Ligand Effects in Gold- and Platinum-Catalyzed Cyclization of Enynes: Chiral Gold Complexes for Enantioselective Alkoxycyclization

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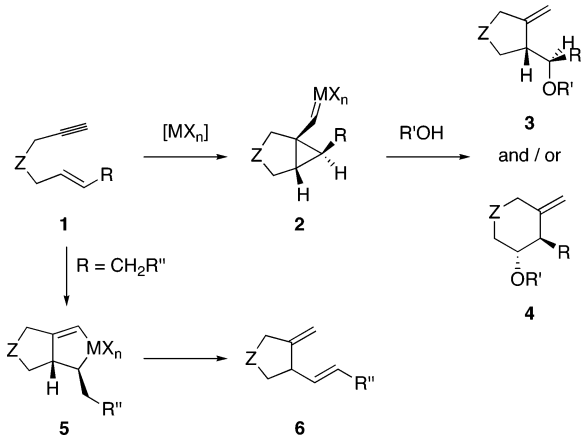
Phosphine and bidentate N−N ligands inhibit the Alder-ene-type cycloisomerization of enynes catalyzed by Pt(II) and favor the alkoxycyclization process. The enantioselective Pt(II)-catalyzed alkoxycyclization has been studied in the presence of chiral mono- and bidentate phosphines, as well as chiral bidentate N−N ligands. Modest levels of enantioselection (up to 50% ee) have been obtained with Tol-BINAP as ligand. The alkoxycyclizations with a catalyst formed from [Au(L)Cl]/AgX proceed more readily, and up to 94% ee's have been obtained using [$(AuCl)_2$(Tol-BINAP)] (**47**) as the precatalyst. The X-ray crystal structures of Au(I) complexes **47** and chloro-(*R*)-2-(*tert*-butylsulfenyl)-1-(diphenylphosphino)ferrocene gold(I) (**39**) show the AuCl fragments monocoordinated with the P centers of the chiral phosphine ligands.

Introduction

The addition of alcohols or water to 1,6-enynes **1** in the presence of $PtCl_2$ as catalyst proceeds via Pt cyclopropyl carbene intermediates **2** (MX_n = $PtLCl_2$, L = R′OH or H_2O) to give five- or six-membered ring alkoxy- or hydroxycyclized compounds **3** and **4** by 5-*exo-trig* or 6-*endo-trig* pathways, respectively.[1,2] The regiochemistry of the process is controlled by substitution pattern on the enyne, in particular by substituents at the alkene and the tether Z.[1,2] Some of these cyclizations are also catalyzed by $AuCl_3$,[1c] Ru(II),[1a,b] and Pd(II)[3] complexes, although the reactions with these catalysts are more limited in scope. Similar intermediates **2** are also involved in other transition-metal-catalyzed cyclization of enynes.[4] For the reactions catalyzed by Pt(II), a competing pathway is the oxidative cyclometalation leading to intermediate **5**, which suffers β-hydrogen elimination to form dienes **6** by a formal Alder-ene process.[1,2] This Alder-ene-type cycloisomerization also proceeds with other d^8 metal complexes as catalysts, such as those based on Pd(II) and Rh(I), as well as d^6 Ru(II) complexes.[1−5] However, in the presence of d^{10} Au(I) complexes $[Au(L)]^+X^-$ (L = phosphine ligand), prepared in situ from [Au(L)Me] and a protic acid, no competing Alder-ene-type cycloisomerization was observed.[6]

Scheme 1



Here we report the effect of phosphines and oxazolines as ligands in the selectivity of the Pt-catalyzed alkoxycyclization versus Alder-ene-type cycloisomerization of enynes **1**. Modest enantioselectivities are obtained by using chiral bidentate phosphines. We also report the first examples of enantioselective alkoxycyclization by using chiral Au(I) catalysts. While our work was in

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progress, the groups of Michelet, Genêt, and Gladiali reported that Pt(II) cationic complexes of (*R*)- or (*S*)-Ph-BINEPINE, a monodentate phosphine ligand, gave up to 85% ee in this reaction.[7]

Results and Discussion

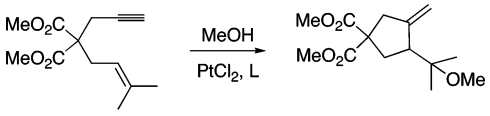
Pt(II) Catalysts with P- or N-Donor Ligands. We analyzed the effect of ligands in the reaction of enyne **7**, with MeOH as solvent in the presence of Pt(II) complexes prepared in situ from $PtCl_2$, and ligands L (Table 1). In the absence of ligand, the reaction of **7** provided a 2:1 mixture of **8** and **9** (Table 1, entry 1).[1b,d] In contrast, in the presence of mono- and bidentate phosphines, exclusive methoxycyclization was observed in all cases. It is interesting to note that the potentially competitive addition of MeOH to the alkyne to form an enol ether[8] does not compete with the cyclization process. Better results were obtained by using $P(C_6F_5)_3$ or P(*o*-Tol)$_3$ than PPh_3 (Table 1, entries 2−4). The use of a 2:1 ratio of phosphine to Pt(II) led only to a small decrease in the yield of **8** (Table 1, compare entries 4 and 5). Bulky, biphenyl-based phosphine **10** gave a good yield of **8**, although the reaction was not complete after 17 h (Table 1, entry 6). The reaction was very slow with phosphine **11**[9] (Table 1, entry 7). Bidentate phosphines dppe, dppp, dppb, dppf, and **12** gave satisfactory results (Table 1, entries 8−12), dppp being the best ligand (Table 1, entry 9).

