Atropisomerism

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Axial Chirality Control of Gold(biphep) Complexes by Chiral Anions: Application to Asymmetric Catalysis**

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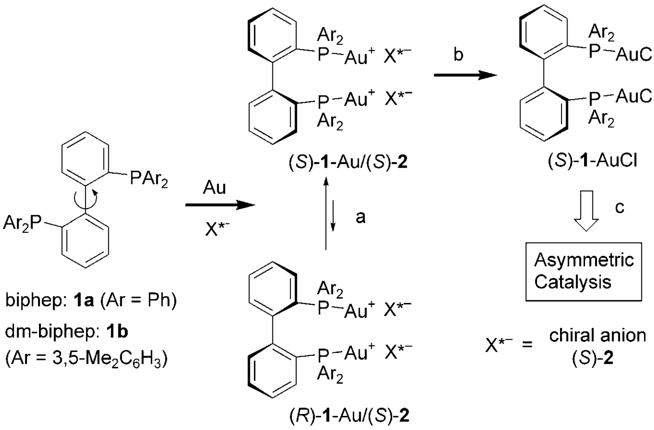
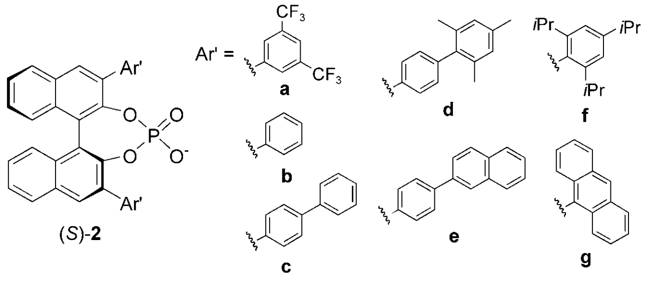
In transition-metal-catalyzed reactions, the design of chiral ligands is important to achieve a high level of asymmetric induction. A dramatic increase in catalytic activity and enantioselectivity can result from a subtle change in the conformational, steric, and electronic properties of chiral ligands.[1] Many efficient chiral phosphine ligands, especially atropisomeric (atropos)[2] ones, have been reported to induce high enantioselectivity and yield.

However, does the pursuit of atropos ligands always result in efficient asymmetric catalysis? Because of the substrate dependence of many catalyst systems, tunable and readily synthesized chiral ligands are strongly desirable. Chirally flexible (tropos)[2b,c] ligands, which are highly modular, versatile, and easy to synthesize without resolution, have thus been a recent topic in asymmetric catalysis;[2,3] We have focused on the tropos bis(phosphanyl)biphenyl (biphep) ligands **1**[4] to develop a new strategy for asymmetric catalysis. The biphep ligands can behave dynamically as chiral bidentate ligands for Ru,[5] Rh,[6] Pd,[7] and Pt[8] complexes when their axial chirality is controlled by chiral diamine or diene ligands. We report herein that axial chirality can be controlled in gold–biphep complexes in a highly stereospecific manner by using the binaphthol-derived phosphate anion **2**,[9,10,11] and that high levels of enantioselectivity can be attained in intramolecular hydroamination (Scheme 1). In contrast to our previous reports,[5–8] chirality control can be attained by monodentate coordination of the chiral anion **2** as a supramolecular chiral auxiliary. The control of the axial chirality of a metal complex by a chiral anion[12] with a high degree of stereospecificity has been a long-standing challenge.



Scheme 1. Strategy of this work. a) Axial chirality control of tropos biphep–gold complexes **1** by using chiral anion **2**. b) Isolation of chirally stable enantiopure biphep–gold complexes below room temperature. c) Application of enantiopure biphep–gold complexes to asymmetric catalysis.



