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Gold Catalysis

Use of Planar Chiral Ferrocenylphosphine-Gold(I) Complexes in the Asymmetric Cycloisomerization of 3-Hydroxylated 1,5-Enynes

Zhiyong Wu,[a,b] Pascal Retailleau,[a] Vincent Gandon,[a,b] Arnaud Voituriez,*[a] and Angela Marinetti*[a]

Abstract: Chiral monodentate phosphines based on *ortho*-disubstituted ferrocene units have been prepared and used for the synthesis of gold(I) complexes. These complexes are highly active catalysts for the cycloisomerization of 3-hydroxy-1,5-enynes into bicyclo[3.1.0]hexanones. Their high catalytic activity is ascribed to their structural analogy to the biaryl-based Buchwald phosphines. This paper discloses the first enantioselective variant of these reactions based on gold catalysis (*ee*'s up to 80 %).

Introduction

The biarylphosphines **I** (Figure 1), initially developed by Buchwald,[1] represent a privileged family of ligands in both palladium and gold catalysis, due to the exceptional catalytic activity of the corresponding metal complexes. The use of these ligands in gold catalysis was first reported by Echavarren,[2] and their scope has subsequently been investigated further by many research groups.[3]

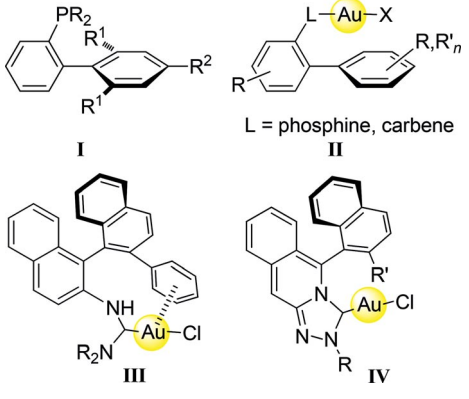

Figure 1. Biaryl ligands and gold complexes.

The increased catalytic activity of complexes containing these ligands is mainly due to the stabilization of cationic gold intermediates, either by steric effects, or by weak coordination of the pendant aryl unit to the gold centre.[4] With this in mind, it would be an attractive idea to apply an analogous design to chiral ligands in which a biaryl unit would ensure both high catalytic activity and enantiocontrol. However, gold complexes of such ligands (**II**, L = phosphine or carbene, including chiral variants of Buchwald phosphines themselves) have hardly been used in catalysis. The most common strategy for building chiral ligands of this class involves the use of NHC's (N-heterocyclic carbenes) or NAC's (nitrogen acyclic carbenes) as ligands, combined with binaphthyl units. This is typified by compounds **III**, in which flexible NAC units are connected to a binaphthyl scaffold bearing an additional aryl substituent.[5] High asymmetric induction is driven here by an appropriate conformation of the triaryl scaffold, which gives the so-called "in" rotamer in which the phenyl group becomes closer to the gold centre and creates a suitable chiral pocket. Alternatively, high enantioselectivity has been achieved with ligands containing rigid NHC units fused to a biaryl scaffold, as in **IV**.[6] In terms of biaryl-based phosphorus ligands, gold complexes of chiral biaryl-monophosphines (**II** with L = PR_2) have only recently been investigated as catalysts for intramolecular hydroamination reactions, with moderate success in terms of chiral induction (ee_{max} = 29 %).[7]

At the start of our studies, we noticed that a three-dimensional arrangement analogous to that of biarylmonophosphines could be generated in gold complexes by pseudobiaryl ferrocene-based phosphines with planar chirality (see **V** in Figure 2; aryl-MOPFs = aryl-monophosphino ferrocenes).