As shown in Figure 1, a monodentate phosphine such as P(*o*-Tol)$_3$ accelerates the reaction of **7**, the methoxycyclization being complete in less than 1 h. On the other hand, in the presence of [Pt(dppf)Cl_2],[10] formed in situ under the conditions of entry 11 (Table 1), the methoxycyclization is considerably retarded.

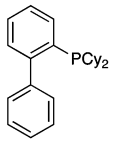
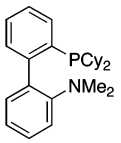
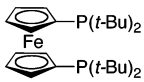
These results indicate that the Alder-ene-type cycloisomerization reaction is inhibited by phosphine ligands, which is somewhat surprising since that process involves a formal 2-e oxidation at the metal to form a Pt(IV) metallacycle (see **5**, Scheme 1) that should be stabilized by stronger donor ligands. The inhibition may be explained by the displacement of weaker alkene ligand[1b] by the phosphine in the initial Pt(II)-enyne complex, thus preventing the oxidative cyclometalation. The exclusive formation of methoxycyclization products in the presence of phosphine ligands strongly supports the proposal of two different mechanisms for these two reactions.

Bidentate ligands such as 4,4′-bipyridine, 4,4′-dimethylbipyridine, or phenantroline (Table 2, entries 1−3) gave poor results.[11] Less basic quinoline led to a mixture of **8** and **9** in moderate yield (Table 2, entry 4). Oxazolines have shown to be excellent ligands in transition metal chemistry.[12] We decided to employ pyridine-oxazoline (**13**) and py-box (**14**)[13] in the methoxycycliza-

Table 1. Influence of Phosphine Ligands in the $PtCl_2$-Catalyzed Reaction of Enyne 7[a]



7 **8** + **9**

entry	L (mol%)	yield (%)	**8**:**9** ratio
1	-	97	63:34
2	PPh_3 (5)	59	>99:<1
3	$P(C_6F_5)_3$ (5)	76	>99:<1
4	P(*o*-Tol)$_3$ (5)	76	>99:<1
5	P(*o*-Tol)$_3$ (10)	69	>99:<1
6	 **10** (5)	87[b]	>99:<1
7	 **11** (5)	50[b]	>99:<1
8	dppe (5)	83[b]	>99:<1
9	dppp (5)	93	>99:<1
10	dppb (5)	76	>99:<1
11	dppf (5)	82	>99:<1
12	 **12** (5)	72	>99:<1

[a] All reactions were carried out in MeOH under refluxing conditions with 5 mol % of $PtCl_2$ for 16 h. Unless otherwise stated, conversions were >99%. [b] Conversion < 90%. In this case, the yield was determined by ^{1}H NMR.

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(10) Clemente, D. A.; Pilloni, G.; Corain, B.; Longato, B.; Tiripicchio-Camellini, M. *Inorg. Chim. Acta* **1986**, *115*, L9-L11.
(11) Complexes of the type [Pt(N−N)(alkyne)X_2] (N−N = bidentate N-donor ligand) prefer a five-coordinate trigonal-bipyramidal structure when the alkyne is a strong π-accepting ligand. Otherwise, even with rigid phenantroline ligands, the resulting Pt(II) complexes are square-planar four-coordinated. See: Fanizzi, F. P.; Maresca, L.; Natile, G.; Lanfranchi, M.; Tiripicchio, A.; Pacchioni, G. *Chem. Commun.* **1992**, 333−335.
(12) For Pt(II)-oxazoline complexes, see: (a) Motoyama, Y.; Mikami, Y.; Kawakami, H.; Aoki, K.; Nishiyama, H. *Organometallics* **1999**, *18*, 3584−3588. (b) Wang, X.; Chakrapani, H.; Madine, J. W.; Keyerleber, M. A.; Widenhoefer, R. A. *J. Org. Chem.* **2002**, *67*, 2778−2788. (c) Motoyama, Y.; Kawakami, H.; Shimozono, K.; Aoki, K.; Nishiyama, H. *Organometallics* **2002**, *21*, 3408−3416. (d) Fossey J. S.; Richards, C. J. *Organometallics* **2004**, *23*, 367−373.

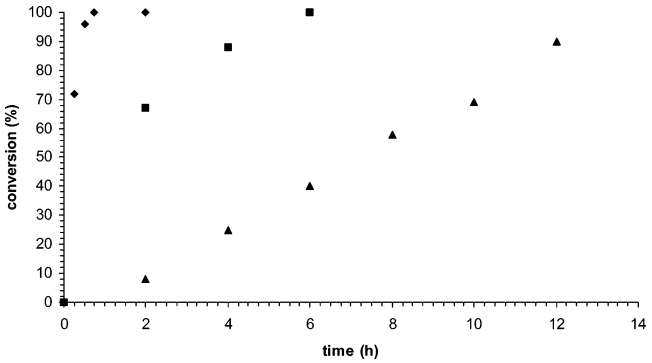
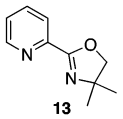
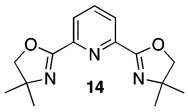


Figure 1. Reaction of **7** in MeOH in the absence or presence of phosphines (refluxing conditions): (■) reaction without phosphine to give a 67:33 mixture of **8** and **9**; (◆) reaction with 5 mol % of P(*o*-Tol)$_3$ to give **8**; (▲) reaction with 5 mol % of dppf to give **8**.

