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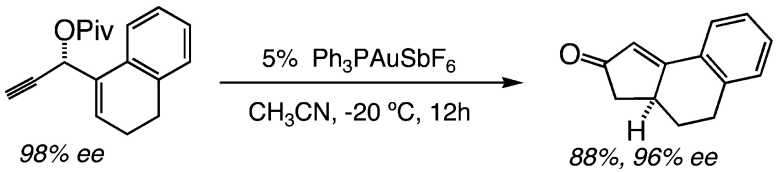


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# Synthesis of 2-Cyclopentenones by Gold(I)-Catalyzed Rautenstrauch Rearrangement

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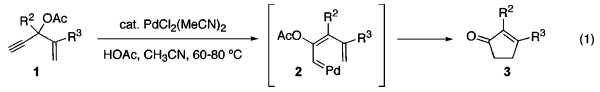
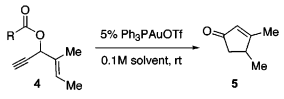
The importance of cyclopentenones as building blocks for organic synthesis continues to inspire the development of general methods for their stereoselective preparation.[1−3] In 1984, Rautenstrauch reported that palladium(II) complexes catalyzed the isomerization of 1-ethynyl-2-propenyl acetates (**1**) to cyclopentenones (eq 1).[4] This reaction and related rearrangements[5] are proposed to proceed through a metal carbene intermediate, such as **2**, arising from a 1,2-acetate migration. While the Rautenstrauch rearrangement provided an efficient route to cyclopentenones, it was limited to the preparation of achiral cyclopentenones substituted at the 2 and 3 positions (eq 1). On the basis of recent examples of gold(I)-catalyzed cyclizations of enynes,[6] we hypothesized that these catalysts might afford an increase in the scope of this reaction and allow the preparation of chiral cyclopentenones.



(1)

In light of our previous success employing $Ph_3PAuOTf$ in methylene chloride for carbon−carbon bond formation,[6b,7] we chose this catalyst system in preliminary studies of the rearrangement (eq 2). To develop catalysts that would permit the synthesis of chiral cyclopentenones, we initiated our investigation with a substrate (**4**) containing a trisubstituted olefin. We were pleased to find that rearrangement of **4**, catalyzed by 5 mol % $Ph_3PAuOTf$ in methylene chloride, did afford desired cyclopentenone **5**, however, in only 30% yield. Examination of the effect of solvent on the reaction revealed that acetonitrile produced the desired adduct with a marked improvement in yield. The yield was further improved by changing the ester from acetate to pivaloate.[8]



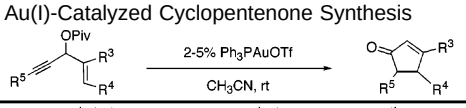

| R | solvent | rxn time | yield[a] |
|---|---|---|---|
| Me | $CH_2Cl_2$ | 0.5 h | 30% |
| Me | MeOH | 14 h | <5% |
| Me | THF | 14 h | 37% |
| Me | $CH_3NO_2$ | 1.5 h | 52% |
| Me | $CH_3CN$ | 6 h | 77% |
| Ph | $CH_3CN$ | 6 h | 76% |
| *t*-Bu | $CH_3CN$ | 6 h | 100% |

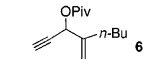
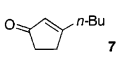
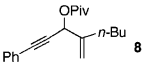
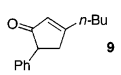
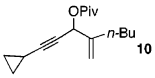
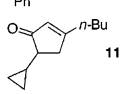
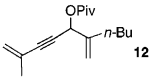
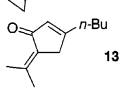
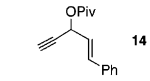
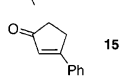
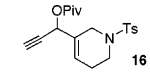
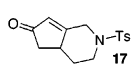
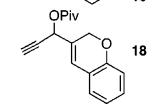
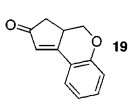
[a] yield determined by $^1$H-NMR versus an internal standard (1,2,3-trimethoxybenzene)

(2)

With optimized reaction conditions in hand, we set out to define the scope of the cyclopentenone synthesis. The reaction is highly tolerant of substitution at the acetylenic position of the 1-ethynyl-2-propenyl pivaloates (Table 1). In addition to unsubstituted alkynes, the gold(I)-catalyzed reaction proceeded smoothly with substrates containing aryl- (entry 2), alkyl- (entry 3), and vinyl-substituted alkynes (entry 4). Cyclization of the latter produced *exo*-methylene cyclopentenone **13** after isomerization of the *iso*-propenyl group into conjugation with the ketone. The reaction also showed excellent scope with respect to substitution on the olefin. Specifically, 1,1-disubstituted (entries 1−4), 1,2-disubstituted (entry 5), and cyclic (entries 6 and 7) alkenes participated in the cyclization. Rearrangement of styrenyl substrates **14** and **18** afforded 3-phenylcyclopentenones **15** and **19** as a result of olefin isomerization into conjugation with the aryl group.