Although several palladium– and copper–MOPF complexes have been synthesized and used in catalysis,[8] the use of gold–MOPF complexes is extremely rare. Only Echavarren has recently reported on two complexes of this family, which gave up to 50 % *ee* in a [4+2] cycloaddition reaction.[9]

In this context, we were interested in a more extended investigation of the potential of gold complexes **V** in enantioselect-

[a] *Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, 1, av. de la Terrasse, 91198 Gif-sur-Yvette, France*
E-mail: arnaud.voituriez@cnrs.fr
angela.marinetti@cnrs.fr
http://www.icsn.cnrs-gif.fr/
[b] *ICMMO (UMR CNRS 8182), Université Paris-Sud, 91405 Orsay, France*

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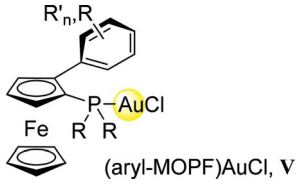


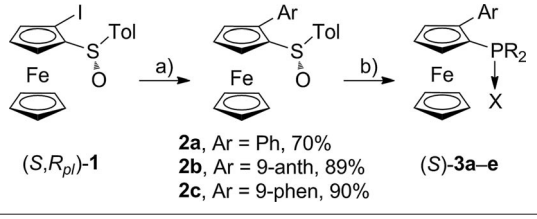
Figure 2. MOPF–gold(I) complexes.

ive catalysis. In this paper, we report the results of our systematic screening of new MOPF–gold complexes in the cycloisomerization of 1,5-enynes into bicyclo[3.1.0]hexanones. Enantioselective variants of these reactions[10] have not been reported to date with gold catalysts. Our previous work has shown that MonoPhos–platinum(II) complexes promote these skeletal rearrangements with moderate to good efficiency.[11]

Results and Discussion

This work started with the synthesis of a series of MOPF ligands, following an established strategy.[8a] The method makes use of (S,R_{pl})-1-iodo-2-*p*-tolylsulfinylferrocene (**1**) as the starting material. This compound was easily obtained in enantiopure form by diastereoselective *ortho*-directed lithiation/iodination of (*S*)-*p*-tolylsulfinylferrocene.[12] Palladium-catalysed Suzuki couplings of (S,R_{pl})-**1** with three different boronic acids allowed us to introduce various aromatic groups onto the ferrocene backbone. Disubstituted chiral ferrocenyl sulfoxides (S,S_{pl})-**2a**–**2c** were obtained in 70–90 % yield, depending on the aryl group used [Ar = phenyl, 70 %; Ar = 9-anthracenyl (Anth), 89 %; Ar = 9-phenanthryl (Phen), 90 %; step a] (Table 1).

Table 1. Synthesis of planar chiral ferrocenyl-phosphines [(*S*)-**3a**] or their BH_3 complexes [(*S*)-**3b**–**3e**].

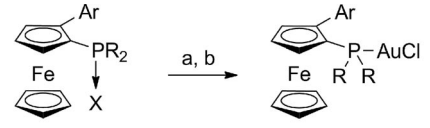


Product	Ar	R	X	Yield [%]
3a	Ph	Ph	–	77
3b	9-anthracenyl	Ph	BH_3	28
3c	9-phenanthryl	Ph	BH_3	39
3d	9-phenanthryl	3,5-$Me_2C_6H_3$	BH_3	25
3e	9-phenanthryl	cyclohexyl	BH_3	35

[a] Reaction conditions: $Pd(SPhos)_2Cl_2$ (Sphos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl), $ArB(OH)_2$, Cs_2CO_3, toluene/THF, 80 °C, 16 h. [b] (i) *t*BuLi, THF, R_2PCl; (ii) BH_3·DMS (DMS = dimethyl sulfide).

The desired phosphines [(*S*)-**3a**] or their borane adducts [(*S*)-**3b**–**3e**] could be synthesized then through sulfoxide/lithium exchange by the addition of *t*BuLi, followed by trapping of the carbanionic ferrocenyl intermediate with a chlorodiaryl- or a chlorodialkylphosphine (step b).[13] Ferrocenyl diphenylphosphine (*S*)-**3a**[8a] was isolated in 77 % yield. The same procedure was used for the synthesis of 9-anthracenyl and 9-phenanthryl-substituted phosphines, which were isolated as the corresponding borane complexes (i.e., **3b** and **3c**), after in-situ protection with BH_3. The phosphorus substituents were varied, going from phenyl (**3a**–**3c**) to more bulky aryl groups in **3d** (R = 3,5-$Me_2C_6H_3$), or to cyclohexyl substituents in **3e**. Phosphine boranes **3d** and **3e** were isolated in moderate yields.[14]

