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Gold(I)-Catalyzed Asymmetric Synthesis of Planar Chiral Arene Chromium Complexes

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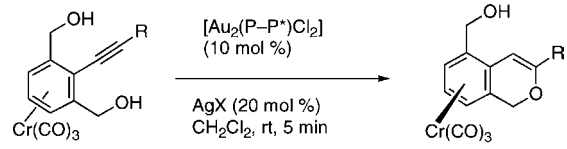
ABSTRACT



a: R = Me; **b** = *n*-Bu, **c**: R = Ph

up to 99% ee

Gold(I)-catalyzed asymmetric cyclization of 1,3-dihydroxymethyl-2-alkynylbenzene chromium complexes gave planar chiral isochromene chromium complexes with high enantioselectivity. Enantiomeric excess of the cyclization products was largely affected by a combination of axially chiral diphosphine(AuCl)$_2$ precatalysts and silver salts. A system of segphos(AuCl)$_2$ with AgBF$_4$ resulted in the formation of the corresponding antipode.

Planar chiral tricarbonyl(arene)chromium complexes have been widely employed in asymmetric synthesis, natural product synthesis and as chiral ligands in asymmetric catalysis.[1,2] Enantiomerically enriched planar chiral arene chromium complexes are accessible by a resolution[3] and asymmetric synthesis,[4] e.g., diastereoselective complexation, diastereoselective or enantioselective lithiation/electrophilic quenching, and nucleophilic addition/hydride abstraction. In

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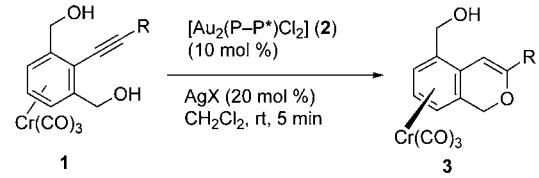
contrast to these methods, efforts to perform catalytic asymmetric synthesis of the planar chiral arene tricarbonylchromium complexes have met with little success. A potentially attractive catalytic route is a desymmetrization[5] of prochiral compounds by a chiral catalyst. We reported the first catalytic asymmetric desymmetrization of a prochiral *o*-dichlorobenzene chromium complex by palladium-catalyzed Suzuki−Miyaura cross-coupling reaction.[6] However, both yield and enantiomeric excess of the mono coupling products were moderate. After that, some catalytic asymmetric synthesis of the planar chiral arene chromium complexes have been reported by Schmalz et al.,[7] Kündig et al.,[8] and us,[9] but satisfactory results regarding both yield and asymmetric induction were not optimal.

The number of reports on the utility of gold(I) complexes as homogeneous catalysts for organic synthesis has recently increased dramatically.[10] Furthermore, asymmetric versions have emerged over 5 years, leading to the development of effective gold(I)-catalyzed enantioselective reactions.[11] Gold(I)-catalyzed intramolecular asymmetric addition of heteroatom and carbon nucleophiles to allenes has been particularly achieved with high enantioselectivity.[12] Some gold(I)-catalyzed asymmetric reactions such as cycloisomerization, cycloaddition, and cyclopropanation have been also performed in enyne or alkyne compounds,[13] while direct asymmetric addition of heteroatom nucleophiles to the alkynes has not yet been reported.[14] As an extension of the gold(I)-catalyzed organic reaction of tricarbonylchromium coordinated alkynyl arenes,[15] we would like to report herein asymmetric version of an intramolecular hydroalkoxylation to the alkynes of alkynylbenzene chromium complexes for an efficient induction of the planar chirality.

We were pleased to find that an intramolecular nucleophilic addition of a hydroxy group of prochiral 1,3-dihydroxymethyl-2-alkynylbenzene chromium complexes **1** took place smoothly by the reaction with axially chiral diphosphine(AuCl)$_2$ precatalyst **2** and silver salt with good to excellent enantioselectivity (Table 1). The reaction was performed at room temperature within 5 min with 10 mol % diphosphine(AuCl)$_2$ catalyst **2** and 20 mol % silver salt

Table 1. Gold(I)-Catalyzed Asymmetric Hydroalkoxylation of (1,3-Dihydroxymethyl-2-alkynyl)benzene Chromium Complexes



