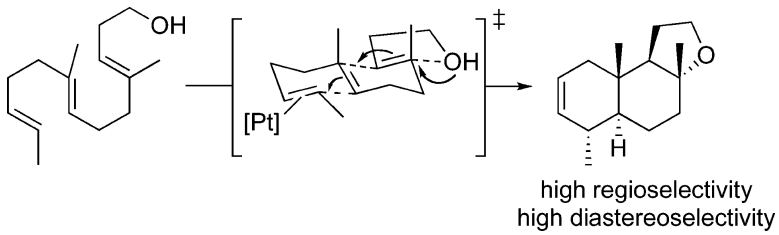
Communication

Regioselective Oxidative Cation-Olefin Cyclization of Poly-enes: Catalyst Turnover via Hydride Abstraction

Charles A. Mullen, and Michel R. Gagn

J. Am. Chem. Soc., **2007**, 129 (39), 11880-11881• DOI: 10.1021/ja073573l • Publication Date (Web): 13 September 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 7 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 09/13/2007

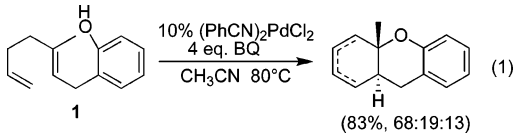
Regioselective Oxidative Cation-Olefin Cyclization of Poly-enes: Catalyst Turnover via Hydride Abstraction

Charles A. Mullen and Michel R. Gagné*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

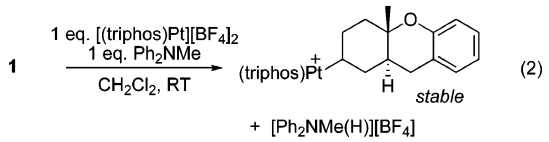
Received May 18, 2007; E-mail: mgagne@unc.edu

Biomimetic polyolefin cascade reactions are among the most challenging problems in reaction design,[1] and since few catalysts initiate *ligand controlled* cation−olefin cyclizations,[2,3] we became interested in developing one around the reactive core of electrophilic Pd(II) and Pt(II).[4] In contrast to H^+, Br^+, and other carbophilic metals, Pd(II) and Pt(II) preferentially coordinate and activate the less substituted alkene,[5] which directs the point of coordination/activation to the terminus in substrates such as **1**.



(1)

As outlined in eq 1 $(PhCN)_2PdCl_2$ in combination with benzoquinone (BQ) effectively catalyzes the oxidative cyclization of poly-enes.[6] Although the diastereoselectivity was high, this methodology's regioselectivity was problematic owing to alkene isomerization after β-hydride elimination. Additionally, all attempts to develop an asymmetric variant of this catalyst failed as added ligands inhibited the catalysis. We[7] and others[5c,d] have also reported that (tris-phosphine)Pt-dications efficiently initiate cation−olefin transformations that mediate the cycloisomerization of dienes into bicyclopropanes.[7a−c] However, with substrates such as **1**, which contain an internal cation trap, the resulting cyclic Pt−alkyl is resistant to β-H elimination (no open cis coordination sites to allow for hydride migration), and the reaction does not turn over. The cyclized product is recoverable, however, by reductive cleavage using $NaBH_4$.[7d]

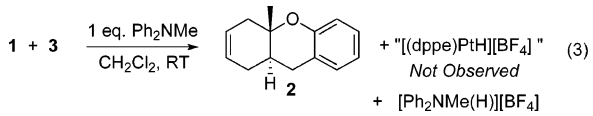


(2)

Rationalizing that an open cis site would enable β-H elimination from a putative alkyl intermediate, we initiated an examination of P_2Pt-dication catalysts for the oxidative cyclization of **1**. These studies led to a novel catalyst system for the *regioselective* oxidative cyclization of poly-enols that additionally utilizes trityl cation to achieve catalyst turnover.

The combination of $[(dppe)Pt][BF_4]_2$ (**3**),[8] **1**, and a weak base at room temperature generated **2** as a single diastereomer and regioisomer (eq 3). This product reasonably results from a *regioselective* β-hydride elimination of an intermediate $(P_2)Pt$−cycloalkyl cation. The contrast to Pd-based methods is striking (cf. eq 1). We presume a $[(dppe)Pt(H)][BF_4]$ byproduct but it appears to decompose.

