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Platinum(II)-Catalyzed 1,6-Diene Cycloisomerizations: Turnover in the Absence of β-Hydride Elimination

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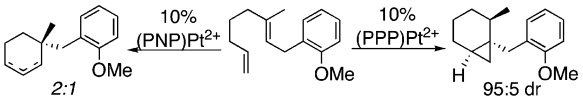
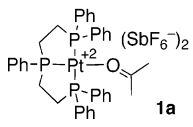
ABSTRACT

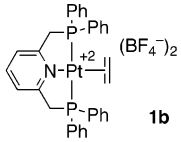


Electrophilic pincer-ligated Pt(II)-dications are efficient catalysts for the cycloisomerization of 1,6-dienes, initiated by alkene activation. The tridentate ligands inhibit β-hydride elimination and thus enable cationic mechanisms that turnover by Pt(II) extrusion. PPP ligands lead to cyclopropane products, while PNP ligands provide cyclohexene products; mechanistic issues are also discussed.

The cationic cyclization of polyolefins is an important biosynthetic process that has been extensively studied in the past 50 years.[1] Because large increases in molecular complexity can be obtained in a single step, synthetic chemists have developed analogous nonenzymatic processes that employ electrophilic reagents to activate polyolefins.[2] A wide range of Brønsted and Lewis acids have been examined;[3] the intermediate carbocations often have low barriers to rearrangement/cyclization, the reactions are extremely sensitive to reaction conditions, and both kinetic and thermodynamic control is possible.[4]



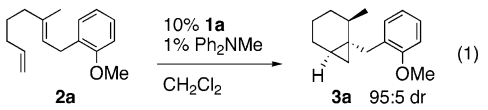
1a



1b

Group 10 metals are well-known to activate olefins toward nucleophilic addition; however, turnover in these systems often hinges on β-hydride elimination of the resulting metal−alkyl.[5] In contrast, Vitagliano has recently reported that **1b** dimerizes olefins and that the tridentate ligand inhibits β-hydride elimination, which promotes cationic intermediates and turnover by extrusion of Pt(II) from a β-cation-containing Pt−alkyl.[6]

We have investigated the use of catalysts **1a** and **1b** for the cyclization of 6-methyl-1,6-dienes, which may be considered intramolecular analogues of the Vitagliano alkene dimerization reaction. Unexpectedly, however, 10 mol % catalyst **1a** rearranges diene **2a**, with good selectivity (95:5 dr), to the fully saturated *trans*-[4.1.0] bicyclic product **3a** (eq 1), a common terpene-like fragment with a stereogenic quaternary center.[7]



2a **3a** 95:5 dr

A mechanistic proposal for the formation of **3** is shown in Scheme 1.[8] 6-Exo-endo addition[9] to the activated terminal

(1) (a) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812. (b) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189. (c) Richards, J. H.; Hendrickson, J. B. In *The Biosynthesis of Steroids, Terpenes, and Acetogenins*; Breslow, R., Karplus, M., Eds.; W. A. Benjamin, Inc.: New York, 1964.

(2) (a) Bartlet, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 342. (b) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, England, 1991; Vol. 3, p 341.

(3) See ref 2 and also: (a) Johnson, W. S.; Bartlett, W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R.; Leopold, E. J.; Luedtke, G. R.; Bancroft, K. J. *J. Org. Chem.* **1999**, *64*, 9587 and references therein. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (c) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806. (d) Corey, E. J.; Wood, H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982 and references therein.

(4) See, for example, Bright, S. T.; Coxon, J. M.; Steel, P. J. *J. Org. Chem.* **1990**, *55*, 1338.

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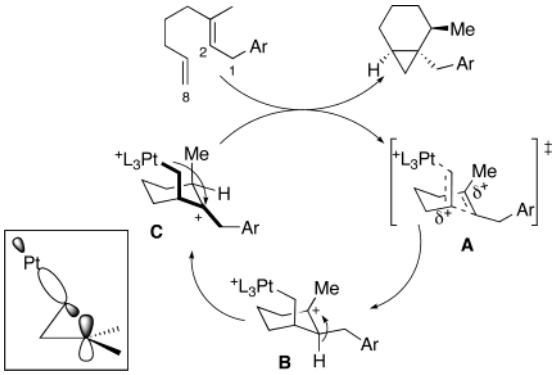
Scheme 1. Proposed Cyclopropanation Mechanism

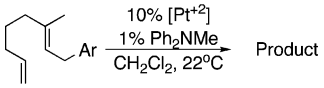


olefin in **A** generates the cyclic Pt−alkyl cation **B**. This intermediate undergoes a 1,2-hydride shift to place the carbocation γ to the metal center, where capture by the Pt−C bond generates the cyclopropane and extrudes Pt(II) (see inset, Scheme 1).

