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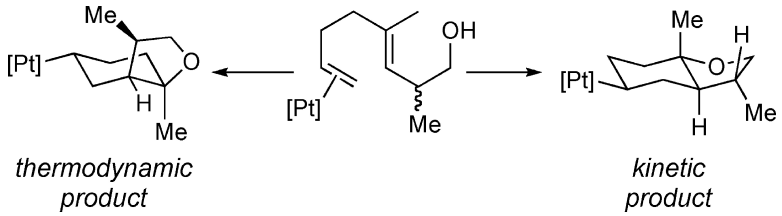

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Reversibility Effects on the Stereoselectivity of Pt(II)-Mediated Cascade Poly-ene Cyclizations

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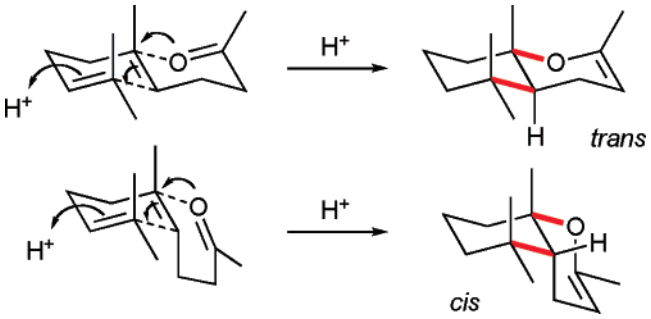
Abstract: Cyclization of 1,5-dienes bearing nucleophilic traps with electrophilic trisphosphine pincer ligated Pt(II) complexes results in the formation of a polycyclic Pt-alkyl via a Pt(η^2-alkene) intermediate. With electron-rich triphosphine ligands, an equilibrium between the Pt(η^2-alkene) and Pt-alkyl was observed. The position of the equilibrium was sensitive to ligand basicity, conjugate acid strength, solvent polarity, and ring size. In cases where the ligand was electron poor and did not promote retrocyclization, the kinetic products adhering to the Stork−Eschenmoser postulate were observed (*E*-alkenes give trans-ring junctions). When retrocyclization was rapid, alternative thermodynamic products resulting from multistep rearrangements were observed (*cis*-[6,5]-bicycles). Under both kinetic and thermodynamic conditions, remote methyl substituents led to highly diastereoselective reactions. In the case of trienol substrates, long-range asymmetric induction from a C-ring substituent was considerably attenuated and only modest diastereoselectivity was observed (~2:1). The data suggest that for a tricyclization, the long-range stereocontrol results from diastereo-selecting interactions that develop during the organization of the nascent rings. In contrast, the bicyclization diastereoselectivities result from reversible cascade cyclization.

Introduction

The stereoselective cascade cyclization of polyprenoids into multicyclic steroid-like structures stands as one of the crowning achievements in organic chemistry.[1] The state of the art synthetic methods reflect the sum of enormous efforts aimed at understanding the rules for controlling the efficiency and selectivity of the nonenzymatic cation−olefin cascade responsible for ring construction. The Stork−Eschenmoser postulate (SEP) was one of the key early findings that enabled the ring-junction stereochemistry to be predicted from the starting olefin geometry; *E*-alkenes give trans-ring junctions and *Z*-alkenes give cis-ring junctions.[2,3] The postulate is a manifestation of a favorable anti addition of electrophile and nucleophile across the original alkene (e.g., Scheme 1). Ultimately, however, the stereochemical outcome of such cascade cyclizations is explainable by evaluating the role that neighboring group participation plays on the kinetics of the cation−olefin reaction;[3] the key being that coordination of a stabilizing group (Lewis base, alkene, etc.) to a carbenium ion simultaneously advances the cyclization reaction coordinate.[4] Interaction of an electron-rich neighboring group on a developing carbenium ion (i.e., stabilizing it) lowers

Scheme 1



the punitive enthalpic cost of localizing a full-positive charge on the center in question at the cost of heightened entropic organization, while simultaneously preserving the stereochemical information (i.e., *E* vs *Z*) stored in the alkene.

The ability of the neighboring group to engage the developing carbenium ion also effects the efficiency and stereospecificity of cyclization reactions.[5] When a good participant is available, the reactions tend to be more favorable and selective since they avoid free carbenium ions and stepwise pathways that can erode stereospecificity.

Another factor influencing the stepwise versus concerted cyclization manifolds is the stability of the initiating carbenium

(1) (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756. (b) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Elmsford, NY, 1991; Vol. 1, pp 341−377. (b) Wendt, K. U.; Schultz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812−2833. (c) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341−409.

(2) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068−5077. (b) Eschenmoser, A.; Ruzika, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890−1904.

(3) For an English translation and historical perspective on the 50th Anniversary of the Eschenmoser, Ruzika, Jeger, and Arigoni 1955 paper, see: Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011−3050.

(4) (a) Johnson, W. S.; Bailey, D. M.; Owyang, R.; Bell, R. A.; Jacques, B.; Crandall, J. K. *J. Am. Chem. Soc.* **1964**, *86*, 1959−1966. (b) Bartlett, P. D.; Clossen, W. D.; Cogdell, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 1308−1314. (c) Poulter, C. D.; King, C. R. *J. Am. Chem. Soc.* **1982**, *104*, 1422−1424.

(5) (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 410−454. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756.

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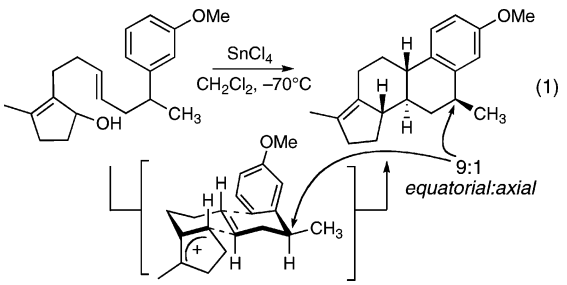
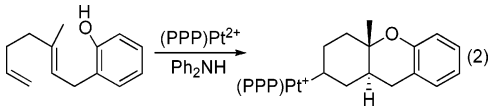
ion or reacting group (oxo-carbenium ion, allyl cation, etc.). When the initiator is highly reactive, it does not need the stabilizing influence of a neighboring group to react with the internal alkene, which leads to free carbenium ions and less selective, possibly nonstereospecific stepwise reactions.[6] Alternatively, when the initiating groups are less reactive, the beneficial effect of a stabilizing group (alkene or terminating protic group) on $\Delta G^{\ddagger}$ can be significant, which favors concerted, stereospecific reactions.

