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Published on Web 11/30/2005

Gold(I)-Catalyzed Stereoselective Olefin Cyclopropanation

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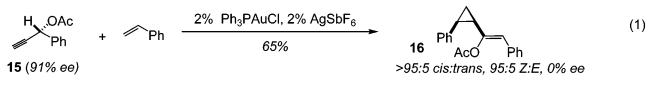
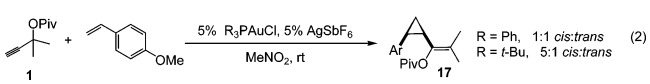
Gold(I) complexes have increasingly found use as catalysts in a variety of organic transformations.[1] While the majority of methods draw on the propensity of gold to activate alkynes toward nucleophilic addition,[2] more recent studies have suggested that carbene-like intermediates may be involved in a number of gold(I)-catalyzed reactions.[3] Similar reactivity has been observed in transition-metal catalyzed olefin cyclopropanation with propargyl acetates which is proposed to proceed via a vinyl carbene generated by transition metal-induced rearrangement of a propargyl ester.[4] On the basis of our observation that cationic phosphinegold(I) complexes catalyze the rearrangement of propargyl pivaloate esters to cyclopentenones,[5] we hypothesized that these complexes might also catalyze an intermolecular olefin cyclopropanation reaction and thereby provide a platform to further examine the apparent generation of gold(I)−carbene intermediates from alkynes.

To this end, reaction of propargyl pivaloate **1** with styrene, catalyzed by 5 mol % cationic triphenylphosphinegold(I), afforded cyclopropane **4** in 74% yield as a 6:1 mixture of *cis*:*trans* diastereomers (Table 1, entry 1). We were pleased to find that the gold(I)-catalyzed cyclopropanation reaction tolerates a wide range of olefin substitution, including monosubstituted (entries 1−3), 1,2-disubstituted (entries 4−6), 1,1-disubstituted (entries 7−8), trisubstituted (entries 9−10), and tetrasubstituted alkenes (entry 11). Functionalized olefins, such as allyltrimethylsilane and dihydropyran, smoothly underwent gold(I)-catalyzed cyclopropanation to afford cyclopropanes **5** and **7**, respectively. Additionally, a variety of common esters undergo the requisite 1,2-migration, including acetate, pivaloate, and benzoate.

To gain insight into the mechanism of this transformation, chirality transfer in the course of the gold(I)-catalyzed reaction of enantioenriched propargyl acetate **15** was examined (eq 1).[5] Gold(I)-catalyzed reaction of **15** with styrene furnished cyclopropane **16** in 65% yield with excellent olefin and cyclopropane diastereoselectivity, but with complete loss of enantiomeric excess, consistent with the formation of a vinyl gold(I)−carbene species. Moreover, the *cis*-selectivity observed in this reaction is consistent with stereochemical models proposed for cyclopropanation reactions involving carbene transfer from a transition metal−carbenoid (Scheme 1).[6]



(1)

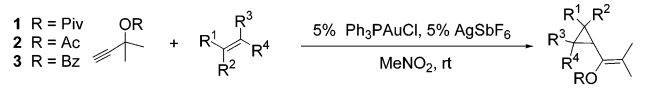


(2)

Notably, the diastereoselectivity of the gold(I)-catalyzed cyclopropanation of 4-methoxystyrene showed a dependence on the phosphine ligand (eq 2). This enhancement in *cis*-selectivity is also consistent with a model in which interaction of the olefin substituent with the ligated metal (in *path B*, Scheme 1) disfavors formation of the *trans*-cyclopropane. The high stereospecificity in the gold(I)-catalyzed cyclopropanation of *cis*- and *trans*-*β*-methyl styrenes (eqs 3 and 4) lends additional support to a mechanism that involves concerted carbene transfer from a gold(I)−carbenoid intermediate. Additionally, the increased diastereoselectivity in the cyclopropanation of the *cis*-isomer is consistent with the proposed model.