The trans stereochemistry of the product requires that the activated terminal alkene adopt a pseudoaxial orientation in **A**. The accessibility of this conformer was previously noted (in a minor product) in the stoichiometric cyclization of 1,6-dienylphenols by **1a** and **1b**.[10,11] Although the observed cyclopropanation was unexpected, stannyl and ferrous γ-carbocations will lose M^+ to form cyclopropanes,[7,12,13] a direct parallel to the postulated loss of Pt^{2+}. Moreover, the stereoelectronic preference for double inversion in the Sn and Fe reactions (W configuration) is accommodated in the putative intermediate **C**. The reactivity of **2a** derivatives labeled with deuterium at C-1, C-2, and C-8 (Scheme 1) was consistent with this mechanism. Since each step in Scheme 1 is stereospecific, the initial C−C bond formation (**A**) sets all three stereocenters in the product. In situ ^{31}P NMR analysis indicates that the catalyst rests at the coordinated alkene stage.

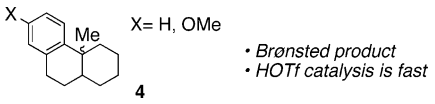
A brief examination of the scope of the cyclopropanation indicated a tolerance for *ortho*- and *para*-OMe donors, but not a *meta*-OMe or an unsubstituted ring (Table 1). In the latter cases, Brønsted background reactions initiate and *cis*- and *trans*-**4** result.[4] This Brønsted mechanism could be suppressed by the addition of excess Ph_2NMe, but at the expense of catalyst turnover. In the case of **2b** and **2d**, unknown catalyst decomposition products were detected by ^{31}P NMR[14] that apparently led to $HSbF_6$ generation. The general requirement for an electron-rich aromatic ring (but one not activated for addition) suggests a possible role for bridging phenonium ions in intermediates such as **C**.[15]

Table 1. Cycloisomerizations Catalyzed by Pt(II) Pincer Complexes

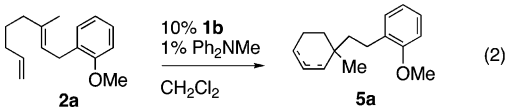


	Ar	diene	[Pt^{2+}][a]	t (h)	product	yield[d]
1	**2a**	*o*-$MeOC_6H_4$	**1a**	16	**3a** (95:5)[b]	83%
2	**2c**	*p*-$MeOC_6H_4$	**1a**	96	**3c** (95:5)[b]	65%
3	**2a**	*o*-$MeOC_6H_4$	**1b**	12	**5a** (2:1)[c]	68%
4	**2b**	*m*-$MeOC_6H_4$	**1b**	12	**5b** (2:1)[c]	70%
5	**2c**	*p*-$MeOC_6H_4$	**1b**	12	**5c** (2:1)[c]	64%
6	**2d**	C_6H_5	**1b**	12	**5d** (2:1)[c]	68%

[a] **1a** was generated in situ from (PPP)PtI_2 and $AgSbF_6$. **1b** was isolated. [b] Dr determined by ^1H NMR. [c] Ratio of 3- to 2-cyclohexene determined by GC. [d] Isolated.



In contrast to the [4.1.0] bicyclic products formed from **1a**, 10 mol % Pt(II) dication **1b** converted the 1,6-dienes **2a**−**d** to a mixture of geminal disubstituted cyclohexenes **5a**−**d** (eq 2 and Table 1, entries 3−6). In each case, the 3-substituted regioisomer was the major product by a 2:1 ratio. The rate of this reaction was somewhat variable, apparently because of small amounts of impurities in the solvent.



Although no data has yet been mechanistically definitive, the loss of one degree of unsaturation in **5** suggests a cycloisomerization that turns over by eliminating Pt(II) from

(5) (a) Hegedus, L. S. In *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994; p 199. (b) Hegedus, L. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: 1991; Vol. 4, p 571.

(6) Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038.

(7) (a) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J. *Tetrahedron* **2003**, *59*, 5623. (b) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625.

(8) Diene cycloisomerization processes do not typically give cyclopropanes; see: (a) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215. (b) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, *35*, 905. Ene-ynes, on the other hand, do typically give cyclopropanes: (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. For a recent Au(I) catalyst, see: (d) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402.

(9) This nomenclature first refers to the bond being activated and then the nucleophilic bond.

(10) Koh, J. H., Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459.

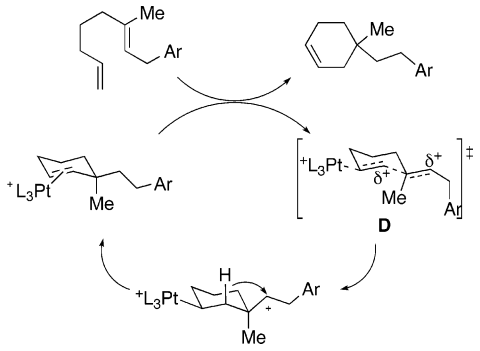
(11) Cation−olefin cyclizations with oxonium initiators also proceed selectively via this conformer; see ref 2a and: (a) Seiders, J. R., II; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406. (b) Johnson, W. S.; van der Gen, A.; Swoboda, J. J. *J. Am. Chem. Soc.* **1967**, *89*, 170.