The debate over stepwise versus concerted reactions is also germane to the discussion of long-range stereocontrol. Numerous examples demonstrate that stereocenters remote from the point of initiation can influence the cascade selectivity (e.g., eq 1).[7] These results were most easily rationalized by invoking the influence of the substituent on the ordered conformation of the polyene in a concerted cyclization (i.e., pseudo-equatorial vs pseudoaxial substituent in a nascent polycycle). Alternatively, a reversible cascade cyclization could account for the selectivity as the retrocyclization provides a means for error correction and access to thermodynamic products. Bartlett, in his authoritative 1982 review, concluded, primarily using free energy arguments, that long-range stereocontrol in sterol cyclizations could not come from a reversible cyclization scenario and that the only logical means for achieving these remarkable effects was through the preorganization that accompanies a concerted cyclization.[1c,8]



Carbophilic transition metal complexes are also known to activate terminal alkenes for cascading cation−olefin reactions.[9] In most of these cases the Stork−Eschenmoser postulate holds, and polyprenoids provide polycyclic structures through chairlike transition structures. Recent advances include oxidative polycyclizations using $PdCl_2$ catalysts in combination with benzoquinone,[10,11] (pyridyl-bisphosphine)Pd^{II} dications,[12] (trisphosphine)Pt^{II} dications,[12] and Hg(II)-mediated polyprenoid cyclizations.[13] In addition to transition metals, several important developments have occurred in the area of chiral electrophilic halonium ions[14] and chiral Brønsted−Lewis acid catalysts[15] for promoting enantioselective cation−olefin polycyclizations. Unlike H^+, Hg(II), and X^+ (X = I, Br, Cl), the carbophilic Pd(II) and Pt(II) Lewis acids have a strong preference for coordinating and activating the least substituted alkene, which provides a strong chemodirecting effect in initiating the cation−olefin cyclization of polyene substrates.[16]

Recent efforts in our laboratory have shown that pincer ligated Pd(II)- and Pt(II)-dications serve as excellent initiators of cation−olefin multicyclizations when the terminus is monosubstituted.[17] The pincer ligands efficiently block migratory deinsertion pathways, resulting in stable polycyclic organometallic products (e.g., eq 2). In the course of evaluating the effect of ligand electronics on the cyclization reaction, it was discovered that ligand basicity not only affected the kinetics of cyclization, but also the thermodynamics. With electron-rich ligands, an equilibrium between cyclized and acyclic (η^2-alkene) structures was discovered, and the position of this equilibrium was responsive to ligand electronics.



Given the potential role of reversibility on the stereoselectivity of biomimetic cation−olefin cascade reactions, a study was initiated to establish its role on the diastereoselectivity of Pt-mediated cyclization reactions. We report herein the effect that solvent, ligand basicity, ring strain, and ring size have on the position of the cyclized/acyclic equilibrium. These data were then utilized to establish conditions wherein retrocyclization was operative and could be utilized to measure the effect of remote substituents on the kinetic and thermodynamic cyclization diastereoselectivity.

Results

Activation Conditions. The Pt(II)-dications for this investigation were generated by one of two means. For complexes bearing more electron-donating tridentate ligands (EtPPPEt, *t*BuPPPEt, and PPPEt; see Chart 1) the dication was preferably generated via protonolysis of the Pt−Me precursor using $[Ph_2NH_2][BF_4]$.[19] A typical activation procedure involved the

(6) (a) Harding, K. E.; Leopold, E. J.; Hudrlik, A. M.; Johnson, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 2540−2549. (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522−523.

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(8) Radical cascade cyclizations can also show remarkable long-range stereoinduction, see: Heinemann, C.; Demuth, M. *J. Am. Chem. Soc.* **1999**, *121*, 4894−4895. For a review of stereoselective radical (and transition metal-catalyzed) multi-cyclizations, see: Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306.

(9) (a) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042−4059. (b) Hahn, C. *Chem. Eur. J.* **2004**, *10*, 5888−5899 and references therein.

(10) Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405−7410.

(11) Prior to our own efforts in this area were discoveries by the Overman group detailing the utility of *catalytic* $PdCl_2(RCN)_2$ to accelerate Cope-like rearrangements. Mechanistic studies pointed to cyclogenerated carbenium ions via chair-like transition structures. See, for example: (a) Overman, L. E.; Renaldo, A. F. *J. Am. Chem. Soc.* **1990**, *112*, 3945−3949, and references therein. For earlier stoichiometric examples, see: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247, and references therein.

(12) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459−3461.

(13) (a) Kang, S. H.; Kim, M. *J. Am. Chem. Soc.* **2003**, *125*, 4684−4685. (b) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Imagawa, T. H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609−1611.

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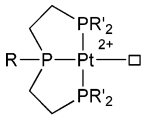
(17) (a) Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, *7*, 3379−3381. (b) Kerber, W. D.; Koh, J. H.; Gagné, M. R. *Org. Lett.* **2004**, *6*, 3013−3015. (c) See also ref 10.

(18) Addition of acetone generated a Pt(II)-acetone adduct which was stable in solution and was readily displaced by dienyl substrates, see 17a.

(19) Protonolysis of the precursor Pt−Me with $[Ph_2NH_2][BF_4]$ to give (EtPPPEt)Pt^{2+} is rapid (<10 min), see: Feducia, J. A.; Campbell, A. N.; Anthis, J. W.; Gagné, M. R. *Organometallics* **2006**, *25*, 3114−3117.

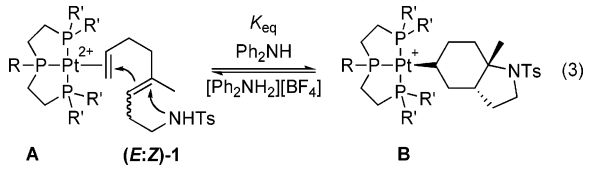
Chart 1



EtPPPEt	R = Et,	R′ = Et
***t*BuPPPEt**	R = *t*Bu,	R′ = Et
PPPEt	R = Ph,	R′ = Et
EtPPP	R = Et,	R′ = Ph
PPP	R = Ph,	R′ = Ph

addition of 10 equiv of $[Ph_2NH_2][BF_4]$ to a solution of [(RPPPR′)Pt−Me][BF_4] and dienyl substrate in the appropriate solvent; at the point of initiation, the reaction thus contained 9 equiv of $[Ph_2NH_2][BF_4]$ and one equiv of Ph_2NH. For complexes bearing the more electron poor PPP and EtPPP ligands (Chart 1), the preferred mode of activation was with $AgBF_4$ and the diiodide [(RPPPR′)Pt−I][I] precursor, followed by the addition of 1 equiv of base (Ph_2NH or Ph_2NMe). Activation via halide abstraction was possible with the more electron-rich Pt complexes; however, this approach required the addition of 2 equiv of acetone to act as a weak labile ligand.[18]