We attempted to control the axial chirality of **1**-Au/(*S*)-**2** complexes by converting the thermodynamically unfavorable diastereomer to the thermodynamically favorable one (Table 1). The combination of *rac*-**1**-AuCl and two equivalents of the silver phosphate complex (*S*)-**2**-Ag in acetone at room temperature produced a mixture of **1**-Au/(*S*)-**2** diastereomers quantitatively within 1 h. The use of anion **2a** initially led to a d.r. value of 52:48, which did not change at room temperature (Table 1, entry 1). However, the isomerization proceeded in acetone at 80 °C over 14 h to give (*S*)-**1a**-Au/(*S*)-**2a** (75:25) as the major diastereomer (Table 1, entry 2). No change of d.r. was observed upon heating up to 100 °C (Table 1, entry 3). Benzene or THF as a solvent resulted in lower diastereoselectivity (Table 1, entries 4 and 5). By introducing a variety of aryl substituents at the 3,3′-positions of the binaphthyl backbone, a series of chiral anions (*S*)-**2** can be generated. When (*S*)-**2** derivatives bearing only phenyl rings or *para*-substituted phenyl rings were used, remarkably high diastereoselectivity resulted (Table 1, entries 6 and 7). Additionally, the **1a**-Au complexes with chiral anions **2d**,**e** isomerized at 100 °C over 14 h to afford exclusively the thermodynamically favored (*S*)-**1a**-Au/(*S*)-**2** complexes (Table 1, entries 8 and 9). As a result of the steric effect of biphep moiety, the **1b**-Au complexes with the chiral anions **2c**

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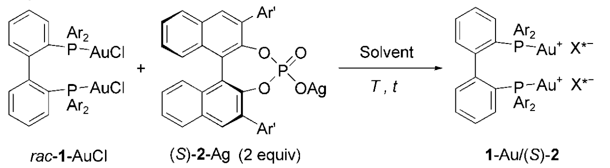
Table 1: Chirality control of biphep–gold complexes using various chiral phosphate anions **2**.[a]



Entry	*rac*-**1**	(*S*)-**2**	Solvent	*T* [°C]	*t* [h]	d.r.[b]
1	**1a**	**2a**	acetone	RT	1	52:48
2	**1a**	**2a**	acetone	80	14	75:25
3	**1a**	**2a**	acetone	100	14	75:25
4	**1a**	**2a**	benzene	100	12	53:47
5	**1a**	**2a**	THF	80	12	71:29
6	**1a**	**2b**	acetone	100	14	96:4
7	**1a**	**2c**	acetone	100	14	99:1
8	**1a**	**2d**	acetone	100	14	100:0
9	**1a**	**2e**	acetone	100	14	100:0
10	**1b**	**2a**	acetone	80	14	87:13
11	**1b**	**2b**	acetone	100	12	89:11
12	**1b**	**2c**	acetone	100	12	100:0
13	**1b**	**2d**	acetone	100	6	decomp.
14	**1b**	**2e**	acetone	100	6	100:0

[a] The use of **2f** and **2g** led to decomposition upon heating. [b] The diastereomer ratio of [(*S*)-**1**-Au/(*S*)-**2**]/[(*R*)-**1**-Au/(*S*)-**2**].

and **2e** gave perfect diastereoselectivity (d.r. 100:0), and the isomerization was found to be faster to afford the single diastereomer (Table 1, entries 12 and 14). The chiral anions **2f,g** with the *ortho*-disubstituted phenyl ring rather than *para*- or *meta*-disubstituted[10] led to decomposition upon heating as a result of strong steric repulsion.

The relative configuration of the major diastereomer (*S*)-**1a**-Au/(*S*)-**2b** was determined by X-ray analysis of a single crystal obtained from a solution of the 96:4 mixture of diastereomers in dichoromethane/ethyl acetate (Figure 1).[13] It was confirmed that the digold complex, in which an oxygen atom of the chiral anion coordinates in a monodentate fashion, has C_2 symmetry. In spite of the presence of the sterically demanding chiral anion, an intramolecular Au–Au contact (2.99 Å) was observed.

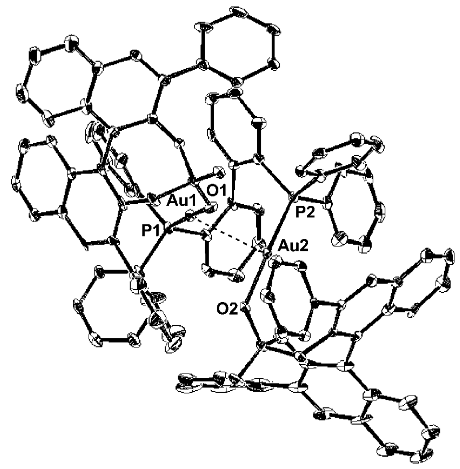


Figure 1. ORTEP view of the diastereopure (*S*)-**1a**-Au/(*S*)-**2b** complex showing Au–Au bonding. Ellipsoids are at the 30% probability level; hydrogen atoms and the solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: Au1–Au2 2.9937(2), Au1–P1 2.2070(12), Au2–P2 2.2178(12), Au1–O1 2.066(3), Au2–O2 2.064(3); P1-Au1-O1 177.64(9), P2-Au2-O 177.03(9).

