Cyclizations

Pd^{II}- and Pt^{II}-Mediated Polycyclization Reactions of 1,5- and 1,6-Dienes: Evidence in Support of Carbocation Intermediates**

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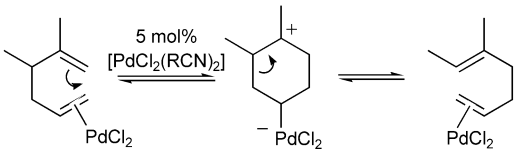
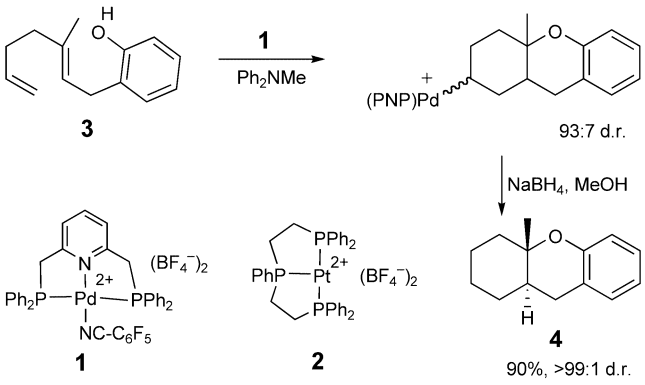
Biomimetic polyolefin cascade reactions[1,2] represent some of the most challenging problems in reaction design, and their products are ubiquitous in the natural world.[3] Since the Brønsted–Lewis acids (BLAs) of Yamamoto et al. are the only known synthetic catalysts for asymmetric catalytic initiation of cation–olefin cyclizations,[4,5] we became interested in an alternative C–C bond-forming cascade wherein activation of a terminal alkene occurs with an electrophilic Pd^{II} source. Although this process is uncommon, it is precedented in the catalysis of the Cope rearrangement with $[PdCl_2(RCN)_2]$ [Eq. (1)] by Overman et al.[6] Fragmentation of a cationic intermediate in the opposite regiodirection was proposed to generate a new diene and a Pd^{II} complex. More recently, Widenhoefer et al.[7] and Toyota, Ihara et al.[8] demonstrated that nucleophilic enols lead to carbocyclic products by β-hydride elimination[9] or protonation.[10]



(1)

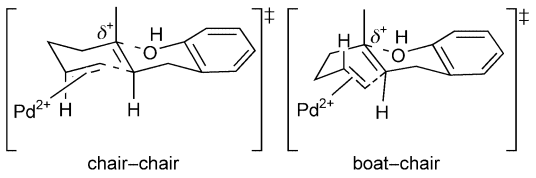
Although substituent effects[11] and stereochemical studies[6c] support a cationic and cyclic intermediate, respectively, the exact nature of this intermediate is unclear, and direct evidence for this cation is lacking.[12] We therefore initiated a plan that first gathered evidence supporting the intermediacy of the carbocyclic cation, while also determining whether it could function as a point for initiating new metal-mediated reactivity. The key to our pursuit was a recent report by Vitagliano et al. of a dicationic Pt complex of a pyridyl bisphosphane pincer ligand $[Pt(PNP)](BF_4)_2$ (PNP = 2,6-bis(diphenylphosphanylmethyl)pyridine) that catalyzes the dimerization of ethylene and 2-methyl-2-butene.[13,14] Intermolecular nucleophilic addition of 2-methyl-2-butene to coordinated ethylene was proposed, with turnover by a sequence of 1,2-hydride shifts. Most importantly, β-hydride elimination did not occur, since no open *cis* coordination sites were available, and this suggests that this complex might be capable of initiating cation formation while preserving the stereochemistry of the M–C bond.

Our first approach to trapping the putative cation utilized the Pd analogue of the Vitagliano complex **1** and dienylphenol **3**. Unlike direct Brønsted acid[4] and Hg^{II}[15] activation/polycyclization, Pd^{II} prefers to coordinate and activate the least substituted alkene,[16] ensuring activation at the terminus. As shown in Scheme 1, the isolable C_6F_5CN adduct[17] efficiently (1 h, RT, CH_2Cl_2) converted **3** to a new metal-containing product devoid of alkene resonances (^{1}H NMR spectroscopy) as a 93:7 mixture of isomers according to ^{31}P NMR spectroscopy. This compound is stable up to 100 °C, though demetalation with $NaBH_4$ at room temperature rapidly[14b] yielded tricycle **4** in 90% yield (two steps) and d.r. > 99:1.[18]



Scheme 1. Phenol trapping of an intermediate cation and reductive cleavage of the stable Pd alkyl complex.