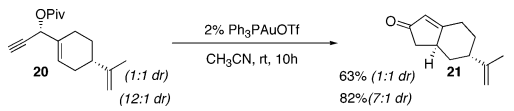
***Table 1.*** Au(I)-Catalyzed Cyclopentenone Synthesis




| entry | substrate | product | rxn time | yield[a] |
|---|---|---|---|---|
| 1 |  **6** |  **7** | 8 h | 80% |
| 2[b] |  **8** |  **9** | 20 h | 73% |
| 3[b] |  **10** |  **11** | 20 h | 85% |
| 4[b] |  **12** |  **13** | 20 h | 81% |
| 5 |  **14** |  **15** | 8 h | 68% |
| 6 |  **16** |  **17** | 14 h | 45% |
| 7 |  **18** |  **19** | 10 h | 48% |

[a] Isolated yield after column chromatography. [b] With 5 mol % $PPh_3AuOTf$ employed.

A 1:1 diastereomeric mixture of **20**, derived from (*S*)-(−)-perillaldehyde, underwent Au-catalyzed isomerization to produce bicyclic enone **21** as a 1:1 mixture of diastereomers (eq 3). We envisioned two scenarios to account for this diastereoselectivity: the stereochemistry of the starting ester is lost in generating a carbene-like intermediate (such as **2**) that undergoes subsequent cyclization with no selectivity, or the stereochemistry of the starting pivaloate influences that of the product. To probe this question, diastereoenriched **20** was subjected to the reaction condition furnishing **21** as a 7:1 mixture of diastereomers, strongly suggesting that stereochemistry of the starting ester influences that of the product cyclopentenone.

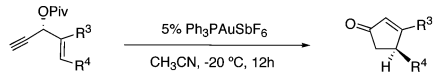


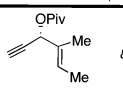
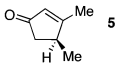
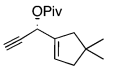
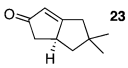
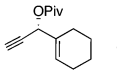
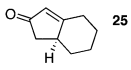
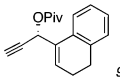
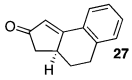
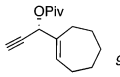
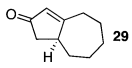
(3)

On the basis of this observation, a series of enantioenriched propargyl pivaloates[9] were prepared in order to examine the chirality transfer in the cyclization. Rearrangement of enantioenriched **24** (93% ee) under the standard conditions ($Ph_3PAuOTf$, $CH_3CN$, rt) cleanly afforded **25**, however, with only 68% ee. Switching the counterion from triflate to hexafluoroantimonate and lowering the temperature to −20 °C allowed for isolation of **25** in 86% yield


**10.1021/ja051689g CCC: $30.25** 

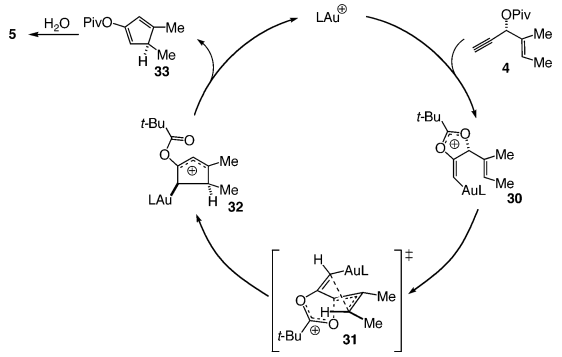
***Table 2.*** Enantioselective Cyclopentenone Synthesis




| entry | substrate (%ee) | product | yield(%ee)[a] |
|---|---|---|---|
| 1 |  **4** *88%ee* |  **5** | 84%(*82%ee*) |
| 2 |  **22** *79%ee* |  **23** | 80%(*77%ee*) |
| 3 |  **24** *93%ee* |  **25** | 86%(*91%ee*) |
| 4 |  **26** *98%ee* |  **27** | 88%(*96%ee*) |
| 5 |  **28** *92%ee* |  **29** | 82%(*83%ee*) |

[a] Isolated yield after column chromatography; % ee determined using chiral HPLC or GC (see Supporting Information for details).

