exo pathways. These vignettes articulate our approach to achieving the desired catalyst control.



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1. INTRODUCTION

Polyenes are the biosynthetic precursors of a massive class of natural products (the terpenes) ranging in complexity from simple C₁₀ carbocycles like menthol and carvone through to complex sterols and beyond. Each member of this class of compounds shares a common progenitor in the cation–olefin reaction (COR), the C–C bond forming workhorse of terpene biosynthesis. For as long as chemists have understood the root sources of these compounds, they have sought to mimic them in the laboratory. While these approaches have become increasingly sophisticated (and powerful), none can escape the basic features of the cation–olefin reaction: (1) it involves reactive intermediates (carbocations), which (2) react exothermically with alkenes to regenerate the same

reactive intermediate. If these two aspects were not sufficiently challenging for methodologists, the diversity of nonproductive means for consuming such reactive intermediates increases multifold the degree of difficulty.

In this Account, we summarize our approach to taming the COR for the purpose of enabling the conversion of polyenes into polycyclic (usually) structures under catalyst control. In the process of developing these methodologies, a number of important facets, often not the key focus of previous publications, have emerged to enrich our understanding and guide our exploration.

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It is these features that this Account addresses, including (1) the nature of the Pt Lewis acid, how it differs from Pd analogues, and its chemoselectivity in alkene activation; (2) the role of catalyst structure on the thermodynamics, kinetics, and selectivity of the COR, how catalyst structure can be utilized to mediate (and diversify) catalyst turnover mechanisms, and induce asymmetry; (3) the recurring observation of reversibility in the ionic cascade cyclization; and (4) the role of neighboring group participation in facilitating the stereochemistry, regiochemistry, and cascade efficiency of the COR.

2. PLATINUM(II): A SOFT LEWIS ACID

The cation–olefin cyclization has long been an efficient synthetic method for converting polyolefins to biologically relevant products.^{1–3} Given the potential for increasing molecular complexity, nonenzymatic electrophiles have been sought to initiate cation–olefin reactivity.^{4,5} While Lewis and Brønsted acid type electrophiles can activate olefins to nucleophilic attack, these species often give nonselective reactions, can be susceptible to rearrangement, or are highly sensitive to reaction conditions.^{6–8} The carbophilic nature of electron deficient group 10 transition metal complexes enables them to behave as capable electrophiles for activating olefins, though the resulting M-alkyl species are often susceptible to reaction-terminating β -hydride elimination (e.g., the Wacker reaction).^{9,10}

Although Pt(II) and Pd(II) complexes are both capable of electrophilic π -activation, there are important elemental properties that affect the reactivity and catalytic potential of Pt(II) species that are not present in Pd(II). Perhaps the most significant differences between these two group 10 metals are the lanthanide contraction and relativistic effects present in the former,¹¹ both of which contribute to more diffuse 5d orbitals that enhance Pt's "soft" character.¹² This, coupled with a slower rate of ligand substitution for Pt(II), allows for the development of catalytic cycles that rely on alternative pathways for M–C bond cleavage: protonolysis, cyclopropanation, and heteroatom insertion.¹³ Important to the genre of polyene reactions is the significantly lower propensity of electrophilic Pt(II) compounds to cause olefin isomerization.¹⁴

In an early study of carbophilic activation of π -bonds by transition metals, Vitagliano and co-workers reported a tridentate ligand that promoted cation-like behavior of Pt and Pd coordinated alkenes while blocking β -hydride elimination from the resultant M-alkyl.^{15,16} These pincer ligands fill the coordination sphere of the square planar geometry and inhibit access to the low energy open coordination sites needed for β -hydride elimination. The apical sites of the square plane, while unoccupied, are higher in energy and not readily accessed (Figure 1).

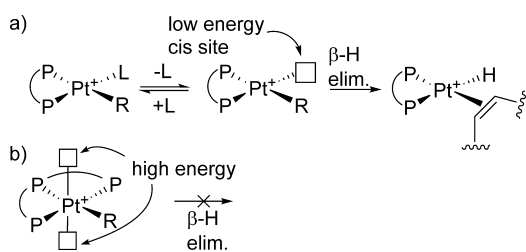
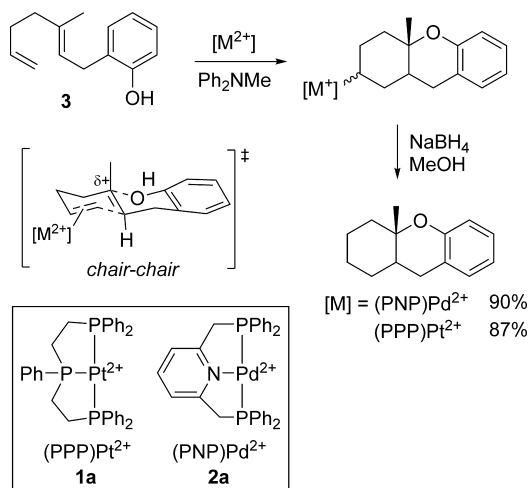


Figure 1. (a) β -H elimination to a low energy open coordination site. (b) High energy open sites inhibit elimination.

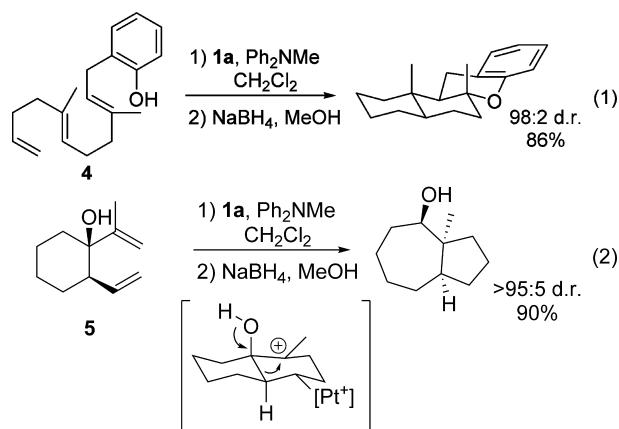
Adapting the Vitagliano concept to a COR cascade format, we employed two different tridentate catalysts, (PPP)Pt²⁺ (**1a**) and (PNP)Pd²⁺ (**2a**), in the cyclization of model substrate **3** (Scheme 1).¹⁷ Cyclization of **3** generated polycyclic organometallic

Scheme 1. Stoichiometric Cyclization of **3** with Tridentate Pd²⁺ and Pt²⁺ Species



products that were stable to chromatography and fully characterizable. In reactions with **3**, the two metal species behaved similarly, with no partially cyclized products detectable, due in part to the propensity of Pd and Pt to coordinate and activate the least substituted, terminal alkene.^{9,18} The observed reactivity is consistent with electrophilic activation of the terminal olefin, nucleophilic addition of the internal double bond to form a tertiary carbocation and rapid/concerted trapping of the tertiary carbocation by the protic terminating group (see proposed *chair–chair* transition state in Scheme 1). In all cases, Brønsted controls gave the monocyclization product resulting from protonation at the more substituted internal alkene.