The isomerization rate of the **1a**-Au/(*S*)-**2e** complex in acetone as a coordinating solvent was influenced by the concentration (Figure 2). The isomerization was complete within 10 h for the 2.5 mM solution but required 20 h at higher concentration (10.0 mM). These results indicate that acetone presumably stabilizes an isomerizing cationic intermediate generated by dissociation of the chiral anion. With the more sterically demanding dm-biphep ligand **1b**, the isomerization of the complex was found to be faster to give the single diastereomer within 6 h.

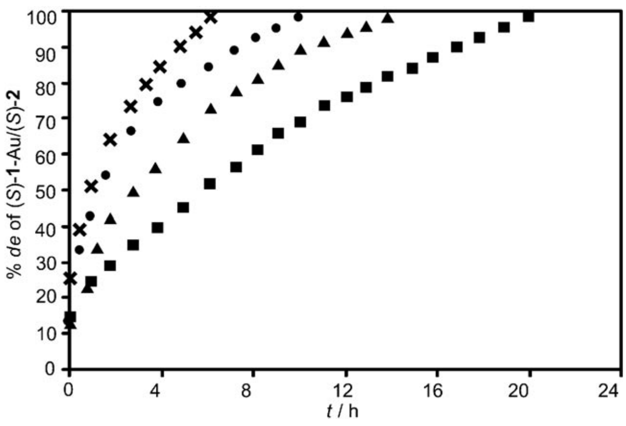
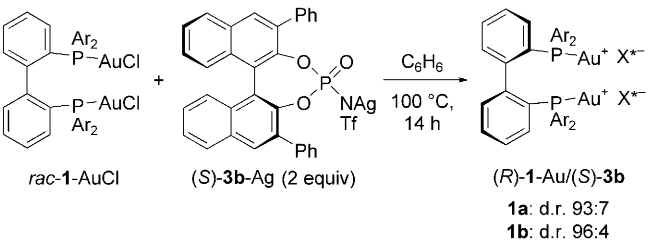


Figure 2. Effect of concentration and substituent on the biphep moiety on the isomerization of **1**-Au/(*S*)-**2e** complexes in acetone at 100 °C. **1a**-Au/(*S*)-**2e:** 2.5 mM (●), 5.0 mM (▲), 10.0 mM (■); **1b**-Au/(*S*)-**2e:** 5.0 mM (×).

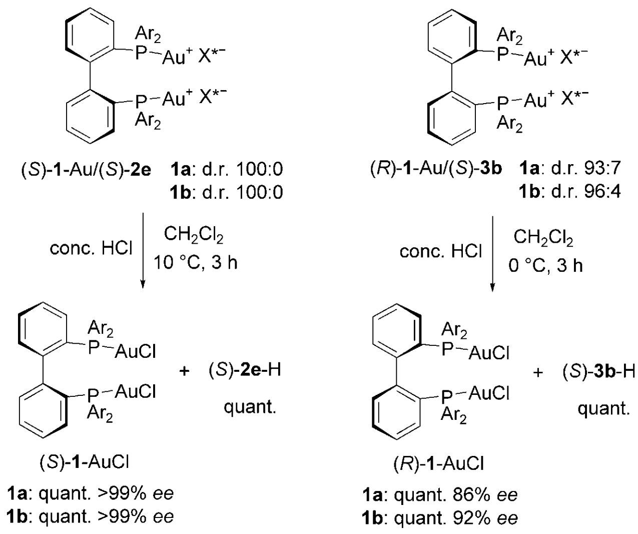
In sharp contract to phosphate anion **2**, *N*-triflyl phosphoramide anion **3**[14] converted the biphep moiety to the previously less favored *R* configuration (Scheme 2). The racemic **1**-AuCl complex was mixed with two equivalents of (*S*)-**3b**-Ag to give a 57:43 mixture of diastereomers in benzene at room temperature; use of acetone as the solvent led to decomposition. Sequentially, the isomerization of the complex by using **3b** proceeded at 100 °C for 14 h to produce (*R*)-**1**-Au/(*S*)-**3b** (**1a**: d.r. 93:7; **1b**: d.r. 96:4) as the major diastereomer.