Table 2. Influence of N Ligands in the $PtCl_2$-Catalyzed Reaction of Enyne 7[a]

entry	ligand (mol%)	AgX (10 mol%)	yield (%)	**8**:**9** ratio
1	4,4'-DiMebipy	-	3[b]	>99:<1
2	Phen	-	9[b]	>99:<1
3	Bipy (5)	$AgBF_4$	20[b]	>99:<1
4	 (10)	-	58	86:14
5	 **13** (5)	-	23[b]	>99:<1
6	**13** (10)	$AgBF_4$	40[b]	>99:<1
7	**13** (10)	AgOTf	96	>99:<1
8	 **14** (5)	AgOTf	91	>99:<1

[a] All reactions were carried out under refluxing conditions with 5 mol % of $PtCl_2$ for 19 h. [b]Conversion ca. 50%. In this case, the yield was determined by ^{1}H NMR.

tion of the enyne **7**. Although, low reactivity was found for the $PtCl_2$·**13** complex, excellent conversions of **7** into methoxycyclization product **8** were obtained in the presence of AgOTf (Table 2, entries 7 and 8).

As a last aspect, the effect of the simple MeCN ligand was also examined in the reaction of substrates **15** and **16** in MeOH to give **17** and **18**, respectively[1] (Scheme 2). Qualitative comparison of the reaction rates should shed light on the nature of the rate-determining step in these processes. Thus, if formation of cyclopropyl Pt(II)-carbenes **19** and **20** is rate determining, **15** should react faster than **16** through intermediate **19** that bears the Ph substituent at the less hindered exo face of the bicyclo[3.1.0]heptene structure. On the other hand, in the event that attack of methanol is the slow step, enyne

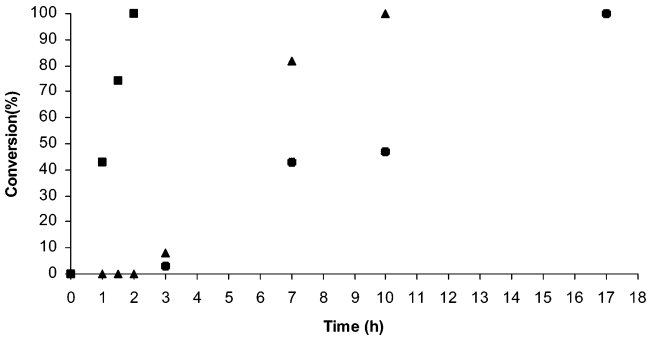
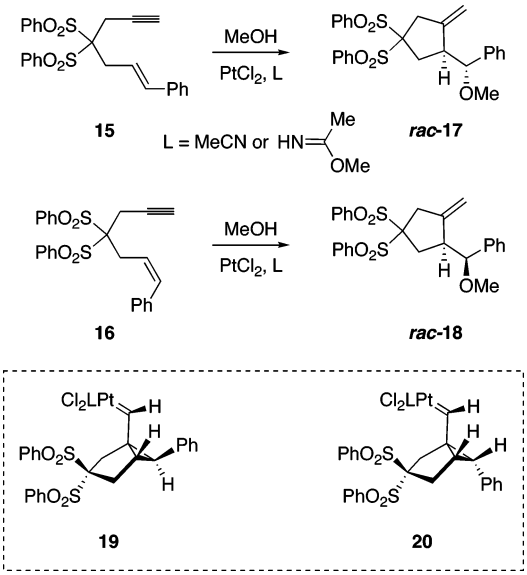


Figure 2. Reaction of enyne **15** in MeOH to give **17**: (●) reaction catalyzed by $PtCl_2$; (▲) reaction catalyzed by $PtCl_2$ preheated in MeOH; (■) reaction catalyzed by $[Pt(MeCN)_2Cl_2]$.

Scheme 2



16 should be more reactive, as the nucleophile would approach the less hindered exo face of the bicyclic intermediate **20**.

When the reaction was carried out by mixing the enyne and 5 mol % of $PtCl_2$ in MeOH at 80 °C, no conversion of the starting material was observed until 3 h. However, the reaction was complete in 17 h, giving a sigmoid curve, showing an induction period (Figure 2).[14] When the reaction was performed preheating the $PtCl_2$ in MeOH for 12 h before the addition of the enyne to the reaction mixture, a similar induction period was observed. However, from this point, the reaction was faster than in the previous case, being complete in 10 h. The low solubility of $PtCl_2$ in MeOH might explain the induction period. In fact, when more soluble $[Pt(MeCN)_2Cl_2]$ was used as the catalyst, no induction period and much faster reaction were observed. It is important to note that it has been described that MeOH reacts with $[Pt(RCN)_2Cl_2]$ to form Pt(II) complexes with iminoesther ligands.[15]

(13) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119−3154.

(14) Reaction of the malonate analogue of **15** takes place in aqueous solvents to give the corresponding hydroxycyclization product.[1] This reaction proceeds similarly in aqueous acetone (86% yield after 6 days with 5% $PtCl_2$) or aqueous dioxane (84% yield after 6 days with 10% $PtCl_2$ or 53% with 5% $PtCl_2$). In ref 7 (Table 1, entry 1), reaction of this substrate with 10% $PtCl_2$ in aqueous dioxane is claimed to give only traces of hydroxycyclization product after a reaction time of 5 days.

