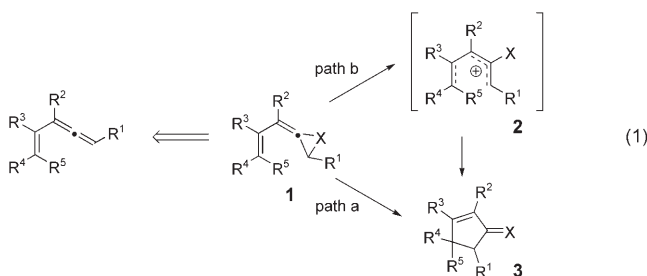


# Gold(I)-Catalyzed Synthesis of Functionalized Cyclopentadienes\*\*

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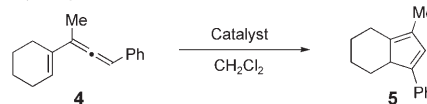
The rearrangement of vinyl allene oxides (**1**, X = O) is a key transformation in the metabolic pathway that converts arachidonic acids into cyclopentenones (**3**, X = O) [Eq (1)].<sup>[1]</sup> These rearrangements can proceed by two distinct



mechanistic pathways:<sup>[2]</sup> a concerted rearrangement (path a) involving direct addition of the olefin on the epoxide or a stepwise mechanism (path b) through a Nazarov cyclization of an oxypentadienyl cation (**2**, X = O<sup>-</sup>).<sup>[3]</sup> The regioselectivity of the cyclization is dictated by donation of the oxyanion into the resulting cation leading to the formation of a ketone. Recently, stabilization of developing positive charge through back-bonding from phosphinegold(I) complexes has been implicated in a number of rearrangement reactions.<sup>[4]</sup> Therefore, we hypothesized that coordination of cationic phosphinegold(I) complexes to a vinyl allene might mimic these reaction pathways through similar back-bonding, leading to metal-carbenoid intermediate **3** (X = R<sub>3</sub>PAu<sup>+</sup>).<sup>[5]</sup> These intermediates would further rearrange into substituted cyclopentadienes, important building blocks in organic and organometallic chemistry.<sup>[6,7]</sup>

In light of our recent success in using [Ph<sub>3</sub>PAuCl] with AgSbF<sub>6</sub> in dichloromethane for carbon-carbon bond-forming reactions,<sup>[4c]</sup> we chose this system for preliminary studies of the proposed cycloisomerization (Table 1). Treatment of vinyl allene **4** with 2 mol % cationic triphenylphosphinegold(I) afforded the desired cyclopentadiene **5** as a single regioisomer in 97 % yield after 1 min at 0 °C (Table 1, entry 1). Similar

Table 1: Catalyst optimization.



Entry	Catalyst	T [°C]	t [min]	Yield [%] <sup>[a]</sup>
1	2 % Ph <sub>3</sub> PAuCl/2 % AgSbF <sub>6</sub>	0	1	97
2	2 % Ph <sub>3</sub> PAuCl/2 % AgSbF <sub>6</sub>	-20	5	93
3	1 % Ph <sub>3</sub> PAuCl/1 % AgSbF <sub>6</sub>	0	1	96
4	5 % Ph <sub>3</sub> PAuCl	23	180	0 <sup>[b]</sup>
5	5 % AgSbF <sub>6</sub>	0	5	0 <sup>[c]</sup>
6	5 % AuCl <sub>3</sub>	0	5	30 <sup>[d]</sup>

[a] Yield of isolated product after column chromatography. [b] Starting material was recovered. [c] Decomposition occurred. [d] Determined by <sup>1</sup>H NMR spectroscopy against an internal standard (1,2,3-trimethoxybenzene).