With these five phosphines in hand, we turned our attention to the synthesis of gold complexes (*S*)-**4a**–**4e** (Scheme 1). Starting with trivalent phosphine (*S*)-**3a**, gold complex (*S*)-**4a** was obtained in 70 % yield after complexation with AuCl·thiodiethanol, obtained in situ by the reaction of $NaAuCl_4$·$(H_2O)_2$ and 2,2′-thiodiethanol. Phosphine boranes (*S*)-**3b**–**3e** were converted into the corresponding gold complexes (*S*)-**4b**–**4e** by in situ deprotection of the borane (2 h at 80 °C in a THF/EtOH solution), followed by reaction with the same gold precursor at 0 °C. Overall yields of 32–75 % were obtained over these two steps.



3a: X = –
3b–**3e**: X = BH_3

4a, Ar = Ph, R = Ph, 70%
4b, Ar = Anth, R = Ph, 75%
4c, Ar = Phen, R = Ph, 32%
4d, Ar = Phen, R = 3,5-$Me_2C_6H_3$, 45%
4e, Ar = Phen, R = Cy, 37%

a) EtOH, THF, 80 °C, 2 h
b) $NaAuCl_4$·$2H_2O$, 2,2'-thiodiethanol, $CHCl_3/H_2O$ (1:5), 0 °C, 40 min

Scheme 1. Synthesis of gold complexes (*S*)-**4a**–**4e**.

The structure and absolute configuration of complex (*S*)-**4c** was ascertained by an X-ray diffraction study. An ORTEP view of this complex is shown in Figure 3.

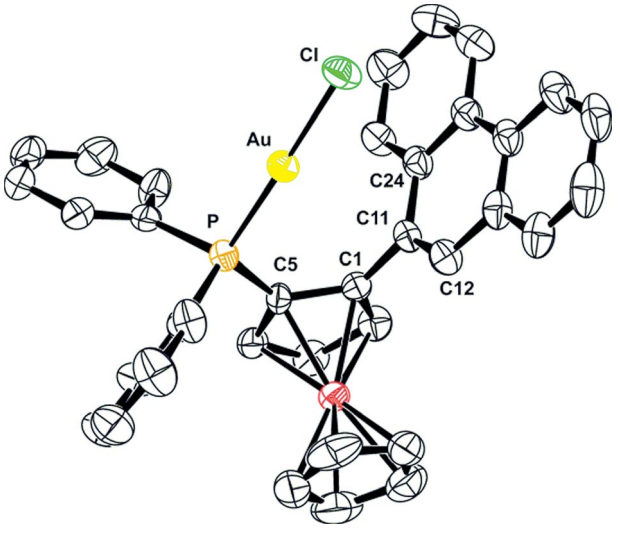
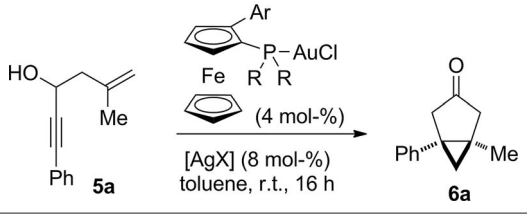


Figure 3. X-ray crystal structure of (*S*)-**4c** showing one molecule in the asymmetric unit. Ellipsoids are drawn at the 50 % probability level, H atoms are not shown for clarity. Selected bond lengths [Å]: Au–P, 2.229(2); Au–Cl, 2.029(2); P–C-5, 1.792(6); Au–C-11, 3.198; Au–C-12, 3.477; Au–C-24, 3.430. Selected bond angles [°]: P–Au–Cl, 178.55(7); Au–P–C-5, 113.1(2); P–C-5–C-4, 126.3(5); C-5–C-1–C-11, 128.1(6).