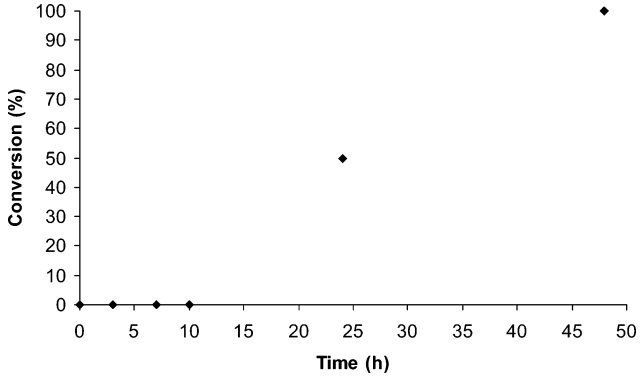
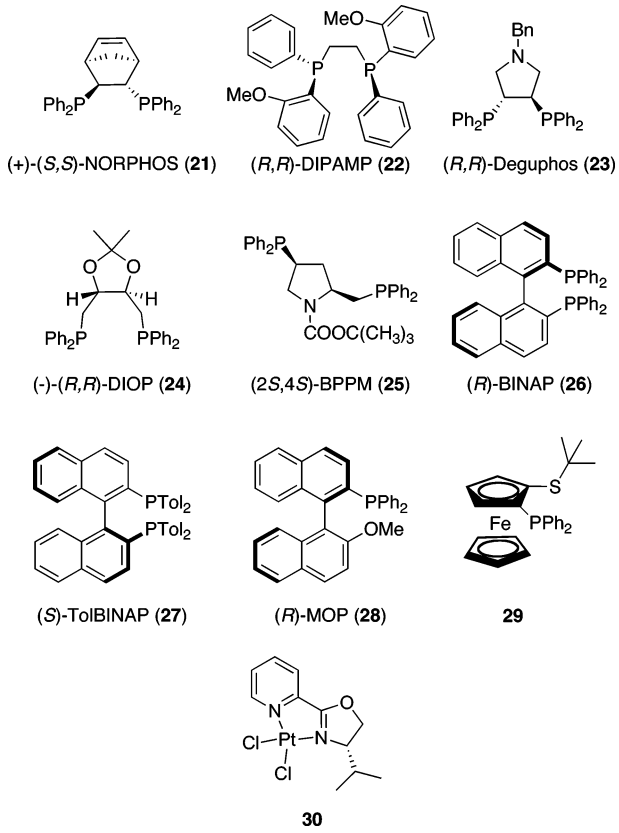


Figure 3. Reaction of enyne **16** in MeOH to give **18** catalyzed by $PtCl_2$.

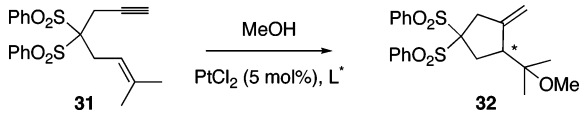
Chart 1



Enyne **16**, bearing a *cis*-disubstituted alkene, reacted more slowly with $PtCl_2$ in MeOH to form **18**, and a longer induction period (ca. 10 h) was observed (Figure 3). This result supports a mechanistic scenario in which formation of cyclopropyl Pt(II)-carbenes as intermediates is the rate-determining step.

Pt(II) Catalysts with Chiral P- or N-Ligands. We tried chiral bidentate phosphines **21**−**27**, monodentate phosphine **28**, potentially bidentate phosphine thioether **29**, and chiral pyridyl oxazoline Pt(II) complex **30** (Chart 1) in the methoxycyclization of enyne **31** to give **32** (Table 3). The reaction in the presence of C_2-symmetric biphosphines, such us NORPHOS (**21**), DIPAMP (**22**), Deguphos (**23**), or DIOP (**24**), as well as with BPPM (**25**) gave good yields of **32**, although the enantioselectivities were very low in all cases (Table 3, entries 1 and 4−7). The addition of silver salts in the case of **21** led to lower yields (Table 3, entries 2 and 3). Better results were obtained with Tol-BINAP (**27**) (Table 3, entries 9 and 10). The reaction with the chiral biscationic platinum complex, $[Pt(PhCN)_2$-(*R*)-BINAP$](BF_4)_2$,[16] gave a good yield of **32**, but no asymmetric induction was observed. In the case of the monophosphine derivative (*R*)-MOP (**28**),[17] an excellent yield was obtained in 48 h, but the enantioselectivity was low (Table 3, entry 11). In the presence of a 2:1 ratio of **28** to $PtCl_2$, no reaction was observed. Reaction in the presence of a ferrocenylphosphine **29**, with planar chirality,[18] led only to traces of the alkoxycyclization product **32** (Table 3, entry 12). Pt(II) complex **30** gives only a productive catalyst in the presence of $AgBF_4$ (Table 3, entries 13 and 14), although the enantioselectivity is low.[19]

Table 3. Alkoxycyclization of Enyne 31 with $[Pt(L^*)Cl_2]$ Complexes with Chiral Ligands 21−29 and Complex 30[a]



entry	L*	additive (10 mol %)	time (h)	yield (%)	% ee (config)
1	**21**		21	99	0
2	**21**	AgOTf	40	59	16 (+)
3	**21**	$AgSbF_6$	40	35	12 (+)
4	**22**		19	100	4
5	**23**		40	87	0
6	**24**		24	97	6
7	**25**		40	99	26 (+)
8	**26**		16	86	32 (−)
9	**27**		24	97	48 (+)
10[b]	**27**		192	62	50 (+)
11	**28**		48	100	12 (+)
12	**29**		48	< 5	
13[c]	**30**		40		
14[c]	**30**	$AgBF_4$	17	97	10 (+)

[a] Unless otherwise stated all reactions were carried under reflux conditions. [b] Reaction carried out at room temperature. [c] Preformed complex **30** was used as precatalyst.