1 **3**

a: R = Me; **b**: R = *n*-Bu; **c**: R = Ph

2a: (*R*)-Binap(AuCl)$_2$,Å@**2b**: (*R*)-Xylylbinap(AuCl)$_2$,Å@
2c: (*R*)-3,5-di-Me-4-MeO-Binap(AuCl)$_2$, **2d**: (*R*)-Segphos(AuCl)$_2$

entry	complex **1**	gold catalyst **2**	X	yield %	% ee[a]
1	**1a**	**2a**	BF_4	86	62
2	**1a**	**2a**	NTf_2	86	95
3	**1a**	**2a**	OTf	78	47
4	**1a**	**2a**	SbF_6	67	95
5	**1a**	**2b**	NTf_2	76	99[b]
6	**1a**	**2b**	SbF_6	87	99
7	**1a**	**2c**	SbF_6	91	99
8	**1a**	**2d**	BF_4	69	−27
9	**1b**	**2a**	NTf_2	87	96
10	**1b**	**2a**	SbF_6	55	93
11	**1b**	**2b**	NTf_2	75	98
12	**1b**	**2b**	SbF_6	87	99[c]
13	**1b**	**2c**	SbF_6	91	98
14	**1b**	**2d**	BF_4	67	−48
15	**1c**	**2a**	NTf_2	79	99
16	**1c**	**2b**	BF_4	73	97
17	**1c**	**2b**	NTf_2	89	99[d]
18	**1c**	**2b**	SbF_6	70	97
19	**1c**	**2c**	BF_4	92	96
20	**1c**	**2d**	BF_4	88	−48

[a] Enantiomeric excess was determined by HPLC with chiralpak AD-H. [b] $[\alpha]^{20}_D = +1116$ (*c* 0.41 in $CHCl_3$). [c] $[\alpha]^{20}_D = +893$ (*c* 0.27 in $CHCl_3$). [d] $[\alpha]^{20}_D = +821$ (*c* 0.27 in $CHCl_3$).

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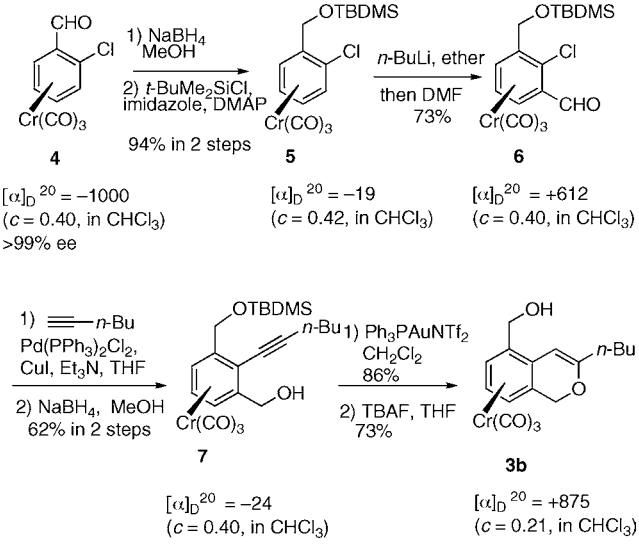
in methylene chloride. It is noteworthy that enantioselectivities of the cyclized isochromene chromium complexes **3** are largely dependent on the combination of gold precatalysts **2** and silver salts. Particularly, an employment of $AgSbF_6$ resulted in excellent enantioselectivities regardless of the nature of the gold precatalyst (entries 4, 6, 7, 10, 12, 13, 18). With $AgNTf_2$, high enantioselectivities were also achieved (entries 5, 9, 11, 15, 17). The use of AgOTf and $AgBF_4$ salts resulted in decreased enantioselectivities of the cyclized chromium complexes **3**. Interestingly, a combination of segphos$(AuCl)_2$ and $AgBF_4$ gave the corresponding antipode of cyclized isochromene chromium complexes (entries 8, 14, 20), although the reason is not clear. In this way, a counterion of the silver salt in the gold-catalyzed asymmetric cyclization of prochiral 1,3-bis(hydroxymethyl)-2-alkynylbenzene chromium complexes controls the enantiopurity dramatically. Thus, the stereochemical information via ion pairs of the anion with the gold cation may have tremendous potential for the enantioselectivity. Use of a smaller amount of the catalysts (e.g., 3 mol % of chiral gold and 6 mol % silver salt) required several hours until disappearance of the starting material. However, chemical yield of the cyclized chromium complex **3** was less than 30% due to instability of the starting chromium complex in a solution, while the enantioselectivity was still excellent. Therefore, a short reaction time is essential for the achievement of high yield with excellent selectivity.