***Scheme 1.*** Proposed Mechanism for the Au(I)-Catalyzed Cyclopentenone Synthesis




and with 91% ee (Table 2, entry 3). Under these conditions, Au(I)-catalyzed rearrangement of enantioenriched propargyl pivaloates delivered cyclopentenones with excellent chirality transfer (Table 2).[10]

A mechanistic hypothesis that accounts for the stereochemical course of the Au(I)-catalyzed rearrangement is shown in Scheme 1. Intramolecular 1,2-addition of the ester onto the alkyne, induced by coordination of the alkyne to a cationic gold(I) complex, affords vinyl gold species **30**. The stereoselectivity of the gold(I)-catalyzed cyclization can be accounted for by an intramolecular cyclization that proceeds through a transition state (**31**) in which the leaving group occupies a position orthogonal to the plane of the olefin.[11] This cyclization produces cationic intermediate **32**, which upon elimination of cationic gold(I), affords diene **33**.[12] Finally, cyclopentadiene **33** is hydrolyzed to cyclopentenone **5**.

In conclusion, we have developed a Au(I) catalyst for the rearrangement of 1-ethynyl-2-propenyl pivaloates to cyclopentenones. The gold(I)-catalyzed reactions are tolerant of substitution at the acetylenic and olefinic positions (except for *Z*-olefins), thus providing access to a wide range of cyclopentenones under exceptionally mild conditions. Additionally, enantioenriched cyclopentenones can be prepared by the gold(I)-catalyzed cyclization of enantioenriched propargyl alcohols. The high degree of chirality transfer in these rearrangements suggests that, in this case, a mechanism involving C−C bond formation prior to scission of the stereogenic C−O bond is operative. Efforts aimed at utilizing Au(I) complexes as catalysts for other rearrangements are ongoing in our laboratories.

**Acknowledgment.** We gratefully acknowledge the University of California, Berkeley, Boehringer Ingelheim, and Merck Research Laboratories for financial support. The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a Sponsoring Member, and Novartis Pharma as a Supporting Member.

**Supporting Information Available:** Experimental procedures and compound characterization data (PDF). This material is available free of charge on the Internet at http://pubs.acs.org.

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(2) For catalytic asymmetric Nazarov cyclizations, see: (a) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544. (b) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075. For asymmetric Nazarov cyclizations of chiral allenes, see: (c) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284.

(3) For alternative asymmetric syntheses of cyclopentenones, see: (a) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296. (b) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Brillet, C.; Garía-Granda, S.; Piñera-Nicolás, A.; Vázquez, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 4516.

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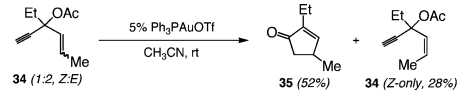
(7) (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350.

(8) Under these conditions (5% catalysts, 0.1 M acetonitrile, rt, 14 h), other metal complexes produced the following results: AgOTf (100% recovered **4**, 0% **5**); $AuCl_3$ (0% **4**, 50% **5**); $PdCl_2(MeCN)_2$ (62% **4**, 0% **5**); $PtCl_2$ (100% **4**, 0% **5**), CuBr (100% **4**, 0% **5**).

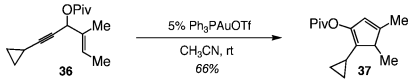
(9) Enantioenriched propargyl alcohols were prepared by reduction of the corresponding ketone with *R*-Alpine−Borane and the absolute stereochemistry assigned according to Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

(10) The absolute stereochemistry of cyclopentenone **23** ($[\alpha]_D = -174$ (*c* 1.25, $CHCl_3$)) was assigned by comparison of optical rotation to that reported in the literature ($[\alpha]_D = -141$ (*c* 0.14, $CHCl_3$)). Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835. The stereochemistry of the remaining cyclopentenones was assigned by analogy.

(11) This transition state also accounts for the observation that rearrangement of a 1:2 mixture of *Z*:*E* olefin isomers (**34**) returned the *Z*-isomer unreacted. Cyclization of the *Z*-isomer would require that the olefin substituent come into close proximity to the vinyl gold.




(12) In accord with this proposed intermediate, diene **37** was isolated from cycloisomerization of **36**.

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