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Towards asymmetric Au-catalyzed hydroxy- and alkoxycyclization of 1,6-enynes

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ABSTRACT

The efficiency of a Au(III)/chiral ligand system has been studied. The association of several chiral mono- and bidentate phosphanes with gold has been tested in the formal addition of an oxygen nucleophile to an alkene followed by a cyclization process, namely the hydroxycyclization reaction of 1,6-enynes. The use of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP ligand led to clean cycloisomerizations and afforded the highest enantiomeric excesses. The enantiomeric excesses were highly dependant on the substrate/nucleophile combination. A ^{31}P NMR study of the catalytic species tends to prove that Au(III) catalyst may be reduced to Au(I) intermediate in the presence of phosphanes.

1. Introduction

Recent years have witnessed a substantial growth in the number of gold-catalyzed reactions implying C–C, C–O or C–N bond formation processes [1]. Despite the rapid development of several synthetic applications, the stereoselective aspects still require investigations and have been scarcely studied [2]. The first report of a gold-catalyzed enantioselective transformation dates from 1986 when Hayashi and Ito described the aldol condensation between isocyanates and aldehydes in the presence of a chiral ferrocenyl-based diphosphane–Au(I) complex [3]. In line with the increasing interest associated with the carbophilic Lewis acid properties of gold complexes, a number of publications describing the asymmetric hydroalkoxylation, hydroamination and hydroarylation of allenes, [2+2] cycloaddition and cycloisomerization of enallenes [2] have recently appeared. Whereas most of these studies deal with the activation of allenes towards nucleophilic attack, only two reports addressed the asymmetric activation of substrates containing an alkyne function (Scheme 1). In 2005, Echavarren et al. synthesized a variety of Au(I)–phosphanes complexes and applied those catalyst to the alkoxycyclization of 1,6-enynes [4a]. The same year, the group of Toste reported the gold-catalyzed cyclopropanation of styrenes with enantioselectivities up to 94% *ee* [4b].

In the course of our ongoing research on metal-catalyzed cycloisomerization reactions of enynes, which are one of the best atom-economical ways for sustainability [5,6], we and others have described novel rearrangements in the presence of external nucleophiles such as alcohols, electron-rich aromatic rings and amines (Scheme 2) [7]. These reactions offer the unique opportunity to create two bonds in a diastereoselective manner. They are based on the hypothesis of a common cyclopropylcarbene intermediate [7m,8], which would be attacked by a nucleophile to give the desired alcohol or ether after rearrangement. To the best of our knowledge, there is only a unique report concerning the asymmetric alkoxycyclization (5 examples) and leading to moderate (*ee* = 2–53%) and excellent (*ee* = 94% in a single case, Scheme 1) enantioselection [4a]. In pursuit of the investigation on atom-economical metal-catalyzed cycloisomerization reactions, [9] we have envisaged to study the asymmetric gold-catalyzed tandem C–C/C–O bond process. We wish therefore to present in this paper our preliminary results leading to enantiomerically enriched functionalized cyclic alkenes starting from 1,6-enynes.

2. Results and discussion

2.1. Optimization of the catalyst system

Initial efforts have focused on the optimization of an efficient system starting from enyne **1a** as a model substrate. We investigated Au(I) and Au(III) catalysts associated with the atropisomeric ligand (*R*)-MeOBIPHEP [10] and first studied the influence of silver salts (Table 1). The absolute configuration of the resulting alcohol was determined based on our studies in the presence of chiral platinum complexes [7b]. The use of AuCl or $AuCl_3$ showed an evident higher efficiency of Au(III) catalyst. The desired alcohol was obtained in a better yield and enantiomeric excess (Table 1, entries 1–2). The influence of silver salts (Table 1, entries 3–5) did not lead to significant modifications as the enantiomeric excesses were determined around 50%. Lowering the catalytic loading of silver

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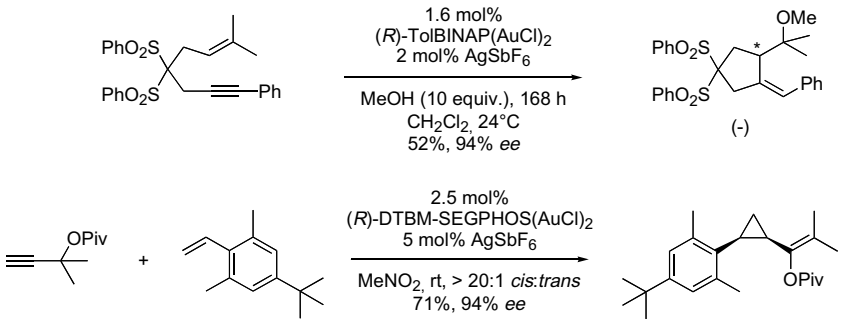
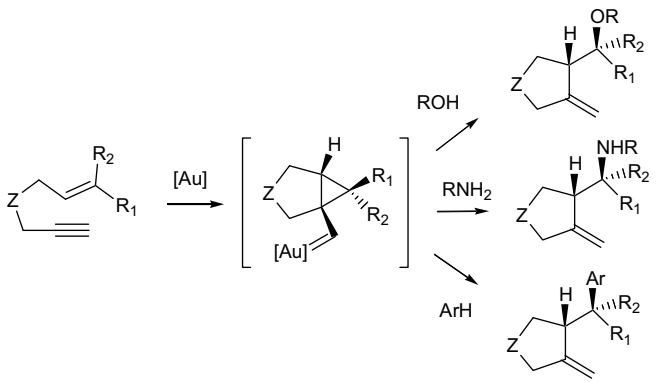


Scheme 1. Asymmetric gold-catalyzed reactions.