Since a single diastereomer was observable in the crude demetalation product, we surmised that the isomer mixture for the Pd alkyl complex must result from epimers at the metal-containing stereocenter, a situation suggestive of competing chair–chair and boat–chair transition states,[19] each with a degree of concertedness in the C–C/C–O bond-forming event, that is, a free carbocation is not likely formed [cf. Eq. (1)].[1,20] Pincer complex $[Pt(PPP)](BF_4)_2$ (**2**, PPP = bis(2-diphenylphosphanylethyl)phenylphosphane),[21] derived from commercially available triphos, provided the intermediate alkyl complex with a slightly higher diastereoselectivity (96:4), and **4** in similarly high yield (87%) and selectivity (> 99:1).



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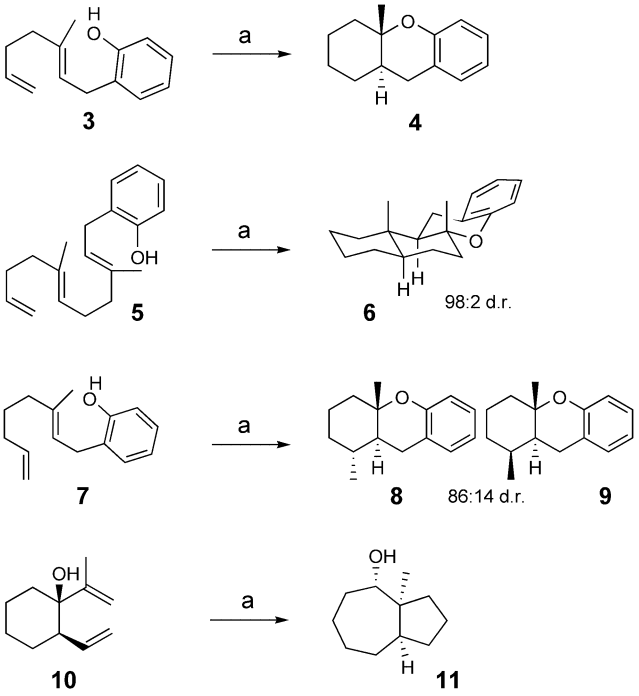
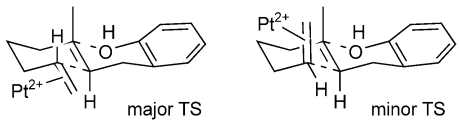
To explore the possibility of cascading the putative cation in a polycyclization reaction,[1] we examined the reaction of trienylphenol **5** with **2** (Scheme 2). As before, cyclization was rapid (4 h), and ^{31}P NMR analysis of the resulting Pt alkyl complex indicated that the product was formed with d.r. ≈ 95%. Treatment with $NaBH_4$ provided tetracyclic **6** as a 96:3:1 mixture of diastereomers (GC), which was isolated as a 98:2 mixture of diastereomers after chromatography (86% yield). Catalyst **1** provided the Pd alkyl complex as a 77:11:8:4 mixture of diastereomers, which simplified to 80:5:minors after treatment with $NaBH_4$; the major diastereomer purified to 98:2 (77% yield).

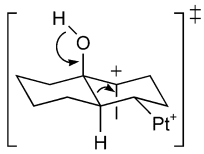


Scheme 2. Interception of cations generated with **2**. Compound **8** was characterized by X-ray crystallography. a: 1) **2**, 1.05 equiv Ph_2NMe, CH_2Cl_2, RT, 1–4 h; 2) $NaBH_4$, MeOH.

Compound **7**, wherein the activated alkene is positioned 6-*exo* to the forming six-membered ring, reacted with **2** to provide a stable Pt alkyl complex as an 86:14 mixture of isomers; reductive cleavage yielded **8** and **9** in the same ratio (Scheme 2, 83% yield). Crystals of the major stereoisomer grew from the oil, and X-ray crystallography confirmed the relative configuration shown in Scheme 2.[22] The major isomer apparently results from a chairlike transition state that places the activated alkene in a pseudo-equatorial orientation. The minor isomer **9** also contained a *trans* ring junction, but a Me···Me NOE suggested a 1,3-diaxial disposition arising from a pseudo-axial position in the putative transition state. The stereo-electronic reasons for this outcome may be related to the pseudo-axial preference of oxonium initiators in polyolefin cascades.[1,23,24] Complex **1** provided **8** with a 78:22 preference (85% yield).

The efficiency of the above cation-trapping experiments prompted us to examine other processes that would support a carbocation intermediate. The reaction of **10** with **2** yielded a new ketone-containing organometallic product that was free of alkene resonances. Reductive removal of the carbocycle ($NaBH_4$) provided *cis*-fused bicyclic alcohol **11** (Scheme 2, 90%, d.r. > 95:5). This reaction is most succinctly explained by cyclogeneration of a carbocation, ring-expanding/contracting pinacol rearrangement (**A**),[25] and Pt–C and C=O reduction. Mechanistic analysis followed from Prins-initiated formation of cations[26] which similarly rearrange to provide *cis*-fused bicyclic ketones. Complex **1** also provided **11** in high yield (93%) and diastereoselectivity (d.r. > 95:5).