Cyclization Reactions. Previous work on the conversion of 1,6-dienes into bicyclopropanes by (PPP)Pt(II) dications indirectly revealed that Pt-mediated C−C bond forming carbenium ion generation was both rapid and reversible.[17] This observation also suggested a similar possibility in cascade cyclization processes. The first evidence for this behavior surfaced while monitoring the cyclization of 10 equiv of a 2:1 *E*:*Z* mixture of 1,5-dienyl sulfonamide **(*E*:*Z*)-1** by (EtPPPEt)Pt^{2+} in CH_2Cl_2 (see Chart 1). Instead of the expected smooth conversion to a Pt-alkyl, an equilibrium between the starting η^2-alkene adduct and the expected product was observed (eq 3).[19] The identity of these complexes was readily apparent from the characteristic J_{Pt-P} of their central phosphorus[20] (Pt(η^2-alkene), **A**, J_{Pt-P} = 2762 Hz; Pt-alkyl, **B**, J_{Pt-P} = 1281 Hz).[21] The presence of uncyclized η^2-alkene adduct was unexpected because all previous cyclizations of dienyl substrates with intramolecular traps had been rapid and proceeded to completion. After 1 h, an **A:B** ratio of ∼1:2 was observed by ^{31}P NMR,[22] and although decomposition occurred over extended times, an equilibrium constant could be measured at early times (∼60).[23]



Solvent and Ligand Effects on K_{eq}. From this starting point, an investigation into the factors controlling the equilibrium position was undertaken.[24] With [(EtPPPEt)Pt][BF_4]$_2$ and **(*E*:*Z*)-1** as the probe, K_{eq} decreases with increasing polarity, presumably by the favorable solvation of the dicationic Pt(η^2-alkene) complex over the monocationic Pt-alkyl (Table 1), though a solvent effect on the acid strength may also contribute. The poor solubility of $[Ph_2NH_2][BF_4]$ limited the accessible solvents. Nitromethane (K_{eq} = 0.68, Figure 1) was selected for further analysis since Pt−olefin complex **A** was favored (Figure 1).

Since previous reports with the more electron poor PPP ligands had not indicated the potential for either reversibility or stepwise cyclization of polyenes, the effect of ligand basicity on the cyclization equilibrium was explored.[25] Table 2 shows the results of modifying the donor properties of the phosphine substituents and the consequent metal electrophilicity.[26] Not surprisingly, more electrophilic complexes shifted the cyclization

Table 1. Solvent Effects on the Cyclization of **(*E*:*Z*)-1**with (EtPPPEt)Pt^{2+}[a]

entry	solvent	K_{eq} (**A:B**)[b]	Δ*G* (kcal/mol)
1	CH_2Cl_2[c]	60 (1:2)	−2
2	$ClCH_2CH_2Cl$[c]	110 (1:3)	−2.8
3	$EtNO_2$	3.2 (4:1)	−0.69
4	$MeNO_2$	0.68 (14:1)	0.23

[a] Conditions: [Pt] = 0.027 M, $[Ph_2NH_2][BF_4]$ = 0.27 M,[1] = 0.27 M, 25(1) °C (see Supporting Information). [b] Relative concentrations determined by ^{31}P NMR. Average of three measurements. [c] [Pt] = 0.012 M.

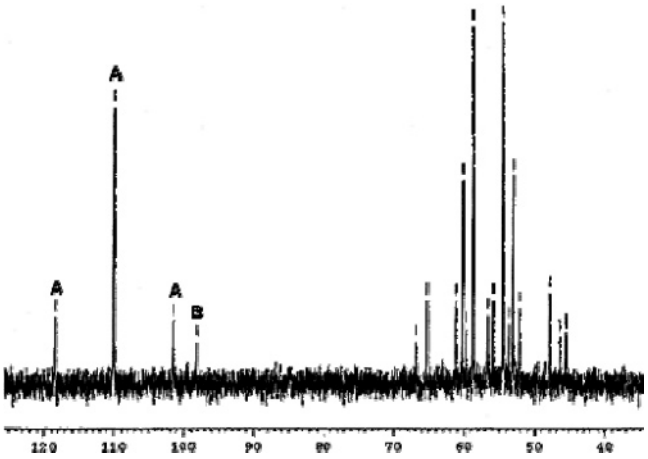


Figure 1. ^{31}P NMR of the cyclization of **1** with (EtPPPEt)Pt^{2+} in $MeNO_2$.

Table 2. Ligand Effects on the Cyclization of **(*E*:*Z*)-1** with (RPPPR′)Pt^{2+} (see Chart 1)[a]

entry	ligand	K_{eq} (**A:B**)[b]	Δ*G* (kcal/mol)
1	EtPPPEt	0.68 (14:1)	0.23
2	*t*BuPPPEt	7.2 (2:1)	−1.2
3	PPPEt	14 (1.2:1)	−1.6
4	EtPPP	1100 (1:10)	−4.1
5	PPP	>4200 (1:>20)	< −4.9

[a] Reaction conditions: [Pt] = 0.027 M, $[Ph_2NH_2][BF_4]$ = 0.27 M,[1] = 0.27 M, 25(1) °C (see Supporting Information). [b] Relative concentrations determined by ^{31}P NMR. Average of three measurements.

(20) Chemical shifts are given for the central P of the triphosphine ligand. This signal is the most diagnostic as the chemical shifts for the terminal phosphines in the Pt(η^2-alkenyl) and the Pt(alkyl) overlap.

(21) Over time in CH_2Cl_2, the ^{31}P NMR spectrum became more complex as chloride abstraction from the solvent generated (EtPPPEt)PtCl (J_{Pt-P} = 3030 Hz), among other decomposition species, see: (a) Liaw, B.; Lobana, T. S.; Lin, Y.; Wang, J.; Liu, C. W. *Inorg. Chem.* **2005**, *44*, 9921−9929. (b) Angulo, I. M.; Bouwman, E.; Lok, S. M.; Lutz, M.; Mul, W. P.; Spek, A. L. *Eur. J. Inorg. Chem.* **2001**, 1465−1473. (c) Oster, S. S.; Lachicotte, R. J.; Jones, W. D. *Inorg. Chim. Acta* **2002**, *330*, 118−124. (d) Wang, Q.; Marr, A. C.; Blake, A. J.; Wilson, C.; Schröder, M. *Chem. Commun.* **2003**, 2776−2777.

(22) The Pt(η^2-alkene) is observed in a 2:1 ratio which correlates to the *E*:*Z* ratio of diene **1** (Figure S1 of the Supporting Information). The complex upfield splitting of the Pt(η^2-alkene) is presumably a result of hindered rotation of the bound olefin by the terminal phosphine substituents. The same splitting pattern is observed in [(EtPPPEt)Pt(1-hexene)][BF_4]$_2$ (Figure S2).

(23) The equilibrium constant was calculated from the following equation where [Pt-alkyl] and [Pt(η^2-alkene)] were obtained from ^{31}P NMR: K_{eq} = ([Pt-alkyl][$Ph_2NH_2^+$])/([Pt(η^2-alkene)][Ph_2NH]).

(24) Equilibrium constant determinations were performed using a C_6D_6 solution of PPh_3 as an external standard (sealed capillary). No net loss of Pt(η^2-alkene) and Pt-alkyl was detected (other than to Pt-Cl in CH_2Cl_2). Additional experimental details are presented in the Supporting Information.

