

Diastereoselective Pt Catalyzed Cycloisomerization of Polyenes to Polycycles

Michael J. Geier and Michel R. Gagné*

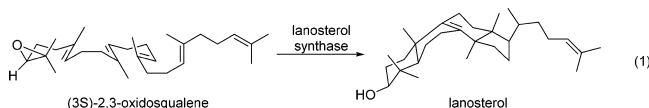
Caudill Laboratories, Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

Supporting Information

ABSTRACT: Application of a tridentate NHC containing pincer ligand to Pt catalyzed cascade cyclization reactions has allowed for the catalytic, diastereoselective cycloisomerization of biogenic alkene terminated substrates to their polycyclic counterparts.

The construction of complex polycyclic hydrocarbon frameworks from simple polyene substrates by cyclaze enzymes (e.g., eq 1) has long been the envy of synthetic chemists.¹ The remarkably selective fashion in which products are formed has attracted a variety of biomimetic approaches.² Of note are recent reports in which cyclization is initiated by organocatalysts,³ M⁺,⁴ H⁺,⁵ and X⁺ reagents.⁶

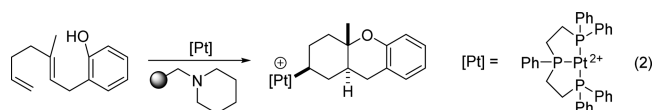
The formation of polycycles via cascade cyclization reactions has long benefitted from the installation of nucleophilic terminating groups, which enhance the efficiency of the cyclization.^{1,2} By contrast, the cyclization of strictly hydrocarbon containing substrates must overcome the lack of H-bond assistance in the terminating alkene, often leading to slow reactions and incomplete cyclization. While aryl terminating groups have been well tolerated as a result of cation- π stability,^{4a,e,5a,b,6a,b} few examples of strictly polyene containing substrates are known.^{4d,7}



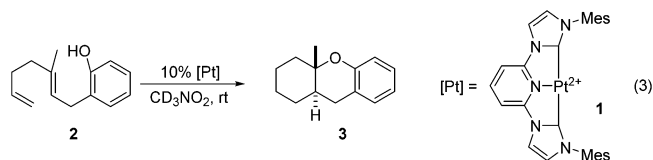
We have previously reported the synthesis of polycyclic Pt-alkyl compounds from simple and complex polyenes using Pt(triphos)²⁺ as the cyclization initiator (eq 2).^{8,9} The triphosphino pincer ligand renders the resulting Pt-alkyl compounds remarkably stable, but susceptible to Pt-C bond functionalization with strongly oxidizing agents (e.g., F⁺ or Cu²⁺).¹⁰ We also considered the feasibility of an alternative oxidant, H⁺, which oxidatively protonates the metal as the first elementary step in the protodemetalation of a Pt^{II}-C bond.¹¹ By following a Pt(II) initiated electrophilic cascade cyclization with an oxidative protonolysis scheme, we sought a cyclization/protonation approach to sterol-like polycyclic compounds. Despite the desirability of such an atom economical cycloisomerization procedure, this goal required a solution to the high stability of Pt-alkyl cations to acid.¹²

To facilitate such a scheme, we required a catalyst that was not only sufficiently electrophilic to initiate the cation olefin cyclization but also electron rich enough to undergo rapid

protodemetalation. Our catalyst design features centered on the hypothesis that the electrophilic activation of a coordinated alkene would be principally controlled by its *trans* ligand, while its two *cis* ligands would primarily impact the facility with which it could be oxidized at the Pt-alkyl stage. This led us to seek a pincer ligand with a poorly donating *trans* ligand and strongly donating *cis* ligands. Limbach et al. have recently reported the hydrovinylation¹³ and hydroamination¹⁴ of ethylene mediated by a series of Pt catalysts engendering these target features, two *cis* NHC ligands and a *trans* pyridine.



We initiated our studies by examining the ability of complex 1 to induce cyclization of 2. Remarkably, after only 3 h at room temperature, complete conversion to the cyclization/protolysis product 3 was observed. Surprisingly, the cyclization proceeded in the absence of added base and provided none of the previously observed Brønsted acid catalyzed monocyclization product 4,¹⁵ which reports on the buildup of acid; i.e., H⁺ is rapidly consumed *in situ*.



Our working mechanism has the reaction being initiated by selective coordination of the Pt electrophile to the least substituted alkene,¹⁶ and subsequent ionic cyclization to B with liberation of H⁺ from the phenol terminating group (Scheme 1). Protodemetalation of B generates 3 and regenerates the Pt catalyst. The lack of 4 indicates that H⁺ never builds up and it reacts more quickly with B than it does with 2.