For neutral gold chloride complex (*S*)-**4c**, the distance between the Au^{I} centre and the nearest carbon of the phenanthryl group, C-11, is 3.198 Å. The adjacent carbons, C-24 and C-12 are at 3.430 and 3.477 Å, respectively, from the gold. The measured Au–C distances are longer than the maximum estimated length for significant arene–Au interactions (2.95 Å).[4c] Based on these structural data, we can only postulate a weak localized gold–*π*(arene) interaction between the metal centre and the phenanthryl group in **4c**, but, as shown below, the high catalytic activity of the corresponding cationic complexes suggests an effective stabilization of the gold centre by these ligands.

The five gold complexes [i.e., (*S*)-**4a**–**4e**] were investigated as catalysts for the cycloisomerization of 3-hydroxy-1,5-enynes into bicyclo[3.1.0]hexan-3-ones, as shown in Table 2.[10] In spite of the established synthetic utility of these reactions, their asymmetric variants are still rare. Asymmetric variants have been carried out with platinum catalysts,[11] but, as far as we are aware, they have not been explored with chiral gold catalysts. From a more general point of view, we can also note that, unlike phosphorus ligands with central, axial, or helical chirality, ligands with planar chirality have been poorly exploited to date in gold catalysis.[15b,16] Enantioselective reactions[17] are commonly carried out with catalysts based on bimetallic gold complexes of atropisomeric diphosphines,[15] chiral counterions (mainly chiral phosphoric acid derivatives),[18] phosphoramidite ligands with bulky and extended substituents,[19] as well as monodentate phosphahelicene ligands.[20] The preliminary screening of monodentate phosphine–gold complexes **4** are reported in Table 2.

Table 2. Screening of gold catalysts (*S*)-**4a**–**4e** in the cycloisomerization of 3-hydroxy-1,5-enynes.



Entry	[Au*]	AgX	Conv. [%][a]	*ee* [%][b]
1	**4a**	$AgBF_4$	93	13
2	**4b**	$AgBF_4$	95	2
3	**4c**	$AgBF_4$	98	31
4	**4d**	$AgBF_4$	100	30
5	**4e**	$AgBF_4$	98	17
6	**4c**	AgOTf	95	44
7[c]	**4c**	AgOTf	100 (85)	46
8[c,d]	**4c**	AgOTf	95 (80)	46

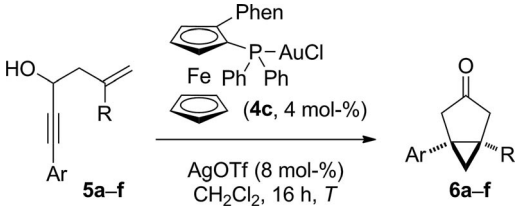
[a] Conversions determined by ^{1}H NMR spectroscopy. Isolated yields in parentheses. [b] Determined by HPLC on a chiral stationary phase. [c] In CH_2Cl_2. [d] At 0 °C.

5-Methyl-1-phenylhex-5-en-1-yn-3-ol (**5a**) was chosen as an initial substrate. The experiments were carried out at room temperature in toluene by using the gold(I) catalyst (4 mol-%) and $AgBF_4$ (8 mol-%). Under these conditions, the reaction proceeded with over 90 % conversion after 16 h. Gold catalysts **4a** and **4b**, where Ar = phenyl and 9-anthracenyl, respectively, gave the corresponding product, 1-methyl-5-phenylbicyclo[3.1.0]-hexan-3-one (**6a**), in good yields, but with very low enantiomeric excess (Table 2, entries 1 and 2).