Compound **1a** was found to be a versatile COR initiator as judged by its reactivity with a variety of polyenes. The cyclization of **4** demonstrated that the cyclogenerated carbocation could cascade through at least one additional olefin prior to termination (eq 1), while the stereoselective cyclization of **5** to a

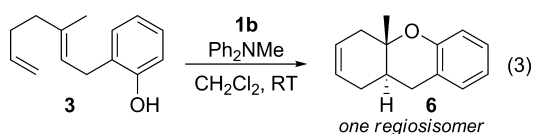


substituted bicyclo[5.3.0]decane (eq 2), showed that the cyclogenerated carbenium ions could also initiate ring-expanding/contracting pinacol rearrangements. Each of these examples (heteroatom addition, COR, pinacol rearrangement) support the

notion that pincer-ligated Pd(II) and especially Pt(II) dications readily cyclogenerate carbenium ions under mild conditions (RT, organic solvents).

3. CATALYTIC OXIDATIVE CASCADE CYCLIZATIONS

Early catalytic studies focused on extending the above cyclizations to the Overman PdCl₂-type Cope rearrangements,^{19–22} which similarly proceed through cyclogenerated carbenium ions. However, the inability to bring this reactivity under ligand control and the unchecked alkene isomerization in the products^{23,24} diverted our efforts to catalysts ligated by more controllable ligands (above). Phosphine coordinated Pt-dications emerged as superior catalysts, partially due to their stronger metal–ligand bonds, their decreased propensity to cause problematic alkene isomerizations, and their ability to initiate catalytic, ligand-controlled cation–olefin cyclizations.²⁵ For example, in contrast to the reaction of **3** with PdCl₂(NCR)₂,^{23,24} the stoichiometric combination of [(dppe)Pt][BF₄]₂ (**1b**) and **3** provided a single diastereomer and regioisomer of **6** at room temperature (eq 3), presumably the result of a regioselective β -hydride



elimination that is *not* accompanied by subsequent alkene isomerization.²⁶ Although the putative Pt–H was not observed, all indications pointed to it as a key reactive intermediate. Converting this stoichiometric reaction into a catalytic method was problematic as productive turnover of the Pt–H intermediate was not well precedented.⁸ One key difference between typical Pd Wacker-type catalysts and Pt systems is that Pt–X bonds (X = Cl, OAc, etc.) are typically not displaced by alkenes, and yet their presence is needed to facilitate metal oxidation.^{27–29} This distinction made traditional M(0) to M(II) oxidizing reagents such as benzoquinone, O₂, and so forth unsuitable.

A solution was discovered in (triphenylcarbenium)BF₄ (TrBF₄), which efficiently abstracted H⁺ from “(dppe)Pt–H” to regenerate the (dppe)Pt²⁺ COR initiator. Most convenient was to buffer the reaction with a weak base (Ph₂NH), whose conjugate acid could promote the fragmentation of commercially available trityl methyl ether into the active hydride abstractor (and MeOH). This technique kept trityl cation (Tr⁺) concentrations low and minimized Tr⁺-mediated side reactions. The proposed catalytic cycle for a resin-bound trityl source is shown in Scheme 2. P₂Pt²⁺ initiates the cyclization by coordination to the least substituted olefin. Cyclization coupled with proton loss, concomitant formation of Tr⁺, regioselective β -hydride elimination to form (P₂)Pt–H⁺, and hydride abstraction by Tr⁺ turns over the conversion of **3** to the oxidative cyclization product **6**.

The reaction works well for a number of dienes and trienes containing a hydroxy or phenoxy terminating group (Table 1) and provides high regioselectivities and only trans ring junctions. In addition to monosubstituted alkene initiation sites, 1,2-disubstituted termini were also tolerated (entries 4 and 5). Terminal tri-substitution, however, was not a viable substitution pattern, a feature we have yet to overcome for any Pd or Pt mediated transformation (entry 6). The selectivity of Pt(II) for coordination and activation of the least-substituted double bond does, however, ensure that activation of internal π -bonds is *not* competitive.³⁰

A number of commercially available chiral diphosphine ligands were screened for enantioselectivity in the oxidative cascade

Scheme 2. Proposed Mechanism for Pt²⁺ Catalyzed Polyene Cyclization

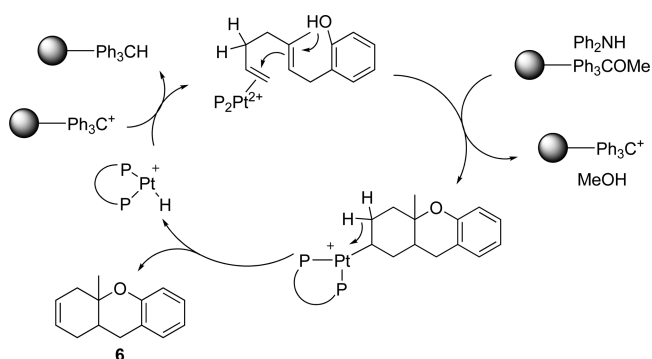


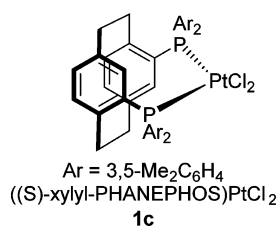
Table 1. Examples of Catalyzed Oxidative Polycyclization with **1b** and **1c**

Entry ^a	Substrate	Product	Yield(%)	
			1b	1c (%ee)
1			73	73 (75)
2			84	75 (79)
3			90	76 (64)
4			65	n.d. ^b (10)
5			72	61 (87)
6		NR		

^aConditions: 10% [Pt], 22% AgBF₄, 2.1 equiv Ph₃COMe resin, EtNO₂.
^bn.d. = not determined.

cyclization.³¹ ((S)-xylyl-PHANEPHOS)PtCl₂ (**1c**), yielded the most promising results, giving the expected product in 75% ee under optimized conditions (Table 1, entry 1). While the trends in reaction efficiencies did not differ much from the achiral to the optimum chiral catalysts, **1c** differed in its response to (*E*)- and (*Z*)-alkene substrates (entries 4, 5); (*E*)-alkenes were unsuitable while (*Z*)-alkenes were well behaved and gave the highest enantioselectivities.

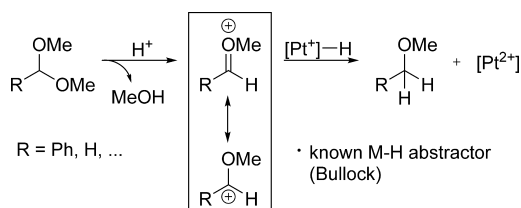
Thus, the viability of various substrate classes exactly reflects the binding propensity of the initiating alkenes to the electrophilic metal, especially with chiral, sterically encumbered catalysts. Unlike typical electrophiles like H⁺, Br⁺, Se⁺, and so forth, which preferentially activate more substituted (i.e., electron rich) alkenes, square planar d⁸ metal complexes have nearly the



opposite trend with η^2 -binding preference arranging as follows: ethylene > mono > 1,2-cis > 1,2-trans \gg 2,2, 1,2,2.^{32,33} In toto, the data show that Pt-alkene coordination chemistry is the key feature in determining the chemoselectivity of polyene activation/cascade initiation.