results were obtained when a lower temperature or lower catalyst loading were used (Table 1, entries 2 and 3). Control experiments employing either 5 mol % [Ph<sub>3</sub>PAuCl] or 5 mol % AgSbF<sub>6</sub> as the sole catalyst did not lead to any conversion of **4** into **5** (Table 1, entries 4 and 5). Other transition-metal complexes showed no catalytic activity; however, gold(III) chloride rapidly consumed **4** to afford a small amount of **5** (Table 1, entry 6).<sup>[8]</sup>

With optimal conditions in hand, the scope of the gold(I)-catalyzed cycloisomerization of vinyl allenes was examined.<sup>[9]</sup> We were pleased to find that the reaction allowed for the regiospecific synthesis of functionalized cyclopentadienes in high yields with a variety of substitution patterns (Table 2). Substitution at the allene terminus was well tolerated, encompassing linear alkyl (Table 2, entries 8 and 9), oxygenated (entries 3–7), secondary benzyl (entry 1), and phenyl substituents (entry 2). Notably, the gold(I)-catalyzed reaction can be easily carried out on a gram scale albeit with a slightly diminished yield (Table 2, entry 1). Furthermore, the stability of acid-labile protecting groups, such as tetrahydropyranil (Table 2, entry 9) and silyl ethers (entries 3, 4, 6, and 7), isopropylidene acetal (entry 5), and an *N*-Boc amine (entry 6), is a testament to the mildness of the reaction conditions. Bicyclic cyclopentadienes are readily produced from the cycloisomerization of vinyl allenes containing cyclic alkenes (Table 2, entries 1–6). Additionally, the gold(I)-catalyzed reaction can be employed for the synthesis of cyclopentadienes with a quaternary carbon center (Table 2, entries 2 and 3). The use of a more electron-rich gold(I) complex, [tBu<sub>3</sub>PAuCl], as a catalyst gave improved yields for some vinyl allenes (Table 2, entries 5, 6, 8, and 9). For example, switching the gold catalyst from [Ph<sub>3</sub>PAuCl] to [tBu<sub>3</sub>PAuCl] resulted in an improved yield for the formation of cyclopentadiene **21** (Table 2, entry 8).

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[\*\*] We gratefully acknowledge the University of California, Berkeley, NIHGMMS (R01 GM073932-01), Merck Research Laboratories, Bristol-Myers Squibb, Amgen Inc., DuPont, GlaxoSmithKline, Eli Lilly & Co., Pfizer, AstraZeneca, and Roche for financial support.

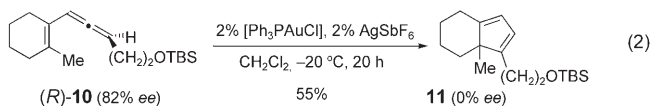
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

**Table 2:** Gold(I)-catalyzed cyclopentadiene synthesis.<sup>[a]</sup>

Entry	Vinyl allene		Cyclopentadiene	Yield [%] <sup>[b]</sup>
1		<b>6</b> <sup>[c]</sup>		<b>7</b> <sup>[c]</sup> 98 (88) <sup>[d]</sup>
2		<b>8</b>		<b>9</b> 92
3		<b>10</b>		<b>11</b> 63
4		<b>12</b>		<b>13</b> 86
5		<b>14</b> <sup>[c]</sup>		<b>15</b> <sup>[c]</sup> 78 <sup>[e]</sup>
6		<b>16</b>		<b>17</b> 53 <sup>[e]</sup>
7		<b>18</b>		<b>19</b> 72
8		<b>20:</b> R = Bn		<b>21</b> 39 (78) <sup>[e]</sup>
9		<b>22:</b> R = THP		<b>23</b> 87 <sup>[d]</sup>

[a] Reaction conditions: [Ph<sub>3</sub>PAuCl] (1.0 or 2.0 mol %), AgSbF<sub>6</sub> (1.0 or 2.0 mol %), vinyl allene in CH<sub>2</sub>Cl<sub>2</sub> (0.05 M), 0 °C, 5 min. [b] Yield of isolated product after column chromatography. [c] 1:1 mixture of diastereomers. [d] 5.3-mmol scale. [e] [tBu<sub>3</sub>PAuCl] (2.0 mol %) was employed. TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, Boc = *tert*-butyloxycarbonyl, Bn = benzyl, THP = tetrahydropyranyl.