The pincer-ligated complexes **1** and **2** uniquely provide a solution to the notion of trapping/cascading the putative intermediate obtained from electrophilic carbocyclization of 1,5- and 1,6-dienes. The variety of trapping reactions (heteroatom addition, cation–olefin, and pinacol rearrangement) are individually consistent with a cationic intermediate, but taken together provide a compelling case for Overman's proposal that cyclization-induced rearrangements proceed through carbenium ion intermediates. Furthermore, the data indicate that 1,5-dienes do not represent a boundary condition for electrophilic carbocyclization/cation generation; other diene arrangements can participate.

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[1] P. A. Bartlett in *Asymmetric Synthesis*, *Vol. 3* (Ed.: J. D. Morrison), Academic Press, New York, **1984**, p. 341.
[2] K. U. Wendt, G. E. Schultz, E. J. Corey, D. R. Liu, *Angew. Chem.* **2000**, *112*, 2930; *Angew. Chem. Int. Ed.* **2000**, *39*, 2812.
[3] B. M. Fraga, *Nat. Prod. Rep.* **2003**, *20*, 392.
[4] See for example: a) K. Ishihara, H. Ishibashi, H. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 3647; b) S. Nakamura, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8131.
[5] Catalytic antibodies show some asymmetric tendencies: J. Hasserodt, K. D. Janda, R. A. Lerner, *J. Am. Chem. Soc.* **2000**, *122*, 40.
[6] a) L. E. Overman, F. M. Knoll, *J. Am. Chem. Soc.* **1980**, *102*, 865; b) L. E. Overman, *Angew. Chem.* **1984**, *96*, 565; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579; c) L. E. Overman, E. J. Jacobsen, *J. Am. Chem. Soc.* **1982**, *104*, 7225.
[7] a) T. Pei, X. Wang, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 648; b) X. Wang, T. Pei, X. Han, R. A. Widenhoefer, *Org. Lett.* **2003**, *5*, 2699; c) T. Pei, R. A. Widenhoefer, *Chem. Commun.* **2002**, 650; d) T. Pei, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2001**, *123*, 11290.
[8] M. Toyota, M. Rudyanto, M. Ihara, *J. Org. Chem.* **2002**, *67*, 3374.

[9] In certain instances cyclohexene products were also observed: L. E. Overman, A. F. Renaldo, *Tetrahedron Lett.* **1983**, *24*, 2235.
[10] X. Wang, R. A. Widenhoefer, *Chem. Commun.* **2004**, 660.
[11] L. E. Overman, A. F. Renaldo, *J. Am. Chem. Soc.* **1990**, *112*, 3945.
[12] For a review of 1,6-diene carbocyclization mechanisms, see: G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215.
[13] C. Hahn, M. E. Cucciolito, A. Vitagliano, *J. Am. Chem. Soc.* **2002**, *124*, 9038.
[14] Vitagliano et al. have extensively documented the addition of weak heteronucleophiles to $[Pd(PNP)]^{2+}$- and $[Pt(PNP)]^{2+}$-activated alkenes: a) C. Hahn, P. Morvillo, E. Herdtweck, A. Vitagliano, *Organometallics* **2002**, *21*, 1807; b) C. Hahn, P. Morvillo, A. Vitagliano, *Eur. J. Inorg. Chem.* **2001**, 419; c) C. Hahn, A. Vitagliano, F. Giordano, R. Taube, *Organometallics* **1998**, *17*, 2060.
[15] M. Nishizawa, H. Takenaka, Y. Hayashi, *J. Org. Chem.* **1986**, *51*, 806.
[16] a) L. S. Hegedus in *Comprehensive Organic Synthesis*, *Vol. 4* (Ed.: B. M. Trost), Pergamon Press, **1991**, p. 571; b) L. S. Hegedus in *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Mill Valley, California, **1994**, p. 199.
[17] J. J. Becker, L. J. V. Orden, P. S. White, M. R. Gagné, *Org. Lett.* **2002**, 727.
[18] The benzylic CH groups are diagnostic: $\Delta\delta = 0.78$ ppm for *cis*, and $\Delta\delta = 0.15$ ppm for *trans*. M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333.
[19] This information would necessarily be lost if β-hydride elimination or β-fragmentation [Eq. (1)] were operative.
[20] a) G. Stork, A. W. Burghstahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068; b) A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890–1904.
[21] The dication was generated in situ from $[PtI_2(PPP)]$ and $AgBF_4$.
[22] CCDC-230057 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
[23] W. S. Johnson, A. van der Gen, J. J. Swoboda, *J. Am. Chem. Soc.* **1967**, *89*, 170.
[24] For a recent example, see: J. R. Seiders II, L. Wang, P. E. Floreancig, *J. Am. Chem. Soc.* **2003**, *125*, 2406.
[25] D. J. Coveney in *Comprehensive Organic Synthesis*, *Vol. 3* (Ed.: G. Pattenden), Pergamon, New York, **1991**, p. 777.
[26] a) L. E. Overman, J. P. Wolfe, *J. Org. Chem.* **2002**, *67*, 6421; b) L. E. Overman, *Acc. Chem. Res.* **1992**, *25*, 352.