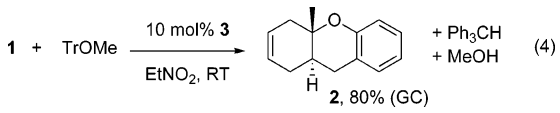
The cyclization/β-elimination step of a putative mechanism for catalysis was thus realized; however, the conversion of "P_2Pt−H^+" to the active dication for reinitiating the cycle (catalyst



(3)

"reoxidation") was not well precedented,[4] in contrast to ubiquitous Pd analogues. One differentiating feature is that these dicationic Pt catalysts lack the coordinating X^- ligands (Cl^-, ^-OAc, etc.), which are key to facilitating metal reoxidation.[9] This makes traditional M(0) to M(II) oxidizing reagents such as benzoquinone, O_2, $CuCl_2$, etc. ineffective for this system.[10]

The hydride abstracting agent (triphenylcarbenium)BF_4 ($TrBF_4$), however, was found to efficiently convert the key intermediate back to the $(dppe)Pt^{2+}$ state for reinitiating catalytic turnover.[11] Thus, 10 mol % $(dppe)Pt^{2+}$ and stoichiometric $TrBF_4$ combined with a weak base (Ph_2NH) serves to absorb the H^- and H^+ generated from the heterolytic loss of H_2 on conversion of **1** to **2**. A more convenient Tr^+ source was trityl methyl ether, which generates Tr^+ and MeOH on reacting with the H^+ expelled on cyclization. This approach keeps Tr^+ concentrations low by only releasing the amount needed for each turn of the cycle, reducing the probability of Tr^+ mediated side reactions while also removing the need for exogenous amine base.



(4)

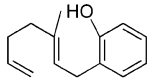
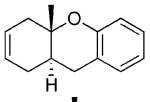
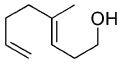
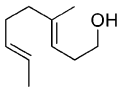
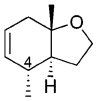
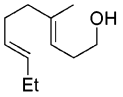
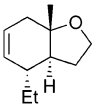
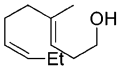
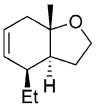
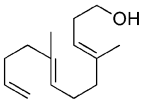
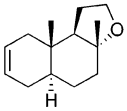
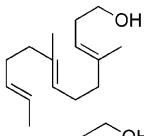
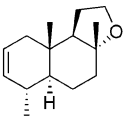
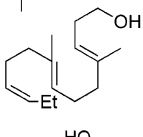
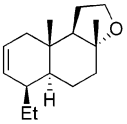
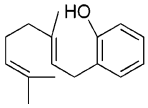
Additional optimization led to a polystyrene resin bound trityl methyl ether that enables simple removal of excess TrOMe and TrH.[12] No loss in yield was observed on using this solid-phase reoxidant. A screen of readily available diphosphines (not shown) indicated that dppe provided the most high-yielding catalyst, and nitroethane was the ideal solvent.

These optimum conditions were applied to a variety of diene- and triene-ol substrates (Table 1).[13] The reactions typically went to completion with 10 mol % **3** and consistently provided high regioselectivities and only trans ring junctions (predicted by the Stork−Eschenmoser postulate[14] for *E* internal olefins). In addition to terminal alkenes, 1,2-disubstituted termini were also tolerated (entries 3−5, 7, 8). These reactions were stereospecific as the *E* and *Z* isomers led to epimeric products at C-4 and suggested chairlike transition states tolerant of unfavorable developing 1,3-diaxial interactions for the *Z* substrates (Scheme 1). Terminal trisubstitution was not tolerated (entry 9).

A proposed catalytic cycle is shown in Scheme 2. Coordination and activation of the less substituted C=C double bond by P_2Pt^{2+} at the terminus of the substrate initiates the cascade cyclization. The trapping of the final cation by the alcohol generates acid which cleaves TrOMe into trityl cation and methanol. The intermediate P_2Pt-alkyl cation **I** has been observed as the resting state of this catalytic cycle by ^{31}P NMR. The fourth coordination site in **I** is

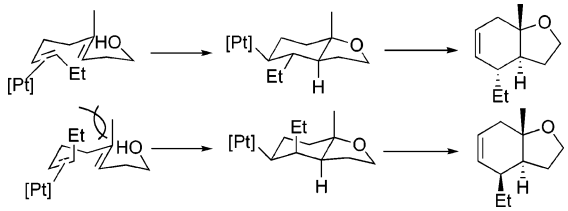
10.1021/ja073573l CCC: $37.00

Table 1. Polycyclizations Catalyzed by (dppe)PtI_2/$AgBF_4$[a]

entry	Substrate	Product	Time(h)	Yield[b]
1	 **1**	 **2**	8	73%[c]
2	 **3**	 **4**	8	84%
3	 **5**	 **6**	12	67%
4	 **7**	 **8**	12	65%
5	 **9**	 **10**	12	72%
6	 **11**	 **12**	12	90%
7	 **13**	 **14**	14	52%
8	 **15**	 **16**	14	45%
9	 **17**			NR

[a] Conditions: 10% (dppe)PtI_2, 22% $AgBF_4$, 2.1 Ph_3COMe resin, $EtNO_2$. [b] Isolated yield of purified material, average of two or more runs; balance of material is largely the product of Brønsted mediated monocyclization. dr > 50:1 (GC) in all cases. [c] 10% Ph_2NH added.