A more atom economical hydride abstractor was discovered by considering the possibility that the acidic reaction conditions could generate oxocarbenium ions from acetals.³⁴ Under conditions analogous to the TrOMe reaction conditions, aromatic acetals like benzaldehyde dimethyl acetal and dimethoxymethane were effective (Scheme 3), and in the latter case provided Me₂O as an easily removed volatile byproduct.

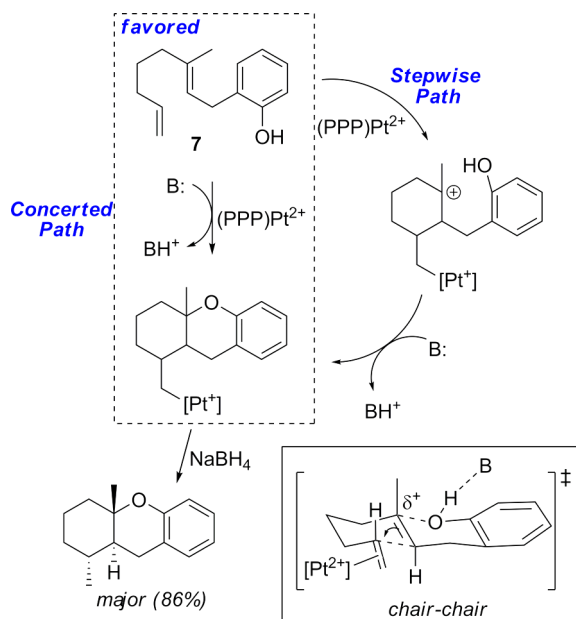
Scheme 3. Oxocarbenium Reductants for Hydride Abstraction



Computational Investigations

In addition to a cascade-initiating 1,5-diene, 1,6-dienylphenol **7** was also shown to be a viable alkene substitution pattern and was computationally investigated in collaboration with the Morokuma group (Scheme 4).³⁵ Density functional theory

Scheme 4. Concerted versus Stepwise Cyclization Pathway for 1,6-Dienylphenols



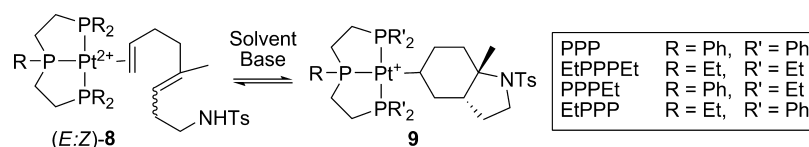
(DFT) calculations compared the concerted and stepwise cyclization pathway and concluded that (1) the major isomer forms from a chairlike transition state that places the terminal alkene in a pseudoequatorial orientation (Scheme 4), and (2) a weak base H-bonded to the terminating group (NH₃) causes the cascade to proceed via a concerted pathway devoid of a significant barrier. This outcome is not unlike the classic calculations reported by Jorgensen and Jenson on cascade cation-olefin cyclizations that show low barriers once properly arranged.³⁶ It is expected that in more flexible polycyclic precursors the cost of preorganizing the structure into the optimum geometry will significantly contribute to the overall barrier.

4. THE ROLE OF REVERSIBILITY IN CASCADE CYCLIZATIONS

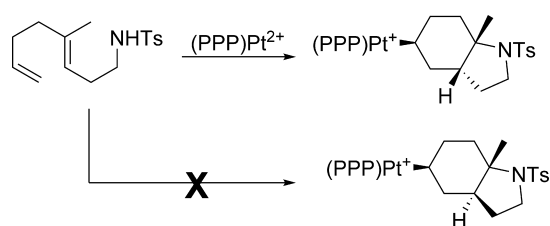
Throughout our studies on Pt-catalyzed or -initiated cation-olefin reactions, we have found that reversibility in the C–C bond forming events is evident.³⁷ Classic studies on CORs suggest that stereocenters remote from the point of initiation can impact the selectivity of the cascade.^{4,38–41} The two dominant hypotheses for this phenomenon suggest that (1) the cyclizations are concerted and the substituent extends its influence by affecting the stability of the nascent chairs of a highly ordered precyclization conformer, or (2) the cyclizations are reversible, which enables error correction and access to thermodynamic products. To probe the viability of either explanation in our platinum(II) systems, the effects of solvent, ligand basicity, and base strength were used to study the position of the cyclized/acyclic equilibrium for (*E:Z*)-**8** (Table 2). With the most electron rich complex (EtPPP)Pt²⁺, an equilibrium was observed by ³¹P NMR between the η^2 -coordinated (*E:Z*)-**8** and **9**. Solvent polarity and base strength had moderate effects on the equilibrium position with more polar solvents decreasing *K*_{eq} (entries 1–3) and stronger bases favoring cyclization (compare entries 3 and 4). More significant was the electronic character of the ligand itself. Strongly electron donating ligands such as EtPPP and PPP (entries 1, 5) gave small *K*_{eq}'s, whereas weakly donating ligands led to **9** being significantly favored (entries 6, 7). In the case of triphos (PPP), no η^2 -alkene could be observed by ³¹P NMR.

In addition to confirming the viability of the retrocyclization, these equilibrium studies provided evidence that when cycloreversion was possible, more complex rearrangements became feasible en route to thermodynamic products. For example, X-ray crystallography confirmed that both isomers of (*E:Z*)-**8** converge onto **9** (cis ring junction), in contrast to that predicted from a kinetically controlled (Stork-Eschenmoerer) concerted cyclization; pure *E* gave only *cis* (Scheme 5). For such a convergence to occur, a reaction pathway capable of interconverting the *E* and *Z* isomers, or their derived intermediates must exist.

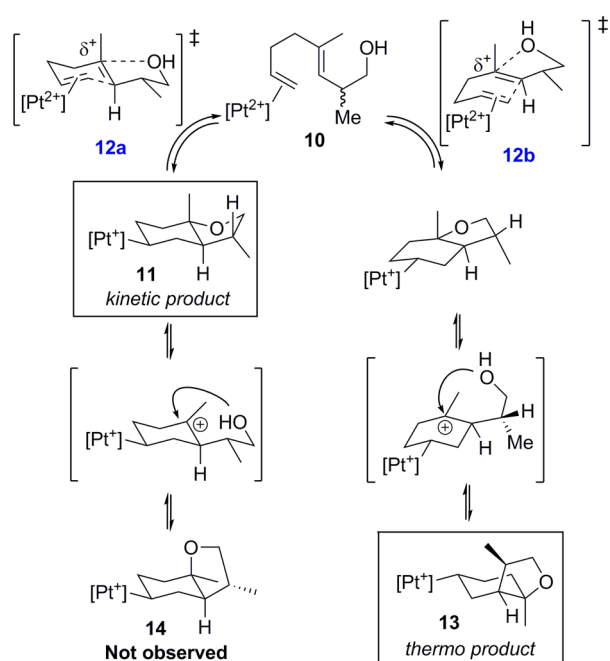
Supporting evidence for such a process came from a detailed analysis of the cyclization of **10**. When the electron deficient PPP ligand was utilized to minimize retro-cyclization, only **11** was observed, reasonably arising from chairlike transition state **12a** (Scheme 6), which orients the methyl group in a pseudoequatorial position. However, when the tridentate ligand is more electron rich than PPP, and thus facilitating of retro-cyclization, the more stable *cis*-fused product **13** is eventually observed, which is not the *cis*-isomer predicted from a simple ionization of the tertiary center and alkoxide recoordination to the opposite face of **11** (**14**). Our analysis suggests that the conversion of kinetic product **11** to the thermodynamic product **13**, must occur by a retrocyclization/boat-recyclization

