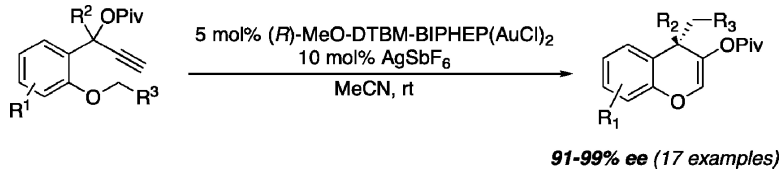
Communication

Gold(I)-Catalyzed Enantioselective Synthesis of Benzopyrans *via* Rearrangement of Allylic Oxonium Intermediates

Minoru Uemura, Iain D. G. Watson, Mikimoto Katsukawa, and F. Dean Toste

J. Am. Chem. Soc., **2009**, 131 (10), 3464-3465• DOI: 10.1021/ja900155x • Publication Date (Web): 24 February 2009



91-99% ee *(17 examples)*

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S COMMUNICATIONS

Published on Web 02/24/2009

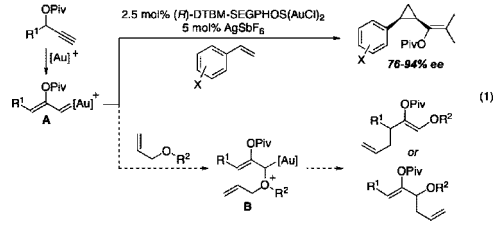
Gold(I)-Catalyzed Enantioselective Synthesis of Benzopyrans *via* Rearrangement of Allylic Oxonium Intermediates

Minoru Uemura, Iain D. G. Watson, Mikimoto Katsukawa, and F. Dean Toste*

Department of Chemistry, University of California, Berkeley, California 94720

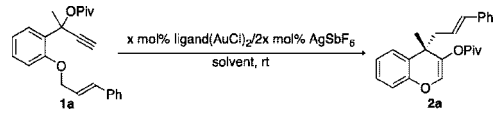
Received January 8, 2009; E-mail: fdtoste@berkeley.edu

The gold-catalyzed 1,2-rearrangement of propargyl esters has provided the basis for the development of a wide range of transformations.[1,2] These reactions are proposed to proceed through gold-stabilized cationic intermediates (**A**) that show reactivity analogous to electrophilic transition metal carbenoids.[3] Despite the current interest in reactions involving these intermediates, very few examples of enantioselective transformations have been described. We have recently reported that chiral biarylphosphinegold(I) complexes catalyze the enantioselective cyclopropanation of alkenes with propargyl esters (eq 1).[3c,i] We hypothesized that related gold(I) complexes might exert enantioface control on the addition of nucleophiles to prochiral vinylcarbenoid intermediate **A**.



On the basis of reported 2,3-rearrangements of oxonium ylides generated from transition metal stabilized carbenoid intermediates,[4] we envisioned that allyl ethers might serve as nucleophiles toward the electrophilic gold(I)−carbenoid intermediate to generate chiral gold(I)−allyl **B**. Subsequent rearrangement of allylic oxonium intermediate **B** would afford the allylated adduct.[3e] To this end, we were pleased to find that the reaction of propargyl ester **1a** with a catalytic amount of *t*-$Bu_3PAuCl/AgSbF_6$ in acetonitrile selectively provided carboalkoxylation[5] product **2a** in 70% yield (Table 1, entry 2). Notably, products derived from a competing formal 2,3-rearrangement of the oxonium ylide or intramolecular olefin cyclopropanation[3i] were not observed.

Table 1. Ligand Effects



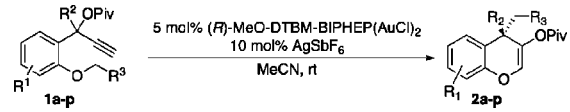
entry	ligand	x	solvent	time	**2a** (%)	ee (%)[a]
1	*t*-Bu_3P	5	$MeNO_2$	10 min	57	−
2	*t*-Bu_3P	5	MeCN	1 h	70	−
3	(*R*)-DTBM-SEGPHOS	2.5	MeCN	1 h	59	97
4	(*R*)-DTBM-SEGPHOS	2.5	$MeNO_2$	10 min	34	96
5	(*R*)-DTBM-SEGPHOS	2.5	CH_2Cl_2	10 min	26	97
6	(*R*)-MeO-BIPHEP	5	MeCN	1 h	69	30
7	(*R*)-MeO-DM-BIPHEP	5	MeCN	1 h	60	35
8	(*S*)-MeO-DTB-BIPHEP	5	MeCN	1 h	74	−96
9	(*R*)-MeO-DTBM-BIPHEP	5	MeCN	1 h	74	97

[a] Enantiomeric excess values were determined by HPLC analysis.