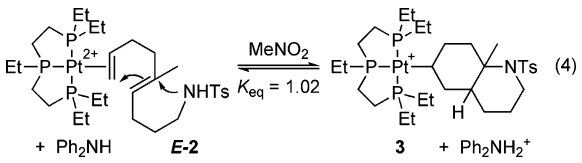
(25) While using **1** as a trapping ligand during protonolysis studies, there was no observation of a Pt(η^2-alkene) when using PPP or EtPPP as the supporting ligand; see ref 19.

(26) ^{31}P NMR data for these compounds is given in Table S1 of the Supporting Information.

equilibrium toward the monocationic Pt-alkyl species, a result of increased activation of the η^2-alkene form and the favorable pairing of the less basic ligand with the more donating alkyl. While no Pt(η^2-alkene) species (<5%) was detected for the most electrophilic case ((PPP)Pt^{2+}), the detectable limit of reversibility was observed using EtPPP as the tridentate ligand ($K_{eq} = 1100$; Figure S3 of the Supporting Information).

On the basis of the cyclization reaction, it was anticipated that stronger bases would drive the equilibrium toward the cyclized product and that stronger conjugate acids would promote retrocyclization to the Pt(η^2-alkene) complex. Experiments to confirm this were limited to bulky diaryl ammonium acids since the conjugate bases of smaller, more electron-rich ammonium acids ligate the metal and poison the complex. With (EtPPPEt)Pt^{2+}, the K_{eq} shifts from 0.68 (**A:B** = 14:1) using [Ph_2NH_2][BF_4] (Table 1), to 11 (**A:B** = 1.4:1) using [Ph_2NMeH]-[BF_4], consistent with the notion that a stronger base such as Ph_2NMe helps promote the cyclization.[27] Adding base or acid to a preequilibrated system also shifted the ratios of **A** and **B** in the expected fashion. Adding 5 equiv of Ph_2NH to a mixture where **A** predominated (entry 4, Table 1) decreased the **A:B** ratio from 14:1 to almost 2:1. Likewise, 5 equiv of [Ph_2NH_2]-[BF_4] shifted the equilibrium to the left; 1:10 to 1:4 (**A**:**B**).[28]

It was anticipated that ring strain in the cyclized organic moiety would also effect the equilibrium in a predictable manner. To investigate this factor, the dienyl sulfonamide ***E*-2**, which should produce a less-strained 6,6 ring structure, was subjected to reversible conditions using (EtPPPEt)Pt^{2+}. The less-strained aza-decalin structure did indeed shift the equilibrium toward the cyclized complex **3** ($K_{eq} = 1.0$; eq 4);[29] however, the magnitude of the shift was less than expected based on generic ring-strain measures (6.3 kcal/mol for *cis*-hydrindan versus −1.9 kcal/mol for *trans*-decalin).[30]



(4)

Stereocontrol in Reversible Polycyclizations. As discussed above, the PPP complex smoothly reacts with 1 equiv of **(*E*:*Z*)-1** to generate alkyl complex **4** with no trace of η^2-alkene (eq 5). This complex was isolated as its BF_4^- salt and characterized by X-ray crystallography. The ORTEP in Figure 2 clearly shows a cis ring juncture for the bicyclic fragment,[31] which contrasts the trans bicyclic products typically obtained from catalytic and stoichiometric cyclizations of *E*-alkenes.[32] To rule out the possibility of a selective cyclization of the minor *Z* isomer present in the 10 equiv of **(*E*:*Z*)-1** (which directly leads to the observed product via the SEP), ***E*-1** was synthesized

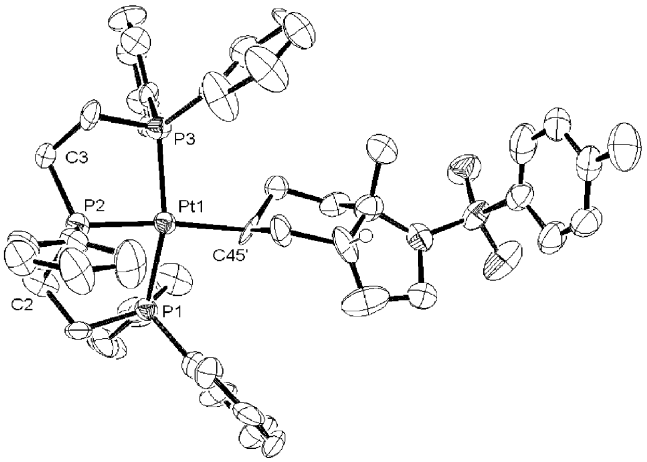
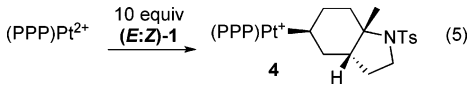


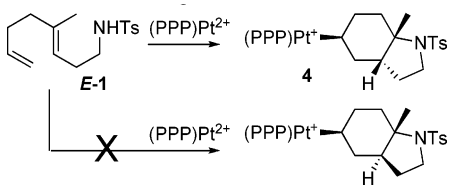
Figure 2. ORTEP representation of **4**. Hydrogen atoms and BF_4^- counterion removed for clarity. Selected bond lengths (Å): Pt−P_1 = 2.269-(4), Pt−P_2 = 2.247(3), Pt−P_3 = 2.308(4), Pt−C_{45} = 2.150(1). Selected bond angles (deg): P_1−Pt−P_2 = 84.51(16), P_2−Pt═P_3 = 84.63(16), P_1−Pt−C_{45} = 92.2(4), P_3−Pt−C_{45} = 100.6(4), C_3−P_2−C_2 = 117.0(6).



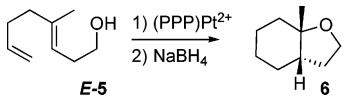
(5)

and cyclized (Scheme 2). By ^{31}P NMR the Pt-alkyl obtained from this reaction was identical to **4**, indicating that both stereoisomers of **1** converge to a single product. This result clearly conflicts with the notion of a concerted cyclization that follows the Stork−Eschenmoser postulate, both because only one product is obtained and because it requires an intermediate-(s) capable of converging the *E* and *Z* isomers of **1** into a single stereoisomer of **4** (vide infra).

Scheme 2



The primary alcohol version of ***E*-1**, ***E*-5**, was also examined as a substrate using the (PPP)Pt^{2+} complex obtained by $HNTf_2$ activation of [(PPP)Pt−Me][BF_4]. In the presence of 1 equiv of Ph_2NMe, compound ***E*-5** cyclized smoothly to a single alkyl product. Cleavage of the bicycle using $NaBH_4$ generated the *cis*-fused octahydrobenzofuran **6**, a product corresponding to a Pt-alkyl that again cannot be the primary cyclization product of ***E*-5** since the SEP predicts a trans ring junction (eq 6). Similar to the cyclization of ***E*-1**, the isolated product is the thermodynamically more stable *cis*-[6,5] ring junction.