Table 2. Effects on the Cyclized/Acyclic Equilibrium for (*E:Z*)-8

entry	ligand	solvent	base	K_{eq}
1	EtPPPEt	CH ₂ Cl ₂	Ph ₂ NH	60
2	EtPPPEt	EtNO ₂	Ph ₂ NH	3.2
3	EtPPPEt	MeNO ₂	Ph ₂ NH	0.68
4	EtPPPEt	MeNO ₂	Ph ₂ NMe	11
5	PPPEt	MeNO ₂	Ph ₂ NH	14
6	EtPPP	MeNO ₂	Ph ₂ NH	1100
7	PPP	MeNO ₂	Ph ₂ NH	>4200

Scheme 5. Stereochemical Outcome of Cyclization of Diene (*E*)-8

Scheme 6. Mechanistic Pathways for Formation of the Kinetic and Thermodynamic Products of Pt-Catalyzed Cyclization of 10

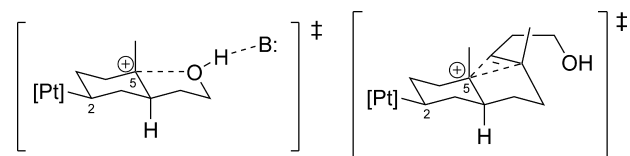


sequence that traverses a high energy trans-fused product capable of reCOORDINATING to provide a cis-fused product with the methyl disposed on the convex face of the structure. The conversion of **10** to **13** thus bypasses the Stork-Eschenmoser guidelines by facilitating a retrocyclization pathway that enables access to an otherwise noncompetitive kinetic pathway(s).

Ligand basicity also affected the ability of the Pt-electrophiles to initiate bi- vs tricyclization reactions. For the tested bicyclization

reactions, all phosphine ligands in Table 2 effectively initiated the cyclization and ligand basicity was predominantly manifested in the cyclized/acyclic equilibrium. Tricyclizations, on the other hand, required the more electron deficient PPP analogues for initiation. This reactivity difference was rationalized by noting that bicyclizations do not require a fully formed carbenium ion that subsequently engages another alkene.⁴² Instead the developing positive charge at C4 can be stabilized by the Lewis base, with or without the aid of a Brønsted base (Scheme 7). B-ring formation

Scheme 7. Neighboring Group Participation in Bi- and Tricyclizations



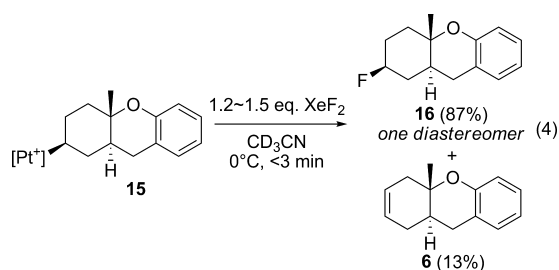
in a tricyclization, however, requires a larger charge buildup at C4 due to the less potent stabilization of the carbenium by the alkene; and hence the need for a more electrophilic Pt species. As described in section 7, such carbonium ions have been observed computationally as transition states with implications for the regiochemistry of A-ring closure.

5. Pt–C BOND FUNCTIONALIZATIONS

Our first successes in delivering cascade cyclizations under catalyst-ligand control took advantage of the inherent ability of organometallic complexes to undergo β -H elimination. The described Pt-catalysts did so with excellent regiocontrol over the elimination to generate products of net oxidative polycyclization. The intermediacy of a group VIII organometallic species suggested the possibility of even more valuable turnover mechanisms (oxygenation, alkylation, halogenation, etc.). Since Pt becomes localized at the C3 position of the polycycle (steroid nomenclature) and this position is commonly functionalized in natural products (e.g., cholesterol) or other artificial bioactive species, the potential to achieve unprecedented cyclization/C3-functionalization reactions began to drive our efforts. Our first successes came from efforts to fluorinate the Pt–C bond with electrophilic F⁺ sources^{43,44} and, thus, achieve a cyclization/C3-fluorination reaction to access steroidal inspired fluorinated carbocycles.^{45–47}

These efforts were initiated with stoichiometric studies on the isolable (PPP)Pt-alkyl⁺ **15**.⁴³ Screening several electrophilic F⁺ sources (Selectfluor, *N*-fluorobenzensulfonamide (NFSI),

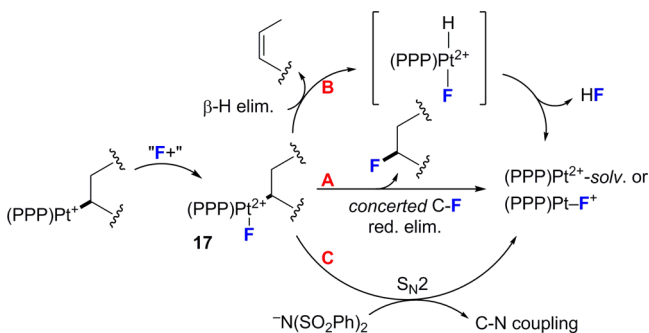
F-pyridinium salts, etc.) revealed that **15** reacts completely with XeF₂ within 3 min at 0 °C (eq 4) to yield **16** by a *stereoretentive*



mechanism. Investigations on various (triphos)Pt-R cations indicated that bulky R groups preferentially fluorinate while smaller groups tend to β -H eliminate, which does not otherwise occur in the absence of oxidant.⁴⁸

Experimental observations as well as previous studies,^{49–53} led to a working mechanism (Scheme 8) that has F⁺ oxidizing

Scheme 8. Proposed Mechanisms for Fluorination of (PPP)Pt–R⁺



the intermediate Pt-alkyl complex to the Pt(IV) intermediate **17**, which can undergo a concerted C–F reductive elimination for sterically congested structures (pathway A), or β -hydride elimination for less bulky arrangements (pathway B). If the alkyl is sterically susceptible to nucleophilic attack by the counterion (e.g., R = CH₃), an S_N2-type amidation can dominate (pathway C).