We turned our attention to the gold(I)-catalyzed asymmetric synthesis of **2a**. We were pleased to find that the complex employed in our gold(I)-catalyzed enantioselective cyclopropanation reaction afforded **2a** in 59% yield and 97% ee (Table 1, entry 3). Moreover, the excellent enantioselectivity was maintained when nitromethane (entry 4) or dichloromethane (entry 5)[6] were employed as solvents; however acetonitrile generally provided higher yields of **2a**.[7] As in the enantioselective cyclopropanation reaction, substitution on the phosphine aryl rings is critical to obtaining the excellent enantioselectivity. For example, the unsubstituted (entry 6) or dimethyl-substituted (entry 7) (*R*)-MeO-BIPHEP$(AuCl)_2$ generated the benzopyran with only 30% and 35% ee, respectively.[8] In contrast, when 3,5-di-*tert*-butyl MeO-BIPHEP derivatives were employed as ligands, the gold-catalyzed rearrangement proceeded with excellent enantioselectivity (entries 8 and 9).[9]

Under the optimized reaction conditions, substitution on the aryl ring was well tolerated. Propargyl pivaloate **1** having halogen (Table 2, entries 2 and 3), sterically demanding (entries 4 and 7), phenyl (entry 5), or electron-donating groups (entry 6) on the aromatic ring afforded **2** in good yields and with excellent enantioselectivities.[10,11] Use of substrates with bulkier substituents in the propargyl position decreased the rate of the reaction; however, enantioselectivities remained excellent in all cases (entries 8−10).[12]

Table 2. Gold(I)-Catalyzed Asymmetric Carboalkoxylation

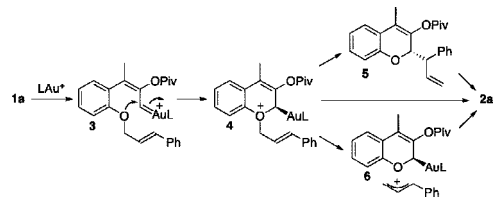


entry	substrate	time (h)	**2** (%)	ee (%)[a]
1	R^1 = H (**1a**)	1	**2a**, 74	97
2	R^1 = 4-Cl (**1b**)	1	**2b**, 69	97
3	R^1 = 4-Br (**1c**)	3	**2c**, 60	94
4	R^1 = 4-*t*-Bu (**1d**)	1	**2d**, 65	99
5[b]	R^1 = 4-Ph (**1e**)	1	**2e**, 64	97
6	R^1 = 4-OPh (**1f**)	1	**2f**, 60	97
7	R^1 = 5-*t*-Bu (**1g**)	1	**2g**, 64	98
8	$R^2 = -CH_2CH_3$ (**1h**)	3	**2h**, 53	99
9	$R^2 = -CH_2CH{=}CH_2$ (**1i**)	3	**2i**, 44	99
10[c]	$R^2 = -CH(CH_3)_2$ (**1j**)	11	**2j**, 35	98
11	Ar = *m*-MeO-C_6H_4 (**1k**)	1	**2k**, 78	99
12	Ar = *p*-Cl-C_6H_4 (**1l**)	3	**2l**, 72	98
13	Ar = *o*-Me-C_6H_4 (**1m**)	3	**2m**, 58	98
14	**1n**	3	**2n**, 55	97
15[c]	**1o**	3	**2o**, 51	97
16	**1p** (61:19, *E*:*Z*)	1	**2p**, 49 (> 95:5, *E*:*Z*)	91

[a] Determined by chiral HPLC analysis. [b] MeCN/CH_2Cl_2 = 19:1 was used as solvent. [c] 10 mol% (*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$/20 mol% $AgSbF_6$.

10.1021/ja900155x CCC: $40.75

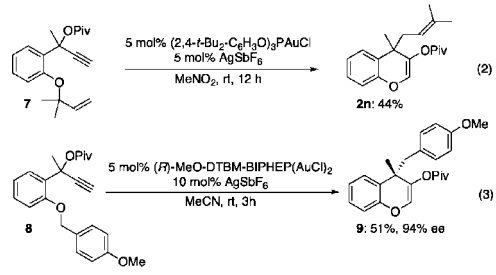
Scheme 1. Proposed Mechanisms



Of particular note is the reaction of allyl substituted ester **1i**, which underwent the desired allyl transfer product **2i** in lieu of the gold-catalyzed 1,5-enyne cycloisomerization[13] (entry 9).

We next examined the scope of the migrating ether substituent. The reaction of cinnamyl ethers bearing an electron-rich methoxy (Table 2, entry 11) or halogen (entry 12) on the aromatic ring provided desired products in good yields and excellent enantioselectivities. *Ortho*-substitution on the aromatic ring did not interfere with the reaction (entry 13). While an unsubstituted allyl group did not undergo the desired transformation, one or more alkyl groups on the alkene moiety efficiently promoted the allyl transfer reaction (entries 14−16). Notably, the reaction of **1p**, which is a mixture of *trans*/*cis* alkene isomers, gave **2p** as a single diastereomer (entry 16).

