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

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Abstract

91-99% ee (17 examples)
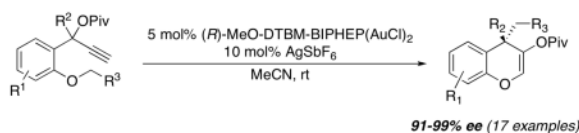
The first transition metal-catalyzed asymmetric carboalkoxylation reaction of propargyl esters is described. The (*R*)-MeO-DTBM-BIPHEP(AuCl)$_2$-catalyzed reactions allows for the construction of benzopyrans containing quaternary stereocenters with excellent enantioselectivity. Experimental evidence supports a mechanism proceeding *via* the generation of a stabilized carbocation from an allylic oxonium intermediate, and subsequent trapping by a chiral allylgold(I) spieces.

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**.
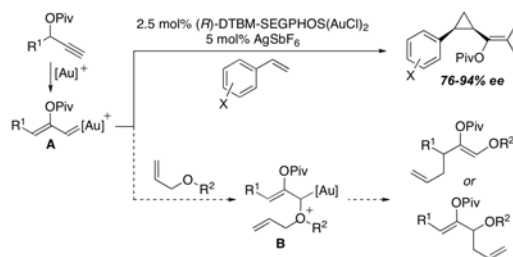
(1)

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 towards the electrophilic gold(I)-carbenoid intermediate to generate chiral gold(I)-allyl **B**.

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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$_3$PAuCl/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 or intramolecular olefin cyclopropanation[3i] were not observed.

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 or dichloromethane[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 the obtaining the excellent enantioselectivity. For example, the unsubstituted (entry 6) or dimethyl-substituted (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] 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).
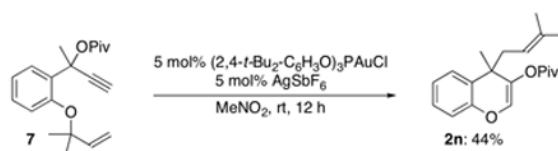
(2)
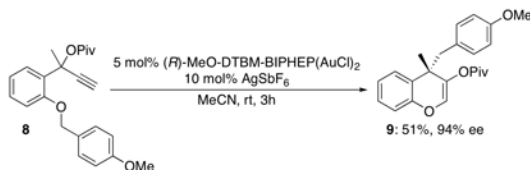
(3)

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 a (*R*)-MeO-DTBM-BIPHEP(AuCl)$_2$-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 towards studying and exploiting the reactivity of these intermediates are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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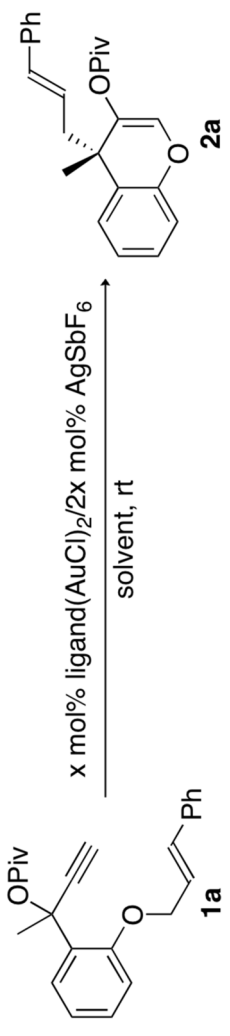
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6. Reactions carried out in acetonitrile minimized the formation of the 2-acetoxyindene product. See: Nakanishi Y, Miki K, Ohe K. Tetrahedron 2007;63:12138.

7. 2a (97% ee) was converted to the corresponding ketone without deterioration of the enantiomeric excess by treatment with 2 equiv. 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 AsSbF$_6$ 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 but diminished yield.

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

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14. A cross-over experiment using 1d and 1k (catalyzed by 5 mol% t-Bu$_3$PAuCl/AgSbF$_6$) produced only 2d (68%) and 2k (70%), indicating that reaction of the allylgold(I) intermediate and the cation must be rapid.
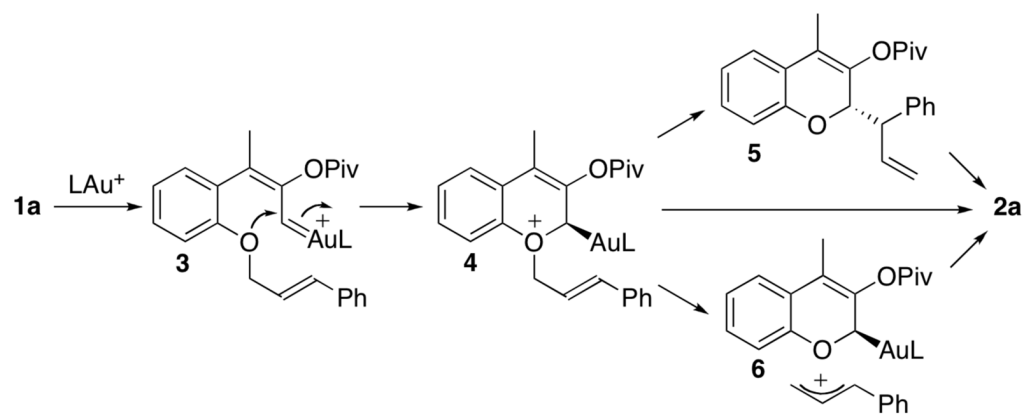
Scheme 1.
Proposed Mechanisms

Table 1

Ligand Effects

$$1a \xrightarrow[\text{solvent, rt}]{x \text{ mol\% ligand(AuCl)}_2/2x \text{ mol\% AgSbF}_6} 2a$$

entry	ligand	X	solvent	time	2a (%)	ee (%)[a]
1	t-Bu$_3$P	5	MeNO$_2$	10 min.	57	--
2	t-Bu$_3$P	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$_2$Cl$_2$	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.

Table 2

Gold(I)-Catalyzed Asymmetric Carboalkoxylation

entry	substrate	time
1	R^1 = H (**1a**)	1
2	R^1 = 4-Cl (**1b**) R^1 = 4-Br (**1c**) R^1 = 4-t-Bu (**1d**) R^1 = 4-Ph (**1e**) R^1 = 4-OPh (**1f**) R^1 = 5-t-Bu (**1g**)	1
3		3
4[b]		1
5		1
6		1
7		1
8	R^2 = −CH$_2$CH$_3$ (**1h**)	3
9	R^2 = −CH$_2$CH=CH$_2$ (**1i**)	3
10[c]	R^2 = −CH(CH$_3$)$_2$ (**1j**)	11
11		1
12	Ar = m-MeO-C$_6$H$_4$ (**1k**)	3
13	Ar = p-Cl-C$_6$H$_4$ (**1l**)	3
14	Ar = o-Me-C$_6$H$_4$ (**1m**)	3
15[c]		3
16	**1n** **1o** **1p** (81:19, E:Z)	1

[a] Determined by chiral HPLC analysis.

[b] MeCN/CH$_2$Cl$_2$=19:1 was used as solvent.

[c]10 mol% (*R*)-MeO-DTBM-BIPHEP(AuCl)$_2$/20 mol% AgSbF$_6$.