Switching to bidentate (*S*-xyllyl-PHANEPHOS)Pt²⁺, **1c**, set up a situation where the intermediate Pt-alkyl could undergo β -H elimination or, as exploited in Table 3, be fluorinated. In the case of the slower reacting F⁺ reagents, the former dominated, but XeF₂ was sufficiently rapid to mediate an efficient and enantioselective cyclization/C3-fluorination reaction (Table 3).⁴⁴ Addition of an HF scavenger (TMS-OMe) increased the yield of numerous dieny and trienyl alcohols. The standard conditions were ineffective for the trienyl phenol in entry 4, but replacing TMS-OMe with a polystyrene-bound piperidine base provided the fluorinated compound in good yield, albeit at the cost of enantioselectivity.

Investigations on the reactivity of the feasible catalytic intermediates revealed that the electrophilic P₂Pt(NCC₆F₅)₂⁺ initiator⁵⁴ is unreactive to XeF₂, suggesting that only after cyclization to a monocationic P₂Pt–alkyl⁺ complex, is the catalyst sufficiently electron rich to trigger the F⁺ oxidation/reductive elimination sequence (Scheme 8). This differential reactivity provides the means to properly sequence the cyclization/fluorination cascade. In situ monitoring by ³¹P NMR spectroscopy reveals that the catalyst rests at the P₂Pt–alkyl⁺ intermediate, making the competitive β -hydride elimination

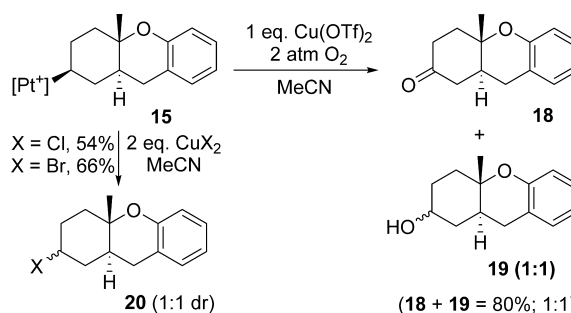
Table 3. Catalytic Enantioselective Fluorination of Polyene Substrates by 10 mol % **1c** and 1.1 equiv of XeF₂

Entry	Substrate	Product	Yield (% e.e.)	Yield β -H elim.
1			67% (75%)	14%
2			67% (73%)	15%
3			80% (81%)	trace
4			69% (10%)	10%
5			56% (78%)	0%

and F⁺ oxidation the likely turnover limiting steps. Unpublished results have demonstrated that kinetically poorer F⁺ sources can serve to turn over a β -H elimination process for the synthesis of **6**, leading to a new cyclization/ β -H elimination scheme that is driven by F⁺ sources rather than Tr⁺ or oxonium ion hydride abstractors (section 3).

In addition to selective Pt–C fluorination reactions, we have also initiated efforts to couple cyclization with Pt–C oxygenation schemes to access C3-oxygenated polycycles.^{55–57} Partial success in achieving this goal was realized by a strategy that intercepts the Pt-alkyl intermediate with a 1-electron oxidant to form a Pt(III)-alkyl. The chemistry of such species has previously been examined by Kochi, Troglor, Baird, and others^{58–62} and is characterized by rapid Pt/Pd–C bond homolysis to reform the divalent state (in a form suitable for initiating the COR) and a free radical. In the context of our own goals, this would generate a C3-free radical which could be trapped with O₂ (and others) to yield C3-oxygenated products. Reaction of (PPP)Pt-alkyl⁺ (**15**) with 1 equiv of Cu(OTf)₂ under O₂ atmosphere gave a combined 80% yield of the C3-oxygenated products **18** and **19** (1:1, Scheme 9).

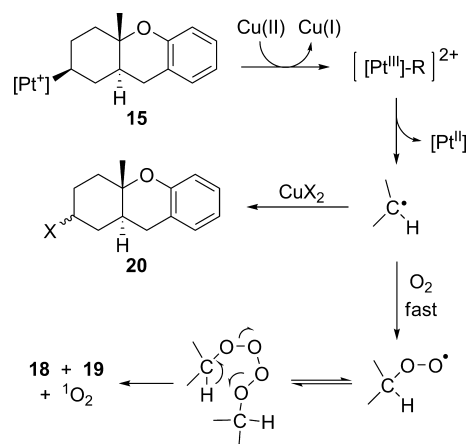
Scheme 9. Pt–Alkyl Bond Functionalizations Mediated by Cu(II) Oxidants



The product distribution is characteristic of the Russell fragmentation of secondary alkyl peroxy radicals (ROO·).⁶³ In the absence of O₂, it was also possible to use copper(II) halides to functionalize the Pt–alkyl bonds, in this case forming the alkyl halide products **20** in a near 1:1 mixture of C3-diastereomers (Scheme 9).

The mechanism diagrammed in Scheme 10 has been proposed to explain these observations. Copper(II) oxidation of

Scheme 10. Proposed Mechanism for C3-Oxygenation of Pt–Alkyls

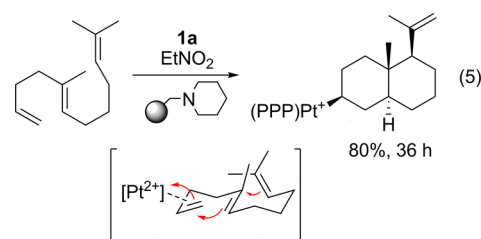


(PPP)Pt–R⁺ to the Pt(III) complex (PPP)Pt–R²⁺ followed by Pt–C bond homolysis releases Pt(II) and the C3-alkyl radical. This radical can either react nondiastereoselectively with CuX₂ to form **20**, or nonselectively with O₂ to form a secondary alkylperoxy radical. Russell disproportionation to give a 1:1:1 mixture of **18**, **19**, and ¹O₂ (not detected) provides the observed products. Initial results indicate that this methodology can operate catalytic in Pt, but the aggressive reaction conditions significantly impact the yields of product (64% at 20 mol % catalyst loading). Although our results thus far confirm our preconceptions that catalytic cyclization/oxygenation schemes would be challenging, the data indicate that success is achievable.

6. NONPROTIC TERMINATING GROUPS

Ionic cyclization reactions that terminate with a protic functional group (OH, NH, etc.) are considerably more efficient than those with simple alkene or arene termini. Computational studies on the cyclization of phenol **3** suggest that Brønsted base effects on the cyclization barrier are considerable. In the absence of a base, the phenol inefficiently stabilizes the developing positive charge on the cyclogenerated carbocation. In contrast, when the phenol has a hydrogen-bonded amine base (NH₃), the cascade is virtually barrier free (section 3). Biomimetic polyene cascades are therefore disadvantaged as alkenes are inherently poorer stabilizers of carbocations than heteroatoms, and the protons on an alkene do not become acidic until the carbocation has been completely formed. These features necessitate considerable positive charge build up on the terminating group, which slows true cation–olefin cascade cyclizations and makes them less efficient.