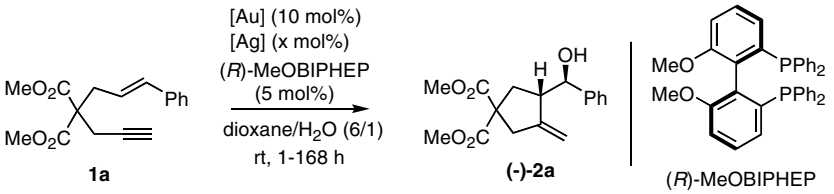


Scheme 2. Cycloisomerization reactions of enynes in the presence of various nucleophiles.

salts to 5 mol% considerably diminished the kinetic of the reaction (168 h instead of 1 h) and induced a large decrease in enantiomeric excess (Table 1, entry 6). Increasing the [Ag]/[Au] ratio accelerated the hydroxycyclization reaction but did not dramatically modify the enantiomeric excesses (Table 1, entries 7–8). A better reproducibility was obtained in the presence of a Au/Ag ratio of 1/3. The use of a higher Au/ligand catalyst ratio (1:1) was also investigated without further improvement (Table 1, entry 9). Further studies implying a different cosolvent or various concentrations did not give better results.

We further pursued our study under the following conditions: 10 mol% of $AuCl_3$, 30 mol% $AgSbF_6$ and 5 mol% ligand at room temperature. We next studied the influence of the chiral ligand on the enantiodiscrimination of the reaction. Few reports were published when we started this work and no enantioselective systems were based on Au(III) precursor. The use of TolBINAP [4a,11] afforded the desired alcohol in a moderate 22% enantiomeric excess (Table 2, entry 1). We investigated the influence of other bidentate phosphorus-based architectures such as the C_2-symmetric (+)-BIPNOR [12] (Table 2, entry 2) or planar chiral diphosphanes ((*R*,*S*)-Josiphos and (*R*)-(*S*)-PPF-P*t*Bu$_2$ [13], (Table 2, entries 3–4), the latter one showing an interesting activity. The use of atropisomeric monophosphanes such as (*S*)-MeO-MOP [14], (*R*)-BINAPO [15] did not give better results (Table 2, entries 5–6).

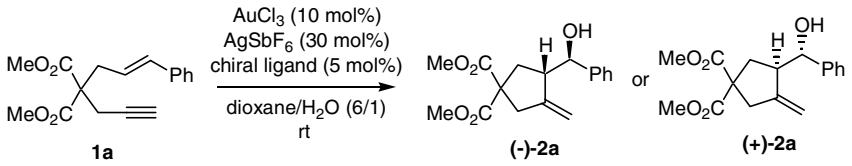
Table 1
Optimization of the gold catalytic system



Entry	[Au] catalyst	[Ag] salts (mol%)	Yield[a] (%)	*ee* (%)[b]
1	AuCl	$AgSbF_6$ (10)	44[c]	29
2	$AuCl_3$	$AgSbF_6$ (30)	83	59
3	$AuCl_3$	$AgBF_4$ (30)	92	54
4	$AuCl_3$	$AgPF_6$ (30)	99	51
5	$AuCl_3$	$AgAsF_6$ (30)	94	53
6	$AuCl_3$	$AgSbF_6$ (5)	57[c]	12
7	$AuCl_3$	$AgSbF_6$ (10)	100[c]	53
8	$AuCl_3$	$AgSbF_6$ (15)	100[c]	55
9[d]	$AuCl_3$	$AgSbF_6$ (30)	95	51

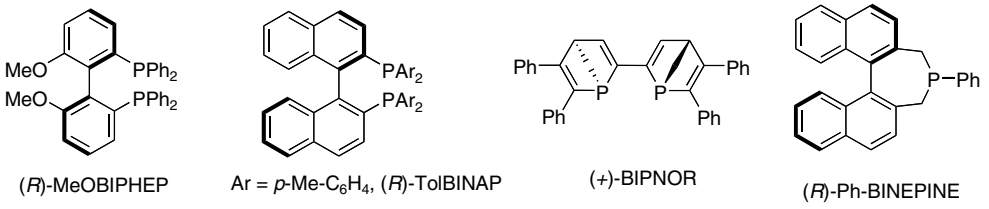
[a] Isolated yield.
[b] Measured by HPLC.
[c] Conversion.
[d] 10 mol% (*R*)-MeOBIPHEP.