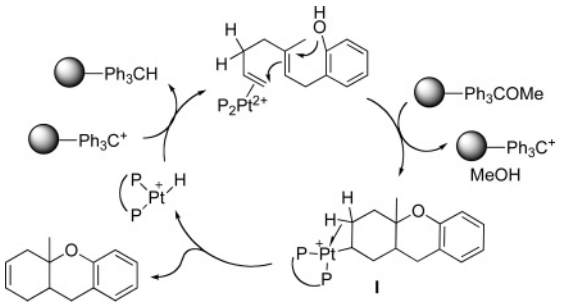
Scheme 1. Chair Transition States for Cyclization of **7** and **9**



filled by a β-agostic interaction from the cyclic alkyl ligand.[15] Since only one agostic complex is observed by ^{31}P NMR (δ 48.4, 41.0 ppm), it is tempting to ascribe the observed regioselectivity to a regio-defining β-agostic interaction. We next propose a turnover limiting β-hydride elimination to generate product and a P_2Pt-H cation, which then looses the hydride on reacting with trityl cation, forming triphenylmethane and regenerating the dicationic Pt species. Other possible mechanisms include a direct β or α abstraction from **I** by Tr^+;[16] however, observation of the same regioselectivity in stoichiometric-Pt mediated reactions suggests that β-hydride occurred.

In conclusion, we have developed a ligand-controlled system for the biomimetic cation-olefin cascade cyclization. We have also demonstrated a new approach to the turnover of oxidative cyclization processes by a Tr^+ mediated hydride abstraction pathway. Studies to further understand the mechanism of this turnover step are underway.

Scheme 2. Proposed Catalytic Cycle



Acknowledgment. We thank the National Institutes of Health, General Medicine for generous support (Grant GM-60578).

Supporting Information Available: Characterization details for all new compounds, and representative synthetic procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756. (b) Bartlet, P. A. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press, Inc.: Orlando, FL, 1984; Vol. 3, pp 341−377. (c) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, England, 1991; Vol. 3, pp 341−409.
(2) (a) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122−11123. (b) Ishirara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647−3655. (c) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131−8140.
(3) Skakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900−903.
(4) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042−4059.
(5) (a) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865−867. (b) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225−7231. (c) Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038−9039. (d) Hahn, C.; Morvillo, P.; Herdtweck, E.; Vitagliano, A. *Organometallics* **2002**, *21*, 1807−1818. (e) Hahn, C. *Chem. Eur. J.* **2004**, *10*, 5888−5899.
(6) Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405−7410.
(7) (a) Kerber, W. D.; Koh, J. H.; Gagné, M. R. *Org. Lett.* **2004**, *6*, 3013−3015. (b) Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, *7*, 3379−3381. (c) Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 13290−13297. (d) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459−3641.
(8) Generated by I^- abstraction of (dppe)PtI_2 by $AgBF_4$.
(9) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071−5075. (c) Helfer, D. S.; Atwood, J. D. *Organometallics* **2004**, *23*, 2412−2420.
(10) For recent examples of H_2O_2-mediated oxidation of alkenes and ketones, see: (a) Colladon, M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G. *J. Am. Chem. Soc.* **2006**, *128*, 14006−14007. (b) Sgarbossa, P.; Scarso, A.; Michelin, R. A.; Strukul, G. *Organometallics* **2007**, *26*, 2714−2719 and references therein.
(11) (a) Cheng, T.-Y.; Bullock, R. M. *Organometallics* **2002**, *21*, 2325−2311. (b) Cheng, T.-Y.; Bullock, R. M. *J. Am. Chem. Soc.* **1999**, *121*, 3150−3155. (c) Chen, T.-Y.; Bullock, R. M. *Inorg. Chem.* **2006**, *45*, 4712−4720.
(12) Fréchet, J. M.; Haque. K. E. *Tetrahedron Lett.* **1975**, *16*, 3055−3056.
(13) It was occasionally beneficial to add 10% Ph_2NH for acid sensitive substrates.
(14) (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.
(15) The assignment of **I** as an agostic complex is primarily based on the ^{31}P NMR, which displays J_{Pt-P} values highly diagnostic of this structure. The P trans to an agostic C−H exhibits a large coupling constant (~4700 Hz) compared to the P trans to the alkyl (~1500 Hz). The ^1H NMR is not particularly diagnostic in the present case, though other P_2Pt-R^+ complexes have demonstrated upfield shifts of the agostic CH (up to −3 ppm). See: (a) Carr, N.; Dunne, B. J.; Orpen, A. G.; Spencer, J. L. *J. Chem. Soc., Chem. Commun.* **1988**, 926−928. (b) Carr, N.; Mole, L.; Orpen, A. G.; Spencer, J. L. *J. Chem. Soc., Dalton Trans.* **1992**, 2653−2662.
(16) (a) Laycock, D. E.; Baird, M. C. *Tetrahedron Lett.* **1978**, *19*, 3307−3308. (b) Hayes, J. C.; Cooper, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 5570−5572.

JA073573L