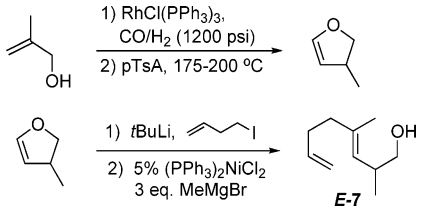


(6)

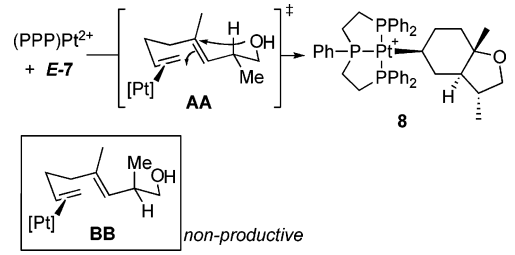
To investigate how existing stereocenters, especially those on remote positions of the polyene, would influence the diastereoselectivity of the cyclization reactions, several readily available dienyl and trienyl alcohols were synthesized.[33] The

(27) DFT calculations on a 1,6-dienyl phenol indicated that in the presence of base, cyclization was semi-concerted. Nowroozi-Isfahani, T.; Musaev, D. G.; Morokuma, K.; Gagné, M. R. *Organometallics* **2007**, *26*, 2540−2549.
(28) These results are presented in Table S2 of the Supporting Information.
(29) We presume an equatorially disposed Pt-C bond in each case.
(30) (a) Wiberg, K. B. *Angew. Chem., Int. Ed.* **1986**, *25*, 312−322. (b) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637−1648.
(31) This structure displays the largest C−P−C angle deviations for PPP at the central phosphorus (117.0°). For a discussion on the importance of C−P−C bond angles, see ref 19.
(32) Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880−11881. Also see refs 10 and 12.
(33) Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682−10691.

Scheme 3



Scheme 4



1,5-dienyl alcohol ***E*-7**, bearing a methyl group β to the trapping −OH, was synthesized as shown in Scheme 3. It underwent rapid cyclization (<20 min) with $(PPP)Pt^{2+}$ (Scheme 4) to generate one cationic (PPP)Pt-alkyl product (**8**) by ^{31}P NMR (89.6 ppm, $J_{Pt-P} = 1316$ Hz), with no evidence for the intermediacy of other compounds.[34] As expected from the previous results with $(PPP)Pt^{2+}$ and **1**, no Pt(η^2-alkene) was observed in the ^{31}P NMR. In contrast to the above cases, however, crystallographic (X-ray) analysis revealed that **8** had a trans ring juncture and a pseudo-equatorially disposed methyl group on the furan ring (Figure 3). The product thus appears to be that predicted from a *concerted*, chairlike transition state that positions the methyl group in a pseudo-equatorial position (**AA**, Scheme 4). The observed 3,5-trans relationship[35] indicates efficient 1,6-stereoinduction, and since one would expect no diastereofacial preference in the alkene coordination step, it also indicates that the **BB** diastereomer either does not cyclize or it rapidly reverts back to starting material upon doing so.[36]

An illuminating observation was made when ***E*-7** was reacted with $[(EtPPP)Pt][BF_4]_2$ under the standard $AgBF_4$ activation conditions. Instead of a smooth conversion to a single alkyl product (or an equilibrium mixture of η^2-alkene and alkyl), the ^{31}P NMR spectrum indicated, after 3 h at RT, a mixture of Pt-(η^2-alkene) at 100.4 ppm ($J_{Pt-P} = 2904$ Hz) and two Pt-alkyl species at 90.9 ($J_{Pt-P} = 1241$ Hz) and 90.2 ppm ($J_{Pt-P} = 1239$ Hz) in a 1:1 ratio. Over time, this mixture converged to a single Pt-alkyl (**9**) at 90.9 ppm (Figure 4) with no trace of the η^2-alkene.

Upon completion of this reaction, **9** was isolated and crystallographically characterized. As shown in Figure 5, the bicyclic fragment has the cis ring junction, and is thus similar to **4** and **6**. As in the case of **4**, **9** has Pt in an equatorial position on the cyclohexyl A-ring and the heteroatom in a 1,4-trans relationship (see Figure 2 for comparison).[37] Additionally, similar to **4** and **6**, the stereochemical outcome cannot be explained by a simple rearrangement (vide infra). When this reaction was stopped after 3 h and treated with $NaBH_4$, it was determined (by GC) that the early forming product was the same trans isomer obtained by cleavage of the cycloalkyl in **8** (see Supporting Information).

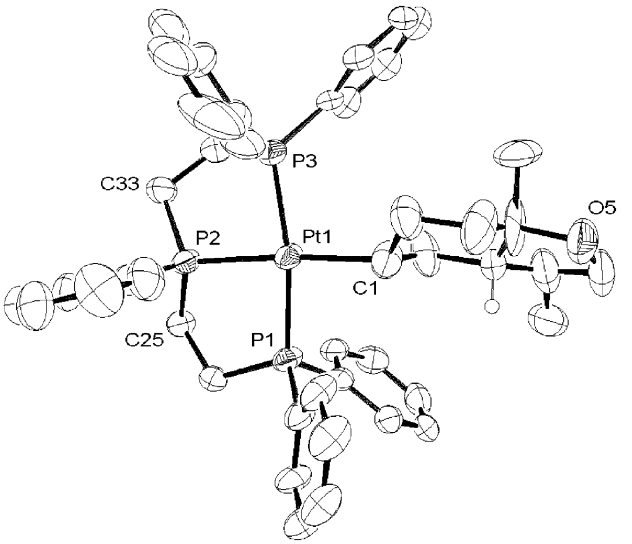


Figure 3. ORTEP representation of **8**. Hydrogen atoms and BF_4^- counterion omitted for clarity. Selected bond lengths (Å): $Pt-P_1 = 2.262(3)$, $Pt-P_2 = 2.290(3)$, $Pt-P_3 = 2.290(3)$, $Pt-C_1 = 2.158(11)$. Selected bond angles (deg): $P_1-Pt-P_2 = 84.80(10)$, $P_2-Pt-P_3 = 83.15(10)$, $P_1-Pt-C_1 = 90.6(4)$, $P_3-Pt-C_1 = 101.7(4)$, $C_{27}-P_2-C_{33} = 112.2(5)$.