We tried determining the configuration of **32** by derivatization of the corresponding alcohol with a chiral ester (i.e., Mosher or mandelate ester). However, attempted demethylation of the methyl ether of **32** with BBr_3 at −78 °C led only to the decomposition of the starting material.

Au(I) Catalysts with Chiral P-Ligands. A chiral ferrocenylphosphine-Au(I) complex has been used in the reaction of aldehydes with α-isocyanoacetate esters with high enantioselectivities.[20] This precedent in Au(I) chemistry led us to synthesize ferrocenylphosphine-Au(I) complexes as potential catalysts for the enantioselective methoxycyclization of enynes.

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(17) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354−362.

(18) (a) García-Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679−3686. For related ligands, see: (b) Priego, J.; García Mancheño, O.; Cabrera, S.; Carretero, J. C. *J. Org. Chem.* **2002**, *67*, 1346−1353. (c) Mancheño, O.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 4566−457. (d) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3944−3947.

(19) For a recent review on applications of oxazoline-containing ligands in asymmetric catalysis, see: McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151−4202.

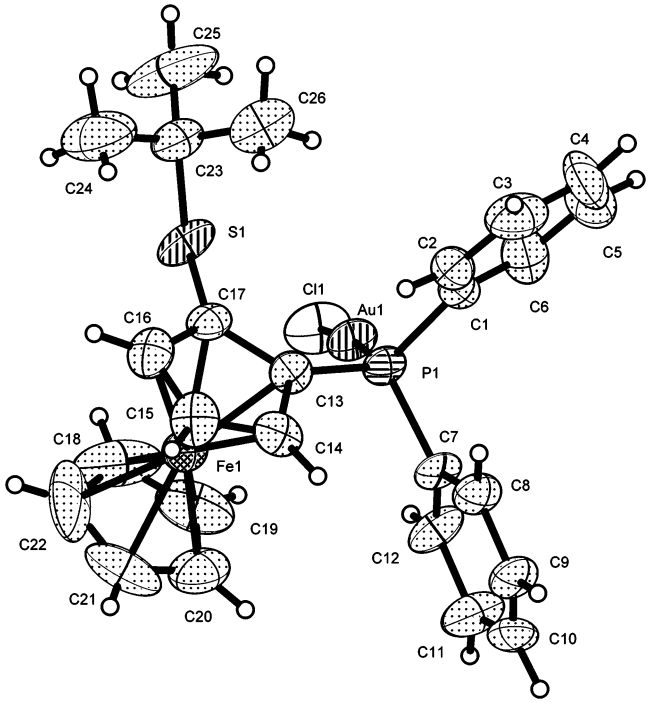
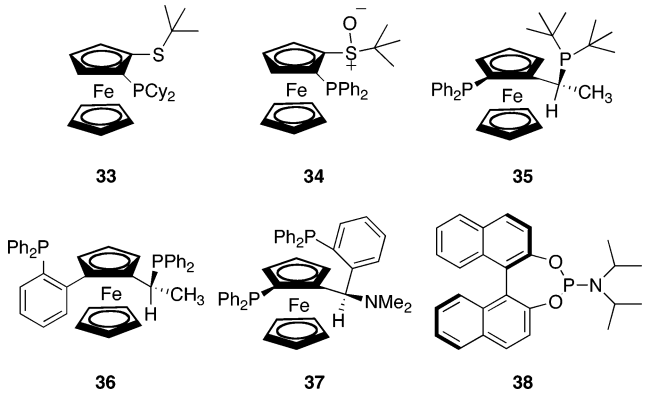


Figure 4. Structure of Au(I) complex **39**. Selected bond distances (Å) and angles (deg): Au(1)−P(1), 2.230(2); Au(1)−Cl(1), 2.289(2); P(1)−Au(1)−Cl(1), 174.25(10); C(1)−P(1)−Au(1), 116.3(3); C(13)−P(1)−Au(1), 114.1(3); C(7)−P(1)−Au(1), 111.2(3).

Chart 2



Au(I) complexes were synthesized from $Na[AuCl_4]\cdot H_2O$ and the corresponding chiral ligands, following the methodology described by Parish et al.[21] As ligands, we used phosphines **26**−**28**, Fesulphos (**29**, **33**, and **34**),[18] Josiphos (**35**), Walphos (**36**), Taniaphos (**37**), and binol derivative **38**[22] (Charts 1 and 2).

The structure of complex **39**, obtained as an orange solid in 96% yield from ligand **29** and $Na[AuCl_4]\cdot 2H_2O$,[21] is shown in Figure 4. Unlike previously reported Pd(II) and Cu(I) complexes of the P,S-ligand **29**,[18] in which both phosphorus and sulfur atoms are coordinated to the metal, this shows that Au(I) coordinates exclusively with the phosphorus atom.[23] The same monodentate character is proposed for complexes **40** and **41** synthesized from the Fesulphos ligands **33** and **34**, respectively (Chart 3).