The enantiomeric excess could be improved to about 31 % *ee* by using catalyst **4c**, which contains a 9-phenanthryl substituent on the ferrocene backbone (Table 2, entry 3). The enantiomeric excess did not improve further by moving to catalysts **4d** and **4e**, in which the diphenylphosphino unit of **4c** was replaced either by a bulkier bis(3,5-dimethylphenyl)phosphino unit (in **4d**) or a more electron-rich dicyclohexylphosphino unit (in **4e**) (Table 2, entries 4 and 5; 30 and 17 % *ee*, respectively). In attempts to optimize the enantioselectivity with catalyst **4c**, we screened several silver salts ($AgPF_6$, $AgSbF_6$, $AgNTf_2$, AgOTf), solvents (dichloroethane, dichloromethane, chloroform, acetonitrile, THF), and reaction temperatures. The highest enantioselectivity was obtained when the reaction was run in dichloromethane at room temperature, with AgOTf as the activating silver salt (Table 2, entry 7, 85 % isolated yield, 46 % *ee*). Decreasing the reaction temperature to 0 °C for this substrate did not improve the enantiomeric excess, but good catalytic activity was still observed (Table 2, entry 8).

The same conditions were then used for the cycloisomerization of other 3-hydroxy-1,5-enynes with catalyst (*S*)-**4c**, as shown in Table 3.

Table 3. Cycloisomerization of 3-hydroxylated 1,5-enynes catalysed by gold complex (*S*)-**4c**.



Entry	Substrate	Ar	R	*T* [°C]	Yield [%]	*ee* [%][a]
1	**5a**	Ph	Me	20	85	46
2	**5b**	3,4-Cl_2-C_6H_3	Me	0	87	43
3	**5c**	3-OMe-C_6H_4	Me	0	91	29
4	**5d**	2-OMe-C_6H_4	Me	0	88	20
5	**5e**	4-OMe-C_6H_4	Me	20	67	56
6	**5e**	4-OMe-C_6H_4	Me	0	82	64
7	**5e**	4-OMe-C_6H_4	Me	–40	72	66
8	**5f**	4-OMe-C_6H_4	Ph	0	76	71
9	**5f**	4-OMe-C_6H_4	Ph	–40	79	80

[a] Enantiomeric excesses determined using chiral HPLC.

Enynes **5b**–**5e**, which have substituted aryl rings on the alkyne group and a methyl group on the olefin moiety (R = Me) gave the corresponding bicyclo[3.1.0]hexan-3-ones in high yields and with moderate enantioselectivities when the reactions were carried out at room temperature or at 0 °C (20–64 % *ee*; Table 3, entries 1–6). Substrate **5f**, in which R = Ph, was converted into the desired bicyclo[3.1.0]hexan-3-one with a higher 71 % *ee* under the same reaction conditions (Table 3, entry 8).[21]

It must be noted here that all these MOPF–gold complexes gave high catalytic activity, and total conversion was reached for all substrates after 16 h at 0 °C. Given the efficiency of the catalyst, we envisioned that the reaction temperature could be

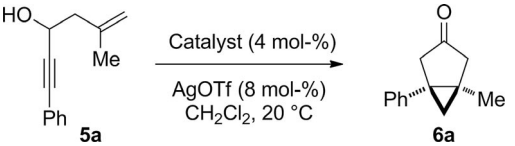
decreased to –40 °C. As a result, the enantiomeric excesses improved to 66 and 80 % *ee* for **6e** and **6f**, respectively (Table 3, entries 7 and 9). Overall, decreasing the reaction temperature resulted in a beneficial effect for these reactions (Table 3, entries 5–7, and entries 8 and 9).

The high catalytic activity of complexes **4** might be due to stabilization of the catalyst through gold–arene interactions. However, the X-ray data in Figure 3 above show long Au–C distances, which preclude strong metal–arene interactions. In spite of this unambiguous structural feature, we cannot exclude the possibility that the Au–arene interactions increase when moving from the neutral complex [i.e., (*S*)-**4c**] to the corresponding cationic gold complex, in which the stabilizing effect of π-arene complexation becomes crucial. This hypothesis was actually corroborated by DFT (density functional theory) calculations. Complex (*S*)-**4c** was optimized using the Gaussian 09 software package at the M06-2X level (see Supporting Information for further details). This functional is known to properly describe noncovalent interactions. SDD (Stuttgart–Dresden basis set) relativistic effective core potentials were used to describe the Au and Fe atoms. The other atoms were described by the 6-31+G(d,p) basis set (Figure 4).

