

REPORT DOCUMENTATION PAGE			Form Approved OMB NO. 0704-0188		
The public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA, 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY)		2. REPORT TYPE New Reprint		3. DATES COVERED (From - To) -	
4. TITLE AND SUBTITLE Terminating Platinum-Initiated Cation-Olefin Reactions with Simple Alkenes			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER W911NF-04-D-0004		
			5c. PROGRAM ELEMENT NUMBER 611102		
6. AUTHORS Joseph G. Sokol, Chandra Sekhar Korapala, Peter S. White, Jennifer J. Becker, Michel R. Gagné			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAMES AND ADDRESSES University of North Carolina - Chapel Hill Office of Sponsored Research The University of North Carolina at Chapel Hill Chapel Hill, NC 27599 -1350			8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Research Office P.O. Box 12211 Research Triangle Park, NC 27709-2211			10. SPONSOR/MONITOR'S ACRONYM(S) ARO		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S) 55041-CH-SR.8		
12. DISTRIBUTION AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.					
13. SUPPLEMENTARY NOTES The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other documentation.					
14. ABSTRACT All for one. Phosphine ligated platinum(II) electrophiles can activate poly-alkenes for cyclase enzyme mimicking cascade cyclizations without the need for special terminating groups. Like the cyclase enzymes, terminal alkenes that generate tertiary cations are good substrates, though the details of the cation termination depend on the alkene arrangement.					
15. SUBJECT TERMS catalysis, poly-ene cyclizations					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON Jennifer Becker
a. REPORT UU	b. ABSTRACT UU	c. THIS PAGE UU			19b. TELEPHONE NUMBER 919-549-4224

Report Title

Terminating Platinum-Initiated Cation-Olefin Reactions with Simple Alkenes

ABSTRACT

All for one. Phosphine ligated platinum(II) electrophiles can activate poly-alkenes for cyclase enzyme mimicking cascade cyclizations without the need for special terminating groups. Like the cyclase enzymes, terminal alkenes that generate tertiary cations are good substrates, though the details of the cation termination depend on the alkene arrangement.

REPORT DOCUMENTATION PAGE (SF298)
(Continuation Sheet)

Continuation for Block 13

ARO Report Number 55041.8-CH-SR

Terminating Platinum-Initiated Cation-Olefin Rea ...

Block 13: Supplementary Note

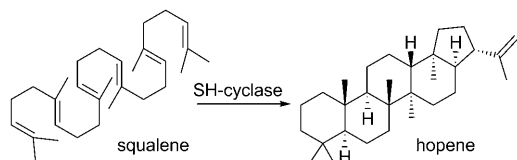
© 2011 . Published in Angewandte Chemie International Edition, Vol. Ed. 0 50, (25) (2011), ((25). DoD Components reserve a royalty-free, nonexclusive and irrevocable right to reproduce, publish, or otherwise use the work for Federal purposes, and to authorize others to do so (DODGARS §32.36). The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other documentation.

Approved for public release; distribution is unlimited.

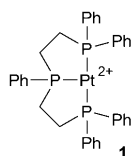
Terminating Platinum-Initiated Cation-Olefin Reactions with Simple Alkenes**

Joseph G. Sokol, Chandra Sekhar Korapala, Peter S. White, Jennifer J. Becker, and Michel R. Gagné*

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

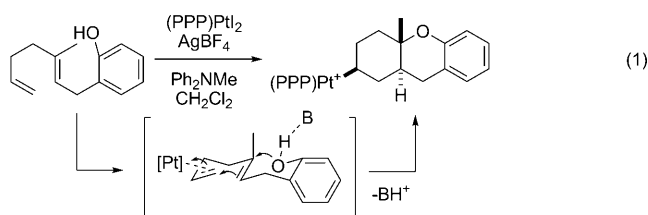


Herein, we describe the development of an alkene-terminated cation-olefin cascade reaction that is initiated by the dicationic platinum complex [(PPP)Pt][BF₄]₂ (PPP = bis-(2-diphenylphosphanylethyl)phenylphosphane), **1**.^[9] Compound **1** is especially efficient at initiating cyclizations wherein the polyene carries a monosubstituted alkene terminus.^[10] In addition to diastereoselectively forming polycyclic products with a broad variety of terminating alkenes, the reactions described herein contrast Hg^{II} reagents by the lack of premature termination processes.^[11]



Our research group previously reported that L_nPt²⁺ sources will initiate the cation-olefin cascade with subsequent termination