Table 2
Ligand screening for the asymmetric hydroxycyclization reaction

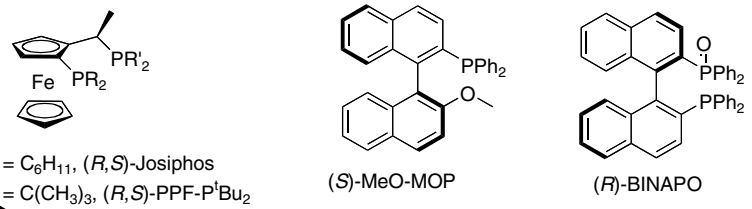


Entry	Chiral ligand	*t* (h)	Yield[a] (%)	*ee* (%) (config.)[b]
1	(*R*)-TolBINAP	72	86	22 (−)
2	(+)-BIPNOR	21	99	9 (+)
3	(*R*,*S*)-Josiphos	36	90	26 (−)
4	(*R*)-(*S*)-PPF-PtBu$_2$	19	96	49 (−)
5[c]	(*S*)-MeO-MOP	20	99	4 (−)
6	(*R*)-BINAPO	20	99	38 (−)
7[c,d]	(*R*)-Ph-BINEPINE	20	0	/
8	(*R*)-(2-furyl)-MeOBIPHEP	17	86	0
9	(*S*)-*p*-Tol-MeOBIPHEP	156	31[e]	14 (+)
10	(*S*)-(4-NMe$_2$)-MeOBIPHEP	60	100[e]	41 (+)
11	(*R*)-3,5-Me-MeOBIPHEP	19	89	22 (−)
12	(*R*)-3,5-*i*Pr-MeOBIPHEP	19	96	33 (−)
13	(*R*)-3,5-*t*Bu-4-MeO-MeOBIPHEP	17	98	72 (−)
14	(*R*)-Cy-MeOBIPHEP	18	100[e]	4 (−)
15	(*S*)-*i*Pr-MeOBIPHEP	18	100[e]	8 (+)
16	(*R*)-3,5-*t*Bu-4-MeO-SEGPHOS	17	99	63 (−)

[a] Isolated yield.
[b] Measured by HPLC.
[c] 10 mol%.
[d] 60 °C.
[e] Conversion.

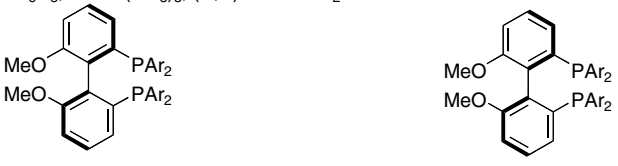


(*R*)-MeOBIPHEP Ar = *p*-Me-C$_6$H$_4$, (*R*)-TolBINAP (+)-BIPNOR (*R*)-Ph-BINEPINE



R = C$_6$H$_5$, R' = C$_6$H$_{11}$, (*R*,*S*)-Josiphos
R = C$_6$H$_5$, R' = C(CH$_3$)$_3$, (*R*,*S*)-PPF-P^{t}Bu$_2$

(*S*)-MeO-MOP (*R*)-BINAPO



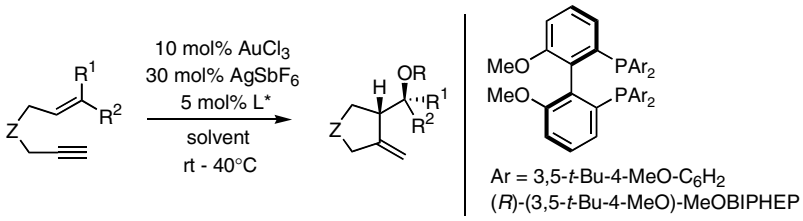
Ar = 4-Me$_2$N-C$_6$H$_4$
(*S*)-(4-NMe$_2$)-MeOBIPHEP
Ar = 4-Me-C$_6$H$_4$
(*S*)-*p*-Tol-MeOBIPHEP

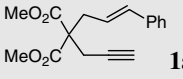
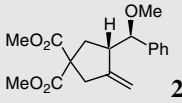
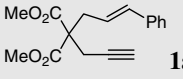
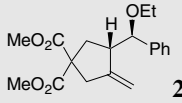
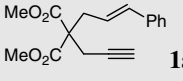
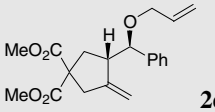
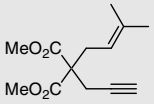
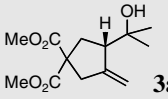
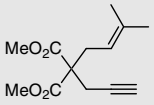
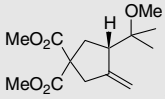
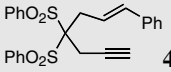
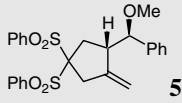
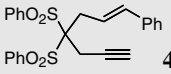
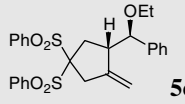
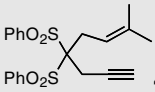
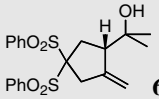
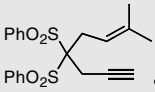
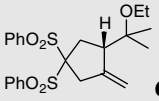
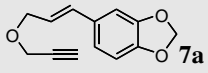
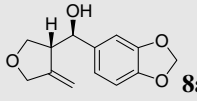
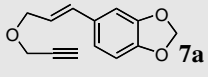
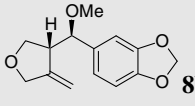
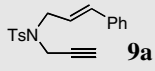
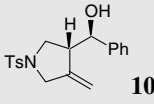
Ar = phenyl, (*R*)-MeOBIPHEP
Ar = furyl, (*R*)-(2-furyl)-MeOBIPHEP
Ar = 3,5-*t*-Bu-4-MeO-C$_6$H$_2$, (*R*)-(3,5-*t*-Bu-4-MeO)-MeOBIPHEP
Ar = 3,5-Me-C$_6$H$_3$, (*R*)-(3,5-Me)-MeOBIPHEP
Ar = 3,5-*i*Pr-C$_6$H$_3$, (*R*)-(3,5-*i*-Pr)-MeOBIPHEP