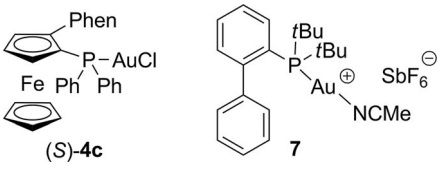
The calculated gas-phase Au–C-11 distance is slightly longer than in the solid state (3.286 vs. 3.198 Å, respectively). On the other hand, the gas-phase Au–C-24 distance was found to be slightly shorter than the solid-state distance (3.385 vs. 3.430 Å, respectively). In the corresponding cationic complex, i.e., after the removal of Cl^- in the calculations, the Au–C-11 distance shortens significantly to become 3.050 Å. More strikingly, the Au–C-24 distance shortens drastically to become as low as 2.802 Å. The maximum electron density along the Au–C-24 axis is indicative of quite a strong noncovalent interaction (ρ_{max} = 0.023 e $Å^{-3}$) in the cationic complex. For comparison, the maximum electron density in (*S*)-**4c** is found along the Au–C-11 axis, and is very modest (ρ_{max} = 0.009 e $Å^{-3}$). Clearly the phenanthryl moiety is well-suited to protecting the active gold centre in the cationic complex, both sterically and electronically, by transferring electron density. This might account for the stability of the cationic gold complex towards reduction to Au^0.

In terms of enantioselectivity, the enantiomeric excesses of up to 80 % *ee* obtained with these catalysts are promising, especially when considering that enynes **6a**–**6f** have a stereogenic carbon at their propargylic position, which means that the substrate might compete with the chiral catalyst for stereochemical control of the cyclization. Indeed, according to the generally assumed mechanism for the cycloisomerization of 1,5-enynes,[22] the stereochemistry of the substrate might be transferred, at least in part, into the product. In our previous work, as well as in literature reports, it has been demonstrated that this is indeed the case with platinum catalysts;[10a,11,23] partial chirality transfer has also been observed by Gagosz in the gold-promoted cycloisomerization of some diastereomeric substrates.[24] Thus, to gain information about the stereochemical control of these cycloisomerization reactions, we carried out the additional experiments shown in Table 4.

Table 4. Stereochemical effect of the stereogenic centre of the substrate.



Entry	Substrate	Catalyst	*ee* [%]
1	(*R*)-**5a**	(*S*)-**4c**	50 (–)
2	(*S*)-**5a**	(*S*)-**4c**	38 (–)
3	*rac*-**5a**	(*S*)-**4c**	46 (–)
4	(*R*)-**5a**	**7**	36 (–)
5	(*R*)-**5a**	$PtCl_2$	21 (–)



We prepared enantiomerically pure substrates (*R*)-**5a** and (*S*)-**5a**,[11a] and submitted them separately to cycloisomerization,