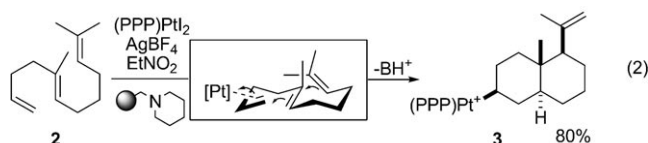
by the intramolecular addition of a protic trap [alcohol, phenol, or sulfonamide, for example; Eq. (1)].^[12] Computa-



tional analysis showed that when a base was hydrogen bonded to the protic terminus and the alkene was in a suitable geometry, the cyclization was highly favorable and virtually barrierless.^[13] In contrast, calculations under base-free conditions were characterized by high-energy intermediates and significantly less favorable thermodynamics.

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

The combination of a polar solvent (EtNO₂) and either Ph₂NMe or, more conveniently, a resin N-bound piperidine base led to an efficient and highly diastereoselective cyclization of triene **2** into **3** [Eq. (2)]. In contrast to protic terminators, however, the reaction proceeds much more



slowly [minutes for Eq. (1) vs. 36 hours for Eq. (2)], a difference which we interpret as reflecting the kinetic cost of generating a discrete tertiary cation.

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

[*] J. G. Sokol, Dr. C. S. Korapala, Dr. P. S. White, Prof. Dr. M. R. Gagné
Department of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-3290 (USA)
E-mail: mgagne@unc.edu

Dr. J. J. Becker
U.S. Army Research Office
P.O. Box 12211, Research Triangle Park, NC 27709 (USA)

[**] We thank the National Institutes of Health, General Medicine (grant no. GM-60578), and the Army Research Office for generous support.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201100463>.

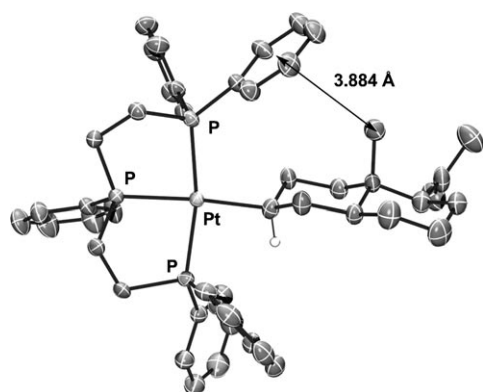


Figure 1. ORTEP plot of **3** showing the diagnostic interaction between the axial methyl group and the Ph ring at phosphorus. Thermal ellipsoids at 50% probability and hydrogen atoms are omitted for clarity.

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

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



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

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

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

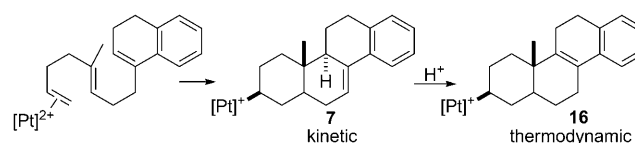
Table 1: Yields and scope of polyene cyclizations initiated by dicationic platinum complex **1**.

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

[a] Reaction conditions: $(\text{PPP})\text{Pt}_2^{2+}$, 2 equivalents of substrate, 2.5 equivalents of AgBF_4 , 3 equivalents of piperidine resin base, and EtNO_2 . [b] $[\text{Pt}]^+ = [(\text{PPP})\text{Pt}]^+$. [c] Yield of isolated product.

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

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



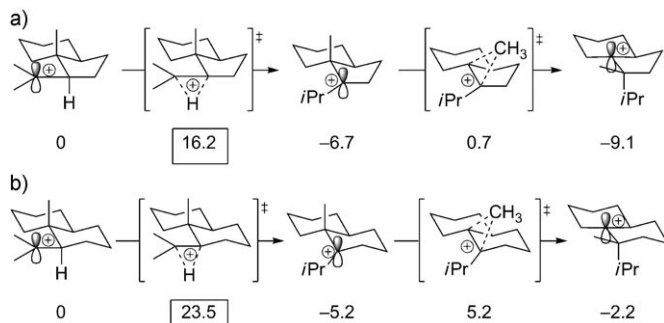
Scheme 2. Reaction termination by selective deprotonation.