Despite these inherent challenges, we have recently demonstrated that aprotic substrates can be effectively cyclized by electrophilic Pt(II) systems,⁶⁴ though with a significant rate decline. As can be seen in eq 5, complete cyclization to the Pt-alkyl



occurs efficiently (80% yield), but requires 36 h instead of minutes for **3**. Nevertheless, a number of olefin-terminated polyenes could be converted to stable Pt–alkyls, with both bi- and tricyclizations proceeding efficiently (Table 4). The stability

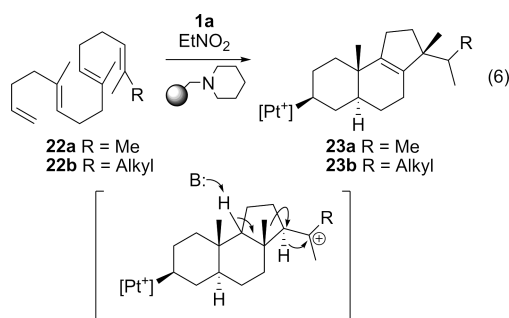
Table 4. Stoichiometric Cyclizations with (PPP)Pt²⁺ (1a)

Entry ^a	Substrate	Product	Yield
1			80%
2			74%
3			95%
4			76%
5			
	21a R = H	R = H	89%
	21b R = OMe	OMe	97%

^aConditions: (PPP)PtI₂, 2.5 equiv of AgBF₄, 3 equiv of piperidine resin base, 2 equiv of substrate, EtNO₂.

(and crystallinity) of the (PPP)Pt–R⁺ complexes enabled the stereochemistry of the cascade to be unambiguously determined to result from sequential chairlike arrangements. The orientation and basicity of the terminal group was found to modestly affect the cyclization rate. For example, the methoxy substituted styryl-terminated **21b** reacts ~4 times faster than the unsubstituted derivative **21a** (entry 5), demonstrating how the nucleophilicity⁶⁵ and/or cation stability of the terminus impacts reaction efficiency even when the terminus would seemingly not be engaged until the cascade has been fully completed. Such observations are in line with decades of observations on terminus effects in the synthetic works of Johnson, van Tamselen, Corey, and so forth.

In contrast to cases where the terminating cyclization occurred by a 6-endo or 6-exo geometry, cyclizations where tertiary carbocations



require the final ring to close with the 5-exo regiochemistry ($R = \text{CH}_3$, eq 6) led to postcyclization rearrangements. For example, reacting **22a** with $(\text{PPP})\text{Pt}^{2+}$ yields a product that, instead of eliminating after C-ring formation, undergoes a Wagner-Meerwein rearrangement to **23a**. Model DFT calculations show the initiating 1,2-hydride shift to be faster for 5-membered rings than for 6-membered C-rings.⁶⁴ When a squalene analogue was investigated ($R = \text{alkyl}$, **22b**, eq 6), the outcome was similar and provided a near 1:1 ratio of diastereomers. Unlike cyclase enzymes, which couple ring-expansion with D-ring annulation,⁶⁶ our 5-exo generated carbenium ions undergo a fast rearrangement that prevents productive ring expansion and additional ring closures.⁶⁷

7. GENERAL PRINCIPLES OF CATALYST CONTROLLED CATION–OLEFIN CASCADES

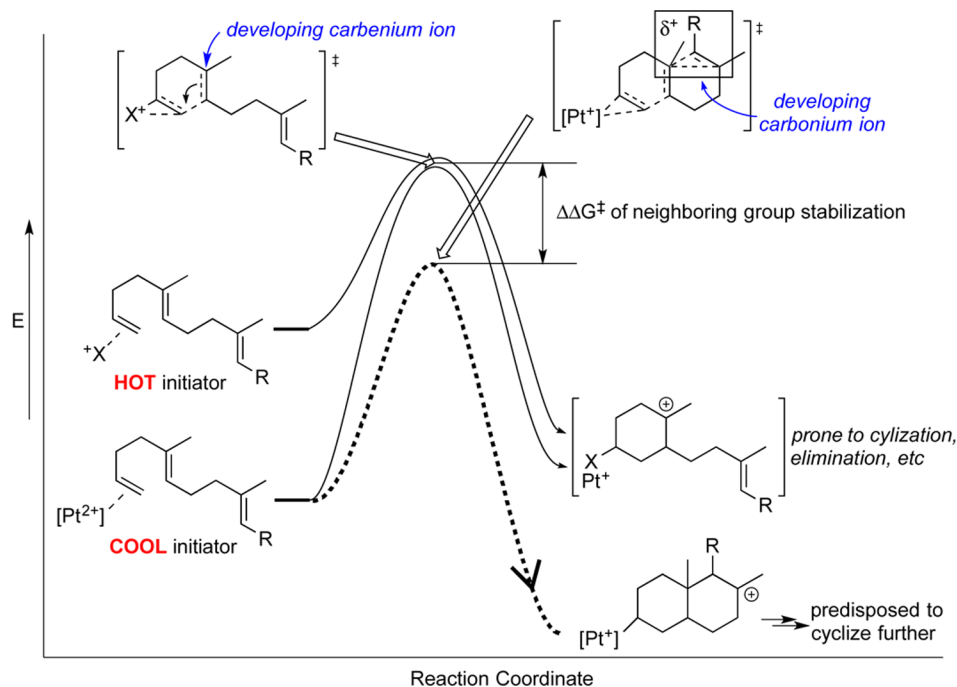
One important feature of the cascade cyclizations described herein is the atypical lack of premature termination, a process that characterizes most polyene cascades.⁶⁸ Our unpublished thoughts on the source of this reaction efficiency have always revolved around the concept of neighboring group participation as described by Eschenmoser et al.^{69,70} Simply put, one can reasonably surmise that the formation of a *carbenium* ion would be more costly than generating a tertiary carbocation that was engaged with and thus delocalized into a neighboring alkene,

(i.e., a *carbonium* ion, Scheme 11).^{71–74} This interaction would lower the enthalpic cost of localizing a full-positive charge, but increase the entropic cost due to heightened preorganization. Invoking neighboring group effects in the COR is particularly appealing as it simultaneously lowers the transition state energy and advances the reaction coordinate of a productive COR. Moreover, the delocalized cation model provides a mechanism for increasing the stereospecificity of cyclization as it bypasses free carbenium ions, which are prone to rearrangements and stepwise pathways that can erode selectivity.

In other words, if the COR initiator is highly reactive (“hot”, Scheme 11), then it should be capable of initiating the COR with little concern over the need to form a reactive carbenium ion.^{75,76} By contrast, a “cooler” initiator does not have the wherewithal to directly react with the alkene nucleophile and must have help, in this case via neighboring group stabilization from the trailing alkene (or heteroatom in the case of protic termini, Scheme 7), the natural consequence being that the B-ring is asynchronously formed in concert with A-ring closure.^{77,78} Taken together with selective coordination to the least substituted, terminal olefin, we have come to believe that these effects account for why our Pt systems tend to fully cyclize without premature termination (Scheme 11). Our confidence in ascribing a special role to Pt-initiators necessarily diminishes as the cascades extend to 3, 4, or more rings. One consequence of the above scenario is that a substrate needs to preorganize multiple nascent rings (usually chairlike) prior to formation of the first ring. While such a hypothesis should be characterized by a large negative $\Delta\Delta G^\ddagger$, we have yet to find a system where this quantity can be precisely measured.