R = Cy, (*R*)-Cy-MeOBIPHEP
R = *i*Pr, (*R*)-*i*-Pr-MeOBIPHEP

Ar = 3,5-*t*-Bu-4-MeO-C$_6$H$_2$,
(*R*)-(3,5-*t*-Bu-4-MeO)-SEGPHOS

Table 3
Asymmetric gold-catalyzed hydroxy- and alkoxycyclization reactions of 1,6-enynes



Entry	1,6-Enyne	Solvent	*t* (h)	Product	Yield[a] (%)	*ee* (%) (config.)[b]
1	 **1a**	MeOH	48	 **2b**	99	30 (−)
2	 **1a**	EtOH	18	 **2c**	88	55 (−)
3	 **1a**	C_3H_5OH	18	 **2d**	89	62 (−)
4	 **1b**	Dioxane/eau (6/1)	96	 **3a**	66	24 (−)
5	 **1b**	MeOH	19	 **3b**	99	30 (−)
6[c]	 **4a**	MeOH	72	 **5b**	99	53 (−)
7[c]	 **4a**	EtOH	72	 **5c**	82	71 (−)
8	 **4b**	Dioxane/eau (6/1)	24	 **6a**	99	72 (−)
9	 **4b**	EtOH	24	 **6c**	99	78 (−)
10	 **7a**	Dioxane/eau (6/1)	22	 **8a**	65	37 (−)
11	 **7a**	MeOH	26	 **8b**	56	33 (−)
12[c]	 **9a**	Dioxane/eau (6/1)	72	 **10a**	99	32 (−)

[a] Isolated yield.
[b] Measured by HPLC.
[c] Reaction at 40 °C.

The case of (*R*)-Ph-BINEPINE [16,17], known as an excellent chiral promoter in the presence of platinum [7b], was particularly surprising as the ligand completely inhibited the reaction (Table 2, entry 7) either at room temperature or at 60 °C. We therefore, decided to screen a set of chiral atropisomeric ligands displaying different stereoelectronic properties. A combination of gold and electron-poor analogue of MeOBIPHEP ligand (Table 2, entry 8) led to the desired alcohol in good yield but in a racemic form. The use of electron-rich analogues of MeOBIPHEP such as (*S*)-*p*-Tol-MeOBIPHEP and (*S*)-(4-NMe_2)-MeOBIPHEP enhanced the enantioselection of the reaction leading to 41% *ee* in the latter case (Table 2, entries 9–10). The influence of steric factors was also observed when performing the reaction in the presence of 3,5-disubstituted MeOBIPHEP analogues (Table 2, entries 11–12). When combining both effects by using (*R*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP ligand, the enantiomeric excess reached 72% (Table 2, entry 13). Further studies with alkyl-substituted ligands (Table 2, entries 14-15) or benzodioxolane-substituted ligand [18] (Table 2, entry 16) did not allow us to obtain better enantiomeric excesses. It is noteworthy that the DTBM-SEGPHOS ligand, known as an excellent chiral promoter in gold catalysis [2], unfortunately did not afford higher enantiomeric excess than 63% (Table 2, entry 16).

The best candidate was therefore the atropisomeric electron-rich and sterically hindered (*R*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP ligand. We performed several other modifications of the reaction conditions (temperature, cosolvents) without success. Having in hand an optimized Au(III)/Ag/chiral ligand system, we then decided to evaluate the scope and limitations on various 1,6-enynes and in the presence of alcohols such as methanol, ethanol and allylic alcohol.

2.2. Scope and limitations

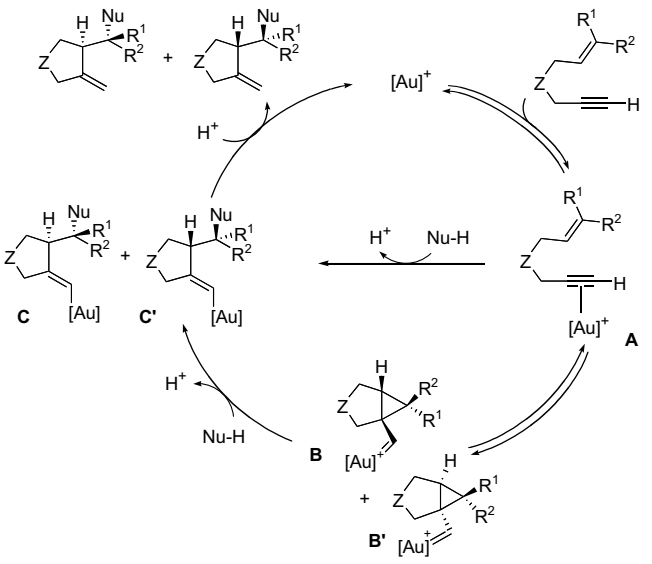
Several carbon-, oxygen- or nitrogen-tethered 1,6-enynes were prepared according to classic and described alkylation reaction procedures [7]. They were then subjected to the catalytic system implying 10 mol% of $AuCl_3$, 30 mol% of $AgSbF_6$ and 5 mol% of (*R*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP ligand (Table 3).