In analogy to the rearrangement of allenoxides, the two mechanistic possibilities shown in Equation (1) were considered. To distinguish between these potential mechanisms, gold(I)-catalyzed cycloisomerization of enantioenriched vinyl allene **10** was examined [Eq. (2)].<sup>[10]</sup> Treatment of vinyl allene

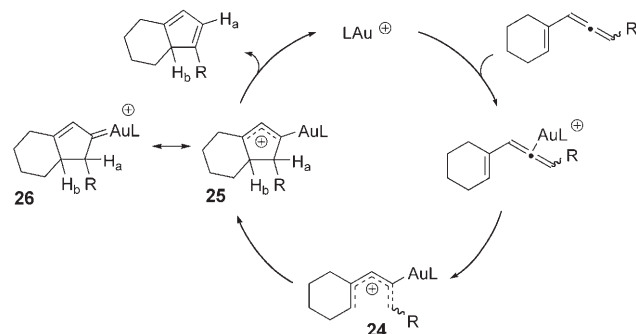


(*S*)-**10** with 2 mol % [Ph<sub>3</sub>PAuCl] and 2 mol % AgSbF<sub>6</sub> in dichloromethane at –20 °C for 20 h furnished cyclopentadiene **11** in 55% yield and with 0% enantiomeric excess. In light of recent examples of excellent chirality transfer in gold-catalyzed additions of nucleophiles to enantioenriched allenes,<sup>[11]</sup> the poor chirality transfer observed in the cyclopentadiene synthesis suggests that the reaction does not proceed through a pathway that involves direct addition of the olefin on a coordinated allene.<sup>[12]</sup>

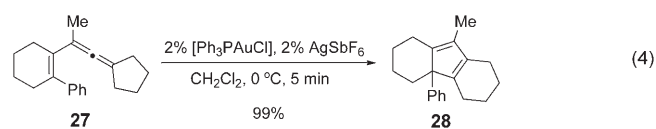
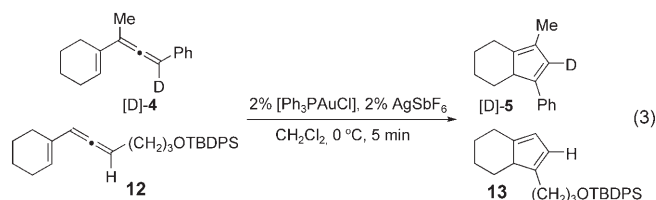
On the basis of this result, a plausible mechanism for this transformation is proposed in Scheme 1. Coordination of a cationic phosphinegold(I) to the allene results in the formation of an achiral pentadienyl cation, **24**, that undergoes electrocyclization to give the cationic intermediate **25**.<sup>[13]</sup> While regioisomeric cyclopentadienes could be formed

through loss of either of two inequivalent protons (H<sub>a</sub> or H<sub>b</sub>) in allyl cation **25**, only a single regioisomer of the cyclopentadiene is formed. The formation of a sole cyclopentadiene product is consistent with gold(I)-carbenoid intermediate **26** undergoing an intramolecular 1,2-hydrogen shift,<sup>[4b,c]</sup> rather than a mechanism involving deprotonation/protonation of a vinyl gold intermediate. This pathway is further supported by the observation of complete deuterium incorporation into [D]-**5** and the lack of crossover in a deuterium-labeling experiment using vinyl allenes [D]-**4** and **12** [Eq. (3)].