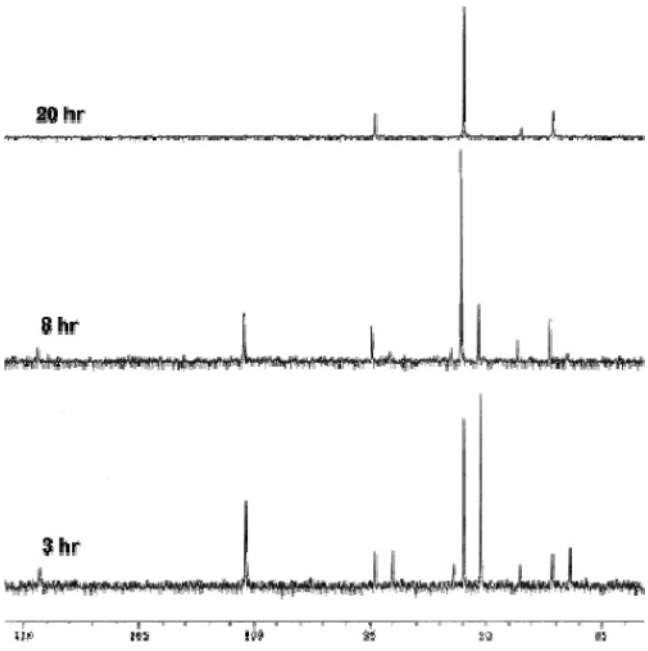


Figure 4. ^{31}P NMR stack plot of the cyclization of ***E*-7** with $(EtPPP)Pt^{2+}$.

To ascertain if the stereoselective reactivity would extend to a tricyclization, the trienol ***E,E*-10**, bearing a −Me substituent β to the trapping −OH on the nascent C-ring, was examined (Scheme 5). The trienol could be efficiently obtained by a sequence of dihydrofuran metalation/alkylation followed by Ni-catalyzed ring opening.[38] A priori, one expects a larger driving force for the complete cyclization of a tricycle as compared to

(34) No detectable quantities of a second isomer was observed either at very short or very long reaction times.
(35) Benzofuran naming convention.
(36) For clarity, the same diastereoface is used with the opposite C-2 stereocenter in Scheme 4, **BB**.
(37) The C−P−C bond angle at the central phosphorus is reduced in **7** (110.8°) compared to **2** (117.0°), which we have previously taken to indicate less strain at the central phosphorus for this square planar complex (ref 19).

(38) Kocienski, P.; Wadman, S.; Cooper, K. *J. Org. Chem.* **1989**, *54*, 1215−1217.

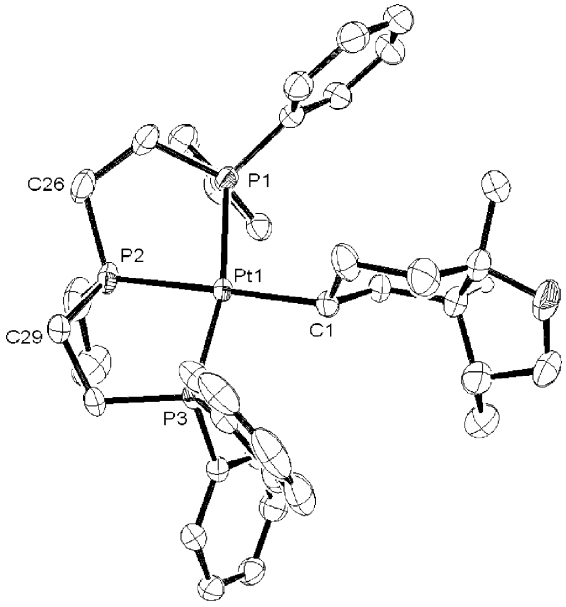
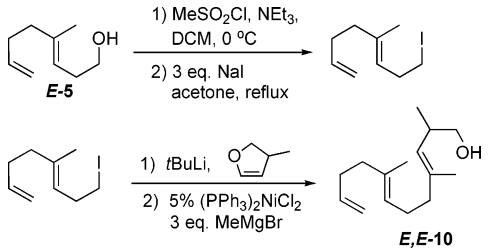
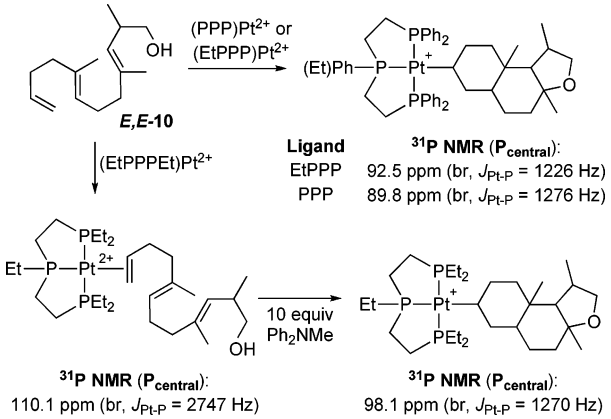


Figure 5. ORTEP representation of **9** with hydrogen atoms and BF_4^- counterion omitted for clarity. Selected bond lengths (Å): Pt−P_1 = 2.3032(8), Pt−P_2 = 2.3016(8), Pt−P_3 = 2.2722(8), Pt−C_1 = 2.134(3). Selected bond angles (deg): 101.07(9), P_3−Pt−C_1 = 90.04(9), C_{26}−P_2−C_{29} = 110.85(18).

Scheme 5



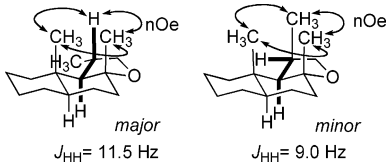
Scheme 6



***E*-7**. The $\Delta H_{cyclization}$ for ***E,E*-10** is relatively straightforward (~20 kcal/mol more negative than ***E*-7**), and although $\Delta S_{cyclization}$ will certainly be more negative, it is difficult to estimate by how much.[1d] In any case, one can reasonably predict a more negative free energy for a tricyclization than a bicyclization, which would then tend to favor alkyl products over the Pt(η^2-alkene) provided that the reaction is kinetically feasible.

Scheme 6 shows the reaction of ***E,E*-10** with the (EtPPPEt)-Pt^{2+}, (EtPPP)Pt^{2+}, and (PPP)Pt^{2+} cyclization initiators. ^{31}P NMR analysis of the combination of (EtPPPEt)Pt^{2+} and ***E,E*-10** under standard reaction conditions showed that although the Pt(η^2-alkene) complex forms normally, it does not cyclize. Ten additional equiv of Ph_2NMe pushes the reaction to ~90% Pt-alkyl and 10% Pt(η^2-alkene); however, additional amine did not complete the reaction. Adding 10 equiv of [Ph_2NHMe][BF_4] to this solution did not change the ratio of Pt-alkyl to Pt(η^2-alkene), suggesting a poorly behaved, but static mixture (cf. ***E*-7**).[39] In contrast, the cyclization of ***E,E*-10** occurred smoothly when the more electron-withdrawing EtPPP and PPP ligands were used. Since the ^{31}P NMR for the (PPP)Pt-alkyls were broad, the cyclization diastereoselectivity was determined by first cleaving the tricycle with $NaBH_4$ and then analyzing by GC. This protocol yielded a 2:1 ratio of diastereomers that were inseparable by column chromatography, but whose structures could be ascertained by careful NMR analysis. These data are most consistent with the major diastereomer having the trans-anti-trans core with the C-ring methyl substituent adopting a pseudo-equatorial orientation, while the minor was most consistent with the trans-anti-trans tricycle having three axial methyl groups (Scheme 7).[40]