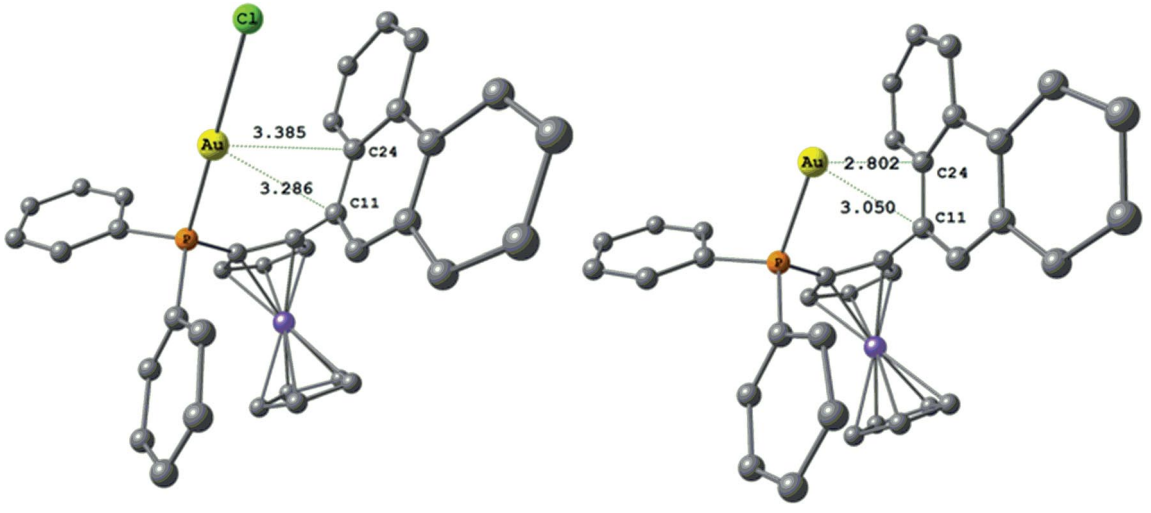


Figure 4. Geometries of calculated complex (*S*)-**4c** (left) and its cationic counterpart (right) (selected distances in Å).

using either enantiopure complex (*S*)-**4c** or the achiral gold complex [(2-biphenyl)di-*tert*-butylphosphine]gold(I)(acetonitrile) hexafluoroantimonate (**7**) as the catalyst. When the chiral catalyst [i.e., (*S*)-**4c**) was used in the cycloisomerization of (*R*)-**5a** and (*S*)-**5a**, enantiomeric excesses of 50 and 38 % *ee*, respectively, were obtained (Table 4, entries 1 and 2). These results are consistent, in terms of enantiomeric excess, with the *ee* obtained starting from the racemic substrate *rac*-**5a** (Table 4, entry 3, 46 % *ee*). The experiments in Table 4, entries 1 and 2 gave bicyclo[3.1.0]hexanone **6a** with the same absolute configuration, which means that the stereochemical control of the chiral catalyst overcomes the effect of the chirality of the substrate. The gap of 12 % *ee* between the two experiments indicates that the stereogenic centre of the substrate has only a rather moderate effect on the stereocontrol. A "matched effect" is observed between (*R*)-**5a** and (*S*)-**4c** (Table 4, entry 1).

On the other hand, starting from enantiomerically pure alcohol (*R*)-**5a**, the achiral gold catalyst **7** gave bicyclo-[3.1.0]hexanone **6a** with 36 % *ee*, and $PtCl_2$ gave the same product with 21 % *ee* (Table 4, entries 4 and 5). Overall, these results demonstrate that enantiopure substrates give partial chirality transfer to the product under gold catalysis, but the chiral gold catalysts (*S*)-**4**, as well as the chiral platinum catalysts reported previously, overcome the effect of the substrate.

Conclusions

In conclusion, we have shown that aryl-substituted, planar chiral ferrocenylphosphines give very active gold catalysts for the cycloisomerization of 3-hydroxy-1,5-enynes into bicyclo[3.1.0]-hexanones. These ligands can be considered to be chiral analogues of Buchwald's phosphines. Their good catalytic activity can be ascribed to a stabilizing effect of the aryl-substituted ferrocene unit, which behaves as a pseudo-biaryl unit. In terms of enantioinduction, these ligands give moderate to good enantiomeric excesses, which are strongly modulated by variations in the aryl substituents on the ferrocene backbone. These results open the way to further optimization of target reactions through structural modification of the chiral ligands.

Experimental Section

Gold Complex 4b: Compound **3b** (20 mg, 0.036 mmol, 1 equiv.) was put into a mixture of ethanol and THF (2:1; 9 mL). The mixture was stirred and heated to reflux (80 °C) for 2 h under an argon atmosphere. The yellow solution was then cooled to room temperature. The volatiles were removed under reduced pressure to give the crude phosphine as a yellow solid, which was used directly in the next step.