With these successes in chirality control of biphep–gold species at 100 °C, we tried to isolate the enantiopure **1**-AuCl



Scheme 2. Chirality control of biphep–gold complexes using chiral *N*-triflyl phosphoramide anion **3b**.

complexes without isomerization (Scheme 3). The single diastereomer (*S*)-**1**-Au/(*S*)-**2e** was found to produce the enantiopure complex (*S*)-**1**-AuCl (> 99 % *ee*) quantitatively upon addition of conc. HCl in dichloromethane at 0 or 10 °C after 3 h. The chiral phosphoric acid (*S*)-**2e**-H corresponding to the protonated (*S*)-**2e** could also be recovered quantitatively by silica gel chromatography. The enantiomeric excess of the dichloride complexes thus obtained was determined by ^{31}P NMR analysis after complexation with two equivalents of (*S*)-**2a**-Ag. Similarly, (*R*)-**1**-Au/(*S*)-**3b** could be transformed into the (*R*)-**1a**-AuCl or (*R*)-**1b**-AuCl bearing opposite absolute configuration quantitatively under the same conditions, without decreasing the enantiomeric integrity of biphep moiety. Interestingly, it was demonstrated that even the *ortho*-disubstituted biphenyl compounds can be resolved as atropos isomers which are chirally stable at room temperature.



Scheme 3. Quantitative isolation of enantiopure (*S*)- and (*R*)-**1**-AuCl complexes without isomerization and recovery of the chiral anion.

The structure of the (*S*)-**1a**-AuCl complex with C_2 symmetry[15] was determined by X-ray analysis of a single crystal obtained from dichoromethane solution (Figure 3).[16] The Au–Au distance was found to be 3.10 Å, which indicates the presence of Au–Au contact.[17] The solid-state structure of (*S*)-**1a**-AuCl was obviously different from the corresponding (tol-binap)gold and (dm-binap)gold complexes (binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) which have π–π stacking interactions between the two aryl groups on the phosphines.[18]

In order to determine the energy barrier of isomerization, enantiopure (*S*)-**1**-AuCl complexes were heated at four different temperatures (60, 70, 80, and 90 °C) in dichloroethane and the ^{31}P NMR signals were monitored after coordination with the chiral anion (*S*)-**2e**. The $\Delta G^{\neq}$ values of (*S*)-**1a**-AuCl and (*S*)-**1b**-AuCl at 27 °C (300 K) were measured to be 26.2 and 27.6 kcal mol^{-1}, respectively (Table 2, entries 1 and 2). Half-life times of biphep (**1a**)- and dm-biphep (**1b**)-AuCl complexes at 300 K were calculated to be 406 and 4097 h, respectively. These results clearly show that the coordination of gold to the biphep ligands significantly increases the energy barrier to block the internal rotation about the biphenyl single bond.[4,19] On the other hand, the use of acetone as a coordinating solvent decreases the torsional barrier to promote the dissociation of Au–Au contact (Table 2, entry 3).

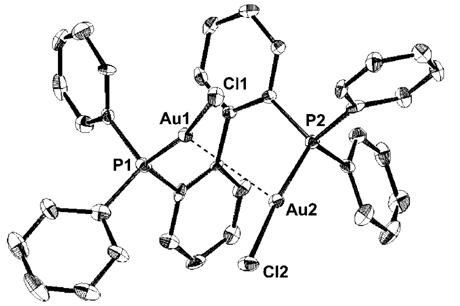


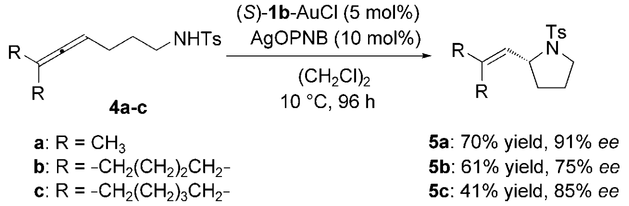
Figure 3. ORTEP view of enantiopure (*S*)-**1a**-AuCl complex showing Au–Au bonding. Ellipsoids are at the 50% probability level; hydrogen atoms and the solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: Au1–Au2 3.0992(3), Au1–P1 2.2347(18), Au2–P2 2.2383(19), Au1–Cl1 2.2965(18), Au2–Cl2 2.2897(19); P1-Au1-Cl1 169.77(6), P2-Au2-Cl2 173.76(6).

Table 2: Thermodynamic data for the isomerization of enantiopure (*S*)-**1**-AuCl complexes.