(12) (a) Davis, D. D.; Johnson, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7576. (b) Fleming, I.; Urch, C. J. *Tetrahedron Lett.* **1983**, *24*, 4591. (c) McWilliam, D. C.; Balasubramanian, T. R.; Kuivila, H. G. *J. Am. Chem. Soc.* **1978**, *100*, 6407. (d) Lambert, J. B.; Salvador, L. A.; So, J. H. *Organometallics* **1993**, *12*, 697.

(13) (a) Casey, C. P.; Smith, L. J. *Organometallics* **1989**, *8*, 2288. (b) Casey, C. P.; Smith Vosejpka, L. J. *Organometallics* **1992**, *11*, 738. (c) Brookhart, M.; Liu, Y.; Goldman, E. W.; Timmers, D. A.; Williams, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 927. (d) Brookhart, M.; Liu, Y. *J. Am. Chem. Soc.* **1991**, 939. Ti is also known, see: (e) Casey, C. P.; Strotman, N. A. *J. Am. Chem. Soc.* **2004**, *126*, 1699.

a β-metalated carbocation (Vitagliano-like),[6] e.g., Scheme 2. This mechanism invokes a 6-endo-exo addition to the Pt-

Scheme 2. Possible Mechanism for Cyclohexene Formation



activated terminal olefin (**D**), followed by an uncommon 1,3-hydride transfer[16] to move the 2° cation into the ring.[17] Extrusion of Pt^{2+} leads to the minor alkene isomer,[6] which can be subsequently isomerized to the major isomer.[18] Unfortunately, efforts to test this hypothesis (and others) with D-labeled **2a** isotopomers were compromised by in situ isotopic scrambling (intermolecular).

Crossover experiments were also performed to determine if **5a** resulted from isomerization of cyclopropane **3a**. In the event, **3a** was unchanged in the presence of 10 mol % **1b**, eliminating this possible mechanism. Similarly, **5a** was not converted to **3a** with catalyst **1a**.

In addition to being sensitive to ligand, the product outcome was also sensitive to metal, as 10 mol % of the Pd analogue of **1b** converted **2a** into *a 3:1 mixture of cyclopropane and cyclohexene* (the Pd analogue of **1a** was unreactive). This departure from Pt reactivity clearly indicates that the competing turnover mechanisms are not only sensitive to metal and ligand but also have sufficiently similar rates to be affected by subtle catalyst changes.[19]

The mechanisms proposed vide supra involve generation of cationic intermediates in dichloromethane, and not surprisingly, ion pairing with the catalyst counteranion proved energetically important. When catalyst **1a** was prepared with the more-strongly coordinating BF_4^- anion, rates of cyclopropanation were significantly retarded. When catalyst **1b** was prepared with the more weakly coordinating SbF_6^- anion, rates of substrate consumption were increased; however, significant decomposition occurred.[20]

Despite mechanistic ambiguities (for cyclohexene formation), these reactions are clean, under catalyst control, and generate chiral quaternary centers from achiral alkene substrates. Mechanistic observations suggest cycloisomerization processes that proceed via intermediate carbocations, each made possible by the inhibition of β-hydride elimination. Our working hypothesis places the platinum alkyl cation intermediates on a relatively flat, multistructural potential energy surface, with product output occurring under catalyst control by the relative energetics of Pt(II) dication extrusion. Encouraging for future development are observations that despite the flat potential energy surface of the intermediate carbocations and their inherent high reactivity, highly selective and diverse transformations are possible through catalyst variations.

Acknowledgment. We gratefully acknowledge the NIGMS (GM60578) for funding. W.D.K thanks Glaxo-Smith-Kline for a graduate fellowship. M.R.G. is a Camille−Dreyfus Teacher−Scholar.

Supporting Information Available: Experimental procedures, deuterium labeling experiments, and structural determination of **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Friedel−Craft-type cyclization on the activated ortho positions is intuitively reasonable, though we have no proof at this time.

(15) For recent examples, see: (a) Nagumo, S.; Ono, M.; Kakimoto, Y.; Furukawa, T.; Hisano, T.; Mizukami, M.; Kawahara, N.; Akita, H. *J. Org. Chem.* **2002**, *67*, 6618. (b) Nagumo, S.; Ishii, Y.; Kakimoto, Y.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 5333.

(16) (a) Schmidt, C. O.; Bouwmeester, H. J.; Franke, S.; König, W. A. *Chirality* **1999**, *11*, 353. (b) Arigoni, D. *Pure Appl. Chem.* **1975**, *41*, 219.

(17) Alternative 1,4- or 1,5-transfers from the ring are also possible. (a) Saunders: M.; Jimenez-Vazquez, H. A. *Chem. Rev.* **1991**, *91*, 375. (b) Watt, C. I. F. In *Advances in Physical Organic Chemistry*; Bethell, D., Ed.; Academic Press: New York, 1988; Vol. 24, p 57.

(18) Control experiments showed that **1b** catalyzes the isomerization of 4,4-dimethylcyclohexene to 3,3-dimethylcyclohexene.

(19) Pt catalysts **1a** and **1b** are completely selective for **3** and **5**, respectively. No traces of cyclohexenes were detected (GC) in the crude cyclopropane reaction mixtures, and vice versa.

(20) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.