On the basis of these results and the influence of ligand on the diastereoselectivity of the cyclopropanation, we initiated studies toward the development of an enantioselective gold(I)-catalyzed cyclopropanation.[7,8] While the diop-gold(I)-catalyzed cyclopropanation of styrene furnished only racemic cyclopropane **22**, we were

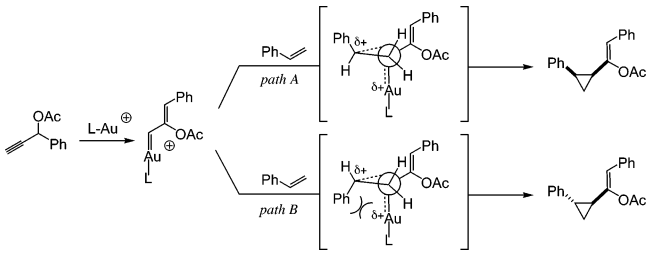
Table 1. Gold(I)-Catalyzed Cyclopropanation[a]



entry	alkene	ester	product	yield (*cis*:*trans*)
1	Ph	**1**	**4**	74% (*6:1*)
2	TMS	**2**	**5**	62% (*1.3:1*)
3	C_5H_{11}	**1**	**6**	48% (*1.3:1*)
4	O	**1**	**7**	61% (*>20:1*)
5	n	**1**	**8** n = 1	68% (*>20:1*)
6	n	**1**	**9** n = 2	69% (*1.2:1*)
7	Ph, Ph	**1**	**10**	73%
8		**3**	**11**	73%
9	Ph	**1**	**12**	84% (*5:1*)
10	Me	**2**	**13**	69% (*1.2:1*)
11		**1**	**14**	67%

[a] Reaction conditions: propargyl ester (0.2 M in nitromethane), alkene (4 equiv.), rt.

Scheme 1. Mechanistic Hypothesis



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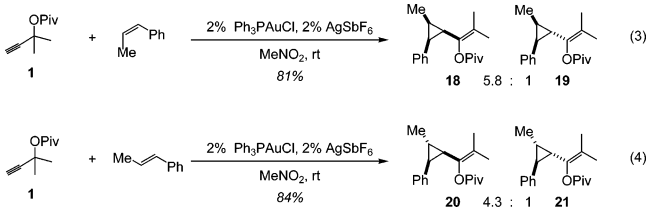
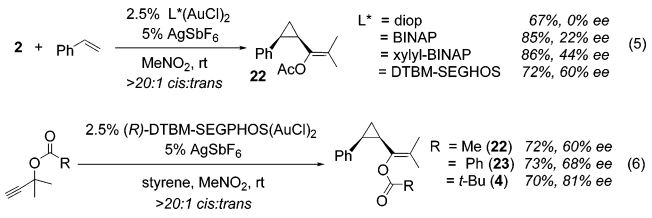


(3)

(4)

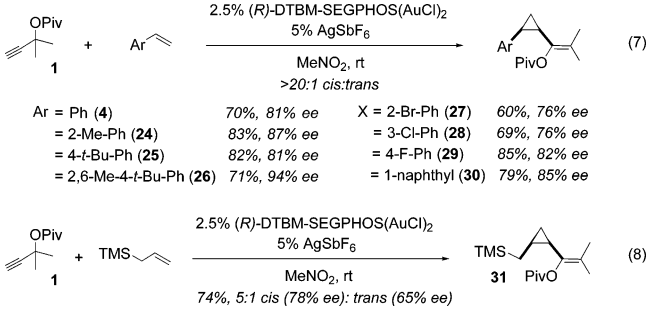
encouraged to find that **22** was generated with 22% ee in the BINAP-gold(I)-catalyzed reaction (eq 5).[9,10] Further ligand optimization identified DTBM-SEGPHOS-gold(I) as the catalyst of choice for the enantioselective olefin cyclopropanation reaction.[11] Alteration of the steric size of the propargyl ester led to the observation that sterically more demanding esters, such as pivaloate, produced cyclopropanes with higher enantiomeric excess (eq 6).[12] Notably, in all cases the gold(I)-catalyzed reaction afforded the *cis*-isomer with high diastereoselectively.