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

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

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

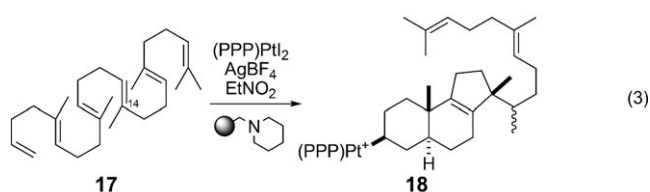
To gain insight into the diverging behavior of 6-*exo* and 5-*exo* terminated reactions, a computational analysis (DFT B3LYP/6-31G*)^[23] of the key 1,2-shifts was carried out on simplified model systems (Scheme 3). Revealing was the



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

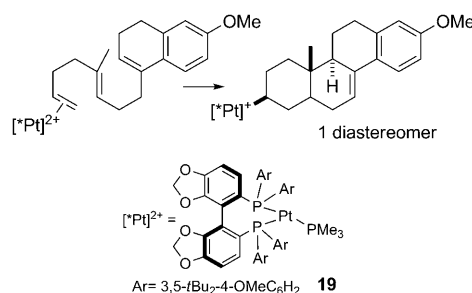
differential activation energy for the initiating 1,2-hydride shift, which was 7.3 kcal mol⁻¹ more favorable for the 5-*exo* terminated ring systems than for the 6-*exo*. The subsequent steps were lower in energy, thus suggesting that it is the slower initiating 1,2-hydrogen transfer in the 6,6 case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

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



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

The viability of performing an asymmetric cascade cyclization was investigated using the chiral [P₂PPt]²⁺ complex (P₂ = DTBM-SEGPHOS, P = PMe₃) **19**. The combination of a chiral P₂ ligand and an achiral monodentate phosphine has been previously shown to catalyze cyclo-rearrangement reactions with high enantiomeric excess.^[27] When **19** was treated with **8** under the standard conditions (Table 1), NMR spectroscopy indicated that a single stereoisomer was obtained (¹H, ³¹P), i.e. the chiral initiator



efficiently and diastereoselectively activates a single olefin face.

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

Experimental Section

Standard cyclization reaction: To 30 mg of [(PPP)PtI₂] was added 15 mg of AgBF₄ followed by 0.75 mL of EtNO₂. The mixture was then stirred for 1 h in the dark. The contents were filtered through a 0.2 μm PTFE syringe filter, washing out the flask and syringe with 0.25 mL EtNO₂, into a flask containing 2 equiv of substrate and 3 equiv of piperidine resin. The reaction mixture was stirred in the dark until the reaction was complete (3–48 h, verified by ³¹P NMR spectroscopy). The reaction mixture was passed through a 0.2 μm PTFE syringe filter, washing out the flask and syringe filter with 0.25 mL EtNO₂. Solvent was then removed under a stream of N₂. The complex was twice reconstituted in a minimum amount of CH₂Cl₂ and force precipitated with cold *t*BuOMe. The mixture was centrifuged and the solvent was decanted off. The crude residue was purified by flash column chromatography on silica gel.

Received: January 19, 2011

Published online: May 5, 2011

Keywords: biomimetic synthesis · cascade cyclization · electrophilic activation · platinum

- [1] a) K. U. Wendt, G. E. Schulz, E. J. Corey, D. R. Liu, *Angew. Chem.* **2000**, *112*, 2930–2952; *Angew. Chem. Int. Ed.* **2000**, *39*, 2812–2833; b) W. S. Johnson, *Acc. Chem. Res.* **1967**, *1*, 1–8; c) P. A. Bartlett in *Asymmetric Synthesis*, Vol. 3 (Ed.: J. D. Morrison), Academic Press, New York, **1984**, pp. 341–409; d) P. A. Bartlett in *Asymmetric Synthesis*, Vol. 3 (Ed.: J. D. Morrison), Academic Press, New York, **1984**, pp. 411–454.
- [2] R. A. Yoder, J. N. Johnston, *Chem. Rev.* **2005**, *105*, 4730–4756.
- [3] a) M. Uyanik, H. Ishibashi, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, *7*, 1601–1604; b) S. Nakamura, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8131–8140.
- [4] a) A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007**, *445*, 900–903; S. H. Kang, S. B. Lee, C. M. Park, *J. Am. Chem. Soc.* **2003**, *125*, 15748–15749.