Possible mechanisms for the gold-catalyzed enantioselective rearrangement are outlined in Scheme 1. Gold(I)-promoted 1,2-migration of propargyl ester **1a** gives gold(I) carbenoid **3**, which subsequently undergoes nucleophilic attack of the ether oxygen to generate oxonium intermediate **4**. We considered several possibilities for the rearrangement of **4** into benzopyran **2a**. First, the direct conversion of **4** to **2a**, *via* a formal 1,4-sigmatropic rearrangement, was excluded by the observation that gold(I)-catalyzed rearrangement of tertiary allyl ether **7** furnished pyran **2n** with inversion of the allyl moiety (eq 2).



Alternatively, **4** could be transformed into **2a** by a 2,3-rearrangement to give **5** followed by a 3,3-rearrangement. However, the observation that, unlike related transition metal catalyzed 2,3-rearrangements of allyl ethers,[4] unsubstituted allyl ethers do not participate suggests that substantial cation character is being generated in the gold-catalyzed rearrangement. Therefore, a mechanism analogous to that proposed for related carboalkoxylation reactions,[5] involving the formation of an allyl cation and allylgold(I) intermediate **6**, seems most likely.[14] In accord with this hypothesis, gold(I)-catalyzed rearrangement of *para*-methoxylbenzyl ether **8**, which is unlikely to proceed through a pathway involving sequential 2,3/3,3-rearrangements, produced pyran **9** in 94% ee (eq 3).

In summary, we have developed an gold(I)-catalyzed carboalkoxylation reaction of propargyl esters that provides benzopyrans containing quaternary stereocenters with excellent enantioselectivity. A mechanism involving reaction of a carbocation with a chiral allylgold(I) intermediate, generated from a gold(I)-stabilized vinylcarbenoid, is proposed. This reactivity significantly expands the class of enantioselective transformations available to transition metal carbenoid intermediates generated from the 1,2-rearrangement of propargyl esters. Experiments aimed toward studying and exploiting the reactivity of these intermediates are ongoing and will be reported in due course.

Acknowledgment. We gratefully acknowledge NIGMS (R01 GM074774), Merck Research Laboratories, Bristol-Myers Squibb, Amgen Inc., and Novartis for financial support. M.U. and I.D.G.W. acknowledge postdoctoral fellowships from JSPS and NSERC, respectively. We thank Solvias for the generous donation of MeO-BIPHEP ligands and Johnson Matthey for a gift of $AuCl_3$.

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

References

(1) For recent reviews of gold-catalyzed reactions, see: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (f) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

(2) (a) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (b) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718.

(3) (a) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505. (b) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546. (c) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (d) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480. (e) Amijs, C. H. M.; López-Carrillo, V.; Echavarren, A. M. *Org. Lett.* **2007**, *9*, 4021. (f) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (g) Davies, P. W.; Albrecht, S. J.-C. *Chem. Commun.* **2008**, 238. (h) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244. (i) Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056.

(4) Enantioselective rearrangements of allylic oxonium ylides catalyzed by **Rh**: (a) Pierson, N.; Fernández-Gárcia, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705. (b) Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 7653. (c) Kitagaki, S.; Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361. (d) Hodgson, D. M.; Petroliagi, M. *Tetrahedron: Asymmetry* **2001**, *12*, 877. **Cu**: (e) Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97.

(5) For examples of gold-catalyzed O to C transfers, see: (a) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (b) Bae, H. J.; Baskar, B.; An, S. E.; Cheong, J. Y.; Thangadurai, D. T.; Hwang, I.-C.; Rhee, Y. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2263. For related Pt-catalyzed reactions, see: (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (d) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024.

(6) Reactions carried out in acetonitrile minimized the formation of the 2-acetoxyindene product. See: Nakanishi, Y.; Miki, K.; Ohe, K. *Tetrahedron* **2007**, *63*, 12138.

(7) **2a** (97% ee) was converted to the corresponding ketone without deterioration of the enantiomeric excess by treatment with 2 equiv of NaOMe in methanol (see Supporting Information).

(8) Other unsubstituted biarylphosphine ligands also gave poor enantioselectivity. For example, the (*R*)-BINAP$(AuCl)_2$ and (*R*)-Cl-MeO-BIPHEP-$(AuCl)_2$ catalyzed reactions in nitromethane gave **2a** in 16% ee and 6% ee, respectively.

(9) Replacing $AgSbF_6$ with $AgBF_4$ (61% yield, 97% ee) or AgOTf (46% yield, 97% ee) in the (*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$ catalyzed reaction afforded **2a** with identical ee's but diminished yields.

(10) The absolute stereochemistry of **2c** was assigned by X-ray crystallography (see Supporting Information), and that of the remaining structures was assigned by analogy.

(11) The corresponding propargyl acetates and benzoates were prone to elimination to form the enyne.

(12) Secondary propargyl esters (R^2 = H) afforded complex mixtures.

(13) (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (b) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858.

(14) A cross-over experiment using **1d** and **1k** (catalyzed by 5 mol% *t*-Bu_3PAuCl/$AgSbF_6$) produced only **2d** (68%) and **2k** (70%), indicating that reaction of the allylgold(I) intermediate and the cation must be rapid.

JA900155X