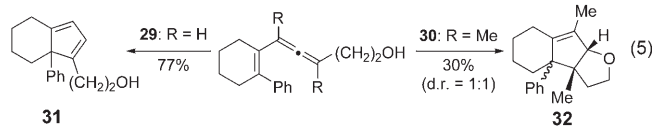
We envisioned that the 1,2-hydrogen shift in cationic intermediate **26** could be replaced by alternative reactions. To this end, we were pleased to find that fully substituted tricyclic cyclopentadiene **28** was generated in excellent yield by reacting bicyclic vinyl allene **27** with 2 mol % cationic triphenylphosphinegold(I) at 0 °C for 5 min [Eq. (4)]. Additionally, we were intrigued by the possibility



**Scheme 1.** Proposed mechanism for gold(I)-catalyzed cyclopentadiene synthesis.



of trapping the cationic intermediate through intramolecular addition of a pendant nucleophile. To examine this possibility, vinyl allenes **29** and **30** bearing a primary alcohol were subjected to the conditions of the gold(I)-catalyzed reaction. While the gold(I)-catalyzed reaction of **29** bearing a hydrogen at the allene terminus afforded cyclopentadienyl carbinol **31** as the sole product in 77% yield, the reaction of **30** bearing a methyl group at the allene terminus led to the formation of tetrahydrofuran derivative **32** [Eq. (5)].



In conclusion, we have developed a gold(I)-catalyzed cycloisomerization of vinyl allenes for the synthesis of cyclopentadienes. The mild reaction conditions of this gold(I)-catalyzed carbon–carbon bond-forming reaction provide a regioselective method for the synthesis of highly functionalized cyclopentadienes, including tricyclic structures through a tandem cycloisomerization/ring-enlargement reaction sequence. Application of the gold(I)-catalyzed reaction to the preparation of optically active metallocenes and asymmetric catalysis is ongoing in our laboratory and will be reported in due course.