(5)

(6)

With these conditions in hand, we examined the effects of styrene aromatic ring substitution on the enantioselective cyclopropanation. As with the propargyl esters, there is a clear correlation between the steric size of the aryl substituent and enantioselectivity. For example, the enantioselectivity of the gold(I)-catalyzed cyclopropanation reaction improved from 81% ee with styrene to 87% ee with *o*-methylstyrene, and further to 94% ee in the synthesis of cyclopropane **26** (eq 7). Halogenated styrenes also participate in

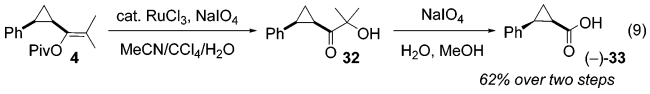


(7)

(8)

the cyclopropanation reaction. For example, 4-fluorostyrene afforded cyclopropane **29** in 85% yield and 82% ee. Gold(I)-catalyzed reaction of propargyl pivaloate **1** with 1-vinylnaphthylene produced *cis*-cyclopropane **30** in 79% yield and 85% ee. Notably, the enantioselective cyclopropanation is not limited to aryl olefins; silylmethylcyclopropane **31** is produced as a 5:1 mixture of *cis: trans* isomers with 78% and 65% ee, respectively (eq 8).

In conclusion, we have developed a triphenylphosphinegold(I)-catalyzed cyclopropanation of olefins using propargyl esters as gold(I)−carbene precursors.[13] This reaction provided the basis for the application of chiral phosphinegold(I) complexes in the enantioselective preparation of vinyl cyclopropanes with high *cis*-selectivity. Subsequent oxidative cleavage of the olefin provides *cis*-cyclopropylcarboxylic acid **32** (eq 9),[14] and therefore complements the *trans*-selectivity often observed in enantioselective olefin cyclopropanations using α-diazoacetates.[7] Moreover, the results reported herein lend further support to the intermediacy of carbene species in gold(I)-catalyzed reactions of alkynes. Further studies on the mechanism and scope of gold(I)-catalyzed cyclopropanation as well as application of chiral phosphinegold(I) complexes to enantioselective catalysis are ongoing and will be reported in due course.



(9)

Acknowledgment. We gratefully acknowledge the University of California, Berkeley, NIHGMS (R01 GM073932-01) Merck Research Laboratories, Bristol-Myers Squibb, Amgen Inc., DuPont, GlaxoSmithKline, Eli Lilly & Co., Pfizer, AstraZeneca. M.J.J. thanks the Swedish Foundation for Strategic Research for financial support. We thank Takasago International Corporation for their generous donation of SEGPHOS ligands and Dr. X. Shi for performing the chirality transfer experiment.

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

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(9) BINAP(AuCl)$_2$-catalyzed reaction in other solvents produced **21** in lower enantiomeric excess and/or lower yield. THF 30%, 0% ee; CH_3CN 28%, 27% ee; DCE 85%, 4% ee; toluene 62%, 12% ee.

(10) 5% MOP−AuCl/5% $AgSbF_6$ produced **22** in 44% yield and only 5% ee.

(11) Other SEGPHOS derivatives gave **23** with lower selectivities: SEGPHOS 43%, 35% ee, DM-SEGPHOS 58%, 61% ee.

(12) The 2,4,6-tri-*iso*-propylbenzoyl ester afforded the cyclopropane in 86% ee but only 24% yield. Other esters (*i*-Pr, 74% ee; diphenylacetyl 70% ee) gave lower enantioselectivity.

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(14) The absolute stereochemistry of **4** was assigned by comparison of the optical rotation of **33** (−17° (c = 0.4, $CHCl_3$)) with that reported in Elling, G. R.; Hahn, R. C.; Schwab, G. *J. Am. Chem. Soc*. **1973**, *96*, 5659. The stereochemistry of the remaining cyclopropanes was assigned by analogy.

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