Scheme 7



Discussion

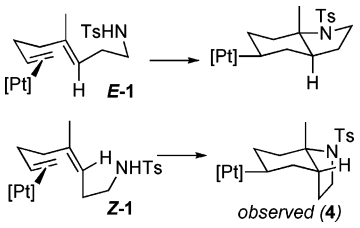
Reversible Polycyclizations using a 1,5-Dienyl Sulfonamide. The reversible cyclization of **1** proved to be a useful tool for establishing the effect of reaction conditions and metal-complex electronics on the thermodynamics of cation−olefin cyclization. Taken together, the data paint an internally consistent picture wherein acid/base strengths, ring strain, ligand basicity, Pt-electrophilicity, and solvent effects all have a predictable effect on the driving force for cascade cyclization. Not surprisingly, cyclization was favored by less polar solvents, more electrophilic metals, stronger bases, and a less strained bicyclic product. The data quantitatively describe the magnitude of these effects while guiding the choice of conditions to establish a reversible cyclization reaction for examining the effect of existing stereogenic centers on cation-olefin polycyclization diastereoselectivities.

Since **(*E*:*Z*)-1** is a 2:1 mixture of *E* and *Z* isomers, generating two diastereomeric Pt-alkyls, one with a trans ring juncture and one with a cis ring juncture, should be possible (Scheme 8). Only one Pt-alkyl was observed by ^{31}P NMR, suggesting that either ***Z*-1** cyclized directly to **4** (Scheme 8) or that ***E*-1** first cyclizes to a trans product and then subsequently isomerizes to the observed product, or both. The smooth conversion of ***E*-1** to **4** (Scheme 2) suggests that the former case is not dominant. Since ***Z*-1** does not build up in the ^{1}H NMR of the ***E*-1** reaction, this eliminates the possibility of a reversible precyclization *E*/*Z*

(39) ^{31}P NMR analysis indicated no decomposition, and so the stoppage is difficult to explain.

(40) Molecular mechanic calculations (AM1, MacSpartan 04) on the minor isomer indicated that the THF β-methyl adopts a position to minimize unfavorable Me−Me interactions, which consequently reduces the key H−C−C−H dihedral angle to 35°. The calculated J_{HH} in this orientation is 6.7 Hz, which helps to explain the unusually large observed coupling constant (9.0 Hz). See: Kemp, W. *Organic Spectroscopy*; W. H. Freeman and Company: New York, 1991, pp 154−155.

Scheme 8



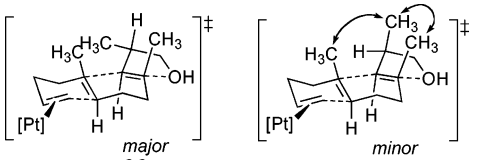
isomerization. It is important to note that isomerization of the *trans* product in Scheme 8 to **4** is not as simple as acid-promoted ionization of the C−N bond and recoordination to the opposite face, as this scenario provides an unobserved diastereomer where the [Pt] and N have a 1,4-cisoid arrangement instead of 1,4-transoid.

The set of experiments carried out on the methylated compound ***E*-7** was mechanistically revealing. Under conditions that minimized retro-cyclization (electron-poor PPP ligand), a single product with a trans ring junction was observed. We favor the hypothesis wherein this is the "kinetic" product, and that it proceeds through the most favorable chair−pseudo-chair transition state **I**, which places the B-ring methyl group in a pseudo-equatorial orientation (**8**, Scheme 9). We qualify the term "kinetic" in this case because under irreversible conditions, one should observe some of the less favored axial methyl product (from **BB**, Scheme 4) since diastereofacial control on η^2-alkene formation should be low. If this product does form, then it reverts to starting material and eventually traps at **8**; nevertheless, we consider this chair−chair product the kinetic product and will refer to it as such (Scheme 9). We suspect that this chair−chair arrangement leads to the kinetic product in each of the cases studied herein, although as outlined below, it may convert to a more stable isomer under certain conditions.

When the triphosphine is more electron-rich than PPP, a scenario conducive to retrocyclization, the kinetic product converts to the more stable *cis* product **9**. Since **9** does not result from a simple ionization of the C−O bond and recoordination to the opposite face of the carbenium ion (leading to **III**), a more complex sequence of steps is needed to invert the C3 stereocenter. One potential mechanism is outlined in Scheme 9, the key steps being a retrocyclization of **8** and re-cyclization via the boat transition state **IV** to **V**, which then ionizes and recoordinates to form **9**.[41] By invoking a boat transition state followed by C−O fragmentation and reformation, it is possible to access a cis ring junction from an *E*-alkene, and thus avoid the constraints of the SEP. The potential for boat-like transition states was previously hinted at in the cyclization of a diene-phenol by (PPP)Pt^{2+} (eq 2). The diastereoselectivity in this reaction was 96:4, and >99:1 after cleavage of the bicycle with $NaBH_4$, a result which was interpreted as being due to competing chair−chair and boat−chair transition structures.[12,41,42] The importance of a B-ring boat transition state is well established in sterol biosynthesis.[1] In the present case, **IV** is higher in energy than **I** and is normally noncompetitive when retrocyclization is slow.

A similar sequence of steps was likely responsible for the formation of **4** and the Pt-alkyl that resulted from the cyclization of ***E*-5**. Less obvious was why ***E*-5** converted to the cis product using (PPP)Pt^{2+}, while ***E*-7** did not. It is possible that the single methyl group on the THF ring reduced the rate of ring opening (an attenuated Thorpe−Ingold effect), with a concomitant lowering of the Pt(η^2-alkene) concentration such that the kinetic product is temporally stabilized. This question will require more experimentation.