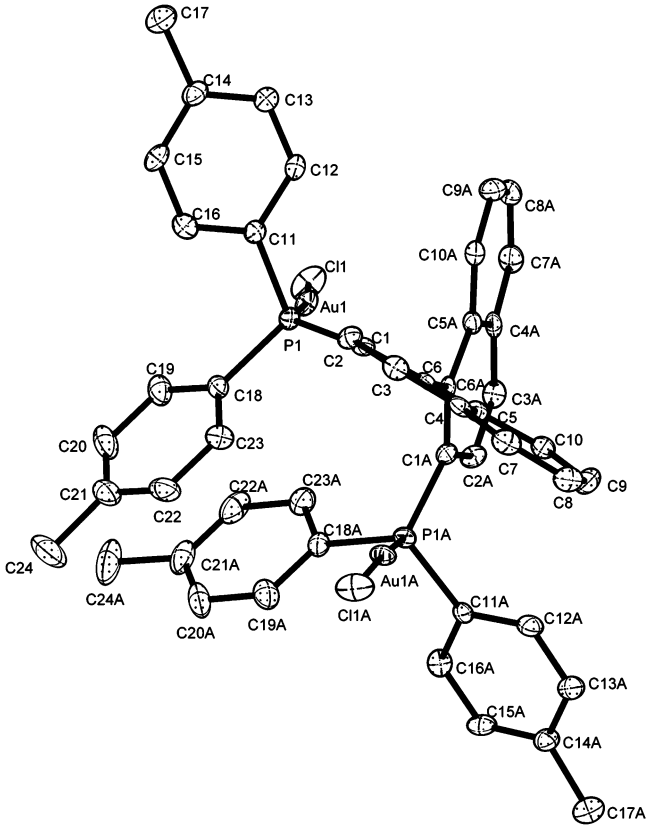
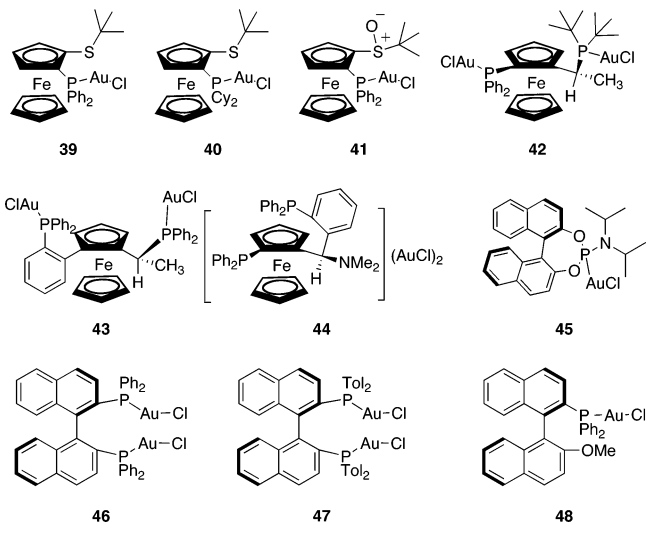


Figure 5. X-ray crystal structure of Au(I) complex **47**. Selected bond distances (Å) and angles (deg): Au(1)−P(1), 2.2353(8); Au(1)−Cl(1), 2.2880(9); P(1)−Au(1)−Cl(1), 172.69(4); C(1)−P(1)−Au(1), 122.55(12); C(11)−P(1)−Au(1), 107.04(11); C(18)−P(1)−Au(1), 109.73(12).

Chart 3



Although ligands **35** and **36** have two P atoms, the $^{31}P\{^1H\}$ NMR spectra of the corresponding Au(I) complexes **42** and **43** (Chart 3) showed two singlet signals,

(20) (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406. (b) Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649−1664. (c) Hughes, P. F.; Smith, S. H.; Olson, J. T. *J. Org. Chem.* **1994**, *59*, 5799−5802.

(21) (a) Al-Sady, A. L.; McAuliffe, C. A.; Parish, R. V.; Sandbank, J. A. *Inorg. Synth.* **1985**, *23*, 191. For the synthesis of gold complexes using this methodology, see: (b) Alder, M. J.; Flower, K. R.; Pritchard, R. G. *J. Organomet. Chem.* **2001**, *629*, 153−159.

(22) de Vries, A. H. M.; Meetsma, A.; Feringa, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374−2376.

(23) For Au(I) complexes dicoordination is preferred, see: Carvajal, M. A.; Novoa, J. J.; Alvarez, S. *J. Am. Chem. Soc.* **2004**, *126*, 1465−1477.

Table 4. Alkoxycyclization of Enyne 31 with Chiral Phosphine Au(I)-L* Complexes[a]

entry	L*	Au(I) complex	time (h)	yield (%)	% ee (config)
1	**29**	**39**	23	92	18 (+)
2	**33**	**40**	3	100	11 (+)
3[b]	**33**	**40**	48	84	5 (+)
4	**34**	**41**	2	100	8 (−)
5	**35**	**42**	96	100	42 (+)
6	**36**	**43**	8	84	38 (+)
7	**37**	**44**	23	99	17 (−)
8	**38**	**45**	48	60	< 2
9	**26**	**46**	22	98	39 (−)
10	(*R*)-**27**	**47**	3	93	43 (−)
11[c]	(*R*)-**27**	**47**	30	98	14 (+)
12[d]	(*R*)-**27**	**47**	4	89	53 (−)
13[e]	(*R*)-**27**	**47**	48	100	34 (−)
14	**28**	**48**	2	94	< 2
15[f]	**26**	**49**	24	100	13 (−)
16	(*R*)-**27**	**50**	8	100	45 (−)

[a] Reactions were carried out in MeOH at room temperature with 2 mol % [Au(L*)Cl] (or 1.6 mol % [L*(AuCl)$_2$] in entries 5, 6, 9, and 10) and 2 mol % $AgSF_6$. [b] Reaction in the absence of silver salt. [c] Reaction performed in CH_2Cl_2 with 10 equiv of MeOH with 2 mol % **47** and 4 mol % $AgSF_6$. [d] Reaction performed in CH_2Cl_2 with 10 equiv of MeOH with 1.6 mol % **47** and 2 mol % $AgSF_6$. [e] Reaction performed with 3 mol % **47** in the absence of Ag(I) salt. [f] Reaction performed with 1.5 mol % **49** and 2 mol % phosphotungstic acid.