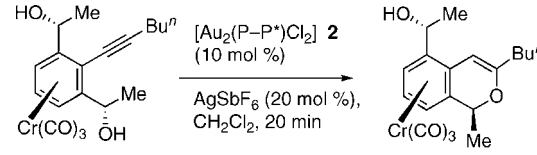
The absolute configuration of the asymmetric gold(I)-catalyzed cyclization product was determined by a comparison of an optical rotation value with that of the authentic compound (Scheme 1). Stereodefined (−)-(1*R*)-*o*-chlorobenzaldehyde tricarbonylchromium[16] (**4**) was converted to the (+)-*tert*-butyldimethylsilyl ether of 2-chloro-3-formylbenzylalcohol chromium complex **6** by *ortho* lithiation of the chromium complex **5** followed by a trap with DMF. Sonogashira coupling of **6** with 1-hexyne followed by reduction of formyl group gave (−)-alkyne chromium complex **7**. The cyclization of **7** with 10 mol % $(PPh_3)AuNTf_2$ in CH_2Cl_2 at room temperature and subsequent desilylation afforded (+)-isochromene chromium complex **3b**. An optical rotation value and chiral HPLC behavior of the authentic complex were completely consistent with those of gold(I)-catalyzed asymmetric cyclized product **3b**, and thus the absolute configuration of the gold-catalyzed asymmetric cyclization compounds **3** was determined as R_p.

Scheme 1. Synthesis of Authentic (+)-3-*n*-Butyl-5-hydroxymethyl-1*H*-isochromene Tricarbonylchromium



The gold(I)-catalyzed asymmetric induction of the planar chirality was further applied to two chromium complexes of *meso*-1,3-bis(α-hydroxyethyl)-2-(hex-1-ynyl)benzene with a chiral center at the benzylic position. In these compounds, two chiral centers beside the planar chirality could be induced by the gold-catalyzed asymmetric cyclization. Treatment of a *meso* chromium complex **8** gave optically active isochromene chromium complex **9** with chiral gold catalyst and silver salt in methylene chloride at room temperature in high enantioselectivity. The employment of $AgSbF_6$ salt resulted in excellent selectivity regardless of the chiral gold catalysts, although the chemical yields were moderate (Table 2).

Table 2. Gold-Catalyzed Asymmetric Cyclization of *meso* Arene Chromium Complex **8**



entry	gold catalyst **2**	temp (°C)	yield (%)	% ee[a]
1	**2a**	rt	24	96
2	**2b**	rt	43	98
3	**2b**	40	34	97
4	**2c**	rt	59	99[b]

[a] Enantiomeric excess was determined by HPLC with chiralpak AD-H. [b] $[\alpha]^{20}_D = +949$ (*c* 0.41 in $CHCl_3$).

A diasteromeric *meso* chromium complex **10** was also cyclized to give an optically active isochromene chromium complex **11** (Table 3). In this case, high enantiomeric excess was obtained by employment of binap$(AuCl)_2$ precatalyst. Particularly, the combination with $AgNTf_2$ resulted in higher selectivity (entry 2). Both *meso* chromium complexes **8** and **10** led to 1-methyl-3-*n*-butyl-5-(α-hydroxyethyl)isochromene chromium complexes with induction of the planar and two central chiralities with excellent enantioselectivity.

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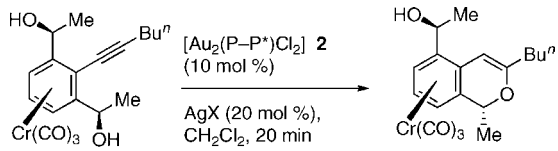
(16) (−)-Enantiopure *o*-chlorobenzaldehyde chromium complex **4** was prepared by diastereoselective *ortho* lithiation of (+)-(benzylidene)methyl-α-D-glucopyranoside chromium complex according to literature procedure. Han, J. W.; Son, S. U.; Chung, Y. K. *J. Org. Chem.* **1997**, *62*, 8264.