- [5] a) R. R. Knowles, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 5030–5032; b) S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027–5029.
- [6] a) S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277; b) C. A. Mullen, A. N. Campbell, M. R. Gagné, *Angew. Chem.* **2008**, *120*, 6100–6103; *Angew. Chem. Int. Ed.* **2008**, *47*, 6011–6014; c) P. Y. Toullec, T. Blarre, V. Michelet, *Org. Lett.* **2009**, *11*, 2888–2891.
- [7] Hg(OTf)₂ cyclizes polyenes in a stepwise fashion that produces partially cyclized products. See for example: H. Takao, A. Wakabayashi, K. Takahashi, H. Imagawa, T. Sugihara, M. Nishizawa, *Tetrahedron Lett.* **2004**, *45*, 1079–1082.
- [8] K. Surendra, E. J. Corey, *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869.
- [9] a) A. R. Chianese, S. J. Lee, M. R. Gagné, *Angew. Chem.* **2007**, *119*, 4118–4136; *Angew. Chem. Int. Ed.* **2007**, *46*, 4042–4059; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449.
- [10] For important contributions to dicationic pincer-platinum alkene activations, see: a) C. Hahn, M. E. Cucciolito, A. Vitagliano, *J. Am. Chem. Soc.* **2002**, *124*, 9038–9039; b) C. Hahn, *Chem. Eur. J.* **2004**, *10*, 5888–5899, and references therein.
- [11] Premature termination of a polyene cyclization can be viewed as an alkene terminated reaction.
- [12] a) J. H. Koh, M. R. Gagné, *Angew. Chem.* **2004**, *116*, 3541–3543; *Angew. Chem. Int. Ed.* **2004**, *43*, 3459–3461; b) J. H. Koh, C. Mascarenhas, M. R. Gagné, *Tetrahedron* **2004**, *60*, 7405–7410.
- [13] T. Nowroozi-Isfahani, D. G. Musaev, K. Morokuma, M. R. Gagné, *Organometallics* **2007**, *26*, 2540–2549.
- [14] Allylsilanes, enolsilanes, enolethers, vinyl fluorides, and vinyl silanes have previously been used as relatively polarized alkene terminators, see references [1, 2, 8, and 16].
- [15] We have previously reported the cycloisomerization of dienes by Pt^{II} wherein a terminal carbenium ion was proposed. See for example: a) W. D. Kerber, J. H. Koh, M. R. Gagné, *Org. Lett.* **2004**, *6*, 3013–3015; b) W. D. Kerber, M. R. Gagné, *Org. Lett.* **2005**, *7*, 3379–3381.
- [16] See the Supporting Information for X-ray data. CCDC c08276 (3), c08373 (9), x1007026 (11), c08380 (13), and c08394 (15) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [17] For examples of simple alkene terminators in classic Johnson cyclizations, see: a) R. L. Carney, W. S. Johnson, *J. Am. Chem. Soc.* **1974**, *96*, 2549; b) W. S. Johnson, L. A. Bunes, *J. Am. Chem. Soc.* **1976**, *98*, 5597; c) W. S. Johnson, G. W. Daub, T. A. Lyle, M. Niwa, *J. Am. Chem. Soc.* **1980**, *102*, 7800–7802.
- [18] H. Mayr, B. Kempf, A. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77.
- [19] MeAlCl₂-initiated cyclization of the terminal epoxy analogue of **8** gave both the tri- and tetrasubstituted alkenes, see reference [8].
- [20] J. A. Feducia, A. N. Campbell, J. W. Anthis, M. R. Gagné, *Organometallics* **2006**, *25*, 3114–3117.
- [21] J. A. Feducia, M. R. Gagné, *J. Am. Chem. Soc.* **2008**, *130*, 592–599.
- [22] For a contrasting example see compound **30** in reference [8].
- [23] MacSpartan 2008 calculations; energies were uncorrected.
- [24] For recent high-level computational studies of cation-olefin reactions and rearrangements in terpene biosynthesis, see: D. J. Tantillo, *Chem. Soc. Rev.* **2010**, *39*, 2847–2854, and references therein.
- [25] a) B. A. Hess, Jr., L. Smentek, *Org. Lett.* **2004**, *6*, 1717–1720; b) R. Rajamani, J. Gao, *J. Am. Chem. Soc.* **2003**, *125*, 12768–12781.
- [26] E. E. van Tamelen, *Acc. Chem. Res.* **1974**, *8*, 152–158. See also, reference [7].
- [27] J. A. Feducia, A. N. Campbell, M. Q. Doherty, M. R. Gagné, *J. Am. Chem. Soc.* **2006**, *128*, 13290–13297.