which indicates that the two phosphorus atoms are not coordinated to the same Au atom. However, the ^{31}P NMR spectrum of the Au(I) complex **44**, synthesized from the Taniaphos ligand (**37**), showed two groups of signals of two species in equilibrium. One of these complexes shows a pair of doublets, which corresponds to the two ^{31}P atoms coordinated to the same Au atom.[24]

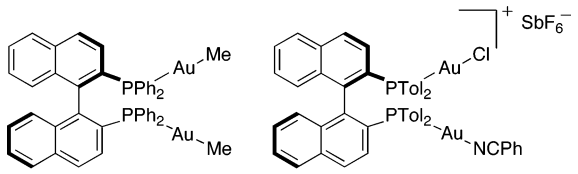
For the methoxycyclization of enynes catalyzed by [Au(PPh$_3$)Me], an acid HX was required as an activator to form the cationic complex.[6] Complex [Au(PPh$_3$)Cl], in the presence of silver salts, did not catalyze the methoxycyclization, which indicates that complexes of the type [Au(PPh$_3$)(MeOH)]X are either not stable or not sufficiently reactive in this reaction. However, in the case of the Au(I) complexes with bulky chiral phosphines, the Au(I)-chloride complexes in the presence of a silver salt gave cationic complexes reactive enough to catalyze the reaction. Results on the enantioselective methoxycyclization of enyne **31** with chiral Au(I) complexes (**39**−**50**) are shown in Table 4.

Complex **39** gave the methoxycyclization product in very good yield, but the asymmetric induction was very low (Table 4, entry 1). Changing the phosphine to a better electron donor in complex **40** improved the reactivity (Table 4, entry 2), although the enantioselectivity was lower. In the absence of silver salt, the reactivity and enantioselectivity decreased (Table 4, entry 3). A similar result was obtained with **41**, although the opposite enantioselection was observed (Table 4, entry 4). Complex **42** was the less reactive, although **32** was obtained with moderate enantioselectivity (42% ee) (Table 4, entry 5). Moderate or low enantioselection was obtained with complex **43** or **44**, respectively (Table 4, entries 6 and 7), while complex **45** prepared from monodentate ligand **38** was not effective (Table 4, entry 8).

Complex **47** with the (*R*)-TolBINAP ligand gave the best results, being considerably more reactive than **46**

(24) For a related equilibrium see ref 20b.

Chart 4



49 **50**

((*R*)-BINAP as ligand) (Table 4, entries 9 and 10). When the ratio of Au/Ag was 1:1, the asymmetric induction decreased and, remarkably, the opposite enantiomer was obtained in excess (Table 4, entry 11). For the activation of complex **47** the best results were obtained by less than stoichiometric amount of Ag(I), 1.6:2 (Table 4, entry 12), which presumably leads to a monocationic complex. This experiment was performed in CH_2Cl_2 containing 10 equiv of MeOH. Similar reactivity was observed in Et_2O, acetone, dioxane, or nitromethane, whereas no reaction took place with 10 equiv of MeOH in toluene, DMF, CH_3CN, or THF. The methoxycyclization proceeded in the absence of silver salt (Table 4, entry 13), although the reaction time increased, and the enantioselectivity decreased. Lowering the reaction temperature to −78 °C led to a very slow conversion, and only traces of the alkoxycyclization products were observed. No methoxycyclization was observed with $AgSbF_6$ (2 mol %) and (*S*)-TolBINAP (2 mol %) in MeOH at room temperature, in the absence of Au(I) after long reaction times. The reaction with complex **48** prepared from the (*R*)-MOP ligand (**28**) was fast, although no enantioselection was obtained (Table 4, entry 14).

All attempts to synthesize a complex with two P coordinated to the same Au(I) atom failed.[25] The X-ray crystal structure of complex **47** reveals that the two atoms of Au(I) are monocoordinating to each P atom (Figure 3). Related BINAP-Ag(I) complexes have been isolated by Yamamoto and were shown to be excellent Lewis acid catalysts in a variety of reactions.[26] However, for the reactions of enynes, Ag(I) complexes proved to be rather poor catalysts.[27] The coordination of Au(I) in **47** is therefore similar to that of the ferrocenyl complexes **39** (Figure 1), **42**, and **43**.

The dimethyl derivative **49** was also synthesized from the chloride complex **46** following the methodology described for [Au(PPh$_3$)Me] (Chart 4).[28] The reaction of **31** with the presumed dicationic complex resulting from **49** (1.5 mol %) and phosphotungstic acid (2 mol %) gave **32** in quantitative yield, although with lower ee than that obtained in Table 4 (compare entries 9 and 15). A cationic complex derived from **47** was isolated and tentatively assigned as **50** based on the NMR data. Reaction of **31** in MeOH with this complex gave **32** quantitatively and with similar enantiomeric excess than that obtained when the cationic complex was formed in situ (Table 4, compare entries 10 and 16).

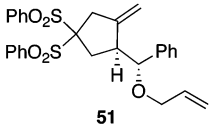
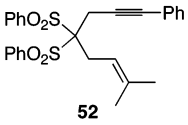
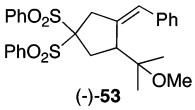
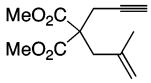
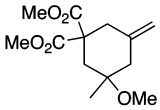
(25) A trinuclear complex with two phosphorus from different ferrocenyl ligands, coordinated to the same gold atom, has been described: Togni, A.; Pastor, S. D.; Rihs, G. *J. Organomet. Chem.* **1990**, *381*, C21−C25.