Intrigued by the efficiency with which 1 induces cyclization in phenol terminating substrate 2, we explored its applicability with the significantly more challenging alkene terminating groups.^{8b} Remarkably, 1 proved effective at initiating the diastereoselective cyclization of a variety of polyene substrates. Bi-, tri-, and tetracyclization reactions all proceeded in the presence of 10% 1. Additionally tolerated were terminating

Received: January 21, 2014

Published: February 11, 2014

The reaction scheme illustrates the catalytic cycle for the [Pt]²⁺ complex. The cycle starts with the catalyst **1** (a [Pt]²⁺ complex) reacting with the substrate **3** (a substituted cyclohexene derivative) to form intermediate **2**. Intermediate **2** then reacts with H⁺ to form intermediate **4**, which is a Pt(IV) complex. Intermediate **4** then releases the product **A** and regenerates the catalyst **1**. The catalyst **1** is also shown reacting with H⁺ to form intermediate **B**, which then reacts with the substrate **3** to form intermediate **2**.

In addition to the **2**→**3** transformation and the faster protonolysis of **B** than **2**, the cyclization of **9**→**10** also reports on a low steady-state concentration of H⁺, as **10** is prone to conversion to **23** under acidic conditions (Scheme 2).¹⁷ In this

Finally, cyclization of **21** provided the tetracycle **22** in 44% yield, forming five stereocenters and providing the 6–6–6–5 sterol framework in a single step. Initial cyclization again

Entry ^{a,b}	Substrate	Product	Solvent	Isolated Yield
1 2			CD ₃ NO ₂ CD ₃ NO ₂	93% ^c 88%(5 mol%)
3 4			CD ₃ NO ₂ CH ₂ Cl ₂	68% ^c 77% ^c
5			CD ₃ NO ₂	80% ^c
6			CD ₃ NO ₂	70%
7 8			CD ₃ NO ₂ CH ₂ Cl ₂	52% 59%
9			CD ₃ NO ₂	61%
10			CD ₃ NO ₂	23%
11			CH ₂ Cl ₂	59%
12			CH ₂ Cl ₂	39%
13			CH ₂ Cl ₂	44%

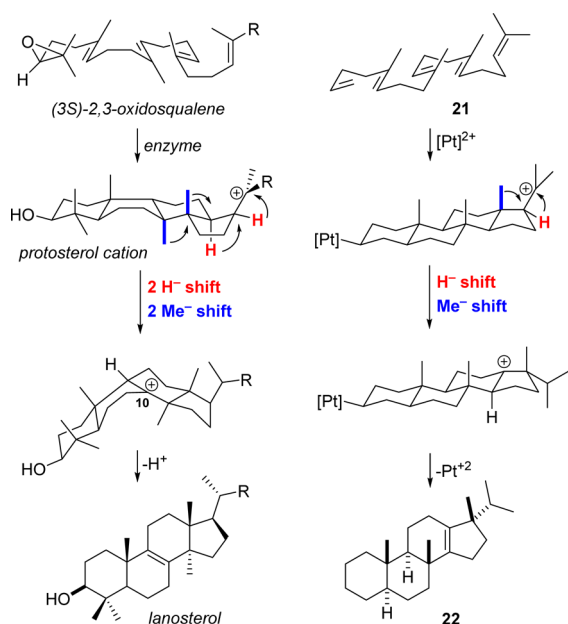
Reaction scheme for the synthesis of **24** and **20** from [Pt]:

[Pt] (a bicyclic carbocation) undergoes an **H⁺ shift** to form an intermediate carbocation. This intermediate then undergoes **1) elimination** and **2) -Pt²⁺** to yield **24** (10%).

Alternatively, [Pt] undergoes a **Me⁻ shift** to form another intermediate carbocation. This intermediate then undergoes **1) elimination** and **2) -Pt²⁺** to yield **20** (39%).

dx.doi.org/10.1021/ja500656k | *J. Am. Chem. Soc.* 2014, 136, 3032–3035

Scheme 4. Terminating Events in Cyclization of 2,3-Oxidosqualene and 21



and two methyl shifts generates a tertiary cation at C10 with elimination to C9 forming the unsaturation at the B/C ring junction of lanosterol.²⁰

Nitromethane proved a suitable solvent in most cases; however, several slow reacting or incomplete cyclizing cases benefitted from a change to dichloromethane. Although **1** has a tendency to abstract chloride from dichloromethane,¹³ it provided shorter reaction times in the case of substrates **17**, **19**, and **21**. It additionally enabled complete consumption of **19** while leaving the product distribution unchanged. Previous studies have shown that the equilibrium position of bicyclizations can be significantly shifted to the product state in the more poorly solvating solvent.²¹ These data additionally suggest that a lower dielectric solvent may also increase the rate of cyclization.