Received: September 29, 2006

Published online: December 14, 2006

**Keywords:** allenes · cycloisomerization · cyclopentadienes · electrocyclic reactions · gold

- [1] a) K. Varvas, L. Järving, R. Koljak, K. Valmsen, A. R. Brash, N. Samel, *J. Biol. Chem.* **1999**, *274*, 9923; b) R. Koljak, O. Boutaud, B.-H. Shieh, N. Samel, A. R. Brash, *Science* **1997**, *277*, 1994; for examples related to biomimetic cyclopentenone annulations, see: c) E. J. Corey, S. P. T. Matsuda, R. Nagata, M. B. Cleaver, *Tetrahedron Lett.* **1988**, *29*, 2555; d) S. J. Kim, J. K. Cha, *Tetrahedron Lett.* **1988**, *29*, 5613.
- [2] a) C. S. López, O. N. Faza, D. M. York, A. R. de Lera, *J. Org. Chem.* **2004**, *69*, 3635; b) B. A. Hess, Jr., L. Smentek, A. R. Brash, J. K. Cha, *J. Am. Chem. Soc.* **1999**, *121*, 5603.
- [3] For recent reviews of Nazarov and related reactions, see: a) A. J. Frontier, C. Collison, *Tetrahedron* **2005**, *61*, 7577; b) H. Pellissier, *Tetrahedron* **2005**, *61*, 6479; c) M. A. Tius, *Eur. J. Org. Chem.* **2005**, 2193.
- [4] a) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 2456; *Angew. Chem. Int. Ed.* **2004**, *43*, 2402; b) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654; c) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858; d) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806; e) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178; f) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260; g) M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002; h) C. Fehr, J. Galindo, *Angew. Chem.* **2006**, *118*, 2967; *Angew. Chem. Int. Ed.* **2006**, *45*, 2901; i) Y. Horino, M. R. Luzung, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 11364; j) S. López, E. Herrero-Gomez, P. Pérez-Galán, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 6175; *Angew. Chem. Int. Ed.* **2006**, *45*, 6029.
- [5] For mercury- and thallium-promoted rearrangements of vinyl allenes to cyclopentenones, see: a) F. Delbecq, J. Goré, *Tetrahedron Lett.* **1976**, 3459; b) R. Baudouy, F. Delbecq, J. Goré, *Tetrahedron* **1980**, *36*, 189; c) R. Baudouy, J. Saartoretti, F. Choplin, *Tetrahedron* **1983**, *39*, 3293.
- [6] For reviews, see: a) *Metallocenes* (Eds.: A. Togni, R. L. Halterman), Wiley-VCH, New York, **1998**; b) R. L. Halterman, *Chem. Rev.* **1992**, *92*, 965; c) E. Winterfeldt, *Chem. Rev.* **1993**, *93*, 827.
- [7] For examples of cyclopentadiene synthesis, see: a) S. Datta, A. Odedra, R.-S. Liu, *J. Am. Chem. Soc.* **2005**, *127*, 11606; b) W. Zhang, S. Luo, F. Fang, Q. Chen, H. Hu, X. Jia, H. Zhai, *J. Am. Chem. Soc.* **2005**, *127*, 18; c) G. Mao, Z. Xi, *Chem. Eur. J.* **2004**, *10*, 3444; d) Z. Xi, Q. Song, J. Chen, H. Guan, P. Li, *Angew. Chem.* **2001**, *113*, 1967; *Angew. Chem. Int. Ed.* **2001**, *40*, 1913; e) Z. Xi, P. Li, *Angew. Chem.* **2000**, *112*, 3057; *Angew. Chem. Int. Ed.* **2000**, *39*, 2950.
- [8] No reaction was observed upon treatment of **4** with PtCl<sub>2</sub>, [PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>], or CuI under the following conditions: 5 mol % catalyst, 0.05 M **4** in CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 3 h.
- [9] For thermal cycloisomerization of vinyl allenes, see: a) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2004**, *126*, 10838; b) D. J. Pasto, W. Kong, *J. Org. Chem.* **1989**, *54*, 4028; For Pd-catalyzed reactions of vinyl allenes see: c) P. H. Lee, K. Lee, Y. Kang, *J. Am. Chem. Soc.* **2006**, *128*, 1139.
- [10] Enantioenriched vinyl allene was prepared from the corresponding propargylic alcohol according to Myers' procedure (see Supporting Information): A. G. Myers, B. Zheng, *J. Am. Chem. Soc.* **1996**, *118*, 4492.
- [11] a) N. Nishina, Y. Yamamoto, *Angew. Chem.* **2006**, *118*, 1930; *Angew. Chem. Int. Ed.* **2006**, *45*, 3314; b) N. T. Patil, L. M. Lutete, N. Nishina, Y. Yamamoto, *Tetrahedron Lett.* **2006**, *47*, 4749; c) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066; d) Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*; e) N. Morita, N. Krause, *Angew. Chem.* **2006**, *118*, 3392; *Angew. Chem. Int. Ed.* **2006**, *45*, 1897; f) B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4489; g) B. D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 8132; h) N. Morita, N. Krause, *Org. Lett.* **2004**, *6*, 4121; i) A. Hoffmann-Roder, N. Krause, *Org. Lett.* **2001**, *3*, 2537.
- [12] Alternatively, rapid allene racemization followed by direct addition of the olefin to a phosphinegold(I)-allene complex could also account for the poor chirality transfer. Gold(I)-catalyzed allene racemization has been previously observed, see: B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978. Furthermore, a small amount (18% yield) of the starting material **10** was also recovered with complete loss of enantiomeric excess.
- [13] a) X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802; b) N. Marison, S. Díez-González, P. de Frémont, A. R. Noble, S. P. Nolan, *Angew. Chem.* **2006**, *118*, 3729; *Angew. Chem. Int. Ed.* **2006**, *45*, 3647; c) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442; d) O. N. Faza, C. S. Lopez, R. Alvarez, A. R. de Lera, *J. Am. Chem. Soc.* **2006**, *128*, 2434.