The influence of the external oxygen nucleophile on the enantiomeric excesses was readily observed. The addition of methanol, leading to the ether **2b** (Table 3, entry 1) induced a decrease of the enantiomeric excess (30%), even though the reaction was extremely performant. The use of ethanol and allylic alcohol gave better enantiomeric excesses (Table 3, entries 2–3) as the corresponding ethers were isolated in good yields and with respectively, 52% and 62% enantiomeric excesses. The challenging case of 1,6-enyne **1b** was then investigated. The addition of water afforded the alcohol **3a** in a modest 24% *ee* (Table 3, entry 4), whereas the use of methanol allowed the formation of the ether **3b** with 30% enantiomeric excess (Table 3, entry 5). It is noteworthy that the control of a unique stereocenter had already been studied in the presence of a Au(I) catalyst [4a] and led to the methyl ether in 2% enantiomeric excess. Anticipating that the carbon-tethered link might also influenced the enantioselection of the reaction, we then tested the cycloisomerization of a *bis*-sulfonyl-substituted derivative **4a**. Indeed, we were pleased to find that the catalytic system was actually more efficient as the corresponding methyl and ethyl ethers were respectively obtained in 53% and 71% enantiomeric excesses (Table 3, entries 6–7). Changing the alkenyl side chain still allowed the formation of the desired alcohol **6a** and ether **6c** in excellent yields (Table 3, entries 8–9) and good enantiomeric excesses (72% and 78%, respectively). In all carbon-tethered enynes, the enantiomeric excesses increased going from methanol to ethanol as a nucleophile. The unexplored case of oxygen- and nitrogen containing enynes was also investigated. Considering the potential weaker Thorpe-Ingold effect [19] of such substrates, we were not surprised to obtain lower enantiomeric excesses. The hydroxy- and methoxycyclization reactions of enynes **7a** and **9a** led to the alcohols **8a**, **10a** and ether **8b** in modest 32–37% enantiomeric excesses.

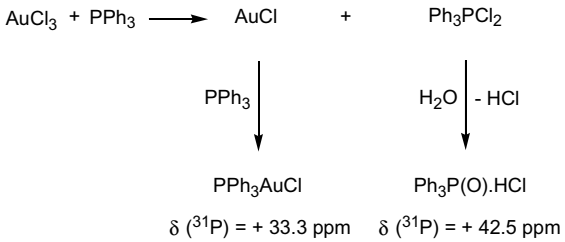
2.3. Mechanistic considerations

An initial complexation of the carbophilic Lewis acid cationic gold catalyst to the alkyne function allows the formation of transient unstable cyclopropylcarbenes [7m,8,20] **B** and **B′** via stereoselective attack of the alkene function on the alkyne (Scheme 3). These two intermediates are diastereomers and virtually in equilibrium via the starting η^2-complex **A**. We may postulate the existence of an equilibrium between complexes **A** and **B** to explain the variation of enantioselectivity observed for a given enyne substrate and different oxygen nucleophiles. Indeed, considering the anti nucleophilic attack on the cyclopropylcarbene intermediates **B**/**B′** as a stereospecific event, the external oxygen nucleophile does not take part in the cyclopropylcarbene formation which therefore represents the enantiodetermining step of this transformation. It is noteworthy that a concerted mechanism based on the addition/cyclization (direct transformation of intermediate **A** to **C** and **C′**) cannot be ruled out and would explain also the influence of the nucleophile on the observed enantioselectivities. Addition of the external nucleophile releases two vinylaurate intermediates **C** and **C′**. Protodemetalation completes the catalytic cycle and affords **2** as an enantiomeric mixture.

In order to get insight into the catalytically active species, we got engaged in a ^{31}P NMR study of the gold complexes formed under our reaction conditions. As a model catalyst, we first investigated the combination of $AuCl_3$, PPh_3 and 3 equiv. of $AgSbF_6$. In a first step, $AuCl_3$ and PPh_3 were mixed in $CDCl_3$. Two phosphorus-containing products were formed in a 1:1 ratio upon mixing for 30 min (Scheme 4, Fig. 1). On the basis of their ^{31}P NMR shifts [21,22], they were respectively, assigned as PPh_3AuCl (δ = +33.3 ppm) and $Ph_3P(O)\cdot HCl$ (δ = +42.5 ppm) [23]. This reactivity can be explained on the basis of an oxidoreduction process involving PPh_3 as a reducing agent. In an initial step, one equivalent of $AuCl_3$ and one equivalent of PPh_3 are converted into AuCl and Ph_3PCl_2. AuCl is then complexed by a second equivalent of PPh_3 to form PPh_3AuCl, whereas Ph_3PCl_2 reacts with traces of water to form $PPh_3P(O)$ and 2 equiv. of HCl. [24] This process is reminiscent to the synthesis of (tht)AuCl involving the reaction of $HAuCl_4$



Scheme 3. Proposed mechanism for the hydroxy- and alkoxycyclization reactions.