In summary, we have reported an efficient, atom economical process for the conversion of a variety of polyene substrates to polycycles. This method hinges upon the paradoxical combination of high electrophilicity at the (CNC)Pt²⁺ stage and ease of protonative oxidation at the (CNC)Pt–R⁺ stage.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as spectroscopic data are available in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

mgagne@unc.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The NIH (GM-60578) is thanked for their generous support. M.J.G. thanks NSERC of Canada for a Postgraduate Scholarship. The authors thank Laura L. Adduci for assistance with

NMR experiments and Dr. Mee-Kyung Chung for assistance with HRMS.

■ REFERENCES

- (1) (a) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812. (b) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (c) Wendt, K. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 3966.
- (2) (a) Kitora, M.; Hessler, F.; Eignerová, B. *Eur. J. Org. Chem.* **2012**, *29*, 29. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.
- (3) (a) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (b) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.
- (4) (a) Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2012**, *134*, 20276. (b) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276. (c) Toullec, P. Y.; Blarrie, T.; Michelet, V. r. *Org. Lett.* **2009**, *11*, 2888. (d) Godeau, J.; Fontaine-Vive, F.; Antoniotti, S.; Duñach, E. *Chem.—Eur. J.* **2012**, *18*, 16815. (e) Surendra, K.; Qiu, W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724. (f) Jeker, O. F.; Kravina, A. G.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12166.
- (5) (a) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, *134*, 11992. (b) Moore, J. T.; Soldi, C.; Fetting, J. C.; Shaw, J. T. *Chem. Sci.* **2013**, *4*, 292. (c) Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130. (d) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122.
- (6) (a) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (b) Sawamura, Y.; Nakatsuji, H.; Sakakura, A.; Ishihara, K. *Chem. Sci.* **2013**, *4*, 4181. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303.
- (7) (a) Takao, H.; Wakabayashi, A.; Takahashi, K.; Imagawa, H.; Sugihara, T.; Nishizawa, M. *Tetrahedron Lett.* **2004**, *45*, 1079. (b) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451. (c) Godeau, J.; Olivero, S.; Antoniotti, S.; Duñach, E. *Org. Lett.* **2011**, *13*, 3320.
- (8) (a) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459. (b) Sokol, J. G.; Korapala, C. S.; White, P. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 5658.
- (9) A catalytic scheme for accessing 2,3-unsaturated polycycles has been developed; see: (a) Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880. (b) Sokol, J. G.; Cochrane, N. A.; Becker, J. J.; Gagné, M. R. *Chem. Commun.* **2013**, *49*, 5046.
- (10) (a) Geier, M. J.; Gagné, M. R. *Organometallics* **2013**, *32*, 380. (b) Zhao, S.-B.; Becker, J. J.; Gagné, M. R. *Organometallics* **2011**, *30*, 3926.
- (11) (a) Labinger, J.; Bercaw, J. In *Higher Oxidation State Organopalladium and Platinum Chemistry*; Canty, A. J., Ed.; Springer: Berlin Heidelberg, 2011; Vol. 35. (b) Hoover, J. M.; DiPasquale, A.; Mayer, J. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 5043. (c) Liu, C.; Bender, C. F.; Han, X.; Widenhoefer, R. A. *Chem. Commun.* **2007**, 3607. (d) Troups, K. L.; Widenhoefer, R. A. *Chem. Commun.* **2010**, *46*, 1712. (e) Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786.
- (12) (a) Butikofer, J. L.; Hoerter, J. M.; Peters, R. G.; Roddick, D. M. *Organometallics* **2004**, *23*, 400. (b) Peters, R. G.; White, S.; Roddick, D. M. *Organometallics* **1998**, *17*, 4493. (c) Feducia, J. A.; Campbell, A. N.; Anthis, J. W.; Gagné, M. R. *Organometallics* **2006**, *25*, 3114. (d) Thorn, D. L. *Organometallics* **1998**, *17*, 348.
- (13) Serra, D.; Cao, P.; Cabrera, J.; Padilla, R.; Rominger, F.; Limbach, M. *Organometallics* **2011**, *30*, 1885.
- (14) Cao, P.; Cabrera, J.; Padilla, R.; Serra, D.; Rominger, F.; Limbach, M. *Organometallics* **2012**, *31*, 921.
- (15) Cochrane, N. A.; Brookhart, M. S.; Gagné, M. R. *Organometallics* **2011**, *30*, 2457.
- (16) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042.
- (17) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865.
- (18) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131.

- (19) Compound **22** devoid of the C10 methyl has been reported;
see: Parker, K. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1974**, 96, 2556.
- (20) Tantillo, D. J. *Nat. Prod. Rep.* **2011**, 28, 1035.
- (21) Feducia, J. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, 130, 592.