Table 3. Asymmetric Cyclization of *meso* Chromium Complex **10**



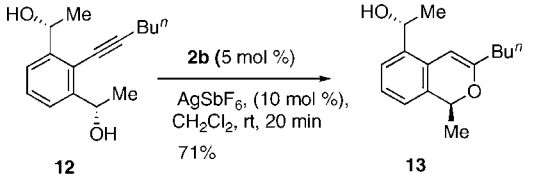
10 **11**

entry	**2**	X	temp (°C)	yield (%)	% ee[a]
1	**2a**	BF_4	rt	53	15
2	**2a**	NTf_2	rt	69	95[b]
3	**2a**	SbF_6	rt	41	88
4	**2a**	SbF_6	40	55	86
5	**2b**	SbF_6	rt	27	56
6	**2b**	SbF_6	40	39	44
7	**2c**	SbF_6	rt	45	75
8	**2d**	SbF_6	rt	23	49

[a] Enantiomeric excess was determined by HPLC with chiralpak AD-H. [b] $[\alpha]^{20}_D = +749$ (*c* 0.08 in $CHCl_3$).

An effect of the tricarbonylchromium fragment for the gold(I)-catalyzed intramolecular asymmetric cyclization of 1,3-dihydroxymethyl-2-alkynylbenzene was next studied. The corresponding chromium-free *meso*-1,3-bis(α-hydroxyethyl)-2-(hex-1-ynyl)benzene (**12**) was treated with 5 mol % [(*R*)-xylyl binap(AuCl)$_2$] (**2b**) and 10 mol % $AgSbF_6$ in CH_2Cl_2 at room temperature to afford an isochromene compound **13** in 71% yield with 84% ee (Scheme 2). The absolute

Scheme 2. Gold-Catalyzed Asymmetric Cyclization of Chromium-Free *meso*-1,3-Bis(α-hydroxyethyl)-2-(hex-1-ynyl)benzene

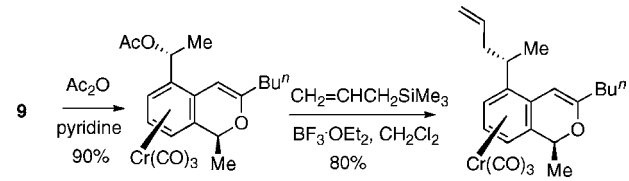


12 **13**

$[\alpha]_D^{20}$ +17 (*c* = 0.3, $CHCl_3$)
84% ee

configuration of major isomer of the compound **13** was consisted with that of dechromium compound of **9** by chiral HPLC (Chiralcel OD-H). This result indicates that the tricarbonylchromium coordination increased the enantioselectivity for gold(I)-catalyzed asymmetric cyclization, although a amount of the catalyst is not identical.

Scheme 3. Stereoselective Carbon−carbon Bond Formation at Benzylic Position of Asymmetric Cyclization Product



14 **15**

$[\alpha]_D^{20} = +497$
(*c* = 0.26, $CHCl_3$)

$[\alpha]_D^{20} = +935$
(*c* = 0.69, $CHCl_3$)

The benzylic hydroxy group of chiral isochromene chromium complex **9** could be further substituted with carbon nucleophiles. The reaction of the corresponding acetate chromium complex **14** with allyl trimethylsilane in the presence of borontrifluoride etherate gave allyl substitution chromium complex **15** with stereochemical retention at the benzylic position in 80% yield.[17] As a double bond of the cyclized isochromene chromium complexes could be stereoselectively reduced to *trans*- and *cis*-1,3-disubstituted isochoman,[15b] the gold(I)-catalyzed asymmetric cyclization of 1,3-dihydroxymethyl-2-alkynylbenzene chromium complexes would be useful for the synthesis of naturally occurring optically active 1,3,5-substituted isochroman derivatives with three central chiralities.

In conclusion, the gold(I)-catalyzed asymmetric cyclization of 1,3-dihydroxymethyl-2-alkynylbenzene chromium complexes has been achieved with excellent enantioselectivity. Enantiomeric excess was largely affected by the nature of silver salts.

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

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