Scheme 4. Proposed catalytic gold species for a $AuCl_3/PPh_3$ mixture.

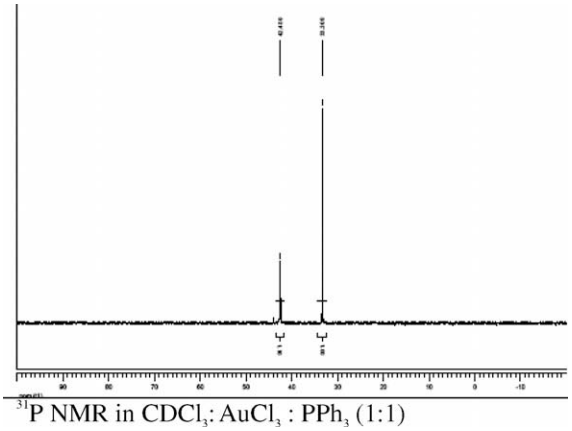


Fig. 1. ^{13}P NMR spectrum for $AuCl_3/PPh_3$ (1/1) mixture.

with 2 equiv. of tetrahydrothiophene (tht) in an alcoholic solution [22].

In a second set of experiments, we studied the nature of the complex formed from the combination of $AuCl_3$ and MeOBIPHEP. Upon mixing a 2:1 ratio of $AuCl_3$ and (*R*)-MeOBIPHEP in CD_3CN, we observed the formation of two products at +23 ppm and +43 ppm after stirring for 30 min (Scheme 5, Fig. 2). The first signal could been assigned to MeOBIPHEP$(AuCl)_2$ complex by comparison with a sample prepared from MeOBIPHEP and (tht)AuCl according to the literature procedure [25]. On the basis of its chemical shift, the second signal was assigned to the hydrochloride adduct of the MeOBIPHEP oxide. Hence, we are assuming that the behavior of the C_2-symmetric chiral bidentate ligand parallels the one observed with PPh_3 and leads to the formation of well-defined Au(I) complexes with a theoretical yield of 50%.

Half of the introduced phosphane playing the role of a sacrificial reductant, it is remarkable to observe that a variation of the P/Au ratio from 1 to 2 did not result in a change of the enantioselectivity (Table 1, entry 9). Under the reaction conditions, we are assuming that the excess $AuCl_3$ may be reduced by a well-known photochemical process to give inactive Au(0) [26,27], thus hampering the possibility to observe a background racemic reaction [28]. Finally, whereas the catalytic active species turned to be the same with both systems, the superior activity observed with the Au(III) precursors versus Au(I) (Table 1, entries 1 and 2) may probably be explained on the basis of Brønsted acid cocatalysis [29], the catalytic amount of HCl produced during the Au(III)/Au(I) reduction process accounting for the difference of reactivity.

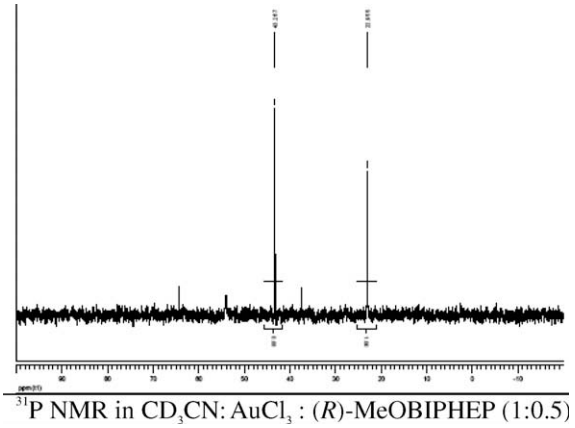


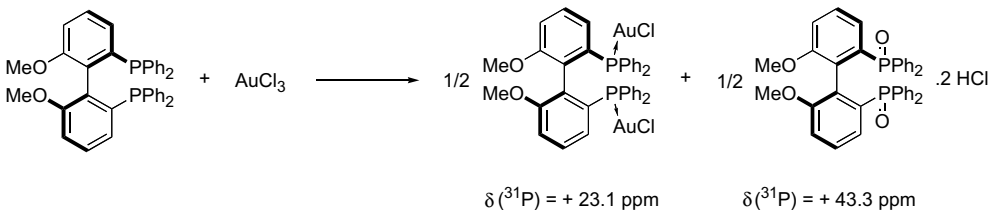
Fig. 2. ^{13}P NMR spectrum for $AuCl_3$/(*R*)-MeOBIPHEP (1/0.5) mixture.

3. Conclusion

The use of $AuCl_3$ associated with a chiral ligand in the presence of silver salts was found to be efficient for the preparation of enantiomerically enriched functionalized alcohols and ethers via hydroxy- and alkoxycyclization reactions. The reaction conditions were optimized, the best chiral inductor being the (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP. The carbon-, oxygen- and nitrogen-tethered enynes reacted smoothly and their cyclization led to various carbocycles and heterocycles in good to excellent yield. The enantioselectivity of the process still needs further optimization as moderate to good enantiomeric excesses are obtained.