(26) (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360−5361. (b) See also: Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yayamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723−4724.

(27) For an interesting side reaction catalyzed by Ag(I), see: Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, in press.

(28) Synthesis of [Au(PPh$_3$)Me]: Tamaki, A.; Kochi, K. *J. Organomet. Chem.* **1973**, *61*, 441−445.

Table 5. Asymmetric Alkoxycyclization of Enynes[a]

entry	enyne	solvent	t (h)	T (°C)	product (yield, %)	% ee
1	**15**	1:1 MeOH-CH_2Cl_2	24	60	**17** (100)	49
2	**15**	CH_2=$CHCH_2OH$	18	24	 **51** (46)	36
3	 **52**	MeOH	168	24	 (-)-**53** (52)	94
4	**7**	MeOH	7	24	**8** (91)	*ca.* 2
5	 **54**	MeOH	72	24	 (+)-**55** (41)	30

[a] Reactions were carried out with 1.6 mol % **47** and 2 mol % of $AgSF_6$.

Although the asymmetric induction obtained in the methoxycyclization of **31** with cationic Au(I) complexes was not high, the reaction proceeds at room temperature, in contrast with that found in the asymmetric version catalyzed by Pt(II), which requires heating at 60−80 °C.[7] We therefore decided to test the performance of the best complex, **47**, in the alkoxycyclization of enynes with different substitution patterns. Thus, enyne **15** gave the methoxycyclization product **17** at 60 °C in excellent yield and moderate enantioselectivity (Table 5, entry 1). Reaction of **15** with allyl alcohol at room temperature provided **51** in 36% ee (Table 5, entry 2). Interestingly, enyne **52**, with a phenyl-substituted alkyne, gives **53** in moderate yield but with an excellent 94% ee (Table 5, entry 3), which exceeded the best result obtained in the Pt(II)-catalyzed hydroxycyclization (85% ee) or methoxycyclization (78% ee) reported by Michelet, Genêt, and Gladiali.[7] This high enantioselectivity might be a consequence of the more crowded nature of the corresponding cyclopropyl Au(I)-carbene intermediate resulting form the phenyl-substituted alkyne. On the other hand, enyne **7** gave almost racemic **8** (Table 5, entry 4). Enyne **54** reacts by a 6-*endo-trig* pathway to afford **55** in only 30% ee (Table 5, entry 4).

Determination of the Configuration. For the determination of the absolute configuration of the carbocycles by derivatization of the corresponding alcohols via the Mosher esters,[29] cleavage the Me−O bond of the methyl ethers was attempted using BBr_3.[30] However, decomposition of the starting material was always observed. As an alternative, Pd-catalyzed deallylation of **51** (36% ee) provided alcohol **56**, which reacted with (*R*)-(−)-MTPACl in pyridine for 2 h at room temperature to give a 2.1:1 mixture (36% de) of two MTPA esters. Analysis of their ^1H and ^{13}C NMR spectra led to the assignment of the absolute configuration for the major alcohol as shown.[31]

51 **56** (57%) (1)

Conclusions

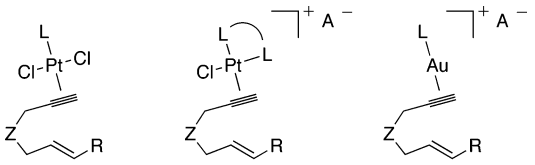
Our results support the proposal for two different mechanisms for the Alder-ene-type cycloisomerization and the alkoxycyclization of enynes as shown in Scheme 1. Thus, the Alder-ene-type cycloisomerization of enynes catalyzed by Pt(II) is inhibited by phosphine ligands L, probably due to displacement of the weaker alkene ligand by the phosphine in the initial Pt(II)-enyne complex, leading to Pt(alkyne)(L)Cl_2 complexes of type **57** (or the corresponding *cis* isomers). Similarly, the methoxycyclization also takes place selectively in the presence of bidentate phosphines, although in this case the reaction, which presumably proceeds through com-

(29) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (c) For application of this method see: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (d) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117.

(30) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773−5780.

(31) (a) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Chapter 7. (b) Details for the configuration assignment are given in the Supporting Information.

plexes of type **58**, are slower that those via **57**. With bidentate pyridine-oxazoline (**13**) and py-box (**14**), the reaction only proceeds satisfactorily in the presence of AgOTf, which suggests that with N−N ligands cationic complexes **58** are the productive intermediates in the alkoxycyclization.



57 **58** **59**

Achieving high levels of enantioselection in the alkoxycyclization appears to be rather challenging, as these reactions probably proceed by means of intermediates such as **57**−**59**, where the attacking alkene is far from the chiral L ligand. With regard to the Pt(II)-catalyzed reactions, the best results were obtained with Tol-BINAP as ligand. In this, and related cases, the addition of Ag(I) salt was not required to form catalytically active Pt(II) complexes. Among the Au(I) complexes studied, [Tol-BINAP($AuCl)_2$] (**47**) gives the best results in the presence of a Ag(I) salt. Although, in general, the asymmetric inductions obtained are not high, the reactions proceed at room temperature, in contrast with that found in the reactions catalyzed by Pt(II), which require heating at 60−80 °C. Enyne **52**, with a less reactive phenyl-substituted alkyne, leads to a good level of enantioselection. Further work to establish the nature of the active catalytic species formed from **47** is underway as a lead to develop more active and enantioselective Au(I) catalysts.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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