The nonclassical carbonium structure in Schemes 7 and 11 were also used to explain the A-ring regioselectivity observed in all of our 1,5-dienyl cascade cyclization reactions. These reliable A-ring 6-endo cyclization preferences are in contrast to monocyclizations with heteroatom nucleophiles, which

Scheme 11. Effect of Initiator Reactivity on the Degree of Neighboring Group Participation in the Cascade



preferentially give kinetic 5-*exo* selectivities. Electrophilic activation of the terminal alkene reasonably leads to π -attack on the terminal (6-*endo* closure) or internal (5-*exo* closure) end of the activated double bond (Figure 2A). In our own

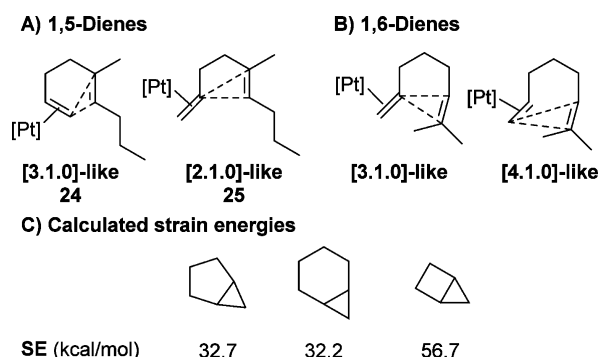


Figure 2. Models to rationalize the regioselectivity of A-ring formation. (A) 6-*endo* versus 5-*exo* intermediates or transition states for 1,5-dienes. (B) For 1,6-dienes. (C) Computed SEs for bicyclo[*n*.1.0]alkanes.⁷⁹

deliberations, we have rationalized the 6-*endo* preference by invoking nonclassical transition states or intermediates that can be described as either proceeding through a bicyclo[3.1.0]-hexane type structure for the 6-*endo* mode, **24**, or a less favorable 5-*exo* bicyclo[2.1.0]pentane type transition states, **25** (Figure 2A). Although one would be unlikely to generate structures encompassing all of the strain energy (SE) of the parent hydrocarbons (Δ SE \sim 24 kcal/mol, Figure 2C), the large difference in ring strain between these two arrangements⁷⁹ led to the suggestion that nonclassical carbonium ions were also at the root of the selectivity. In contrast to 1,5-dienes, trapping studies on 1,6-diene cyclopropanation reactions supported the notion of competitive 5-*exo* and 6-*endo* closures (see Scheme 13, next section). Applying the ring strain argument to these two scenarios would invoke competing [3.1.0]- and [4.1.0]-like transition states. Since the hydrocarbon ring strain of these arrangements is similar (Figure 2B), a significant kinetic preference would not be predicted.

Computational studies led by the Tantillo group at UC Davis provided important insights into the role of nonclassical carbocations in such cyclization reactions.⁸⁰ Figure 3 shows the ground and transition state energies for the 5-*exo* and 6-*endo* ring closure pathways of a substituted 1,5-diene using [Pt(PH₃)₃]²⁺ as the initiator. As the data show, the thermodynamics of the two possible cyclization modes were not significantly different, with the ground state (classical) 6-*endo* carbenium ion being \sim 1 kcal/mol more stable than that derived by the 5-*exo* pathway. In contrast, the 5-*exo* and 6-*endo* transition states were found to be nonclassical in nature, with the former

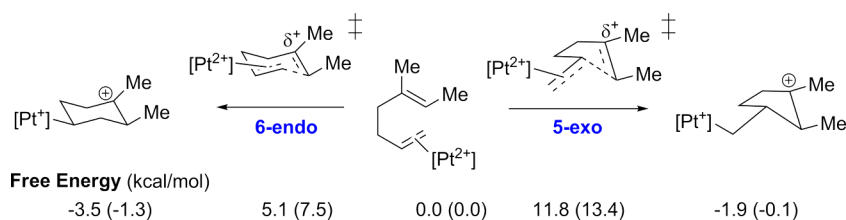
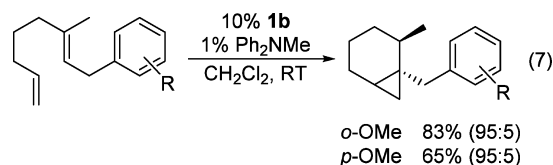


Figure 3. Computed reaction enthalpies (free energies in parentheses; kcal/mol; in DCE) and barriers for [Pt(PH₃)₃]²⁺ promoted 6-*endo* and 5-*exo* cyclizations.

being considerably higher in energy than the 6-*endo* mode ($\Delta\Delta G^\ddagger = 5.9$ kcal/mol). By virtue of being nonclassical, these transition states thus set the stage for a portion of the strain energy associated with the parent bicyclo[*n*.1.0]alkanes to be transferred to these analogous transition states, and hence their rates of cyclization.

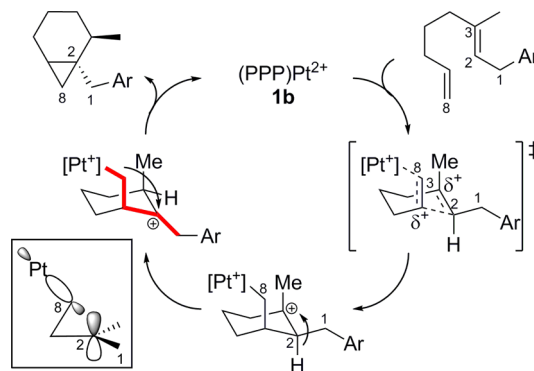
8. IONIC DIENE CYCLOISOMERIZATION: BICYCLOPROPANES

Utilizing a mechanism that parallels that discussed above for cascade cyclizations, (PPP)Pt²⁺ catalyst **1b** was found to cycloisomerize a number of 1,6-dienes to bicyclo[4.1.0] alkanes with high diastereoselectivity (e.g., eq 7).⁸¹ Analogous Pd(II) complexes either were unreactive or gave mixtures of bicyclic and monocyclic products.