4. Experimental section

$AuCl_3$, Ag salts and PPh_3 were commercially available from Cortecnet and Acros and used without further purification. All catalytic manipulations involving air-sensitive reagents were carried out under argon and Schlenk techniques for catalytic tests. Water, dioxane, methanol, ethanol and allylic alcohol were degassed by sparging with argon and/or exposure to vacuum. Column chromatography was performed with 0.040–0.063 mm Art. 11567 silica gel (E. Merck) or Florisil gel 100–200 mesh (Avocado). Optical-rotation measurements were conducted on a Perkin–Elmer 241 polarimeter at 589 nm. High Pressure Liquid Chromatography analyses (HPLC) were performed on Waters instruments (Waters 486 detector, 717 autosampler equipped with Daicel Chiralcel OD-H, OJ and Chiralpak AS-H).



Scheme 5. Proposed catalytic gold species for a $AuCl_3$/(*R*)-MeOBIPHEP mixture.

Enynes **1a–b**, **4a–b**, **7a** and **9a** were prepared according to published procedures [7]. The spectral characterizations of alcohols **2a**, **3a**, **8a** and **10a** and ethers **2b**, **5b** and **6b** are identical to those published in the literature [7].

4.1. Typical procedure for gold-catalyzed hydroxy- and alkoxycyclisation reactions

A mixture of $AuCl_3$ (10 mol%, M = 303.32), (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP (5 mol%, M = 1151.6) and $AgSbF_6$ (30 mol%, M = 343.61), was degassed and stirred 30 min at room temperature in alcohol or dioxane. The enyne was then added to the mixture and water if necessary. The mixture was filtered through a short pad of florisil or silica gel (cyclohexane/EtOAc, 50/50) and the solvents were evaporated under reduced pressure. The crude product was purified if necessary by silica gel flash chromatography (cyclohexane/EtOAc, 90/10).

4.1.1. Dimethyl-4-(1-hydroxy-phenylmethyl)-3-methylene-cyclopentane-1,1-dicarboxylate (**2a**)

Starting from 70 mg of enyne **1a** and following the typical procedure using 1.9 mg (2.5 mol%) of $AuCl_3$, 7.0 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 6.3 mg of $AgSbF_6$ in 0.42 ml of 14% aqueous dioxane at room temperature in one day, compound **2a** was obtained as a pale yellow oil (51 mg, 99%). $[\alpha]_D^{22} = -54.0$ (c = 1.14, $CHCl_3$). HPLC (Chiralcel OD-H, hexane/propan-2-ol (90/10), 1 ml/min, λ = 215 nm): 14′8 and 18′6, *ee* = 72%.

4.1.2. Dimethyl-4-(1-methoxy-phenylmethyl)-3-methylene-cyclopentane-1,1-dicarboxylate (**2b**)

Starting from 50 mg of enyne **1a** and following the typical procedure using 5.3 mg (10 mol%) of $AuCl_3$, 10 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 17.9 mg of $AgSbF_6$ in 0.30 ml of methanol at room temperature in 2 days, compound **2b** was obtained as a pale yellow oil (57 mg, 99%). $[\alpha]_D^{22} = -17.2$ (c = 0.78, $CHCl_3$). HPLC (Chiracel OJ, hexane/propan-2-ol (99/1), 1 ml/min, λ = 215 nm): 36′7 and 39′0, *ee* = 30%.

4.1.3. Dimethyl-4-(1-ethoxy-phenylmethyl)-3-methylene-cyclopentane-1,1-dicarboxylate (**2c**)

Starting from 50 mg of enyne **1a** and following the typical procedure using 5.3 mg (10 mol%) of $AuCl_3$, 10 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 17.9 mg of $AgSbF_6$ in 0.30 ml of ethanol at room temperature in 18 h, compound **2c** was obtained as a pale yellow oil (49 mg, 88%). $[\alpha]_D^{22} = -42.8$ (c = 0.60, $CHCl_3$). HPLC (Chiracel OJ, hexane/propan-2-ol (99/1), 0.5 ml/min, λ = 215 nm): 17′0 and 18′5, *ee* = 55%.

4.1.4. Dimethyl-4-(1-allyloxy-phenylmethyl)-3-methylene-cyclopentane-1,1-dicarboxylate (**2d**)

Starting from 50 mg of enyne **1a** and following the typical procedure using 5.3 mg (10 mol%) of $AuCl_3$, 10 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 17.9 mg of $AgSbF_6$ in 0.30 ml of allylic alcohol at room temperature in 18 h, compound **2d** was obtained as a pale yellow oil (52 mg, 89%). $[\alpha]_D^{22} = -35.2$ (c = 0.63, $CHCl_3$). HPLC (Chiracel OJ, hexane/propan-2-ol (99/1), 0.8 ml/min, λ = 215 nm): 12′2 and 13′8, *ee* = 62%.