$NaAuCl_4 \cdot 2H_2O$ (16 mg, 0.04 mmol, 1.1 equiv.) was dissolved in water (2 mL) under argon, and the solution was cooled to 0 °C. 2,2′-Thiodiethanol (14 mg, 0.11 mmol, 3 equiv.) was then added to the solution, followed by the addition of a solution of the crude phosphine (1 equiv.) in $CHCl_3$ (2 mL). The mixture was stirred for 10 min at 0 °C, then it was stirred at room temperature for 30 min, and then extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, and then concentrated in vacuo. Purification by flash column chromatography on silica gel (heptane/dichloromethane, 30:70) gave gold complex **4b** (21 mg, 75 %) as an orange solid. R_f = 0.29 (dichloromethane/heptane, 70:30). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.36 (d, J = 8.5 Hz, 1 H), 8.32 (s, 1 H), 7.93 (d, J = 8.0 Hz, 1 H), 7.90–7.80 (m, 3 H), 7.70 (dd, J = 8.5, 6.5 Hz, 1 H), 7.53–7.42 (m, 4 H), 7.34 (d, J = 8.5 Hz, 1 H), 7.28–7.21 (m, 1 H), 7.13–7.05 (m, 3 H), 6.95–6.89 (m, 1 H), 6.76–6.68 (m, 2 H), 4.88 (s, 1 H), 4.84 (s, 1 H), 4.65 (s, 1 H), 4.40 (s, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.5 (d, $J_{C,P}$ = 14.6 Hz, CH), 133.6 (d, $J_{C,P}$ = 14.6 Hz, CH), 133.3 (C), 131.8 (d, $J_{C,P}$ = 65.0 Hz, C), 131.7 (CH), 131.3 (C), 131.0 (C), 130.8 (CH), 129.7 (d, $J_{C,P}$ = 19.2 Hz, C), 128.9 (d, $J_{C,P}$ = 4.4 Hz, CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 127.3 (C), 126.7 (CH), 125.2 (d, $J_{C,P}$ = 4.6 Hz, CH), 125.3 (CH), 124.5 (CH), 77.0 (d, $J_{C,P}$ = 8.0 Hz, CH), 73.9 (d, $J_{C,P}$ = 10.1 Hz, CH), 72.3 (C), 69.8 (d, $J_{C,P}$ = 8.0 Hz, CH) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 27.4 ppm. IR: $\tilde{\nu}$ = 3049, 2986, 1518, 1481, 1437, 1333, 1158, 1101, 1001, 889, 829, 740, 694 cm^{-1}. $[\alpha]_D^{25}$ = –28 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{38}H_{30}AuFeNP$ [M – Cl + CH_3CN]$^+$ 784.1131; found 784.1210.

General Procedure for the Enantioselective Cycloisomerization Reactions: Silver salt (8 mol-%) and the substrate (0.10 mmol, in 1.0 mL of CH_2Cl_2) were added sequentially to a solution of the Au^I complex (4 mol-%) in CH_2Cl_2 (0.5 mL) under argon. The mixture was stirred for 16 h. The solvent was removed under reduced pressure, and the crude mixture was checked by NMR spectroscopy. The mixture was then purified by column chromatography on silica gel (heptane/EtOAc, 90:10) to give the final product.

1-(4-Methoxyphenyl)-5-phenylbicyclo[3.1.0]hexan-3-one (6f): 79 % yield, 80 % *ee*. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20–7.10 (m, 2 H), 7.18–7.05 (m, 3 H), 7.01 (d, J = 8.5 Hz, 2 H), 6.70 (d, J = 8.5 Hz, 2 H), 3.72 (s, 3 H), 3.22 (d, J = 19.0 Hz, 1 H), 3.15 (d, J = 18.5 Hz, 1 H), 2.77 (d, J = 19.0 Hz, 1 H), 2.75 (d, J = 18.5 Hz, 1 H), 1.99 (m, 1 H), 1.05 (d, J = 6.5 Hz, 1 H) ppm. HPLC [CHIRALPAK® IB, 20 °C, *i*PrOH/*n*-heptane (0.5:99.5), 0.8 mL/min, 231 nm]: t_R = 36.3 min (major) and 39.3 min (minor).

CCDC-1400309 [for (*S*)-**4c**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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