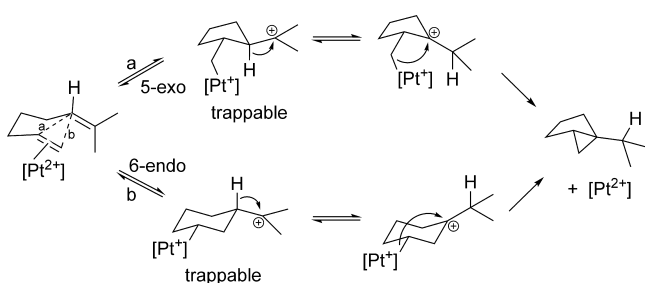


The consistent trend of activating the least substituted, terminal olefin is proposed to also prevail in this reaction (Scheme 12). After the initial cyclization, a 1,2-hydride shift

Scheme 12. Proposed Catalytic Cycle for Cyclopropanation of 1,6-Dienes



generates a carbocation that is γ to the metal center, which initiates a doubly invertive Pt–C bond cleavage/C–C bond formation that annulates the cyclopropane and regenerates Pt(II). Deuterium labeling and trapping experiments provide support for this hypothesis,^{82,83} as do well-studied Ti-, Fe-, and Sn-mediated cyclopropanations.^{84–86} Additional details on the first C–C bond forming event emerged from trapping studies on the conversion of 1,6-dienes to bicyclo[3.1.0]alkanes in Scheme 13. When

Scheme 13. Possible Endo- and Exocyclic Routes to [3.1.0]-Bicyclic Products**Table 5. Cyclopropanation with P₂P-Ligated Pt²⁺ Complexes**

entry	P ₂	bite angle	time (h)	yield	dr
1	dppm	72°	1.5	79%	26:1
2	dppbz	83°	5	25%	12:1
3	dppe	85°	6	56%	19:1
4	dppp	91°	15	45%	5:1
5	dppb	98°	7	16%	7:1

the reaction was carried out in the presence of benzyl alcohol two Pt-containing compounds were obtained, one resulting from the trapping of a 5-exo cyclization (pathway a, Scheme 13), and the other from a 6-endo cyclization (pathway b, Scheme 13). In situ monitoring revealed a dynamic composition that ultimately shifts the near equal speciation to the endocyclic product at equilibrium; once again reflecting reversibility in the C–C bond formation. Computational and experimental studies were consistent with Scheme 13, and additionally demonstrated that both pathways lead to the [3.1.0]-bicyclo product and that cross over between the two manifolds can occur at several points.⁸⁷

Well aware of the laborious routes to (especially chiral) triphos ligand derivatives, we sought to improve these preliminary efforts by investigating the viability of P₂P surrogates (bidentate + monodentate ligands).⁸³ Our first investigations focused on the effect of bidentate ligand bite angle using PMePh₂ as the monodentate ligand. Though clear correlations were murky, dpmp provided the best results with respect to yield, dr, and rate (Table 5), the dpmp catalyst being efficient enough to proceed at room temperature instead of the 40 °C required by the tridentate ligand systems.

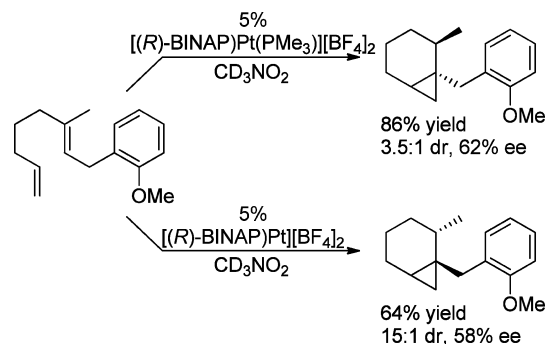
Screening monodentate ligands on the [(dpmp)Pt]²⁺ core, showed that PPh₃ provided the highest diastereoselectivity (dr = 38:1), while PMe₃ gave the best yield (94%). The latter was used to outline a substrate scope (Table 6). In addition to permitting milder reaction conditions than the triphos catalyst system, the P₂P system also gave products for previously unreactive acetal and sulfone substituted substrates. The P₂P strategy also provided an experimentally tractable venue for asymmetric catalysis with chiral P₂* ligands. A survey of commercially available chiral bidentate ligands revealed R-xyl-BINAP and SEGPHOS to be most enantioselective, though yields were slightly lower than with the [(dpmp)(PMe₃)Pt]²⁺ system (Table 6).

Control experiments for the P₂*P-catalyzed experiments led us to investigate the cycloisomerization with a BINAP-based catalyst lacking the PMe₃ (i.e., (BINAP)Pt²⁺). This catalyst proceeded to give the enantiomeric bicyclopropane product with moderate yields and enantioselectivity. The presence or absence of PMe₃ controls the sense of enantioselectivity; that is, both antipodes are accessible from a single enantiomer of BINAP (Scheme 14). Most surprising about this result is the divergence from our notion that blocking the cis sites is a requirement for avoiding β-hydride elimination. In this reaction, at least, such products were not detected by GC-MS. The source of this peculiar behavior is still not known, but it seems likely that the slow substitution kinetics of Pt may be key to reducing the rate of elimination. P₂Pd²⁺ catalysts only give alkene scrambling.

Table 6. Cycloisomerization of Dienes with [(P₂)Pt(PMe₃)] [BF₄]₂^a

Entry	Diene	Product	P ₂	Yield	%ee	dr
1			dppm (R = Me)	72%	--	57:1
			xyl-BINAP (R = H)	55%	92%	--
			SEGPHOS (R = H)	64% ^b	84%	--
2			xyl-BINAP	70%	95%	3.9:1
			SEGPHOS	77% ^b	79%	3:1
3			dppm	73%	--	--
			xyl-BINAP	70%	93%	--
			SEGPHOS	69%	87%	--
4			dppm	78% (5.8:1) ^c	--	--

^aReactions at room temperature. For P₂ = dpmp, 5 mol % cat, for P₂ = BINAP or SEGPHOS, 10 mol % cat. ^bYield by GC. ^cMixture of cycloisomerization and cyclohexene products.

Scheme 14. Effect of PMe_3 on the Absolute Stereochemistry

9. SUMMARY AND OUTLOOK

Platinum(II) catalysts are efficient tools for the cation–olefin cascade of linear polyenes into complex, multicyclic compounds. Their utility emerges from an ability to cyclogenerate reactive carbenium/carbonium ions under *catalyst control*. While they can somewhat inefficiently directly generate carbenium ions (e.g., in cyclopropane synthesis), an important facet of their initiator properties is that they kinetically benefit from the assistance of a neighboring functional group (protic heteroatoms or trailing alkene). The engagement of such groups simultaneously stabilizes the developing charge and advances the reaction coordinate for polycyclization. These features coupled with the strong preference of Pt(II) electrophiles to coordinate to and activate the least substituted alkene provide the means to achieve precision in the activation and propagation of cascade cyclizations.

One of the exciting features of using a transition metal to initiate cascade cyclization reactions is the generation of an organometallic complex at the C3 position of the resulting product (steroid numbering). Opportunities abound for manipulating this Pt–C bond postcyclization. Our initial efforts focused on β -H elimination to yield unsaturated A-ring products, but more recent efforts have focused on processes that first oxidize the Pt(II) alkyl to the Pt(III) or Pt(IV) state, with subsequent productive reactivity. This approach has enabled the cascade to be followed by stereoselective fluorination and oxygenation reactions to yield products wherein the original polyene has been significantly upgraded with regards to complexity and functionality. It is clear that this direction represents an important growth opportunity, but only by properly investing in the fundamental chemistry of these complex organometallic compounds. The ubiquity of organometallic intermediates in important methodologies (cross coupling, insertion, etc.) suggests obvious new directions for expanding the postcyclization derivatization of new carbocycles.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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