While a good case can be made for reversibility affecting the diastereoselectivity of bicyclization reactions, the same was not true for the tricyclization of ***E,E*-10**. Interestingly, under standard reaction conditions, the more electron-rich ligand EtPPPEt was incapable of initiating the cyclization, though it could with 10 equiv of the stronger base Ph_2NMe. With more electron poor ligands, however, a smooth conversion to alkyl products ensued and the diastereoselectivity could be ascertained by cleavage and GC analysis (2:1 dr). Careful NMR analysis of the diastereomer mixture pointed to products of the chair−anti-chair conformation, with the mixture occurring at the beta carbon of the THF ring (pseudo-axial and -equatorial). Although modest, this 2:1 selectivity represents 1,10-stereoinduction,[8] and since the reaction is apparently irreversible,[43] it requires a different rate of cyclizing the two diastereomeric acyclic activated complexes (**CC** and **DD**), consistent with Bartlett's assertion that long-range stereocontrol in sterol cyclizations comes from developing intra-ring interactions in the organizing assembly.[1d] Additionally consistent with a concerted cyclization was the formation of trans-anti-trans products, as reversibility in the C−O bond forming step would access the more stable [6.6.5]-trans-anti-cis products.[44]



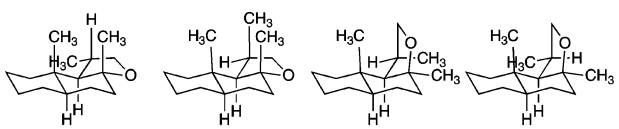
The marked difference in reactivity between the phosphine ligands in bi- vs tricyclization was intriguing. In the former case, the ligands can each catalyze the cyclization, and the observed effect of ligand basicity is on the position of the equilibrium. In the tricyclization case, however, the electron-rich EtPPPEt cannot initiate cyclization (standard conditions), whereas the

(41) Molecular mechanics indicate that the chair conformer of cyclohexane is more stable than the boat conformer by 6.4 kcal/mol, see: (a) Allinger, N. L.; Miller, M. A.; VanCatledge, F. A.; Hirsch, J. A. *J. Am. Chem. Soc.* **1967**, *89*, 4345−4357. (b) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127−8134.

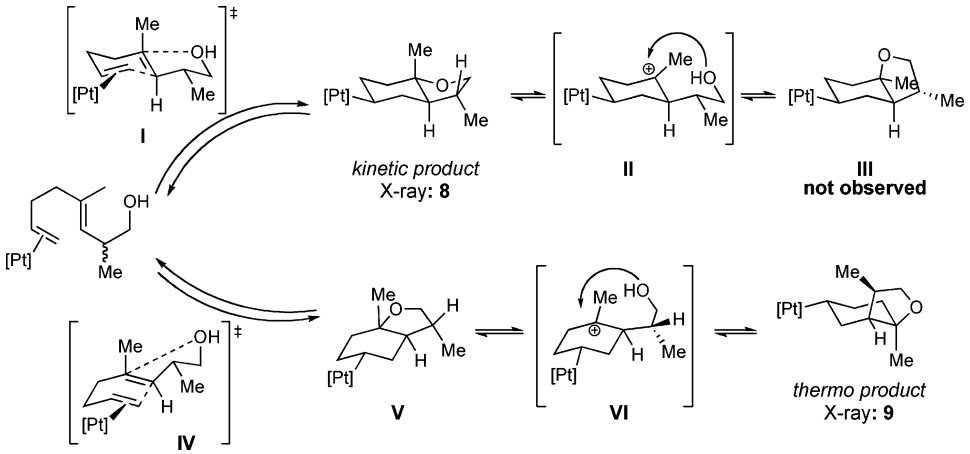
(42) Ref 12 also describes a similar situation with a pyridyl-bisphosphine (PNP) pincer ligand on Pd^{2+}, which gives an initial diastereoselectivity of 93:7 and >99:1 after cleavage. Since both diastereoisomers converge to the same trans product, the initial dr was interpreted as reflecting the boat−chair vs. chair−chair preference.

(43) Since the forward rate is too slow for EtPPPEt under standard conditions, and additional stronger base is poorly behaved, we have not been successful at rigorously proving that the tricyclization is irreversible. However, the expected larger driving force for tri- versus bicyclization, the significant difference in the ground state structures of model structures (ref 44), and the modest dr all suggest otherwise.

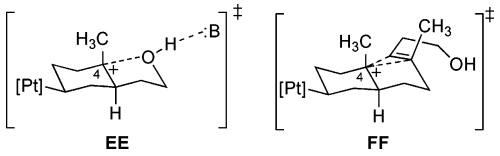
(44) Hartree-Fock calculations (6−31G*) indicate the following ground state relative energies (kcal/mol). Calculations were carried out using MacSpartan 04. The trans-anti-cis structures were not considered viable since a strong nOe between the angular CH_3 and the CH_3 α to the THF oxygen was observed in both diastereomers.



Scheme 9



less basic EtPPP and PPP ligands do so smoothly. This difference can be understood by noting that the bicyclization is not a true cation−olefin reaction since no developing carbenium ion reacts with another alkene, though the activated terminal alkene certainly behaves like one. The developing positive charge at C_4 is stabilized by the hydroxyl center, either with or without the aid of base (**EE**).[27] Since an alcohol will be a good neighboring group for stabilizing such a species, the reaction coordinate may proceed forward without needing to build up a large positive charge. Alternatively, B-ring formation in the tricyclization requires a genuine cation−olefin reaction, and since an alkene is a poorer ligand for the developing carbenium ion (**FF**), the degree of stabilization imparted by the neighboring group will be significantly lessened.[45] Moving the reaction coordinate forward in a tricyclization thus requires the buildup of more positive charge on C_4 to engage the alkene, which concomitantly requires a more electrophilic complex.



Systematically modifying the electrophilicity of the initiating Pt(η^2-alkene) complex in the cation−olefin cyclization provided the means for examining how the cyclization thermodynamics responded. Not surprisingly, the more electrophilic the initiating group, the more favorable is the cyclization. When the cyclization was reversible, high diastereoselectivities were observed, suggesting that this mechanism is indeed effective at error correcting and promoting long-range transfer of stereochemical information.[46] Moreover, when the cyclizations are reversible, alternative reaction pathways are explored that may access more stable products not otherwise accessible under the kinetic control of a typical cascade cyclization that is constrained by the SEP. The ability of pincer-ligated platinum(II) complexes to achieve this enables the formation of cis-ring fused bicyclic complexes that are not predicted by the SEP. Tricyclizations, however, were too favorable to find conditions where the η^2-alkene form was stable enough to enable retrocyclization and electrophilic enough to initiate the forward cascade cyclization.

Acknowledgment. We thank the National Institutes of Health Institute of General Medicine for support of this research. We thank Dr. Peter White for X-ray structural determinations; correspondence regarding them should be directed to his attention at UNC Chapel Hill (pwhite@unc.edu). We also thank Dr. Marc ter Horst (UNC Chapel Hill NMR Facility) and Dr. Tony Ribeiro (Duke University NMR Center) for extensive help with NMR analysis on the mixture of diastereomers produced from the cyclization and subsequent cleavage of **10**.

Supporting Information Available: Tables and Figures for equilibrium studies including sample ^{31}P NMR spectra, full experimental procedures, and X-ray structural data for **4**, **8**, and **9**. This material is free of charge via the Internet at http://pubs.acs.org.

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(45) Such non-classical carbocations form the basis of the early experimental rationalizations for the non-concerted, but stereospecific, cascade cyclizations. See refs 1a, 2, and 3.

(46) For a classic example of this phenomenon in acid promoted bicyclization of farnesic acid derivatives, see: Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191−2198. See also ref 1a.