Entry	Complex	$t_{1/2}$ [h][c]	$\Delta G^{\neq}$ [kcal mol^{-1}][c]	$[\alpha]_D$
1[a]	(*S*)-**1a**-AuCl	406	26.2	+12.8[d]
2[a]	(*S*)-**1b**-AuCl	4097	27.6	+38.6[e]
3[b]	(*S*)-**1b**-AuCl	987	26.8	–

[a] In dichloroethane. [b] In acetone. [c] At 27 °C (300 K). [d] At 25 °C, *c* = 0.5 in CHCl$_3$. [e] At 27 °C, *c* = 0.5 in CHCl$_3$.

Having established the isolation of the enantiopure (*S*)-**1**-AuCl complexes, we investigated their ability as atropos asymmetric catalysts (Scheme 4). These enantiopure complexes were applied to the intramolecular hydroamination of allene **4** in which a new C–N bond is created with a new chiral center α to the N atom.[10,20] Indeed, the reaction of allene **4a** could be catalyzed by treatment of (*S*)-**1b**-AuCl (5 mol %) and AgOPNB (10 mol %) (OPNB = *p*-nitrobenzoate) to afford the product **5a** with high enantioselectivity (91 % *ee*) at 10 °C. Moreover, the use of cyclic allene **4b**,**c** provided good enantioselectivity but lower yield. Reaction of **4a** with complex **1a**-AuCl using **4a** instead of **1b**-AuCl gave



Scheme 4. Enantioselective biphep–gold catalyzed intramolecular hydroamination.

decreased yield and enantioselectivity (27 %, 53 % *ee*). Since the epimerization of the **1b** portion of the cationic Au complex might proceed during the course of the reaction, the change in enantioselectivity of the product was monitored during the course of the reaction at 10 °C. We found that the enantioselectivity was constant with increasing the conversion (after 24 and 48 h; 91 % *ee*). Additionally, it was confirmed by the exchange from the cationic complex to **1b**-AuCl followed by the addition of (*S*)-**2c**-Ag that epimerization of the biphep moiety did not take place even after the reaction.

In summary, we have reported that the axial chirality of biphep–gold complexes can be imprinted by use of phosphate **2** and *N*-triflyl phosphoramide **3** as chiral anions and memorized at room temperature even after the dissociation of chiral anions. The enantiopure (*S*)-**1**-AuCl complexes thus isolated are shown to catalyze the intramolecular hydroamination as atropos asymmetric catalysts. Further mechanistic studies on chirality control and applications of the diastereopure complexes consisting of biphep, gold, and a chiral anion for synergistic asymmetric catalysis are in progress.

Experimental Section

A solution of *rac*-**1a**-AuCl (18.9 mg, 0.02 mmol) and (*S*)-**2b**-Ag (24.3 mg, 0.04 mmol) in acetone (4.0 mL) was stirred at 100 °C for 14 h. After the addition of dichloromethane (4.0 mL) at room temperature, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The yellow solid was dissolved in a minimum amount of dichloromethane and precipitated by dropwise addition of pentane. The complex was washed three times with pentane and then dried in vacuo. The two-diastereomer mixture (*S*)-**1a**-Au/(*S*)-**2b** and (*R*)-**1a**-Au/(*S*)-**2b**, which confirmed by ^{31}P NMR analysis (92 % *de*), was obtained quantitatively. The structure of the (*S*)-**1a**-Au/(*S*)-**2b** complex was proven by X-ray analysis of a single crystal obtained from dichloromethane/ethyl acetate solution. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 5.39$–5.43 (m, 2H), 6.15 (t, $J = 7.8$ Hz, 2H), 6.21–6.32 (m, 6H), 6.74–6.80 (m, 6H), 7.16–7.25 (m, 16H), 7.36–7.39 (m, 6H), 7.44–7.51 (m, 6H), 7.64–7.89 ppm (m, 16H); ^{31}P NMR (121 MHz, CDCl$_3$): $\delta = 4.51$ (s, 2P), 19.63 ppm (s, 2P); Anal. calcd for $C_{100}H_{68}Au_2O_8P_4 \cdot 2.5\,CH_2Cl_2 \cdot 0.5\,CH_3COOC_2H_5$: C 57.79; H 3.57 %; found: C 57.82; H 3.56 %; $[\alpha]_D^{25} = +363.96$ ($c = 0.20$ in CHCl$_3$); (*R*)-**1a**-Au/(*S*)-**2b**: ^{31}P NMR (121 MHz, CDCl$_3$): $\delta = 6.42$ (s, 2P), 19.47 (s, 2P).

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