4.1.5. Dimethyl-4-(1-hydroxy-methylethyl)-3-methylene-cyclopentane-1,1-dicarboxylate (**3a**)

Starting from 50 mg of enyne **1b** and following the typical procedure using 6.1 mg (10 mol%) of $AuCl_3$, 11.6 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 20.7 mg of $AgSbF_6$ in 0.36 ml of 14% aqueous dioxane at room temperature in 4 days, compound **3a** was obtained as a colorless oil (36.1 mg, 66%). $[\alpha]_D^{22} = -38$ (c = 0.16, $CHCl_3$). HPLC (Chiralcel OD-H, hexane/propan-2-ol (98/2), 1 ml/min, λ = 215 nm): 17′7 and 19′6, *ee* = 24%.

4.1.6. Dimethyl-4-(1-methoxy-methylethyl)-3-methylene-cyclopentane-1,1-dicarboxylate (**3b**)

Starting from 50 mg of enyne **1b** and following the typical procedure using 6.1 mg (10 mol%) of $AuCl_3$, 11.6 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 20.7 mg of $AgSbF_6$ in 0.36 ml of methanol at room temperature in 19 h, compound **3b** was obtained as a colorless oil (55 mg, 99%). $[\alpha]_D^{22} = -2.0$ (c = 0.65, $CHCl_3$). HPLC (Chiracel OJ, hexane/propan-2-ol (99/1), 1 ml/min, λ = 215 nm): 8′3 and 9′4, *ee* = 30%.

4.1.7. 1,1-Bis(phenylsulfonyl)-4-(1-hydroxy-methylethyl)-3-methylene-cyclopentane (**6a**)

Starting from 70 mg of enyne **4b** and following the typical procedure using 5.2 mg (10 mol%) of $AuCl_3$, 9.8 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 17.5 mg of $AgSbF_6$ in 0.30 ml of 14% aqueous dioxane at room temperature in 24 h, compound **6a** was obtained as a colorless oil (70.9 mg, 99%). $[\alpha]_D^{22} = -30.8$ (c = 0.81, $CHCl_3$). HPLC (Chiralpak AS-H, hexane/propan-2-ol (90/10), 1 ml/min, λ = 215 nm): 51′7 and 61′3, *ee* = 72%.

4.1.8. 1,1-Bis(phenylsulfonyl)-4-(1-ethoxy-methylethyl)-3-methylene-cyclopentane (**6c**)

Starting from 60 mg of enyne **4b** and following the typical procedure using 4.7 mg (10 mol%) of $AuCl_3$, 8.8 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 15.8 mg of $AgSbF_6$ in 0.26 ml of ethanol at room temperature in 24 h, compound **6c** was obtained as a yellow oil (66 mg, 99%). $[\alpha]_D^{22} = -25.5$ (c = 0.51, $CHCl_3$). HPLC (Chiralpak AS-H, hexane/propan-2-ol (90/10), 1 ml/min, λ = 215 nm): 17′8 and 19′7, *ee* = 78%.

4.1.9. 4-[1-Hydroxy-(3,4-methylenedioxy)phenylmethyl]-3-methylene-tetrahydrofuran (**8a**)

Starting from 50 mg of enyne **7a** and following the typical procedure using 5.8 mg (10 mol%) of $AuCl_3$, 10.9 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 19.6 mg of $AgSbF_6$ in 0.34 ml of 14% aqueous dioxane at room temperature in 3 days, compound **8a** was obtained as a brown oil (35 mg, 65%). $[\alpha]_D^{22} = -13.6$ (c = 0.66, $CHCl_3$). HPLC (Chiralcel OD-H, hexane/propan-2-ol (98/2), 1 ml/min, λ = 215 nm): 39′7 and 47′1, *ee* = 37%.

4.1.10. 4-[1-Methoxy-(3,4-methylenedioxy)phenylmethyl]-3-methylene-tetrahydrofuran (**8b**)

Starting from 70 mg of enyne **7a** and following the typical procedure using 9.7 mg (10 mol%) of $AuCl_3$, 18.4 mg of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP and 33 mg of $AgSbF_6$ in 0.57 ml of methanol at room temperature in 26 h, compound **8b** was obtained as a colorless oil (45 mg, 56%). $[\alpha]_D^{22} = -10.1$ (c = 0.53, $CHCl_3$). HPLC (Chiralpak AS-H, hexane/propan-2-ol (95/5), 1 ml/min, λ = 215 nm): 9′2 and 10′0, *ee* = 33%.

4.1.11. 3-[(1-Hydroxy)phenylmethyl]-4-methylene-N-tosyl-pyrrolidine 10a

Starting from 70 mg of enyne 9a and following the typical procedure using 6.3 mg (10 mol%) of $AuCl_3$, 13 mg of (R)-4-MeO-3,5-(t-Bu)$_2$-MeOBIPHEP and 22.1 mg of $AgSbF_6$ in 0.39 ml of 14% aqueous dioxane at room temperature in 3 days, compound 10a was obtained as a pale yellow oil (75 mg, 99%). $[\alpha]_D^{22} = -22.3$ (c = 0.67, $CHCl_3$). HPLC (Chiralpak AS-H, hexane/propan-2-ol (90/10), 1 ml/min, λ = 215 nm): 41′0 and 45′5, *ee* = 32%.

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